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Rapprocher les études sur le placebo et la kinésithérapie : une thèse exploratoire

Bridging placebo studies with physiotherapy: An exploratory thesis

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THESIS SUMMARY

This thesis explores the potential for physiotherapy to learn from and contribute to placebo studies. It argues that placebo studies may offer valuable insights into how physiotherapy interventions can be optimized for patient benefit while also contributing to placebo studies. The thesis reports on three through three individual studies examining the use of placebo treatments and contextual factors (CFs) in physiotherapy.

The first study is a non-inferiority randomized controlled study on healthy participants that compared the effectiveness of an open-label placebo (OLP) to a deceptive placebo (DP) in relieving experimentally induced pain. The results indicate that the OLP, when delivered with an educational video, is not inferior to the DP. The second study explored the acceptability of both these treatments through semi-structured interviews of eight trial participants who had experienced either a DP or an OLP. The results suggest the acceptability of placebo treatments depends on individual preferences. Some viewed effectiveness as the primary factor in deciding whether the treatment was acceptable, while others emphasized the importance of respecting their autonomy and voiced a preference not to be deceived, even if the treatment is effective.

The third study examined the use of CFs among healthcare professions through a web-based survey. The survey was administered in French-speaking European countries and results revealed that the use of CFs may be even more widespread than placebo treatment use. Communication was the most commonly reported CF used to elicit placebo effects. Factors grouped within the therapeutic relationship and patient characteristics categories were most often employed. The results emphasized the need for further research to gain a deeper understanding of practitioner thought processes when implementing these approaches, as well as the establishment of an ethical framework to ensure their justified use.

The thesis concludes that considerably more research is required before OLPs can be clinically utilised in physiotherapy. Ethical guidelines for the use of CFs to

enhance placebo effects should be developed, and education on placebo and nocebo effects, including into healthcare ethics, should be integrated into physiotherapy training and continuing education. Future research directions could focus on developing placebo controls to better evaluate the effectiveness of physiotherapy interventions.

RÉSUMÉ DE LA THÈSE

Cette thèse explore le potentiel de la kinésithérapie à s'enrichir des études sur le placebo et à contribuer à ces dernières. Elle soutient que les études sur le placebo peuvent offrir des informations précieuses sur la façon dont les interventions en kinésithérapie peuvent être optimisées au bénéfice du patient. La thèse rapporte les résultats de trois études distinctes examinant le cas des traitements placebo puis des facteurs contextuels (CFs).

La première étude est une étude randomisée contrôlée de non-infériorité comparant l'efficacité d'un placebo ouvert (OLP) à un placebo associé au mensonge (DP) pour le soulagement d'une douleur expérimentalement induite chez des participants sains. Les résultats indiquent que les effets induits par l'OLP, lorsqu'il est accompagné d'une vidéo éducative, ne sont pas inférieurs à ceux induits par le DP. La seconde étude explore l'acceptabilité de ces deux formes de traitements (OLP et DP) par le biais d'entretiens semi-structurés avec huit participants de l'essai clinique précédemment mentionné. Les résultats suggèrent que l'acceptabilité des traitements relève de préférences individuelles. Certains considèrent l'efficacité comme un facteur déterminant pour décider si le traitement est acceptable, tandis que d'autres soulignent l'importance de respecter leur autonomie de décision et expriment leur préférence à ne pas être trompés, indépendamment de l'efficacité.

La troisième étude examine l'utilisation des CFs par les professionnels de santé par le biais d'une enquête en ligne diffusée dans des pays francophones européens. Les résultats révèlent que l'utilisation des CFs semble être davantage répandue que celle des traitements placebo. Les facteurs inclus dans les catégories de la relation thérapeutique et des caractéristiques du patient sont les plus souvent utilisées. Parmi eux, la communication est le plus fréquemment utilisé pour augmenter les effets placebo. Dans leur ensemble, les résultats obtenus soulignent la nécessité de poursuivre les recherches sur l'utilisation de CFs et de mettre en place un cadre éthique pour en garantir une utilisation adaptée.

Dans leur ensemble, les résultats de nos travaux laissent penser que des recherches supplémentaires sont nécessaires avant que les OLPs puissent être utilisés cliniquement en kinésithérapie. En outre, les enseignements en formation initiale et continue doivent intégrer des notions relatives aux effets placebo et nocebo, et les leviers de mobilisation de ces effets ne devraient être enseignés qu'accompagnés de notions d'éthique médicale. De futures de recherche devraient se concentrer sur le développement de traitements placebo contrôles spécifiques à la kinésithérapie afin de mieux en évaluer l'efficacité.

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ABBREVIATIONS LIST

CF: Contextual Factor

DP: Deceptive Placebo

OLP: Open-label Placebo

PCE: Proportion of effect attributable to Contextual Effects

RCT: Randomised Controlled Trial

PART ONE: THEORETICAL FRAMEWORK

1. GENERAL INTRODUCTION

1.1. A BRIEF HISTORY AND EPISTEMOLOGY OF PHYSIOTHERAPY

1.1.1. History of physiotherapy and physical treatment techniques in France

Physiotherapy was created as a profession approximately at the same time all around the world. Historical contexts and social pressures, such as the rise of chronic diseases among which tuberculosis, or global events such as World War I, highlighted the need for rehabilitation. The profession's history has been shaped by influential figures such as Mary McMillan, the "mother" of physical therapy (Elson, 1964), Georgii Lind and Robin McKenzie. Yet, despite a (roughly) common date of birth, the physiotherapy profession as we know it today, has developed independently in every country, resulting in unique trajectories. As a result, the profession's evolution in each country reflects distinct cultural and historical contingencies explaining some of the variations between regions. Nicholls argues that physiotherapy needs to be "understood as a specific historical agent, rather than merely as an extension of, or handmaiden to, medicine" (Nicholls, 2021). Physiotherapy itself, as a set of treatment techniques, has been around even longer. It was simply not practiced by what we now identify as the physiotherapist profession. Nowadays, although there is much in common between these rehabilitation professions, some differences are explained by their history. Lessons from the origins of the profession can illuminate current prevailing challenges.

Focusing on its history in France, it is challenging to pinpoint exactly where contemporary physiotherapy originates from, and what led to its social creation, in 1946 through a State Diploma of [*Masseur-Kinésithérapeute*][1] (Loi N°46-857 Du 30

[1] Translated to Masseuse-Physiotherapist in English. This is still the current name in France for physiotherapists. It stems from kinés(i), Greek for movement.

Avril 1946 Tendant à La Réglementation de l'exercice Des Professions de Masseur Gymnaste Médical, de Masseur-Kinésithérapeute et de Pédicure, 1946). The challenge is partly owed to the fact physiotherapy is the result of the merger of multiple professions. Furthermore, past techniques have inspired more than just current physiotherapy, and similarly, contemporary physiotherapy has not been shaped solely by its past techniques (Monet, 2006). However, one entry point to understanding the emergence of the profession is to explore the history of the treatments nowadays practiced by contemporary physiotherapists.

Although physical treatments have been used as long as medicine exists, a good place to start is 1780 when a landmark essay entitled "[Essay on the usefulness of movement, or of the different exercises of the body, and of rest in the cure of diseases]"[2] was published by the surgeon Claude Joseph Tissot. This essay was a precursor of functional rehabilitation. Tissot describes the importance of exercise, rest, manual treatment and mobilisation manoeuvres. In this essay, he described key notions that shaped the development of physical treatment techniques[3] such as the notions of active, passive and mixed exercises (or activities). He distinguishes military and Olympic gymnastics, which were commonplace, from medicinal gymnastics, tailored for patients. At the time, this was revolutionary. Located in this essay comes a deep conviction about the importance of movement: "[Movement is the soul of all nature; with it we begin our existence, we end it when it abandons us. It leads us to death by working to maintain our life]"[4]. A little under seventy years later, the word kinesitherapy[5], literally meaning treatment through movement, was first suggested in an essay on movement as a treatment by Carl Augustus Georgii (Georgii, 1847). In this essay, Georgii recounts the legacy of the man who first combined physical exercise and massage for medical purposes by creating Swedish Gymnastics: Pehr Henrik Ling.

[2] Essai sur l'utilité du mouvement, ou des différents exercices du corps, et du repos dans la cure des maladies

[3] Physical treatments are grouped by Dr Mac Auliffe in 1904 as treatments by the use of air, heat, cold, light, water and also by exercise and manual therapy (Monet, 2006)

[4] « Le mouvement est l'âme de toute la nature ; c'est avec lui que nous commençons notre existence, que nous la terminons quand il nous abandonne. Il nous conduit à la mort en travaillant à maintenir notre vie »

[5] We will use this word as a translation of the French word "Kinésithérapie" as used by Georgii in his essay. This will allow to accentuate the distinction between kinesitherapy from physiotherapy as it used nowadays. It is amusing to see the term physiotherapy is world-wide except for "a small village of indomitable Gauls" as Asterix would put it who still use [*Kinésithérapie*] ('The Word', 2023).

Once again, focusing more exclusively on the emergence of the physiotherapy profession in France. During this period, physical treatments were neglected by the medical profession as they carried with them a "[smell of charlatanism because the public was long exploited by ignorant and cupid people]" (Monet, 2006). To add to this, physical treatments were sometimes a cover-up for illegal prostitution (Nicholls & Cheek, 2006; 'The Massage Scandals.', 1899). In the beginning of the 20th century, kinesitherapy, treating with movement, was grouped with electrotherapy, treating with electrical currents, to become [*physiothérapie*]. At the time in French, [*physiothérapie*] was not defined as physiotherapy is now. It was simply the use of both physical agents and electricity as modes of treatment. As a demonstration of its establishment in France, the 3rd international congress of physiotherapy was held in Paris in 1910. It included nearly 1000 congressmen with members of the French government and notably the president of the French Republic, Armand Fallières (Monet, 2003). As such, in France, kinesitherapy was born in the beginning of the 20th century from a set of techniques with no obvious effect which doctors did not want to perform anymore. Kinesitherapy was a mixture of abandoned medical specialties and ancient practices (for example bonesetters)(Monet, 2003). What these practices shared was that they were believed to have little therapeutic benefit considering the time and effort they required. As such, they were seen as dishonourable for the medical profession to practice. Indeed, they were themselves facing a crisis both of number of professionals and of illegal practice[6].

Following a period of "therapeutic nihilism"[7] (Shapiro & Shapiro, 1997b) during the 19th century, scientific medicine emerged and as such in France, all treatments that were believed to have little therapeutic benefits were seen as dishonourable for the doctors who were more and more inclined to advocate the so-called therapeutic medicine (Monet, 2003). This is why kinesitherapy was born from a set of abandoned treatments with little therapeutic benefit. It was, at that time, no more than a set of

[6] During this period in France, the medical profession also wanted to heavily regulate the practice of medicine. As such, to limit charlatanism there was no other option that delegate the techniques they no longer wanted to perform to another regulated profession: the masseuse-nurses. This profession will later be at the origin of the profession of physiotherapists.

[7] Therapeutic nihilism refers to the common scepticism, in that time, about the capacity of medicine to generally and significantly improve health (Stegenga, 2018)

physical treatment techniques that were not considered to have much therapeutic value. Today, we could say that physiotherapy was born amidst techniques with no recognized therapeutic value but that may have been effective thanks to their capacity to harness placebo effects. As Shapiro and Shapiro pointed out, "until recently, the history of medical treatment is essentially the history of the placebo effect, because all medical treatments, with rare exceptions, were at best placebos, at worst unknowingly deadly" (Shapiro & Shapiro, 1997a). The relationship between physiotherapy and placebo studies will be the subject of this thesis.

1.1.2. Contemporary physiotherapy in France

Fast-forward to present times and the profession in France has evolved and undergone several transformations. The curriculum has changed and now gives major importance to science in the basic training of future physiotherapists (Décret N° 2015-1110 Du 2 Septembre 2015 Relatif Au Diplôme d'Etat de Masseur-Kinésithérapeute, 2015). Today, the profession is undergoing numerous changes (Rollin, 2022). Not only are aspiring physiotherapists trained at universities, but there are also more and more physiotherapists producing research. As a result, the French government established in 2019 a new section in the [National Council of Universities](CNU91)[8](Décret N° 2019-1107 Du 30 Octobre 2019 Modifiant Le Décret N° 87-31 Du 20 Janvier 1987 Relatif Au Conseil National Des Universités Pour Les Disciplines Médicales, Odontologiques et Pharmaceutiques, 2019).

Created after the liberation of France from the Nazi occupation (Ordonnance N°45-2631 Du 2 Novembre 1945 Comité Consultatif Des Universités, n.d.), the CNU is a national institution in charge of the management of researchers within a discipline. It plays a key role in the evaluation and recruitment of professors and researchers in higher education institutions across France. It is responsible for assessing and ranking candidates for academic positions based on their research, teaching, and academic contributions in their respective fields. The CNU operates through disciplinary sections, each covering a specific academic field or subject area. The CNU's evaluations are highly regarded and carry significant weight in academic

[8] CNU91 as in the 91st section in the "Conseil National des Universités" in French

recruitment and promotion processes in France. This political organisation was created to guarantee researchers liberty and independence within scientific research in France. Its members are elected from French universities and research institutions. The creation of a new section for rehabilitation research is an institutional recognition placing research on rehabilitation in France as an autonomous section on a par with other disciplines such as psychology (CNU16), philosophy (CNU17), mathematics (CNU25), neuroscience (CNU69) or medicine (CNU42-58 depending on specialty). Before this, rehabilitation researchers were integrated within other sections and were under the control of medical sections. The organization may be said to serve the purpose of internal regulation of a scientific communities as defined by the American sociologist Robert Merton[9] (Merton, 1979).

However, what does the recognition of being an autonomous section mean? Nurses are currently in a similar professional dynamic as physiotherapists among the allied healthcare professions (Lecordier, 2012). Nurse and sociologist Didier Lecordier claims that a profession and scientific discipline go hand-in-hand, and cannot be disassociated (Lecordier, 2012). Ljiljana Jovic, also a nurse and sociologist, adds that nursing, as a professional discipline, has professional, educational and scientific roles. As such, it does not interest itself only in the production of knowledge but also at how knowledge can aid practice. She states that a professional discipline is "[the reflection of the reciprocal influence between knowledge and practice]" (Jovic, 2008). Jovic suggests 5 conditions for the creation of a new discipline: specific knowledge, structured production and transmission of knowledge, a collective approach, environments for the dissemination of knowledge, a political understanding of the situation (Jovic, 2008). On this perspective, the creation of a professional discipline is the result not only of the production of knowledge but also of a social and political organisation (Lecordier et al., 2013).

These conditions are similar to what the sociologist of science Joseph Ben-David had theorised much earlier about how scientific disciplines are created. He insisted on the importance of a scientific identity for researchers which he understands as encompassing three conditions: researchers must conduct empirical work in their new

[9] When defining sciences as an Ethos of Science through its ethic norms CUDOS.

field, they must not have another identity and they must be a part of an on-going group of scientists rather than work as isolated individuals (Ben-David & Collins, 1966). The third point implies that scientists have students that identify themselves with this new scientific identity. As such, the role that is given to them by the academic institutions and more specifically its internal regulation, is foundational to the growth of a discipline (Ben-David, 1991). We can see here how the creation of the CNU91 may help foster conditions contributing to the development of knowledge in physiotherapy in France.

The emergence of new disciplines is not uncommon in the history of science and they all start by building upon existing knowledge gathered by other fields (Jovic, 2008). A notable example of this is psychology which emerged as a discipline from speculative philosophy and physiology in the 19th century (Ben-David & Collins, 1966). This is also the case for nursing or physiotherapy building upon the production of other disciplines such as biology, physiology, neuroscience, psychology, and related fields. This can be said for any discipline seeking to settle within already established scientific academia: namely, they should integrate and be commensurate with an existing body of knowledge. Epistemologist Susan Haack's crossword metaphor[10] for scientific evidence[11] illustrates this well (Haack, 1997). In her book first published in 1993 entitled "Evidence and Inquiry: Towards Reconstruction in Epistemology", Susan Haack compared scientific inquiry to a crossword puzzle, where new pieces are added through trial and error, gradually refining the overall picture (Haack, 1995). Each clue and answer are analogous to a hypothesis and its corresponding evidence. Just as crossword puzzles require that individual clues and answers be consistent with one another, scientific inquiry requires that hypotheses and evidence be consistent with each other and with the broader body of knowledge in each field. The metaphor emphasizes the importance of building upon existing knowledge and understanding,

[10] Metaphors have been argued to be pragmatic, interactive phenomenon and Quine adds they "flourish in playful prose and high poetic art but are vital also at the growing edge of science and philosophy" (Haack, 1994) where sometimes "there can be mutual reinforcement between an explanation and what it explains" (Quine & Ullian, 1970). Following the lead of such scholars, we will also take the liberty of sometime distilling metaphors into this manuscript.

[11] Initially the metaphor only described scientific inquiry in relation to foundationalism but took on a broader explanation once published to also include the epistemology of scientific disciplines as "epistemologically distinguished" (Haack, 1997).

rather than starting from scratch each time. It also highlights the idea that scientific inquiry is an ongoing and collaborative process, in which different researchers can contribute different pieces to the puzzle. The trial-and-error process of adding new pieces to the crossword puzzle also highlights the iterative nature of scientific inquiry, as researchers continually refine their understanding of a particular phenomenon through successive rounds of testing and revision. Overall, Haack's crossword metaphor provides a memorable way of thinking about the complex and multifaceted process of scientific inquiry, and it has become widely used in the philosophy of science as a way of explaining the epistemological principles that underlie scientific research.

As noted, for medicine the shift in paradigm to a science-informed discipline happened much earlier than physiotherapy[12]. Notwithstanding, it is difficult to clearly establish when medicine went from being empirical to being scientific (Fagot-Largeault, 2012)[13]. Some refer to the landmark publication led by Sackett in 1992 discussing the now wide-spread model of evidence-based medicine (Guyatt et al., 1992). Others, such as Archie Cochrane, might argue it began around 1950 with Sir Austin Bradford Hill introducing into healthcare the principles of the randomised controlled trials (RCTs) previously suggested by Ronald Fischer for agriculture (Cochrane, 1999). Even before that, in 1865, one might argue is the beginning of experimental medicine with Claude Bernard who strongly insisted that young doctors should be wary of clinical observations alone[14] (Bernard, 1865). He stated trainees should instead complement their clinical observations with comparative experiments such as that carried out by Lint in 1757 (Milne, 2012).

[12] This is true when we consider the dates at which the shift happened. However, relatively to its creation, the shift happened quite quickly for the physiotherapy profession.

[13] Fagot-Largeault suggests three turning points: with Claude Bernard and the emergence of so-called "experimental medicine", after Claude Bernard with Evidence-Based Medicine, before Claude Bernard with numerical medicine giving an increasing importance to numeric figures.

[14] "Un médecin qui essaye un traitement et qui guérit ses malades est porté à croire que la guérison est due à son traitement. Souvent des médecins se vantent d'avoir guéri tous leurs malades par un remède qu'ils ont employé. Mais la première chose qu'il faudrait leur demander, ce serait s'ils ont essayé de ne rien faire, c'est-à-dire, de ne pas traiter d'autres malades car, autrement, comment savoir si c'est le remède ou la nature qui a guéri ?" Claude Bernard in 1865 cited by (Fagot-Largeault, 2012) translated as "[A doctor who tries a treatment and cures his patients is inclined to believe that the cure is due to his treatment. Often doctors boast that they have cured all their patients by a remedy they have used. But the first thing they should be asked is whether they have tried to do nothing, that is, not to treat other patients, for otherwise how can we know whether it is the remedy or nature that has cured?]"

Once a discipline has emerged, it faces numerous challenges for it to persist (Debout, 2008; Lecordier et al., 2013). It must build its foundations upon the production of specific knowledge useful to the population and in the case of a profession to its professional practice. It must also build its foundations on the study of research questions that are rooted in the needs of professional practice. The production of knowledge on this research object must bring forward the mobilisation and elaboration of concepts, models, and methods. In relation to these challenges, Schneider, building on philosopher and historian Thomas Kuhn's contributions, suggests 4 stages of a scientific discipline, each stage requiring specific researcher profiles, evaluation and development (Kuhn, 1996; Shneider, 2009). The first step is to introduce new objects and phenomena as a subject matter. For example, in physiotherapy, this could be the questions emerging from professional practice. Next, the discipline must develop tools and methods to study these objects and phenomena. The third stage, the most productive one, consists in applying the tools and methods to the research object. Lastly, the fourth stage is to maintain, update and pass on the knowledge that has been developed.

Overall, we observe a growing recognition of science within physiotherapy, as evidenced by the increasing emphasis on its production and application in this field. This is similar to the changes that occurred with the emergence of scientific medicine. However, as with any other healthcare profession, physiotherapy is not a science in itself. It is first and foremost a profession. Its application relies on a combination of scientific knowledge, clinical reasoning, and practical skills. It draws on a range of existing scientific disciplines such as anatomy, physiology, biomechanics, neuroscience and exercise science.

1.1.3. Physiotherapy as a technology

Particularly striking is that the history of physiotherapy in France is marked by a significant shift in its practice. Initially, physiotherapy emerged from the relegation of treatment techniques that were considered useless when scientific medicine gained prominence. However, over time, physiotherapy has evolved into a critical component of modern healthcare. In contrast with two hundred years ago when doctors were debating the use of movement as a treatment, it has advanced; it also evolved

compared to 73 years ago[15] with its professionalisation in France. Just as medicine has embraced an evidence-based model, physiotherapy in France in now striving to do the same. For example, the legal texts that currently regulate professional practice in France require physiotherapists to provide patients "[with conscientious and attentive care based on the acquired data of science]"(*Article R4321-1 - Code de La Santé Publique - Légifrance*, n.d.)[16]. As such, physiotherapy practice must be based on scientific evidence. Kell and Owen highlight how the evidence-based practice movement "challenged physiotherapists to discuss more overtly the ontological basis of its professional knowledge" (Kell & Owen, 2008). This model requires healthcare providers to critically assess health knowledge, questioning the foundation of their epistemological beliefs and their therapeutic health concepts (Bientzle et al., 2014).

Several physiotherapists have tried to offer epistemological foundations for physiotherapy. Kerry did this by drawing from the philosophers of science Popper, Kuhn, Lakatos and Feyerabend (Kerry et al., 2008). Earlier[17], a specific paradigm for physiotherapy was suggested by Noronen and Wikstrom-Grotell (Noronen & Wikstrom-Grotell, 1999). Lindquist et al. suggested three different professional identities: the *empowerer* (of patients), the educator and the treater. Each identity, it is argued, shapes how physiotherapists approach knowledge and practice (Lindquist et al., 2006). With a more empirical approach, Wikström-Grotell et al. analysed over 400 abstracts from doctoral dissertations in physiotherapy in Denmark, Norway, Finland and Sweden. The results showed that Nordic doctoral dissertations in physiotherapy were clinically orientated relying mainly on quantitative methods and more rarely employing qualitative and mixed methods (Wikström-Grotell et al., 2018). Shaw and DeForge compared physiotherapists' "practice epistemology"[18] to a that of a *bricoleur* using all tools at his or her disposal, emphasising embracing multiple epistemologies (Shaw & DeForge, 2012). The *bricoleur* characterisation

[15] Here we used 2019 as the date for the recognition of the discipline in France and 1946 as the date for the creation of the physiotherapist state diploma, thus 73 years apart.

[16] « Dès lors qu'il a accepté de répondre à une demande, le masseur-kinésithérapeute s'engage personnellement à assurer au patient des soins consciencieux, attentifs et fondés sur les données acquises de la science. »

[17] Although physiotherapy as a discipline is nascent in France, it can be traced back to the 1980's in other regions and in particular Scandinavian countries.

[18] Edwards and Richardson define practice epistemology as « theories about how knowledge is sought and applied in clinical practice » (Edwards & Richardson, 2008).

might be said to favour engagement with ontological and epistemological issues by encouraging physiotherapists to "embrace multiple epistemologies, discovering new ways of knowing" (Shaw & DeForge, 2012). From this perspective, professional practice cannot be reduced solely to a method of producing knowledge, a science; but instead as a way of using and interacting with knowledge and its practical (i.e., clinical) applications.

Physiotherapy emerged from a given set of techniques and is now advancing closer to a science-informed practice. However, it cannot be considered a science itself. Looking further into the distinction between techniques and science, the epistemologist Dominique Raynaud gave a detailed account of these notions (Raynaud, 2016b). He recounts the positions of several philosophers of science on the distinction between science, technique and technology which are illuminating when it comes to conceiving the advancement of physiotherapy as an evidence-based practice (Raynaud, 2016a).

Although technique and technology are often conflated, Raynaud insists on distinguishing them. To this end, he starts by arguing that a technique is an object or process regardless of how it is justified. For example, in physiotherapy, a treatment technique such as a specific manual therapy manipulation or a diagnostic process are examples of techniques. Raynaud continues with Mario Bunge's definition for technology which "is defined as technique that uses scientific knowledge". In other words, technology is the application of science to an end. In the case of physiotherapy, the end is to treat patients. Technology, it is argued, therefore includes all techniques that are based on scientific knowledge[19]. In the previous example, if the manual therapy technique is justified through tradition, it would only be considered a technique. However, if it is delivered to the patient based on evidence from clinical trials applying rigorous scientific methods to test its effectiveness, it will be considered a technology. The same can be said for a diagnostic process. If the diagnostic reasoning is based on reactions to a prayer for example, it will only be considered a technique. Instead, if it is based on scientific evidence, it will be a technology.

[19] Bunge goes into more detail stating that knowledge can be considered a technology if and only if it is compatible with contemporary science and if it is used to control, transform and create things or natural or social processes.

Raynaud insists on the fact that a sequence of operations whether material or intellectual, for example when diagnosing a medical condition, can be considered a technological process.

However, a technology is not a science. Raynaud proposes three main differences should be considered. The first proposed distinction[20] is that science aims to know the world where technology aims to change it. The second proposed distinction is that science progresses through falsification, illustrated in Popper's refutability criteria, whereas technology proceeds by confirmation. Lastly, Raynaud proposes that science and technology are distinguished through their relationship with new knowledge. Science is cumulative: new knowledge builds upon the previous body of evidence. Technology is not: a technology can be forgotten due to progress if a new technology replaces it. New treatments replace older ones. Finally, Raynaud states "[the articulation between science (which pursues a goal of knowledge) and technology (which pursues a goal of action on reality) can serve as a starting point to characterise technological reasoning]"[21] (Raynaud, 2016a). These distinctions suggest it may be more accurate to describe healthcare not as a science but as a technology.

In line with this stance, Pinsault and Monvoisin suggest that physiotherapy is nowadays in continuity with so-called Bernardian theories common with other medical specialties (Pinsault & Monvoisin, 2014). It has shifted from a set of techniques operating without evidence-based justifications to a science-based practice akin to a technology. Nowadays, physiotherapy tries to find evidence-based foundations for its interventions. It anchors itself within known medical knowledge as do other healthcare disciplines.

Initially, physiotherapy mainly drew its foundations from the fields of anatomy, biomechanics and physiology. However, recent changes suggest moving from a biomedical paradigm to a biopsychosocial paradigm. One way to observe the impact of the arrival of the biopsychosocial model is to consider the sciences that physiotherapy draws from. Nowadays, physiotherapy still draws from biology,

[20] Also attributed by Raynaud to Mario Bunge.

[21] L'articulation entre la science (qui poursuit un but de connaissance) et la technologie (qui poursuit un but d'action sur le réel) peut servir de point de départ pour caractériser le raisonnement technologique.

anatomy, physiology but also from neurosciences and psychology[22]. The addition of these new sources of knowledge illustrates physiotherapy is more and more rooted in a biopsychosocial model. This is also outlined by the use of the International Classification of Functioning[23] (World Health Organization, 2001) in physiotherapy (Allet et al., 2008).

As healthcare professionals continue to prioritize evidence-based practice, demonstrating the effectiveness and value of physiotherapy interventions with compelling evidence is a major challenge for physiotherapists. In fact, in an editorial of Chartered Society of Physiotherapy's Magazine in 2008, it was argued that "if physiotherapy failed to demonstrate its worth to those who hold the public purse, the profession could find itself isolated and ignored" (Kell & Owen, 2008). How could physiotherapy demonstrate its worth? This can be done by embracing its shift from a set of techniques to a technology, and therefore finding justifications to physiotherapy interventions in healthcare and as such improve the effect of our interventions. One straightforward[24] strategy could be to seek evidence for the specific effects of interventions. Some authors refer to this as the 'cure' in healthcare (Jecker & Self, 1991). This is already the main subject of study in most research. However, another strategy, complementary to the first although currently less popular in physiotherapy research, is to study the other effects related to interventions. This is sometimes referred to as the 'care' in healthcare (Jecker & Self, 1991). The context of care has been the subject of much research in fields such as medicine or psychology. Recent development of research on the placebo effect gives reasonable insights into how the context of care may influence health outcomes.

[22] Here we distinguish psychology from clinical psychology which can be considered a technology applying knowledge from several sciences such as psychology, biology, or even some less scientific sources such as Freud's psychoanalysis (which according to Bunge would in turn transform it back into a technique and not a technology).

[23] As opposed to the International Classification of Diseases (World Health Organization, 1992) which is closer to the biomedical understanding of diagnostic and treatment.

[24] Albeit only in thought!

1.2. PLACEBO CONCEPTS

Few concepts in medicine are both as widely embedded and contentious as placebo. Grunbaüm, in his landmark article on the topic (Grünbaum, 1986), describes it as a real "Tower of Babel". To prevent the "tower" from collapsing on itself, the conceptual framework developed here will aim to anchor solid foundations for the rest of the thesis. We'll briefly explore current placebo concepts for this manuscript and discuss some conceptual variations giving an overview of disagreements surrounding them[25]. This groundwork will be necessary before exploring, in greater detail, how physiotherapy research could be informed by placebo studies.

1.2.1. PLACEBO CONTROLS

Although placebo treatments have been used throughout time in clinical settings[26], the reason they are popularly conceptualized is due to their omnipresence as controls in clinical experimentations and trials. Annoni recounts historical moments in which the deceptive use of inert substances was used to evaluate treatment effects (Annoni, 2020). One of the earlier examples of this was the experimentation regarding Mesmer's claim of an "animal fluid". In 1784, the French King Louis XVI commissioned a scientific report from a group led by Benjamin Franklin including notable scientists such as Antoine de Lavoisier. Later, blind controls were used to evaluate other popular claims of effectiveness such as for Hahnemann's homeopathy (Annoni, 2020). Each time the treatment failed to outperform the deceptive control the observed effects were attributed to the patient's "imagination". Progressively, the use of inert treatments – placebo treatments – gained popularity as useful tools to compare treatments to (Annoni, 2020).

After the Second World War, medical research adopted the components of the double-blind RCTs as a standard for evaluating treatment effect. These features included blinded assessment, random assignment to comparable groups, and the use of inferential statistics (Kaptchuk, 1998). The placebo treatment became the "emblem

[25] Our ambition here is not exhaustiveness but only to set a sufficient framework in which we can progress in the rest of the thesis. For a more detailed account on this topic, we recommend reading (Annoni, 2020; C. Blease, 2018; C. Blease & Annoni, 2019).

[26] This will be discussed in 2.1.1

of all the healing occurring in the disguised "no-treatment" arm" (Kaptchuk, 1998). At that time, the placebo effect itself was held responsible for any effect taking place in the control group. Kaptchuk suggests this conflation was used as a justification for the use of randomisation in a sceptical medical community at the time (Kaptchuk, 1998). After the RCT became accepted, a treatment had to perform better than a placebo to be deemed effective.

One of the first accounts of modern-day placebo research is the "Conferences on therapy" that took place in Cornwell University in 1946. During these conferences, a shift from *suggestion* and *imagination* to *placebo effect* took place (Annoni, 2020). Closely following, in landmark article "The powerful Placebo" written in 1955, the American anaesthesiologist Henri Beecher claimed that 35,2% of patients across 15 clinical trials had experienced therapeutic benefits from placebo treatments (Beecher, 1955). Beecher argued that the placebo could "produce gross physical changes" including "objective changes at the end organ which may exceed those attributable to potent pharmacological action." Not very surprisingly, many readers understood his estimations as the magnitude of the placebo effect. Yet, this is not the case as Beecher's study suffered several important flaws (Kienle & Kiene, 1997) which we will shortly explore. Additionally, Beecher presented the placebo effect as a "single and stable power that behaved in a consistent manner" and, exaggerated its power in an attempt, Kaptchuk suggests, to increase acceptability of the RCT (Kaptchuk, 1998). This was done by overlooking many other effects present in the control group that we will now turn to.

1.2.2. Differentiating the placebo response and placebo effects

Although Beecher had aggregated all effects taking place when patients received a placebo treatment, since then, researchers have further revised and refined these concepts. To distinguish them it is necessary to differentiate between the placebo response and the placebo effect which are still to date the source of much confusion. In 2018, an expert consensus defined the placebo response to include "all health changes that result after the administration of an inactive treatment" (Evers et al., 2018). This includes spontaneous evolution and regression to the mean. The source

of the confusion between placebo response and effect could be due to how placebo treatments are used in RCTs as shown in Figure 1.

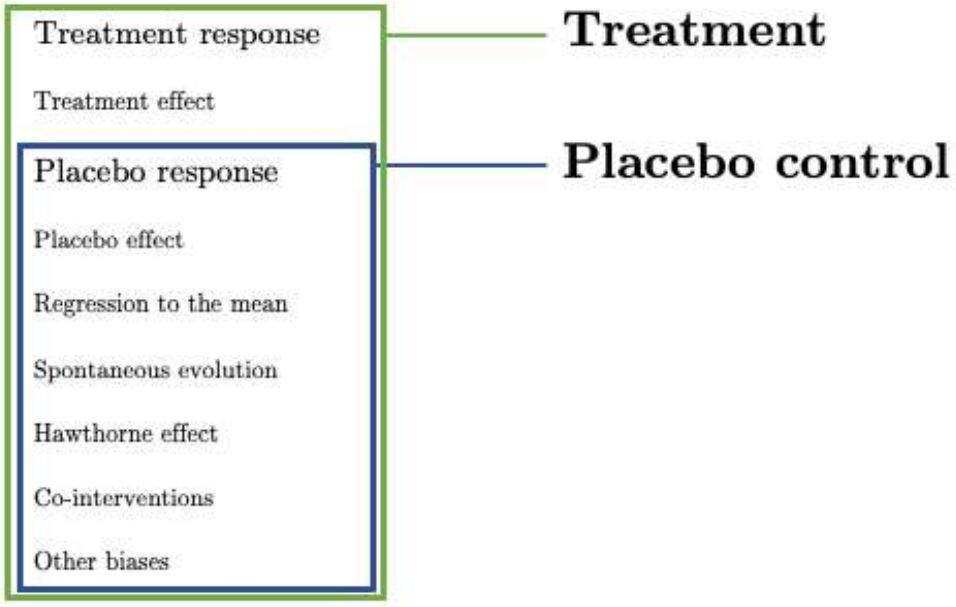

Figure 1: Separating treatment effect, placebo effect and placebo response

Complicating matters further, some authors describe the placebo response as synonymous with non-specific effects (Kleijnen et al., 1994; A. H. Roberts et al., 1993). This difference can be sometimes only semantic and other times highlight underlying conceptual differences (see Section 1.2.4)(Gøtzsche, 1994).

1.2.3. Placebo and nocebo effects

Owing to the function of RCTs, it was not necessary to understand the black box of effects that properly can be called the placebo response. This patchwork of effects was only useful in the necessity of subtracting it from the effects of the treatment to explore its potential potency as suggested by Figure 1. However, starting in the latter half of the Twentieth century, scientists tried to understand how placebo treatments could still produce an effect even though the constituents of the treatment were therapeutically inert. This way of perceiving placebos seemed to give rise to an oxymoron: an effect out of nothing (Kelley, 2018). This brought forth the need to

reconceptualise placebo effects as something more than the effect of an "empty" pill. It was the starting point for interest in the mechanisms of the placebo effect.

In his historical review, Annoni describes this as one of the notable epistemological shifts in the last 50 years of placebo research (Annoni, 2020). Seeking to understand what was happening within the placebo response was the first shift, he argues. Elaborate study designs drawing from the principles of the RCT were now attempting to open the black box of effects in the control group. This was done by looking at mechanisms of the placebo effect, using no-treatments groups or using hidden-open treatment administration designs (Benedetti, Maggi, et al., 2003). These experiments led to the understanding that there may be many placebo effects and, contrary to Beecher's assumption, there was not a unique stable placebo effect across all contexts.

In 2018, an expert consensus proposed placebo and nocebo effects refer "to the changes specifically attributable to placebo and nocebo mechanisms, including the neurobiological and psychological mechanisms of expectancies" (Evers et al., 2020). Placebo effects refer to positive expectancies prompting beneficial health changes, and nocebo effects to negative expectancies causing negative health changes. There are now thought to be several neurobiological mechanisms underpinning the placebo effect as shown in Figure 2 (Benedetti et al., 2011a). In addition, the use of functional imaging has contributed greatly to identify specific neurobiological pathways of placebo effects (Zunhammer et al., 2021). Placebo effects may provide meaningful conditions common that are commonly presented in physiotherapy practice such as pain analgesia (Finniss et al., 2009) as well as in movement disorders such as Parkinson's disease (de la Fuente-Fernández et al., 2001) and physical performance (Hurst et al., 2020).

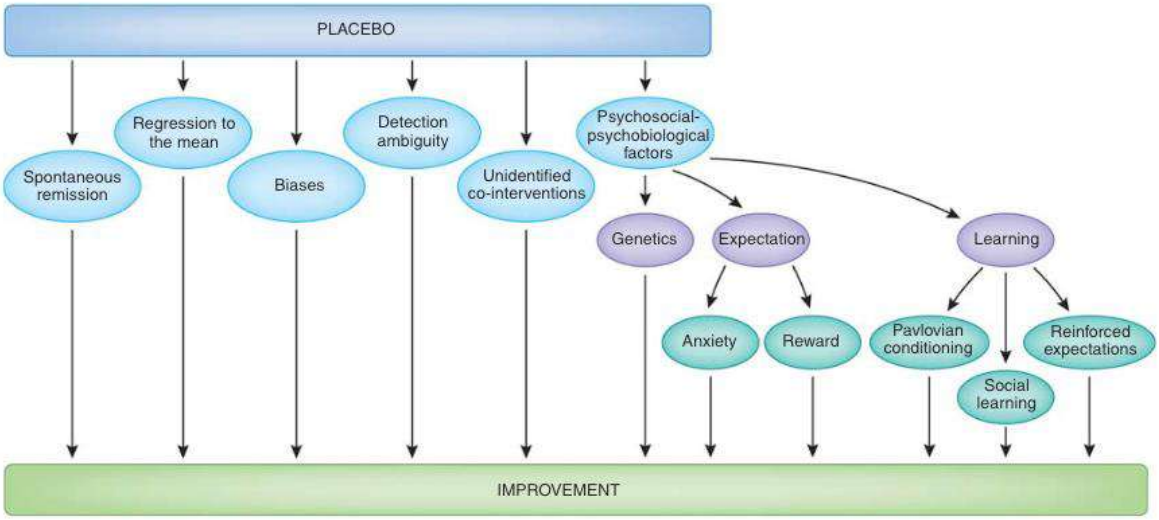

Figure 2: Schematization of the placebo response. The placebo effect is defined here by Benedetti et al. as the improvement due to psychosocial-psychobiological effects and its mechanisms (Benedetti et al., 2011a).

However, as the foregoing commentary strongly demonstrates, there are still many disagreements surrounding the definition of placebo effects (C. Blease, 2018; C. Blease & Annoni, 2019). One of the most contentious issues is the amalgam of placebo effects and responses presented earlier. Similarly, conflation of several semantic meanings behind the term *placebo* has also led to disagreements and confusions (Sussex, 2018). For example, conflation of the term placebo as a control and placebo in a clinical context, meaning a treatment not known to work but still given to patients, is problematic since the term functions differently in distinctive contexts (C. R. Blease, 2019). To this end, some authors suggest changing the *placebo* terminology in hopes this will resolve conceptual disputes by providing a blank canvas upon which to build (Turner, 2011, 2018). Alternate terms have been suggested such as response expectancy (Kirsch, 2018), the meaning response (Moerman & Jonas, 2002), context effects (Di Blasi et al., 2001) or positive care effect (C. Blease, 2012; Louhiala & Puustinen, 2008). Although all these alternatives pinpoint problematic features of the term *placebo*, Blease and Annoni suggest none justify overhauling the current terminology (C. Blease & Annoni, 2019). Going further than terminological changes, some say the concept itself is flawed, has become too broad (Miller, 2018),

doesn't exist (Szawarski, 2004), requires change or should be abandoned (Traeger & Kamper, 2017; Turner, 2011, 2018)[27].

To date, Blease argues that there is room for optimism since, despite the conflict and dissent, there is "considerable underlying agreement about definitional matters" when it comes to placebo effects (C. Blease, 2018). Placebo effects are widely considered to be genuine psychobiological effects that engage perceptual and cognitive processes to elicit therapeutic benefits (Kaptchuk & Miller, 2015). It is variously proposed that the placebo effect might be usefully harnessed in clinical settings (Miller, 2018).

1.2.4. Contextual factors

Another important shift in placebo research, argues Annoni, arose when researchers sought to understand the key determinants of the placebo effect. This was pivotal in understanding its modulation (Annoni, 2020). It led to understanding that the characteristics of a treatment as well as other contextual cues of the clinical encounter are important in eliciting placebo effects. It is believed that these cues trigger placebo and nocebo effects via mechanisms of patient expectations and conditioning. Benedetti suggested that the placebo "is not the inert substance alone, but rather its administration within a set of sensory and social stimuli that tell the patient that a beneficial treatment is being given" (Benedetti et al., 2011a). These cues have been referred to as contextual factors (CFs) and have been divided into five categories: patient characteristics, clinician characteristics, the nature of the treatment, healthcare setting features and the patient-clinician relationship including verbal and non-verbal communication (Bernstein et al., 2020; Claridge, 1970; Di Blasi et al., 2001; Rossettini, Carlino, et al., 2018; Testa & Rossettini, 2016)[28].

It is worth noting that CFs can also have other effects on healthcare outcomes. In addition to their direct effect as triggers of placebo and nocebo effects, they can have indirect effects by increasing satisfaction, reducing anxiety or providing

[27] Traeger and Kamper wrote this in a letter to the editor to which the authors of the study replied to their rebuttals (Carvalho, 2017).

[28] Not being able to find a copy of Claridge's book we trust Szawarski in her reporting of Claridge's words (Szawarski, 2004). However, it seems better practice to attribute the words of Claridge to Claridge.

reassurance which in turn allow better physical health (Street, Jr et al., 2009). In the case of physiotherapy for example, there is evidence that communication influences patient adherence to physiotherapist-prescribed home-rehabilitation (Lonsdale et al., 2017). Regarding their direct effects, they might modulate placebo effects through expectations and conditioning and directly produce improvements. When reviewed systematically, interventions on communication provided significant but small effects on pain (Mistiaen et al., 2016). Unfortunately, due to the diversity of the interventions no meta-analysis could be conducted. In the case of the patient-clinician relationship, its overall effect on healthcare outcomes is small but significant with a standardised mean difference (Cohen's *d*) of 0.11 (Kelley et al., 2014).

Derived from these CFs, "contextual effects" is sometimes used to talk about placebo effects in everyday clinical care. In addition, Benedetti talks about placebo-like effects for effects that are akin to placebo effects but without the use of placebo treatments (Benedetti, 2008). However, problematically, in recent years, several studies have used the term contextual effect as synonymous to placebo response. As such they proposed the term proportion of effect attributable to contextual effects (PCE) to study the fraction of the overall treatment attributable to the placebo response (Hafliðadóttir et al., 2021; Tsutsumi et al., 2023; Whiteside et al., 2017; Zou et al., 2016). The findings from these studies suggest that overall, across all conditions, the proportion attributable to placebo response was 0.65 (95%CI 0.59 to 0.72) with high variability between studies (Tsutsumi et al., 2023). In ailments common in physiotherapy, such as pain relief in fibromyalgia, the placebo response was responsible for 60% of the overall effect (95%CI 0.56 to 0.64) also with very high variability between studies (Whiteside et al., 2017). In osteoarthritis, on average 75% (95%CI 72% to 79%) of the overall treatment effect was due to the placebo response (Zhang, 2019; Zou et al., 2016). This highlights that the PCE is higher than average in conditions commonly presented in physiotherapy practice. However, it is important to keep in mind these studies look at the placebo response and not merely the placebo effect. Unfortunately, this creates, once more, a potential source for confusion.

Nonetheless, within this shaky tower of Babel, it is reassuring to see that there is sufficient agreement among researchers to pursue research on the placebo effect

(C. Blease, 2018). However, it is also important to be cautious and attentive to nuanced, definitional differences that still persist and which may undermine research methodologies (C. Blease et al., 2023).

1.3. PHYSIOTHERAPY, CONTEXTUAL FACTORS AND PLACEBO STUDIES

Section 1.1 suggested that placebo studies could be a valuable source of knowledge for physiotherapy. Following this, section 1.2 attempted to disambiguate several, often conflated, important placebo concepts. This section will now explore the link between placebo studies and physiotherapy research.

Firstly, it is important to note that placebo research is inter-disciplinary. Due to its prevalence in healthcare, it has been studied by several fields ranging from, among others, philosophy, psychology, medicine, history. For example, the international society advocating for placebo research founded in June 2014[29] is itself multi-disciplinary in nature. Interdisciplinary research aims to bring together experts from different scientific disciplines to provide a more comprehensive understanding of placebo phenomena. However, the success of such research depends on the ability of the researchers to collaborate effectively. For example, one of the main challenges of interdisciplinary research is avoiding redundancy in the findings or of researchers talking at cross purposes. The former can occur when each discipline focuses only on its area of expertise without considering the findings of other disciplines. This, in turn, may lead to researchers talking at cross purposes by perpetuating conceptual variations which may in turn create challenges to mutual learning, especially across disciplinary divides. Therefore, as the previous conceptual overview has emphasized, it is crucial to strike a critical attitude toward different perspectives and ensure that the research findings are collaborative, and not repetitive. Only then can an interdisciplinary approach be worthy of the name, yielding meaningful insights and advance scientific knowledge.

Secondly, the sociologist of science Joseph Ben-David highlights the importance of *outsiders* and *role hybridisation* for scientific growth (Ben-David, 1991). The psychologists Lilienfeld adds the need for "big-picture thinkers" to the list (Lilienfeld,

[29] Society for Interdisciplinary Placebo Studies (SIPS)(*SIPS: Home*, n.d.)

2017). In the case of role hybridisation, researchers have hybrid profiles; they bring methods from one discipline to another and therefore bring innovation. This is one of the strengths of interdisciplinary research. As such, when researching placebo effects, it is reasonable to assume that having several disciplines is beneficial to the scientific growth of the domain.

Lastly, exploring which fields of research are currently most heavily interested in placebo studies is useful. A recent bibliometric analysis from Weimer et al.[30] listed the main contributors to recent placebo research[31] represented in Figure 3. Among them we can find many psychologists (e.g., Colaguiri, Evers, Vase), clinical psychologists (e.g., Kirsch, Kelley, Rief), a philosopher (e.g., Blease) and academic physicians (e.g., Benedetti, Colloca, Meissner, Amanzio). According to this database, it seems the role of physiotherapists and physiotherapy is limited in placebo studies. Testing this preliminary observation, searching the JIPS database for publications specifically studying physiotherapy, revealed, after screening titles and abstracts, only two relevant publications (Hohenschurz-Schmidt et al., 2022; Rossettini, Camerone, et al., 2020). Undertaking the same in the PubMed database using the MeSH headings "Placebo Effect" and "Physiotherapy" or "Physical Therapy" added one extra article (Stack, 2006). Again, repeating the process in Google Scholar while completing the search with a snowball research strategy added seven more articles (Bisconti et al., 2021; Clemence, 2001; Rossettini, Carlino, et al., 2018; Rossettini et al., 2019; Rossettini, Geri, et al., 2020; Rossettini, Palese, et al., 2018). Of note among these articles, one editorial suggested physiotherapy could be considered the ultimate placebo (Stack, 2006). Three narrative reviews described the psychoneurobiological underpinnings of CFs relevant to physiotherapy (Hohenschurz-Schmidt et al., 2022; Rossettini, Camerone, et al., 2020; Rossettini, Carlino, et al., 2018). Four surveys described physiotherapists' knowledge about CFs (Bisconti et al., 2021; Rossettini et al., 2019; Rossettini, Palese, et al., 2018, 2018). Finally, a viewpoint by

[30] Dr Weimer and Pr. Enck manually archive all articles regarding placebo and nocebo effects into a database for placebo research: the JIPS. Such an effort is crucial when a research object is interdisciplinary.

[31] To do so, they analysed the JIPS database. One side-effect of this is that is contains articles referenced in the PubMed database. This excludes some literature such as philosophy, social sciences etc. However, a quick search of the most cited Google Scholar Profiles with the label "placebo" seem to confirm the description of the professions implicated in placebo research.

physiotherapist Mark Clemence describing placebo concepts concludes that "the profession has yet to develop a model of placebos and ethics relevant to its own clinical practice" (Clemence, 2001).

This rapid review suggests, at the very least, that physiotherapy is not currently well integrated into the interdisciplinary field of placebo studies – yet.

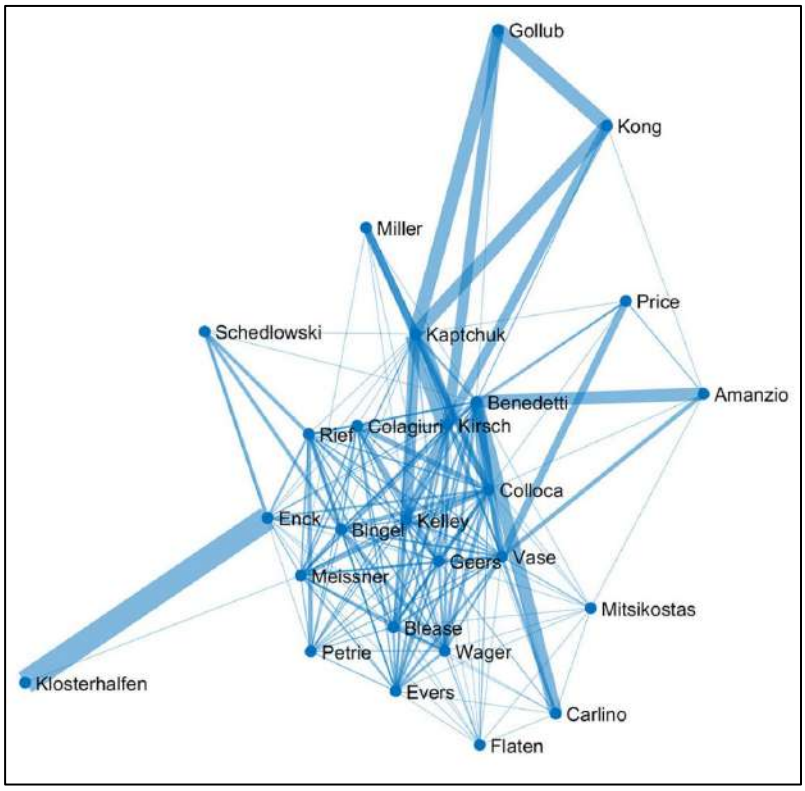

Figure 3: From Weimer et al. (Weimer et al., 2022). Network of the most prolific authors in the JIPS database.

Therefore, it seems apparent that few physiotherapists currently contribute to placebo research, and, in turn, there is scarce attention in placebo studies to physiotherapy. Of course, this brief literature review does not preclude the possibility that some physiotherapists may be contributing to placebo research independently of the actual field of physiotherapy. Notwithstanding, the interest in the present thesis is, in a preliminary sense, begin to address this gap and to bridge these two fields.

Notably, other researchers have begun to consider similar limitations with respect to other health professions. For example, Annoni et al. find that the nursing profession is less studied in placebo research (Annoni et al., 2021). Yet, they argue

that the responsibilities and proportion of nursing staff in the health processions is expected to increase in the forthcoming years. They also postulate, drawing on high levels of satisfaction with nurses, that there may be enhanced placebo effects when patients interact with nurses. Annoni and colleagues' reasoning for nursing also holds true for physiotherapy. In France, physiotherapists are already seeing an increase in their responsibilities with patients gaining direct access to physiotherapists without the need for physician referral as of January 2023 (*Proposition de loi portant amélioration de l'accès aux soins par la confiance aux professionnels de santé*, n.d.). Patients also show high satisfaction and associated enhancers of placebo effects in physiotherapy care (Bak Bødskov et al., 2022).

Additionally, physiotherapy may be more predisposed to be a source of potent placebo effects than many other health interventions[32]. Linde et al. notes that general practice physicians are "seeing patients for sometimes unclear, non-specific complaints or minor ailments as well as chronic chronically ill patients coming back from specialists without a fully satisfying therapy" (Linde et al., 2018). The same is true of physiotherapy, and indeed, patients with these conditions or presenting such symptoms are often referred to physiotherapists. Further justification for exploring placebo effects in physiotherapy comes from its focus on quality-of-life[33], the fundamental importance of touch in treatments (Roger et al., 2002; Rothstein, 1992) and the high prevalence of subjective disorders as reasons for consultations in physiotherapy such as pain, musculoskeletal disorders, or improvement of quality of life[34].

In summary, there are crucial reasons to believe it is important to extend placebo studies to physiotherapy and for physiotherapists to study placebo effects.

[32] Curiously, the term placebo is often attributed to the psalm 116 translated from the Latin « placebo Domino in regione vivorum » meaning « I shall please the Lord in the land of the living », Latin sentence itself a translation from the Hebrew sentence: « et'halekh liphnay adonai b'artzot hakhayim » meaning « I will walk before the Lord in the land of the living ». The Latin translation for this would then be « Deambulo ». Another amusing common point between physiotherapy (in French *Kinésithérapie* meaning treatment through movement) and the placebo effect's history. Thank you to Richard Monvoisin for pointing this out. (Aronson, 1999; Monvoisin, 2020)

[33] As illustrated above with the placebo given to the ICF in physiotherapy.

[34] These are the missions cited by World Physiotherapy in their description of the profession (*Policy Statement*, n.d.)

Further support comes from the need for wider interdisciplinary research to advance scientific knowledge about placebo phenomenon and the prevalence of subjective disorders in physiotherapy that may make it particularly disposed to placebo effects. Knowledge about placebo effects could contribute to the evidence-base of physiotherapy going forward.

1.4. RESEARCH AIM

To recap: Physiotherapy in France originated as a set of techniques: physical treatments delegated by the medical profession when scientific medicine emerged (section 1.1). Medicine took the paradigmatic turn of becoming more scientific and evolved toward the current widely accepted evidence-based approach to treatment. Nowadays, physiotherapy itself has also taken this turn and current best practice of physiotherapy is also one informed by scientific evidence. This is reflected by increasing integration of the professional curriculum to universities and manifested in France also by the creation of a CNU section in 2019. This evolution from its origins requires the profession to seek justifications to our interventions in healthcare leading to consider physiotherapy as a technology. This has led to a shift towards establishing evidence for the effectiveness of physiotherapy interventions through RCT and placebo-controlled trials.

However, improving the effectiveness of interventions can also be achieved by considering the context in which they are administered, including via the care provided to patients. Furthermore, research into placebo effects has the potential to identify how care can influence health outcomes, thereby improving healthcare outcomes through the placebo effect (section 1.2). Despite its potential, placebo knowledge seems to have been largely neglected in the field of physiotherapy (section 1.3). To establish its relevance, it is necessary to explore how placebo knowledge may contribute to physiotherapy practices, and how physiotherapy may mutually learn from placebo studies. Therefore, the goal of the present exploratory thesis is to begin to address the following research aim: **How can placebo studies inform the practice of physiotherapy?**

Given the fact there is little mutual exploration between the two fields, the thesis will attempt, in a preliminary way, to bridge this gap. Due to the considerable

vastness of this research aim, the objectives of this thesis are modest: namely, to initiate exploration of this question through two overlapping objectives. First, to advance placebo studies in specific areas where gaps in research have been identified, and second, to explore how knowledge from placebo studies might be applied to physiotherapy. The thesis strives to achieve reciprocal learning in these two areas of research.

1.5. THESIS STRUCTURE

The research question is inherently complex, cross-disciplinary, and open-ended, giving rise to numerous subsidiary questions that can be argued in multiple ways. As a result, this thesis adopts an exploratory approach that aims to uncover how placebo effects can be leveraged to enhance healthcare, particularly in the field of physiotherapy. Recognizing that several approaches could be undertaken to this end, this thesis is solely focused on two main questions. Other approaches will be discussed as future research directions in section 5. From the overarching aim, and two objectives of the thesis, two research questions have been derived that are discussed in the present thesis:

Question 1. Under which conditions should placebo treatments be used in physiotherapy?

Question 2. How are contextual factors used in physiotherapy?

Reflecting on the overarching research question implies the need for different research perspectives. Additionally, given the nature of the topic, it was important to study the placebo effect in an interdisciplinary manner. This involved drawing upon insights from diverse fields, including psychology, philosophy, and physiotherapy, to develop a comprehensive understanding of the phenomenon. This also resulted in the use of various methodologies including survey research, quantitative research, and also qualitative research. Due to this approach, the most suitable way to present the results is in the form of an article collection of individual projects linked together by this thesis[35]. Part two: Experimental results will present

[35] This presentation may lead to necessary redundancy with the articles' introductions and discussions which was minimised as best as possible.

the experimental results of this thesis. Question 1 will be discussed in section 2 and Question 2 in section 3 (see Figure 4).

Section 2 starts by presenting different forms of placebo treatments along with their ethical and evidence-based dimensions with focus on examples relevant to physiotherapy. This leads to identifying a gap in placebo research: comparing OLPs and DPs. To address this, we conducted a non-inferiority randomised controlled study with detailed methodology detailed in Articles 1 and results presented in Article 2. Advancing the question of placebo treatment use, we conducted a qualitative study on the acceptability of both DPs and OLPs in Article 3.

Section 3 will start by detailing CFs relevant to physiotherapy practice identifying the need to describe how physiotherapists and other healthcare providers perceive the use of CFs in routine care. This is the aim of Article 4. To fill this research gap, we conducted a web-based survey in French-speaking countries.

Lastly, in Part three: General Discussion, although each result will be discussed with respect to each article, the overall contributions of this thesis are discussed. Contributions to the field of placebo studies are presented first, followed by contributions to physiotherapy research. Finally, the thesis closes by offering contributions on new ways in which placebo knowledge could contribute to physiotherapy will bring the thesis essay to a close. This section will discuss the evaluation of physiotherapy effectiveness. Here, further research discussing the applications of placebo studies to improve research in physiotherapy by reflecting on methodological insights from placebo studies is presented. Figure 4 summarises the structure of the manuscript.

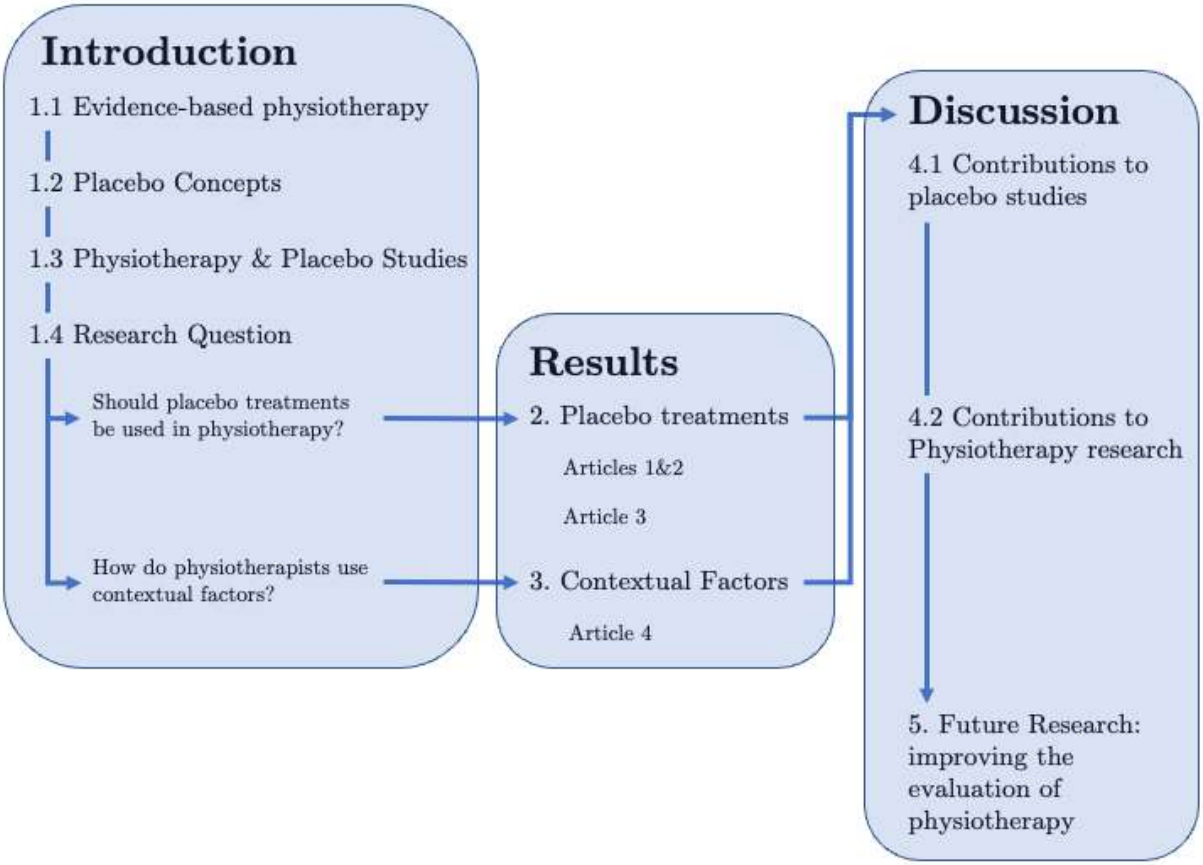

Figure 4: Graphical presentation of thesis structure

PART TWO: EXPERIMENTAL RESULTS

2. USE OF PLACEBOS AS STANDALONE TREATMENTS

2.1. BACKGROUND

2.1.1. Placebo treatment use

The use of placebo treatments is not new although they were not necessarily conceived as such by practioners in the past. Curiously, one form of placebo treatments was sold (very expensively) as ground unicorn horn (Czerniak & Davidson, 2012). Placebos were also commonly used in France during the 16th century as tricks to debunk fake "possessions". Priests would administer ordinary water presented as holy water or holy water presented as normal water (Kaptchuk et al., 2009). The first non-religious use of the term placebo is believed to be in the landmark medical lexicon written in 1772 by Willam Cullen who described them as treatments given with no intent of curing the patient but "prescribed therefore in pure placebo", meaning to please (Kerr et al., 2008). Perhaps less recognized is that healers dating all the way back to medieval Egypt such as Qustā Ibn Lūqā had already started to grasp the effect of placebo treatments approximately seven hundred year before Cullen (Wilcox & Riddle, 1995). The term was added to the medical lexicon by Hooper and Quincy's Medical dictionary of 1817 defining placebo as "an epithet given to any medicine adapted more to please than benefit the patient" (Hooper & Quincy, 1817).

To this day, one of the main predictors of the decision to prescribe medication is the physician's belief that patients expect a prescription (Britten & Ukoumunne, 1997; Md Rezal et al., 2015). However, physicians may overestimate patient's expectations (Lado et al., 2008). This can lead to the prescription of treatments that have no indication in the given clinical setting but are delivered more to please the patient. For example, when looking at why primary care providers would use placebo treatments, in one study in Switzerland, close to two-third of practitioners replied doing so was "to comply with the requests of the patient" (Fässler et al., 2009).

Another study reported that those patients who are considered more difficult or more demanding were more likely to receive a placebo (Fässler et al., 2010).

Nowadays, placebo treatments are believed to be widespread (Fässler et al., 2010; Linde et al., 2018). A recent meta-analysis found general practitioners' use of placebo treatments in the last year ranged from 46% to 95%. However, there was a very high heterogeneity between studies included as shown in Figure 5.

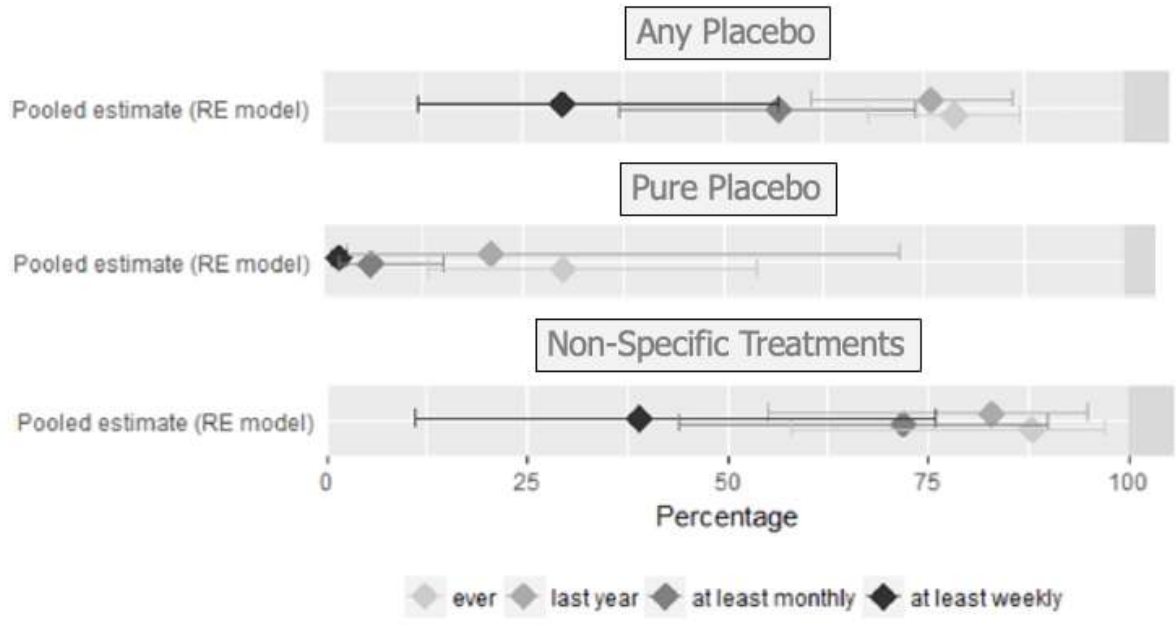

Figure 5 Use of Placebo treatments adapted from Linde et al. 2018

Percentages (95% confidence intervals) of GPs having used a placebo intervention (upper part), a pure placebo or a non-specific therapy (lower part) at least once in their career (light grey), last year (grey), using it at least monthly (dark grey) or at least weekly (black).

Surveys investigating placebo use often distinguish two cases: pure and impure placebos (Brody, 1982). Pure placebo treatments which are understood as interventions with no specific therapeutic effect on the organism nor the symptom. Such examples could be low doses of sugar, low doses of caffeine, or an even more inert component such as cellulose which humans don't digest. In physiotherapy, such examples could be an chemically inert cream or saline cream or electrotherapy which the physiotherapists doesn't turn on, or forgets to activate (Stack, 2006). On the

other hand, impure placebo are treatments that are believed to incorporate an active component through their mode of transmission, but which that active component is not believed to have any effect on the given symptom.

Some authors prefer to refer to impure placebos as non-specific therapies because some definitions also include interventions with unclear or unproven specific effects (Linde et al., 2018). The use of impure placebos far outnumber the use of pure placebos (Linde et al., 2018), with one survey finding prescription by doctors at least once in their career of up to 97% for impure placebos and only 12% for pure placebos (Howick et al., 2013). This usage appears to be particularly prevalent in primary care settings whereas pure placebos seem to be more common in hospital settings (Fässler et al., 2010). Commonly used impure placebo include over-the-counter analgesics, vitamins or, less frequently, sedatives or antibiotics (Tilburt et al., 2008).

There are instances where non-indicated physiotherapy was identified as one form of impure placebo physicians could prescribe (Howick et al., 2013; Hróbjartsson & Norup, 2003). This may arise when physicians refer to a physiotherapist when treatment is not indicated. One example of this is found in

Table 1 where up to 60% of physicians reported already prescribing physiotherapy as a placebo. In physiotherapy, examples of impure placebos are abundant. For example, in shoulder pathologies, they include laser therapy, extracorporeal shockwave therapy, pulsed electromagnetic energy, and therapeutic ultrasound (Pieters et al., 2020). For pain relief, manual therapy is also sometimes considered impure placebo (Bialosky et al., 2011, 2017; Puentedura & Flynn, 2016).

Notably, impure placebos, due to their active components, may carry individual and populational-level adverse effects. In the case of antibiotics, impure placebo use can significantly contribute to overprescribing. For example, Pouwels et al. found that 92% of consultations for bronchitis led to antibiotic prescription when only 13% of consultations required it (Pouwels et al., 2018). Moreover, the justification for using these treatments as impure placebo to promote positive psychological effects rather than simply being prescription errors is unclear (Linde et al., 2018). It is believed that over-prescribing contributes to the increase of microbial resistance which is listed as one of the 10 major challenges healthcare will face according to the WHO (Scheres & Kuszewski, 2019). In the case of physiotherapy, both pure and

impure placebos may also lead to maladaptive beliefs such as low back pain requires "adjusting" or "realigning" the spine (Darlow et al., 2012; Demoulin et al., 2016).

Types of Placebo Interventions

Placebo Interventions Reported to Have Been Used at Least Once During the Past Year	*General Practitioners (n = 182)*	*Hospital-Based Physicians (n = 185)*	*Private Specialists (n = 136)*
Antibiotics	70% (63-77)	33% (26-40)	18% (11-25)
Physiotherapy	59% (52-66)	24% (18-30)	13% (7-19)
Sedatives	45% (38-52)	24% (18-30)	10% (5-15)
B vitamins	48% (41-55)	10% (6-14)	9% (4-13)
Saline injections	5% (2-8)	1% (0-2)	0%
Other	26% (20-32)	14% (6-19)	15% (9-21)

NOTE: Ninety-five percent confidence intervals in parentheses. $N_{total} = 503$.

Table 1 Results from Hróbjartsson & Norup, 2003

It is also worth adding, the pertinence of the concepts of pure and impure placebos is debated. One critic is the Finish medical philosopher and ethicist Pekka Louhiala, who argues that the concepts make little clinical sense when considering treatments with uncertain effects (Louhiala et al., 2015).

To recap: Placebo treatments are used widely in primary care. In some cases, referral to a physiotherapist can also be considered as a placebo intervention. Additionally, although placebo use has not been specifically measured or prevalence explored in physiotherapy, as noted, numerous potential placebo treatments likely exist in physiotherapy practice.

2.1.2. Deceptive Placebos

When considering the conditions under which general practitioners report prescribing placebos, the most frequently chosen justification was that it "can be used as long as the physician and patient work together in partnership" (Fässler et al., 2009). Paradoxically, however, in the same survey most placebo treatments were administered with patients being told either "this is a drug or a therapy" or nothing at all in 89% of pure placebo uses and 73% of impure placebo uses (Fässler et al., 2009). Tilburt et al. also found that placebo treatments are most often administered unbeknownst to patients - that is, they are administered deceptively and often identified in the literature as deceptive placebos (DP)(Tilburt et al., 2008).

Even though some patients could benefit from placebo treatments, their use brings forth several ethical concerns regarding if and how they can be used clinically (Annoni, 2018b). When physicians consider the ethicality of prescribing DPs, Beauchamp and Childress' four principles of beneficence, non-maleficence, justice and respect for autonomy should be considered (F. L. Bishop, Howick, et al., 2014). Although DPs are often considered, from a clinician's perspective, to be unethical (Fässler et al., 2011; Howick et al., 2013) from the point of view of ethicists things are not as clear cut. Supposing placebo treatments provide an actual therapeutic benefit[36], the administration of a DP could be seen as a classic case of paternalism: a patient's autonomy is overridden for a therapeutic benefit which is in the patient's best interest. On these grounds, some medical ethicists suggest the use of deception when prescribing placebos is acceptable or may be acceptable in some limited cases (O'Neill, 1984). Sokol even suggests a flowchart to help decide when deception could be, according to him, morally acceptable (Sokol, 2007). Foddy justifies DP use because, he argues, it does not infringe on any morally important form of autonomy and because the benefits of placebo far outweigh the risks which he considers to be non-existent[37] (Foddy, 2009).

Other authors suggest the issue is not one of paternalism where autonomy is overruled for a benefit. Instead, they argue DPs can be administered while respecting patient autonomy (Allen, 2019; Gold & Lichtenberg, 2014). Gold and Lichtenberg also distinguish between lying to patients and deceiving them[38] (Gold & Lichtenberg, 2014). This distinction classifies a sentence accompanying a DP prescription such as "this treatment is morphine to help you get better" or "this manual therapy will realign your back" to be a lie; whereas saying "I believe this treatment will help you and think it's a good therapeutic option" would be a deception. They argue that the former would be a clear infringement upon patient autonomy when the latter would be acceptable as it's in the patient's interest (Gold & Lichtenberg, 2014). Deception

[36] This is a controversial point which will be further discussed in 4.1.1

[37] This is a controversial stance as well brought forward by Foddy who does not look at indirect or long-term consequences of DPs as argued by Annoni: "The idea that placebos are "inert" and therefore "harmless," however, is misleading: deceptive placebos may harm individual patients and society in different and important ways" (Annoni, 2018b).

[38] This distinction is borrowed from Carson (Carson, 2010)

is "not carried out to interfere with or obstruct the function of the will, but merely to make possible a means to the patient's ends" (Allen, 2019). Such a means, it is argued, is only used to reach an otherwise unobtainable end[39] that is in the interest of the patient thus respecting the patient's will[40] and rendering it acceptable. Another situation where DPs are argued by Lichtenberg to be acceptable is when the patient's will does not respect the HCP's professional autonomy or when patients feel a benefit before having reached the required dose to reach specific effectiveness (Lichtenberg et al., 2004). Here discontinuing the DP treatment, it is argued, could be considered unethical.

However, the idea that DPs are acceptable is not the dominant ethical position in health ethics: most authors argue against their use. For example, Schwab directly challenges Foddy's justifications. Firstly Schwab argues that the examples of deception are actually lies and secondly that the deception involved is in fact meaningful (Schwab, 2009). As such, claims such as "this treatment may help" should be considered deceptive when administering a DP because "in contemporary clinical settings patients may reasonably expect that all prescribed medicines have been tested and approved for their specific efficacy" violating the HCP's duty of truthfulness (Annoni, 2018b). Furthermore the risk of deceiving or lying to patients may undermine trust in the doctor-patient relationship (Schwab, 2009).

To administer treatments openly, Annoni discusses three possible solutions (Annoni, 2018b). The first is to neither use deceptive nor transparent disclosures. This could for example be administering a placebo manual therapy while saying: "there is research showing that this treatment could help reduce your pain with minimal side-effects." However, this statement, Annoni argues, does not respect the healthcare provider's duty to truthfulness as Schwab has also argued above.

[39] In Allen's ideal placebo described as one where a DP is the best or only treatment option and supposing both the deception is required, and that placebo have actual therapeutic benefit. Both points are discussed in 4.1

[40] This is also debatable. The previous section outlined situations where healthcare providers did not correctly predict what patients want. Although some literature, confirmed in study 3, show that patients prefer efficacy over autonomy, this is not absolute and some patients' will is first and foremost to be informed to exercise their own will rather than be deceived for a potential benefit even in Allen's ideal placebo situation (F. L. Bishop, Aizlewood, et al., 2014; Druart et al., 2023).

The second option Annoni suggests would be to obtain "negative informed consent" or "authorized concealment." In these cases, patient could consent in advance to the use of placebo treatments. Examples of this could be situations where patients agree to receive DPs while not knowing when they would be administered. There are examples in which these uses of placebo treatments could complement physiotherapy care. For instance, an example could consist in adding one or two placebo pills to a 10-pill box of opioids. In this example, placebo treatments are used as dose-extenders. In such a case they would be associated with active treatments to extend the effect of the treatment (Colloca et al., 2016). This could be useful to limit total dose intake and thus reduce side-effects all while reducing treatment cost and limiting dose escalation. Such a strategy might be useful in the treatment of pain or Parkinson's disease where dose escalation proves a real challenge for rehabilitation. However, this solution also has limitations. Firstly, warning patients they may receive a placebo treatment in advance may lower their expectations which in turn reduces the usefulness of placebo treatments. Second, increasing suspicion of receiving a placebo treatment may also reduce patient compliance with effective medication and usual care.

Therefore, both these solutions are unsatisfactory (Annoni, 2018b). Lastly, Annoni suggests that placebos could be used openly in the form of open-label placebos (OLPs) (which we will turn to, next). Overall, DPs are often not ethically justifiable and their use in physiotherapy is no exception. Annoni concludes that it is impossible to prescribe DP while respecting patient autonomy concluding: either placebos are to be administered openly or paternalism needs to be, independently, morally justified (Annoni, 2018a).

2.1.3. Open-Label Placebos

Although many investigators have discussed the ethicality of using DP, their main ethical pitfall is linked to the need to deceive patients to administer them and the infringement upon patient autonomy this necessitates. Underlying this ethical concern, is the notion that deception is necessary to elicit the placebo effect (F. L. Bishop, Howick, et al., 2014) and is, as such, deemed unethical by most primary care practitioners (Howick et al., 2013). On this view, should patients become aware of

the inert nature of the treatment they received, the placebo effect would vanish. However, as early as 1965, and later on in 2003, pioneering authors proposed that maybe this was not the case after all (Aulas & Rosner, 2003; Park & Covi, 1965). More recently in 2010, Kaptchuk et al., in a landmark trial, showed that deception did not seem to be necessary to elicit placebo effects (Kaptchuk et al., 2010).

Combined, this research suggests that honestly administered placebos, so called OLPs, could present a solution to the ethical conundrum of administering placebo treatments. Multiple uses in physiotherapy can be imagined. To illustrate: placebo treatments could also be interesting in situations where other treatments are proscribed; for example, among pregnant women who are limited in their drug intake due to the potential adverse effects of some drugs on the foetus: in the case of low back pain during pregnancy placebo treatments could complement physiotherapy treatment. Other situations where this could be useful include, for example, whereby pain may prevent patients from performing certain exercises or movements. In rehabilitation this could arise in the case of fibromyalgia or post-operative conditions. Using an OLP in such a case may allow to reduce the acute pain just enough to carry out the rehabilitation care for long-term benefits.

However, Annoni continues stating "it is still unclear whether open-label placebos are as effective as DPs, or whether they imply a trade-off between veracity and effectiveness" (Annoni, 2018b). This is a research gap that will be necessary to probe further before we can resolutely consider clinical applications of placebo treatments in physiotherapy.

2.2. ARTICLES 1 & 2: PLACETHIC STUDY

This study resulted in two publications with distinct objectives. The first is a protocol article where we presented the methodological considerations pertaining to our study protocol. It was published in *Medicines (Basel)* in January 2020 under the title: "*Can an open-label placebo be as effective as a deceptive placebo? Methodological considerations of a study protocol*". Publishing the study protocol separately allowed to delve deeper into the methodological choices that were made and discuss them independently from the results. Particularly in placebo studies, it is crucial to carefully consider the methodology employed and its underlying justifications.

The second article presents the study results. It was submitted to The Journal of Pain on the 8th of March under the title "If only you knew! A non-inferiority randomized controlled trial comparing deceptive and open-label placebo treatments in healthy subjects". It is currently under review.

medicines

MDPI

Protocol

Can an Open-Label Placebo Be as Effective as a Deceptive Placebo? Methodological Considerations of a Study Protocol

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Abstract: Background: Placebo has been studied for many years and is ever-present in healthcare. In clinical practice, its use is limited by ethical issues raised by the deception entailed by its administration. **Objective:** To investigate whether, when given detailed information about pain and underlying placebo mechanisms, subjects will have a response similar to that of those subjected to a procedure in which they receive a conventional placebo treatment. **Methods:** The study is designed as a non-inferiority randomized, parallel with a nested crossover trial. In addition, 126 subjects without any known pathology will be included. They will be randomized into two groups. Each subject will undergo three Cold Pressor Tests (CPT): calibration, condition of interest (deceptive placebo or educated placebo), and control. Our main judgment criterion will be the comparison in pain intensity experienced on the visual analog scale between the two CPTs with placebo conditions. **Results:** This study will allow us to rule on the non-inferiority of an "educated" placebo compared to a deceptive placebo in the context of an acute painful stimulation. It is another step towards the understanding of open-label placebo and its use in clinical practice. **Conclusions:** This study has been approved by the ethics committee in France (2017-A01643-50) and registered on ClinicalTrials.gov (NCT03934138).

Keywords: open label placebo; pain; cold pressor test; ethics; clinical trial; placebo

1. Introduction

The placebo effect has been studied for decades and is present in medical and paramedical care. Though placebo treatments have shown their efficacy in numerous pathologies, their use in common practice is limited because of ethical issues. Placebos are utilized mostly as a methodological tool in control groups to demonstrate the efficiency of studied therapies.

Placebo was initially described as an inert substance or therapeutic procedure devoid of any pharmacological effect. Benedetti highlights an important nuance and describes the placebo not only as the inert substance but "its administration within a set of sensory and social stimuli that tell the patient that a beneficial treatment is being given" [1]. Indeed, the placebo effect can be in part defined as a "psychobiological phenomenon occurring in the patient's brain after the administration of an inert substance, or of a sham physical treatment along with verbal suggestions (or any other cue) of clinical benefit" [2]. Although there is no consensus on the taxonomy of the terms, the placebo effect and the placebo response are not interchangeable terms—the latter being the sum of all non-specific effects taking place after administration of a placebo treatment and the placebo effect being precisely

the psychosocial and psychobiological non-specific effects [1,3–5]. However, some authors suggest different definitions [6].

Many factors have been identified as potentially influencing the placebo effect and several mechanisms have been studied that elicit it [1,4]. The two main mechanisms implicated are learning and expectations. Other mechanisms such as social learning, memory, concentration, reward, and decreased anxiety [7] have also been studied and can either be classified into learning processes or expectations' modulation. A third mechanism of keen interest in recent research explores the genetics involved in the placebo effect [8]. Several genes have been identified in the dopaminergic, opioidergic, endocannabinoidergic, and serotoninergic pathways as modulators of a subject's placebo response.

Throughout recent decades, endogenous placebo mechanisms have been investigated. They refer to endogenous cascades triggered by expectancy, learning, and their combination, whereas exogenous mechanisms depend on pharmacologically induced effects [6]. Levine brought up this hypothesis for the first time in 1978 and since then many studies have confirmed it [9,10]. The authors described an endogenous response triggered by a positive expectancy [11]. Studies using fMRI [12,13] and PEI [14] have shown common mechanisms for placebo-induced and opioid-induced analgesia, particularly the activation of common cerebral regions. These findings have been confirmed and further studied as shown by recent reviews [15,16]. There is now solid evidence identifying the areas of the brain in play during placebo analgesia for example.

The expectation modulation mechanism includes the patient's expectations and that of the practitioner. A group of subjects hoping for a positive effect of a placebo treatment is more likely to experience the expected improvement of the symptoms [17]. The trial proposed in the present article attempted to modulate the subject's positive expectations using their understanding of underlying placebo mechanisms.

1.1. The Use of Placebo in Contemporary Clinical Practice

Numerous studies have explored the use of placebo treatments in clinical practice in industrialized countries. In the United Kingdom, in 2013, a survey involving interviews with 783 physicians [18] showed that 78% used placebo treatments at least once a week. In addition, they indicated that at least 97% of physicians had used them, most often impure ones (meaning derived from its original use yet inert on the symptom treated [5]), at least once in their careers. Pure placebos such as saline injection were very rarely utilized. In Denmark, the 2003 study by Hrobjartsson and Norup showed that 86% of general practitioners reported using at least one "intervention with no specific effect on the condition to be treated but a possible non-specific effect" in the previous year [19]. The main reason given was to avoid confrontation with the patient. In Tilburt et al.'s. study in 2008 [20], 334 interns and 345 rheumatologists in the United States were interviewed. Results demonstrated that 55% of practitioners used a placebo at least once during the previous year and 46% at least two or three times a month. Again, the majority of prescriptions were for impure placebos. Of these, 70% were antibiotics, which raises issues for the patient and for the community as well. More recently, a review from Linde and collaborators [21] confirmed these results on a large-scale meta-analysis. Firstly, we can see large intervals of responses (from 29 to 97% used placebo treatments at least once in their career) that seem to indicate that the concepts are quite differently defined in each study. Secondly, we can see that placebo treatments are widely used in practice and that these treatments are more often impure than pure.

1.2. Ethical Concerns

The ethical issues raised by the deception associated with placebo treatments limit its use. Indeed, "most physicians agree that the placebo effect plays a significant role, but that the use of placebo is often associated with uncertainty regarding the ethical dimensions of whether and how to communicate the use of a placebo to the patient" [22]. In addition, in the field of research, opinions are divided and, in most countries, there are no official regulations.

A first option is the use of placebo as a lure. That is, the inert nature of the given treatment is hidden from the patient in order to provide a placebo effect. Some authors such as Foddy justify lying to or omitting information from the patient because the treatment is administered in the patient's interest [23]. However, this represents a hindrance to the patient's autonomy and strengthens the doctor's paternalistic relationship with the patient. In this context, the patients cannot give informed consent nor can they refuse the treatment.

Moreover, this deceptive use of placebos can harm the therapist–patient relationship when the deception is discovered or revealed. "When a patient finds that a real illness was treated by a fake drug, the doctor–patient relationship will rupture, and may have long-term consequences on the patient's capacity to trust any medical advice" [24]. However, placebos can be a useful solution when there is no effective treatment available.

Considering previous arguments, in November 2006, the American Medical Association adopted an ethical policy prohibiting the use of placebo associated with deception in clinical practice. Added to that, many authors favor the use of open-label placebo [25] mostly because of the ease in manipulating patients that is underlined by the discovery of physiological mechanisms involved in the therapeutic ritual [4].

1.3. Placebos without Deception

However, if the patient takes a placebo treatment with full disclosure in regard to the nature of the treatment, will the therapeutic effect observed in the previously cited studies still be present? This question had started to raise interest as early as 2003. Authors such as Aulas and Rosner conducted a clinical trial on non-blind placebos as treatments for anxiety, in subjects suffering from depression, to answer this question [26]. This trial was a good starting point yet suffered from important methodological limitations. To overcome these limitations, Kaptchuk et al. designed one of the first randomized controlled trials on placebos without deception. This study compared an open-label placebo (OLP) to a no treatment arm with patients suffering from irritable bowel syndrome (IBS) [27]. In the OLP group, patients knew "that the placebo pill was an inactive (i.e., «inert») substance like a sugar pill that contained no medication." About 15 min were set aside to provide information about placebo. The symptom improvement in this group was clinically and statistically superior to the control condition. Results were surprisingly high: "finally, the percentage of patients reporting adequate relief (59%) is comparable with the responder rates in clinical trials of drugs currently used in IBS," demonstrating that, in a context of persuasive reasoning, OLP may show effectiveness comparable to the established treatments in IBS.

Other studies have confirmed Kaptchuk's team's hypothesis [28]: placebos without deception seem to improve a range of clinical symptoms while maintaining patient autonomy and trust in the physician. Recent reviews found OLP treatments to be clinically effective compared to no-treatment groups [29] on several conditions including: IBS, depression, allergic rhinitis, chronic low back pain, and attention deficit hyperactivity disorder (ADHD).

Nonetheless, it is still unclear how OLPs work [30] and how to increase their effectiveness. One variable that is to be considered is the rationale given during its administration.

Such explanations are starting to be studied more and more. For example, Locher et al. [31] compared OLP and deceptive placebos with a focus on the rationale given to the patients. The research hypothesis was that the educated placebo would still be less effective than the deceptive placebo. Other studies such as Schaefer et al.'s RCT [32] looked at information as a trigger of positive expectancy in allergic rhinitis.

This protocol's hypothesis is that knowledge and understanding of the mechanisms at work in the placebo effect will increase the intensity of the open placebo response towards a non-inferiority compared with deceptive placebo. This is the reason the group with the variable of interest is called "educated" placebo. This study will be the first, to our knowledge, to test for non-inferiority between an educated placebo and a deceptive one.

2. Materials and Methods

2.1. Objectives

The main objective of this study is to investigate whether or not an educated placebo is non-inferior to a deceptive placebo treatment on treating acute pain intensity. Secondary objectives of the study include verifying the superiority of both placebo treatments with a no-treatment Cold Pressor Test (CPT). We will also assess the effect of both placebo treatments on anxiety. This study also aims to measure whether or not the educational video was effective in transmitting knowledge about the placebo effect.

2.2. Design

We will conduct a non-inferiority randomized, parallel with a nested crossover trial comparing educated open-label placebo to deceptive placebo. This monocentric study will be carried out by two licensed physiotherapists in a University Hospital near the campus.

Written informed consent will be obtained from subjects prior to their participation in the study. The investigation will consist of a single two-hour session. Participants will receive a 20€ participation compensation.

The subjects meeting the inclusion criteria (detailed below) will be randomized into two groups: (1) educated placebo or (2) conventional/deceptive placebo. Each will be subjected first to a calibration CPT, and then, in a randomized order, will receive the CPT under the condition of interest (either the Conventional placebo CPT (CPTp) or the Educated placebo CPT (CPTe)) and a Control CPT (CPTc). This is represented in Figure 1.

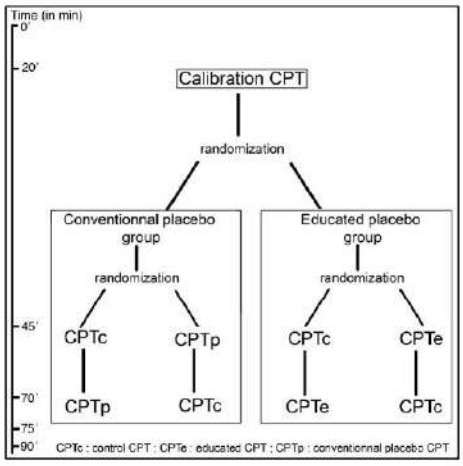

Figure 1. CPT order diagram.

Regarding blinding, investigators will not be blind as they deliver the treatment openly in the educated group. Patients in the deceptive placebo group will be blinded. However, patients in the educated placebo group will not be due to the nature of OLP. The analysis will be done blindly as the analyst will not know which group received which treatment.

2.3. Assessment

The primary end point will be the difference in pain intensity, assessed on a 100-point visual analogue scale (VAS), between the educated OLP and the deceptive placebo treatments at the end of

the placebo condition CPT. We have chosen pain intensity as opposed to pain threshold because it involves less motivational and cognitive components [33].

The main secondary end point will be, for each subject, the difference in pain intensity, also assessed by VAS, between open or deceptive placebo versus no-treatment control. Secondarily, a questionnaire (inspired by Hughes et al.'s data [34]) measuring knowledge regarding the placebo effect will be completed by all the subjects after the study and also before the educational video for the educated placebo group. In addition, all the subjects will complete another questionnaire about their perception of the investigators and of the study [35]. Blood pressure (BP) and heart rate (HR) values will be obtained before, during, and after each CPT by means of an automatic blood pressure monitor. Finally, subject's anxiety will be evaluated through heart rate variability. Before the CPT treatment, an expectancy questionnaire will be used [36].

We expect to find a non-inferiority between both groups on the main end point. Considering the nature of the dependent variables and the choice of the painful stimulation, we expect a high interindividual variability. This has been limited as best as possible by the cross-over conducted in both arms of the study.

2.4. Subjects

Participants are to be recruited via advertisements for a study of a painkiller cream, on the Grenoble University campus. Inclusion criteria are: being aged between 18 and 40 years old, registered to the national healthcare, having understood and signed the written consent. Non-inclusion criteria were the following: legal impossibility to participate to the protocol (i.e., pregnant women, people deprived of their liberty) or affections modifying the painful stimulus used (any known pathology affecting the venous, arterial, or lymphatic system, diabetes, cardiac affections, asthma, frostbite on the hand, epilepsy, hand arthritis, lupus erythematosus, and allergic reactions to the cream, under pain regulation medication).

All medication that could impact pain sensation, such as painkillers or psychotropics, have to be stopped three weeks prior to experiment, as will alcohol in the 24 h prior to the experiment.

Socio-demographic information will be collected in order to control the impact of these variables in the representation of the placebo effect and consequently expectations towards the treatments.

2.5. Ethical Considerations Regarding the Study Protocol

During conceptualization of the protocol, several ethical questions were raised. The first was about the information given while administering the cream as a deceptive placebo. While it was first considered to present it as "an analgesic cream", this was deemed too much of a deception and unethical. The committee in charge of ethics agreed on the use of the sentence "This is a cream useful for treating pain" as it was argued that was true due to its non-specific effect.

Secondly, the choice of reaching 7/10 as a threshold on the VAS was debated. It was argued that this was a high level of pain. However, the duration of this intense pain was deemed short enough to present little risks and be a probable situation in a clinical setting. The treatments used in the case of pain rated over 7/10 are also those with the most side-effects and thus these types of intense pain experiences would benefit most from OLP treatments. The time frame required to obtain a score of 7 on the VAS with a CPT is still within a reasonable duration.

Lastly, among the often-used pain stimulation methods, the choice of using a CPT was also questioned. This point is discussed in the discussion below.

2.6. Material

The Cold Pressor Test (CPT), Dip Cooler RU 200 from Techne® (Cole Parmer, Staffordshire, United-Kingdom) will deliver the pain stimulus. The duration of the immersion will be calibrated during the first CPT and maintained for an identical time in the two others. More on the use of the CPT is presented below.

Tablets will be used to fill out the assessments as well as watch the videos. The content of the educational video will be detailed below. The control video (about the history of hygiene and Semmelweis) was taken from a well-known video broadcasting website with written consent from the creator.

The placebo treatment used for both groups is a neutral cream with no active pharmacological substance: CremaFluid Phytomedica® (Laboratoires Phytomedica, Aix-en-Provence France). It will be presented as a placebo cream in group 1 (educated placebo) and as a painkiller in group 2 (deceptive placebo).

2.7. Randomization

Randomization was carried out in several steps. Firstly, an analyst from inside the team wrote the code to get a randomized spreadsheet of groups and CPT orders. The rest of the procedure was conducted by the research team's staff not involved in the protocol. Another analyst was asked to attribute to each group an unidentifiable name in order to blind the analysis of results (group A and group B) as well as choose a random seed. Lastly, another person made individual, numbered, and sealed envelopes with the randomization results inside. This entire process was done with no involvement from the investigators. The envelopes are kept under lock and key.

This process allows for preservation of the blinding of the analyst (not knowing which treatment group A and B received) and maintains the investigator in the dark regarding group attribution until the envelope is opened.

2.8. CPT Procedure

Each volunteer will be initially subjected to a calibration test according to the CPT procedure and then to the experimental tests. After this, a debriefing and two questionnaires will conclude the inclusion.

Each CPT procedure is as follows. Every CPT is preceded by a 3 min monitored resting period where heart rate and respiratory rate are measured. Blood pressure is measured at the end of this 3 min baseline assessment. The hand and forearm temperature will be checked on both sides for reference. The non-dominant hand and distal third of the forearm will be immerged into the CPT at 1 °C +/− 1 °C. The forearm length submerged in the cold-water tank will be determined as follows: 1/3 of the distance between the ulnar styloid and the tip of the olecranon. The elbow will be placed on the outer rim of the water tank and the hand relaxed with no contact with the bottom of the tank.

For the calibration CPT, patients will be asked to record the intensity of their pain on the VAS every 5 s approximately. When the intensity exceeds 7/10 on the VAS, the subject will be told to remove his or her hand from the water. The time at which this event occurs will be referenced as (t). For both of the other CPTs, patients will be asked to keep the hand in the tank during (t) seconds and complete a VAS as soon as the hand is taken out of the water.

In between each CPT, a 20 min pause is mandatory and skin temperature is checked before the next CPT. If needed, a tank of warm water at approximately 25 °C can be used to warm up the hand until it reaches contralateral temperature.

2.9. Part I: Calibration

The protocol can be described in three different phases described below. The first phase is the calibration. Subjects are greeted by the main investigator who will explain in detail the nature of the pain stimulation applied and inform subjects of their rights regarding data privacy and protocol interruption. Inclusion and non-inclusion criteria are checked before signing a written consent. Once consent is obtained, the randomization envelope is opened to allocate subjects to a group and determine the order of the CPTs. The calibration CPT can then start following the procedure stated above in part 2.8.

This calibration will enable us to use a constant duration for the immersion of the hand in the water for the two remaining CPTs, and will allow us to ensure that the intensity of pain is homogeneous.

2.10. Part II: Experimental CPTs

During the break between calibration and the second CPT, the subject will receive the information related to the group they are randomized into. For the deceptive placebo group, the video will describe the history of hygiene and correct method for washing hands. For the educated placebo group, the video will be an educational video about placebo, its physiology, and the use of OLP. Movies are similar in terms of duration (~11 min), image quality, and format. After both videos, there will be a time where questions can be answered by the investigators. The educated placebo group will fill out a questionnaire regarding their knowledge of the placebo effect before watching the educational video.

The test phase will be divided into two parts in a random sequence to compensate for habituation effect: deceptive placebo CPT (CPTp) or educated placebo (CPTe) and control CPT (CPTc). For the CPTp and CPTe, two milliliters of the neutral placebo cream are applied beforehand following a standardized procedure: four round-trips on the forearm along its submerged part and on the dorsal and palmar side of the hand and an expectancy questionnaire is filled out. The immersion time (t) in cold water will be that previously calibrated.

While applying the neutral cream, the examiner will explain to the deceptive placebo group, that "it is a cream effective in fighting cold-related pain." In the Educated placebo condition, the examiner states that it is "a placebo cream, containing no active substance that is effective in fighting cold-related pain. All the mechanisms shown in the previous film will be at work. In a way, your brain will be secreting the active components itself."

Under the control condition, no cream will be applied.

The examiner will be aware that the same placebo cream is used for the two groups, in order to simulate real situations in which the practitioner administering or prescribing the placebo does so with full knowledge of its presence. The patient will not be blinded in the OLP group and will be blinded in the deceptive placebo group. The analyst will be blinded to group allocation.

2.11. Part III: Subject Debriefing

After all three CPTs, all subjects are asked to fill out the questionnaire on their knowledge of the placebo effect. One group (deceptive placebo group) is naive to this questionnaire and the other is filling it out again after having viewed an educational video approximately 40 min ago. This will allow for controlling information retention. Subjects then fill out a questionnaire on their perception of the research hypothesis as well as their perception of the investigators.

After the inclusion is finished, a debriefing session is conducted by the main investigator in order to explain the research protocol and the deception if one has taken place. This is done in order to be sure patients understand what the research was about and to answer any questions left by the protocol. This debriefing also allows to be sure the pain stimulation was well lived through.

Figure 2 is a detailed flow chart of the research protocol. From top to bottom are the three phases of the protocol. The white boxes are the procedures common to both groups.

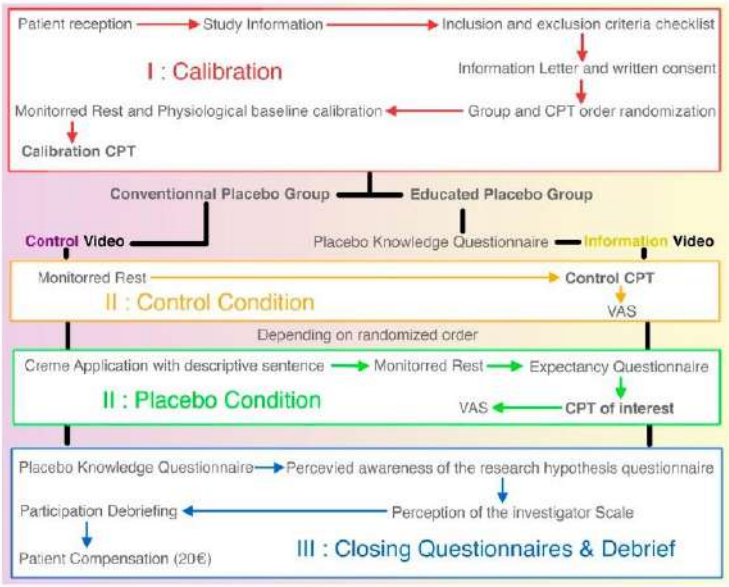

Figure 2. Detailed study flow for a subject. From top to bottom for an animated version of this figure, see: http://bit.ly/Placethic-Figure.

2.12. Sample Size

As previously stated by the FDA and confirmed by the MCID recommended by Myles et al. [37], we set the margin of non-inferiority at 10 mm. Based on a 21.9 mm standard-deviation of the VAS score[38] and assuming an alpha of 0.05, the minimum sample size required to achieve a power of 80% to reject the inferiority null hypothesis was 60 per group. Adding to that a 5% margin of estimated non-usable data the total number of subjects will be of 126.

Streff et al. [38] had a similar utilization of experimental pain in their study using a CPT on healthy subjects and a visual analog scale (VAS) to estimate pain. In the dataset they present, a standard deviation of 21.9 mm is calculated.

2.13. Statistical Analysis

We will perform the statistical analysis with alpha = 0.05. Unless stated otherwise, all tests will be bilateral. We will perform the tests with an Intention To Treat population: all participants will be analyzed in the group in which they were initially randomized.

Missing data on the primary endpoint will be imputed by multiple imputation if between 5% and 20% of the measurements are missing. If less than 5% are missing, we will not impute the missing data. If more than 20% of the data are missing, the results will be interpreted with caution. We will not perform missing data imputation on the other endpoints.

We will test the non-inferiority of the Educated Placebo compared to the Conventional Placebo using the unilateral 95% confidence interval of the difference of the pain intensity. The non-inferiority margin is set to 10 mm on the VAS. We will estimate the confidence interval by linear regression. The linear regression will account for the pain intensity without placebo and the sequence of the CPTs. As an Intention to Treat analysis can be biased when evaluating a non-inferiority [39], we will also test the non-inferiority with a per protocol analysis: subjects will be included in the group only if there

were no deviations from the protocol. If the results of the two analysis are discordant, we will interpret the results with caution.

We will also test the superiority of the Conventional Placebo compared to no-treatment by a cross-over ANOVA. Similarly, we will test the superiority of the Educated Placebo compared to no-treatment by a cross-over ANOVA. We will test the other between group differences by Student's *t*-test for two independent samples.

We will test the effect of the education in the Educated Placebo group by Student's *t*-test for paired samples comparing the knowledge about Placebo before and after the educational video.

This study will allow us to rule on the non-inferiority of an educated placebo compared to conventional placebo in the context of an acute painful stimulation. We have highlighted the need to study the different determinants increasing the placebo effect, and in particular the understanding of underlying placebo mechanisms. This study is the first step in a series of research works that could allow an ethical use of placebo in clinical practice.

Analysis will be conducted on Stata software, version 15 (StataCorp LLC, College Station, TX, USA) or higher.

3. Results

This research protocol has been approved by the Ethical Committee (Comité de Protection des Personnes Sud Ouest et Outre mer III) on the 28th of February 2018 under the identification 2017-A01643-50 and registered on ClinicalTrials.gov under the identification number NCT03934138. Funding has been acquired through the APICIL Foundation to conduct the investigation and compensate patients. Recruitment has started during May 2019 and will take place until the required number of subjects is recruited.

Pre-testing was conducted in order to assess logistical needs and train the investigators. Slight modifications were adopted such as the reduction of intervals between each VAS during the calibration CPT from 10 to 5 s. The instructions for the CPT were also made more precise to include instructions in regard to not touching the bottom of the tank or moving the hand during the procedure. During these pre-tests, we were able to better estimate the time needed for set-up during which the cooling of the CPT is time-consuming. The average time for inclusion is closer to one hour and a half compared to the initial two hours announced to the subjects. However, this extra time allows for a technical margin.

The final set-up is illustrated in Figure 3. Monitoring was conducted through the computer to the left. Patients had to their right the CPT tank as well as the warm water if needed. Investigators were wearing lab coats over casual clothing.

Figure 3. Clinical trial set-up during a CPT test.

4. Discussion

4.1. Methodological Justifications

Many of the methodological choices made during conceptualization of the protocol need to be argued and explained. The first choice made during conception was to conduct a non-inferiority trial. Such trials are useful in asserting the non-inferiority between two procedures when one has a clear advantage over the other whether it being economical, iatrogenic, or ethical. In the present protocol, the educated placebo has a distinct ethical advantage over the deceptive placebo, and this justifies the choice of resorting to a non-inferiority analysis.

At the time of obtaining ethical authorizations in 2016, too few open-label placebo studies were published and none were conducted in France to justify its use on patients in the eyes of ethical committees. Therefore, the ethical committee authorized a trial conducted on healthy volunteers with an experimental pain. This is another step towards justifying OLP use with patients.

Experimental pain modalities are numerous although common techniques involve either heat, cold, or electrical stimulations. In this case, we opted for the use of a CPT with water at 1 °C. This method is broadly used and has well described modalities towards its use as a pain stimuli [38,40–42]. Although CPTs present a high inter-subject variability, the cross-over design will mitigate any effect this would have on the results of the secondary endpoint variables. Setting the temperature at 1 °C allows for average times of 40 s before reaching pain tolerance [43]. Regarding setting the VAS limit at 70/100 before taking the hand out of the tank, this is justified because of the patients we wish to treat in future protocols. These patients suffer from intensive pain (>7/10) that requires special treatments often associated with strong adverse events. These patients would benefit the most from innovative solutions to treat pain such as OLP.

Another choice made for this protocol is the use of VAS as the main evaluation criterion. This measure of pain intensity is not influenced by the cognitive and motivational components that influence pain tolerance or pain threshold or duration of immersion [33]. Its ease of use and of comprehension is another advantage [44]. The numerous secondary criteria will allow to assess the anxiety subjects felt via measure of their heart and respiratory rate. Expectancy and perception of the study and the investigator will be measured with questionnaires. Both groups will fill out a placebo knowledge questionnaire with no prior explanation on the effect. Only the educated placebo group will take this test again once the protocol is finished. This will allow us to control the understanding of the educational video.

The choice of using a cross-over methodology when comparing placebo to no-treatment allows us to control for each subject and each group with a no-treatment measure. This is a methodological strength of the protocol. The randomization of the order in which these control and placebo CPTs are done allows for adjusting on habituation that other studies have found [45]. Each CPT takes place after a 20 min wash-out period where vasodilatation may return to its baseline state. This is verified by a check that hand temperature is comparable on both hands as well as having the VAS return to 0 before performing a new test.

One crucial element of the protocol resides in the choice of using a video capsule to deliver the rationale as well as constructing the rationale. To do so, we contacted authors in several other open-label placebo trials to use their scripts as a starting point. Once this was done, we took the most common misconceptions found by Hughes et al. [34] and discussed them in the video. To give credibility to the video and reinforce the positive expectations of patients watching the video, we described several landmark articles and trials about placebos and open label placebos as well as gave feedback from patients from those trials. The video was illustrated with several everyday life examples. A cartoonist was hired to give visual graphical illustrations over which a text was read. To ensure proper understanding, any questions patients could have regarding the video are answered. The control group is also presented with a video to watch. This video is presented as a video to distract subjects

from the painful experience before starting the interventional phase of the study. Both videos are similar in regard to length and format.

During this trial, the subject's knowledge about the placebo effect needed to be measured in order to check for effectiveness of the education. To our knowledge, there are no questionnaires specifically validated for our population to this end. However, a recent study [34] constructed a 15-item questionnaire to survey placebo knowledge among trial participants. We adapted this questionnaire to use in our study (available in French and English in the Supplementary Files S1 and S2). After coming up with a first version of the questionnaire, we pre-tested it with 10 subjects meeting our inclusion criterion and five people older than the age limit set in the protocol. Pre-tests were conducted via cognitive interviews. The questions were clear for all subjects and allowed us to proceed with this questionnaire in our trial. During the trial, the need for a naive response from the educated placebo groups imposes to fill the questionnaire before the CPT of interest. This may be considered as part of the intervention as this condition is not present in the deceptive placebo group (to complete Figure 2 we added in the Supplementary Files a table comparing the interventions received in both groups). In any case, every element of the questionnaire is addressed in the video and analysis will check for any influence of the questionnaire on the placebo response.

4.2. Future OLP Research

As stated during the 2019 SIPS conference, future research on open-label placebo will be faced with several challenges in order to justify a potential use in a clinical setting. Among these challenges is the investigation of the mechanisms behind open-label placebos' efficacy and what triggers exist that modulate this efficacy. Current hypotheses revolve around the patient–therapist relationship, the treatment in itself and/or the rationale given to the patients. This study will allow for gaining insight regarding the latter. The modalities of the educational intervention, explained and argued in the previous subsection, will allow for interesting discussion once the results are obtained.

Another challenge future research needs to take into account is to conduct investigations on subjects that are not healthy subjects. This protocol helps towards justifying the use of OLP with patients once used with healthy subjects with no risks and shows potential benefits. At the time of conceptualization of this protocol, too few studies allowed for ethical justification of the use of OLP with patients.

One of the major difficulties in regard to OLP research is the difficulty in using control groups as a reference. Past studies have used no treatment or treatment as usual groups as controls. This study suggests an original methodology with two parallel groups as well as an intra-group control. This allows for intra-subject control as well as comparison between a no treatment condition and a treatment condition. Of course, this means that the statistical analysis must show, in order to conclude a non-inferiority with clinical relevance, that both the deceptive placebo and the open-label placebo are statistically superior to the no treatment condition while also finding the open-label placebo condition to be non-inferior to the deceptive placebo. This methodological challenge of having a valid control group seems to justify the necessity in publishing protocols allowing for a detailed peer-review process. This allows going in-depth into the process used to elicit a placebo response as well as give a detailed account of the context present during the inclusions.

Lastly, there persists a difficulty in the blinding of the different people involved. To be close to a clinical setting, it is impossible to blind the patient and the therapist. However, an independent assessor could help in blinding the assessment. This was not done in this protocol for material reasons. Instead, the primary outcome is self-reported and the analysis is done blindly by the statistical team.

To address these multiple challenges and avoid discrediting future OLP research, we argue that there is a need to give in-depth explanations of what happens during research protocols that elicit placebo responses whether they are open or not. However, the current scientific publication process often restrains authors towards the number of words used in an article. This is done for obvious reasons, yet does not allow for the exhaustive detail to be given in regard to the protocols and their justifications.

This is why it seems crucial to encourage authors to publish their detailed research protocols and methodological considerations either in separate articles or in formats with a less restrained approach to the word limits.

In regard to this protocol, depending on the results, future research will be conducted to investigate the cognitive levers associated with the rationale that can increase OLP effectiveness. Comparisons between an optimized open-label placebo and several treatments in patients affected with persistent pain such as fibromyalgia or low back pain will also be designed and carried out.

Supplementary Materials: The following are available online at http://www.mdpi.com/2305-6320/7/1/3/s1, File S1: Questionnaire Placebo French Version, File S2: Questionnaire Placebo English Version

Author Contributions: Conceptualization, L.D., S.G.L., and N.P.; Methodology, L.D., S.G.L., C.R., M.D., H.T., J.-L.B., and N.P.; Software, L.D. and H.T.; Validation, L.D., S.G.L., C.R., and N.P.; Formal Analysis, M.D. and H.T.; Investigation, L.D., S.G.L., and N.P.; Resources, C.R.; Data Curation, H.T.; Writing—original draft preparation, L.D., S.G.L., and N.P.; Writing—review and editing, L.D., S.G.L., C.R., M.D., H.T., and N.P.; Visualization, L.D. and S.G.L.; Supervision, N.P.; Project administration, L.D. and S.G.L.; Funding acquisition, L.D., S.G.L., and N.P. All authors have read and agreed to the published version of the manuscript.

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References

1. Benedetti, F.; Carlino, E.; Pollo, A. How placebos change the patient's brain. *Neuropsychopharmacology* **2011**, *36*, 339–354. [CrossRef] [PubMed]
2. Price, D.D.; Finniss, D.G.; Benedetti, F. A comprehensive review of the placebo effect: Recent advances and current thought. *Annu. Rev. Psychol.* **2008**, *59*, 565–590. [CrossRef] [PubMed]
3. Ernst, E.; Resch, K.L. Concept of true and perceived placebo effects. *BMJ* **1995**, *311*, 551–553. [CrossRef] [PubMed]
4. Benedetti, F. Placebo and the new physiology of the doctor-patient relationship. *Physiol. Rev.* **2013**, *93*, 1207–1246. [CrossRef] [PubMed]
5. Kelley, J.M. Lumping and Splitting: Toward a Taxonomy of Placebo and Related Effects. *Int. Rev. Neurobiol.* **2018**, *139*, 29–48. [PubMed]
6. 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. [CrossRef] [PubMed]
7. Colloca, L.; Miller, F.G. How placebo responses are formed: A learning perspective. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **2011**, *366*, 1859–1869. [CrossRef]
8. Colagiuri, B.; Schenk, L.A.; Kessler, M.D.; Dorsey, S.G.; Colloca, L. The placebo effect: From concepts to genes. *Neuroscience* **2015**, *307*, 171–190. [CrossRef]
9. Levine, J.D.; Gordon, N.C.; Fields, H.L. The mechanism of placebo analgesia. *Lancet* **1978**, *2*, 654–657. [CrossRef]
10. Gracely, R.H.; Dubner, R.; Wolskee, P.J.; Deeter, W.R. Placebo and naloxone can alter post-surgical pain by separate mechanisms. *Nature* **1983**, *306*, 264–265. [CrossRef]
11. Amanzio, M.; Benedetti, F. Neuropharmacological dissection of placebo analgesia: Expectation-activated opioid systems versus conditioning-activated specific subsystems. *J. Neurosci.* **1999**, *19*, 484–494. [CrossRef] [PubMed]
12. Wager, T.D.; Rilling, J.K.; Smith, E.E.; Sokolik, A.; Casey, K.L.; Davidson, R.J.; Kosslyn, S.M.; Rose, R.M.; Cohen, J.D. Placebo-induced changes in FMRI in the anticipation and experience of pain. *Science* **2004**, *303*, 1162–1167. [CrossRef] [PubMed]

13. Eippert, F.; Finsterbusch, J.; Bingel, U.; Büchel, C. Direct evidence for spinal cord involvement in placebo analgesia. *Science* **2009**, *326*, 404. [CrossRef] [PubMed]
14. Petrovic, P.; Kalso, E.; Petersson, K.M.; Ingvar, M. Placebo and opioid analgesia–imaging a shared neuronal network. *Science* **2002**, *295*, 1737–1740. [CrossRef]
15. Palermo, S.; Benedetti, F.; Costa, T.; Amanzio, M. Pain anticipation: An activation likelihood estimation meta-analysis of brain imaging studies. *Hum. Brain Mapp.* **2015**, *36*, 1648–1661. [CrossRef]
16. Amanzio, M.; Benedetti, F.; Porro, C.A.; Palermo, S.; Cauda, F. Activation likelihood estimation meta-analysis of brain correlates of placebo analgesia in human experimental pain. *Hum. Brain Mapp.* **2013**, *34*, 738–752. [CrossRef]
17. Aulas, J.-J. Placebo et effet placebo. *Ann. Pharm. Fr.* **2005**, *63*, 401–415. [CrossRef]
18. Howick, J.; Bishop, F.L.; Heneghan, C.; Wolstenholme, J.; Stevens, S.; Hobbs, F.D.R.; Lewith, G. Placebo use in the United kingdom: Results from a national survey of primary care practitioners. *PLoS ONE* **2013**, *8*, e58247. [CrossRef]
19. Hróbjartsson, A.; Norup, M. The use of placebo interventions in medical practice–a national questionnaire survey of Danish clinicians. *Eval. Health Prof.* **2003**, *26*, 153–165. [CrossRef]
20. Tilburt, J.C.; Emanuel, E.J.; Kaptchuk, T.J.; Curlin, F.A.; Miller, F.G. Prescribing "placebo treatments": Results of national survey of US internists and rheumatologists. *BMJ* **2008**, *337*, a1938. [CrossRef]
21. Linde, K.; Atmann, O.; Meissner, K.; Schneider, A.; Meister, R.; Kriston, L.; Werner, C. How often do general practitioners use placebos and non-specific interventions? Systematic review and meta-analysis of surveys. *PLoS ONE* **2018**, *13*, e0202211. [CrossRef] [PubMed]
22. Fent, R.; Rosemann, T.; Fässler, M.; Senn, O.; Huber, C.A. The use of pure and impure placebo interventions in primary care—A qualitative approach. *BMC Fam. Pract.* **2011**, *12*, 11. [CrossRef] [PubMed]
23. Foddy, B. A duty to deceive: Placebos in clinical practice. *Am. J. Bioeth.* **2009**, *9*, 4–12. [CrossRef] [PubMed]
24. Powell, T.; Bailey, J. Against placebos. *Am. J. Bioeth.* **2009**, *9*, 23–25. [CrossRef]
25. Miller, F.G.; Colloca, L. The legitimacy of placebo treatments in clinical practice: Evidence and ethics. *Am. J. Bioeth.* **2009**, *9*, 39–47. [CrossRef]
26. Aulas, J.-J.; Rosner, I. Efficacy of a non blind placebo prescription. *L'Encéphale* **2003**, *29*, 68–71.
27. Kaptchuk, T.J.; Friedlander, E.; Kelley, J.M.; Sanchez, M.N.; Kokkotou, E.; Singer, J.P.; Kowalczykowski, M.; Miller, F.G.; Kirsch, I.; Lembo, A.J. Placebos without deception: A randomized controlled trial in irritable bowel syndrome. *PLoS ONE* **2010**, *5*, e15591. [CrossRef]
28. Colloca, L.; Howick, J. Placebos Without Deception: Outcomes, Mechanisms, and Ethics. *Int. Rev. Neurobiol.* **2018**, *138*, 219–240.
29. Charlesworth, J.E.G.; Petkovic, G.; Kelley, J.M.; Hunter, M.; Onakpoya, I.; Roberts, N.; Miller, F.G.; Howick, J. Effects of placebos without deception compared with no treatment: A systematic review and meta-analysis. *J. Evid. Based Med.* **2017**, *10*, 97–107. [CrossRef]
30. Kaptchuk, T.J. Open-Label Placebo: Reflections on a Research Agenda. *Perspect. Biol. Med.* **2018**, *61*, 311–334. [CrossRef]
31. Locher, C.; Frey Nascimento, A.; Kirsch, I.; Kossowsky, J.; Meyer, A.; Gaab, J. Is the rationale more important than deception? A randomized controlled trial of open-label placebo analgesia. *Pain* **2017**, *158*, 2320–2328. [CrossRef] [PubMed]
32. Schaefer, M.; Sahin, T.; Berstecher, B. Why do open-label placebos work? A randomized controlled trial of an open-label placebo induction with and without extended information about the placebo effect in allergic rhinitis. *PLoS ONE* **2018**, *13*, e0192758. [CrossRef] [PubMed]
33. Handwerker, H.O.; Kobal, G. Psychophysiology of experimentally induced pain. *Physiol. Rev.* **1993**, *73*, 639–671. [CrossRef] [PubMed]
34. Hughes, J.; Greville-Harris, M.; Graham, C.A.; Lewith, G.; White, P.; Bishop, F.L. What trial participants need to be told about placebo effects to give informed consent: A survey to establish existing knowledge among patients with back pain. *J. Med. Ethics* **2017**, *43*, 867–870. [CrossRef] [PubMed]
35. Rubin, M. *The Perceived Awareness of the Research Hypothesis Scale: Assessing the Influence of Demand Characteristics*; The University of Newcastle: Callaghan, NSW, Australia, 2016.
36. Devilly, G.J.; Borkovec, T.D. Psychometric properties of the credibility/expectancy questionnaire. *J. Behav. Ther. Exp. Psychiatry* **2000**, *31*, 73–86. [CrossRef]

37. Myles, P.S.; Myles, D.B.; Galagher, W.; Boyd, D.; Chew, C.; MacDonald, N.; Dennis, A. Measuring acute postoperative pain using the visual analog scale: The minimal clinically important difference and patient acceptable symptom state. *Br. J. Anaesth.* **2017**, *118*, 424–429. [CrossRef]
38. Streff, A.; Kuehl, L.K.; Michaux, G.; Anton, F. Differential physiological effects during tonic painful hand immersion tests using hot and ice water. *Eur. J. Pain* **2010**, *14*, 266–272. [CrossRef]
39. Wiens, B.L.; Zhao, W. The role of intention to treat in analysis of noninferiority studies. *Clin. Trials* **2007**, *4*, 286–291. [CrossRef]
40. Kyle, B.N.; McNeil, D.W. Autonomic arousal and experimentally induced pain: A critical review of the literature. *Pain Res. Manag.* **2014**, *19*, 159–167. [CrossRef]
41. Ferreira-Valente, M.A.; Pais-Ribeiro, J.L.; Jensen, M.P. Validity of four pain intensity rating scales. *Pain* **2011**, *152*, 2399–2404. [CrossRef]
42. McManus, F.J.; Ward, A.R.; Robertson, V.J. The analgesic effects of interferential therapy on two experimental pain models: Cold and mechanically induced pain. *Physiotherapy* **2006**, *92*, 95–102. [CrossRef]
43. Mitchell, L.A.; MacDonald, R.A.R.; Brodie, E.E. Temperature and the cold pressor test. *J. Pain* **2004**, *5*, 233–237. [CrossRef] [PubMed]
44. Price, D.D.; McGrath, P.A.; Rafii, A.; Buckingham, B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. *Pain* **1983**, *17*, 45–56. [CrossRef]
45. LeBlanc, J.; Potvin, P. Studies on habituation to cold pain. *Can. J. Physiol. Pharmacol.* **1966**, *44*, 287–293. [CrossRef]

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If only you knew! A non-inferiority randomized controlled trial comparing deceptive and open-label placebo treatments in healthy subjects

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Abstract:	This study aimed to compare the use of deceptive placebo treatments (DP) and open-label placebo treatments (OLP) to reduce pain in healthy volunteers. A non-inferiority, randomized, controlled trial was conducted at a university clinic in France. We conducted a parallel, randomised, controlled trial, which also included a nested cross-over no-treatment condition. We included 60 subjects and the main result shows that the OLP was not inferior to the DP by a margin of 10mm, with a unilateral alpha risk of 5%. The mean difference between both groups regarding intensity of pain was 0.7mm and a 95%CI of]-∞; 5.4]. Secondary outcomes require cautious interpretation of the effect of placebo versus no-treatment due to a time-treatment interaction. The study indicates that OLP may perform just as well as DP and could provide support for the use of OLP as an ethical alternative to DP when they are to be used in a clinical setting. Trial Registration: French national ethical committee n°2017-A01643-50 & ClinicalTrials n°NCT03934138
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Title Page

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If only you knew! A non-inferiority randomized controlled trial comparing deceptive and open-label placebo treatments in healthy subjects

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- The authors declare no competing of conflicts of interest.
- Data and code for analysis are available upon request to the corresponding author.

Abstract (unstructured 153 words)

This study aimed to compare the use of deceptive placebo treatments (DP) and open-label placebo treatments (OLP) to reduce pain in healthy volunteers. A non-inferiority, randomized, controlled trial was conducted at a university clinic in France. We conducted a parallel, randomised, controlled trial, which also included a nested cross-over no-treatment condition. We included 60 subjects and the main result shows that the OLP was not inferior to the DP by a margin of 10mm, with a unilateral alpha risk of 5%. The mean difference between both groups regarding intensity of pain was 0.7mm and a 95%CI of]-∞; 5.4]. Secondary outcomes require cautious interpretation of the effect of placebo versus no-treatment due to a time-treatment interaction. The study indicates that OLP may perform just as well as DP and could provide support for the use of OLP as an ethical alternative to DP when they are to be used in a clinical setting.

Trial Registration: French national ethical committee n°2017-A01643-50 & ClinicalTrials n°NCT03934138

Perspective: Open-label placebos (OLPs) were non-inferior to deceptive placebos (DPs) in reducing pain in our randomized controlled study on healthy subjects. This suggests that OLPs can be as effective as DPs while having ethical advantages. If deception is not a necessary condition for efficacy, OLPs should be preferred over DPs.

Keywords: Pain, Deceptive Placebo, Open-Label Placebo, Experimental Pain, Randomized Controlled Trial

Introduction (437 words)

Vigorous debate surrounds the clinical use of deceptive placebo treatments (DP). Although their use is believed to be widespread [26], a major ethical pitfall in their use is the need to deceive patients in administering such treatments [1,3]. In response to these pitfalls, honestly prescribed, so-called 'open label placebos' (hereafter, OLP) have been suggested as a more ethical solution to the use of placebo treatments in a clinical setting [23]. As such, the efficacy of honestly prescribed placebo treatments have been studied [2]. Two recent meta-analyses showed a moderate effect size when compared to no-treatment [9,37]: more precisely the most recent meta-analysis of the two an effect size of 0.79 with a 95% compatibility interval (95%CI) of 0.38 to 1.20 (we choose here to use the term compatibility interval instead of confidence intervals as suggested by Rafi & Greenland [32]). However, although OLPs have a supposed ethical advantage over DPs, some patients consider effectiveness over autonomy when deciding whether a placebo treatment is acceptable or when choosing their preferred placebo administration [4,16]. As pointed out by Charlesworth and colleagues: "it is often suggested that open-label placebos are likely to be less effective than placebos delivered deceptively" [9]. To date, several trials have compared the effectiveness of DP and OLP on pain [14,25,27,30]. Mundt et al. [30], Locher et al. [27], Kube et al. [25] and Disley et al. [14] all found no statistical difference between DP and OLP when testing for superiority. However, no studies have tested OLP and DP for non-inferiority.

Interestingly, Locher et al. [27] also found no difference between an OLP administered without a rationale and no-treatment showing the necessity of the rationale when administering OLPs. Indeed, one of the reasons for OLP's effectiveness could be the suggested benefit through information [8]. Similarly, when administering DPs, information about treatment mechanisms boosts the placebo response [36]. However, in published trials on OLPs,

there are important variations in the rational given to patients before treatment administration [21,37]. These variations mean clinical applications might depend on the rational given by the therapist. To this end, using a standardised rationale could be interesting to ease replication and clinical transferability.

Adding to the need to replicate previous studies, we need better comparisons of DP and OLP. As there is no superiority of DP compared to OLP and there is a supposed ethical benefit of OLP compared to DP, non-inferiority (or equivalence) design and analysis is indicated. Therefore, this study aimed to compare OLP and DP through a non-inferiority analysis. Our hypothesis is that OLP provided with standardised information upon administration will be non-inferior to perform as well as DP.

Methods (no word limit)

This trial and analysis plan have been approved by the French national ethical committee (n°2017-A01643-50) and registered on ClinicalTrials (NCT03934138). The protocol along with the analysis plan has been published in a separate article [15].

Trial Design

We conducted a non-inferiority, randomised, controlled trial comparing the use of DP and OLP. Due to both the supposed ethical superiority of the OLP over the DP and previous studies showing no superiority of DP over OLP, a non-inferiority trial is the appropriate design. The trial was a parallel study comparing a group receiving a DP and one receiving an OLP. Within the parallel design was nested a cross-over where each participant also received a no-treatment condition. This allows comparing OLP and DP (parallel design) while comparing both placebos to no-treatment as a secondary outcome (nested cross-over). This design limits the impact of this secondar outcome on the number of subjects. It is also appropriate when expecting high inter-individual variability. Both the allocation to the group as well as the order

of the placebo and no-treatment condition were randomised. This is made apparent in the flowchart in **Figure 1**. At the end of the study, some participants were also invited to participate in a qualitative study regarding the acceptability of placebo treatments [16].

Participants

We recruited healthy participants aged between 18 and 40 to participate in a study on pain. Participants were informed before the study that the study involved administration of three painful stimulations via cold water. Written consent was given by all participants. Participation was compensated 20€. Participants were recruited via advertisements for a study of a painkiller cream, on the Grenoble University campus and on social media. Inclusion criteria were being aged between 18 and 40 years old, registered to the national healthcare system, having understood and signed the written consent. Non-inclusion criteria were the following: legal impossibility to participate to the protocol (i.e., pregnant women, people deprived of their liberty) or affections modifying the perception of pain due to cold (any known pathology affecting the venous, arterial, or lymphatic system, diabetes, known cardiac ailments, asthma, frostbite on the hand, epilepsy, hand arthritis, lupus erythematosus, allergic reactions to the cream, or being under psychotropic or pain medication).

Interventions

Each participant visited the research platform during a single face-to-face individual visit lasting two hours with two physiotherapists well-versed in placebo effects conducting the study. This visit was divided in three phases: preparation, experimentation and debriefing.

The preparation phase was identical for both groups. During this part of the study, participants were allowed to ask any questions they had regarding the study procedure. The narrative of the study at that moment was that the aim of the study was to study the effect of a cream on pain. Participants were informed once again of the fact they would undergo

three painful stimulations during the trial. Inclusion and exclusion criteria were checked, and a written consent was signed. The first Cold Pressor Test (CPT) stimulation was the calibration CPT. During this CPT, participants immersed their hand and the distal third of their forearm in water at 1°C. A twenty-minute break was respected between each of the following CPTs to ensure a correct wash-out period for pain. They filled out a Visual Analog Scale (VAS) rating for pain intensity every five seconds and were told to take their hands out once the VAS reached 7 out of 10 at least. This time was recorded and set as the duration of the following experimental CPTs for this individual.

The experimental phase started after the calibration CPT. After completing a survey on knowledge regarding placebo effects, the OLP group watched a video revealing the cream studied in this trial was inert and explaining mechanisms behind the placebo effect as well as a brief explanation on the mechanisms of pain (http://bit.ly/Placethic-Video). To ensure structural equivalence [8,28], the DP group watched a control video on the history of washing hands under the pretence that they had to take their mind off the calibration before the experimental part of the study (https://www.youtube.com/watch?v=WQVYWUsrfbk). During the experimental phase, each participant underwent two more CPT procedures: one with no-treatment and one with a placebo treatment either deceptive or open. The order between the no-treatment condition and the placebo condition (whether deceptive or open) was randomised. For both CPTs, participants immersed their arms in the CPT for the duration recorded during calibration and evaluated their pain intensity on the VAS once the time was up. In one case they immersed their arm with no additional treatment and in the placebo condition an inert cream was applied before immersion. Investigators wore a white coat and carried a stethoscope during the trial. The cream was conditioned in a small 2mL plastic syringe and administered using vinyl gloves and a short one-minute massage saying it was to

help the skin "absorb" the cream. The OLP Group was administered the inert cream along with the sentence: "[I will now apply a placebo cream that does not contain any active substance. It will make it easier to bear the pain during the next test through the placebo mechanisms seen in the video.]" The DP Group was administered the inert cream along with the sentence: "[I will now apply an effective cream to combat pain due to the cold. It will make it easier to bear the pain of the next test.]" Before immersing their arm with the placebo cream, participants filled out a questionnaire measuring treatment credibility and expectancy [12,13,29].

During the debriefing of the study, both groups filled out several questionnaires. The first measured perceived knowledge of the research hypothesis, [33] the second measured the perception of the investigators ("During the study, I trusted the investigator" on a 5 point Likert scale) and the last one measured knowledge regarding placebo effects. The questionnaire on placebo effect knowledge was designed for this study. It was inspired by the main misconceptions surrounding placebo effects [22]. It was pre-tested via cognitive interviews to check understandability and reading difficulty with 15 volunteers drawn from a convenience sample from the authors' network sharing the same characteristics as our study sample.

After study participation, all recruits were offered the 20€ compensation and investigators debriefed participants. During this discussion, we disclosed the purpose of the trial and also answered honestly any questions they had [5].

Blinding

During the study, only the analyst was blinded. Participants in the DP group were blind to the inert nature of their treatment and participants in the OLP group were aware they were receiving an inert treatment. Investigators were not blind to the treatment they were administering.

Sample Size

In accordance with the Food and Drug Administration and supported by the minimal clinically-interesting difference (MCID) recommended by Myles et al. [31], we set the non-inferiority margin at 10 mm. Streff et al. had a similar utilization of experimental pain in their study using a CPT on healthy subjects and a VAS to estimate pain. In the dataset they present, a standard deviation of 21.9 mm is observed [35]. Taking this into account and assuming a unilateral alpha of 0.05, the minimum sample size required to achieve a power of 80% to reject the inferiority null hypothesis was 60 per group. Adding to that a 5% margin of estimated non-usable data the necessary number of subjects was set at 126.

Randomisation

Subjects were randomly allocated to a group determining which placebo they received (either DP or OLP) and to the order in which they received their placebo treatment (either placebo then no-treatment or no-treatment then placebo). Both the group and order of treatment randomisation were blocked with random block sizes between 2 and 4 participants. Group allocation for each participant was stored in a sealed envelope, its content unbeknownst to investigators. A participant's envelope was opened only once he or she had signed the consent form and the experimentation had started.

Outcomes & Statistical Methods

We performed the statistical analysis with alpha = 0.05. Non-inferiority was unilateral, and all other tests were bilateral. We used an Intent-to-treat population approach: all participants were analysed in the group in which they were initially randomized. For the primary endpoint, we planned to impute missing data by multiple imputation if between 5% and 20% of the measurements were missing. If less than 5% were missing, we planned

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complete cases analysis. If more than 20% of the data were missing, the results would be interpreted with caution. We planned complete case analysis on the other endpoints.

The primary endpoint was the difference in pain intensity, on a 100-point VAS, between the OLP and the DP treatments at the end of the placebo condition CPT. Pain intensity was chosen as it seems to involve less motivational and cognitive components than pain threshold [20]. We tested the non-inferiority of the OLP condition compared to the DP condition using the unilateral 95%CI of the difference in pain intensity. The non-inferiority margin was set to 10 mm. We estimated the compatibility interval by linear regression. The linear regression accounted for pain intensity during no-treatment condition and the CPT's order. As an intent-to-treat analysis can be biased when evaluating non-inferiority [38], to check the consistency of our results, we also tested non-inferiority with a per protocol analysis: subjects were included in the group only if there were no deviations from the protocol.

The main secondary endpoint was the difference in pain intensity between each placebo condition and no-treatment. The superiority of the DP condition compared to no-treatment was tested by a cross-over ANOVA including an interaction effect between time and treatment. Similarly, we also tested the superiority of the OLP condition compared to no-treatment by a cross-over ANOVA.

Other secondary outcomes include the questionnaire measuring knowledge developed for this study, ranging from 0 to 17, which was compared between both groups as well as before and after watching the video for the OLP group. This questionnaire is available in the supplementary materials. In addition, all subjects completed a questionnaire about their perception of the investigators and of the research hypothesis [35]. We tested these between group differences with Student's t-test for two independent samples. To compare the knowledge about placebo before and after the educational video in the OLP group, we

used Student's t-test for paired samples. Lastly, before each placebo condition CPT, participants filled out treatment credibility and expectancy questionnaire [12,13,29]. Credibility and expectancy were each scored out of 100.

Blood pressure (BP) and heart rate (HR) values were obtained before, during, and after each CPT to ensure the CPT is well tolerated.

Analysis was conducted on Stata software, version 17.0 (StataCorp LLC, College Station, TX, USA).

Results (no word limit)

Recruitment & Participant Flow & Harms

Recruitment spread over the 3rd of May 2019 to the 15th of October 2021 with periods of interruption due to the COVID pandemic and lockdowns. During the end of 2021, due to the sanitary situation's impact on the trial, recruitment had to be halted.

In this timeframe, we recruited 60 volunteers. Of which, one person did not receive the intervention due to an adverse event (fainting after calibration CPT). **Figure 1** shows the flow of participants in the study.

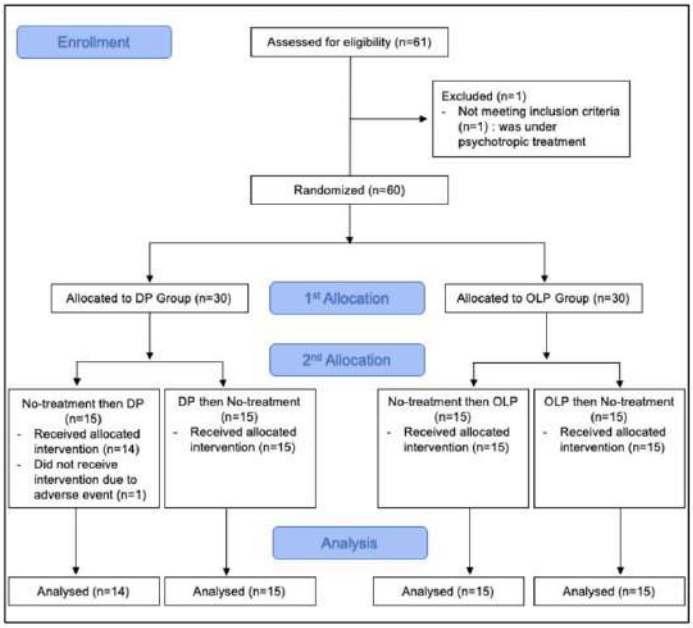

Figure 1: Flowchart of participants in the clinical trial

Population description

Our analysed population included 59 subjects. Their characteristics are presented in **Table 1**.

Group	DP	OLP
Number of subjects	29	30
Women[1]	20 (69.0)	19 (63.3)
Age in years[2]	21.0 [19.0; 27.0]	22.0 [21.0; 22.0]
Time in seconds to reach 7/10 during calibration CPT[2]	31.0 [21.0; 46.0]	30.5 [24.0; 53.0]

Table 1: Description of the participants. [1]n (%) [2]median[Q1-Q3]

Outcomes and estimation

Table 2 show the results for each outcome depending on group. For the primary outcome, results are shown also depending on the order of treatment received.

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Group	DP	OLP
Number of participants	29	30
Treatment order: NT then Placebo	**14 (48.3)**	**15 (50.0)**
VAS_{NT} (mm)	60.5 [59.0; 66.0]	66.0 [55.0; 73.0]
$VAS_{placebo}$ (mm)	55.5 [51.0; 69.0]	60.0 [48.0; 73.0]
Treatment order: Placebo then NT	**15 (51.7)**	**15 (50.0)**
$VAS_{placebo}$ (mm)	64.0 [62.0; 70.0]	66.0 [60.0; 81.0]
VAS_{NT} (mm)	68.0 [60.0; 79.0]	71.0 [66.0; 88.0]
Knowledge before educative video	-	13.0 [11.0; 14.0]
Knowledge at end of trial	13.0 [11.0; 14.0]	15.5 [14.0; 16.0]
Treatment Credibility (%)	66.7 [58.3; 83.3]	56.3 [33.3; 66.7]
Treatment Expectancy (%)	60.8 [46.7; 71.7]	47.5 [35.0; 60.8]

Table 2: Descriptive results of primary and secondary outcomes

The main result of our study is the non-inferiority comparison of the intensity of pain of the DP and the OLP groups measured by VAS. This was calculated through an ANOVA adjusted for group, treatment order and pain intensity during calibration. The results show that the mean difference (VAS_{OLP}-VAS_{DP}) was 0.7mm with a unilateral 95%CI of]-∞; 5.4]. The upper bound of the 95%CI is within our non-inferiority margin of 10mm, allowing us to draw the following conclusion: in our study the OLP condition was not inferior to the DP condition by a margin of 10mm and with a unilateral alpha risk of 5%. There do not appear to be any significant deviation from the assumptions of the linear model.

The first secondary outcome that was of interest was the difference between the placebo conditions and no-treatment. There was a significant interaction between time and treatment in the analysis of this outcome. During the second CPT, both placebo conditions showed no difference with the no-treatment condition. In the DP group, the mean difference (VAS_{DP}-VAS_{NT}) was 2.7 with a 95%CI of [-5.5; 10.9]. In the OLP group, the mean difference (VAS_{OLP}-VAS_{NT}) was 6.9 with a 95%CI of [-2.2; 15.9]. During the third CPT, both groups showed a statistically significant difference to no-treatment. In the DP group, the mean difference (VAS_{DP}-VAS_{NT}) was -9.3 with a 95%CI of [-17.5; -1.1]. In the OLP group, the mean difference (VAS_{OLP}-VAS_{NT}) was -15.4 with a 95%CI of [-24.5; -6.3]. In both groups, one outlier was

abnormally low. Sensitivity analysis was conducted to see if excluding this data point would change interpretation of results. This was not the case indicating the outlier had little impact on interpretation. In summary for this outcome, these results indicate there is no difference when comparing placebo conditions and no-treatment during the second CPT and a statistically significant difference during the third CPT. **Figure 2** represents the findings for the previously mentioned endpoints.

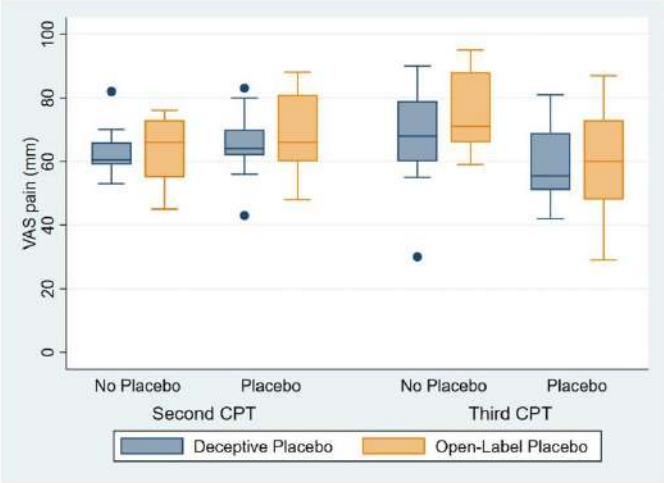

Figure 2: Main endpoint graphical representation measuring pain intensity with a Visual Analog Scale (VAS) ranging from 0 to 100mm. Participants receiving no-treatment during the second Cold Pressor Test (CPT) are those receiving placebo in the third CPT and vice-versa.

Another secondary outcome was our participant's knowledge regarding placebo. This was measured thanks to a questionnaire ranging from 0 to 17. Results were compared with a Satterthwaite test due to a difference in variability between groups. When comparing both groups (OLP_{after}-DP) the difference was 2.4 with a 95%CI of [1.4; 3.4]. This can be interpreted as the OLP group scoring significantly higher than the DP group. We also compared the score of the OLP group before and after watching the educational video. The difference (OLP_{after}-OLP_{before}) was 2.4 with a 95%CI of [1.6; 3.3]. **Figure 3** represents these findings.

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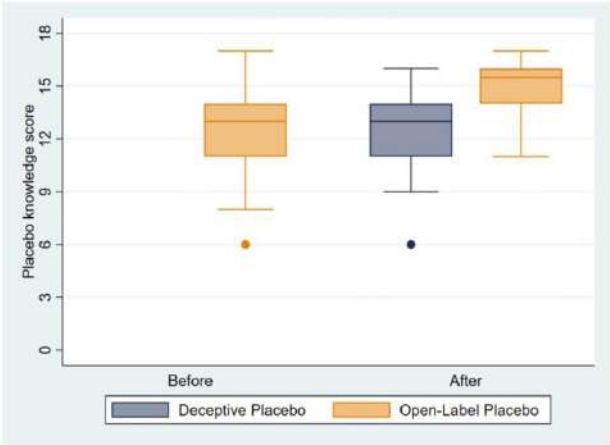

Figure 3: Graphical evolution of scores on the placebo knowledge questionnaire. For the OLP group, knowledge was evaluated before and after watching the educational video.

Just after treatment administration and while the treatment was "taking effect on the skin", we asked participants to fill out scores regarding their expected effects and the credibility of the treatment. These questionnaires were scored out of 100. When comparing treatment credibility (OLP-DP), the difference was -16,6% with a 95%CI of [-27.3; -5.9]. This indicates there was a significantly lower credibility of the OLP treatment compared to the DP. Similarly, the difference in treatment expectancy was -11.2% with a 95%CI of [-20.9; -1.4] indicating there also was a significantly lower expectancy for the OLP than for the DP treatment. These are illustrated of **Figure 4**.

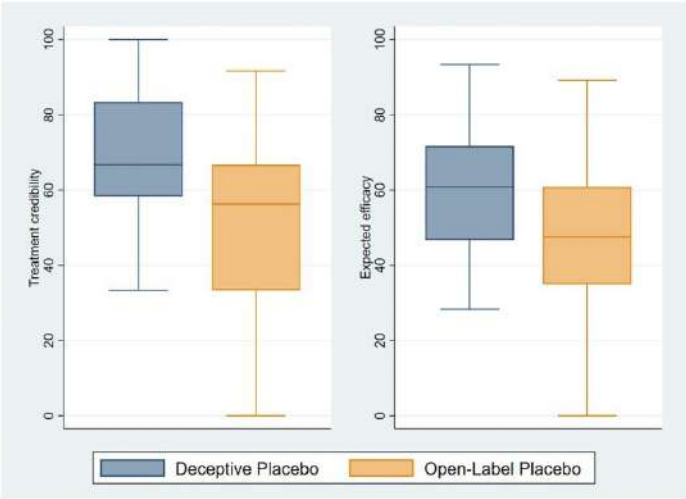

Figure 4: Credibility and Expectancy of treatment effect out of 100 just after application of the placebo cream.

Lastly, there was no statistically significant difference in how both groups trusted the investigators and it seems that the OLP were more confident they had understood the research hypotheses (results available in supplementary materials).

Discussion (1345 words)

- Findings and interpretations

In this study, we showed that an OLP with a convincing rationale was non-inferior to a DP with a 10mm margin on the VAS and a 5% alpha risk. This study contributes to replicate and confirm the findings from previous trials comparing OLP and DP [14,25,27,30]. It also allows further interpretation than previous studies finding no superiority as it concludes to a non-inferiority.

Secondary outcomes are interesting to interpret and especially the comparison with the no-treatment conditions. Surprisingly, during the second CPT there were no differences between placebo conditions and no-treatment. However, during the third CPT, there were significant differences. This differs from our initial hypothesis of showing a superiority of

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placebo treatments compared to no-treatment on both CPTs as shown in some published comparisons of OLP with no-treatment [37]. However, in reality our results show that time had an impact on the result of our study. This is different to initial hypothesis of generating placebo effects (superiority to no-treatment) on both occasions. One way this could be explained is that participants may have been influenced by their *a priori* experiences. As such, during the second CPT they may have re-assessed their pain intensity due to the difference between the first and second CPT (filling a VAS every 5 seconds or waiting for the time to be up). Once this was done, they noted a change during the third CPT: participants to whom we took away the treatment worsened and participants to whom we added a placebo treatment improved. This could be in line with findings from Colloca et al. showing that *a priori* experiences modulate response to DP more than expectancy [10,11]. The role of expectation has also been questioned for OLPs [34]. This would also be consistent with the credibility and expectancy scores we measured for each treatment. Indeed, although DP and OLP were non-inferior, OLP showed significantly lower expectancy and credibility. Haas et al. also showed lower credibility and expectancy score for OLP rather than DP using the same questionnaire [19].

Another point of discussion in our findings pertains to the rational content and format we choose to use. This is an important point to discuss when administering OLPs as Blease et. al propose it is unclear what explains the potential effect of OLPs (e.g., whether it the rationale, the pill or the doctor-patient relationship, or some combination thereof) [8]. OLPs in clinical trials have been administered with highly variable rationales [37]. In contrast some authors have suggested key information to include in the OLP rationale [21]. In our study, we chose a video format with mostly informative content. Other studies have used appeals to other patient's experience, boosting hopefulness or increasing expectations [34]. Our results show that our participants may indeed have benefited from the educational video to improve their

knowledge about placebo. However, a video rationale may have also taken away part of the doctor-patient relationship during administration. The use of this format allowed for a better replicability of our findings, to limit variability in future research and, if future results call for it, an easier clinical application.

- Strengths and limitations

Several methodological considerations should be discussed in this study. Some have already been reviewed in a separate article [15]. Firstly, the use of a cross-over nested in the parallel trial allowed to look at inter-individual comparison as well as consider how a priori experiences changed pain experience. This also allowed to have a no-treatment condition in addition to our two placebo conditions without increasing the number of subjects needed allowing for additional power. However, in hindsight, we planned for a cross-over because we hypothesized there would only be a small interaction of time on the treatment effect. This was not the case as the interaction of time in our linear regression was important. Therefore, in this study the interpretation of the difference, or lack thereof, between placebo conditions and no-treatment requires caution because of the discordance. If we had planned for three groups (OLP vs DP vs NT), this would have facilitated the interpretation. However, other studies have already shown the effect of OLPs versus no-treatment [37]. Another major point of discussion, common to most OLP studies to date, is the lack of patient and therapist blinding. Indeed, due to the nature of the treatment, patients are aware of the inertness of what they are receiving. However, we could have improved the blinding in the administration of the OLP and DP [8]. Our study did not do better than other studies in this regard. Due to this, results must always be interpreted with caution as they are difficult to distinguish from reporting bias from patients or investigators. Relatedly, we cannot rule out whether the effectiveness of DP or OLP was owed to placebo effects proper, or participant responder biases. As has been

argued, conflating placebo responses with placebo effects means researchers often tend to inflate the size of placebo effects [6,8,24].

Underpowered studies are an issue in medical research and placebo research is no exception [6]. In our study we had initially planned for 126 subjects considering our 10 mm non-inferiority margin and an estimated standard deviation of 21.6 mm. Due to the pandemic we were unable to recruit this many participants. However, we are confident this did not affect the results for two main reasons. Firstly, the observed standard deviation was significantly lower in our study than anticipated. This is probably thanks to our first CPT functioning as calibration. This made our population more homogeneous in pain ratings and increased our power. Secondly, as our results show H0 is unlikely, there would be no type-II risk. We accept H1 accepting with a type-I risk. Thus, although our study did not recruit the initially planned number of subjects, we believe this had no impact on our power nor our interpretation.

Lastly, for the knowledge questionnaire, we could add that in our study design one outcome was not balanced for both groups because structural equivalence was not perfect [8,28]. The knowledge questionnaire was completed twice by our OLP group and only once by our DP group. Although there was at least an hour between both completions for the OLP group, there is no guarantee that this did not bias their responses as we have not checked the test-retest reliability of our questionnaire.

- Implications

Nevertheless, these findings have two major implications. Firstly, amidst a replication crisis in medical and particularly in placebo research, replication and confirmation of findings are important contributions to scientific knowledge [6]. Secondly, our findings bring serious doubts to the pertinence and justification of the currently widespread clinical uses of DPs [26]. Indeed, several studies have found no superiority between a DP and a well-explained OLP and we add

to this by showing non-inferiority. If placebo treatments are to be used, OLPs should be favoured over DPs. However, looking at how OLPs should best be administered is still to be determined. For example, in our nested qualitative study [16] participants suggested the following conditions to administer OLPs in the clinical setting: a convincing rationale, time to discuss this treatment option with their healthcare provider, proven effectiveness compared to DP, appropriateness regarding the clinical situation and being included in the decision to take an OLP.

- Future Studies

Moving further, research comparing the effect of DPs and OLPs with patients instead of healthy subjects are needed before any clinical applications are suggested. It is reasonable to assume that findings with healthy subjects will be similar among patients as placebo effects seem to have a smaller effect size for healthy subjects rather than patients [17]. Another important area of research that need to be addressed is to better understand what we are measuring in no-treatment conditions. As such, in our study it seems that reverting to a no-treatment condition after having been given a placebo treatment could have worsened the pain similar to a nocebo effect. Furukawa et al. suggest considering some no-treatment conditions such as waiting-lists as nocebo effects and thus poor tools to distinguish the placebo effect from the placebo response [18]. Finally, further research is needed to explore the acceptability of placebos, including OLPs, among patients [7,16].

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References

1. **Annoni M, Miller FG: Placebos in clinical practice: an ethical overview. Douleur et Analgésie Lavoisier; 27:215–20, 2014.**

2. **Aulas J-J, Rosner I: [Efficacy of a non blind placebo prescription]. Encephale 29:68–71, 2003.**

3. **Barnhill A: What it takes to defend deceptive placebo use. Kennedy Inst Ethics J 21:219–50, 2011.**

4. **Bishop FL, Aizlewood L, Adams AEM: When and why placebo-prescribing is acceptable and unacceptable: a focus group study of patients' views. PLoS One 9:e101822, 2014.**

5. **Bishop FL, Jacobson EE, Shaw J, Kaptchuk TJ: Participants' experiences of being debriefed to placebo allocation in a clinical trial. Qual Health Res 22:1138–49, 2012.**

6. **Blease C, Colagiuri B, Locher C: Replication crisis and placebo studies: rebooting the bioethical debate. J Med Ethics :jme-2022-108672, 2023.**

7. **Blease CR: The role of placebos in family medicine:'Implications of evidence and ethics for general practitioners'. Australian journal of general practice 48:700–5, 2019.**

8. **Blease CR, Bernstein MH, Locher C: Open-label placebo clinical trials: is it the rationale, the interaction or the pill? BMJ Evid Based Med [Internet] , 2019. Available from: https://doi.org/10.1136/bmjebm-2019-111209**

9. **Charlesworth JEG, Petkovic G, Kelley JM, Hunter M, Onakpoya I, Roberts N, Miller FG, Howick J: Effects of placebos without deception compared with no treatment: A systematic review and meta-analysis. J Evid Based Med 10:97–107, 2017.**

10. **Colloca L, Akintola T, Haycock NR, Blasini M, Thomas S, Phillips J, Corsi N, Schenk LA, Wang Y: Prior therapeutic experiences, not expectation ratings, predict placebo effects: An experimental study in chronic pain and healthy participants. Psychother Psychosom :1–8, 2020.**

11. **Colloca L, Benedetti F: How prior experience shapes placebo analgesia. Pain 124:126–33, 2006.**

12. Coste J, Tarquinio C, Rouquette A, Montel S, Pouchot J: Cross-cultural adaptation and validation of the French version of the credibility/expectancy questionnaire. Further insights into the measured concepts and their relationships. Psychologie Française 65:173–84, 2020.

13. Devilly GJ, Borkovec TD: Psychometric properties of the credibility/expectancy questionnaire. Journal of Behavior Therapy and Experimental Psychiatry 31:73–86, 2000.

14. Disley N, Kola-Palmer S, Retzler C: A comparison of open-label and deceptive placebo analgesia in a healthy sample. J Psychosom Res 140:110298, 2021.

15. Druart L, Graham Longsworth S, Rolland C, Dolgopoloff M, Terrisse H, Bosson J-L, Pinsault N: Can an open-label placebo be as effective as a deceptive placebo? Methodological considerations of a study protocol. Medicines (Basel) [Internet] 7:, 2020. Available from: https://doi.org/10.3390/medicines7010003

16. Druart L, Vauthrin O, Pinsault N, Locher C, Blease C: `It's not my greengrocer, it's someone from the medical profession': A qualitative study regarding acceptability of deceptive and open-label placebo prescribing in France. British Journal of Health Psychology [Internet] Wiley; , 2022. Available from: https://doi.org/10.1111%2Fbjhp.12624

17. Forsberg JT, Martinussen M, Flaten MA: The Placebo Analgesic Effect in Healthy Individuals and Patients: A Meta-Analysis. Psychosom Med 79:388–94, 2017.

18. Furukawa TA, Noma H, Caldwell DM, Honyashiki M, Shinohara K, Imai H, Chen P, Hunot V, Churchill R: Waiting list may be a nocebo condition in psychotherapy trials: a contribution from network meta-analysis. Acta Psychiatr Scand 130:181–92, 2014.

19. Haas JW, Rief W, Doering BK: Open-label placebo treatment: Outcome expectations and general acceptance in the lay population. Int J Behav Med [Internet] , 2020. Available from: https://doi.org/10.1007/s12529-020-09933-1

20. Handwerker HO, Kobal G: Psychophysiology of experimentally induced pain. Physiol Rev 73:639–71, 1993.

21. Heiss U, Rosenfield M, Bernstein M: Can the open-label placebo rationale be optimized? Frontiers in Pain Research Frontiers; :61, 2021.

22. Hughes J, Greville-Harris M, Graham CA, Lewith G, White P, Bishop FL: What trial participants need to be told about placebo effects to give informed consent: a survey to establish existing knowledge among patients with back pain. J Med Ethics [Internet] , 2017. Available from: http://dx.doi.org/10.1136/medethics-2016-103964

23. Kaptchuk TJ, Miller FG: Open label placebo: can honestly prescribed placebos evoke meaningful therapeutic benefits? BMJ 363:k3889, 2018.

24. Kirsch I: The placebo effect revisited: Lessons learned to date. Complementary Therapies in Medicine 21:102–4, 2013.

25. Kube T, Rief W, Vivell M-B, Schäfer NL, Vermillion T, Körfer K, Glombiewski JA: Deceptive and Nondeceptive Placebos to Reduce Pain: An Experimental Study in Healthy Individuals. Clin J Pain 36:68–79, 2020.

26. Linde K, Atmann O, Meissner K, Schneider A, Meister R, Kriston L, Werner C: How often do general practitioners use placebos and non-specific interventions? Systematic review and meta-analysis of surveys. PLoS One 13:e0202211, 2018.

27. Locher C, Frey Nascimento A, Kirsch I, Kossowsky J, Meyer A, Gaab J: Is the rationale more important than deception? A randomized controlled trial of open-label placebo analgesia. Pain 158:2320–8, 2017.

28. Locher C, Gaab J, Blease C: When a Placebo Is Not a Placebo: Problems and Solutions to the Gold Standard in Psychotherapy Research. Front Psychol 9:2317, 2018.

29. Mertens V-C, Moser A, Verbunt J, Smeets R, Goossens M: Content Validity of the Credibility and Expectancy Questionnaire in a Pain Rehabilitation Setting. Pain Practice 17:902–13, 2017.

30. Mundt JM, Roditi D, Robinson ME: A comparison of deceptive and non-deceptive placebo analgesia: Efficacy and ethical consequences. Ann Behav Med 51:307–15, 2017.

31. Myles PS, Myles DB, Galagher W, Boyd D, Chew C, MacDonald N, Dennis A: Measuring acute postoperative pain using the visual analog scale: the minimal clinically important difference and patient acceptable symptom state. Br J Anaesth 118:424–9, 2017.

32. Rafi Z, Greenland S: Semantic and cognitive tools to aid statistical science: replace confidence and significance by compatibility and surprise. BMC Med Res Methodol 20:244, 2020.

33. Rubin M: The Perceived Awareness of the Research Hypothesis Scale: Assessing the influence of demand characteristics. figshare; , 2016 [cited 2023 Jan 23]. Available from: https://figshare.com/articles/journal_contribution/The_Perceived_Awareness_of_the_Research_Hypothesis_Scale_Assessing_the_influence_of_demand_characteristics/4315778/2

34. Schaefer M, Sahin T, Berstecher B: Why do open-label placebos work? A randomized controlled trial of an open-label placebo induction with and without extended information about the placebo effect in allergic rhinitis. PLoS One 13:e0192758, 2018.

35. Streff A, Kuehl LK, Michaux G, Anton F: Differential physiological effects during tonic painful hand immersion tests using hot and ice water. Eur J Pain 14:266–72, 2010.

36. Tang CW, Colagiuri B: Can an educational handout enhance placebo analgesia for experimentally-induced pain? PLoS One 8:e77544, 2013.

37. von Wernsdorff M, Loef M, Tuschen-Caffier B, Schmidt S: Effects of open-label placebos in clinical trials: a systematic review and meta-analysis. Sci Rep 11:3855, 2021.

38. Wiens BL, Zhao W: The role of intention to treat in analysis of noninferiority studies. Clin Trials 4:286–91, 2007.

2.3. ARTICLE 3

As stated, OLPs are proposed as an ethical means to circumvent deception when using placebo treatments. They might prove an effective way to use placebo treatments provided their effectiveness is demonstrated. Our results suggest they may perform as well as DPs. However, much of the literature on the ethicality of DPs was written by ethicists postulating, a priori, whether patients would or would not want to be deceived; OLPs have been considered more ethical mainly by those same authors (C. Blease et al., 2016). In section 2.1.1 of the thesis, it was argued that healthcare provider's representations of patients' views and actual patient views show dissension. For example, Fässler et al. reported that patients were 7.4 times more likely to accept a placebo treatment if it allowed to gain a therapeutic advantage through the placebo effect than to refuse; in contrast, physicians believed this ratio would be closer to 0.9 (Fässler et al., 2011). As such, the assumption that OLPs are acceptable should be explored more deeply to examine both OLP and DP acceptability. If physiotherapists are to offer OLPs to their patients, it is crucial to understand patient views on the matter. This is the research gap our second research project begins to address.

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ARTICLE

'It's not my greengrocer, it's someone from the medical profession': A qualitative study regarding acceptability of deceptive and open-label placebo prescribing in France

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Abstract

Objectives: To explore participants' views regarding clinical use of deceptive placebo (DP) and open-label placebo (OLP) treatments.

Design: Qualitative thematic analysis.

Methods: We conducted eight semi-structured interviews with healthy participants in an experimental trial comparing the efficacy of OLP and DP (Clinical trials n°NCT03934138). Interviewees' opinions were solicited following administration of placebos during the trial. Interviews were analysed using data-driven analysis.

Results: We identified three themes. First, participants considered trust central in judging a placebo treatment to be acceptable. They expressed the importance of an implicit trust both in their health care professionals' (HCPs') competency as well as in the profession at large. A second theme was the perception of how placebo treatments might solve health problems. Acceptability of both types of placebo treatments was dependent on the perception patients had about the treatment solving their problem and/or doubts regarding the effectiveness of placebos The third theme encompassed perceived risks associated with placebo prescribing. Some

comments viewed placebos positively as facilitating reduced medication intake. However, participants also identified the potential of placebos to generate adverse side effects.

Conclusions: Treatment acceptability by patients is a prerequisite, alongside effectiveness, to harness OLPs in clinical care. Our study identified the importance of trust in HCPs prescribing placebos, the clinical effectiveness of placebos and the potential risks of these interventions in assessing their acceptability. Future research is needed to explore the contexts in which placebos might be used, and how best to communicate information about placebo interventions.

KEYWORDS
ethics, open-label, patients' attitude, placebo, placebo attitudes

Statement of contribution

What is already known?

- In clinical settings, placebos are widely used.
- Deceptive placebo (DP) prescribing raises specific ethical concerns.
- Honestly prescribed – or so-called 'Open-Label Placebos' (OLPs) may have the potentially to harness beneficial placebo effects while also respecting patient autonomy.
- The premise that OLPs will be less infringing on patient autonomy, however, does not mean patients will consider them acceptable.
- Aside from establishing the effectiveness of OLPs to harness placebo effects, it is also important to investigate whether patients find OLPs acceptable.
- In some previous studies, participants have been requested to offer their opinions which were not informed nor based on experience with placebos.
- In this study, we interviewed participants after disclosure about this intervention and after they had experienced either DP or OLP in a clinical trial setting.

What does this study add?

- Participants considered trust central in judging a placebo treatment to be acceptable. Trust was affected differently by DPs and OLPs.
- Intervention preference was far from unanimous, suggesting acceptability of placebos may be patient-dependent.
- This is the first study, to explore the acceptability of DP and OLP in France.

INTRODUCTION

Placebo interventions are used in clinical research to evaluate a treatment's specific efficacy (Ernst & Resch, 1995); however, clinical uses also exist. In clinical settings, placebo use may even be quite common (Fässler et al., 2010; Linde et al., 2018). A recent meta-analysis (Linde et al., 2018) showed usage among general practitioners in the previous year ranged from 46% to 95% with a pooled estimate of 76% (95% CI: 61%–86%).

Despite these findings, it should also be emphasized that many disagreements persist with respect to defining placebo concepts (Blease & Annoni, 2019). For example, Miller suggests restricting the definition of placebo effects to situations where intentional inert interventions are used (Miller, 2018). Benedetti appears to consider a larger scope for defining placebo effects. He writes that the placebo effect is the difference of effect between an expected and unexpected treatment even when no placebo treatment has been given (Benedetti, 2020). This was illustrated in a well-known experience comparing open and hidden administration of morphine injections (Benedetti et al., 2011). Other scholars suggest abandoning the term of placebo altogether. Alternatives have been suggested such as Moerman's 'meaning response' focusing on social and cultural significance of treatments where the *meaning response* is defined as 'the psychological and physiological effect of meaning in the origins or treatment of illness' (Moerman & Jonas, 2002). Howick in his recently proposed revision of Grunbaüm's model attempts to co-define the terms 'placebo' and 'placebo effects' and describes placebos largely as treatments whose effects are not based on characteristic features of treatments but rather on incidental factors (Grünbaum, 1986; Howick, 2017). For example, the characteristic features of amoxicillin are its antibiotic constituent; the incidental features include its coloration, taste, bulking agent, branding and price. Howick proposed that, 'a treatment process is a [generic] placebo when none of the characteristic treatment factors C are effective… in patients X for D'; he interprets 'characteristic features' as a feature of treatments that '(1) is not expectancy that a treatment is effective; and (2) that has an incremental benefit on the target disorder over a legitimate placebo control' (Howick, 2017). According to Howick, a placebo effect is, 'either (a) a remedial effect produced by the incidental features of some treatment… or (b) any effect of a generic placebo' (Howick, 2017). While Turner argues the terms 'placebo' and 'placebo effects' may ultimately prove not to be analytically useful, Blease argues that the terms should be independently defined. In clinical settings the term placebo may be variously used to refer to treatments that are prescribed, which have no known effects other than potential for placebo effects, or which are used to placate patients for whom no treatment is available (Blease, 2019; Blease & Annoni, 2019). Blease also argues scientific advances can legitimately be described as constituting a mature 'placebo effect paradigm' replete with progress and empirical growth (Blease, 2018).

Conceptual disagreements are not merely philosophical, but carry ethical and practical consequences for the use of placebos, and how to adequately interpret the size of placebo effects (Blease & Annoni, 2019; Hardman et al., 2020; Turner, 2011). Notwithstanding disagreements, many researchers in the field of placebo studies consider placebo effects to be genuine psychobiological effects that engage perceptual and cognitive processes to elicit therapeutic benefits (Kaptchuk & Miller, 2015). To this end, it is variously proposed that the placebo effect might be usefully harnessed in clinical settings. This may be achieved via particular vigilance to contextual factors that might elicit placebo effects in everyday care (Di Blasi et al., 2001). Additionally, strengthening communication and therapeutic alliance in clinical settings may harness improved outcomes (Kelley et al., 2014; Street et al., 2009), including via placebo effects. As Locher and colleagues propose, the ritual of prescribing a pill could also be conducted in a deliberate manner (Locher et al., 2019). Lastly, non-verbal communicating and artefacts in the context of care could elicit placebo effects (Bernstein, Locher, Kube, et al., 2020; Howe et al., 2019).

Although some patients might potentially benefit from placebo effects arising from placebo use, deceptive placebo (DP) prescribing invites ethical concerns. For one, deception in clinical practice may violate the patient's autonomy with regard to making informed decisions about the treatment. Potential harm to the therapeutic relationship, as well as in general trust towards healthcare professionals (HCPs), is also a concern. At the same time, health ethicists are not in agreement (Foddy, 2009) with some arguing that the benefits outweigh the risks, or that deceptive placebo prescribing does not infringe on morally important forms of patient autonomy.

Treatments that rely on the placebo effect while being open and honest with patients regarding the inert nature of the treatment, might present a way to respect these ethical dilemmas (Blease et al., 2016). Such interventions, called open-label placebos (OLPs) depend on the rationale given before administration and can take several different modalities; from an inert pill, to a cream or taping. It is proposed that OLPs optimize treatment response while respecting patient autonomy. Although deception was

previously believed to be crucial to obtain placebo effects, a growing body of research suggests that this might not be necessary (Charlesworth et al., 2017; von Wernsdorff et al., 2021). In multiple studies, OLPs have been compared to no treatment. A first meta-analysis (Charlesworth et al., 2017) in 2017 found a standardized mean difference of .88 (95% CI: .62, 1.14) and a more recent meta-analysis (von Wernsdorff et al., 2021) showed a standard mean difference of .72 (95% CI: .39, 1.05). However, studies regarding OLP are still nascent and suffer from methodological difficulties regarding blinding for example (Blease et al., 2019). It is also unclear if and how the results found in experimental and clinical trials translate to routine clinical practice (Miller, 2018). To date, the small number of studies, their heterogeneity and the risk of bias calls for caution when drawing conclusions on efficacy. While effectiveness is being evaluated, the premise that these treatments will be less of a hindrance on patient autonomy does not mean patients will consider them acceptable. Perhaps most importantly, it is necessary to probe whether patients themselves consider deceptive placebos to be unethical (Bishop et al., 2014). However, aside from the transparency in its administration, there is little information today about the information given or not to the patient during the administration of an OLP (Heiss et al., 2021; von Wernsdorff et al., 2021), or whether patients find these treatments acceptable (Blease, 2019).

A limited body of research has explored whether patients consider deceptive placebos to be ethical. Fässler et al. found that HCPs thought DP treatments to be less acceptable than patients did (Fässler et al., 2011). As such, patients were seven times more likely than the physicians thought to accept a placebo intervention if it would allow them to gain a therapeutic advantage through the placebo effect.

Several recent studies included patients when considering DP's acceptability criteria (Bishop et al., 2014; Fässler et al., 2011; Hammami et al., 2019; Köteles & Ferentzi, 2012; Ortiz et al., 2016; Pugh et al., 2016). Surveys and focus group studies reveal that acceptability is influenced by expected benefits (Bishop et al., 2014; Fässler et al., 2011; Hammami et al., 2019) as well as lack of harm (Ortiz et al., 2016). It also seems the closer the information was to a lie rather than indirect information (Marsili, 2014), the less acceptable treatments were considered to be (Pugh et al., 2016). Some patients even consider benefits and therapist intentions to be more important than deception (Hammami et al., 2019). These findings might be said to describe a pragmatic view of placebo interventions (Köteles & Ferentzi, 2012). However, such views are not ubiquitously held. A subgroup of patients appear to place more importance on trust and truthfulness and, therefore, value honesty above all else (Bishop et al., 2014).

Regarding OLPs, only a few theoretical studies so far have looked at treatment acceptability. These studies suggest OLPs are ethically valid treatments (Blease et al., 2016). Fewer studies included patients such as Haas et al.'s study (Haas et al., 2021) comparing DP and OLP treatment acceptability through online vignettes. These results showed a higher acceptability towards DP than OLP among lay people. This was correlated to a higher expectancy towards DP rather than OLP (Haas et al., 2021). However, previous studies included participants requesting them to offer opinions not informed nor based on experience. This is one of the major difficulties when including patients into studies regarding OLP acceptability. Even more so as OLP treatments are not widely used; and therefore, only a few people have experienced them. Similarly, physicians sometimes consider OLP to be disrespectful to patients and at risk of offending them (Bernstein, Locher, Stewart-Ferrer, et al., 2020). One qualitative study interviewed healthy participants to explore OLP usability but with an aim less focused on acceptability rather than on the plausibility of the treatment rationale (Locher et al., 2021). This study looked at lay people's attitudes towards OLP treatments after use focused on the rationale rather than the acceptability of the treatment (Locher et al., 2021) without informing participants of the existence of OLP treatments in the non-OLP groups. Again, however, there are documented discrepancies in how the information is communicated to participants during the administration of OLPs in clinical trials (Heiss et al., 2021; von Wernsdorff et al., 2021). These differences could influence the acceptability of the intervention.

The objective of this qualitative thematic analysis is to build on this body of research into patients' views about DPs and OLPs. We interviewed participants after an education on these interventions and after they had experienced one or the other in a clinical trial setting. To our knowledge, this is the first

TABLE 1 Topics and questions in semi-structured interviews

Topic	Description	Initial question	Example prompts
Open-label placebo use	These topics looked at the attitude participants had regarding open-label or deceptive placebo treatments, whether or not they would deem their use acceptable or not, how this would impact the way they judge their healthcare professional and what factors drive their opinion	'Imagine you go to see a healthcare professional. He or she suggests an open-label placebo treatment for pain management after explaining that it is a placebo treatment, what we know about it and how it works. How would you judge this situation?'	• Could you explain what would make this situation more/less acceptable to you? • Could you describe a situation where you would/would not accept this intervention? • How would you feel if you were in this situation? • How would this situation impact your relationship with your HCPs?
Deceptive placebo use		'Imagine you go to see a healthcare professional. He or she suggests a deceptive placebo (previously explained) for pain management. From an outside perspective, meaning you are aware of the situation, how would you judge this situation?'	• Could you explain what would make this situation more/less acceptable to you? • Could you describe a situation where you would/would not accept this intervention? • How would you feel if you were in this situation? • If you were to learn about this, how would this impact your relationship with your HCPs?
Treatment preference	This topic looks at which treatment is preferred in a given situation	'Given everything we have discussed, regardless of the conditions, which treatment between OLP and DP would you prefer to take for pain management?'	• Could you develop your answer further? • What drove you to choose this view?

study, to explore acceptability of DP and OLP among lay participants in France. It is also one of the first to interview participants after having experienced either of these treatments.

MATERIALS AND METHODS

Study design and participants

The qualitative study was nested in a non-inferiority randomized trial aimed at comparing the efficacy of DP and OLP on experimental pain with healthy participants (Druart et al., 2020). The study took place at the University of Grenoble and was approved by the national ethics committee (2017-A01643-50). All research participants gave informed consent. In this clinical trial, 60 subjects were randomized into two groups: one received a DP and the other received an OLP. Both groups also underwent a no-treatment (NT) condition in which the pain stimulus was delivered with no treatment. The method used in the clinical trial as well as its registration information are detailed in a separate paper (Druart et al., 2020).

During the trial, participants from the OLP group watched a video (bit.ly/Placethic-Video) aimed at explaining the mechanisms of placebo on pain relief before receiving their treatment. A video on a completely different subject was viewed by the DP group (https://youtu.be/WQVYWUs1fbk). Before interviews, the DP group was given the time to watch the video the OLP group had seen during the trial. This allowed for both groups to be offered the same information about OLPs and simulate the setting in which an OLP could be proposed to a patient (i.e. after information regarding OLP).

Qualitative interviews all took place immediately afterwards. This allowed us to explore the views of participants immediately after experiencing an OLP or DP treatment.

Data collection

Data were collected through face-to-face eight semi-structured interviews lasting 30–40 min following common-practice methodological recommendations (Braun & Clarke, 2019). We aimed to recruit four to eight participants in our study in line with similar studies in placebo research (Bishop et al., 2012). Our qualitative thematic analysis was exploratory, and we did not aim for data saturation as the concept is not always desired (Braun & Clarke, 2019). The number of participants was also limited due to logistical constraints in scheduling interviews among members of the research team. We invited eight participants who enrolled in the trial to participate in interviews. All persons approached accepted. Although participation in the clinical trial was compensated by 20€, participants did not receive extra compensation for their time in the interviews.

The interviews were conducted by O.V. The interviewer started by debriefing participants about the clinical study. Then, the aim of the interview ('We want to understand what you think about placebo treatments') and its process ('The interview will be recorded for transcription purposes however anything you say will be anonymous and confidential') were explained. All participants of the DP group were invited to watch the video about the OLP approach before the interview.

The interviews addressed three topics (described in detail in Table 1). The order in which the topics of OLP and DP treatments were discussed was chosen randomly for each participant. This was done to minimize overrepresentation of one treatment over the other. Prompts and probes were used to ensure questions were answered as deeply as possible (see Table 1).

Data analysis

Thematic analysis was undertaken using a data-driven (or inductive) analysis (Braun & Clarke, 2006, 2013) and comprising five steps: pre-analysis, coding, categorization, refining and interpreting. (1)

Pre-analysis consisted of the transcription of the interviews by O.V. and proof-read by L.D. to increase reliability of the transcription. Next, O.V. and L.D. familiarized themselves the material by reading through the transcripts several times. (2) Coding was then conducted by L.D. and O.V. where '[nodes of meaning]' (Bardin, 2013) were identified and coded for presence and direction. During this phase, analysts can choose between a semantic (words used) or latent (meaning of text) approach. The latter was chosen in this study to allow for more in-depth understanding (Coolican, 2017). When discrepancies were found between coding, both analysts discussed and, if needed, a third author (N.P.) weighed in to resolve disagreements. (3) Next, via a process of higher-order categorization we sorted the codes into themes with the help of a thematic map. This was undertaken by O.V. and L.D. (4) The themes were then refined by all authors. All sample quotes were translated into English by L.D. and O.V.

The online software was used (https://www.qcamap.org/) to assist with coding the data.

RESULTS

Interviews were conducted with eight people (three males and five females) of the 60 participants of the trial; ages of participants varied between 19 and 34 years (see Table 2). Among the participants, four interviewees received a DP in the experimental trial and four received an OLP.

After analysis, we coded 92 categories (39 regarding OLP, 39 regarding DP and 14 regarding placebo effects in general). These categories were organized into three main themes, which were further subdivided into subthemes (see Table 3).

Trust in HCPs and placebo prescribing

Implicit trust in HCPs

Many participants signalled implicit trust in their HCPs as influencing whether they considered placebo treatments acceptable. Among these comments, some participants described their trust in HCPs' competency, for example: 'if he prescribes it to me I guess it's the best thing to take so I'm glad he prescribes it to me' [A]; and also '[I]f he is convinced it is because he also has a scientific background, I suppose it is his role also to have made sure that the effectiveness was proven' [G].

Some participants implied trusting the fact it's an HCP's function to treat them; for example:

> the fact that it is recommended by eh, well, my doctor or my physiotherapist it is someone who is knowledgeable.
>
> [D]

TABLE 2 Sample description

Subject	Trial group	Gender	Age	Occupation	Interview order
A	OLP	Male	21	Student	OLP then DP
B	DP	Male	24	Unemployed	OLP then DP
C	OLP	Female	21	Student	DP then OLP
D	OLP	Female	28	Employed	DP then OLP
E	DP	Female	27	Employed	OLP then DP
F	DP	Female	19	Student	OLP then DP
G	DP	Male	34	Manager	DP then OLP
H	OLP	Female	28	Manager	DP then OLP

TABLE 3 List of themes

Trust in HCPs and placebo prescribing	Implicit trust in HCPs
	Potential to breach trust
	Trust and the use of OLPs
Perception about solving the clinical problem	Effectiveness matters most
	Treating physical causes
	Doubts about potency of the effect
	Other treatment options
Perceived risks associated with placebos	Avoid risks of medications
	Side effects of placebo
	Balancing benefits with risks

> in the end it's the practitioner who chooses according to the results that there are in the studies. I mean it's his job to choose the best option possible. It's not as if we went to the garage and we had a quote and that we had to choose a quote… He won't offer you a choice between an open placebo or a closed placebo and say which one do you take? No, but it is up to him to decide according to his knowledge.
>
> [G]

> [I]t's not my greengrocer [prescribing the treatment], it's someone from the medical profession, it's ok […] If the doctor thinks that [DP] can solve the problem as the main treatment and that there is no need for another treatment I will say yes.
>
> [D]

This trust went further for some patients who saw it as justification for a more paternalistic approach in the therapeutic relationship: "in any case when we are not a doctor, we listen to what we are told to do." [H]

Potential to breach trust

Some participants described use of DPs as a breach of trust; for example: 'you trust someone and the person does not tell you everything. Even though it is your body, it is your injury, it is your pain, it is you who takes it, it is your side effects… it's easy to be on the doctor's side but since you are the patient uh…. I would take it badly' [F]. This was especially true if the trust was not already established in the therapeutic relationship: 'If with the practitioner we are already lacking a little in trust, it would be a kind of betrayal' [C].

Other participants voiced their wish to be included in the decision process concerning them, and described breaches of trust following DP administration as decisive in their future relationship with their clinician; for example,

> I would never see him again […] saying: Why didn't you tell me? I would listen to these explanations. But, after that, I do not think I will return. The trust would have died.
>
> [F]

> I'm going to be a little mad and I'm not going to go back to see him. It's going to offend me actually. […] Because I'm very trusting, I trust [my HCPs] etc., and I think that everything depends on trust and not on lies. Either we talk about it and we make the decision together or..[not]. […] Frankly unless I am in a coma and not conscious and that they can lie to me without me having a reaction; but otherwise no I do not want to be lied to, no […]. I think I will not trust him anymore and change [HCP].
>
> [E]

Some participants questioned the intent of HCPs to use placebos and signalled the potential to diminish trust of these treatments. For example, 'I think he/she shouldn't do that just to get rid of you and make money off you otherwise it would be a shame' [G]. Again, this questioning about intent in relation to trust was, for some participants, an important factor in deciding whether or not the treatment was acceptable:

> What are the objectives? If their goal is just to avoid paying or doing something that takes them longer or if it's a thing that benefits them and not you well all the sudden it's sad. But if it's always with the moral goal of helping you get better, well in that case I'm always ok.
>
> [B]

Trust and the use of OLPs

Some participants suggested OLPs might enhance trust in the HCP; for example: 'if I was logical enough I would say I prefer open, the advantage is that we are perhaps more integrated into the thing, it is true that it is more appealing and gives greater trust' [G]. In comparison with DPs, participants suggested that OLPs could help protect trust in HCPs; for example:

> Suggesting an open placebo like: 'ok, I suggest this treatment, I give my opinion, yes or no' where I can choose. […] At least there's honesty, we both know what we are engaged in and in the end it is still my body and I think that there's no justification to lie about what we are giving me.
>
> [E]

> [T]he advantage is that we are perhaps more integrated into the [process]. It is true that it is more desirable, gives greater confidence… it's sure that if she/he explains well, the practitioner explains everything well, and then tells us "we do it like that" and everyone is aware of everything, there is not this impression of lying a little bit.
>
> [G]

According to multiple comments, how OLPs were described could have potential to either strengthen or strain trust; for example:

> [it is] how [the practitioner] sells his/her thing.
>
> [B]

> I have to feel that I have free will. That I don't feel manipulated.
>
> [F]

> [This can be done]…by telling me that there are studies. In any case they showed me that there were studies that proved it so I have a little desire to believe a little bit. If he explains to me and he manages to demonstrate that there is an efficiency.
>
> [G]

One participant indicated that overselling OLPs could undermine trust in the HCP: 'He has to explain it objectively enough so that I can make up my mind rather than trying to sell me the thing like a shaman there' [F].

Other participants considered trust in their prior relationship with their HCP as crucial to whether they considered OLPs acceptable:

> I will give more importance to the advice of someone that has already helped me.
>
> [B]

> [If] this is the first time I see the person I'm going to be skeptical.
>
> [F]

> [I]t depends on which health professional offers me this. If it's someone I trust or if it's someone I'm a little suspicious of.
>
> [H]

Perceptions about solving the clinical problem

Effectiveness matters most

Some participants were explicit in emphasizing effectiveness as the most important factor in deciding if a placebo treatment was acceptable; for example:

> the goal of taking a treatment is that it works.
>
> [G]

> if there is an effectiveness it will not bother me ethically that I am not told the truth […] if you go to the doctor, it is to have a result no matter how you get there.
>
> [H]

> if I encounter pain and if it allows me to suffer less I am open to everything.
>
> [D]

Other participants offered more nuanced perspectives, even while suggesting effectiveness was a leading concern; for example: 'it depends if […] it is beneficial for me and if I was deceived on part of the treatment that had no negative impact on me, that just had the aim of being positive. In which case it's just beneficial' [B]. Relatedly, some participants were focused on whether the HCP considered the treatment effective: 'if he thinks it can relieve me I don't see any problem. […] if it's to do tests, I'm not ok' [D].

One participant noted that a placebo treatment would not be acceptable, on the grounds that HCPs have the power to offer something more potent:

> [B]y default when I have pain I will try to work with placebos by myself and if I go to see the doctor it is that I am at a stage where I want a solution.
>
> [B]

Treating physical causes

Some comments suggested placebo treatments were perceived as useful for treating symptoms, but not the cause of the health problem:

> it has an efficiency but if I understood correctly it generates endorphins and endorphins do not solve the problem. It makes the pain more bearable. Whereas if I go to see the doctor, it's that I want to solve the problem.
>
> [B]

It was important to some respondents that the cause of the symptomatology be treated before considering a placebo treatment; for example:

> I would not accept being given false morphine. Once I am treated with a cast for example, it does not bother me. All the same, if I have a serious disease like cancer and that my cancer is not treated, it would bother me. But if I am given a placebo for the pain related to cancer [it's ok].
>
> [H]

> if I tell him I have tendonitis and he tells me to take a placebo I will tell him ok for pain management but it will not change that I have tendonitis.
>
> [B]

Relatedly, one participant noted that the placebo effect could only have a psychological effect on symptoms: 'the principle of placebo is that, I mean… It's empty. It's psychological.' [F].

Doubts about potency of the effect

Regardless of whether participants were offered OLP or DP, a number of comments suggested placebos were perceived as less potent than drugs: for example: 'If it works, all the better. If it doesn't work I would tell [the HCP] I want something stronger' [A]. Some participants also doubted the clinical relevance of placebos saying '[I'd say] that me, I actually want to be treated' [C] or even 'I am skeptical. […] I will not be in the right mode. Actually, I think it will not work because I would say: anyway it's psychological' [F].

Such views led one participant having received a DP during the trial to question the legitimacy of their perceived improvement during the experiment: 'Frankly, I really felt a difference so uh… but I think it is not related to the fact I took the cream' [E]. In contrast, when the pain in the experiment was not completely remedied by the placebo treatment, one participant that had received a OLP during the trial felt 'a little embarrassed, […] I had a small disappointment that it was not as huge as what I had been told. I thought I would be almost pain free' [H].

Other treatment options

Some comments also indicated placebo treatments would be more acceptable in scenarios where no other treatment options were available: 'if you are in therapeutic failure, if there is no other treatment or if the treatment is not effective… Well yes anyway might as well try' [E] or 'I will accept even more because it may be the only option that will help me' [D]. One participant hinted that not only clinical effectiveness but conventionality in offering a mainstream treatment was also important: 'if there is a more obvious solution to the problem, well I will find it a pity that he does not suggest it' [B].

Perceived risks associated with placebos

Avoid risks of medications

Participants identified avoidance of medication intake as one advantage of placebos over other treatments; for example: 'So I think it's good at first to use a placebo, to avoid drug substances [. . .] not necessarily use anti-inflammatory drugs' [C]. This benefit was especially cited in relation to potential for medication side effects, for example: 'less risks of side effects than a drug' [G]. However, other participants were more nuanced in their comments, and still perceived the necessity of medications, for example: '[I]f it can limit the amount of drugs I take it's cool but I also don't want it to take care of everything' [D].

It was also apparent that placebos were seen as less invasive than medications, for example: 'It's a little less substance that's not supposed to be in your body I would say. If there is a placebo that can replace so much the better' [A].

Side effects of placebos

However, participants also considered the potential side effects of the placebo treatment itself, for example: 'as long as there are no negative repercussions for the patient' [G]. Pain was a commonly identified potential side-effect of placebos:

> if I treat one pain to have another pain, suddenly I'll question it a little.
>
> [D]

> Too many side effects that are more disabling than my pain in itself because suddenly it would not be good and if I suffer more afterwards.
>
> [D]

Relatedly, the administration of the placebo treatment was cited as a potential source of side effects:

> There is the method of administration of the OLP that should not be too painful.
>
> [H]

> I will have more concern about invasive [placebo] surgery.
>
> [G]

Notably, for one participant, placebos were perceived as less invasive than medication but also having potential for side effects: 'We can try because if it is less intrusive at the level of the body and as long as the pain can be bearable' [E].

Balancing benefits with risks

Another concern was that the benefits should be balanced against the risks when it comes to decisions about placebos versus other treatments, for example: '[I]t's always the same comparison between the benefits and then the risks you take' [G].

The benefit–risk ratio implied weighing up multiple different factors: 'if there are possible side effects or, I don't know, anything that can change something or the disease, [. . .] or, I don't know, if for example the disease absolutely must be treated now I prefer to have something where I am already convinced of the effectiveness' [A]. Several participants reported elements of the clinical situation that they

believed would influence acceptability of a placebo treatment including the chronicity and the intensity of pain, the seriousness of the pathology and the urgency of a treatment. For example, to illustrate the impact of the chronicity of pain: 'if it is a pain even that has been there for a long time but is sustainable, I think that precisely it is almost more logical if it has been going on for a long time to use a placebo' [A]. For other participants, chronicity was a deterrent towards placebo treatments: 'if [the pain] lasts for a very long time, I will be less likely to accept [the placebo]' [B].

One participant identified the risk of opting for a placebo treatment if it did not improve the situation thereby forfeiting other, potentially more effective, options: 'I would tell myself that I do not want to take the risk that it does not have the effect that I want it to' [H].

DISCUSSION

This study aimed to explore lay people's viewpoints on deceptive and open-label placebo treatments. Undertaking interviews and qualitative thematic analysis, we identified three overarching themes related to both placebo interventions. First, our participants considered trust central in judging placebo treatments acceptable. Participants expressed the importance of implicit trust both in their HCPs' competency, as well as in what it meant to be an HCP, and related the importance of trust in acceptability of placebos. A second major theme was the perception of how the treatment could solve presenting health problems. Our results found acceptability of both types of placebo treatments was dependent on the perception patients had about the treatment solving their problem as well as the doubts they had regarding the effectiveness of placebo treatments. The third major theme encompassed perceived risks associated with placebo prescribing. Some comments positively endorsed placebos as facilitating reduced medication intake. However, participants also identified the potential of placebo treatments to generate potentially adverse side effects. Participants expressed the need for risks to be balanced with regards to potential benefits of placebos.

Comparing our results to the current literature reveals some similarities to previous studies. Expected benefits and perceived risks were major themes highlighted in other qualitative research about DP (Bishop et al., 2014; Fässler et al., 2011; Hammami et al., 2019; Ortiz et al., 2016). These themes are also present in physician views regarding the prescription of placebo treatments (Bliamptis & Barnhill, 2021). We also found other participant responses previously identified in the literature. Some participants preferred effectiveness over honesty (Köteles & Ferentzi, 2012) whereas others value honesty over all else (Bishop et al., 2014). However, beyond currently published qualitative studies, but in line with published ethical analyses (Annoni, 2018; Annoni & Miller, 2014), our findings added a novel perspective by revealing an important focus on trust with regard to placebo treatments. Our results also hinted that OLPs and DPs impacted trust differently. DPs were seen by some participants as a breach of trust and a potential threat to the therapeutic relationship bringing doubts regarding the intent of the HCP. In contrast, prior trust in the HCP and plausibility of the treatment rationale appeared to be regarded by our participants as important for OLP acceptability.

Interestingly, in contrast with other qualitative studies, our participants identified the potential for side effects of placebo treatments. This could be due to: a misunderstanding of the inert medical nature of placebo treatments, anticipation of potential nocebo effects or even in some cases suggestions that side effects could be due to the administration method of the placebo intervention (sham surgery for example). Alternatively, participants may have interpreted this to mean stigmatization or other negative psychological effects prompted by the administration of placebos (Blease, 2019; Blease et al., 2019; Specker Sullivan, 2021). Another point of interest is that placebo definitions from the public may influence their views of placebo and, therefore, acceptability (Hardman et al., 2019). This seemed to be the case in our study. For example, people viewing the placebo effect as treating only imaginary affections were less likely to find it acceptable.

It is important to reflect whether choosing the preferred treatment modality is linked to what is expected of an HCP and more largely of the preferred model of patient-clinician partnership. Our

results suggest different representations of what participants expected of their HCPs. Some expected to be included in the decision-making process (adopting a so-called patient-centred model) and others expected the HCP to know what was best and act upon it (adopting a more paternalistic model of care). In our data, there were different patient profiles. Some patients seemed to prioritize treatment efficacy over autonomy and others appeared to favour autonomy even if with a loss of efficacy. Similar studies on placebo acceptability have found such stances labelling one a 'consequentialist' point of view and another an 'autonomy respecting' point of view (Bishop et al., 2014). Although our study was limited, placebo preference does not appear to be unanimous. It may be that the answer to whether an OLP is more acceptable than DP is patient-dependent, which could also be true when comparing acceptability of placebos with conventional treatments. Although OLPs were initially thought and tested as ethically more acceptable interventions compared with deceptive placebos, our results seem to hint participants were not in agreement with respect to the ethical acceptability of OLPs. The question of comparing DP to OLP regarding efficacy is even more relevant with this in mind and is currently under investigation in published and undergoing trials (Druart et al., 2020; Locher et al., 2017).

We also note, among participants, placebo treatments appeared to prompt common acceptability criteria that might arise with any other clinical treatment: Sekhon et al. defined acceptability as 'a multi-faceted construct that reflects the extent to which people delivering or receiving a healthcare intervention consider it to be appropriate, based on anticipated or experienced cognitive and emotional responses to the intervention' (Sekhon et al., 2017). Our results hint at the seven dimensions comprising acceptability: affective attitude, burden, perceived effectiveness, ethicality, intervention coherence, opportunity costs and self-efficacy (Sekhon et al., 2017). This leads us to consider that placebo treatments could have similar levers influencing treatment acceptability as any other treatment.

Strengths and limitations

This study has several strengths and limitations. First, our trial is one of the few studies to date that has been conducted on placebo acceptability in France. Treatment acceptability can vary depending on socio-cultural context (Bhugra & Ventriglio, 2015; Ventriglio et al., 2018) and this is worth highlighting. This is also one of the few studies, to our knowledge including lay perspectives about treatment acceptability both for DP and OLP. In addition, few studies have conducted qualitative research into placebo interventions in a pragmatic setting: participants actually experienced the intervention allowing them to give a retrospective (i.e. experienced) feedback on the placebo to which they were allocated and a prospective (i.e. anticipated) view about the other placebo modality (Sekhon et al., 2017). Even fewer studies have compared the acceptability of DP and OLP. To the extent of our knowledge only one other study had these similar strengths (Locher et al., 2021). Few studies discussed the variety of administration of placebo interventions ranging from an inert pill to manual therapy, surgery or other non-pharmacological interventions. Our patients also benefited from a standardized information capsule, although not validated by a separate study, provided during the trial or before the interview depending on the group to which they were randomized. Minimal information was given to participants following the video as researchers' conceptual views on placebos may heavily influence the answers given by participants later on. This is especially true regarding placebos and the multiple conceptual differences that exist surrounding them (Hardman et al., 2020).

Our study also has limitations. The sample size was restricted. Although the concept of data saturation is not always a desired goal (Braun & Clarke, 2019), and our survey was exploratory in nature, we note it was not clear from our interviews whether we achieved data saturation. Inferences on the basis of the sample are further limited because our subjects were healthy and mainly young. Acceptability modalities could vary in other settings or populations. The clinical trial setting, although allowing a pragmatic study, invited other methodological shortcomings. Although our participants experienced the treatments, this is still research conducted in an experimental setting and it is unclear if and whether these findings translate to a clinical context. For example, there is reason to believe that experimental

pain is different to the experience of chronic pain and that this could have repercussion in the acceptability of the treatments. In addition, our participants only tried one of the two modalities (i.e., either DP or OLP) before the qualitative interview. We also are unable to say if the participants recruited in the clinical trial had a specific set of attitudes towards placebo or mind–body treatments that led them to enrol in the first place. In addition, the interviewer was not blind to the group allocation, which might have led to a bias in the non-verbal framing of the questions and to participants' responses. Finally, our study only had a single experience with the placebo treatments. In other studies, patients were offered a course of OLP interventions, which might also influence acceptability factors (Carvalho et al., 2016).

Future studies

The results from this study would usefully be supported by further in-depth qualitative interviews with patients. More specific HCP and patient characteristics might be explored to further understand acceptability of these interventions. For example, demographic factors relating to patients (such as gender, age, education, health insurance status and socio-economic status) may influence acceptability. In addition, HCPs characteristics such as gender, age, communication style, tone of voice, personality factors, accents or perceived attractiveness might influence acceptability. Acceptability might be further complicated by dyadic factors relating to the particular configuration of patients with HCPs (Friesen & Blease, 2018; Howe et al., 2022).

We strongly suggest future studies should focus on providing solid evidence for the effectiveness of OLP before clinical use can be considered. Our study identified the importance to patients of establishing clinical effectiveness of placebo interventions. This also suggested the importance of studying how best to communicate OLP rationale (Heiss et al., 2021; Locher et al., 2017). The preference of DP or OLP seemed to be an individual choice and further studies into what motivates one or the other intervention, for what condition and for whom, are recommended. Trials also need to cover more diversity in the clinical trial samples to better represent the general population. Again, participant diversity could be better included with different pathologies, different cultures, different ages.

Finally, our results suggest that placebo efficacy and acceptability are intertwined. In healthcare, a treatment is usually considered effective if it has a superior effect to a similar inert treatment. However, maybe patients and HCPs do not unanimously define effectiveness in the same way. Our results also showed that effectiveness was sometimes considered a higher priority than autonomy in regard to preference to DP and OLP. This suggests future clinical trials could also compare the effectiveness of OLP to DP through superiority or non-inferiority trials. Going further, if such trials showed positive results, seeing how one positive aspect of placebo treatments was allowing to reduce drug intake, we could also suggest trials comparing the effectiveness and acceptability of OLP and analgesic medications as well as dose-extending OLP in combination with analgesic medications to find the most dose-effective method of administration.

CONCLUSION

Treatment acceptability by patients is a pre-requisite, alongside effectiveness, to harnessing OLP interventions in clinical care. The acceptability of placebo treatments depends on the trust patients have in their HCP, anticipated benefits of treatments and the risks associated with their intake. The preference for DP or an OLP appeared to be a matter of individual choice and context. Finding ways to improve both trust in HCP but also in the OLP rationale when prescribing may be an important next step in studying OLP treatment acceptability. Future research should also focus on what patients want to know about OLP treatments and how to best communicate effectiveness. This goes in tandem with the prerequisite of a patient-centred paradigm whereby communicating benefits and risks as well as preserving trust are fundamental to uphold informed patient decisions.

AUTHOR CONTRIBUTIONS

Leo Druart: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; validation; visualization; writing – original draft; writing – review and editing. **Oriana Vauthrin:** Conceptualization; data curation; formal analysis; investigation; methodology; validation; visualization; writing – original draft; writing – review and editing. **Nicolas Pinsault:** Conceptualization; formal analysis; funding acquisition; methodology; project administration; resources; supervision; validation; visualization; writing – original draft; writing – review and editing. **Cosima Locher:** Formal analysis; methodology; project administration; supervision; validation; visualization; writing – original draft; writing – review and editing. **Charlotte Blease:** Formal analysis; methodology; project administration; supervision; validation; visualization; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. The funding for the clinical trial was provided by APICIL Foundation, which had no part in the methodology or design or data collection or analysis of this study.

DATA AVAILABILITY STATEMENT

The raw data from the interviews that support the findings of this study are available in French from the corresponding author upon reasonable request.

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REFERENCES

Annoni, M. (2018). The ethics of placebo effects in clinical practice and research. *International Review of Neurobiology*, *139*, 463–484.

Annoni, M., & Miller, F. G. (2014). Placebos in clinical practice: An ethical overview. *Douleur et Analgésie*, *27*, 215–220.

Bardin, L. (2013). *L'analyse de contenu*. Presses Universitaires de France.

Benedetti, F. (2020). *Placebo effects*. Wiley.

Benedetti, F., Carlino, E., & Pollo, A. (2011). Hidden administration of drugs. *Clinical Pharmacology and Therapeutics*, *90*, 651–661.

Bernstein, M. H., Locher, C., Kube, T., Buergler, S., Stewart-Ferrer, S., & Blease, C. (2020). Putting the 'Art' into the 'Art of Medicine': The under-explored role of artifacts in placebo studies. *Frontiers in Psychology*, *11*, 1354.

Bernstein, M. H., Locher, C., Stewart-Ferrer, S., Buergler, S., DesRoches, C. M., Dossett, M. L., Miller, F. G., Giese, D., & Blease, C. R. (2020). Primary care providers' use of and attitudes towards placebos: An exploratory focus group study with US physicians. *British Journal of Health Psychology*, *25*, 596–614.

Bhugra, D., & Ventriglio, A. (2015). Do cultures influence placebo response? *Acta Psychiatrica Scandinavica*, *132*, 227–230.

Bishop, F. L., Aizlewood, L., & Adams, A. E. M. (2014). When and why placebo-prescribing is acceptable and unacceptable: A focus group study of patients' views. *PLoS One*, *9*, e101822.

Bishop, F. L., Jacobson, E. E., Shaw, J., & Kaptchuk, T. J. (2012). Participants' experiences of being debriefed to placebo allocation in a clinical trial. *Qualitative Health Research*, *22*, 1138–1149.

Blease, C. (2018). consensus in placebo studies: Lessons from the philosophy of science. *Perspectives in Biology and Medicine*, *61*, 412–429.

Blease, C., & Annoni, M. (2019). Overcoming disagreement: A roadmap for placebo studies. *Biology and Philosophy*, *34*, 1–26.

Blease, C., Colloca, L., & Kaptchuk, T. J. (2016). Are open-label placebos ethical? Informed consent and ethical equivocations. *Bioethics*, *30*, 407–414.

Blease, C. R. (2019). The role of placebos in family medicine: 'Implications of evidence and ethics for general practitioners'. *Australian journal of general practice*, *48*, 700–705.

Blease, C. R., Bernstein, M. H., & Locher, C. (2019). Open-label placebo clinical trials: Is it the rationale, the interaction or the pill? *BMJ Evidence-based Medicine*, *25*, 159–165.

Bliamptis, J., & Barnhill, A. (2021). Physician perspectives on placebo ethics. *Journal of Medical Ethics*. https://doi.org/10.1136/medethics-2021-107446

Braun, V., & Clarke, V. (2006). Using thematic analysis in psychology. *Qualitative Research in Psychology*, *3*, 77–101.

Braun, V., & Clarke, V. (2013). *Successful qualitative research: A practical guide for beginners*. SAGE.

Braun, V., & Clarke, V. (2019). To saturate or not to saturate? Questioning data saturation as a useful concept for thematic analysis and sample-size rationales. *Qualitative Research in Sport, Exercise and Health*, *13*, 201–216.

Carvalho, C., Caetano, J. M., Cunha, L., Rebouta, P., Kaptchuk, T. J., & Kirsch, I. (2016). Open-label placebo treatment in chronic low back pain: A randomized controlled trial. *Pain*, *157*, 2766–2772.

Charlesworth, J. E. G., Petkovic, G., Kelley, J. M., Hunter, M., Onakpoya, I., Roberts, N., Miller, F. G., & Howick, J. (2017). Effects of placebos without deception compared with no treatment: A systematic review and meta-analysis. *Journal of Evidence-Based Medicine*, *10*, 97–107.

Coolican, H. (2017). *Research methods and statistics in psychology*. Routledge.

Di Blasi, Z., Harkness, E., Ernst, E., Georgiou, A., & Kleijnen, J. (2001). Influence of context effects on health outcomes: A systematic review. *Lancet*, *357*, 757–762.

Druart, L., Graham Longsworth, S., Rolland, C., Dolgopoloff, M., Terrisse, H., Bosson, J.-L., & Pinsault, N. (2020). Can an open-label placebo be as effective as a deceptive placebo? Methodological considerations of a study protocol. *Medicines (Basel)*, *7*, 3.

Ernst, E., & Resch, K. L. (1995). Concept of true and perceived placebo effects. *BMJ*, *311*, 551–553.

Fässler, M., Gnädinger, M., Rosemann, T., & Biller-Andorno, N. (2011). Placebo interventions in practice: A questionnaire survey on the attitudes of patients and physicians. *The British Journal of General Practice*, *61*, 101–107.

Fässler, M., Meissner, K., Schneider, A., & Linde, K. (2010). Frequency and circumstances of placebo use in clinical practice – a systematic review of empirical studies. *BMC Medicine*, *8*, 15.

Foddy, B. (2009). A duty to deceive: placebos in clinical practice. *The American Journal of Bioethics*, *9*, 4–12.

Friesen, P., & Blease, C. (2018). Placebo effects and racial and ethnic health disparities: An unjust and underexplored connection. *Journal of Medical Ethics*, *44*, 774–781.

Grünbaum, A. (1986). The placebo concept in medicine and psychiatry. *Psychological Medicine*, *16*, 19–38.

Haas, J. W., Rief, W., & Doering, B. K. (2021). Open-label placebo treatment: Outcome expectations and general acceptance in the lay population. *International Journal of Behavioral Medicine*, *28*, 444–454. https://doi.org/10.1007/s12529-020-09933-1

Hammami, M. M., Hammami, S., Aboushaar, R., & Aljomah, A. S. (2019). Lay people's ethical attitudes to placebo treatment: A Q-Methodology Study. *Patient Preference and Adherence*, *13*, 1599–1617.

Hardman, D. I., Geraghty, A. W., Howick, J., Roberts, N., & Bishop, F. L. (2019). A discursive exploration of public perspectives on placebos and their effects. *Health Psychology Open*, *6*, 2055102919832313.

Hardman, D. I., Geraghty, A. W., Lewith, G., Lown, M., Viecelli, C., & Bishop, F. L. (2020). From substance to process: A meta-ethnographic review of how healthcare professionals and patients understand placebos and their effects in primary care. *Health (London, England)*, *24*, 315–340.

Heiss, U., Rosenfield, M., & Bernstein, M. (2021). Can the Open-Label Placebo rationale be optimized? *Frontiers in Pain Research*, *2*, 734882. https://doi.org/10.3389/fpain.2021.734882

Howe, L. C., Hardebeck, E. J., Eberhardt, J. L., Markus, H. R., & Crum, A. J. (2022). White patients' physical responses to healthcare treatments are influenced by provider race and gender. *Proceedings of the National Academy of Sciences of the United States of America*, *119*, e2007717119.

Howe, L. C., Leibowitz, K. A., & Crum, A. J. (2019). When your doctor "Gets It" and "Gets You": The critical role of competence and warmth in the patient-provider interaction. *Frontiers in Psychiatry*, *10*, 475.

Howick, J. (2017). The relativity of 'placebos': Defending a modified version of Grünbaum's definition. *Synthese*, *194*, 1363–1396.

Kaptchuk, T. J., & Miller, F. G. (2015). Placebo effects in medicine. *The New England Journal of Medicine*, *373*, 8–9.

Kelley, J. M., Kraft-Todd, G., Schapira, L., Kossowsky, J., & Riess, H. (2014). The influence of the patient-clinician relationship on healthcare outcomes: A systematic review and meta-analysis of randomized controlled trials. *PLoS One*, *9*, e94207.

Koteles, F., & Ferentzi, E. (2012). Ethical aspects of clinical placebo use: What do laypeople think? *Evaluation and the Health Professions*, *35*, 462–476.

Linde, K., Atmann, O., Meissner, K., Schneider, A., Meister, R., Kriston, L., & Werner, C. (2018). How often do general practitioners use placebos and non-specific interventions? Systematic review and meta-analysis of surveys. *PLoS One*, *13*, e0202211.

Locher, C., Buergler, S., Frey Nascimento, A., Kost, L., Blease, C., & Gaab, J. (2021). Lay perspectives of the open-label placebo rationale: A qualitative study of participants in an experimental trial. *BMJ Open*, *11*, e053346.

Locher, C., Frey Nascimento, A., Kirsch, I., Kossowsky, J., Meyer, A., & Gaab, J. (2017). Is the rationale more important than deception? A randomized controlled trial of open-label placebo analgesia. *Pain*, *158*, 2320–2328.

Locher, C., Gaab, J., Blease, C., Inderbinen, M., Kost, L., & Koechlin, H. (2019). Placebos are part of the solution, not the problem. An exemplification of the case of antidepressants in pediatric chronic pain conditions. *Frontiers in Psychiatry*, *10*, 998.

Marsili, N. (2014). Lying as a scalar phenomenon. In *Certainty-uncertainty–and the attitudinal space in between* (pp. 153–173). John Benjamins Publishing Company.

Miller, F. G. (2018). Reining in the placebo effect. *Perspectives in Biology and Medicine*, *61*, 335–348.

Moerman, D. E., & Jonas, W. B. (2002). Deconstructing the placebo effect and finding the meaning response. *Annals of Internal Medicine*, *136*, 471–476.

Ortiz, R., Chandros Hull, S., & Colloca, L. (2016). Patient attitudes about the clinical use of placebo: Qualitative perspectives from a telephone survey. *BMJ Open*, *6*, e011012.

Pugh, J., Kahane, G., Maslen, H., & Savulescu, J. (2016). Lay attitudes toward deception in medicine: Theoretical considerations and empirical evidence. *AJOB Empirical Bioethics*, *7*, 31–38.

Sekhon, M., Cartwright, M., & Francis, J. J. (2017). Acceptability of healthcare interventions: An overview of reviews and development of a theoretical framework. *BMC Health Services Research*, *17*, 88.

Specker Sullivan, L. (2021). More than consent for ethical open-label placebo research. *Journal of Medical Ethics*, *47*(12), e7.

Street, R. L., Jr., Makoul, G., Arora, N. K., & Epstein, R. M. (2009). How does communication heal? Pathways linking clinician-patient communication to health outcomes. *Patient Education and Counseling*, *74*, 295–301.

Turner, A. (2011). 'Placebos' and the logic of placebo comparison. *Biology and Philosophy*, *27*, 419–432.

Ventriglio, A., Magnifico, G., Borraccino, L., Rinaldi, A., & Bellomo, A. (2018). Placebo and cultural responses. *Nordic Journal of Psychiatry*, *72*, S33–S35.

von Wernsdorff, M., Loef, M., Tuschen-Caffier, B., & Schmidt, S. (2021). Effects of open-label placebos in clinical trials: A systematic review and meta-analysis. *Scientific Reports*, *11*, 3855.

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2.4. SUMMARY

From these results, we see that one major component of the acceptability of placebo treatments is effectiveness (Article 3) and that OLPs seems to be non-inferior to DP (Article 2). However, that doesn't mean placebo treatments are ready for clinical use in physiotherapy. For instance, participants in our study suggested, that placebo treatments seem acceptable when no other treatment is available. This is one of the challenges with placebo treatments: they may risk taking the place of other more effective interventions. Adding to this, ethical concerns over OLPs exist which will be discussed further in section 4.1.1. One example is the question of whether OLPs involve deception. Blease et al. argue this depends on the information given during the rationale (C. Blease et al., 2016).

Combined these findings and considerations invite us to inquire whether other existing, ethical ways of eliciting placebo effects in physiotherapy might be harnessed without relying on placebo treatments.

3. USES OF PLACEBO EFFECTS AS TREATMENT ENHANCERS

3.1. BACKGROUND

3.1.1. PLACEBO EFFECTS WITHOUT PLACEBO TREATMENTS

Although placebo use is widespread, as the discussion on CFs in section 1.2.4 emphasized, they may not be the only way to harness placebo effects in clinical practice. The idea of increasing placebo effects in everyday care is not new and has already been suggested for some time (Chaput de Saintonge & Herxheimer, 1994). More recently, psychologist and placebo scholar Irving Kirsch summarized six lessons learnt from his research, and proposed the potential of enhancing the placebo effects in treatment (Kirsch, 2013). This view was also shared by a recent expert consensus which proposed clinicians should maximize placebo effects and minimize nocebo effects in everyday care (Evers et al., 2018, 2020). Similarly, the American Medical Association has given the following recommendation in 2008: "Physicians can avoid using a placebo yet produce a placebo-like effect through the skilful use of reassurance and encouragement. In this way, the physician builds respect and trust, promotes the patient-physician relationship, and improves health outcomes" (Bostick et al., 2008).

Interventions which benefit from the characteristic effect of the treatment as well as the incidental factors, in turn increasing the placebo effect, could be named *superverums* (Gaab et al., 2016). Brody gave examples of *superverum*s such as "the sustained partnership approach, working with patients on the narratives they construct to explain illness, listening to patients, providing them with satisfactory explanations, expressing care and concern, and enhancing their sense of control" (Brody, 2000). The "skilful use of verbal communication" is also suggested as a way to increase placebo effects (Annoni & Miller, 2016).

To recap: these recommendations propose the use of placebo effects without placebo treatments as potential treatment enhancers[41]. Mechanistic research, outlined

[41] This supposes that the placebo effect and treatment effect are additive. Recently, this postulate has been challenged. Several reviews have questioned the additive model and rather suggested an interactive model. As Kube and Rief state: "given that the evaluation of drug treatments in RCTs is based on the assumption of additivity, its violation has far-reaching consequences" (Boussageon et al., 2022; Coleshill et al., 2018; Kube & Rief, 2017; Lund et al., 2014; Vase, 2020). However, other reviews have found inconsistencies in examinations

in section 1.2.3, has shown that placebo effects can foster genuine psychobiological effects that could in turn elicit therapeutic benefits. As then discussed in section 1.2.4, the placebo effect is now no longer considered merely the effect of an inert treatment but rather can be influenced by multiple factors in the context of treatment and care.

3.1.2. Contextual Factors

Various cues, presented in the introduction, which can be described as CFs could elicit, or influence the strength of placebo and nocebo effects. As previously noted in section 1.2.4, CFs can be classified in five categories: patient characteristics, clinician characteristics, patient-clinician relationship, the nature of the treatment and healthcare setting features (Di Blasi et al., 2001). However, studies most often link CFs to expectations and not to placebo and nocebo effects and more generally healthcare outcomes.

Currently, most studies on CFs have focused on physicians. More recently, bridging physiotherapy and CFs, two reviews led by Italian physiotherapists have suggested that CFs could also arise in physiotherapy, leading to placebo effects (Rossettini, Carlino, et al., 2018; Testa & Rossettini, 2016); these are presented in Figure 6 and will be detailed hereinafter.

of the additivity assumption concluding that to date "at least under some conditions the assumption of additivity does not hold" (Coleshill et al., 2018).

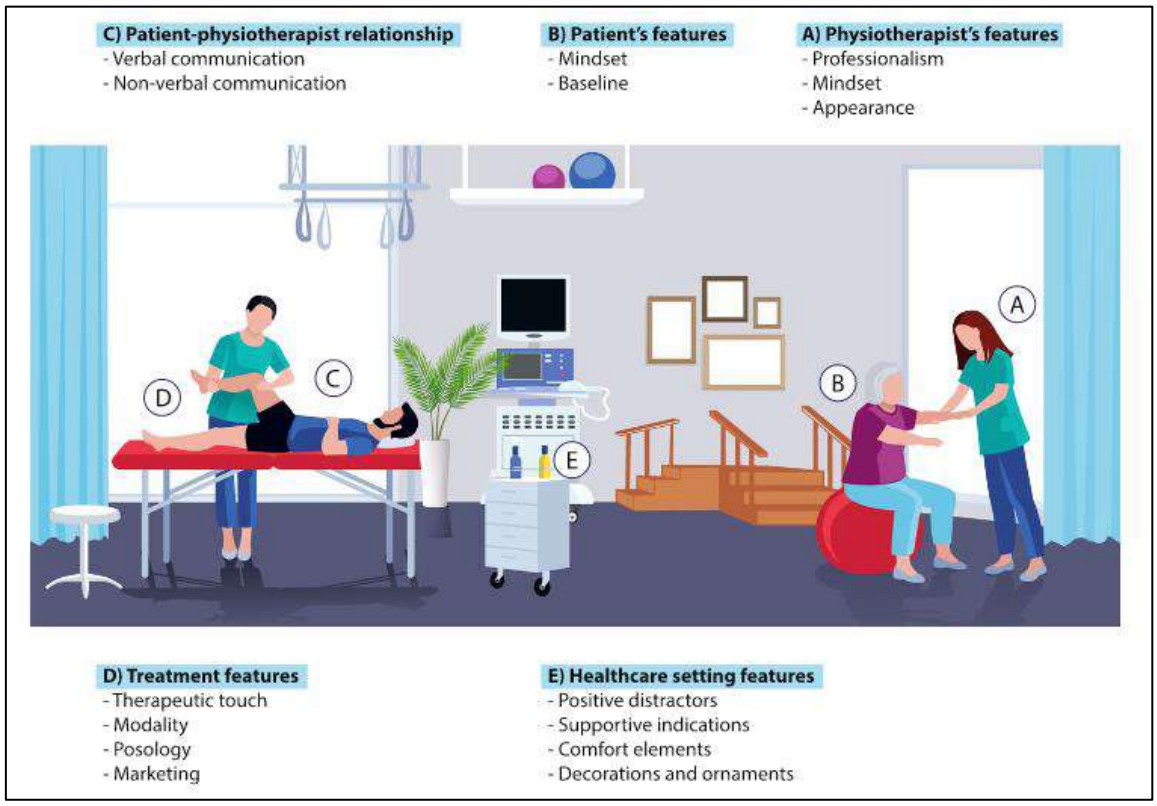

Figure 6: From Rossettini et al. this figure shows contextual factors in physiotherapy clinical practice (Rossettini, Camerone, et al., 2020).

3.1.2.1. PHYSIOTHERAPIST CHARACTERISTICS

Patient's expectancies can be influenced by both the appearance and reputation of the physiotherapist. The perception of the professional's expertise, competency, qualification and level of training may influence patient's expectations, which in turn may augment or diminish placebo effects. For instance, Howe et al. suggested, in a RCT of 164 participants, that expectations and placebo effects were mediated by cues related to warmth and competency (Howe et al., 2017). This may also arise in physiotherapy since perceived expertise is considered an important factor of quality of care for patients (Del Baño-Aledo et al., 2014). When patients are referred to physiotherapists by a physician, it seems possible that doctors' recommendations may also play a part in how patients perceive physiotherapists' expertise and the relevance of rehabilitation to their condition. Similarly, the professional's appearance also carries influence on expectations. The "white coat effect" for instance has been described as impacting patients' perceptions of physician confidence, trust and their

openness in discussing sensitive matters (Bernstein et al., 2020). In the case of physiotherapy, Mercer et al. showed that, in Canada, patients deemed physiotherapists with lab coats as the most professional. However, they preferred to visit physiotherapists wearing a tailored outfit, such as dressed with a shirt and a chino (Mercer et al., 2008). How factors such as dress might be successfully combined in physiotherapy to augment perceptions of both competence and warmth, is not yet understood.

In addition, the physiotherapist's belief in the treatment's effect may be important too. Gracely had shown this in a study of dentistry: in one group, dentists were told they would either be injecting fentanyl, naloxone or placebo and in the other group they were told they could only be injecting naloxone, or placebo. The results suggested that dentists convinced that they could not deliver effective treatment provided less pain relief than those who believed they could be injecting active fentanyl (Gracely et al., 1985). This seems to translate to physiotherapy, as there is evidence that, among patients with low back pain, beliefs regarding rehabilitation effectiveness were correlated to their therapist's own views about the effectiveness of the treatment (Darlow et al., 2012).

3.1.2.2. PATIENT CHARACTERISTICS

Regarding patient characteristics, as we've noted, expectations play a major role in placebo effects (Benedetti et al., 2011a). They have also been directly linked to healthcare outcomes: better expectations lead to better health outcomes (Mondloch et al., 2001). The same could be said for the trust patients feel regarding therapists (Birkhäuer et al., 2017). Positive or negative experiences in previous consultations can influence expectations (Colloca & Benedetti, 2006). As such patient's perception and experience of care are crucial to take into consideration when analysing placebo effects (Vase et al., 2011).

Studies suggest satisfaction with physiotherapy care is determined more often by interpersonal elements of care and its process and organisation rather than by the results of the treatments itself (Hush et al., 2011). Irish physiotherapist O'Keefe and colleagues showed that not taking into account patient preferences had a negative impact on physiotherapist interactions (O'Keeffe et al., 2016). This could in turn

contribute to nocebo effects. Patient age and gender also contribute to shape experience of care differently. Hush et al., in their review of the factors contributing to patient experience in physiotherapy, find that older patients tend to be more sensitive to access to services and to the effectiveness of communication (Hush et al., 2011). Similarly, patients with acute conditions were more sensitive to physiotherapist expertise, reputation, level of training and professional behaviour than those with chronic conditions who perceived the organization of care as more significant (Hush et al., 2011). The severity of the initial symptoms also modulated what patients expected of physiotherapy. A study showed a more sudden onset of pain or an increasing disability both lead to higher expectation of treatment relief (M. D. Bishop et al., 2019). Regarding patient gender, the main predictors of satisfaction for male patients with neck or low back pain were physiotherapist features and treatment outcome, whereas female patients considered organizational and communication components of care more important (Stenberg et al., 2012).

3.1.2.3. Patient-Physiotherapist relationship

Rossettini and Testa group under this category many CFs that include the interaction between the physiotherapist and the patient including verbal and non-verbal communication, and the therapeutic alliance (Testa & Rossettini, 2016). A recent Delphi survey found that musculoskeletal practitioners, including physiotherapists, believed the patient-clinician relationship the most important category of CFs (Sherriff et al., 2023). Kirsch suggests that optimising placebo effects can be achieved by taking more care in forming a therapeutic alliance and by spending more time with patients[42] (Kirsch, 2013). In physiotherapy, it seems the therapeutic alliance is a consistent predictor of low-back pain treatment outcomes (Ferreira et al., 2013). This was supported by a RCT including 117 patients with low back pain: Fuentes et al. found that an enhanced therapeutic alliance reduced pain intensity and

[42] Economical constraints on a healthcare system have a large role to play in the duration of consultations. For instance, in France a physiotherapy consultation is set at 30 minutes and a physician consultation at a little under 15 minutes on average. However, although reducing consultation time with patients may allow a direct reduction of costs for the healthcare system, it could also prove to be cost-effective to enhance the placebo component of treatment while also improving the conditions of labour for healthcare providers. To date, too few studies allow to say this is the case (Hamberger et al., 2019).

improved muscle pain sensitivity (Fuentes et al., 2014). However, Babatunde et al.'s scoping review of the literature nuances this as they conclude the therapeutic alliance has been studied "in a limited extent in the rehabilitation literature with conflicting frameworks and findings" (Babatunde et al., 2017).

Communication has been the focus of many empirical studies which demonstrate that verbal suggestions can generate placebo effects (Vase et al., 2002, 2009; Voudouris et al., 1990). When congruent with a conditioning procedure, verbal suggestions can increase the placebo effect (Benedetti, Pollo, et al., 2003). Additionally, a negative suggestion, incongruent with conditioning, can dispel the placebo effect (Benedetti, Pollo, et al., 2003; Corsi et al., 2019). As we will see, verbal communication not only includes what is said but also how it is said. A recent meta-analysis found that if communication conveys empathy and warmth it can improve health outcomes (Howick et al., 2018).

Relatedly, it has been shown that the effect of treatment depends on the information provided during the treatment administration. When a treatment's administration is hidden, its effect diminishes by approximately 50% in Amanzio et al.'s study (Amanzio et al., 2001). The simple fact that patients expect to receive a treatment changes the overall treatment response (Amanzio et al., 2001; Benedetti et al., 2011b; Colloca et al., 2004). This highlights how placebos effects may arise in already prescribed treatments. In addition, nocebo effects may also occur. One such context is the disclosure of potential side-effects of treatments by practioners. In this case, disclosure of potential adverse effects could be self-fulling by risking increasing the likelihood of negative expectancies, and thereby adverse effects via nocebo effects. On the other hand, concealing these potential side effects may be considered as undermining the duty to adequately inform patients about treatments. This was illustrated in the case of finasteride, a drug for benign prostatic hyperplasia. In about 15% of cases, finasteride is believed to induce adverse sexual effects such as erectile dysfunction or decreased libido. In one study, one hundred and seven patients were randomised into two groups: one group was informed of the potential side-effects of the treatment and the second were not. Results indicated that the participants in the group informed of potential uncommon side-effects reported significantly more side-effects that the other groups (44% versus 15%)(Mondaini et al., 2007).

Yet, verbal suggestions have also been studied in situations other than the disclosure of side-effects. This was the topic of an early study by Thomas in 1987 (Thomas, 1987). He randomised 200 patients into 4 groups. Two groups would receive a consultation led in a "positive manner" with or without treatment and the last two received a "non-positive" consultation with or without treatment. Thomas found better results for patients receiving "positive" suggestions independently of whether they were treated or not. Since this study, many other studies have looked at the influence of verbal suggestions on healthcare outcomes. For instance, one noteworthy example is the study conducted by Varelmann et al. (Varelmann et al., 2010): 140 patients were divided in two groups during local anaesthetic injection. The only difference between groups was the words used to describe the injection. One group was told "you are going to feel a big sting and burn in your back now, like a bee sting; this is the worst part of the procedure." The other group was told "we are going to inject the local anaesthetic that will numb the area where we are going to do the epidural anaesthesia and you will be comfortable during the procedure." The results show that, not only was there significantly higher rates of pain reported during the injection in the nocebo suggestion group, but this difference in pain intensity carried over to the rest of the procedure. This is crucial for physiotherapy as communicating to patients represents up to twice as much time than hands-on treatment (L. Roberts & Bucksey, 2007).

As noted, non-verbal behaviour, defined as behaviour without linguistic communication, is also something that can influence health outcomes (Mast, 2007). They can convey positive expectations which seem to produce higher placebo effects. Examples of this in the literature include smiling, strong tone of voice, more eye contact, more leaning towards the patient (Daniali & Flaten, 2019). On the other hand, negative behaviours such as no smile, monotonous tone of voice, no eye contact or leaning backward from the patient may lead to nocebo effects (Daniali & Flaten, 2019). Indeed, face expressions have been shown to influence pain processing and enhance placebo analgesia (Valentini et al., 2014). Conversely, absence of smiling or looking away from the patient led to negative effects specifically during physiotherapy consultation (Ambady et al., 2002). However, Mast warns that nonverbal cues can be interpreted differently depending on the situation. For example, a recent study "found

that patient satisfaction was related to female gender stereotypical nonverbal behaviour (e.g., more gazing at patient, less interpersonal distance, softer voice, less looking at medical chart) for female physicians and that patient satisfaction was especially high if male physicians adhered to male gender stereotypical nonverbal behaviour (e.g., more interpersonal distance, more expansiveness, louder voice)" (Mast & Kadji, 2018; Schmid Mast et al., 2007). To summarize what clinicians could retain from research on nonverbal behaviours, Stickley suggest the acronym SURETY: namely, "Sit at an angle"; "Uncross legs and arms"; "Relax"; "Eye contact"; "Touch"; "Your intuition" (Stickley, 2011).

3.1.2.4. NATURE OF THE TREATMENT

Treatment characteristics may bear influence on expected effectiveness of drugs. Meissner and Linde recently published an overview of different treatment characteristics to consider amongst which colour, size number and shape of drugs (Meissner & Linde, 2018). However, most of these results suffer important limitations as they originate from studies with limited sample sizes and lack replication (C. Blease et al., 2023). More specifically for physiotherapy, a subgroup analysis from a Cochrane meta-analysis revealed a greater efficacy of physical placebos (e.g. acupuncture or a machine turned off) over pharmacological placebos (e.g. a pill)(Hróbjartsson & Gøtzsche, 2010). Among physical placebos, sham acupuncture was the most potent.

Regarding other characteristics present in physiotherapy treatments, Testa and Rossettini suggested the importance of touch during physical treatments (Testa & Rossettini, 2016). Touch is often considered an important component of physiotherapy's identity as argued by the physiotherapist Rothstein (Rothstein, 1992). Roger et al. found several reasons physiotherapists had to touch their patients including assistive touch, caring touch, touch to provide a therapeutic intervention, and touch used to perceive information (Roger et al., 2002). In their study, a caring touch was a touch used to comfort, encourage, and to show a caring attitude. They also described uses of touch for "building rapport" and also touch used "to produce a feeling of safety or reassurance for a patient whether or not it was physically needed" (Roger et al., 2002). When touch is needed to treat the patient, for example in the case of manual therapy, other treatment features may play a role. Demoulin et al.

showed that the cracking joint sounds during spinal manipulation led patients to believe that a manual therapy technique was successful (Demoulin et al., 2018). Indeed, believing low back pain treatment requires to "realign" the spine or repair tissue is a maladaptive belief which may contribute to expecting manual therapy or a joint sound during treatment (Demoulin et al., 2016).

3.1.2.5. Healthcare setting features

There is less research into the role of the environment in modulating placebo and nocebo effects (Bernstein et al., 2020). However, environmental factors may provide cues to the patient that they can expect a positive effect following treatment. Frank and Frank point out that this includes "symbol[s of] the therapist's role as a healer" (Frank & Frank, 1993). For physiotherapists, these symbols may take the form of displayed diplomas or certification, decorative artifacts, or even the colour of the walls. Displaying evidence of the therapist's clinical expertise could help build expectancies. In their review, Testa and Rossettini suggest an optimal setting has natural lighting, low noise levels and relaxing and soft music. The therapeutic setting should be private, comfortable and include nature artworks (Testa & Rossettini, 2016). Moreover, providing an enriched therapeutic environment could be one way to influence a positive interaction (Rossettini, Camerone, et al., 2020). This could also be achieved by adding apparatus that is distinctive to physiotherapy such as pictures of anatomy or model skeletons.

3.1.3. Other considerations on contextual factors

It is worth noting that contextual categorisations also carry inherent limitations. For instance, this classification is suggested with a focus on the "source" of the CF. However, these factors could also be grouped depending on other features; for example, whether they are potentially modifiable or changeable. As such past experiences could be classified as non-modifiable factors whereas communication could be considered a modifiable factor. Alternatively, they could be categorised depending on whether they are modulated during the appointment or not. Developing this line of reasoning, treatment delivery would be included whereas the physiotherapist's belief that such a treatment is effective would not.

Another difficulty worth noting is that categorising tends to shift focus away from possible interactions between factors. For example, there could be an interaction between CFs linked to the practitioner and those linked to the treatment. Alternatively, there could also be an interaction between characteristics of the patient and of the physiotherapist. This could be the case regarding the dyadic features of the physiotherapist and patient. For example, gender dyads have a significant impact on communication (Sandhu et al., 2009). Another example could be looking at how physiotherapist race and gender could influence the placebo effect. Howe et al.'s study suggests that unconscious biases[43] led to lower treatment responses in white patients when the healthcare provider was black or female (Howe et al., 2022). Such considerations are scarcely taken into account in current research on CFs (Friesen & Blease, 2018). Another example of an interaction between characteristics of the treatment and of the therapist could be a supposed difference in expectations from a sham acupuncture treatment depending on if the provider fits the patient's expectations or even stereotypes associated with providers and modalities, for example, as an elderly Asian man. In physiotherapy, Harman et al. reported a "preconceived image of a physiotherapist as being fit and active" (Harman et al., 2021). If these are the stereotypes patients carry about physiotherapists, clinicians that do not fit these expectations may have a negative impact on treatment expectations.

Another limitation to current research on CFs is few RCTs have examined the impact of manipulating CFs on the overall treatment effect (Bernstein et al., 2020). This is likely because research on CFs is much more recent than that on placebo treatments. Generally, there is a progression in development phases for clinical research. When clinical research is introduced to undergraduate students, it's often divided into different phases based on the study's objective. These classifications typically include efficacy studies, mechanistic studies, effectiveness studies, pragmatic studies, and efficiency studies. Efficacy studies aim to answer the question of whether

[43] The authors tested for perceived competency and warmth. The women were on average rated both warmer and more competent. Black and Asian providers were rated as warmer and equally competent. This suggests the biases were unconscious. The topic is well covered by the book by Banaji presenting implicit association tests (Banaji, 2013).

an intervention can have an effect in ideal conditions. Mechanistic studies focus on understanding how an intervention works. Effectiveness studies explore whether the intervention works for the intended population. Pragmatic studies evaluate the effectiveness of an intervention in a clinical setting outside of research labs. Lastly, efficiency studies analyse how the intervention uses resources compared to other interventions, weighing resource usage against benefits provided. In general, researchers typically begin by studying the efficacy of a treatment, focusing on whether the intervention can have an effect. At the same time, they also conduct mechanistic studies to understand how the intervention works. Once the intervention has been shown to have an effect in ideal conditions, researchers can then move on to testing its effectiveness. This is followed by efficiency and pragmatic trials. By following this progression, researchers can gain a comprehensive understanding of the intervention and its potential impact.

With respect to research on CFs, we can observe that verbal suggestions (Varelmann et al., 2010) have been shown effective but few other CFs have been studied just as extensively. Research has focused on linking CFs and expectancies as Mercer et al. did with clothing (Mercer et al., 2008). Still, mechanistic studies confirm expectations influence placebo effects (Bingel, 2020; Voudouris et al., 1990). Nonetheless, actual efficacy of effectiveness studies linking CFs and healthcare outcomes are scarce. Again, this could be explained in part due to the novelty of this approach but also to methodological restrictions or even the need for large samples to show relatively small effect sizes.

Overall, CFs may offer a promising solution to maximizing placebo effects and minimizing nocebo effects in physiotherapy. However, this will require to verify if CFs meaningfully influence healthcare outcomes while testing if their manipulation is effective or efficient.

3.2. ARTICLE 4

In such a burgeoning topic within placebo studies, it is reasonable to start with an exploration of healthcare providers' practices related to CFs. Similar to investigations into the use of placebo treatment in clinical settings, it is necessary to study how healthcare providers currently use CFs. Indeed, if we assume that

healthcare providers should maximize placebo effects and minimize nocebo effects, it is vital to inquire how they conceive the various therapeutic potential of distinct factors in their work too. Furthermore, examining if there are any specificities in CF use in physiotherapy compared to other healthcare professions is also important to fill current research gaps pertaining to physiotherapy and placebo studies. This is where our third study fits in.

This study was submitted to PLOS One on the 13th of January 2023 under the title "Perception and use of contextual factors in eliciting placebo and nocebo effects: an online survey of healthcare providers in French-speaking countries in Europe". It is currently under review. It was also accepted as a poster presentation in the 2023 SIPS congress.

PLOS ONE

Perception and use of contextual factors in eliciting placebo and nocebo effects: an online survey of healthcare providers in French-speaking countries in Europe

--Manuscript Draft--

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Keywords:	General Practice; Pain; Professional Practice; Placebo effect; Nocebo effect; Surveys and Questionnaires
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Healthcare providers' use of contextual factors

Title

Perception and use of contextual factors in eliciting placebo and nocebo effects: an online survey of healthcare providers in French-speaking countries in Europe

Running Title
Healthcare providers' use of contextual factors

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Keywords
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Abbreviations
CF: Contextual Factors
HCP: Healthcare providers.

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Abstract (word count: 250)

Contextual factor use by healthcare professionals has been studied mainly among nurses and physiotherapists. Preliminary results show that healthcare professionals use contextual factors without specifically labelling them as such. The main objective of this study was to explore voluntary contextual factor use among various healthcare professions. Our goal was hypothesis-generating to initiate further research explaining and characterising contextual factor use. We conducted a web-based questionnaire cross-sectional observational study on a non-probabilistic convenience sample. Face and content validity were tested through cognitive interviews. Data were analysed descriptively. The target population was, or final-year healthcare students as defined by the French public health code. The countries of distribution of the questionnaire were the French-speaking European countries. Among our 1236 participants, the use of contextual factors was widespread. Those relating to the therapeutic relationship (e.g., communication) and the patient characteristics (e.g., past experiences) are the most used. Meanwhile, contextual factors related to the healthcare providers' characteristics and their own beliefs are reported as less used. Despite high variability, respondents suggested contextual effects contribute to approximately half of the overall effect in healthcare and were perceived as more effective on children and elderly adults. Conceptual variations that exist in the literature are also present in the way healthcare providers consider contextual effects. Interestingly, there seems to be common ground on how physiotherapists, nurses and physicians use different contextual factors. We can also see that although there are similarities in usage, there seems to lack both an epistemological as well as an ethical common ground.

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Background

Several reasons can explain treatment improvement. Kleijnen[1] and, more recently, Wampold suggest grouping these reasons into three categories: "natural" effects, specific effects and contextual effects[2]. The so-called "natural" effects are effects that occur spontaneously, due to the dynamics of the condition itself, including the cyclic evolution of symptoms and regression to the mean, without any link to the strategies put in place. These effects are estimated in clinical trials with no-treatment groups[3]. Specific effects are the effects inherently due to a medication or treatment. In the case of medication, they are related to the active pharmacological substance. Clinical trials have been thought out to test these specific effects. They are observed when compared to placebos in randomised clinical trials[3].

Finally, contextual effects are those obtained within the context of the healthcare interaction. This includes behavioural, cognitive and emotional care provided by the therapist[4,5]. Some authors use the term contextual effects as a substitute for placebo effects[4] while others use the term more broadly, including all behavioural, cognitive or emotional care provided[2]. Lastly, an even broader definition exists, including all non-specific effects[6] : i.e. placebo effects, natural history and regression to the mean. This definition is particularly used in studies aiming to determine effect sizes of these categories. Regardless of these, if not simply semantic, conceptual variations, contextual factors (CFs) play a part in patient expectations, the symbolic meaning of a healing setting or the relationship between the healer and the patient[7], influencing non-specific effects by different biological, psychological and social factors.

Although clinical research has aimed to justify treatment use through evaluating specific effects, non-specific effects (i.e., contextual and "natural"

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effects as defined by Wampold) also contribute significantly to patient improvement. As an example, a recent meta-analysis showed that, across all conditions, half (0.54, 95%CI 0.46 to 0.64) of the overall treatments' effects could be attributed to contextual effects[8]. For osteoarthritis, this proportion was closer to 75% (0.75, 95%CI 0.24 to 0.68)[6] and for fibromyalgia around 60% (0.60, 95%CI 0.56 to 0.64)[9]. These high proportions justify the need to understand them better.

Although the proportion of contextual effects attributable to placebo effects is still unclear[10,11], Hafliðadóttir et al. showed that the proportion of the treatment effect attributable to context was closely influenced by placebo effects[8]. Interestingly, research has shown that CFs can be used as triggers for placebo and nocebo effects[7,12]. Therefore, we could expect a positive impact on healthcare outcomes if healthcare providers (HCPs) optimise the use of CFs. This implies that HCPs should be aware that placebo effects are part of everyday care, and that CFs lead to maximised placebo effects and minimised nocebo effects[13,14]. However, it is unclear what HCPs currently know about CFs and, more importantly, if and how they consciously use them in their everyday clinical activities. However, before training HCPs to maximise placebo effects, we need a better understanding of how CFs are currently used across professions. This would allow for a more practice-based education of HCPs, as well as serve as a screening of potential unreasonable use.

Initial studies regarding the use of placebo effects or CFs have been conducted in Italy on specialised physiotherapists[15–17], nurses[18] and nursing students[19]. In the Netherlands, a survey focused on nurses and general HCPs[20]. Several studies were also conducted on surgeons both in the United-Kingdom[21,22] and Sweden[23]. These studies, including samples

of 100 to 791 respondents, show that HCPs have some knowledge regarding contextual effects and believe they are effective on healthcare outcomes. The percentage of HCPs that deliberately used CFs was estimated to be 52% for physiotherapists[17] and 53% among nurses[20]. When asked what CFs they believed to be most effective in generating placebo or nocebo effects, respondents put forth the therapeutic relationship and patient expectations in Bisconti et al.[15]. Whereas in Rossettini et al.'s sample[17] they added the patient-centred approach Whether it was nurses or physiotherapists, the factors believed to be less effective were those linked to the HCP[17,18].

These preliminary results indicate that it is likely that HCPs use CFs without specifically labelling them as such. This form of empirical use is forged through clinical practice and through professional know-how learnt before graduating. These surveys mainly focus on specific professions (physiotherapists, nurses, surgeons). However, it is conceivable that distinct health professions perceive the relative importance of CFs differently[24]. Various factors, such as the diverse nature of their activities, the selective processes to access the studies or even the perception of their discipline's epistemology, could influence HCPs' views of CFs. Therefore, comparisons across different healthcare professions would be of interest. The main objective of this study was to evaluate the knowledge and explore the use of CFs among various healthcare professionals and last year students in France and French-speaking Belgium, and Switzerland. Secondly, our goal was hypothesis-generating, to initiate further research into explaining and characterising CFs use across HCPs.

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Methods

Study design

To meet this study's objectives, we conducted a cross-sectional observational study on a non-probabilistic convenience sample. Ethical approval was obtained from the local ethics committee for research in the Grenoble-Alpes University (CERGA) on 07/12/2020 with IRB : CERGA-Avis-2020-2.

Participants and setting

We surveyed HCPs from European French-speaking countries (France, Switzerland and Belgium). Our participants were required to be currently employed in clinical activities. As there is a broad definition of which professions involved in healthcare are considered HCPs, we based our selection on the French public health law[25].

As a result, our study targeted:

a) HCPs and students in their last year of teaching in the following professions: medical doctors, midwives, dentists, pharmacists, nurses, physiotherapists, occupational therapists, psychomotor therapists, speech therapists, nursing assistants, radiographers, nurse assistants, and orthoptists.

b) Practising or studying in a General Data Protection Regulation (GDPR) compliant country; and

c) Understood the French language.

Questionnaire development and validity testing

We searched the literature for questionnaires investigating contextual factor use in HCPs that could be adapted in our study and found three[16–18]. However, they were targeted only at physiotherapists or nurses and were

172 therefore not completely suitable for use in this study. Therefore, relying on
173 these questionnaires, we created a more generic, questionnaire suitable for all
174 professions.

175 To check the face and content validity, we ran cognitive interviews[26]
176 through video-calls due to the sanitary restrictions in place at the time. During
177 this step, interviewees were invited to complete the questionnaire while reading
178 and thinking aloud. Meanwhile, the interviewer filled another copy out based on
179 oral justifications given by the participants. Interviewers can probe the
180 understanding of the questions to test the content validity of the questionnaire.
181 They are a robust way of testing this as we can observe how the survey is
182 handled and the cognitive process behind its completion[27]. Face validity was
183 assessed by observing usability and technical functionality through the screen
184 sharing of the interviewees. One person from each profession was interviewed
185 as well as one student in a medical profession, one in a nonmedical profession
186 and one in a pharmaceutical profession. They were recruited through the
187 professional networks of the authors. Before the interview, an email containing
188 the consent form and information about the study was sent to the participants.
189 The data from the cognitive interviews were anonymized.

190 In addition, the questionnaire was reviewed by an expert committee
191 composed of a panel of 4 experts, with both researchers and clinicians (G.R.,
192 A.K. and N.P.), with expertise in the field of placebo studies and/or survey-
193 based research.

194

195 **Questionnaire description**

196 The questionnaire, available in French and a forward-translated English
197 version in the supplementary materials 1-3, was divided into three parts:

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knowledge of contextual effects, voluntary use of CFs, and socio-demographics.

Participants began with five closed questions about their knowledge on what contextual effects are. First, respondents used 5-point Likert scale to self-assess their level of knowledge and then the estimated influence these CFs have on their practice. Then, they were asked about the definition, parameters, impact, and mechanisms of contextual effects through closed-ended questions.

In the second part of the questionnaire, participants specify their active use of these effects, and their representations of CFs in their care with 4 closed questions. We first asked to evaluate the perceived importance of several CFs on a linear scale ranging from 0 (no impact on healthcare outcomes) to 100 (fundamental impact on healthcare outcomes). Participants then reported their frequency of intentional use for 12 example CFs identified from literature reviews[4,7] (for example, "Have you ever used titles or status, real or not, to improve the clinical outcome of your care?" followed by the question "how often" if the reply was positive). Respondents were asked about their perceptions of the proportion of the overall effect of care attributable to contextual effects according to patient age, gender, and symptomatology on a scale of 0% to 100%. Finally, we asked participants about their conditions for using CFs. The question was formulated as such: "After having completed the following questionnaire, do you use CFs?" and could be answered "Yes", "No, but I plan to", or "No". To all respondents that didn't answer "No", we asked for their motivations for using CFs. Adaptive questioning reduced the length of this section of the questionnaire. A definition of contextual effects was reminded on pages 3 and 8 of the questionnaire to obtain informed responses and reduce the disparity between participants over lexical discrepancies they could have.

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The third part surveys demographic data. Participants provided information on their status, their health disciplines, their ages, and the conditions of their practice.

Respondents were not able to review and change their answers between pages of the survey. Only one question (definition of Contextual Effects) had a randomization of items. Incomplete questionnaires were not registered.

Recruitment process

This survey was open and self-administered and recruited during two periods of time. The first spread between the 15th of February 2021 to the 1st of April, and the second from the 6th of July 2021 to the 1st of October 2021. LD and EBB distributed the link to the questionnaire by emailing all communication departments of hospitals associated with universities, several healthcare schools and institutes, and health and social institutions available (public information in France). Communication regarding the study was also conducted on social networks with professional and student associations or unions of various professions. This started a snowballing recruitment process as participants were invited to share the survey.

Due to the recruitment process, participants in this study formed a non-probabilistic convenience sample. This does not allow for the calculation of response rates, nor does it offer generalisations about the wider HCP population. In addition, the process was based on voluntary participation without any incentive.

Data collection procedure

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The questionnaire was encoded on Sphinx Online (www.sphinxonline.com) in conformity with the General Data Protection Regulation of the European Union. When participants click on the link of the questionnaire, an information notice about the survey, data protection, and informed consent appear. Respondents give their consent to participate by clicking on "next".

Data was anonymous as we collected no cookies, no IP check, no log file analysis, no registration. Data collected were anonymous and non-identifiable. All data generated by this research project was stored in compliance with GDPR regulations.

Statistical analysis

Survey data were downloaded from Sphinx into R software with a compatible database.

Because we were in an exploratory phase, we collected numerous potential predictors of the use of CFs. The absence of a single outcome of interest has three direct implications for inferential statistical analysis:

First, as the p-value is the probability of getting a test statistic at least as extreme as what was observed if the targeted null hypothesis is true, this last point is mandatory for the statistical test to be relevant. If the null hypothesis of no association is indeed true in the context of randomisation, it cannot be the case in the context of observational data.

Second, as no minimal clinically important difference is stated, no *a priori* sample size has been determined. That is, the power of each predictor test is unknown. This is problematic for both "negative" and "positive" results. In the context of low power, it is well admitted that absence of evidence is not

evidence of absence, but it is less known that a significant result is subject to overestimation or direction error (referred respectively as Magnitude and Sign errors by Gelman and Carlin[28]). This means that any result obtained in a context of possible low power is uninterpretable.

Lastly, as every predictor is equally of interest to the authors, every association should be tested, leading to an inflation of the alpha significance level. One possibility would be to adjust for the multiple comparisons, but this does not alleviate the power issue discussed above.

For these reasons, we did not rely on statistical significance to discuss the presence or absence of association. Instead, we discussed graphical representation, whether a pattern emerges and whether the hypothesis is worth testing in future studies.

Results

We recruited 1236 participants, which were all analysable since incomplete answers were not registered. The median time of completion was 11"49'. A little under half (49.8% n=616) of our sample accessed our questionnaire through e-mail communications, and 38.6% (n=477) through social media.

Sample description

Through a period of five months, we recruited a sample of 1236 HCPs, of which 80.5% (n=995) were professionals, and 19.5% (n=241) were final-year healthcare students. Among professionals, physiotherapists, nurses and medical doctors were the main professions represented with respectively 33%, 20% and 20%. For students, physiotherapist students, medical students and speech therapists were most represented with respectively 31%, 20% and 11%.

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The distribution of our population is detailed in table 1. Among the professionals, private practice, and public employees (42% and 39%, respectively) were the most represented.

Table 1: Demographic characteristics of the respondents. [1] n (%); [2] Median (IQR)

Knowledge regarding contextual effects and contextual factors

Our sample estimated their knowledge of contextual effects to be average (3.08 out of 5 with a SD of 0.89), and that this knowledge had a moderate impact on their clinical practice (3.74 out of 5 with a SD of 0.92). When asked for the definition of contextual effects, we presented our sample with several definitions from the literature: of an inert treatment, the spontaneous course of the disease, a therapeutic encounter, or a placebo/nocebo effect. The two most represented unique choices of our participants were for 67% (n=833) the definition of placebo or nocebo effects, and 21% (n=262) selected the definition of the therapeutic encounter.

We then asked our sample what influences contextual effects: 95% of the sample agreed that the therapeutic relationship was an influencing factor. The characteristics of the clinical setting, of the therapist and of the patient were influencing factors for 86%, 85% and 82%, respectively. Lastly, the characteristics of the treatment were least consensual as only 68% of our sample thought they influenced contextual effects.

Several specific situations were then presented where we asked if contextual effects were present. We suggested situations when a non-pharmacological treatment is administered (such as manual therapy), when the consultation takes place at the home of a patient, a home-visit (i.e. the consultation does not take place in a specialised medical environment), when

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no treatment is delivered during the consultation, when the consultation takes place by means of telecare, when the patients self-medicate (i.e. no HCP is involved in the administration). Although all these situations have the potential to generate contextual effects, of these propositions, only 53% of the panel answered there were contextual effects when the patients self-medicated. The results for the other propositions are presented in Figure 1.

Figure 1: Specific situations with contextual effects (multiple responses variables, n=1236). Participants were asked whether the following situations were subject to contextual effects: when the treatment was non-pharmacological, in the case of home-visits (i.e. did not take place in a medical setting), when there was no-treatment (i.e. an examination with no prescription), in the case of telecare (i.e. there was no physical presence of a therapist) or when the patients self-medicated (i.e. there was no direct health-encounter) Figure shows the percentage of people who answered "yes".

Lastly, we asked about the mechanisms that were responsible for contextual effects. This question allowed for multiple responses and showed that 92% of the sample believed psychological mechanisms were implicated, 81% for suggestions, 67% for conditioning and only 40% for biological mechanisms. For 43% of our sample, these effects were the effect of self-healing processes, and 23% considered them to be due to natural evolution. Lastly, 22% believed other non-identified immaterial entities, such as energies or spirituality, were responsible for these effects. Figure 2 represents these findings.

Figure 2: Mechanisms behind contextual effects (multiple responses variables, n=1236).

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Perception of effect size and contextual factor relative importance

Participants were asked to rate on a 100-point scale the weight of several individual CFs to the global contextual effect. The most effective contextual factor, according to our sample, was the therapeutic relationship, followed closely by verbal and non-verbal communication. The CFs related to the patient, such as past experiences and their beliefs and expectations, came next. Physical contact as well as the treatment price were the factors which were perceived as less potent closely followed by the CFs pertaining to the HCP, such as status or therapist expectations. The detailed results for this question are available in the Supplementary Material 4.

When asked to estimate the average effect size of CFs, our sample replied on average 50% of the total effect of treatment. We then suggested certain situations where the effect size of contextual effects could vary, such as when working with men or women, children, or older adults or when measuring subjective or objective symptoms. Figure 3 shows these results. Our panel seems to show no sensible difference between men and women. However, they perceive CFs to work more effectively on younger and older patients compared to average aged patients. There was also a belief that CFs had more of an influence on subjective symptoms rather than objective symptoms. However, these questions were all subject to heavy variability, as seen graphically by the distribution of answers.

Figure 3: Perceived proportion of effect attributable to contextual effects depending on patient gender, age, or nature of symptoms (n=1236). From top to bottom: in all conditions, among men, women, older adults, adults, children and on objective and subjective symptoms. Box plots were generated with Q1, Q2 and Q3 quartiles. Distribution is represented by probability density.

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Contextual factor use

When asked if they already voluntarily use CFs in their clinical activity, the large majority (91.7%, n = 1133) of the sample replied that they did, and 5% (n = 67) replied they did not, although they intended to do so in the future. Only 3% (n = 36) replied that they did not use CFs in their clinical activity.

The respondents were presented with a list of an example CFs and asked if they used this particular factor. For those replying yes, they were then asked the pace at which they had used this factor. Figure 4 presents the results of this question and supplementary material 5 shows the pace of use. We can see the most used CF is communication, declared by 95% of our HCP sample, followed by patient's past experiences used by 93% of clinicians interviewed. Indeed, the most used CFs are related to either the therapeutic alliance or the patient's characteristics. The least used CFs are those related to the HCP such as a colleague's reputation (52%), own reputation (35%) or one's status (doctor, professor, etc) (31%).

Figure 4: Contextual factor use (n=1236). Participants answered whether, yes or no, they voluntarily use each contextual factor.

Healthcare providers' motivation for using contextual factors

The last part of our survey took an interest in the motivations of the HCPs using contextual effects. This question allowed for multiple choices and showed that 83% of the sample actively used CFs to optimise care and 74% to improve patient satisfaction. Some situations were less consensual such as using CFs to limit undesirable effects of a treatment which only 43% declared or using CFs when in a therapeutic impasse which was justified by 32% of the sample. Lastly, 24% of the interviewed HCPs claim to use CFs to compensate for the lack of specific efficacy of a given treatment.

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Intra group comparison

During analysis, as stated in the introduction, we plotted CF use for each profession. Figure 5 shows, for each CF, the use in the three most represented professions in our sample (n>200): physiotherapists, nurses, and physicians, since the sample sizes are insufficient in other professions. The complete version of this data visualisation is available as supplementary material 6. From Figure 5, the use of CFs seems homogenous among physiotherapists, nurses, and physicians.

Figure 5: Use of each contextual factor for physiotherapists (n=400), nurses (n=246) and physicians (n=223).

Discussion

This study aimed to describe the voluntary use of CFs among healthcare professionals in France and French-speaking Belgium and, Switzerland. Through a web-survey, we led a cross-sectional observational study on a non-probabilistic convenience sample. We gathered 1236 replies, of which all were analysed. From our data, CFs use is widespread. CFs related to the therapeutic relationship (e.g., communication) and the patient (e.g., patients' past experiences or patients' beliefs) are the most used. Meanwhile, CFs regarding the HCP's status or reputation and their own beliefs and past experiences are reported to be less used. Respondents suggested that contextual effects contribute to approximately half of the overall effect in healthcare, although a multimodal distribution showed high variability in responses. Contextual effects were perceived to be more effective on children and elderly adults and were perceived to be similar for men and women. For our participants, subjective symptoms are more susceptible to contextual effects than objective symptoms.

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Comparing our results regarding conceptual definitions to previous studies, we notice that, to the best of our knowledge, we are in line with other surveys also showing much diversity in perceptions of definitions[15,17–19,23]. We can find more homogenous answers but only when asking if participants agreed to their suggested definition[21,22]. This is quite different from asking to choose a definition among a set number of propositions as done in our study. Thus, the heterogeneity could be due to the fact participants sometimes refer to a broad definition of contextual effects and sometimes restrict their definition to placebo effects. As such, this could reflect the conceptual variations among experts outlined in the introduction section[29,30].

Originally, we also wanted to examine whether participants perceived the omnipresence of contextual effects in care. To this end, we chose to question several situations where contextual effects were present, but which differed from a usual healthcare encounter. This allowed us to situate our question within a clinical frame to obtain responses less influenced by the question framing. For example, we asked our participants whether they thought contextual effects took place during telecare instead of asking if they existed when the HCP was not physically present. This could have introduced other differentiation factors than those we aimed to investigate (e.g. not the physical presence but the use of technology in our previous example). However, our pre-testing did not lead us to believe this was the case. Interestingly, we can underline inconsistencies between answers on mechanisms and practical implications. As an example, whereas a large majority of participants declared contextual effects were due to psychological mechanisms and conditioning (Fig. 2), only 53% considered it was not necessary to meet a HCP for contextual effects to be present (Fig. 1). Suggesting that they did not understand those

454 psychological and conditioning mechanisms were not linked to the presence of
455 a HCP. These original results show that contextual effects are not well
456 understood all while their mechanisms seem to be known by most participants.
457 We found a much higher percentage of CF use (92% for communication)
458 than other surveys (52% for PTs[17] and 53% for nurses[20] for example). We
459 could hypothesise that presenting examples leads to a better illustration of the
460 underlying concepts and thus increases the perception of use. This could be
461 due to using numerous examples of specific CFs in our questions or due to
462 users' over-reporting.
463 Regarding the proportion of the overall effect attributable to contextual
464 effects, our participants were in line with recent literature[8] although we can
465 reasonably assume that they answered empirically. In fact, considering that the
466 majority (67%) of our sample defined contextual effects as placebo effects, this
467 assumption is quite probable. Similarly to other studies[15,17,18], our panel
468 suggested that the therapeutic alliance was the most impactful CF. Without
469 comparing to other CFs, recent published literature shows that the therapeutic
470 alliance can, in itself, have a clinically significant impact on outcomes[31]. Some
471 studies have highlighted that his viewpoint is shared by patients[32]. However,
472 and in contrast to previous findings[15,17–19], our panel showed a belief,
473 unseen-before in the literature, that the least effective CFs were linked to the
474 HCP and the treatment price. This could be interpreted considering cultural
475 specificities of how treatment prices are considered by the social systems in
476 place. Interestingly enough, the most used CFs were those that were perceived
477 as the most effective (linked to the relationship or the patient). However, CFs
478 linked to the therapist were perceived as moderately effective yet were amongst

the least used. This suggests that other reasons led our participants not to use them.

These reasons could be linked to the ethics of using CFs in clinical care. Looking closer at the question regarding reasons for the use of CFs, we can see that there is diversity in what some HCPs find acceptable. Although the motivations are quite broad, they show that HCPs seem to find it acceptable to use CFs in everyday clinical work. However, some motivations might be limited in terms of ethical acceptability. For instance, using CFs to compensate for the lack of a specific treatment efficacy seems questionable. A better demonstration of clinically meaningful effects in situations where CFs are optimised needs to be demonstrated. Our results support the need for ethical guidelines regarding the use of CFs preventing unreasonable use, as was previously hinted by expert committees[13,14].

Implications

Three main implications arise from these findings. Firstly, we can see that the conceptual variations that exist in the literature are also present in the way HCPs consider contextual effects. Secondly, there seems to be common ground on how physiotherapists, nurses and physicians use different CFs. Lastly, we can also see that although there are similarities in usage, there seems to lack both an epistemological (1 of 5 people answered that contextual effects resulted from immaterial entities such as spirits, energies, etc.) as well as an ethical (1 in 4 people saw CFs as a way to justify a treatment otherwise lacking specific effect) common ground.

Strengths and limitations

Regarding our study, we can outline a few strengths. Firstly, to the best of our knowledge, our study has the largest sample yet regarding

characterisation of CF use. This is mainly due to the recruitment strategy, which had broader inclusion criteria than other studies in the literature since we recruited all professions. Moreover, this is the first study examining the use of CFs in France and, more modestly, other European French-speaking countries. Another originality in this study is to have focused on harnessing placebo and nocebo effects through other means than placebo treatments, whose use is well described in the literature. We focused solely on CFs as enhancers of routine care and not on placebo treatments. This study is also one of the first to have questioned how HCPs perceived the effect size of contextual effects. Although the mean is close to what can be observed in meta-analyses when considering a broad definition of contextual effects, there is an important variance in responses. In some cases, the third quartile reaches up to 80% of the overall effect. These overestimations are not surprising as they are also present for many treatments, as shown, for example, in a survey where 87.7% of general physicians overestimated treatment effects and risks[33]. Lastly, another feature of this questionnaire was its usability for several professions allowing for comparisons between professions. Through pre-testing, we were able to use a questionnaire adapted to multiple professions. We also investigated all categories of CFs through a thorough list.

Even though our study design allowed the strengths mentioned above, it also led to some limitations. Firstly, as our observational study was retrospective, it shares the same bias as other retrospective studies and carries a risk of memory bias from respondents. Secondly, regarding the questionnaire administration, we had no way to determine the number of people who gave up on answering or the total number of people who were exposed to the questionnaire to calculate the participation rate. This could mask a potential

selection bias. Although our sampling strategy allowed for a large number of participants, our sample was heterogenous. It had a high proportion of physiotherapists and was constrained in professions such as dentists, surgeons, or nurse assistants. However, the main represented professions are also those who are the most numerous in French HCPs demographics. The same can be observed regarding the geographical localisations of our participants, which are almost exclusively practising in France. Thirdly, regarding the content of our questionnaire, asking about knowledge could have led our participants to have been biased in their responses later. Additionally, we did not check if the responses to questions measuring knowledge were correctly understood. In other surveys, this was done through the use of open-ended questions[20] asking for examples which could be verified for appropriateness.

Future research

Future research is needed, and the hope is that this exploratory study will inspire follow-up work. Regarding knowledge of contextual effects, qualitative studies (e.g., focus groups or semi-structured interviews) could deepen our knowledge about HCPs' understanding of these effects in routine care and better circumscribe inconsistencies in understanding among HCPs. This could also be completed by qualitative studies looking at how patients perceive effectiveness such as has been done with psychiatric inpatients[32]. Regarding the use of CFs in clinical practice, using the same questionnaire among all professions allows comparable results. Further investigation of CF uses among dentists, nurse assistants, or pharmacists, for example, could be of interest. Similarly, most studies regarding CF use are focused on European countries. More quantitative studies (e.g., surveys) are needed in extra-

Healthcare providers' use of contextual factors

European countries. This would help better understand if and how cultural determinants could influence HCPs' use of CFs. Furthermore, these studies would only look at the voluntary use of CFs, and qualitative studies are needed on lived experiences of HCPs to better understand their voluntary and involuntary CF use during their clinical reasoning and decision-making process. More diversity could also be sought out by looking at different categories of impairments (e.g. musculoskeletal, neurological, cardio-circulatory, etc.). This could show if some specific types of pathologies are more prone to HCPs using CFs. In line with this, quantifying the declaration bias of such questionnaires would be interesting to see if perceived use matches externally observed use. Finally, researches about CFs and healthcare have to be linked to the discussion about the epistemological foundations that underlie professional practices of each healthcare profession, such as done in psychology[34].

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574 **Conflict of interest**

575 The authors report no conflict of interest.

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579 **References**

580 1. Kleijnen J, de Craen AJ, van Everdingen J, Krol L. Placebo effect in double-
581 blind clinical trials: a review of interactions with medications. Lancet Lond
582 Engl. 1994;344: 1347–9. doi:10.1016/s0140-6736(94)90699-8

583 2. Wampold BE. Healing in a social context: The importance of clinician and
584 patient relationship. Front Pain Res. 2021;2. doi:10.3389/fpain.2021.684768

585 3. Ernst E, Resch KL. Concept of true and perceived placebo effects. BMJ.
586 1995;311: 551–3.

587 4. Di Blasi Z, Harkness E, Ernst E, Georgiou A, Kleijnen J. Influence of context
588 effects on health outcomes: a systematic review. Lancet Lond Engl. 2001;357:
589 757–62.

590 5. Di Blasi Z, Kleijnen J. Context effects. Powerful therapies or methodological
591 bias? Eval Health Prof. 2003;26: 166–79. doi:10.1177/0163278703026002003

592 6. Zou K, Wong J, Abdullah N, Chen X, Smith T, Doherty M, et al. Examination of
593 overall treatment effect and the proportion attributable to contextual effect in
594 osteoarthritis: meta-analysis of randomised controlled trials. Ann Rheum Dis.
595 2016;75: 1964–1970. doi:10.1136/annrheumdis-2015-208387

596 7. Rossettini G, Carlino E, Testa M. Clinical relevance of contextual factors as
597 triggers of placebo and nocebo effects in musculoskeletal pain. BMC
598 Musculoskelet Disord. 2018;19: 27. doi:10.1186/s12891-018-1943-8

599 8. Hafliðadóttir SH, Juhl CB, Nielsen SM, Henriksen M, Harris IA, Bliddal H, et
600 al. Placebo response and effect in randomized clinical trials: meta-research with
601 focus on contextual effects. Trials. 2021;22: 493. doi:10.1186/s13063-021-
602 05454-8

603 9. Whiteside N, Sarmanova A, Chen X, Zou K, Abdullah N, Doherty M, et al.
604 Proportion of contextual effects in the treatment of fibromyalgia—a meta-
605 analysis of randomised controlled trials. Clin Rheumatol. 2017;37: 1375–1382.
606 doi:10.1007/s10067-017-3948-3

10. Vase L, Petersen GL, Riley, 3rd JL, Price DD. Factors contributing to large analgesic effects in placebo mechanism studies conducted between 2002 and 2007. Pain. 2009;145: 36–44. doi:10.1016/j.pain.2009.04.008

11. Hróbjartsson A, Gøtzsche PC. Placebo interventions for all clinical conditions. Cochrane Database Syst Rev. 2010; CD003974. doi:10.1002/14651858.CD003974.pub3

12. Testa M, Rossettini G. Enhance placebo, avoid nocebo: How contextual factors affect physiotherapy outcomes. Man Ther. 2016;24: 65–74. doi:10.1016/j.math.2016.04.006

13. Evers AWM, Colloca L, Blease C, Annoni M, Atlas LY, Benedetti F, et al. Implications of placebo and nocebo effects for clinical practice: Expert consensus. Psychother Psychosom. 2018;87: 204–210. doi:10.1159/000490354

14. Evers AWM, Colloca L, Blease C, Gaab J, Jensen KB, Atlas LY, et al. What should clinicians tell patients about placebo and nocebo effects? Practical considerations based on expert consensus. Psychother Psychosom. 2020; 1–8. doi:10.1159/000510738

15. Bisconti M, Venturin D, Bianco A, Capurso V, Giovannico G. Understanding contextual factors effects and their implications for italian physiotherapists: Findings from a national cross-sectional study. Healthc Basel Switz. 2021;9. doi:10.3390/healthcare9060689

16. Rossettini G, Geri T, Palese A, Marzaro C, Mirandola M, Colloca L, et al. What physiotherapists specialized in orthopedic manual therapy know about nocebo-related effects and contextual factors: Findings from a national survey. Front Psychol. 2020;11: 582174. doi:10.3389/fpsyg.2020.582174

17. Rossettini G, Palese A, Geri T, Fiorio M, Colloca L, Testa M. Physical therapists' perspectives on using contextual factors in clinical practice: Findings from an Italian national survey. PloS One. 2018;13: e0208159. doi:10.1371/journal.pone.0208159

18. Palese A, Cadorin L, Testa M, Geri T, Colloca L, Rossettini G. Contextual factors triggering placebo and nocebo effects in nursing practice: Findings from a national cross-sectional study. J Clin Nurs. 2019;28: 1966–1978. doi:10.1111/jocn.14809

19. Cadorin L, Rossettini G, Testa M, Geri T, Palese A. The awareness of contextual factors, placebo and nocebo effects among nursing students: Findings from a cross-sectional study. Nurse Educ Pract. 2019;42: 102670. doi:10.1016/j.nepr.2019.102670

20. Smits RM, Veldhuijzen DS, van Middendorp H, van der Heijden MJE, van Dijk M, Evers AWM. Integrating placebo effects in general practice: A cross-sectional survey to investigate perspectives from health care professionals in the netherlands. Front Psychiatry. 2021;12: 768135. doi:10.3389/fpsyt.2021.768135

21. Baldwin MJ, Wartolowska K, Carr AJ. A survey on beliefs and attitudes of trainee surgeons towards placebo. BMC Surg. 2016;16: 27. doi:10.1186/s12893-016-0142-5

22. Wartolowska K, Beard DJ, Carr AJ. Attitudes and beliefs about placebo surgery among orthopedic shoulder surgeons in the United Kingdom. PloS One. 2014;9: e91699. doi:10.1371/journal.pone.0091699

23. Rosén A, Sachs L, Ekdahl A, Westberg A, Gerdhem P, Kaptchuk TJ, et al. Surgeons' behaviors and beliefs regarding placebo effects in surgery. Acta Orthop. 2021;92: 507–512. doi:10.1080/17453674.2021.1941627

24. Annoni M, Buergler S, Stewart-Ferrer S, Blease C. Placebo studies and patient care: Where are the nurses? Front Psychiatry. 2021;12: 591913. doi:10.3389/fpsyt.2021.591913

25. Code de la santé publique ; quatrième partie : Profession de santé : Articles L4001-1 à L4444-3). Available: https://www.legifrance.gouv.fr/codes/section_lc/LEGITEXT000006072665/LEGISCTA000006125348/#LEGISCTA000006125348

26. Shafer K, Lohse B. How to conduct a cognitive interview: A nutrition education example. US Dep Agric Natl Inst Food Agric. 2005.

27. Drennan J. Cognitive interviewing: verbal data in the design and pretesting of questionnaires. J Adv Nurs. 2003;42: 57–63.

28. Gelman A, Carlin J. Beyond power calculations: Assessing type S (sign) and type M (magnitude) errors. Perspect Psychol Sci J Assoc Psychol Sci. 2014;9: 641–51. doi:10.1177/1745691614551642

29. Blease C, Annoni M. Overcoming disagreement: a roadmap for placebo studies. Biol Philos. 2019;34: 1–26.

30. Kelley JM. Lumping and splitting: Toward a taxonomy of placebo and related effects. Int Rev Neurobiol. 2018;139: 29–48. doi:10.1016/bs.irn.2018.07.011

31. Del Re AC, Flückiger C, Horvath AO, Wampold BE. Examining therapist effects in the alliance-outcome relationship: A multilevel meta-analysis. J Consult Clin Psychol. 2021;89: 371–378. doi:10.1037/ccp0000637

32. Locher C, Mansour R, Koechlin H, Büchi S. Patient-appraised beneficial moments during inpatient psychiatric treatment. BMC Health Serv Res. 2020;20: 734. doi:10.1186/s12913-020-05617-4

33. Treadwell JS, Wong G, Milburn-Curtis C, Feakins B, Greenhalgh T. GPs' understanding of the benefits and harms of treatments for long-term conditions: an online survey. BJGP Open. 2020;4. doi:10.3399/bjgpopen20X101016

34. Gaab J, Blease C, Locher C, Gerger H. Go open: A plea for transparency in psychotherapy. Psychol Conscious Theory Res Pract. 2016;3: 175–198. doi:10.1037/cns0000063

Table 1 Click here to access/download;Figure;Table1.docx

Characteristic	Professional N = 995 (80.5%)	Student N = 241 (19.5%)	Total N = 1236
Gender[1]			
Other	2 (0.2%)	2 (0.8%)	4 (0.3%)
Female	679 (68%)	183 (76%)	862 (70%)
Male	314 (32%)	56 (23%)	370 (30%)
Age[2]	38 (30, 50)	24 (23, 26)	34 (26, 47)
Profession[1]			
Physiotherapist	326 (33%)	74 (31%)	400 (32%)
Nurse	201 (20%)	22 (9.1%)	246 (20%)
Physician	197 (20%)	49 (20%)	223 (18%)
Other	100 (10%)	29 (12%)	129 (10%)
Midwife	38 (3.8%)	16 (6.6%)	54 (4.4%)
Speech Therapist	11 (1.1%)	27 (11%)	38 (3.1%)
Radiographer	28 (2.8%)	8 (3.3%)	36 (2.9%)
Pharmacist	21 (2.1%)	11 (4.6%)	32 (2.6%)
Nurse Assisstant	23 (2.3%)	0 (0%)	23 (1.9%)
Dentist	19 (1.9%)	3 (1.2%)	22 (1.8%)
Occupational	16 (1.6%)	2 (0.8%)	18 (1.5%)
Surgeon	8 (0.8%)	Non-Applicable	8 (0.6%)
Psychomotor therapist	7 (0.7%)	0 (0%)	7 (0.6%)
Orthoptist	0 (0%)	0 (0%)	0 (0%)
Activity[1]			
Private practice	422 (42%)		
Public sector employee	391 (39%)		
Private sector employee	120 (12%)		
Mixed	55 (5.5%)		
Other	7 (0.7%)		

[1] n (%); [2] Median (IQR)

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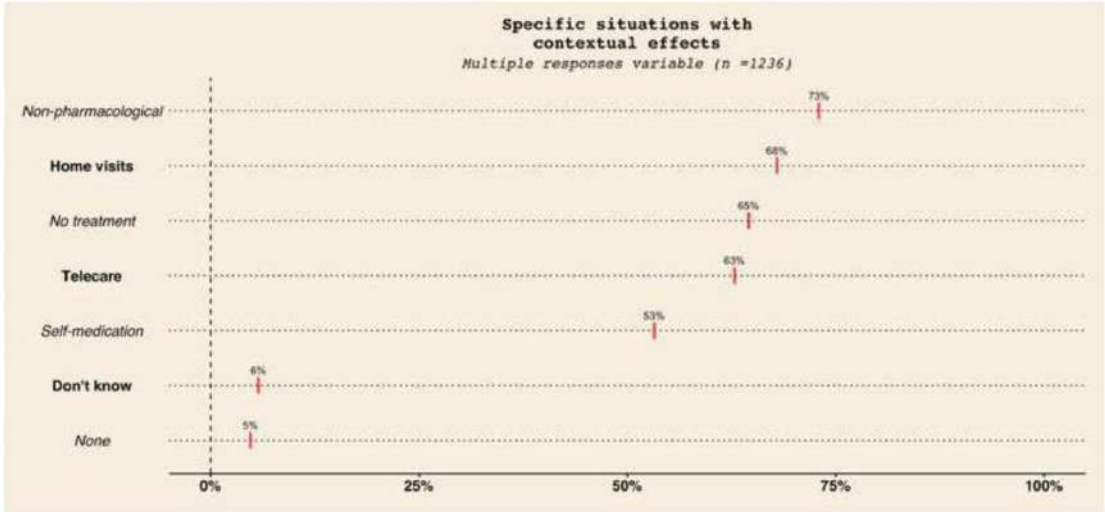

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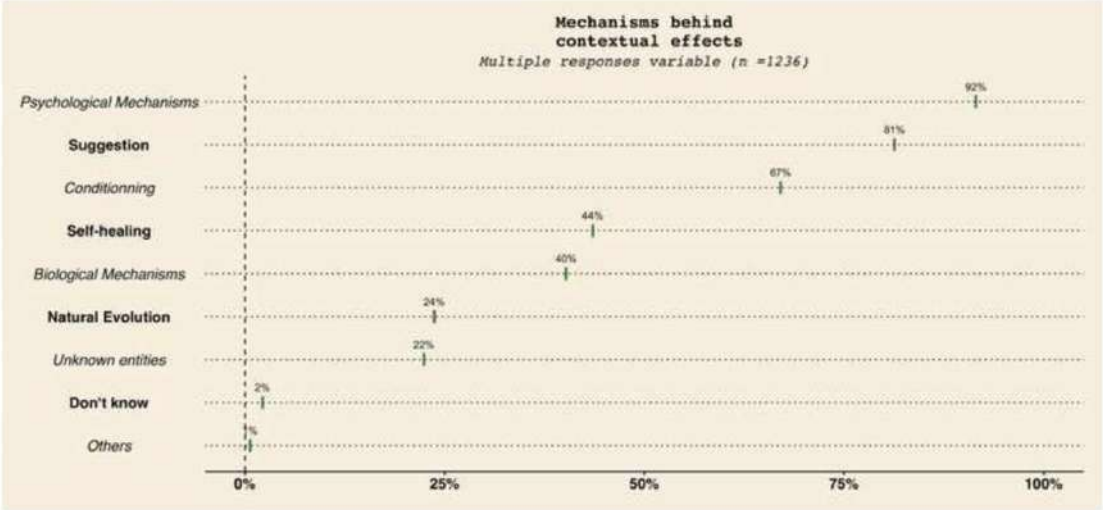

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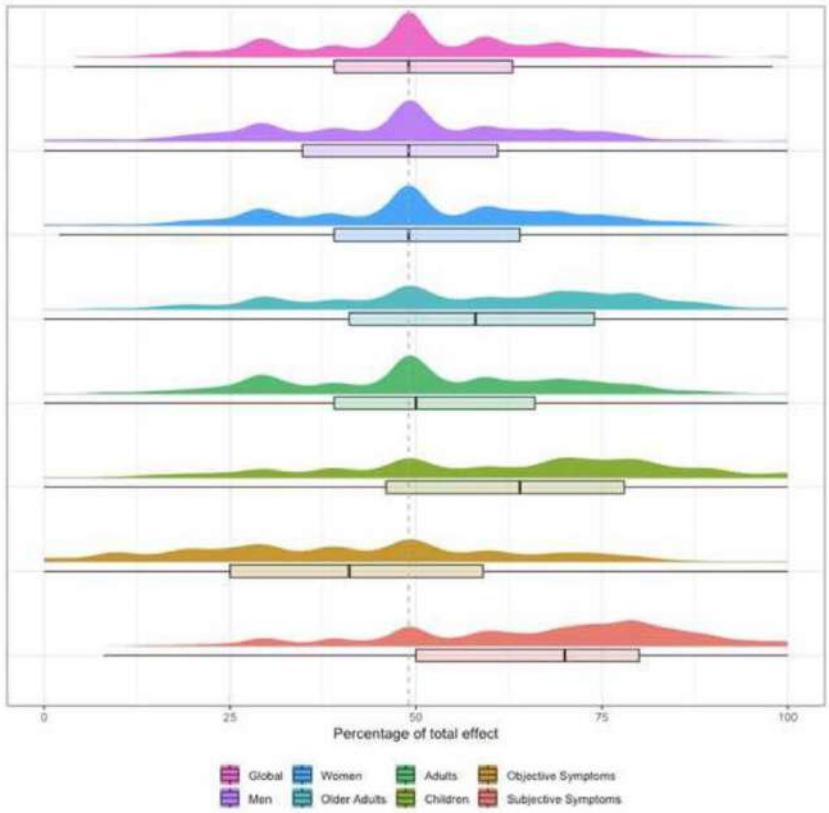

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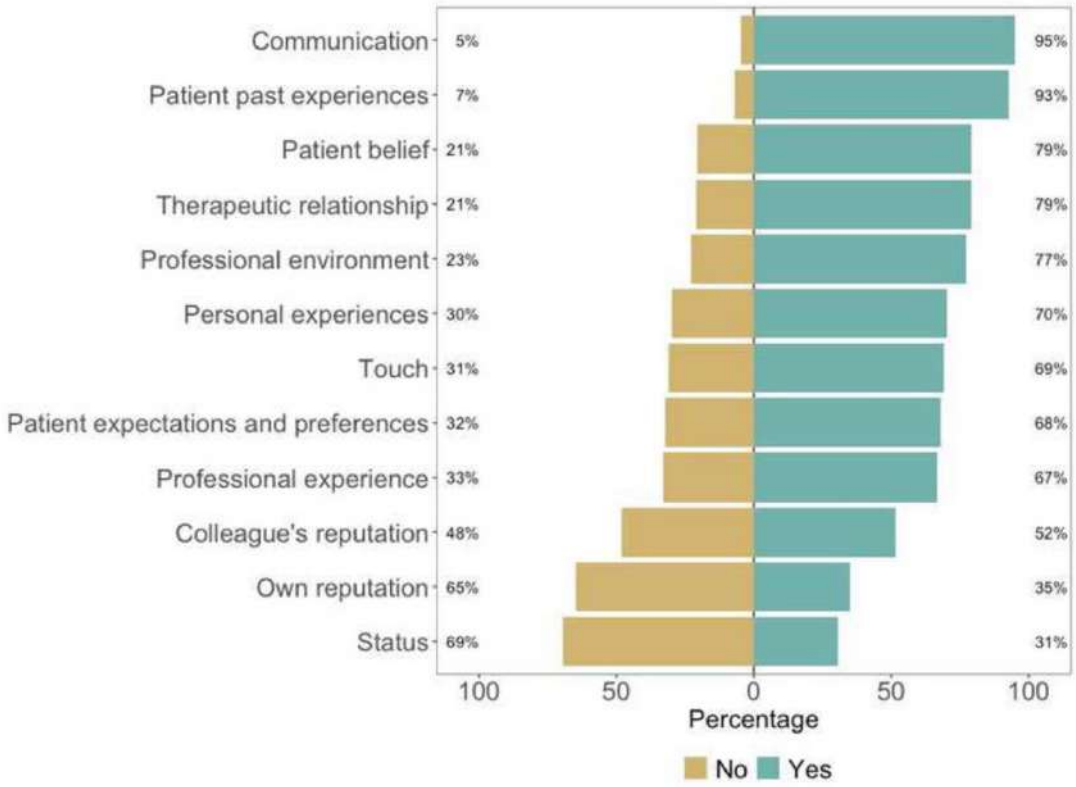

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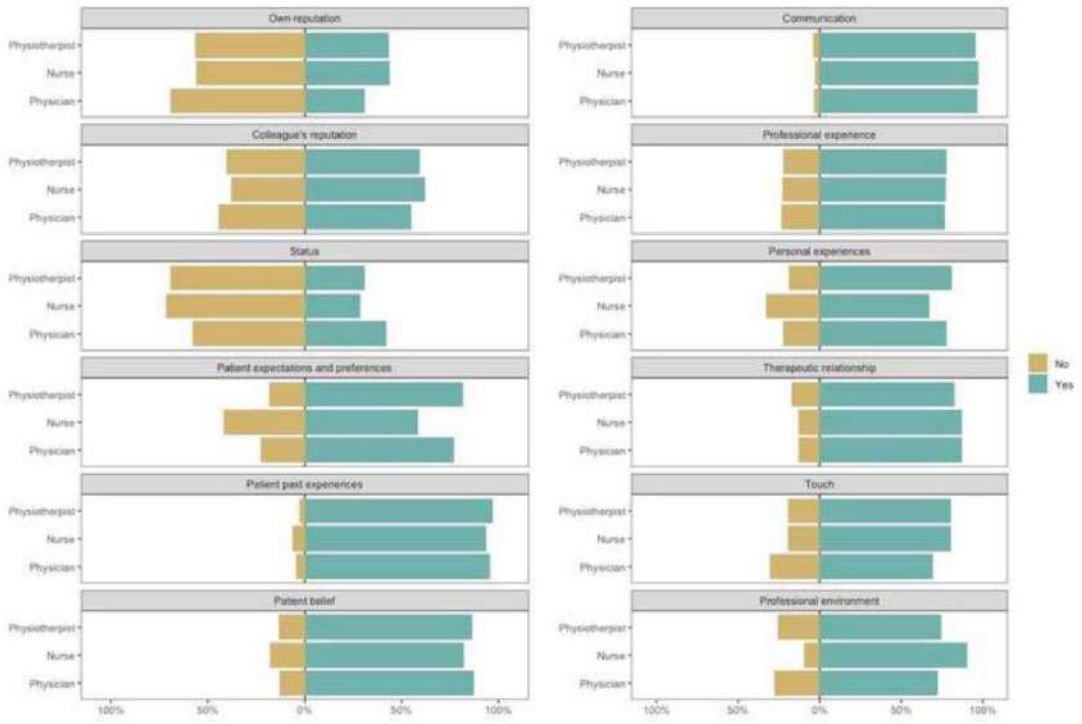


PART THREE: GENERAL DISCUSSION

4. SUMMARY OF RESULTS

This thesis contributed original results in three separate research studies. The first study (2.2) was a randomised controlled study comparing the effectiveness of DP and OLP. The major novelty of the study is that it is the first to test for non-inferiority between the two placebo interventions. The second study (2.3) was a qualitative study exploring the acceptability of DPs and OLPs. The originality of this study was in examining and contrasting participants' views on both placebo treatments. Finally, the third study, presented in 3.2, was a web-based survey in French-speaking countries investigating the use of CFs in clinical settings. Compared with previous questionnaires evaluating CF-use, it gathered the largest sample of participants including physiotherapists and was administered across a variety of healthcare professions. This allowed a comparison of how different professions in French-speaking countries routinely consider CFs in care.

Combined, the results showed that the acceptability of OLPs may not be as straight forward as initially thought. Although DPs are predominantly perceived to be unethical by ethicists, not all participants in our study viewed them negatively. To some, effectiveness was the main deciding factor in deeming a treatment to be acceptable. Our participants trusted the healthcare providers to act in their best interest and to be knowledgeable enough to choose the right treatment. However, for others, this was not the case. They focused more heavily on respect for their autonomy and strongly voiced a preference not to be lied to, disregarding effectiveness as a sufficient justification for deception. Furthermore, building on this, we found that, in our trial, OLPs performed as well as DPs provided the former was sufficiently explained. This new information, once replicated and confirmed, might change the acceptability of both placebo treatments. However, it was not clear in our study if the placebo treatments outperformed the no-treatment condition. Adding to this there were no comparisons with other specific kinds of treatments that may benefit patients.

There are also limitations with the findings including the small sample size in the explorative qualitative study.

Beyond DPs and OLPs, study 4 suggested that, in a clinical setting and as a potential means to harness placebo effects, CF use may be even more prevalent than placebo use as reported in Linde et al.'s meta-analysis (Linde et al., 2018). Moreover, use of CFs appeared to be widespread across all professions with similar usage. The most common CF reportedly used to elicit placebo effects was communication. More generally, factors grouped in the therapeutic relationship and patient characteristics categories were the most frequently reported to be used. However, there appeared to be divergent ethical and epistemological reasoning behind CF usage among survey participants.

Section 1.5 advanced two questions (Question 1 [Under which conditions should placebo treatments be used in physiotherapy?] & Question 2 [How are contextual factors used in physiotherapy?]) to explore how placebo studies could contribute to physiotherapy practice. This thesis sought to offer new contributions both to placebo studies and to research on physiotherapy practice. These contributions will now be discussed separately before summarizing answers to both questions. Finally, future research directions will be discussed.

4.1. CONTRIBUTIONS TO PLACEBO STUDIES

4.1.1. GOING FURTHER WITH PLACEBO TREATMENTS

The results of these studies offer new contributions to placebo studies. When Allen defended the use of DPs, he made two assumptions that can be considered conventional wisdom in placebo studies literature. Firstly, he supposed that for a placebo to have an effect, deception was required, and second he supposed that it was possible for placebo treatments to have actual therapeutic benefits (Allen, 2019). While recognizing that these points were controversial, he nonetheless built his defence of DPs on these premises.

Our results challenge the first premise suggesting that there may not be any loss of effectiveness when using an OLP rather than a DP. They add to other findings which show that OLPs could be substitutes for DPs (Disley et al., 2021; Kube et al.,

2020; Locher et al., 2017; Mundt et al., 2017). Therefore, recalling Annoni's claims (cited in section 2.1.3): "it is still unclear whether open-label placebos are as effective as DPs, or whether they imply a trade-off between veracity and effectiveness" (Annoni, 2018b), at least on the strength of Article 2 combined with the results of other studies, it seems that OLPs may not require to compromise effectiveness for truthfulness.

It is fundamentally important to dwell on Allen's second point before any clinical use of placebo treatments is recommended. Indeed, results of study 2 are equivocal on this matter: the placebo conditions did not perform better than the no-treatment condition at T1 but did at T2. Indeed, this showed that the sequence order had a significant impact on the placebo effect which renders the cross-over difficult to interpret. Returning to the literature, questions about the placebo effect's effect size are not new. Several meta-analyses have been conducted on the topic concluding the placebo effect is variable, showing effects that range from small but significant to large. Contributing to its variability, placebo mechanism studies, patient-reported outcomes and continuous subjective outcomes such as pain provide higher placebo effects (Hróbjartsson & Gøtzsche, 2001, 2010; Vase et al., 2002, 2009). Results on OLPs seem to give similar conclusions when compared to no-treatments conditions (Charlesworth et al., 2017; von Wernsdorff et al., 2021).

However, to obtain more definitive conclusions about whether OLPs are as effective as DPs, several shortcomings in placebo research must first be addressed. Currently, there remain important ongoing, but often overlooked, points of discussion concerning the methodology of research conducted into OLPs: Blease et al. suggest "although these issues are intricate, they are not merely academic: without due diligence to conceptual, and as a consequence, methodological considerations, OLP effect sizes may be over- or underestimated" (C. R. Blease et al., 2019). For example, depending on the control (or worse, lack of control) used to evaluate the effectiveness of OLPs, results will vary. This is one strength of study 2's design, discussed in depth in Article 1, as the study included both a control condition (the DP group) and a no-treatment condition. However, although the cross-over nested in the parallel design allowed to include all three conditions and within subject control, it also proved difficult to interpret the comparison of the placebo conditions with no-treatment, as

discussed above. Thus, comparing the placebo treatments to no-treatment did not allow to draw clear conclusions in our trial.

Another concern is lack of blinding of the investigators and participants. Failure to blind may lead to non-intentional inflation of OLP effects via researcher degrees of freedom and increase the risk of responder bias (C. Blease et al., 2023). This is one limitation that should be considered when interpreting the results discussed in Article 2. Neither the investigators nor the participants receiving OLPs were blinded to treatment allocation. OLPs by nature require patients as providers are always aware of the administration of the treatment. However, adding an independent assessor, blind to group allocation, without using a patient-reported outcome measure may have had the potential to limit risk of bias (C. R. Blease et al., 2019). Similar to many OLP studies, lack of blinding may lead to researcher allegiance or nocebo effect during the no-treatment condition (C. R. Blease et al., 2019). Additionally, the use of no-treatment conditions as means to differentiate the placebo effect from the placebo response may prove ineffective (C. R. Blease et al., 2019). Such limitations across several OLP studies led clinicians, such as Australian physiotherapist Christopher Maher and colleagues, to recommend caution on the enthusiastic claims on clinical use of OLPs (Amorim et al., 2020; Maher et al., 2021).

In addition to these methodological considerations, there is a need for more fundamental research into OLPs. Firstly, in light of the findings of study 3 presented in this thesis, effectiveness may be a major deciding factor when evaluating preferences of DPs versus OLPs (Druart et al., 2023), therefore, further research should be aimed at substantiating the findings of study 2. Results should be replicated and compared to confirm the findings that OLPs and DPs may be equivalent (C. Blease et al., 2023). Currently, meta-analyses examining OLPs show an effect compared to no-treatment but have yet to compare OLPs and DPs (Charlesworth et al., 2017; von Wernsdorff et al., 2021).

Secondly, other research endeavours regarding OLP could usefully encompass a deeper understanding of how they work. This could better allow identification of the conditions under which OLPs are most effective (C. R. Blease et al., 2019). Currently, one suggested explanation for OLP effects lies within the rationale administered with it. Preliminary results from Locher et al. suggest that furnished with no rationales,

OLPs were not effective (Locher et al., 2017). Considering these results, von Wernsdorff et al. in their systematic review reported the rationales of the studies they included in their meta-analysis (von Wernsdorff et al., 2021). On closer inspection one can observe significant differences in how OLPs are administered. This leads Heiss et al. to suggest that the rationale should be optimised (Heiss et al., 2021).

However, it seems possible some rationales may risk overstating the effectiveness of OLPs. This raises the question about whether some OLPs are simply a way of generating expectancies while replacing one lie (stating the treatment is something other than inert) with a deception or even another lie (implying or outright stating it will have positive therapeutical effects). Given the potentially important role of the rationale in OLPs, one major feature of study 2 was to use a video to administer the rationale. This may have diminished expectations by reducing patient-physiotherapist interactions, it allows better replication in other studies.

Aside from the fundamental research about what cues enhance their effectiveness, investigating the physiological mechanisms behind OLPs will also be important. To date, all meta-analyses on OLPs offer similar conclusions: the intervention is promising but further research should investigate the role of expectations and explore the underlying mechanisms (Charlesworth et al., 2017; Spille et al., 2023; von Wernsdorff et al., 2021). On this topic, precursor studies show that OLPs may be regulated by mechanisms similar to DPs, namely through the involvement of endogenous opioids (Benedetti et al., 2022). This could be an indicator that OLPs trigger the same mechanisms accompanying DPs, but further research is needed.

In addition to the need for basic research, further applied research is also invaluable. For instance, finding clinical applications for OLPs or establishing their cost-effectiveness will be necessary before any clinical use can be recommended (Hamberger et al., 2019). Moreover, establishing whether OLPs are ethical is crucial. Study 3 of this thesis found treatment acceptability was not as straight forward as initially presumed, this could also be the case regarding wider acceptability of OLPs among patients. For instance, Blease et al. argue this point by stating that the question of whether OLPs involve deception depends on the information given during the rationale (C. Blease et al., 2016). Furthermore, the ideal disclosure for OLPs may

be difficult to achieve in practice as, giving exhaustive information or detailed information may undermine patient understanding and could thereby compromise the informed consent and respect for patients' autonomy.

American medical ethicist Specker-Sullivan argues that deception is not the only factor to consider when deciding if an OLP is ethical (Specker Sullivan, 2020). She argues clinicians' proposed use of OLPs may be the product of epistemic injustice. On this line of reasoning, some groups could be systematically driven towards placebo treatments if their narratives are less believed by healthcare providers. Examples of such situations are commonplace in healthcare with a prominent illustration being gender and racial biases in the treatment of pain (Samulowitz et al., 2018). Currently, OLP trials are mainly conducted on female participants and the conditions that are studied are conditions that mainly affect women (Specker Sullivan, 2020). Additionally, there may be other long-term harms, Blease argues that, after being offered an OLP, some patients may self-stigmatise or feel guilt, perhaps by diminishing the medical importance of their symptoms as being "all in their heads"(C. R. Blease, 2019). This is something two participants in study 3 had also hinted at: if a physiotherapist suggested an OLP, participant [C] would "[have the impression that the doctor does not care about me]"[44] or participant [F] would believe "[I'm going to say to myself that you're actually making fun of me.]"[45] Even if OLPs prove effective, patients may not want OLPs or placebo treatments at all (C. Blease et al., 2023).

Overall, OLPs show promise for potential clinical applications but considerably more research is needed before any clinical use is recommended.

4.1.2. Going further with contextual factors

When considering CF use, study 4 offers an overview of how healthcare providers routinely consider these factors. One interesting finding was professionals did not use all CFs in the same way. For example, 95% of participants reported routinely using communication to increase healthcare outcomes whereas only 31% reported using title or status to improve outcomes. Similarly, they perceived some CFs to be more effective than others. Interestingly, they did not necessarily report using the CFs they

[44] "Au contraire j'ai l'impression que le médecin se fout de moi quoi"

[45] "Non parce que je vais me dire là vous vous foutez de ma gueule en fait"

perceived most effective. An example of this is the use of touch which was considered the 2nd least effective out of 12 yet was the 7th most used.

Future research endeavours could usefully explore the effect of individual CFs on placebo effects. First, this would allow to verify whether these factors actually provide meaningful health benefits to patients. Secondly, comparing the impact of several CFs on placebo effects could help establish which enhance placebo effects the most.

Building on this idea, studying the interaction between separate CFs should also be considered. As argued in section 3.1.3, CFs' effect may be modulated by their interaction. Currently, this aspect of CFs has been neglected. For example, it seems reasonable to assume that some CFs' impact on expectancies and placebo effects may be modulated by localized or cultural differences. This hypothesis seems to be supported by findings of a systematic review conducted by Lorié et al. which reported that nonverbal empathy was expressed variably across cultural groups (Lorié et al., 2017). Similarly, cultural differences with respect to clinician uniforms or dress style, may influence expectancies and placebo effects (Bernstein et al., 2020).

Bernstein et al. suggested experimental designs aimed at evaluating the extent to which CFs influence the placebo effect (Bernstein et al., 2020). For example, this might be achieved by comparing the same sham treatment administered in various settings. An example relevant to physiotherapy could be a design where all study arms receive sham manual therapy with one arm receiving it within a favourable setting (dependant on the specific CF to be examined), another group with a neutral setting and finally one with a negative setting. Another method could be inspired by a so-called balanced placebo design (Kube & Rief, 2017). One variation of this design might include four groups. Two groups would receive the verum treatment and two groups would receive the sham treatment. One verum and one sham group would receive their treatments within an enriched CF context. The two other groups would receive their treatments in impoverished CF setting. To illustrate, one example of such a trial for manual therapy on pain relief could go as follows. One group would receive manual therapy within an enriched setting (physiotherapist with a white coat, explaining the treatment, providing warm touch, and so on) while another would receive a sham manual therapy with the same setting. A third and fourth group would

receive active or sham manual therapy within an impoverished setting (therapist with cold hands, no explanations, no reassurance, explaining manual therapy may cause adverse effects and so on). Comparing all 4 groups would allow the opportunity to estimate the interaction between CFs, placebo effects and treatment effects.

Finally, following section 1.2, research on CFs also brings forth more definitional questions regarding placebo effects. Study 4 suggested there was also strong disagreement between participants on what were placebo effects. Dissecting the placebo effect can lead to viewing it as the sum of individual effects of CFs. Therefore, the placebo effect could be the addition of, for example, the effects of the provider's clothing, the treatment's colour or branding, and so on. In that case, the placebo effect could be likened to a bunch of grapes: each grape would be the specific effect of one CF and the bunch of grapes itself the placebo effect[46]. However, among the bunch of grapes would also be the effect of showing empathy or the effect of the physiotherapist's warmth. Do such grapes belong in the bunch? Should empathetic communication be considered a placebo effect? According to Enck et al., this is the biggest threat to placebo research since placebo studies may "outdate itself by declaring all and everything as a placebo effect" (Enck et al., 2017). Going against some of his earlier writings, bioethicist Franklin Miller now also worries that the definition of placebo effects may be stretched too wide (Miller, 2018). Perhaps just as Blease and Annoni argued the necessity to distinguish placebo controls from clinical uses of placebos (C. Blease & Annoni, 2019), it may also be useful to distinguish harnessing placebo effects by using placebos and by using CFs.

4.2. CONTRIBUTIONS TO PHYSIOTHERAPY

4.2.1. USING PLACEBO TREATMENTS IN PHYSIOTHERAPY

The thesis also aimed to contribute to physiotherapy research. One of the two research questions formulated in section 1.5 was: Question 1 Under which conditions should placebo treatments be used in physiotherapy? The discussion in section 4.1.1

[46] This metaphor, as the classification of contextual factors, also poorly represents possible interactions between contextual factors, or metaphorical grapes.

emphasized the need for considerably more research before any clinical uses of OLP can be recommended.

Particularly, before any clinical applications are possible in physiotherapy, specific research will need to be carried out by both physiotherapists and placebo scholars. First, the hypothesis OLPs perform as well as DPs will need to be tested among rehabilitation patients and not only on healthy subjects as was the case in Article 2. Considering a recent meta-analysis found that OLPs produced small but significant effects among healthy subjects on patient-reported outcomes (Spille et al., 2023), there is reason to believe that these results may carry over to patients as placebo effects are typically larger for patients (Forsberg et al., 2017). Patients with pain may benefit from OLPs, but they could also be used for conditions such as post-operative movement disorders, or kinesiophobia in elderly patients after a fall, or movement apprehension in the case of instability; conditions which may be more specific to physiotherapy which could respond well to placebo effects. Investigating OLP uses for pain, good candidate pathologies for future clinical trials could be fibromyalgia or low back pain. Fibromyalgia shows a PCE of up to 60% of the overall effect (Whiteside et al., 2017) while in the case of low back pain, OLPs have previously showed that they may help reduce pain combined with treatment-as-usual (Carvalho et al., 2016, 2020; Kleine-Borgmann et al., 2019). Replicating study 2 in patients with low back pain may prove particularly fruitful. It may then lead to go further and compare OLPs to active drugs. For example, Kleine-Borgmann argued, in their response to Amorin et al., that OLPs provided similar treatment effects as other active treatments such as nonsteroidal anti-inflammatory drugs or opioid tramadol (Amorim et al., 2020; Kleine-Borgmann et al., 2020). They proposed that the benefit-risk ratio may be in favour of OLPs. However, further follow-up research is required to explore these claims, particularly for conditions and patient populations within physiotherapy.

In study 2, the placebo treatment used was a cream. This is a treatment which could be commonly used in physiotherapy practice (e.g. for articular pain, delayed onset muscle soreness, as an adjuvant to massages) and was chosen for this reason while also being used in other placebo studies showing its potential to provide placebo effects (Voudouris et al., 1990). In the future, OLPs could also take the form of

treatments even more specific to physiotherapists' expertise. Examples of these could be sham manual therapy or assisted guidance while a patient performs an active movement or taping an articulation or a muscle. OLPs could also be imagined with the possibility that patients may administer it themselves after designing the treatment with their physiotherapist, for example, if the OLP is a prescription for a protocolised non-specific stretching routine. In such a case, patients could be co-design of the OLP which best suits them. This may increase their expectations of relief and adherence to treatment. It may also provide the benefit of allowing patients to administer the OLP themselves without being dependant of a physiotherapist. Innovating the design of OLPs may come from role hybridisation of physiotherapists and placebo scholars, alongside patients. Overall, there are several areas of research specific to physiotherapy to investigate if there is any potential to use OLPs in this field. Both patients and physiotherapists well-versed in placebo studies will need to be actively engaged in research if the end-products are to be meaningful, and ultimately, used in practice.

There are other important issues outlined by some authors when advocating for the use of placebo treatments. Indeed, promoting placebo treatments could have two other undesirable effects clinicians should be aware of. Firstly, regardless of their effect, some situations do not call for placebo treatments. Braillon highlights how placebo treatments can be unnecessarily offered to patients who may only require explanations or reassurance instead of treatments. He adds that "by defining vague symptoms as an entity requiring a treatment, healthy people are converted into patients" (Braillon, 2009). It is also worth considering that placebo treatments might also risk taking the place of more effective treatments, indicating that comparing OLPs to active treatments may be even more relevant.

Secondly, if the placebo effect is considered a sufficient justification for a treatment, then any treatment might be deemed acceptable. As such, placebo effects should not be a sufficient justification to use a treatment. As stated in section 2.1.1, treatments relying solely on placebo effects are likely to be common in physiotherapy. As a result, physiotherapists should be cautious of their use. Indeed, medical philosopher Friesen warns that acknowledging placebo use could "lead to creating or further cementing inaccurate beliefs about where the placebo treatments can be

effective" (Friesen, 2019). She is not alone in proffering such claims. Fabrizio Benedetti observed a rise in the number of pseudoscientific assertions regarding the placebo effect (Benedetti, 2019). He considers the dangers associate with inappropriate use of placebo knowledge is likely to be underestimated and suggests that there has been an increase in the justification of "bizarre objects and procedures" purely on the grounds that they may elicit expectations through placebo effects. Worryingly enough, the conditions on which these procedures are claimed to work are often ones on which the placebo effect does not function such as reducing malignant tumour size, as antibiotics or in blood coagulation. Benedetti puts forward a word of caution: "placebos do not cure, but rather, they may sometimes improve quality of life."

In light of these considerations, Beedie et al. suggest being upfront with patients about the use of treatments with uncertain effects (Beedie et al., 2018). Drawing on our results in study 2 and 3, such a strategy may be relevant while not trading off placebo effects. This will require further replication both through clinical trials and to establish patient acceptability. The latter could be tested by interviewing patients directly about the open use of impure placebos in physiotherapy. Replicating study 3, semi-structured interviews with patients of specific demographics and conditions relevant to physiotherapy, such as those mentioned above, would be valuable. Additionally, asking physiotherapists how they view placebo treatments in physiotherapy could prove useful in describing current use of impure placebos in physiotherapy which section 2.1.1 showed was lacking. Combined these results could allow to investigate relevant situations in physiotherapy where OLPs, if at all, be most appropriate. This could suggest potential situations in which patients and physiotherapists suggest is the best manner to consider and disclose impure placebos in physiotherapy care.

Overall, in response to Question 1, although there is some promising evidence of benefits regarding clinical applications of OLPs, there are still points of caution that need to be addressed contrary to the unbridled enthusiastic claims that are sometimes made regarding placebo treatments. Once OLPs are demonstrated to be effective, ethical and acceptable for patients, their use may complement physiotherapy practice.

4.2.2. Using contextual factors in physiotherapy

The second research question of this thesis from section 1.5 was: Question 2 How are contextual factors used in physiotherapy? Study 4 provided insights which allow to state CFs seem to be used frequently by the majority of healthcare providers. When comparing physiotherapists, nurses and physicians, there seems to be few significant differences in which CFs are used. However, some differences can be noted for consideration in future exploration. For example, physiotherapists were the profession which considered patient past expectations and preferences the most. This may be hypothesised to be due to professional specificity considering, for example, the importance of participatory treatments in rehabilitation. Physiotherapy, along with nursing, are the professions which use touch the most whereas pharmacists were the professionals to use touch the least. This did not seem to be due to a difference in perceived effectiveness of this CF. Again, this may be linked to the specificity of professional practice; as Roger et al. found, there are many ways touch may be used in physiotherapy (Roger et al., 2002). The same could be true for other CFs. Further qualitative research should be aimed at investigating how physiotherapists use CFs as well as their thought process surrounding use. This could take the form of reviewing a video tape of varieties of consultations with physiotherapists or instruction by the use of stand-ins. Such methods would furnish researchers with greater insights into the thought processes behind CF use and could also help inspect differences between reported use and observed use of CFs.

Weighing the benefits of influencing the context of care with the potential risk on patients' autonomy and healthcare will also be important. For example, in our survey, we found that 24% of our respondents considered using CFs to compensate for lack of effect of their treatment. This compensatory approach may be considered an unethical motivation for increasing placebo effects, by continuing to peddle ineffective treatments. Upon inspection of the open-ended answers to the question "why do you use CFs" of study 4, one physiotherapist (participant 191) answered "because it's very fun to use, I see it as a game.[47]" Such a response, if it is intended to take seriously, leads to fundamental questions about the motivations for

[47] "Parce que c'est très drôle à utiliser, je vois ça comme un jeu"

manipulating[48] aspects of the healthcare encounter and setting. This shows that unethical uses of CFs exist and suggest that education into CFs and placebo and nocebo effects must be paired with healthcare ethics. Currently, it is unknown what physiotherapists are taught about CFs and placebo and nocebo effects within established or hidden curricula. This could be investigated through mixed methods with both a survey of current education programs across physiotherapy curricula and qualitative interviews with physiotherapy teachers, and students, to understand any current learning on placebo topics. In turn, the profession could also adapt the recommendations from the expert consensus on what healthcare providers should know about placebo and nocebo effects to physiotherapy (Evers et al., 2018, 2020). This could lead to professional recommendations by the French chartered society of physiotherapy similar akin to the American Medical Association's stance (Bostick et al., 2008) as well as specific recommendations for physiotherapists on what they should be taught about placebo phenomena.

Adding to empirical results from study 4, further impact on patient autonomy can be seen when some positive cues increase expectancy more than is reasonable, that is, as the state of evidence permits. Annoni warns this can lead to an ethical dilemma if providers "resort to misleading communication" (Annoni, 2018). Kolber concurs stating that "there are limits on the amount of reassurance a physician can give; otherwise, we have simply traded one form of deception for another"[49] (Kolber, 2007). For example, only using positive suggestions in physiotherapy could lead to an exaggeration of a treatment's effect. The imbalance of creating expectations above what the treatment can realistically achieve could in turn lead to nocebo effects. In response to these concerns, some authors suggest to aim for "realistic optimism" (Bystad et al., 2015). Annoni and Miller suggest that considering helpfulness, truthfulness and pragmatism is necessary when considering the ethics of therapeutic communication (Annoni & Miller, 2016).

[48] It may be useful here to clarify, as Annoni and Miller did, that manipulate is morally neutral. Manipulation of context can lead both to good or bad outcomes (Annoni & Miller, 2016).

[49] In his article, he compares the use of placebo effects through deceptive placebo treatments and with reassurance and enhanced doctor-patient relationship.

Again, the examples outline the use potential of CFs and raise ethical questions. An expert consensus in 2018 concurs stating "experts agreed that medical ethics education encompassing placebo and nocebo effects should be a routine part of clinical training" (Evers et al., 2018). Our survey results give empirical evidence this is a necessity. Due to the specificity of questions involving the use of CFs, there seems to be a need for an ethical framework before any clinical recommendations can be made.

Lastly, while it should improve the quality of care that physiotherapists "spend more time with patients, listen carefully to their complaints, demonstrate that they understand and empathize with patient concerns, and so forth, these activities cost time and money" (Kolber, 2007). Given the current strain on healthcare resources, it's important to consider whether allocating resources towards enhancing patient-physiotherapist interactions to boost placebo response might divert attention from other patients being neglected, undertreated or receiving inadequate treatment. This is all the truer in a model where collective decisions determine consultations duration and honoraria through an operating agreement with the social security administration such as is the case in France. Adding to this, the current healthcare system for physiotherapy, among others, in France is already under heavy strain.[50] For example, for strokes where immediate rehabilitation is considered urgent, French physiotherapists only average approximately 4 consultations. This contrasts with an increase in the number of physiotherapists in France (reaching just over 100 000 physiotherapists in 2023) while the average number of consultations for each patient diminishes. However, it seems difficult to explain this decrease through one hypothesis when it could be due to an increase of health demands (ageing population, increase of chronic pathologies, etc.) but also a decrease of health offer (physiotherapists leaving due to burn-out, physiotherapists working part-time, diversification of activities to increase income, etc.). As stated in part 3.1.1, medico-economic research could usefully investigate whether increasing placebo effects through the use of CFs is a safe, ethical and cost-effective use of healthcare resources. At the moment, too few studies focus on this issue (Hamberger et al., 2019).

[50] Data from the following paragraph comes from the 2022 report on the demographics of the chartered society of physiotherapy (CNOMK, 2023) and the open data from the national healthcare system (*Accueil — Data Pathologies*, n.d.).

To recap: most physiotherapists reported using CFs. Future research should focus on gaining deeper understanding of physiotherapists' justifications and thought processes with respect to invoking CF. In tandem, an ethical framework preventing unethical use of CFs should be added to physiotherapy curricula.

5. FUTURE DIRECTIONS

The aim of this thesis presented in section 1.4 was to explore how placebo studies could inform the practice of physiotherapy. Having presented and discussed the findings of this thesis and outlining specific future studies, it is also valuable to briefly consider additional new directions to advance the overarching research aim. Indeed, while this thesis has focused on direct clinical applications of placebo knowledge, indirect applications exist. These new considerations advance and elaborate potential future directions in the continuing exploration of this research aim.

5.1. CHALLENGES IN EVALUATING NON-PHARMACOLOGICAL INTERVENTIONS

There are specific challenges with evaluating non-pharmacological interventions such as surgery, psychology and physiotherapy. Notwithstanding, it is crucial to use placebo controls in non-pharmacological randomised trials in order to estimate effect sizes (K. A. Wartolowska et al., 2022). Failure to do so may result in systematic biases and conflation of treatment response and treatment effects (as described in Figure 1). Adequate use of placebo controls relies on adequate blinding which refers to investigators, assessors and patients not knowing whether the patient is receiving the treatment or the control. Blinding traditionally serves two purposes. Firstly, it allows to equivalent expectations about benefits in groups receiving the intervention and the control. Second it helps prevent the influence of researcher allegiance on the outcomes of treatments (Locher et al., 2018). Although there may be difficulties in blinding during pharmacological trials, this is more difficult in the case of non-pharmacological interventions (Boutron et al., 2004). Since physiotherapy involves physical interventions and high levels of patient engagement and interaction with the therapist, it may be difficult to blind patients and therapists to treatment allocation

(Boutron et al., 2004; Locher et al., 2018). Indeed, physiotherapy interventions among which manual therapy, exercise programs, and patient education may prove difficult to blind for these reasons (Annaswamy et al., 2023). Additionally, physiotherapy often prioritises subjective outcomes which depend on patient perception and are particularly prone to bias from lack of blinding (K. A. Wartolowska et al., 2022). Adding to this, when patients or researchers are not blinded, they may become disappointed or biased against their allocated treatment intervention which in turn may lead to nocebo effects (Armstrong & Watts, 1981; Torgerson & Roland, 1998; Zelen, 1979). For example, this might happen when comparing the effects of 10 sessions of gentle massage compared to a motor control targeted rehabilitation program for example. Overall, failure to correctly blind has important consequences often leading to an overestimation of effect sizes (Hohenschurz-Schmidt, Draper-Rodi, Vase, Scott, McGregor, Soliman, MacMillan, Olivier, Cherian, Corcoran, Abbey, Freigang, Chan, Phalip, Nørgaard Sørensen, et al., 2023; Hohenschurz-Schmidt, Draper-Rodi, Vase, Scott, McGregor, Soliman, MacMillan, Olivier, Cherian, Corcoran, Abbey, Freigang, Chan, Phalip, Sørensen, et al., 2023).

To recap: this difficulty in blinding in RCTs is in part due to the placebo controls used. If the placebo control is not well designed to mimic the intervention and be indistinguishable from it, blinding proves difficult. This has been illustrated in non-pharmacological interventions such as orthopaedic surgery (Anderson et al., 2022; K. Wartolowska et al., 2017) and psychology (Gaab et al., 2016, 2018; Locher et al., 2018). In physiotherapy interventions there is scant reflection on these challenges.

However, initial assessment of placebo fidelity show placebo controls are not optimal. For example, in trials evaluating manual therapy, D'Alessandro et al. found that there was limited fidelity between experimental and sham interventions (D'Alessandro et al., 2022). More problematically, participants allocated to controls showed significantly lower expectations than those allocated to experimental interventions (Machado et al., 2008). This suggests many trial results are prone to bias due to improper control design.

5.2. IMPROVING THE DESIGN OF PLACEBO CONTROLS

Several solutions exist to increase the quality of the randomised placebo-controlled trial. Because it is difficult to estimate the placebo effect size (Hróbjartsson, 2002; Hróbjartsson et al., 2011), it is important to consider the fidelity between the placebo control and the experimental intervention (Beard et al., 2020). To do so, investigators should strive for structural equivalence which requires adequately describing the interventions that were used (Gaab et al., 2018; Locher et al., 2018). This is why specific reporting guidelines have been developed to this end both for interventions and controls namely the TiDieR Reporting Guidelines (Howick et al., 2020).

Looking closer at the example of musculoskeletal surgery, significant advances have been made on this front. For instance, the use of placebo controls was shown to be possible, desirable, and acceptable by surgeons (K. Wartolowska, Beard, et al., 2014; K. Wartolowska et al., 2017; K. Wartolowska, Judge, et al., 2014). After identifying limitations to the reporting of placebo controls in surgery (Cousins, Blencowe, Tsang, Lorenc, et al., 2020), guidelines detailing when placebo controls are justified as well as the rationale to implement them have been recently developed (Beard et al., 2020, 2021). Additionally, a specific framework was established to help researchers construct surgical placebo controls (Cousins, Blencowe, Tsang, Chalmers, et al., 2020). Although there is still room for progress in design of sham surgeries (Sochacki et al., 2020), such initiatives could be adapted for other non-pharmacological placebo controls for physiotherapy interventions. This would constitute a major aid to produce quality physiotherapy research.

To this end, knowledge about placebo effects may help designing placebo controls in physiotherapy. Vase and Wartolowska insist it is crucial to "personalise the placebo control" (Vase & Wartolowska, 2019). This implies customising the placebo control to be indistinguishable from the intervention treatment. For instance, if manual therapy produces a joint sound the sham should also. This leads to suggestions of including more active placebos which produce side-effects (Jensen et al., 2017) which could also be applicable to physiotherapy. Finding credible shams for physical intervention in physiotherapy is challenging and requires methodological

innovation. For example when considering manual therapy targeted at the shoulder, Michener et al. suggested a sham procedure where "the clinician applied minimal pressure and slid the hands across the skin to mimic the manipulative thrust" (Michener et al., 2013, 2015). Another attempt at producing controls comes from a recent Delphi study which included experts on deception, including magicians, to suggest criteria to create sham treatments for physical treatments (Braithwaite et al., 2020). However, only five criteria among seventy-nine reached consensuses for both research methodologists and experts on deception. Hancock et al. also found minimal agreement among physiotherapists as to which controls may be appropriate, credible and inert (Hancock et al., 2006).

Overall, the best hope for solutions to help overcome the challenges in evaluating non-pharmacological treatments, and specifically physiotherapy, could come from the continued conversation between placebo studies and physiotherapy. Physiotherapy would increase the internal validity of its studies by striving to improve the design of the placebo controls it uses.

CONCLUSION

In conclusion, physiotherapy can both learn from and contribute to placebo studies. Nowadays, physiotherapy is an evidence-informed profession that is enthusiastic about establishing the effectiveness of its various interventions. However, fulfilling this new direction will requires ongoing focus on establishing the effectiveness of treatments; for that, as we have seen, placebos need to be adequately designed. Another less common approach is to focus on other effects in physiotherapy care. Research into the placebo effect may lead to meaningful impacts of care on healthcare outcomes. As such, placebo studies may offer valuable insights into how physiotherapy interventions can be optimized for patient benefit.

To date, there is little attention from placebo studies to physiotherapy and vice versa. Therefore, this thesis aimed to explore how placebo studies could contribute to the knowledge base of physiotherapy and its practice. By examining the use of placebo treatments and CFs, the thesis aimed to shed light on how placebo effects could be harnessed to enhance patient outcomes in physiotherapy. This was done by contributing both to placebo and physiotherapy studies through three individual studies.

The first two studies focused on the use of placebo treatments. Combined, the results suggest that OLP acceptability was not as straight forward as initially thought. Some participants in the study deemed the effectiveness of placebo treatments as the primary factor in deciding whether the treatment was acceptable. These participants placed trust in healthcare providers to act in their best interest and make informed decisions regarding treatment. However, for others, respect for their autonomy was of utmost importance, and they strongly voiced their preference not to be deceived, even if the treatment was effective. In such cases, these participants did not view effectiveness as a sufficient justification for deception.

In the second study, OLPs performed as well as DPs, provided that OLPs were sufficiently explained. While this new information is promising, it is important to note that it is not clear from these results whether the placebo treatments

outperformed no-treatment. Additionally, the study only included healthy volunteers which limits the transferability of results to patients. Thus, while there may be some evidence of potential benefits of OLPs for clinical applications, caution is still necessary. Once OLPs can be demonstrated to be both effective and ethically acceptable to patients, they may then be a possibility for this to serve as a complementary approach within physiotherapy practice.

Finally, aside from placebo treatments, CFs may be a useful solution to harness placebo effects in clinical care without placebo treatments. A survey conducted in French-speaking European countries revealed that the use of CFs may be even more widespread than placebo treatment use. Communication was the most commonly reported CF used to elicit placebo effects. Overall, factors within the therapeutic relationship and patient characteristics categories were most often employed. The widespread use of CFs among physiotherapists highlights the need for further research to gain a deeper understanding of their thought processes and clinical decision-making when implementing these approaches. However, there are varying ethical and epistemological justifications behind the use of CFs. An ethical framework must also be established to ensure that the use of CFs is reasonable and justifiable among patient populations. Therefore, future studies should focus on exploring the mechanisms and rationale behind the use of CFs in physiotherapy, while also developing guidelines and standards for their appropriate and ethical use.

In addition to these clinical uses, future research directions could include investigating how placebo knowledge may help improve the design of controls in physiotherapy. This may prove fruitful in illuminating current challenges in blinding and controlling in the evaluation of non-pharmacological interventions.

To further advance the relationship between placebo studies and physiotherapy, it will be necessary to integrate education about placebo and nocebo effects, including healthcare ethics, to physiotherapy initial training and continuous education. Other strategies should also include special interest groups about placebo effects in physiotherapy professional societies. These groups could collaborate on a framework for the use of placebo effects in physiotherapy or establish methodological guidelines to design placebo controls in physiotherapy. Complementary to these efforts, greater attention to the field could be established via special issues in physiotherapy journals

regarding placebo effects in physiotherapy. However, the relationship should go both ways. This thesis has argued that it is also important to consider what placebo studies can learn from physiotherapists too. To this end, for example, the SIPS might fruitfully include a workshop or panel on this topic during its future conferences.

To conclude, this thesis seeks to contribute to the establishment of a long and fruitful relationship which has potential to be mutually beneficial for both placebo studies and physiotherapy.

BIBLIOGRAPHY

1. *Accueil—Data pathologies*. (n.d.). Retrieved 25 April 2023, from https://data.ameli.fr/pages/data-pathologies/

2. Allen, A. (2019). A Kantian defence of placebo deception. *Monash Bioethics Review*, *37*(3–4), 81–93. https://doi.org/10.1007/s40592-019-00102-z

3. Allet, L., Bürge, E., & Monnin, D. (2008). ICF: Clinical relevance for physiotherapy? A critical review. *Advances in Physiotherapy*, *10*(3), 127–137. https://doi.org/10.1080/14038190802315941

4. Amanzio, M., Pollo, A., Maggi, G., & Benedetti, F. (2001). Response variability to analgesics: A role for non-specific activation of endogenous opioids. *PAIN*, *90*(3), 205. https://doi.org/10.1016/S0304-3959(00)00486-3

5. Ambady, N., Koo, J., Rosenthal, R., & Winograd, C. H. (2002). Physical therapists' nonverbal communication predicts geriatric patients' health outcomes. *Psychology and Aging*, *17*, 443–452. https://doi.org/10.1037/0882-7974.17.3.443

6. Amorim, A. B., Machado, G. C., & Maher, C. G. (2020). Enthusiastic claims for open-label placebo pills ignore the evidence. *Pain*, *161*(5), 1124. https://doi.org/10.1097/j.pain.0000000000001803

7. Anderson, D. B., Beard, D. J., Sabet, T., Eyles, J. P., Harris, I. A., Adie, S., Buchbinder, R., Maher, C. G., & Ferreira, M. L. (2022). Evaluation of placebo fidelity and trial design methodology in placebo-controlled surgical trials of musculoskeletal conditions: A systematic review. *PAIN*, *163*(4), 637. https://doi.org/10.1097/j.pain.0000000000002432

8. Annaswamy, T., Cunniff, K., Rizzo, J. R., Naeimi, T., Kumbhare, D., & Batavia, M. (2023). Methodological Issues Relevant to Blinding in Physical Medicine and Rehabilitation Research. *American Journal of Physical Medicine & Rehabilitation*, 10.1097/PHM.0000000000002228. https://doi.org/10.1097/PHM.0000000000002228

9. Annoni, M. (2018a). Lying, deception, equivocation and the ethics of prescribing placebos in clinical practice. *Rivista Italiana Di Filosofia Del Linguaggio*, *12*(1), Article 1. http://www.rifl.unical.it/index.php/rifl/article/view/472

10. Annoni, M. (2018b). The ethics of placebo effects in clinical practice and research. *International Review of Neurobiology*, *139*, 463–484. https://doi.org/10.1016/bs.irn.2018.07.031

11. Annoni, M. (2020). Better than nothing: A historical account of placebos and placebo effects from modern to contemporary medicine. *International Review of Neurobiology*, *153*, 3–26. https://doi.org/10.1016/bs.irn.2020.03.028

12. Annoni, M., Buergler, S., Stewart-Ferrer, S., & Blease, C. (2021). Placebo studies and patient care: Where are the nurses? *Frontiers in Psychiatry*, *12*, 591913. https://doi.org/10.3389/fpsyt.2021.591913

13. Annoni, M., & Miller, F. G. (2016). Placebo effects and the ethics of therapeutic communication: A pragmatic perspective. *Kennedy Institute of Ethics Journal*, *26*(1), 79–103. https://doi.org/10.1353/ken.2016.0004

14. Armstrong, P. W., & Watts, D. G. (1981). Clinical trials: randomization before consent. *Biomedicine / [Publiee Pour l'A.A.I.C.I.G.]*, *34*(2), 65–66.

15. Aronson, J. (1999). Please, please me. *BMJ: British Medical Journal*, *318*(7185), 716.

16. *Article R4321-1—Code de la santé publique—Légifrance*. (n.d.). Retrieved 28 February 2023, from https://www.legifrance.gouv.fr/codes/article_lc/LEGIARTI000006913983

17. Aulas, J.-J., & Rosner, I. (2003). [Efficacy of a non-blind placebo prescription]. *L'Encephale*, *29*(1), 68–71.

18. Babatunde, F., MacDermid, J., & MacIntyre, N. (2017). Characteristics of therapeutic alliance in musculoskeletal physiotherapy and occupational therapy practice: A scoping review of the literature. *BMC Health Services Research*, *17*(1), 375. https://doi.org/10.1186/s12913-017-2311-3

19. Bak Bødskov, E., Palmhøj Nielsen, C., Ramer Mikkelsen, L., Martin Klebe, T., Terp Høybye, M., & Nørgaard Madsen, M. (2022). High Patient Satisfaction with Examination by Advanced Practice Physiotherapists in an Orthopaedic Outpatient Shoulder Clinic: A Cross-Sectional Study Using Quantitative and Qualitative Methods. *Physiotherapy Canada*, *74*(4), 342–352. https://doi.org/10.3138/ptc-2021-0043

20. Banaji, M. R. (2013). *Blindspot: Hidden biases of good people* (1st ed.). Delacorte Press.

21. Beard, D. J., Campbell, M. K., Blazeby, J. M., Carr, A. J., Weijer, C., Cuthbertson, B. H., Buchbinder, R., Pinkney, T., Bishop, F. L., Pugh, J., Cousins, S., Harris, I. A., Lohmander, L. S., Blencowe, N., Gillies, K., Probst, P., Brennan, C., Cook, A., Farrar-Hockley, D., ... Cook, J. A. (2020). Considerations and methods for placebo controls in surgical trials (ASPIRE guidelines). *The Lancet*, *395*(10226), 828–838. https://doi.org/10.1016/S0140-6736(19)33137-X

22. Beard, D. J., Campbell, M. K., Blazeby, J. M., Carr, A. J., Weijer, C., Cuthbertson, B. H., Buchbinder, R., Pinkney, T., Bishop, F. L., Pugh, J., Cousins, S., Harris, I., Lohmander, L. S., Blencowe, N., Gillies, K., Probst, P., Brennan, C., Cook, A., Farrar-Hockley, D., ... Cook, J. A. (2021). Placebo comparator group selection and use in surgical trials: The ASPIRE project including expert workshop. *Health Technology Assessment*, *25*(53), 1–52. https://doi.org/10.3310/hta25530

23. Beecher, H. K. (1955). The powerful placebo. *Journal of the American Medical Association*, *159*(17), 1602–1606.

24. Beedie, C., Whyte, G., Lane, A. M., Cohen, E., Raglin, J., Hurst, P., Coleman, D., & Foad, A. (2018). 'Caution, this treatment is a placebo. It might work, but it might not': Why

emerging mechanistic evidence for placebo effects does not legitimise complementary and alternative medicines in sport. *British Journal of Sports Medicine*, *52*(13), 817–818. https://doi.org/10.1136/bjsports-2017-097747

25. Ben-David, J. (1991). *Scientific Growth: Essays on the Social Organization and Ethos of Science*. University of California Press.

26. Ben-David, J., & Collins, R. (1966). Social Factors in the Origins of a New Science: The Case of Psychology. *American Sociological Review*, *31*(4), 451–465. https://doi.org/10.2307/2090769

27. Benedetti, F. (2008). Mechanisms of placebo and placebo-related effects across diseases and treatments. *Annual Review of Pharmacology and Toxicology*, *48*, 33–60. https://doi.org/10.1146/annurev.pharmtox.48.113006.094711

28. Benedetti, F. (2019). The dangerous side of placebo research: Is hard science boosting pseudoscience? *Clinical Pharmacology and Therapeutics*. https://doi.org/10.1002/cpt.1579

29. Benedetti, F., Carlino, E., & Pollo, A. (2011a). How placebos change the patient's brain. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *36*(1), 339–354. https://doi.org/10.1038/npp.2010.81

30. Benedetti, F., Carlino, E., & Pollo, A. (2011b). Hidden administration of drugs. *Clinical Pharmacology and Therapeutics*, *90*(5), 651–661. https://doi.org/10.1038/clpt.2011.206

31. Benedetti, F., Maggi, G., Lopiano, L., Lanotte, M., Rainero, I., Vighetti, S., & Pollo, A. (2003). Open versus hidden medical treatments: The patient's knowledge about a therapy affects the therapy outcome. *Prevention & Treatment*, *6*, No Pagination Specified-No Pagination Specified. https://doi.org/10.1037/1522-3736.6.1.61a

32. Benedetti, F., Pollo, A., Lopiano, L., Lanotte, M., Vighetti, S., & Rainero, I. (2003). Conscious expectation and unconscious conditioning in analgesic, motor, and hormonal placebo/nocebo responses. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *23*(10), 4315–4323.

33. Benedetti, F., Shaibani, A., Arduino, C., & Thoen, W. (2022). Open-label nondeceptive placebo analgesia is blocked by the opioid antagonist naloxone. *PAIN*, 10.1097/j.pain.0000000000002791. https://doi.org/10.1097/j.pain.0000000000002791

34. Bernard, C. (1865). *Introduction à l'étude de la médecine expérimentale*. Baillière.

35. Bernstein, M. H., Locher, C., Kube, T., Buergler, S., Stewart-Ferrer, S., & Blease, C. (2020). Putting the 'art' into the 'art of medicine': The under-explored role of artifacts in placebo studies. *Frontiers in Psychology*, *11*, 1354. https://doi.org/10.3389/fpsyg.2020.01354

36. Bialosky, J. E., Bishop, M. D., George, S. Z., & Robinson, M. E. (2011). Placebo response to manual therapy: Something out of nothing? *The Journal of Manual & Manipulative Therapy*, *19*(1), 11–19. https://doi.org/10.1179/2042618610Y.0000000001

37. Bialosky, J. E., Bishop, M. D., & Penza, C. W. (2017). Placebo mechanisms of manual

therapy: A sheep in wolf's clothing? *The Journal of Orthopaedic and Sports Physical Therapy*, *47*(5), 301–304. https://doi.org/10.2519/jospt.2017.0604

38. Bientzle, M., Cress, U., & Kimmerle, J. (2014). Epistemological beliefs and therapeutic health concepts of physiotherapy students and professionals. *BMC Medical Education*, *14*(1), 208. https://doi.org/10.1186/1472-6920-14-208

39. Bingel, U. (2020). Placebo 2.0: The impact of expectations on analgesic treatment outcome. *Pain*, *161*, S48–S56.

40. Birkhäuer, J., Gaab, J., Kossowsky, J., Hasler, S., Krummenacher, P., Werner, C., & Gerger, H. (2017). Trust in the health care professional and health outcome: A meta-analysis. *PLOS ONE*, *12*(2), e0170988. https://doi.org/10.1371/journal.pone.0170988

41. Bisconti, M., Venturin, D., Bianco, A., Capurso, V., & Giovannico, G. (2021). Understanding contextual factors effects and their implications for italian physiotherapists: Findings from a national cross-sectional study. *Healthcare (Basel, Switzerland)*, *9*(6). https://doi.org/10.3390/healthcare9060689

42. Bishop, F. L., Aizlewood, L., & Adams, A. E. M. (2014). When and why placebo-prescribing is acceptable and unacceptable: A focus group study of patients' views. *PloS One*, *9*(7), e101822. https://doi.org/10.1371/journal.pone.0101822

43. Bishop, F. L., Howick, J., Heneghan, C., Stevens, S., Hobbs, F. D. R., & Lewith, G. (2014). Placebo use in the UK: a qualitative study exploring GPs' views on placebo effects in clinical practice. *Family Practice*, *31*(3), 357–363. https://doi.org/10.1093/fampra/cmu016

44. Bishop, M. D., Mintken, P., Bialosky, J. E., & Cleland, J. A. (2019). Factors shaping expectations for complete relief from symptoms during rehabilitation for patients with spine pain. *Physiotherapy Theory and Practice*, *35*(1), 70–79. https://doi.org/10.1080/09593985.2018.1440676

45. Blease, C. (2012). The principle of parity: The 'placebo effect' and physician communication. *Journal of Medical Ethics*, *38*(4), 199–203. https://doi.org/10.1136/medethics-2011-100177

46. Blease, C. (2018). Consensus in placebo studies: Lessons from the philosophy of science. *Perspectives in Biology and Medicine*, *61*(3), 412–429. https://doi.org/10.1353/pbm.2018.0053

47. Blease, C., & Annoni, M. (2019). Overcoming disagreement: A roadmap for placebo studies. *Biology & Philosophy*, *34*(2), 1–26.

48. Blease, C., Colagiuri, B., & Locher, C. (2023). Replication crisis and placebo studies: Rebooting the bioethical debate. *Journal of Medical Ethics*, jme-2022-108672. https://doi.org/10.1136/jme-2022-108672

49. Blease, C., Colloca, L., & Kaptchuk, T. J. (2016). Are open-Label placebos ethical? Informed consent and ethical equivocations. *Bioethics*, *30*(6), 407–414. https://doi.org/10.1111/bioe.12245

50. Blease, C. R. (2019). The role of placebos in family medicine:'Implications of evidence and ethics for general practitioners'. *Australian Journal of General Practice*, *48*(10), 700–705.

51. Blease, C. R., Bernstein, M. H., & Locher, C. (2019). Open-label placebo clinical trials: Is it the rationale, the interaction or the pill? *BMJ Evidence-Based Medicine*. https://doi.org/10.1136/bmjebm-2019-111209

52. Bostick, N. A., Sade, R., Levine, M. A., Stewart, Jr, D. M., & American Medical Association Council on Ethical and Judicial Affairs. (2008). Placebo use in clinical practice: Report of the American Medical Association Council on Ethical and Judicial Affairs. *The Journal of Clinical Ethics*, *19*(1), 58–61.

53. Boussageon, R., Howick, J., Baron, R., Naudet, F., Falissard, B., Harika-Germaneau, G., Wassouf, I., Gueyffier, F., Jaafari, N., & Blanchard, C. (2022). How do they add up? The interaction between the placebo and treatment effect: A systematic review. *British Journal of Clinical Pharmacology*, *88*(8), 3638–3656. https://doi.org/10.1111/bcp.15345

54. Boutron, I., Tubach, F., Giraudeau, B., & Ravaud, P. (2004). Blinding was judged more difficult to achieve and maintain in nonpharmacologic than pharmacologic trials. *Journal of Clinical Epidemiology*, *57*(6), 543–550. https://doi.org/10.1016/j.jclinepi.2003.12.010

55. Braillon, A. (2009). Placebo is far from benign: It is disease-mongering. *The American Journal of Bioethics: AJOB*, *9*(12), 36–38. https://doi.org/10.1080/15265160903234078

56. Braithwaite, F. A., Walters, J. L., Moseley, G. L., Williams, M. T., & McEvoy, M. P. (2020). Towards more credible shams for physical interventions: A Delphi survey. *Clinical Trials (London, England)*, *17*(3), 295–305. https://doi.org/10.1177/1740774520910365

57. Britten, N., & Ukoumunne, O. (1997). The influence of patients' hopes of receiving a prescription on doctors' perceptions and the decision to prescribe: A questionnaire survey. *BMJ*, *315*(7121), 1506–1510. https://doi.org/10.1136/bmj.315.7121.1506

58. Brody, H. (1982). The Lie That Heals: The Ethics of Giving Placebos. *Annals of Internal Medicine*, *97*(1), 112–118. https://doi.org/10.7326/0003-4819-97-1-112

59. Brody, H. (2000). The placebo response. Recent research and implications for family medicine. *The Journal of Family Practice*, *49*(7), 649–654.

60. Bystad, M., Bystad, C., & Wynn, R. (2015). How can placebo effects best be applied in clinical practice? A narrative review. *Psychology Research and Behavior Management*, *8*, 41–45. https://doi.org/10.2147/PRBM.S75670

61. Carson, T. L. (2010). *Lying and Deception: Theory and Practice*. OUP Oxford.

62. Carvalho, C. (2017). Reply. *Pain*, *158*(6), 1179–1180. https://doi.org/10.1097/j.pain.0000000000000885

63. Carvalho, C., Caetano, J. M., Cunha, L., Rebouta, P., Kaptchuk, T. J., & Kirsch, I. (2016). Open-label placebo treatment in chronic low back pain: A randomized controlled trial. *Pain*, *157*(12), 2766–2772. https://doi.org/10.1097/j.pain.0000000000000700

64. Carvalho, C., Pais, M., Cunha, L., Rebouta, P., Kaptchuk, T. J., & Kirsch, I. (2020). Open-label placebo for chronic low back pain: A 5-year follow-up. *Pain*. https://doi.org/10.1097/j.pain.0000000000002162

65. Chaput de Saintonge, D. M., & Herxheimer, A. (1994). Harnessing placebo effects in health care. *Lancet (London, England)*, *344*(8928), 995–998. https://doi.org/10.1016/s0140-6736(94)91647-0

66. Charlesworth, J. E. G., Petkovic, G., Kelley, J. M., Hunter, M., Onakpoya, I., Roberts, N., Miller, F. G., & Howick, J. (2017). Effects of placebos without deception compared with no treatment: A systematic review and meta-analysis. *Journal of Evidence-Based Medicine*, *10*(2), 97–107. https://doi.org/10.1111/jebm.12251

67. Claridge, G. (1970). *Drugs and human behaviour*. London, Allen Lane. http://archive.org/details/drugshumanbehavi0000clar

68. Clemence, M. (2001). Developing the Ethics of Placebos in Physiotherapy. *Physiotherapy*, *87*(11), 582–586. https://doi.org/10.1016/S0031-9406(05)61125-X

69. CNOMK. (2023, January 9). La démographie des kinésithérapeutes en 2022. *Ordre des masseurs-kinésithérapeutes*. https://www.ordremk.fr/actualites/ordre/la-demographie-des-kinesitherapeutes-en-2022/

70. Cochrane, A. L. (1999). *Effectiveness & Efficiency: Random Reflections on Health Services*. Taylor & Francis.

71. Coleshill, M. J., Sharpe, L., Colloca, L., Zachariae, R., & Colagiuri, B. (2018). Placebo and Active Treatment Additivity in Placebo Analgesia: Research to Date and Future Directions. *International Review of Neurobiology*, *139*, 407–441. https://doi.org/10.1016/bs.irn.2018.07.021

72. Colloca, L., & Benedetti, F. (2006). How prior experience shapes placebo analgesia. *Pain*, *124*(1–2), 126–133. https://doi.org/10.1016/j.pain.2006.04.005

73. Colloca, L., Enck, P., & DeGrazia, D. (2016). Relieving pain using dose-extending placebos: A scoping review. *Pain*, *157*(8), 1590–1598. https://doi.org/10.1097/j.pain.0000000000000566

74. Colloca, L., Lopiano, L., Lanotte, M., & Benedetti, F. (2004). Overt versus covert treatment for pain, anxiety, and Parkinson's disease. *The Lancet Neurology*, *3*(11), 679–684. https://doi.org/10.1016/S1474-4422(04)00908-1

75. Corsi, N., Emadi Andani, M., Sometti, D., Tinazzi, M., & Fiorio, M. (2019). When words hurt: Verbal suggestion prevails over conditioning in inducing the motor nocebo effect. *The European Journal of Neuroscience*. https://doi.org/10.1111/ejn.14489

76. Cousins, S., Blencowe, N. S., Tsang, C., Chalmers, K., Mardanpour, A., Carr, A. J., Campbell, M. K., Cook, J. A., Beard, D. J., & Blazeby, J. M. (2020). Optimizing the design of invasive placebo interventions in randomized controlled trials. *British Journal of Surgery*, *107*(9), 1114–1122. https://doi.org/10.1002/bjs.11509

77. Cousins, S., Blencowe, N. S., Tsang, C., Lorenc, A., Chalmers, K., Carr, A. J., Campbell, M. K., Cook, J. A., Beard, D. J., & Blazeby, J. M. (2020). Reporting of key methodological issues in placebo-controlled trials of surgery needs improvement: A systematic review. *Journal of Clinical Epidemiology*, *119*, 109–116. https://doi.org/10.1016/j.jclinepi.2019.11.016

78. Czerniak, E., & Davidson, M. (2012). Placebo, a historical perspective. *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology*, *22*(11), 770–774. https://doi.org/10.1016/j.euroneuro.2012.04.003

79. D'Alessandro, G., Ruffini, N., Aquino, A., Galli, M., Innocenti, M., Tramontano, M., & Cerritelli, F. (2022). Differences between experimental and placebo arms in manual therapy trials: A methodological review. *BMC Medical Research Methodology*, *22*(1), 219. https://doi.org/10.1186/s12874-022-01704-8

80. Daniali, H., & Flaten, M. A. (2019). A qualitative systematic review of effects of provider characteristics and nonverbal behavior on pain, and placebo and nocebo effects. *Frontiers in Psychiatry*, *10*, 242. https://doi.org/10.3389/fpsyt.2019.00242

81. Darlow, B., Fullen, B. m., Dean, S., Hurley, D. a., Baxter, G. d., & Dowell, A. (2012). The association between health care professional attitudes and beliefs and the attitudes and beliefs, clinical management, and outcomes of patients with low back pain: A systematic review. *European Journal of Pain*, *16*(1), 3–17. https://doi.org/10.1016/j.ejpain.2011.06.006

82. de la Fuente-Fernández, R., Ruth, T. J., Sossi, V., Schulzer, M., Calne, D. B., & Stoessl, A. J. (2001). Expectation and dopamine release: Mechanism of the placebo effect in Parkinson's disease. *Science (New York, N.Y.)*, *293*(5532), 1164–1166. https://doi.org/10.1126/science.1060937

83. Debout, C. (2008). Sciences des soins infirmiers: Réflexions épistémologiques sur le projet d'une discipline. *Recherche en soins infirmiers*, *93*(2), 72–82. https://doi.org/10.3917/rsi.093.0072

84. Décret n° 2015-1110 du 2 septembre 2015 relatif au diplôme d'Etat de masseur-kinésithérapeute, 2015-1110 (2015).

85. Décret n° 2019-1107 du 30 octobre 2019 modifiant le décret n° 87-31 du 20 janvier 1987 relatif au Conseil national des universités pour les disciplines médicales, odontologiques et pharmaceutiques, 2019-1107 (2019). https://www.legifrance.gouv.fr/loda/id/JORFTEXT000039296788/

86. Del Baño-Aledo, M. E., Medina-Mirapeix, F., Escolar-Reina, P., Montilla-Herrador, J., & Collins, S. M. (2014). Relevant patient perceptions and experiences for evaluating quality of interaction with physiotherapists during outpatient rehabilitation: A qualitative study. *Physiotherapy*, *100*(1), 73–79. https://doi.org/10.1016/j.physio.2013.05.001

87. Demoulin, C., Baeri, D., Toussaint, G., Cagnie, B., Beernaert, A., Kaux, J.-F., & Vanderthommen, M. (2018). Beliefs in the population about cracking sounds produced during spinal manipulation. *Joint, Bone, Spine: Revue Du Rhumatisme*, *85*(2), 239–242. https://doi.org/10.1016/j.jbspin.2017.04.006

88. Demoulin, C., Roussel, N., Marty, M., Mathy, C., Genevay, S., Henrotin, Y., Tomasella, M., Mahieu, G., & Vanderthommen, M. (2016). [THE MALADAPTIVE BELIEFS OF PATIENTS WITH LOW BACK PAIN. A NARRATIVE REVIEW]. *Revue Medicale de Liege*, *71*(1), 40–46.

89. Di Blasi, Z., Harkness, E., Ernst, E., Georgiou, A., & Kleijnen, J. (2001). Influence of context effects on health outcomes: A systematic review. *Lancet (London, England)*, *357*(9258), 757–762.

90. Disley, N., Kola-Palmer, S., & Retzler, C. (2021). A comparison of open-label and deceptive placebo analgesia in a healthy sample. *Journal of Psychosomatic Research*, *140*, 110298. https://doi.org/10.1016/j.jpsychores.2020.110298

91. Druart, L., Vauthrin, O., Pinsault, N., Locher, C., & Blease, C. (2023). 'It's not my greengrocer, it's someone from the medical profession': A qualitative study regarding acceptability of deceptive and open-label placebo prescribing in France. *British Journal of Health Psychology*, *28*(2), 273–290. https://doi.org/10.1111/bjhp.12624

92. Edwards, I., & Richardson, B. (2008). Clinical reasoning and population health: Decision making for an emerging paradigm of health care. *Physiotherapy Theory and Practice*, *24*(3), 183–193. https://doi.org/10.1080/09593980701593797

93. Elson, M. O. (1964). The Legacy of Mary McMillan. *Physical Therapy*, *44*(12), 1067–1072. https://doi.org/10.1093/ptj/44.12.1067

94. Enck, P., Klosterhalfen, S., & Weimer, K. (2017). Unsolved, forgotten, and ignored features of the placebo response in medicine. *Clinical Therapeutics*, *39*(3), 458–468. https://doi.org/10.1016/j.clinthera.2016.11.016

95. Evers, A. W. M., Colloca, L., Blease, C., Annoni, M., Atlas, L. Y., Benedetti, F., Bingel, U., Büchel, C., Carvalho, C., Colagiuri, B., Crum, A. J., Enck, P., Gaab, J., Geers, A. L., Howick, J., Jensen, K. B., Kirsch, I., Meissner, K., Napadow, V., ... Kelley, J. M. (2018). Implications of placebo and nocebo effects for clinical practice: Expert consensus. *Psychotherapy and Psychosomatics*, *87*(4), 204–210. https://doi.org/10.1159/000490354

96. Evers, A. W. M., Colloca, L., Blease, C., Gaab, J., Jensen, K. B., Atlas, L. Y., Beedie, C. J., Benedetti, F., Bingel, U., Büchel, C., Bussemaker, J., Colagiuri, B., Crum, A. J., Finniss, D. G., Geers, A. L., Howick, J., Klinger, R., Meeuwis, S. H., Meissner, K., ... Consortium of Placebo Experts. (2020). What should clinicians tell patients about placebo and nocebo effects? Practical considerations based on expert consensus. *Psychotherapy and Psychosomatics*, 1–8. https://doi.org/10.1159/000510738

97. Fagot-Largeault, A. (2012). *L'émergence de la médecine scientifique*. Editions Matériologiques. https://doi.org/10.3917/edmat.fagot.2012.01

98. Fässler, M., Gnädinger, M., Rosemann, T., & Biller-Andorno, N. (2009). Use of placebo interventions among Swiss primary care providers. *BMC Health Services Research*, *9*(1), 144. https://doi.org/10.1186/1472-6963-9-144

99. Fässler, M., Gnädinger, M., Rosemann, T., & Biller-Andorno, N. (2011). Placebo

interventions in practice: A questionnaire survey on the attitudes of patients and physicians. *The British Journal of General Practice: The Journal of the Royal College of General Practitioners*, *61*(583), 101–107. https://doi.org/10.3399/bjgp11X556209

100. Fässler, M., Meissner, K., Schneider, A., & Linde, K. (2010). Frequency and circumstances of placebo use in clinical practice–a systematic review of empirical studies. *BMC Medicine*, *8*, 15. https://doi.org/10.1186/1741-7015-8-15

101. Ferreira, P. H., Ferreira, M. L., Maher, C. G., Refshauge, K. M., Latimer, J., & Adams, R. D. (2013). The therapeutic alliance between clinicians and patients predicts outcome in chronic low back pain. *Physical Therapy*, *93*(4), 470–478. https://doi.org/10.2522/ptj.20120137

102. Finniss, D. G., Nicholas, M. K., & Benedetti, F. (2009). Placebo analgesia—Understanding the mechanisms and implications for clinical practice. *Reviews in Pain*, *3*(2), 15–19. https://doi.org/10.1177/204946370900300205

103. Foddy, B. (2009). A duty to deceive: Placebos in clinical practice. *The American Journal of Bioethics: AJOB*, *9*(12), 4–12. https://doi.org/10.1080/15265160903318350

104. Forsberg, J. T., Martinussen, M., & Flaten, M. A. (2017). The Placebo Analgesic Effect in Healthy Individuals and Patients: A Meta-Analysis. *Psychosomatic Medicine*, *79*(4), 388–394. https://doi.org/10.1097/PSY.0000000000000432

105. Frank, J. D., & Frank, J. B. (1993). *Persuasion and Healing: A Comparative Study of Psychotherapy*. JHU Press.

106. Friesen, P. (2019). Placebos as a source of agency: Evidence and implications. *Frontiers in Psychiatry*, *10*, 721. https://doi.org/10.3389/fpsyt.2019.00721

107. Friesen, P., & Blease, C. (2018). Placebo effects and racial and ethnic health disparities: An unjust and underexplored connection. *Journal of Medical Ethics*, *44*(11), 774–781. https://doi.org/10.1136/medethics-2018-104811

108. Fuentes, J., Armijo-Olivo, S., Funabashi, M., Miciak, M., Dick, B., Warren, S., Rashiq, S., Magee, D. J., & Gross, D. P. (2014). Enhanced therapeutic alliance modulates pain intensity and muscle pain sensitivity in patients with chronic low back pain: An experimental controlled study. *Physical Therapy*, *94*(4), 477–489. https://doi.org/10.2522/ptj.20130118

109. Gaab, J., Blease, C., Locher, C., & Gerger, H. (2016). Go open: A plea for transparency in psychotherapy. *Psychology of Consciousness: Theory, Research, and Practice*, *3*(2), 175–198. https://doi.org/10.1037/cns0000063

110. Gaab, J., Locher, C., & Blease, C. (2018). Placebo and psychotherapy: Differences, similarities, and implications. *International Review of Neurobiology*, *138*, 241–255. https://doi.org/10.1016/bs.irn.2018.01.013

111. Georgii, A. A. du texte. (1847). *Kinésithérapie, ou Traitement des maladies par le mouvement selon la méthode de Ling, par A. Georgii. Suivi d'un abrégé des applications de Ling à l'éducation physique*. https://gallica.bnf.fr/ark:/12148/bpt6k56859395

112. Gold, A., & Lichtenberg, P. (2014). The moral case for the clinical placebo. *Journal of Medical Ethics*, *40*(4), 219–224. https://doi.org/10.1136/medethics-2012-101314

113. Gøtzsche, P. C. (1994). Is there logic in the placebo? *Lancet (London, England)*, *344*(8927), 925–926.

114. Gracely, R. H., Dubner, R., Deeter, W. R., & Wolskee, P. J. (1985). Clinicians' expectations influence placebo analgesia. *Lancet (London, England)*, *1*(8419), 43.

115. Grünbaum, A. (1986). The placebo concept in medicine and psychiatry. *Psychological Medicine*, *16*(1), 19–38. https://doi.org/10.1017/s0033291700002506

116. Guyatt, G., Cairns, J., Churchill, D., Cook, D., Haynes, B., Hirsh, J., Irvine, J., Levine, M., Levine, M., Nishikawa, J., Sackett, D., Brill-Edwards, P., Gerstein, H., Gibson, J., Jaeschke, R., Kerigan, A., Neville, A., Panju, A., Detsky, A., ... Tugwell, P. (1992). Evidence-Based Medicine: A New Approach to Teaching the Practice of Medicine. *JAMA*, *268*(17), 2420–2425. https://doi.org/10.1001/jama.1992.03490170092032

117. Haack, S. (1994). "Dry Truth and Real Knowledge": Epistemologies of Metaphor and Metaphors of Epistemology. In J. Hintikka (Ed.), *Aspects of Metaphor* (pp. 1–22). Springer Netherlands. https://doi.org/10.1007/978-94-015-8315-2_1

118. Haack, S. (1995). Evidence and Inquiry: Towards Reconstruction in Epistemology (1993). In *Philosophy and Phenomenological Research* (Vol. 56). Blackwell. https://doi.org/10.1023/A:1004924514117

119. Haack, S. (1997). The Puzzle of 'Scientific Method'. *Revue Internationale de Philosophie*, *51*(202 (4)), 495–505.

120. Hafliðadóttir, S. H., Juhl, C. B., Nielsen, S. M., Henriksen, M., Harris, I. A., Bliddal, H., & Christensen, R. (2021). Placebo response and effect in randomized clinical trials: Meta-research with focus on contextual effects. *Trials*, *22*(1), 493. https://doi.org/10.1186/s13063-021-05454-8

121. Hamberger, J., Meissner, K., Hinterberger, T., Loew, T., & Weimer, K. (2019). Placebo economics: A systematic review about the economic potential of utilizing the placebo effect. *Frontiers in Psychiatry*, *10*, 653. https://doi.org/10.3389/fpsyt.2019.00653

122. Hancock, M. J., Maher, C. G., Latimer, J., & McAuley, J. H. (2006). Selecting an appropriate placebo for a trial of spinal manipulative therapy. *Australian Journal of Physiotherapy*, *52*(2), 135–138. https://doi.org/10.1016/S0004-9514(06)70049-6

123. Harman, K., Sim, M., LeBrun, J., Almost, J., Andrews, C., Davies, H., Khalili, H., Sutton, E., & Price, S. (2021). Physiotherapy: An active, transformational, and authentic career choice. *Physiotherapy Theory and Practice*, *37*(5), 594–607. https://doi.org/10.1080/09593985.2019.1639230

124. Heiss, U., Rosenfield, M., & Bernstein, M. (2021). Can the open-label placebo rationale be optimized? *Frontiers in Pain Research*, 61.

125. Hohenschurz-Schmidt, D., Draper-Rodi, J., Vase, L., Scott, W., McGregor, A., Soliman, N., MacMillan, A., Olivier, A., Cherian, C. A., Corcoran, D., Abbey, H., Freigang, S., Chan, J., Phalip, J., Nørgaard Sørensen, L., Delafin, M., Baptista, M., Medforth, N. R., Ruffini, N., ... Rice, A. S. C. (2023). Blinding and sham control methods in trials of physical, psychological, and self-management interventions for pain (article I): A systematic review and description of methods. *PAIN*, *164*(3), 469. https://doi.org/10.1097/j.pain.0000000000002723

126. Hohenschurz-Schmidt, D., Draper-Rodi, J., Vase, L., Scott, W., McGregor, A., Soliman, N., MacMillan, A., Olivier, A., Cherian, C. A., Corcoran, D., Abbey, H., Freigang, S., Chan, J., Phalip, J., Sørensen, L. N., Delafin, M., Baptista, M., Medforth, N. R., Ruffini, N., ... Rice, A. S. C. (2023). Blinding and sham control methods in trials of physical, psychological, and self-management interventions for pain (article II): A meta-analysis relating methods to trial results. *PAIN*, *164*(3), 509. https://doi.org/10.1097/j.pain.0000000000002730

127. Hohenschurz-Schmidt, D., Thomson, O. P., Rossettini, G., Miciak, M., Newell, D., Roberts, L., Vase, L., & Draper-Rodi, J. (2022). Avoiding nocebo and other undesirable effects in chiropractic, osteopathy and physiotherapy: An invitation to reflect. *Musculoskeletal Science and Practice*, *62*, 102677. https://doi.org/10.1016/j.msksp.2022.102677

128. Hooper, R., & Quincy, J. (1817). *Quincy's Lexicon-medicum: A new medical dictionary, containing an explanation of the terms in anatomy, physiology, practice of physic, materia medica, chymistry, pharmacy, surgery, midwifery, and the various branches of natural philosophy connected with medicine*. Philadelphia: Published by E. & R. Parker, M. Carey & Son, and Benjamin Warner. http://archive.org/details/2557010R.nlm.nih.gov

129. Howe, L. C., Goyer, J. P., & Crum, A. J. (2017). Harnessing the placebo effect: Exploring the influence of physician characteristics on placebo response. *Health Psychology: Official Journal of the Division of Health Psychology, American Psychological Association*, *36*(11), 1074–1082. https://doi.org/10.1037/hea0000499

130. Howe, L. C., Hardebeck, E. J., Eberhardt, J. L., Markus, H. R., & Crum, A. J. (2022). White patients' physical responses to healthcare treatments are influenced by provider race and gender. *Proceedings of the National Academy of Sciences of the United States of America*, *119*(27), e2007717119. https://doi.org/10.1073/pnas.2007717119

131. Howick, J., Bishop, F. L., Heneghan, C., Wolstenholme, J., Stevens, S., Hobbs, F. D. R., & Lewith, G. (2013). Placebo use in the United Kingdom: Results from a national survey of primary care practitioners. *PloS One*, *8*(3), e58247. https://doi.org/10.1371/journal.pone.0058247

132. Howick, J., Moscrop, A., Mebius, A., Fanshawe, T. R., Lewith, G., Bishop, F. L., Mistiaen, P., Roberts, N. W., Dieninytė, E., Hu, X.-Y., Aveyard, P., & Onakpoya, I. J. (2018). Effects of empathic and positive communication in healthcare consultations: A systematic review and meta-analysis. *Journal of the Royal Society of Medicine*, *111*(7), 240–252. https://doi.org/10.1177/0141076818769477

133. Howick, J., Webster, R. K., Rees, J. L., Turner, R., Macdonald, H., Price, A., Evers, A. W. M., Bishop, F., Collins, G. S., Bokelmann, K., Hopewell, S., Knottnerus, A., Lamb, S., Madigan, C., Napadow, V., Papanikitas, A. N., & Hoffmann, T. (2020). TIDieR-Placebo: A

guide and checklist for reporting placebo and sham controls. *PLoS Medicine*, *17*(9), e1003294. https://doi.org/10.1371/journal.pmed.1003294

134. Hróbjartsson, A. (2002). What are the main methodological problems in the estimation of placebo effects? *Journal of Clinical Epidemiology*, *55*(5), 430–435.

135. Hróbjartsson, A., & Gøtzsche, P. C. (2001). Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *The New England Journal of Medicine*, *344*(21), 1594–1602. https://doi.org/10.1056/NEJM200105243442106

136. Hróbjartsson, A., & Gøtzsche, P. C. (2010). Placebo interventions for all clinical conditions. *The Cochrane Database of Systematic Reviews*, *1*, CD003974. https://doi.org/10.1002/14651858.CD003974.pub3

137. Hróbjartsson, A., Kaptchuk, T. J., & Miller, F. G. (2011). Placebo effect studies are susceptible to response bias and to other types of biases. *Journal of Clinical Epidemiology*, *64*(11), 1223–1229. https://doi.org/10.1016/j.jclinepi.2011.01.008

138. Hróbjartsson, A., & Norup, M. (2003). The use of placebo interventions in medical practice–a national questionnaire survey of Danish clinicians. *Evaluation & the Health Professions*, *26*(2), 153–165. https://doi.org/10.1177/0163278703026002002

139. Hurst, P., Schipof-Godart, L., Szabo, A., Raglin, J., Hettinga, F., Roelands, B., Lane, A., Foad, A., Coleman, D., & Beedie, C. (2020). The Placebo and Nocebo effect on sports performance: A systematic review. *European Journal of Sport Science*, *20*(3), 279–292. https://doi.org/10.1080/17461391.2019.1655098

140. Hush, J. M., Cameron, K., & Mackey, M. (2011). Patient satisfaction with musculoskeletal physical therapy care: A systematic review. *Physical Therapy*, *91*(1), 25–36. https://doi.org/10.2522/ptj.20100061

141. Jecker, N. S., & Self, D. J. (1991). Separating care and cure: An analysis of historical and contemporary images of nursing and medicine. *The Journal of Medicine and Philosophy*, *16*(3), 285–306. https://doi.org/10.1093/jmp/16.3.285

142. Jensen, J. S., Bielefeldt, A. Ø., & Hróbjartsson, A. (2017). Active placebo control groups of pharmacological interventions were rarely used but merited serious consideration: A methodological overview. *Journal of Clinical Epidemiology*, *87*, 35–46. https://doi.org/10.1016/j.jclinepi.2017.03.001

143. Jovic, L. (2008). Les conditions d'émergence d'une discipline scientifique et professionnelle. *Recherche en soins infirmiers*, *93*(2), 68–71. https://doi.org/10.3917/rsi.093.0068

144. Kaptchuk, T. J. (1998). Powerful placebo: The dark side of the randomised controlled trial. *Lancet (London, England)*, *351*(9117), 1722–1725. https://doi.org/10.1016/S0140-6736(97)10111-8

145. Kaptchuk, T. J., Friedlander, E., Kelley, J. M., Sanchez, M. N., Kokkotou, E., Singer, J. P., Kowalczykowski, M., Miller, F. G., Kirsch, I., & Lembo, A. J. (2010). Placebos without

deception: A randomized controlled trial in irritable bowel syndrome. *PloS One*, *5*(12), e15591. https://doi.org/10.1371/journal.pone.0015591

146. Kaptchuk, T. J., Kerr, C. E., & Zanger, A. (2009). Placebo controls, exorcisms, and the devil. *Lancet (London, England)*, *374*(9697), 1234–1235.

147. Kaptchuk, T. J., & Miller, F. G. (2015). Placebo effects in medicine. *The New England Journal of Medicine*, *373*(1), 8–9. https://doi.org/10.1056/NEJMp1504023

148. Kell, C., & Owen, G. (2008). Physiotherapy as a profession: Where are we now? *International Journal of Therapy and Rehabilitation*, *15*(4), 158–167. https://doi.org/10.12968/ijtr.2008.15.4.29034

149. Kelley, J. M. (2018). Lumping and splitting: Toward a taxonomy of placebo and related effects. *International Review of Neurobiology*, *139*, 29–48. https://doi.org/10.1016/bs.irn.2018.07.011

150. Kelley, J. M., Kraft-Todd, G., Schapira, L., Kossowsky, J., & Riess, H. (2014). The influence of the patient-clinician relationship on healthcare outcomes: A systematic review and meta-analysis of randomized controlled trials. *PloS One*, *9*(4), e94207. https://doi.org/10.1371/journal.pone.0094207

151. Kerr, C., Milne, I., & Kaptchuk, T. (2008). William Cullen and a missing mind-body link in the early history of placebos. *Journal of the Royal Society of Medicine*, *101*(2), 89–92. https://doi.org/10.1258/jrsm.2007.071005

152. Kerry, R., Maddocks, M., & Mumford, S. (2008). Philosophy of science and physiotherapy: An insight into practice. *Physiotherapy Theory and Practice*, *24*(6), 397–407. https://doi.org/10.1080/09593980802511797

153. Kienle, G. S., & Kiene, H. (1997). The powerful placebo effect: Fact or fiction? *Journal of Clinical Epidemiology*, *50*(12), 1311–1318.

154. Kirsch, I. (2013). The placebo effect revisited: Lessons learned to date. *Complementary Therapies in Medicine*, *21*(2), 102–104. https://doi.org/10.1016/j.ctim.2012.12.003

155. Kirsch, I. (2018). Response expectancy and the placebo effect. *International Review of Neurobiology*, *138*, 81–93. https://doi.org/10.1016/bs.irn.2018.01.003

156. Kleijnen, J., de Craen, A. J., van Everdingen, J., & Krol, L. (1994). Placebo effect in double-blind clinical trials: A review of interactions with medications. *Lancet (London, England)*, *344*(8933), 1347–1349. https://doi.org/10.1016/s0140-6736(94)90699-8

157. Kleine-Borgmann, J., Schmidt, K., Hellmann, A., & Bingel, U. (2019). Effects of open-label placebo on pain, functional disability, and spine mobility in patients with chronic back pain: A randomized controlled trial. *Pain*, *160*(12), 2891–2897. https://doi.org/10.1097/j.pain.0000000000001683

158. Kleine-Borgmann, J., Schmidt, K., Hellmann, A., & Bingel, U. (2020). Reply to Amorim et al. *Pain*, *161*(5), 1124–1125. https://doi.org/10.1097/j.pain.0000000000001804

159. Kolber, A. J. (2007). A Limited Defense of Clinical Placebo Deception. *Yale Law & Policy Review*, *26*, 75.

160. Kube, T., & Rief, W. (2017). Are placebo and drug-specific effects additive? Questioning basic assumptions of double-blinded randomized clinical trials and presenting novel study designs. *Drug Discovery Today*, *22*(4), 729–735. https://doi.org/10.1016/j.drudis.2016.11.022

161. Kube, T., Rief, W., Vivell, M.-B., Schäfer, N. L., Vermillion, T., Körfer, K., & Glombiewski, J. A. (2020). Deceptive and Nondeceptive Placebos to Reduce Pain: An Experimental Study in Healthy Individuals. *The Clinical Journal of Pain*, *36*(2), 68–79. https://doi.org/10.1097/AJP.0000000000000781

162. Kuhn, T. S. (1996). *The Structure of Scientific Revolutions* (3rd edition). University of Chicago Press.

163. Lado, E., Vacariza, M., Fernández-González, C., Gestal-Otero, J. J., & Figueiras, A. (2008). Influence exerted on drug prescribing by patients' attitudes and expectations and by doctors' perception of such expectations: A cohort and nested case-control study. *Journal of Evaluation in Clinical Practice*, *14*(3), 453–459. https://doi.org/10.1111/j.1365-2753.2007.00901.x

164. Lecordier, D. (2012). Recherche en soins infirmiers et paramedicaux, une question de point de vue disciplinaire. *Recherche en soins infirmiers*, *108*(1), 5–5. https://doi.org/10.3917/rsi.108.0005

165. Lecordier, D., Rémy-Largeau, I., & Jovic, L. (2013). Comment aborder la question de la discipline « sciences infirmières » en France? *Recherche en soins infirmiers*, *112*(1), 6–13. https://doi.org/10.3917/rsi.112.0006

166. Lichtenberg, P., Heresco-Levy, U., & Nitzan, U. (2004). The ethics of the placebo in clinical practice. *Journal of Medical Ethics*, *30*(6), 551–554. https://doi.org/10.1136/jme.2002.002832

167. Lilienfeld, S. O. (2017). Psychology's Replication Crisis and the Grant Culture: Righting the Ship. *Perspectives on Psychological Science: A Journal of the Association for Psychological Science*, *12*(4), 660–664. https://doi.org/10.1177/1745691616687745

168. Linde, K., Atmann, O., Meissner, K., Schneider, A., Meister, R., Kriston, L., & Werner, C. (2018). How often do general practitioners use placebos and non-specific interventions? Systematic review and meta-analysis of surveys. *PloS One*, *13*(8), e0202211. https://doi.org/10.1371/journal.pone.0202211

169. Lindquist, I., Engardt, M., Garnham, L., Poland, F., & Richardson, B. (2006). Physiotherapy students' professional identity on the edge of working life. *Medical Teacher*, *28*(3), 270–276. https://doi.org/10.1080/01421590600605272

170. Locher, C., Frey Nascimento, A., Kirsch, I., Kossowsky, J., Meyer, A., & Gaab, J. (2017). Is the rationale more important than deception? A randomized controlled trial of open-label placebo analgesia. *Pain*, *158*(12), 2320–2328. https://doi.org/10.1097/j.pain.0000000000001012

171. Locher, C., Gaab, J., & Blease, C. (2018). When a Placebo Is Not a Placebo: Problems and Solutions to the Gold Standard in Psychotherapy Research. *Frontiers in Psychology*, *9*, 2317. https://doi.org/10.3389/fpsyg.2018.02317

172. Loi n°46-857 du 30 avril 1946 tendant à la réglementation de l'exercice des professions de masseur gymnaste médical, de masseur-kinésithérapeute et de pédicure, 46-857 (1946). https://www.legifrance.gouv.fr/jorf/id/JORFTEXT000000315340

173. Lonsdale, C., Hall, A. M., Murray, A., Williams, G. C., McDonough, S. M., Ntoumanis, N., Owen, K., Schwarzer, R., Parker, P., Kolt, G. S., & Hurley, D. A. (2017). Communication skills training for practitioners to increase patient adherence to home-based rehabilitation for chronic low back pain: Results of a cluster randomized controlled trial. *Archives of Physical Medicine and Rehabilitation*, *98*(9), 1732-1743.e7. https://doi.org/10.1016/j.apmr.2017.02.025

174. Lorié, Á., Reinero, D. A., Phillips, M., Zhang, L., & Riess, H. (2017). Culture and nonverbal expressions of empathy in clinical settings: A systematic review. *Patient Education and Counseling*, *100*(3), 411–424. https://doi.org/10.1016/j.pec.2016.09.018

175. Louhiala, P., Hemilä, H., & Puustinen, R. (2015). Impure placebo is a useless concept. *Theoretical Medicine and Bioethics*, *36*(4), 279–289. https://doi.org/10.1007/s11017-015-9336-6

176. Louhiala, P., & Puustinen, R. (2008). Rethinking the placebo effect. *Medical Humanities*, *34*(2), 107–109. https://doi.org/10.1136/jmh.2008.000307

177. Lund, K., Vase, L., Petersen, G. L., Jensen, T. S., & Finnerup, N. B. (2014). Randomised Controlled Trials May Underestimate Drug Effects: Balanced Placebo Trial Design. *PLOS ONE*, *9*(1), e84104. https://doi.org/10.1371/journal.pone.0084104

178. Machado, L. A. C., Kamper, S. J., Herbert, R. D., Maher, C. G., & McAuley, J. H. (2008). Imperfect placebos are common in low back pain trials: A systematic review of the literature. *European Spine Journal*, *17*(7), 889–904. https://doi.org/10.1007/s00586-008-0664-3

179. Maher, C. G., Traeger, A. C., Shaheed, C. A., & O'Keeffe, M. (2021). Placebos in clinical care: A suggestion beyond the evidence. *Medical Journal of Australia*, *215*(6). https://www.mja.com.au/journal/2021/215/6/placebos-clinical-care-suggestion-beyond-evidence

180. Mast, M. S. (2007). On the importance of nonverbal communication in the physician-patient interaction. *Patient Education and Counseling*, *67*(3), 315–318. https://doi.org/10.1016/j.pec.2007.03.005

181. Mast, M. S., & Kadji, K. K. (2018). How female and male physicians' communication is perceived differently. *Patient Education and Counseling*, *101*(9), 1697–1701. https://doi.org/10.1016/j.pec.2018.06.003

182. Md Rezal, R. S., Hassali, M. A., Alrasheedy, A. A., Saleem, F., Md Yusof, F. A., & Godman, B. (2015). Physicians' knowledge, perceptions and behaviour towards antibiotic prescribing: A systematic review of the literature. *Expert Review of Anti-Infective Therapy*,

13(5), 665–680. https://doi.org/10.1586/14787210.2015.1025057

183. Meissner, K., & Linde, K. (2018). Are blue pills better than green? How treatment features modulate placebo effects. *International Review of Neurobiology*, *139*, 357–378. https://doi.org/10.1016/bs.irn.2018.07.014

184. Mercer, E., Mackay-Lyons, M., Conway, N., Flynn, J., & Mercer, C. (2008). Perceptions of outpatients regarding the attire of physiotherapists. *Physiotherapy Canada. Physiotherapie Canada*, *60*(4), 349–357. https://doi.org/10.3138/physio.60.4.349

185. Merton, R. K. (1979). *The Sociology of Science: Theoretical and Empirical Investigations* (N. W. Storer, Ed.). University of Chicago Press. https://press.uchicago.edu/ucp/books/book/chicago/S/bo28451565.html

186. Michener, L. A., Kardouni, J. R., Lopes Albers, A. D., & Ely, J. M. (2013). Development of a sham comparator for thoracic spinal manipulative therapy for use with shoulder disorders. *Manual Therapy*, *18*(1), 60–64. https://doi.org/10.1016/j.math.2012.07.003

187. Michener, L. A., Kardouni, J. R., Sousa, C. O., & Ely, J. M. (2015). Validation of a sham comparator for thoracic spinal manipulation in patients with shoulder pain. *Manual Therapy*, *20*(1), 171–175. https://doi.org/10.1016/j.math.2014.08.008

188. Miller, F. G. (2018). Reining in the placebo effect. *Perspectives in Biology and Medicine*, *61*(3), 335–348. https://doi.org/10.1353/pbm.2018.0046

189. Milne, I. (2012). Who was James Lind, and what exactly did he achieve. *Journal of the Royal Society of Medicine*, *105*(12), 503. https://doi.org/10.1258/jrsm.2012.12k090

190. Mistiaen, P., van Osch, M., van Vliet, L., Howick, J., Bishop, F. L., Di Blasi, Z., Bensing, J., & van Dulmen, S. (2016). The effect of patient-practitioner communication on pain: A systematic review. *European Journal of Pain (London, England)*, *20*(5), 675–688. https://doi.org/10.1002/ejp.797

191. Moerman, D. E., & Jonas, W. B. (2002). Deconstructing the placebo effect and finding the meaning response. *Annals of Internal Medicine*, *136*(6), 471–476.

192. Mondaini, N., Gontero, P., Giubilei, G., Lombardi, G., Cai, T., Gavazzi, A., & Bartoletti, R. (2007). Finasteride 5 mg and sexual side effects: How many of these are related to a nocebo phenomenon? *The Journal of Sexual Medicine*, *4*(6), 1708–1712. https://doi.org/10.1111/j.1743-6109.2007.00563.x

193. Mondloch, M. V., Cole, D. C., & Frank, J. W. (2001). Does how you do depend on how you think you'll do? A systematic review of the evidence for a relation between patients' recovery expectations and health outcomes. *CMAJ*, *165*(2), 174–179.

194. Monet, J. (2003). *Emergence de la kinésithérapie en France à la fin du XIXe et au début du XXe siècle: Une spécialité médicale impossible : genèse, acteurs et intérêts de 1880 à 1914* [These de doctorat, Paris 1]. https://www.theses.fr/2003PA010575

195. Monet, J. (2006, January). Construction historique d'une spécilisation médicale

impossible: La kinésithérapie. *Kinésthérapie Scientifique*, *462*.

196. Monvoisin, R. (2020, November 5). *Question reçue: Source de l'erreur de traduction sur le terme placebo* -. https://www.monvoisin.xyz/question-recue-source-de-lerreur-de-traduction-sur-le-terme-placebo/

197. Mundt, J. M., Roditi, D., & Robinson, M. E. (2017). A comparison of deceptive and non-deceptive placebo analgesia: Efficacy and ethical consequences. *Annals of Behavioral Medicine: A Publication of the Society of Behavioral Medicine*, *51*(2), 307–315. https://doi.org/10.1007/s12160-016-9854-0

198. Nicholls, D. A. (2021). Where history is concerned: An editorial for the special issue on physiotherapy history. *Physiotherapy Theory and Practice*, *37*(3), 355–358. https://doi.org/10.1080/09593985.2021.1887065

199. Nicholls, D. A., & Cheek, J. (2006). Physiotherapy and the shadow of prostitution: The Society of Trained Masseuses and the massage scandals of 1894. *Social Science & Medicine*, *62*(9), 2336–2348. https://doi.org/10.1016/j.socscimed.2005.09.010

200. Noronen, L., & Wikstrom-Grotell, C. (1999). Towards a paradigm-oriented approach in physiotherapy. *Physiotherapy Theory and Practice*, *15*(3), 175–184. https://doi.org/10.1080/095939899307720

201. O'Keeffe, M., Cullinane, P., Hurley, J., Leahy, I., Bunzli, S., O'Sullivan, P. B., & O'Sullivan, K. (2016). What influences patient-therapist interactions in musculoskeletal physical therapy? Qualitative systematic review and meta-synthesis. *Physical Therapy*, *96*(5), 609–622. https://doi.org/10.2522/ptj.20150240

202. O'Neill, O. (1984). Paternalism and partial autonomy. *Journal of Medical Ethics*, *10*(4), 173–178. https://doi.org/10.1136/jme.10.4.173

203. Ordonnance n°45-2631 du 2 novembre 1945 Comité Consultatif des Universités. Retrieved 19 February 2023, from https://www.legifrance.gouv.fr/jorf/id/JORFTEXT000000522125

204. Park, L. C., & Covi, L. (1965). Nonblind Placebo Trial: An Exploration of Neurotic Patients' Responses to Placebo When Its Inert Content Is Disclosed. *Archives of General Psychiatry*, *12*(4), 336–345. https://doi.org/10.1001/archpsyc.1965.01720340008002

205. Pieters, L., Lewis, J., Kuppens, K., Jochems, J., Bruijstens, T., Joossens, L., & Struyf, F. (2020). An Update of Systematic Reviews Examining the Effectiveness of Conservative Physical Therapy Interventions for Subacromial Shoulder Pain. *Journal of Orthopaedic & Sports Physical Therapy*, *50*(3), 131–141. https://doi.org/10.2519/jospt.2020.8498

206. Pinsault, N., & Monvoisin, R. (2014). *Tout ce que vous n'avez jamais voulu savoir sur le thérapies manuelles*. PUG - Presses universitaires de Grenoble.

207. *Policy statement: Description of physical therapy.* (n.d.). World Physiotherapy. Retrieved 16 April 2023, from https://world.physio/policy/ps-descriptionPT

208. Pouwels, K. B., Dolk, F. C. K., Smith, D. R. M., Robotham, J. V., & Smieszek, T. (2018). Actual versus 'ideal' antibiotic prescribing for common conditions in English primary care. *The Journal of Antimicrobial Chemotherapy*, *73*(suppl$_2$), 19–26. https://doi.org/10.1093/jac/dkx502

209. *Proposition de loi portant amélioration de l'accès aux soins par la confiance aux professionnels de santé*. (n.d.). vie-publique.fr. Retrieved 16 April 2023, from http://www.vie-publique.fr/loi/288203-acces-aux-soins-proposition-de-loi-rist

210. Puentedura, E. J., & Flynn, T. (2016). Combining manual therapy with pain neuroscience education in the treatment of chronic low back pain: A narrative review of the literature. *Physiotherapy Theory and Practice*, *32*(5), 408–414. https://doi.org/10.1080/09593985.2016.1194663

211. Quine, W., & Ullian, J. (1970). *The web of belief*. https://www.semanticscholar.org/paper/The-web-of-belief-Quine-Ullian/57f1d9744b841944e9d7dd67001d88e706037319

212. Raynaud, D. (2016a). Chapitre 1. Science, technique, technologie. In *Qu'est-ce que la technologie ?* (pp. 21–55). Éditions Matériologiques; Cairn.info. https://www.cairn-sciences.info/qu-est-ce-que-la-technologie--9782373610444-p-21.htm

213. Raynaud, D. (2016b). *Qu'est-ce que la technologie ?* Éditions Matériologiques; Cairn.info. https://www.cairn.info/qu-est-ce-que-la-technologie--9782373610444.htm

214. Roberts, A. H., Kewman, D. G., Mercier, L., & Hovell, M. (1993). The power of nonspecific effects in healing: Implications for psychosocial and biological treatments. *Clinical Psychology Review*, *13*(5), 375–391. https://doi.org/10.1016/0272-7358(93)90010-J

215. Roberts, L., & Bucksey, S. J. (2007). Communicating with patients: What happens in practice? *Physical Therapy*, *87*(5), 586–594. https://doi.org/10.2522/ptj.20060077

216. Roger, J., Darfour, D., Dham, A., Hickman, O., Shaubach, L., & Shepard, K. (2002). Physiotherapists' use of touch in inpatient settings. *Physiotherapy Research International*, *7*(3), 170–186. https://doi.org/10.1002/pri.253

217. Rollin, J. (2022). *Un corps en mouvement: Déplacements sociaux et professionnalisation de la kinésithérapie* [These de doctorat, Lyon, École normale supérieure]. https://theses.fr/2022ENSL0031

218. Rossettini, G., Camerone, E. M., Carlino, E., Benedetti, F., & Testa, M. (2020). Context matters: The psychoneurobiological determinants of placebo, nocebo and context-related effects in physiotherapy. *Archives of Physiotherapy*, *10*, 11. https://doi.org/10.1186/s40945-020-00082-y

219. Rossettini, G., Carlino, E., & Testa, M. (2018). Clinical relevance of contextual factors as triggers of placebo and nocebo effects in musculoskeletal pain. *BMC Musculoskeletal Disorders*, *19*(1), 27. https://doi.org/10.1186/s12891-018-1943-8

220. Rossettini, G., Geri, T., Palese, A., Marzaro, C., Mirandola, M., Colloca, L., Fiorio, M.,

Turolla, A., Manoni, M., & Testa, M. (2020). What physiotherapists specialized in orthopedic manual therapy know about nocebo-related effects and contextual factors: Findings from a national survey. *Frontiers in Psychology*, *11*, 582174. https://doi.org/10.3389/fpsyg.2020.582174

221. Rossettini, G., Palese, A., Geri, T., Fiorio, M., Colloca, L., & Testa, M. (2018). Physical therapists' perspectives on using contextual factors in clinical practice: Findings from an Italian national survey. *PloS One*, *13*(11), e0208159. https://doi.org/10.1371/journal.pone.0208159

222. Rossettini, G., Palese, A., Geri, T., Mirandola, M., Tortella, F., & Testa, M. (2019). The knowledge of contextual factors as triggers of placebo and nocebo effects in patients with musculoskeletal pain: Findings from a national survey. *Frontiers in Psychiatry*, *10*, 478. https://doi.org/10.3389/fpsyt.2019.00478

223. Rothstein, J. M. (1992). Our identity and the power of touch. *Physical Therapy*, *72*(4), 249–250. https://doi.org/10.1093/ptj/72.4.249

224. Samulowitz, A., Gremyr, I., Eriksson, E., & Hensing, G. (2018). 'Brave Men' and 'Emotional Women': A theory-guided literature review on gender bias in health care and gendered norms towards patients with chronic pain. *Pain Research & Management*, *2018*, 6358624. https://doi.org/10.1155/2018/6358624

225. Sandhu, H., Adams, A., Singleton, L., Clark-Carter, D., & Kidd, J. (2009). The impact of gender dyads on doctor-patient communication: A systematic review. *Patient Education and Counseling*, *76*(3), 348–355. https://doi.org/10.1016/j.pec.2009.07.010

226. Scheres, J., & Kuszewski, K. (2019). The Ten Threats to Global Health in 2018 and 2019. A welcome and informative communication of WHO to everybody. *Zdrowie Publiczne i Zarządzanie*, *17*(1), 2–8. https://doi.org/10.4467/20842627OZ.19.001.11297

227. Schmid Mast, M., Hall, J. A., & Roter, D. L. (2007). Disentangling physician sex and physician communication style: Their effects on patient satisfaction in a virtual medical visit. *Patient Education and Counseling*, *68*(1), 16–22. https://doi.org/10.1016/j.pec.2007.03.020

228. Schwab, A. P. (2009). When subtle deception turns into an outright lie. *The American Journal of Bioethics: AJOB*, *9*(12), 30–32. https://doi.org/10.1080/15265160903234128

229. Shapiro, A. K., & Shapiro, E. (1997a). The placebo: Is it much ado about nothing? In *The placebo effect: An interdisciplinary exploration* (pp. 12–36). Harvard University Press.

230. Shapiro, A. K., & Shapiro, E. (1997b). *The powerful placebo: From ancient priest to modern physician* (pp. xi, 280). Johns Hopkins University Press.

231. Shaw, J. A., & DeForge, R. T. (2012). Physiotherapy as bricolage: Theorizing expert practice. *Physiotherapy Theory and Practice*, *28*(6), 420–427. https://doi.org/10.3109/09593985.2012.676941

232. Sherriff, B., Clark, C., Killingback, C., & Newell, D. (2023). Musculoskeletal practitioners' perceptions of contextual factors that may influence chronic low back pain outcomes: A modified Delphi study. *Chiropractic & Manual Therapies*, *31*(1), 12.

https://doi.org/10.1186/s12998-023-00482-4

233. Shneider, A. M. (2009). Four stages of a scientific discipline; four types of scientist. *Trends in Biochemical Sciences*, *34*(5), 217–223. https://doi.org/10.1016/j.tibs.2009.02.002

234. *SIPS: Home*. (n.d.). Retrieved 1 March 2023, from https://placebosociety.org/home

235. Sochacki, K. R., Mather, R. C., Nwachukwu, B. U., Dong, D., Nho, S. J., Cote, M. P., & Harris, J. D. (2020). Sham surgery studies in orthopaedic surgery may just be a sham: A systematic review of randomized placebo-controlled trials. *Arthroscopy: The Journal of Arthroscopic & Related Surgery: Official Publication of the Arthroscopy Association of North America and the International Arthroscopy Association*, *36*(10), 2750-2762.e2. https://doi.org/10.1016/j.arthro.2020.05.001

236. Sokol, D. K. (2007). Can deceiving patients be morally acceptable? *BMJ (Clinical Research Ed.)*, *334*(7601), 984–986. https://doi.org/10.1136/bmj.39184.419826.80

237. Specker Sullivan, L. (2020). More than consent for ethical open-label placebo research. *Journal of Medical Ethics*. https://doi.org/10.1136/medethics-2019-105893

238. Spille, L., Fendel, J. C., Seuling, P. D., Göritz, A. S., & Schmidt, S. (2023). Open-label placebos—A systematic review and meta-analysis of experimental studies with non-clinical samples. *Scientific Reports*, *13*(1), Article 1. https://doi.org/10.1038/s41598-023-30362-z

239. Stack, E. (2006). Physiotherapy: The ultimate placebo. *Physiotherapy Research International: The Journal for Researchers and Clinicians in Physical Therapy*, *11*(3), 127–128. https://doi.org/10.1002/pri.342

240. Stegenga, J. (2018). *Care and Cure: An Introduction to Philosophy of Medicine*. University of Chicago Press. https://press.uchicago.edu/ucp/books/book/chicago/C/bo29193227.html

241. Stenberg, G., Fjellman-Wiklund, A., & Ahlgren, C. (2012). 'Getting confirmation': Gender in expectations and experiences of healthcare for neck or back patients. *Journal of Rehabilitation Medicine*, *44*(2), 163–171. https://doi.org/10.2340/16501977-0912

242. Stickley, T. (2011). From SOLER to SURETY for effective non-verbal communication. *Nurse Education in Practice*, *11*(6), 395–398. https://doi.org/10.1016/j.nepr.2011.03.021

243. Street, Jr, R. L., Makoul, G., Arora, N. K., & Epstein, R. M. (2009). How does communication heal? Pathways linking clinician-patient communication to health outcomes. *Patient Education and Counseling*, *74*(3), 295–301. https://doi.org/10.1016/j.pec.2008.11.015

244. Sussex, R. (2018). Describing placebo phenomena in medicine: A linguistic approach. *International Review of Neurobiology*, *139*, 49–83. https://doi.org/10.1016/bs.irn.2018.07.032

245. Szawarski, Z. (2004). The concept of placebo. *Science and Engineering Ethics*, *10*(1), 57–64. https://doi.org/10.1007/s11948-004-0063-z

246. Testa, M., & Rossettini, G. (2016). Enhance placebo, avoid nocebo: How contextual

factors affect physiotherapy outcomes. *Manual Therapy*, *24*, 65–74. https://doi.org/10.1016/j.math.2016.04.006

247. The Massage Scandals. (1899). *The Lancet*, *153*(3950), 1310–1311. https://doi.org/10.1016/S0140-6736(01)50360-8

248. The Word. (2023, February 13). *HISTORY.PHYSIO*. https://history.physio/projects/the-word/

249. Thomas, K. B. (1987). General practice consultations: Is there any point in being positive? *British Medical Journal (Clinical Research Ed.)*, *294*(6581), 1200–1202.

250. Tilburt, J. C., Emanuel, E. J., Kaptchuk, T. J., Curlin, F. A., & Miller, F. G. (2008). Prescribing 'placebo treatments': Results of national survey of US internists and rheumatologists. *BMJ (Clinical Research Ed.)*, *337*. https://doi.org/10.1136/bmj.a1938

251. Torgerson, D. J., & Roland, M. (1998). What is zelen's design? *BMJ (Clinical Research Ed.)*, *316*(7131), 606. https://doi.org/10.1136/bmj.316.7131.606

252. Traeger, A. C., & Kamper, S. J. (2017). The effect of nothing? Time to abandon the concept of placebo. *PAIN*, *158*(6), 1179. https://doi.org/10.1097/j.pain.0000000000000884

253. Tsutsumi, Y., Tsujimoto, Y., Tajika, A., Omae, K., Fujii, T., Onishi, A., Kataoka, Y., Katsura, M., Noma, H., Sahker, E., Ostinelli, E. G., & Furukawa, T. A. (2023). Proportion attributable to contextual effects in general medicine: A meta-epidemiological study based on Cochrane reviews. *BMJ Evidence-Based Medicine*, *28*(1), 40–47. https://doi.org/10.1136/bmjebm-2021-111861

254. Turner, A. (2011). `Placebos' and the logic of placebo comparison. *Biology &amp Philosophy*, *27*(3), 419–432. https://doi.org/10.1007/s10539-011-9289-8

255. Turner, A. (2018). What are the benefits of a new placebo language? *Perspectives in Biology and Medicine*, *61*(3), 401–411. https://doi.org/10.1353/pbm.2018.0052

256. Valentini, E., Martini, M., Lee, M., Aglioti, S. M., Iannetti, G. D., & Iannetti, G. (2014). Seeing facial expressions enhances placebo analgesia. *Pain*, *155*(4), 666–673. https://doi.org/10.1016/j.pain.2013.11.021

257. Varelmann, D., Pancaro, C., Cappiello, E. C., & Camann, W. R. (2010). Nocebo-induced hyperalgesia during local anesthetic injection. *Anesthesia and Analgesia*, *110*(3), 868–870. https://doi.org/10.1213/ANE.0b013e3181cc5727

258. Vase, L. (2020). Can insights from placebo and nocebo mechanisms studies improve the randomized controlled trial? *Scandinavian Journal of Pain*, *20*(3), 451–467. https://doi.org/10.1515/sjpain-2019-0183

259. Vase, L., Nørskov, K. N., Petersen, G. L., & Price, D. D. (2011). Patients' direct experiences as central elements of placebo analgesia. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *366*(1572), 1913–1921. https://doi.org/10.1098/rstb.2010.0402

260. Vase, L., Petersen, G. L., Riley, 3rd, J. L., & Price, D. D. (2009). Factors contributing to large analgesic effects in placebo mechanism studies conducted between 2002 and 2007. *Pain*, *145*(1–2), 36–44. https://doi.org/10.1016/j.pain.2009.04.008

261. Vase, L., Riley, 3rd, J. L., & Price, D. D. (2002). A comparison of placebo effects in clinical analgesic trials versus studies of placebo analgesia. *Pain*, *99*(3), 443–452.

262. Vase, L., & Wartolowska, K. (2019). Pain, placebo, and test of treatment efficacy: A narrative review. *British Journal of Anaesthesia*, *123*(2), e254–e262. https://doi.org/10.1016/j.bja.2019.01.040

263. von Wernsdorff, M., Loef, M., Tuschen-Caffier, B., & Schmidt, S. (2021). Effects of open-label placebos in clinical trials: A systematic review and meta-analysis. *Scientific Reports*, *11*(1), 3855. https://doi.org/10.1038/s41598-021-83148-6

264. Voudouris, N. J., Peck, C. L., & Coleman, G. (1990). The role of conditioning and verbal expectancy in the placebo response. *Pain*, *43*(1), 121–128.

265. Wartolowska, K. A., Hohenschurz-Schmidt, D., Vase, L., & Aronson, J. K. (2022). The importance of using placebo controls in nonpharmacological randomised trials. *PAIN*, 10.1097/j.pain.0000000000002839. https://doi.org/10.1097/j.pain.0000000000002839

266. Wartolowska, K., Beard, D., & Carr, A. (2017). Blinding in trials of interventional procedures is possible and worthwhile. *F1000Research*, *6*, 1663. https://doi.org/10.12688/f1000research.12528.2

267. Wartolowska, K., Beard, D. J., & Carr, A. J. (2014). Attitudes and beliefs about placebo surgery among orthopedic shoulder surgeons in the United Kingdom. *PloS One*, *9*(3), e91699. https://doi.org/10.1371/journal.pone.0091699

268. Wartolowska, K., Judge, A., Hopewell, S., Collins, G. S., Dean, B. J. F., Rombach, I., Brindley, D., Savulescu, J., Beard, D. J., & Carr, A. J. (2014). Use of placebo controls in the evaluation of surgery: Systematic review. *BMJ (Clinical Research Ed.)*, *348*, g3253. https://doi.org/10.1136/bmj.g3253

269. Weimer, K., Buschhart, C., Broelz, E. K., Enck, P., & Horing, B. (2022). Bibliometric properties of placebo literature from the JIPS database: A descriptive study. *Frontiers in Psychiatry*, *13*, 853953. https://doi.org/10.3389/fpsyt.2022.853953

270. Whiteside, N., Sarmanova, A., Chen, X., Zou, K., Abdullah, N., Doherty, M., & Zhang, W. (2017). Proportion of contextual effects in the treatment of fibromyalgia—A meta-analysis of randomised controlled trials. *Clinical Rheumatology*, *37*(5), 1375–1382. https://doi.org/10.1007/s10067-017-3948-3

271. Wikström-Grotell, C., Noronen, L., & Lenné, R. (2018). Physiotherapy as an academic discipline – from the perspective of Nordic doctoral dissertations. *European Journal of Physiotherapy*, *20*(2), 79–84. https://doi.org/10.1080/21679169.2017.1374453

272. Wilcox, J., & Riddle, J. M. (1995). Qustā Ibn Lūqā's Physical Ligatures and the Recognition of the Placebo Effect. *Medieval Encounters*, *1*(1), 1–25.

https://doi.org/10.1163/157006795X00046

273. World Health Organization. (1992). *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. World Health Organization.

274. World Health Organization. (2001). *International Classification of Functioning, Disability and Health: ICF.* World Health Organization.

275. Zelen, M. (1979). A new design for randomized clinical trials. *The New England Journal of Medicine*, *300*(22), 1242–1245. https://doi.org/10.1056/NEJM197905313002203

276. Zhang, W. (2019). The powerful placebo effect in osteoarthritis. *Clinical and Experimental Rheumatology*, *37 Suppl 120*(5), 118–123.

277. Zou, K., Wong, J., Abdullah, N., Chen, X., Smith, T., Doherty, M., & Zhang, W. (2016). Examination of overall treatment effect and the proportion attributable to contextual effect in osteoarthritis: Meta-analysis of randomised controlled trials. *Annals of the Rheumatic Diseases*, *75*(11), 1964–1970. https://doi.org/10.1136/annrheumdis-2015-208387

278. Zunhammer, M., Spisák, T., Wager, T. D., Bingel, U., & Placebo Imaging Consortium. (2021). Meta-analysis of neural systems underlying placebo analgesia from individual participant fMRI data. *Nature Communications*, *12*(1), 1391. https://doi.org/10.1038/s41467-021-21179-3

SUPPLEMENTARY MATERIALS

1. ARTICLE 2 SUPPLEMENTARY MATIERIALS

- Questionnaire evaluating knowledge on placebo effects
- Complementary Data from Article 2

Supplementary Material 1

Auto-évaluation à propos des effets placebos :

Consignes : Cochez les réponses correctes. Il peut y avoir d'aucune à et toutes les réponses justes. Le questionnaire comporte 17 questions réparties sur 3 pages.

Connaissez-vous le placebo ?

- o Non pas du tout
- o J'en ai déjà entendu parler
- o J'ai quelques notions
- o Oui je sais ce qu'est le placebo

1. **Le placebo :**
   - o A un effet seulement chez les personnes qui y croient
   - o Fonctionne uniquement si le patient ignore qu'il s'agit d'un placebo
   - o A un effet si le patient sait qu'il s'agit d'un placebo

2. **Le mécanisme de l'effet placebo est**
   - o Inexistant
   - o Psychologique
   - o Psychologique et physiologique

3. **Les traitements placebo ne sont efficaces que sur les patients qui mentent à propos de leurs symptômes**
   - o Vrai
   - o Faux

4. **Un comprimé de paracétamol utilisé contre la douleur est un placebo**
   - o Vrai
   - o Faux

5. **Les effets placebo fonctionnent notamment grâce aux attentes des patients**
   - o Vrai
   - o Faux

6. **Les effets placebos ne sont efficaces que chez les personnes optimistes**
   - o Vrai
   - o Faux

7. **Les traitements placebo peuvent traiter des douleurs**
   - o Vrai
   - o Faux

1

8. **Les traitements placebo ne peuvent pas résoudre des symptômes nécessitant une médication précise**
   - o Vrai
   - o Faux

9. **Les traitements placebo dits « antalgiques » ne soulagent que les douleurs imaginaires (i.e. douleurs n'étant pas liées à une lésion/maladie)**
   - o Vrai
   - o Faux

10. **Un comprimé sans substance pharmacologique est un placebo**
    - o Vrai
    - o Faux

11. **Les effets placebo fonctionnent grâce au contexte dans lequel est administré le soin**
    - o Vrai
    - o Faux

12. **Des modifications physiologiques, comme la sécrétion de molécules chimiques, ont lieu dans le cerveau quand vous recevez un placebo**
    - o Vrai
    - o Faux

13. **Les effets placebo sont imaginaires et n'ont d'effets que sur notre psychique et non sur notre corps**
    - o Vrai
    - o Faux

14. **Les effets placebo n'ont lieu que lors des expériences, en recherche clinique**
    - o Vrai
    - o Faux

15. **Un comprimé placebo peut avoir des effets secondaires**
    - o Vrai
    - o Faux

16. **Il n'existe pas d'effets placebo lors d'un traitement médical classique**
    - o Vrai
    - o Faux

17. La couleur, la forme et le conditionnement d'un comprimé placebo peuvent modifier son efficacité

- ○ Vrai
- ○ Faux

3

Supplementary Material 1

Complementary Data :

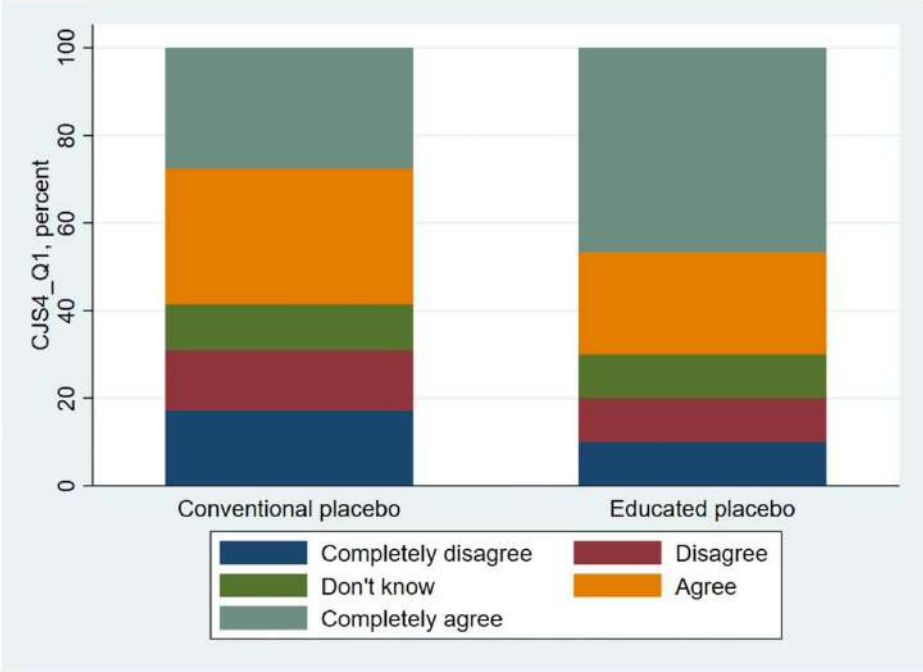
CJS4

Tableau descriptif

Groupe	Placebo classique	Placebo éduqué
N	29	30
Q1 Je savais ce que les chercheurs étudiaient dans cette recherche.		
Tout à fait en désaccord	5 (17.2)	3 (10.0)
Plutôt en désaccord	4 (13.8)	3 (10.0)
Sans Avis	3 (10.3)	3 (10.0)
D'accord	9 (31.0)	7 (23.3)
Tout à fait d'accord	8 (27.6)	14 (46.7)
Q2 Je n'étais pas sûr de ce que les chercheurs essayaient de démontrer dans cet		
Tout à fait en désaccord	6 (20.7)	13 (43.3)
Plutôt en désaccord	10 (34.5)	7 (23.3)
Sans Avis	2 (6.9)	3 (10.0)
D'accord	9 (31.0)	5 (16.7)
Tout à fait d'accord	2 (6.9)	2 (6.7)
Q3 J'ai eu une bonne idée de ce que les hypothèses ont été dans cette recherche		
Tout à fait en désaccord	3 (10.3)	1 (3.3)
Plutôt en désaccord	2 (6.9)	2 (6.7)
Sans Avis	4 (13.8)	3 (10.0)
D'accord	17 (58.6)	14 (46.7)
Tout à fait d'accord	3 (10.3)	10 (33.3)
Q4 Je ne savais pas exactement ce que les chercheurs visaient à prouver dans ce		
Tout à fait en désaccord	5 (17.2)	15 (50.0)
Plutôt en désaccord	11 (37.9)	9 (30.0)

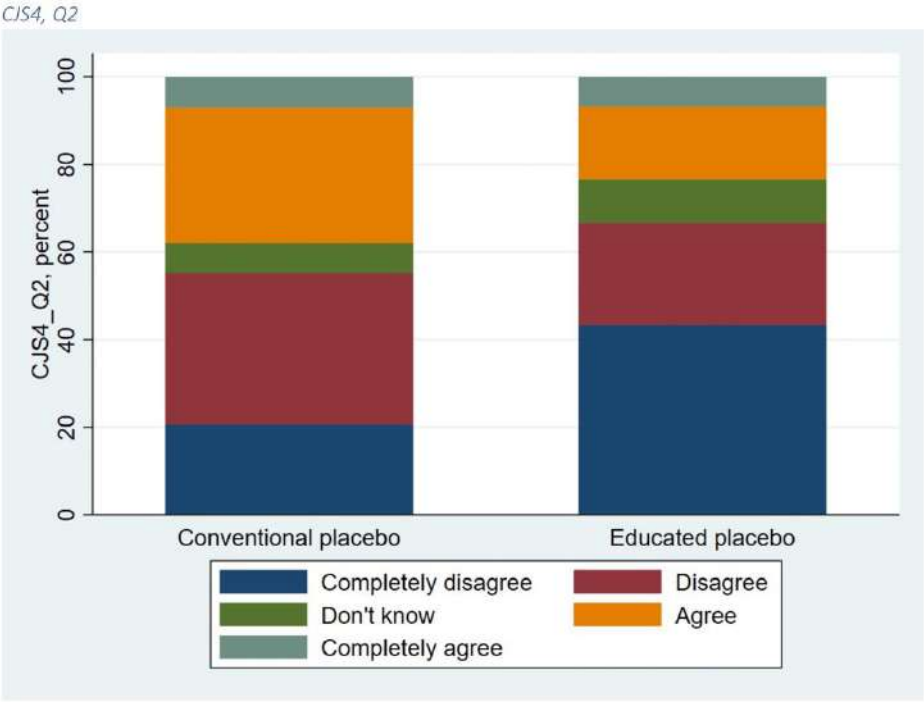
Sans Avis	3 (10.3)	1 (3.3)
D'accord	7 (24.1)	4 (13.3)
Tout à fait d'accord	3 (10.3)	1 (3.3)

CJS4, Q1



Résultat du test des rangs de Wilcoxon : p = 0.156

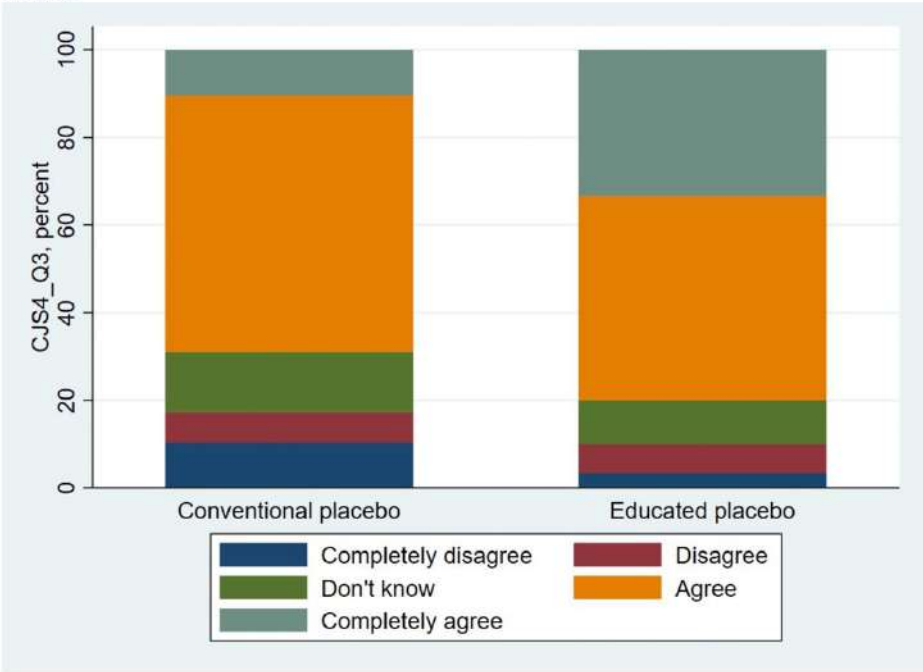
Interprétation : Nous n'avons pas mis en évidence de différence statistiquement significative entre les deux groupes.



Résultat du test des rangs de Wilcoxon : p = 0.123

Interprétation : Nous n'avons pas mis en évidence de différence statistiquement significative entre les deux groupes.

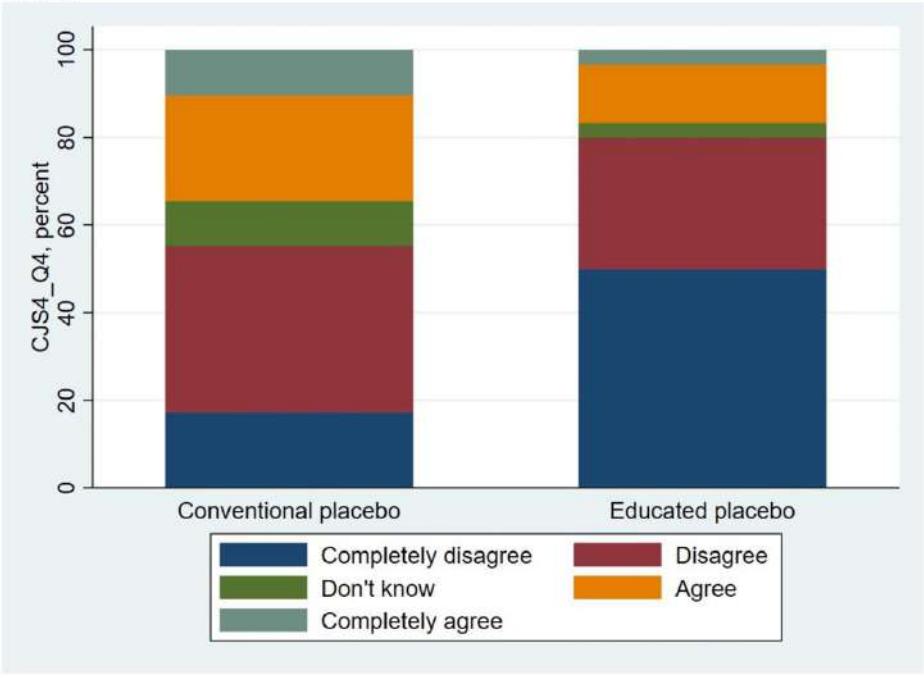
CJS4, Q3



Résultat du test des rangs de Wilcoxon : p = 0.056

Interprétation : Nous n'avons pas mis en évidence de différence statistiquement significative entre les deux groupes.

CJS4, Q4

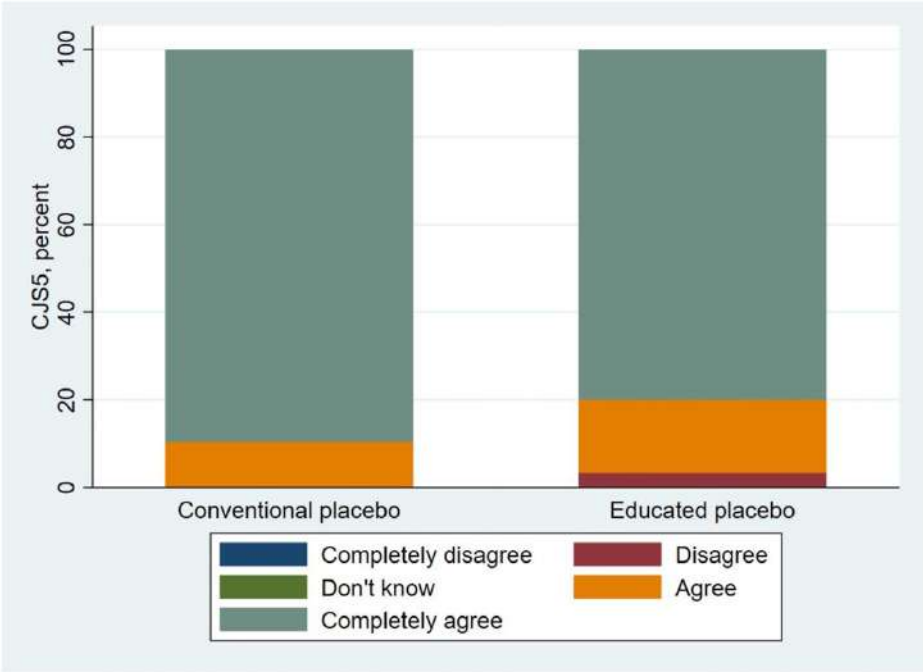


Résultat du test des rangs de Wilcoxon : p = 0.007

Interprétation : Les participants du groupe placebo éduqué sont statistiquement significativement moins en accord avec la question 4 que les participants du groupe placebo classique.

CJS5

Groupe	Placebo classique	Placebo éduqué
N	29	30
Durant l'étude, j'avais confiance en l'investigateur ou l'investigatrice.		
Plutôt en désaccord	0 (0.0)	1 (3.3)
D'accord	3 (10.3)	5 (16.7)
Tout à fait d'accord	26 (89.7)	24 (80.0)



Résultat du test des rangs de Wilcoxon : p = 0.391

Interprétation : Nous n'avons pas mis en évidence de différence statistiquement significative entre les deux groupes.

2. ARTICLE 4 SUPPLEMENTARY MATERIALS

- CF Questionnaire FR
- CF Questionnaire EN
- Questionnaire logic sheet
- Supplementary figure: Estimated effect size for each CF
- Supplementary figure: Use and pace of use for each CF
- Supplementary figure: Inter-healthcare provider CF use

Introduction

Bienvenue dans cette enquête !

Chers consœurs, confrères, étudiantes, étudiants,

Cette enquête vise à étudier dans quelle mesure les professionnel(le)s de santé utilisent le contexte dans lesquels ils prennent en charge leurs patients. Celui-ci peut améliorer ou détériorer le résultat des traitements qu'ils administrent.
En effet, il est admis que des facteurs en lien avec la relation soignant-soigné ou l'environnement peuvent influencer les résultats des traitements : on les nomme les facteurs contextuels. Par exemple, les termes utilisés pour s'adresser au patient, la posture adoptée par le professionnel ou le fait de porter une blouse peuvent influencer la perception de la douleur, le niveau d'anxiété ou la performance physique d'un patient.

Les professionnels de santé en exercice en France, en Suisse et en Belgique comme les étudiants des filières de santé en formation en France, Suisse ou Belgique peuvent répondre à ce questionnaire.

Dans les questions qui suivent, **nous vous demandons de bien vouloir répondre <u>en fonction de votre propre expérience</u>**.

Votre participation à l'étude nécessite 10 à 15 minutes et votre contribution ne sera enregistrée que si l'ensemble du questionnaire est complété. Ainsi, si vous choisissez de ne pas aller au bout du remplissage du questionnaire, aucune donnée ne sera enregistrée. La participation à cette étude ne présente aucun risque ou bénéfice direct pour les participant(e)s. À cet égard, cette étude a fait l'objet d'une déclaration auprès du Comité d'Éthique de la Recherche de l'Université Grenoble Alpes.
Les réponses sont pseudo-anonymes et ne seront utilisées qu'à des fins de recherche. Les données produites sont stockées et traitées dans le respect du RGPD sur des serveurs de l'Université Grenoble Alpes conformes aux exigences du RGPD. Le traitement des données est conforme avec une méthodologie de référence (MR004) de la CNIL.

En cliquant sur "Suivant", vous acceptez de participer à l'étude et consentez à l'utilisation des données produites par la réponse à ce questionnaire dans les conditions décrites plus haut. Les résultats de cette recherche-ci feront l'objet d'une publication scientifique ainsi que de présentations en congrès. En aucun cas, l'anonymat de la participation ne peut être levé et les résultats ne seront présentés que de manière groupée.

Si au terme de l'étude vous souhaitez retirer votre participation ou que vous souhaitez obtenir un renseignement, vous pouvez contacter le coordinateur de l'étude : leo.druart@univ-grenoble-alpes.fr.

Autoévaluation des connaissances

D'après vous, quel est l'état de vos connaissances sur les effets contextuels :

Pas de connaissances — Excellente connaissance du sujet

D'après vous, est-ce que ces connaissances influencent votre pratique clinique ?

Pas du tout — Beaucoup

D'après vous, l'effet contextuel est défini comme :

- ○ Je ne sais pas
- ○ Un traitement n'ayant pas d'efficacité propre ou spécifique
- ○ Aucune des propositions
- ○ Une manifestation des différents symptômes d'une maladie et de leur évolution au cours du temps en l'absence de traitement
- ○ Un effet de l'interaction ou de la présence avec un(e) soignant(e)
- ○ Un effet psycho-physiologique positif (bénéfique) ou négatif (dommageable) observé après un soin quel qu'il soit

L'ordre des items est aléatoire

Connaissances générales

Dans la suite du questionnaire nous considérerons l'effet contextuel comme étant un effet psycho-physiologique positif (bénéfique) ou négatif (dommageable) observé après un soin quel qu'il soit. Celui-ci peut améliorer ou détériorer le résultat des traitements administrés. En effet, il est admis que certains éléments du contexte peuvent influencer les résultats des traitements : on les nomme les facteurs contextuels. Le langage courant associe souvent le terme effet placebo à ce qui est ici défini comme effet contextuel.

D'après vous, les effets contextuels dépendent fortement des paramètres suivants (plusieurs options possibles) :

- ☐ Les caractéristiques du traitement (nature, durée, mode d'administration, durée, etc)
- ☐ Les caractéristiques du patient
- ☐ Les caractéristiques du thérapeute
- ☐ Les caractéristiques de l'environnement de soin
- ☐ Les caractéristiques de la relation thérapeutique
- ☐ Aucune des propositions
- ☐ Je ne sais pas

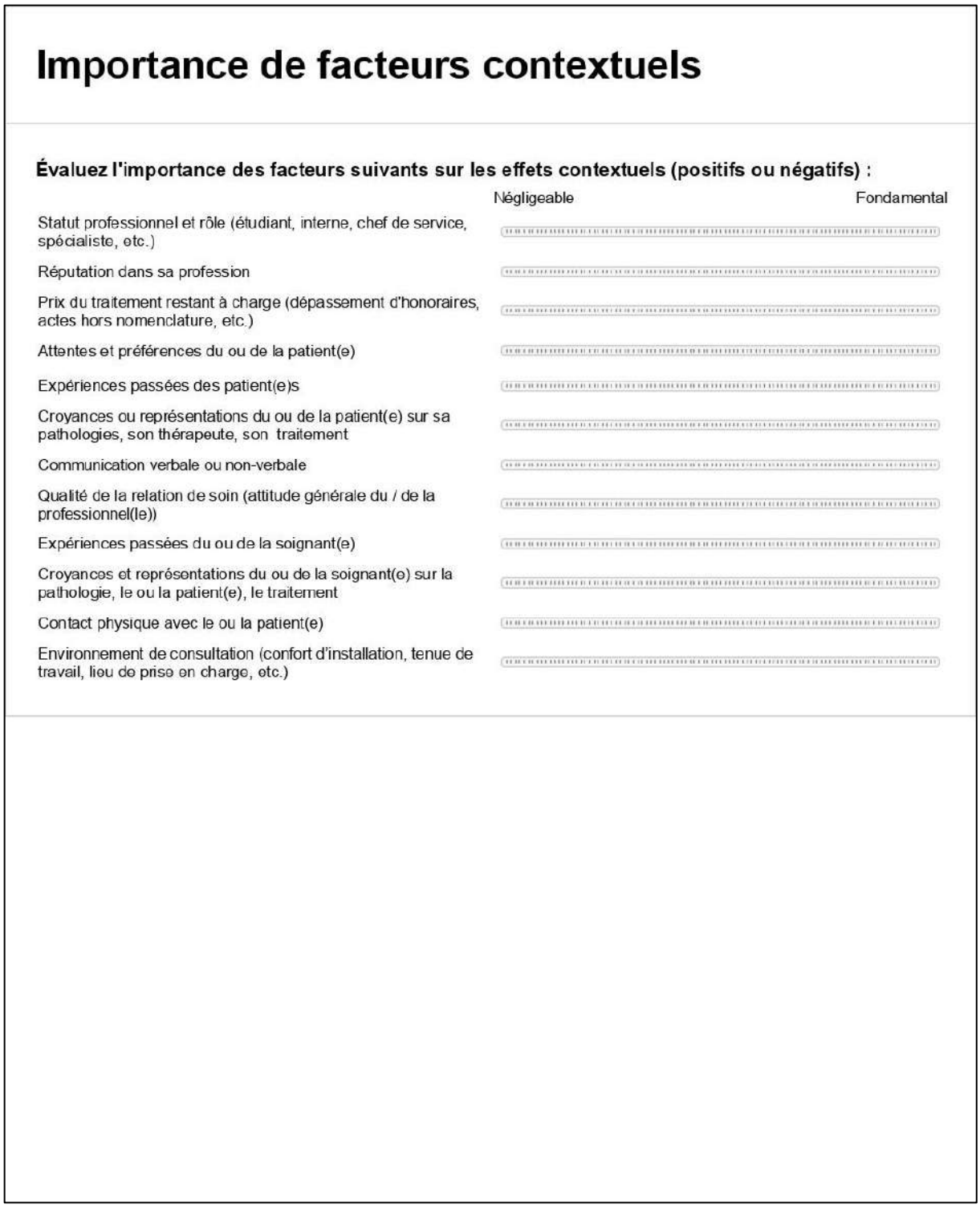
Sélectionnez, parmi ces situations spécifiques, celle(s) où les effets contextuels sont présents :

- ☐ Lorsque le patient prends un traitement sans avis, ni interaction avec un professionnel de santé (i.e. automédication)
- ☐ Lorsque le traitement n'est pas médicamenteux
- ☐ Lorsque la consultation ne conduit pas à un traitement
- ☐ Lorsque la consultation a lieu au domicile du patient
- ☐ Lorsque la consultation a lieu en télé-soin
- ☐ Aucune des propositions
- ☐ Je ne sais pas

Fonctionnement des Effets Contextuels

D'après vous, quelles sont les explications des mécanismes d'action des effets contextuels ?

- ☐ Histoire naturelle de la maladie
- ☐ Auto guérison (mécanisme basé sur la relation corps-esprit)
- ☐ Mécanismes psychologiques
- ☐ Suggestion verbale ou non-verbale
- ☐ Conditionnement
- ☐ Mécanismes biologiques
- ☐ Entités immatérielles (énergies, spiritualité, etc.)
- ☐ Je ne sais pas
- ☐ Autres



Importance de facteurs contextuels

Évaluez l'importance des facteurs suivants sur les effets contextuels (positifs ou négatifs) :

	Négligeable	Fondamental
Statut professionnel et rôle (étudiant, interne, chef de service, spécialiste, etc.)		
Réputation dans sa profession		
Prix du traitement restant à charge (dépassement d'honoraires, actes hors nomenclature, etc.)		
Attentes et préférences du ou de la patient(e)		
Expériences passées des patient(e)s		
Croyances ou représentations du ou de la patient(e) sur sa pathologies, son thérapeute, son traitement		
Communication verbale ou non-verbale		
Qualité de la relation de soin (attitude générale du / de la professionnel(le))		
Expériences passées du ou de la soignant(e)		
Croyances et représentations du ou de la soignant(e) sur la pathologie, le ou la patient(e), le traitement		
Contact physique avec le ou la patient(e)		
Environnement de consultation (confort d'installation, tenue de travail, lieu de prise en charge, etc.)		

Utilisation des facteurs contextuels

Avez-vous déjà mis en place des stratégies pour valoriser ou influencer votre réputation professionnelle dans le but d'améliorer le résultat clinique de vos prises en charge ?

- ○ Oui
- ○ Non

À quelle fréquence ?

Avez-vous déjà mis en place des stratégies pour valoriser ou influencer la réputation professionnelle d'un(e) confrère dans le but d'améliorer le résultat clinique de vos prises en charge ?

- ○ Oui
- ○ Non

À quelle fréquence ?

Avez-vous déjà usé de titres ou d'un statut (étudiant, interne, docteur, professeur, chef de service, spécialiste, etc.), réels ou non, dans le but d'améliorer le résultat clinique de vos prises en charge ?

- ○ Oui
- ○ Non

À quelle fréquence ?

Avez-vous mis en place des stratégies pour influencer les attentes et préférences du ou de la patient(e) dans le but d'améliorer les résultats cliniques de vos prises en charge ?

- ○ Oui
- ○ Non

À quelle fréquence ?

Avez-vous déjà modifié vos prises en charge en fonction des expériences passées du ou de la patient(e) ?

- ○ Oui
- ○ Non

À quelle fréquence ?

Avez-vous déjà modifié votre prise en charge en fonction des croyances ou représentations du ou de la patient(e) sur sa pathologie, son thérapeute, son traitement ?

- ○ Oui
- ○ Non

À quelle fréquence ?

Avez-vous déjà mis en place des stratégies pour adapter votre communication verbale et/ou non-verbale dans le but d'améliorer les résultats cliniques de vos prises en charge ?

- ○ Oui
- ○ Non

À quelle fréquence ?

Avez-vous déjà mis en avant votre expérience professionnelle dans le but d'améliorer le résultat clinique de vos prises en charge ?

- Oui
- Non

À quelle fréquence ?

Avez-vous déjà mis en avant votre vécu personnel dans le but d'améliorer le résultat clinique de vos prises en charge ?

- Oui
- Non

À quelle fréquence ?

Avez-vous déjà mis en place une stratégie d'adaptation de votre relation de soin dans le but d'améliorer le résultat clinique de votre prise en charge ?

- Oui
- Non

À quelle fréquence ?

Avez-vous déjà utilisé le contact physique lors d'un examen ou d'un traitement aux seules fins d'améliorer le résultat clinique de votre prise en charge ?

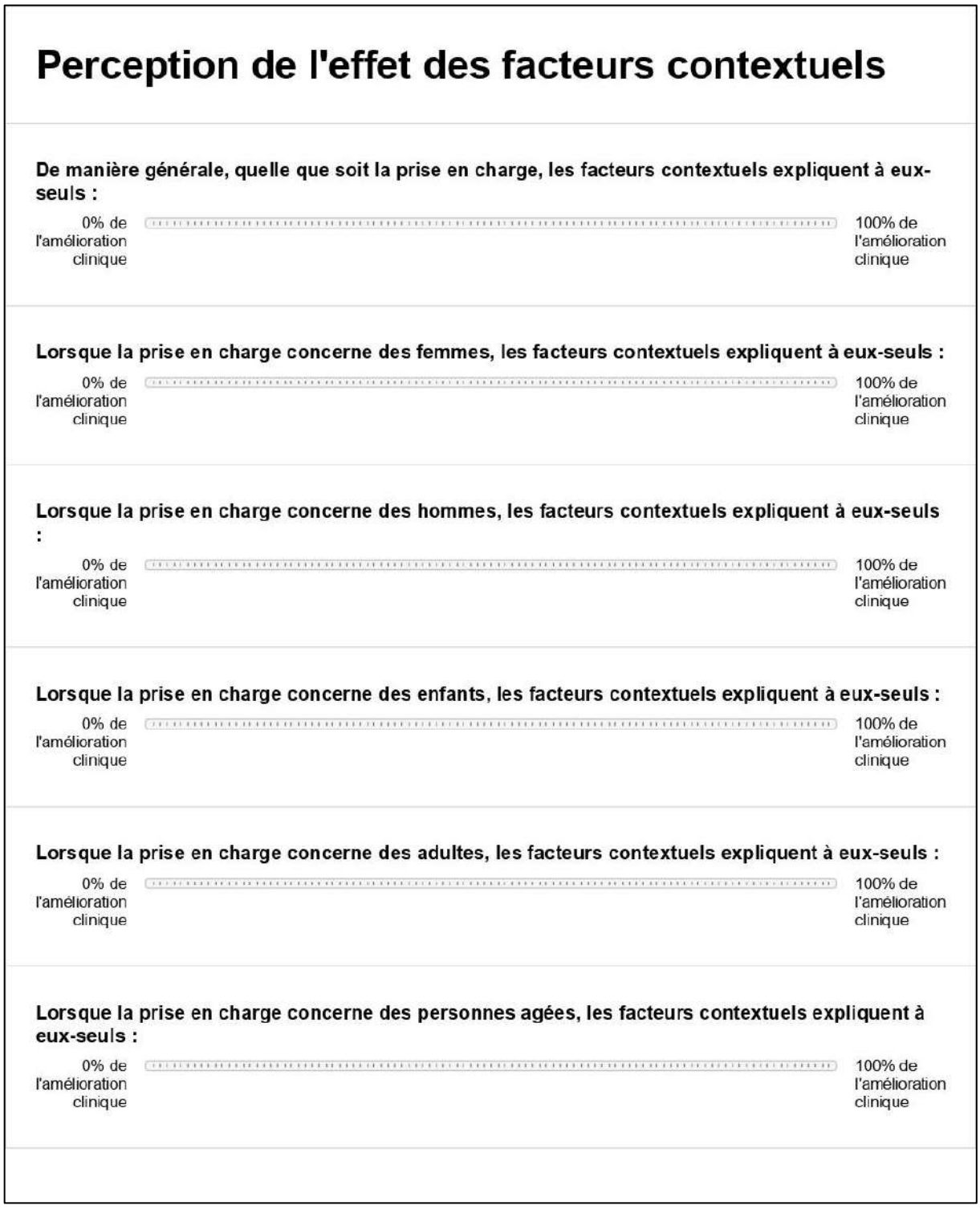
- ○ Oui
- ○ Non

À quelle fréquence ?

Avez-vous déjà mis en place des stratégies d'adaptation de l'environnement de soin (confort d'installation, tenue de travail, lieu de prise en charge) dans le but d'améliorer le résultat clinique de vos prises en charge ?

- ○ Oui
- ○ Non

À quelle fréquence ?


Perception de l'effet des facteurs contextuels
De manière générale, quelle que soit la prise en charge, les facteurs contextuels expliquent à eux-seuls :
0% de l'amélioration clinique
100% de l'amélioration clinique
Lorsque la prise en charge concerne des femmes, les facteurs contextuels expliquent à eux-seuls :
0% de l'amélioration clinique
100% de l'amélioration clinique
Lorsque la prise en charge concerne des hommes, les facteurs contextuels expliquent à eux-seuls :
0% de l'amélioration clinique
100% de l'amélioration clinique
Lorsque la prise en charge concerne des enfants, les facteurs contextuels expliquent à eux-seuls :
0% de l'amélioration clinique
100% de l'amélioration clinique
Lorsque la prise en charge concerne des adultes, les facteurs contextuels expliquent à eux-seuls :
0% de l'amélioration clinique
100% de l'amélioration clinique
Lorsque la prise en charge concerne des personnes agées, les facteurs contextuels expliquent à eux-seuls :
0% de l'amélioration clinique
100% de l'amélioration clinique

Lorsque la prise en charge vise à traiter des symptômes subjectifs (fatigue, anxiété, douleur, etc), les facteurs contextuels expliquent à eux-seuls :

0% de l'amélioration clinique — 100% de l'amélioration clinique

Lorsque la prise en charge vise à traiter des symptômes objectifs (fréquence cardiaque, glycémie, sécrétion de dopamine, saturation en oxygène, etc), les facteurs contextuels expliquent à eux-seuls :

0% de l'amélioration clinique — 100% de l'amélioration clinique

Conditions personnelles d'utilisation

Suite aux éléments du questionnaire précisant la définition (rappelée ci-dessous) des facteurs contextuels, les utilisez-vous ?

- ○ Oui, je les utilise déjà
- ○ Non
- ○ Non mais j'envisage de les utiliser

Dans quel objectifs ?

- ☐ Dans le cadre des prises en charges efficaces dispensés afin d'optimiser les résultats cliniques
- ☐ Pour compenser le manque d'effet d'un traitement sans efficacité démontrée
- ☐ Pour répondre à un besoin d'amélioration de la satisfaction du ou de la patient(e)
- ☐ Lorsque vous êtes dans une impasse thérapeutique
- ☐ Afin de mieux supporter les effets indésirables des traitements efficaces
- ☐ Autres motivations

Rappel de définition :

L'effet contextuel est un effet psycho-physiologique positif (bénéfique) ou négatif (dommageable) observé après un soin quel qu'il soit. Celui-ci peut améliorer ou détériorer le résultat des traitements administrés. En effet, il est admis que certains éléments du contexte peuvent influencer les résultats des traitements : on les nomme les facteurs contextuels. Le langage courant associe souvent le terme effet placebo à ce qui est ici défini comme effet contextuel.

Démographie

Quel est votre genre ?

- Homme
- Femme
- Autre

Quel âge avez-vous ?

Comment avez-vous entendu parler de ce questionnaire ?

- Réseaux Sociaux
- Mailing
- Bouche à oreille
- Autre

Vous exercez / étudiez

- en France métropolitaine
- en France non-métropolitaine
- en Suisse
- en Belgique
- Autre

Vous êtes :

- Professionnel(le)
- Étudiant(e)

Démographie des Professionnels

Quelle est votre profession ?

- ○ Aide-soignant(e)
- ○ Chirurgien
- ○ Dentiste
- ○ Ergothérapeute
- ○ Infirmier(e)
- ○ Kinésithérapeute / Physiothérapeute
- ○ Manipulateur(rice) en électroradiologie médicale
- ○ Médecin
- ○ Orthophoniste
- ○ Orthoptiste
- ○ Pharmacien(ne) d'officine
- ○ Psychomotricien(ne)
- ○ Sage-femme
- ○ Autre (préciser)

Avez-vous une pratique de spécialité ?

- ○ I.P.A.
- ○ I.B.O.D.E.
- ○ I.A.D.E.
- ○ Puériculteur/trice
- ○ Aucun

Depuis combien de temps êtes vous diplômé(e) (en années entières) ?

Quel est votre mode d'exercice clinique principal ?

- ○ Salarié du secteur public
- ○ Salarié du secteur privé
- ○ Libéral ou indépendant
- ○ Mixte
- ○ Autre

Quel exercice préférentiels avez-vous ?

☐ Biologie médicale	☐ Cardiologie	☐ Chirurgie
☐ Dermatologie et vénéréologie	☐ Esthétique et reconstruction	☐ Endocrinologie - Maladies métaboliques
☐ Gastro-entérologie et hépatologie	☐ Génétique médicale	☐ Gériatrie
☐ Gynécologie et obstétrique	☐ Hématologie	☐ Maladie infectieuse
☐ Maxillo-faciale	☐ Médecine du travail	☐ Médecine générale
☐ Médecine interne	☐ Médecine nucléaire	☐ Médecine physique et de réadaptation
☐ Néphrologie	☐ Neurologie	☐ Ophtalmologie
☐ ORL	☐ Orthopédie et traumatologie	☐ Oncologie
☐ Pédiatrie	☐ Pneumologie	☐ Psychiatrie
☐ Radiologie et imagerie médicale	☐ Réanimation et anesthésie	☐ Rhumatologie
☐ Santé publique	☐ Urologie	☐ Autres :

Intervenez vous auprès d'une catégorie de population particulière ?

- ○ Oui
- ○ Non

Si oui, laquelle ?

- ☐ Nouveaux-nés
- ☐ Nourrissons
- ☐ Adolescents - Enfants
- ☐ Adultes
- ☐ Personnes âgées
- ☐ Patients en fin de vie
- ☐ Patients avec maladies professionnelles
- ☐ Sportifs
- ☐ Patients avec une atteinte cognitive
- ☐ Douleurs persistantes
- ☐ Population précaires
- ☐ Affections de longue durée
- ☐ Autres :

Démographie Étudiants

Vous êtes étudiants :

- ○ En Orthophonie
- ○ En Kinésithérapie / En Physiothérapie
- ○ En Ergothérapie
- ○ En Médecine
- ○ En Maïeutique
- ○ En Pharmacie
- ○ En Manipulation radio
- ○ En Puériculture
- ○ En Aide-soignant(e)
- ○ En Soins infirmiers
- ○ En Odontologie
- ○ En Orthoptie
- ○ En Psychomotricité
- ○ Autres (préciser)

Vous êtes :

- ○ Externe
- ○ Interne de spécialité médicale
- ○ Interne de spécialité chirurgicale

Vous êtes :

- ○ Externe
- ○ Interne de pharmacie d'officine
- ○ Interne de pharmacie d'une autre spécialité

En quelle année êtes-vous de votre parcours (exemple 3ème année depuis le bac hors redoublement, mettre "3") ?

Introduction

Welcome to this survey !

Dear colleagues and students,

The aim of this survey is to investigate the extent to which health professionals use the context in which they care for their patients. This can improve or worsen the outcome of the treatments they administer.
Indeed, it is recognized that factors related to the provider-patient relationship or the environment can influence treatment outcomes: these are known as contextual factors. For example, the words used to address the patient, the posture adopted by the professional or the fact of wearing a gown can influence the perception of pain, the level of anxiety or the physical performance of a patient.

Practicing health professionals in France, Switzerland and Belgium as well as healthcare students in France, Switzerland or Belgium can answer this questionnaire.

In the following questions, **we ask you to answer according to your own experience**.

Your participation in the survey takes 10-15 minutes and your contribution will only be recorded if the whole questionnaire is completed. Therefore, if you choose not to complete the questionnaire, no data will be recorded. There is no direct risk or benefit to participants in this study. In this respect, this study has been declared to the Research Ethics Committee of Grenoble Alpes University.
The responses are pseudo-anonymous and will only be used for research purposes. The data produced is stored and processed in compliance with the RGPD on Université Grenoble Alpes servers that comply with the RGPD requirements. The data processing complies with a national methodology of reference (MR004) of the CNIL.

By clicking on "Next", you agree to participate in the study and consent to the use of the data produced by the response to this questionnaire under the conditions described above. The results of this research will undergo scientific publication and be presented at conferences. Under no circumstances can the anonymity of participation be lifted and the results will only be presented in an aggregate.

If at the end of the study you wish to withdraw your participation or if you need information, you can contact the study coordinator: EMAIL ADRESS

Knowledge self-evaluation

What do you think is the state of your knowledge about contextual effects?

No knowledge — Excellent knowledge on the topic

In your opinion, does this knowledge influence your clinical practice?

Not at all — A lot

According to you, the contextual effect is defined as :

- A manifestation of symptoms of a condition or their evolution, positive or negative, in absence of treatment
- I don't know
- A treatment with no specific efficacy
- A positive (beneficial) or negative (detrimental) psycho-physiological effect observed after a treatment regardless of its specific efficacy
- An effect of the interaction with a therapist
- None of the following

The order of items is random

General understanding

In the rest of the questionnaire we will consider the contextual effect as being a positive (beneficial) or negative (damaging) psycho-physiological effect observed after any kind of treatment. This can improve or deteriorate the outcome of the treatments administered. Indeed, it is accepted that certain elements of the context can influence the results of treatments: these are called contextual factors. Commonly the term placebo effect is often associated with what is defined here as a contextual effect.

In your opinion, the contextual effects depend strongly on the following parameters (several options possible):

- ☐ Treatment characteristics (type, duration, administration mode, etc)
- ☐ Patient characteristics
- ☐ Therapist characteristics
- ☐ Healthcare environnement setting characteristics
- ☐ Therapeutic relationship characteristics
- ☐ None of the above
- ☐ I don't know

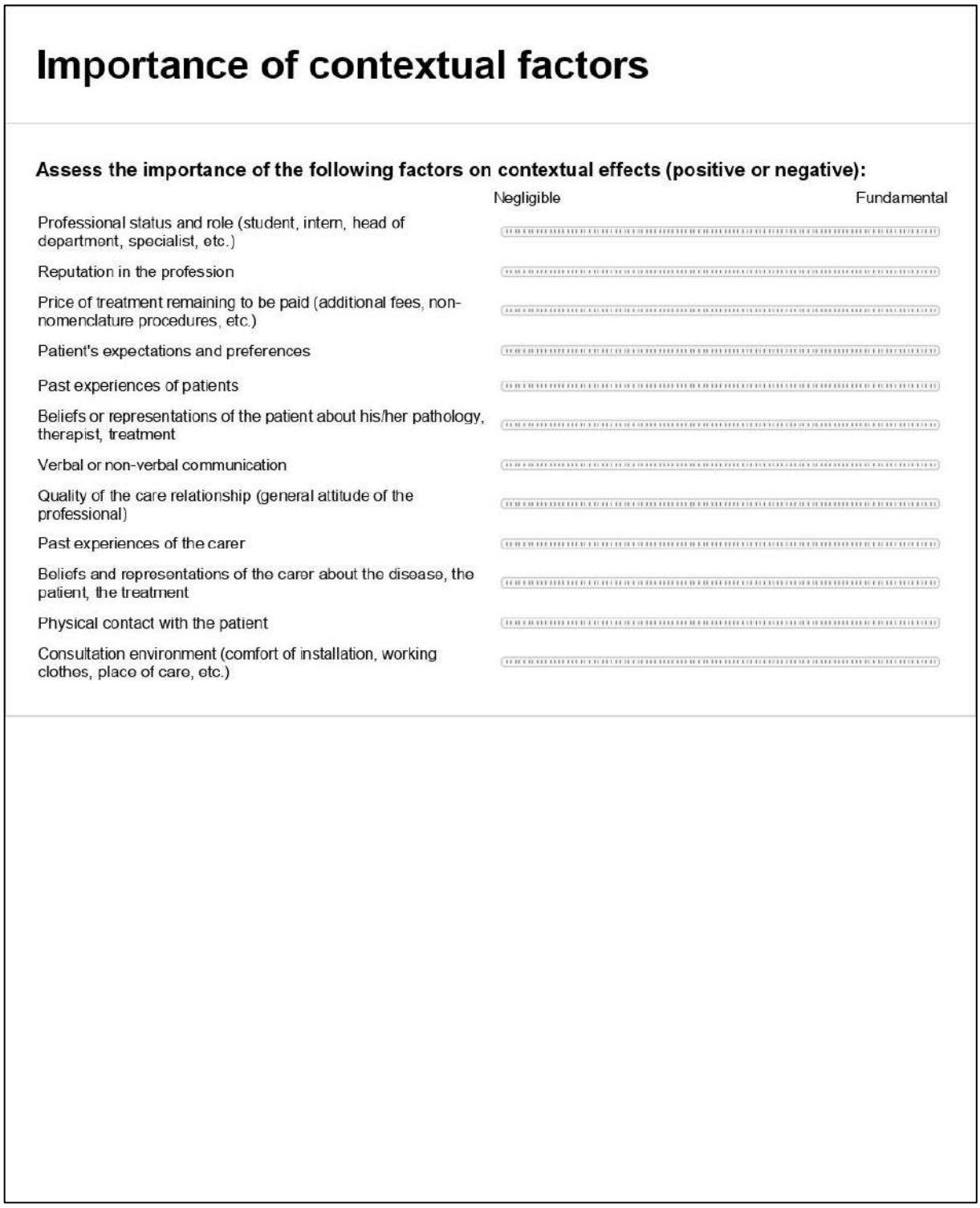
Select the specific situation(s) where contextual effects are present:

- ☐ When the patient takes a treatment without advice from or interaction with a health professional (i.e. self-medication)
- ☐ When the treatment is not medicinal
- ☐ When the consultation does not lead to treatment
- ☐ When the consultation takes place at the patient's home
- ☐ When the consultation takes place via telecare
- ☐ None of the above
- ☐ I don't know

How contextual effects work

What do you think are the explanations for the mechanisms of action of contextual effects?

- ☐ Spontaneous evolution of the disease
- ☐ Self-healing (based of the mind-body relationship)
- ☐ Psychological mechanisms
- ☐ Verbal or non-verbal sugestions
- ☐ Condtionning
- ☐ Biological mechanisms
- ☐ Immaterial entities (energies, spirituality, etc.)
- ☐ I don't know
- ☐ Other



Importance of contextual factors

Assess the importance of the following factors on contextual effects (positive or negative):

	Negligible	Fundamental
Professional status and role (student, intern, head of department, specialist, etc.)		
Reputation in the profession		
Price of treatment remaining to be paid (additional fees, non-nomenclature procedures, etc.)		
Patient's expectations and preferences		
Past experiences of patients		
Beliefs or representations of the patient about his/her pathology, therapist, treatment		
Verbal or non-verbal communication		
Quality of the care relationship (general attitude of the professional)		
Past experiences of the carer		
Beliefs and representations of the carer about the disease, the patient, the treatment		
Physical contact with the patient		
Consultation environment (comfort of installation, working clothes, place of care, etc.)		

Contextual Factors Use

Have you ever implemented strategies to enhance or influence your professional reputation in order to improve the clinical outcome of your care?

- ○ Yes
- ○ No

How often ?

Have you ever implemented strategies to enhance or influence the professional reputation of a colleague in order to improve the clinical outcome of your care?

- ○ Yes
- ○ No

How often ?

Have you ever used titles or status (student, intern, doctor, professor, head of department, specialist, etc.), real or not, in order to improve the clinical outcome of your care?

- ○ Yes
- ○ No

How often ?

Have you used strategies to influence patient expectations and preferences in order to improve clinical outcomes?

- Yes
- No

How often ?

Have you ever modified your treatments according to the patient's past experiences?

- Yes
- No

How often ?

Have you ever modified your approach according to the patient's beliefs or representations about his or her pathology, therapist or treatment?

- Yes
- No

How often ?

Have you ever implemented strategies to adapt your verbal and/or non-verbal communication in order to improve the clinical outcomes of your care?

- Yes
- No

How often ?

Have you ever put forward your professional experience to improve the clinical outcome of your treatments?

- ○ Yes
- ○ No

How often ?

Have you ever put forward your personal experiences to improve the clinical outcome of your care?

- ○ Yes
- ○ No

How often ?

Have you ever put in place a strategy to adapt your therapeutic relationship in order to improve the clinical outcome of your care?

- ○ Yes
- ○ No

How often ?

Have you ever used physical contact during an examination or treatment for the sole purpose of improving the clinical outcome of your care?

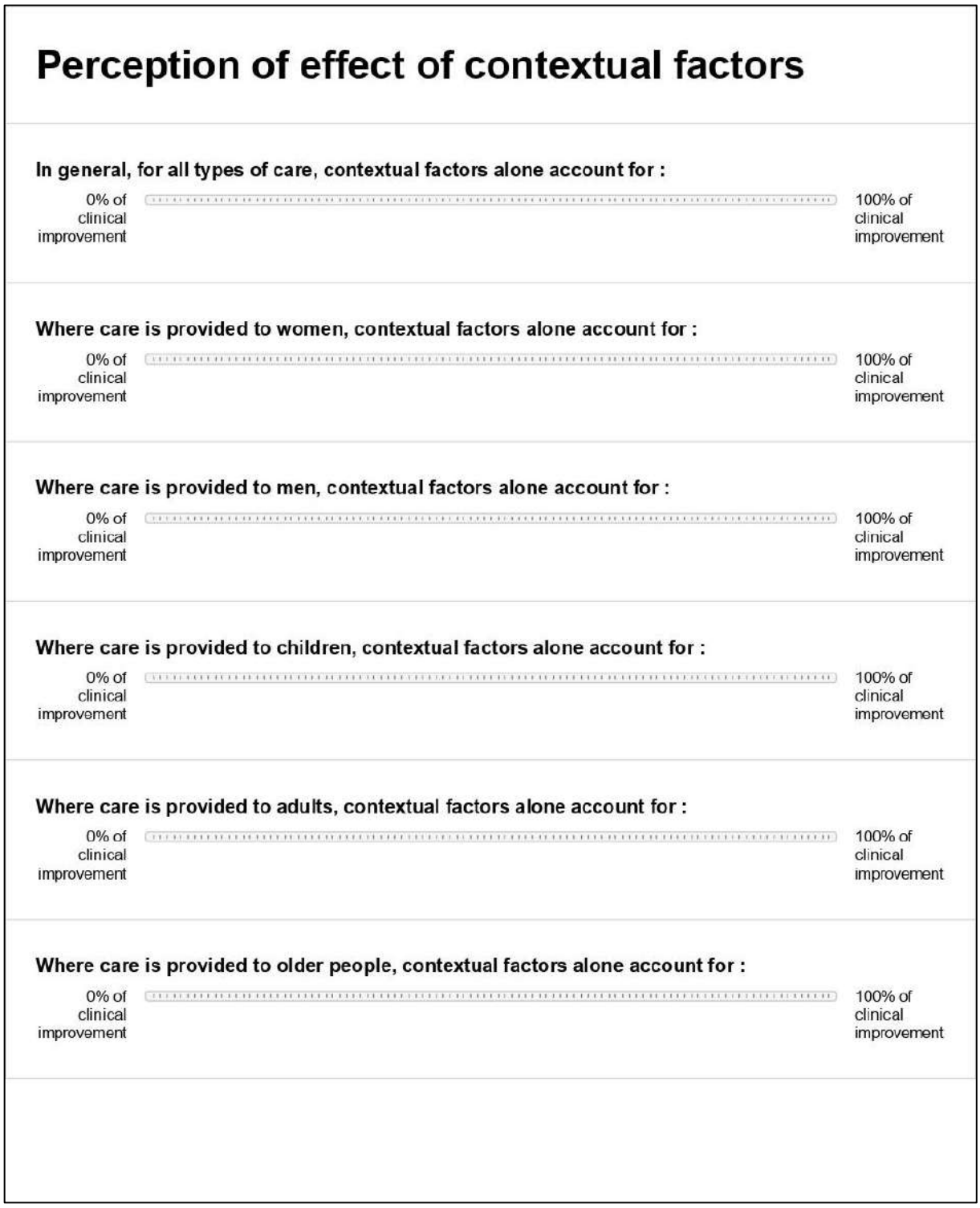
- ○ Yes
- ○ No

How often ?

Have you already implemented strategies for adapting the care environment (comfort of installation, working clothes, place of care) in order to improve the clinical outcome of your care?

- Yes
- No

How often ?


Perception of effect of contextual factors
In general, for all types of care, contextual factors alone account for :
0% of clinical improvement
100% of clinical improvement
Where care is provided to women, contextual factors alone account for :
0% of clinical improvement
100% of clinical improvement
Where care is provided to men, contextual factors alone account for :
0% of clinical improvement
100% of clinical improvement
Where care is provided to children, contextual factors alone account for :
0% of clinical improvement
100% of clinical improvement
Where care is provided to adults, contextual factors alone account for :
0% of clinical improvement
100% of clinical improvement
Where care is provided to older people, contextual factors alone account for :
0% of clinical improvement
100% of clinical improvement

When dealing with subjective symptoms, contextual factors alone account for :

0% of clinical improvement — 100% of clinical improvement

When dealing with objective symptoms, contextual factors alone account for :

0% of clinical improvement — 100% of clinical improvement

Personal terms of use

Following the questionnaire items specifying the definition (recalled below) of contextual factors, do you use them?

- ○ Yes, I already use them
- ○ No
- ○ No but I plan to use them

For what purposes ?

- ☐ In the context of effective treatments provided to optimise clinical outcomes
- ☐ To compensate for the lack of effect of a treatment without proven effectiveness
- ☐ To meet a need to improve patient satisfaction
- ☐ When you are in a therapeutic impasse
- ☐ To better cope with the side effects of effective treatments
- ☐ Other motivations

Reminder of definition :
The contextual effect is a positive (beneficial) or negative (damaging) psycho-physiological effect observed after any treatment. It can improve or deteriorate the outcome of the treatments administered. Indeed, it is accepted that certain elements of the context can influence the results of treatments: these are called contextual factors. Commonly, the term placebo effect is often associated with what is defined here as a contextual effect.

Demography

What is your gender ?

- Man
- Woman
- Other

How old are you ?

How did you hear about this questionnaire ?

- Social media
- Email
- Word of mouth
- Other

You work / study:

- in mainland France
- in non-metropolitan France
- in Switzerland
- in Belgium
- Other

You are a:

- Professional
- Student

Demography for Professionals

What is your profession ?

- Carer
- Surgeon
- Dentist
- Occupational Therapist
- Nurse
- Physiotherapist
- Medical Electroradiology Technician
- Physician
- Speech Therapist
- Orthoptist
- Pharmacist
- Psychomotor therapist
- Midwife
- Autre (préciser)

Do you have a speciality practice ?

- I.P.A.
- I.B.O.D.E.
- I.A.D.E.
- Childcare
- None

How long have you been a graduate (in whole years)?

What is your main clinical practice?

- ○ Employed public sector
- ○ Employed private sector
- ○ Private Practice
- ○ Mixed
- ○ Other

What is your preferred exercise?

- ☐ Medical Biology
- ☐ Dermatology
- ☐ Gastroenterology and hepatology
- ☐ Gynaecology and obstetrics
- ☐ Maxillofacial
- ☐ Internal Medicine
- ☐ Nephrology
- ☐ ENT
- ☐ Pediatrics
- ☐ Radiology
- ☐ Public Health
- ☐ Cardiology
- ☐ Plastic Surgery
- ☐ Medical Genetics
- ☐ Hematology
- ☐ Occupational medicine
- ☐ Nuclear Medicine
- ☐ Neurology
- ☐ Orthopaedics and traumatology
- ☐ Pneumology
- ☐ Resuscitation and anaesthesia
- ☐ Urology
- ☐ Surgery
- ☐ Endocrinology
- ☐ Geriatrics
- ☐ Infectious diseases
- ☐ General Medicine
- ☐ Physical and Rehabilitation Medicine
- ☐ Ophtalmology
- ☐ Oncology
- ☐ Psychiatry
- ☐ Rhumatology
- ☐ Other

Do you work with a particular category of population?

- ○ Yes
- ○ No

If yes, which one ?

- ☐ Newborns
- ☐ Infants
- ☐ Teenagers - Children
- ☐ Adults
- ☐ Older people
- ☐ End of life patients
- ☐ Patients with occupational diseases
- ☐ Sportsmen and women
- ☐ Patients with cognitive impairment
- ☐ Peristant pain
- ☐ Low-income population
- ☐ Long-term conditions
- ☐ Other

Demography for students

You are a student:

- ○ In Speech Therapy
- ○ In Physiotherapy
- ○ In Occupational Therapy
- ○ In Medicine
- ○ Of Maieutics
- ○ In Pharmacy
- ○ In Medical Imagery Techniques
- ○ In Childcare
- ○ to be a carer
- ○ In Nursing
- ○ In Odontology
- ○ In Orthoptics
- ○ In Psychomotor Therapy
- ○ Other

You are:

- ○ Medical Extern
- ○ Medical Specialty Resident
- ○ Surgical Specialty Resident

You are:

- ○ Extern
- ○ Resident in Clinical Pharmacology
- ○ Resident in another Pharmacology Speciliaty

In which year of your course are you (e.g. 3rd year since the baccalaureate without counting repeated years, put "3")?

Questionnaire Logic

- All questions are mandatory
- Questions with circle before the items allow for a unique choice and questions with boxes in front of items allow multiple answers
- Questions with answer options such as "Other" allow for free text responses if the item is selected.

Page : Knowledge Self-Evaluation
- Question 2 is only shown when answer to Question 1 is different from "No knowledge"
- Scales range from 1 to 5 with text modalities for variable 1 and 5

Page : Importance of Contextual Factors
- Answers vary on a scale of 1 to 101 with extreme modalities shown as "Negligible" and "Fundamental"

Page : Contextual Factors Use
- Questions regarding pace of use are only displayed in the specific CF is used, i.e. the answer is "Yes"
- Options for frequency of use are "Systematically"; "Regularly"; "Sometimes"; "Rarely"; "Exceptionally" and "I don't know".

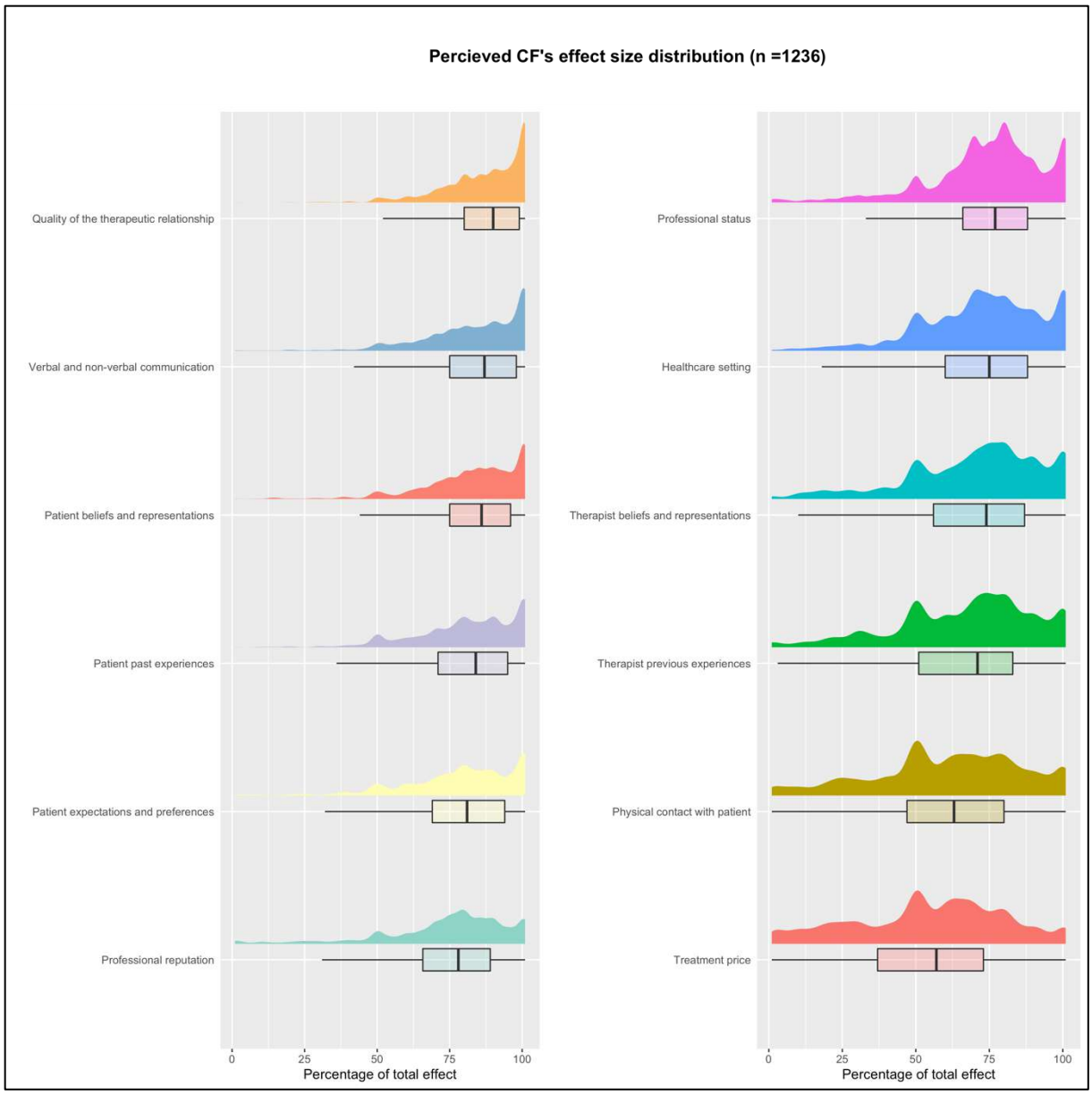
Page : Perception of effect of contextual factors
- Answers vary from 1 to 101 with text modalities at both extremes shown as "0% of clinical improvement" and "100% of clinical improvement"

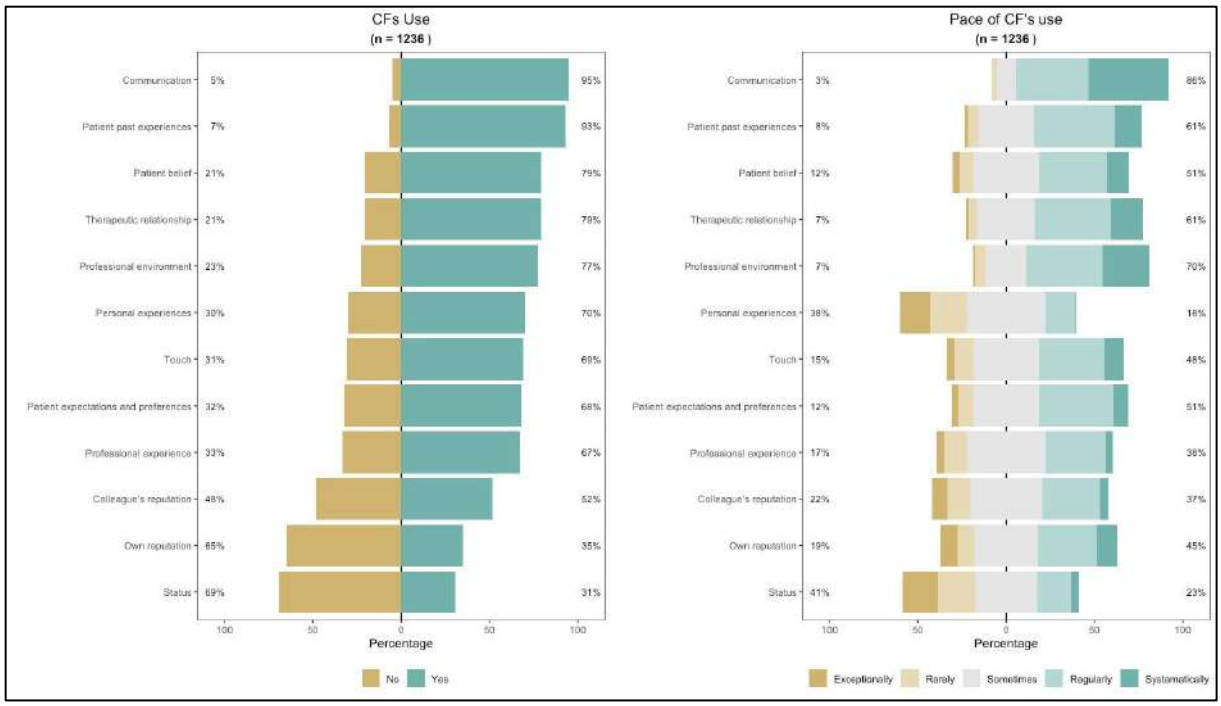
Page : Personal terms of use
- The second question "For what purposes" only shows if the answer to the previous question is different from "No".

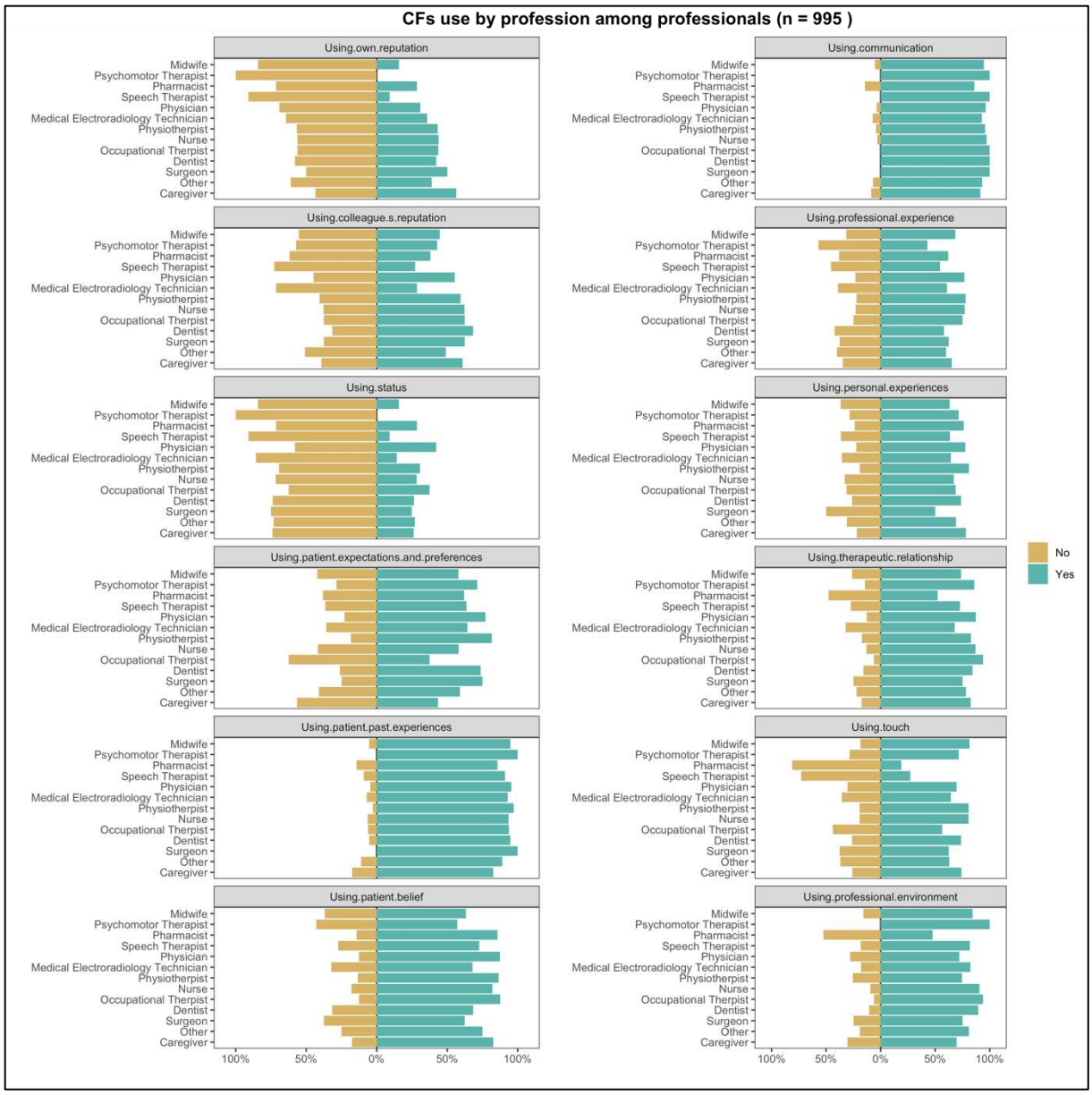
Page : Demography
- Depending on the answer to the last question, participants are either directed to the page "Demography for professionals" or "Demography for students"

Page : Demography for Professionals
- The question "Do you have a specialty practice ?" is only shown for nurses
- The question "What is you preferred exercice?" is only shown to physicians and surgeons
- The question "If yes, which one?" is only shown to people having replied "yes" to the previous question

Page : Demography for students
- The first question "You are" is only for medical students
- The second question "You are" is only for pharmacy students


Percieved CF's effect size distribution (n =1236)
Quality of the therapeutic relationship
Verbal and non-verbal communication
Patient beliefs and representations
Patient past experiences
Patient expectations and preferences
Professional reputation
Professional status
Healthcare setting
Therapist beliefs and representations
Therapist previous experiences
Physical contact with patient
Treatment price
0
25
50
75
100
Percentage of total effect
0
25
50
75
100
Percentage of total effect


CFs Use
(n = 1236)
Communication 5% 95%
Patient past experiences 7% 93%
Patient belief 21% 79%
Therapeutic relationship 21% 79%
Professional environment 23% 77%
Personal experiences 30% 70%
Touch 31% 69%
Patient expectations and preferences 32% 68%
Professional experience 33% 67%
Colleague's reputation 48% 52%
Own reputation 65% 35%
Status 69% 31%
100 50 0 50 100
Percentage
No Yes
Pace of CF's use
(n = 1236)
Communication 3% 86%
Patient past experiences 8% 61%
Patient belief 12% 51%
Therapeutic relationship 7% 61%
Professional environment 7% 70%
Personal experiences 38% 18%
Touch 15% 48%
Patient expectations and preferences 12% 51%
Professional experience 17% 38%
Colleague's reputation 22% 37%
Own reputation 19% 45%
Status 41% 23%
100 50 0 50 100
Percentage
Exceptionally Rarely Sometimes Regularly Systematically


CFs use by profession among professionals (n = 995)
Using.own.reputation
Using.communication
Using.colleague.s.reputation
Using.professional.experience
Using.status
Using.personal.experiences
Using.patient.expectations.and.preferences
Using.therapeutic.relationship
Using.patient.past.experiences
Using.touch
Using.patient.belief
Using.professional.environment
Midwife
Psychomotor Therapist
Pharmacist
Speech Therapist
Physician
Medical Electroradiology Technician
Physiotherpist
Nurse
Occupational Therpist
Dentist
Surgeon
Other
Caregiver
100%
50%
0%
50%
100%
No
Yes