



UNIVERSITY OF GENOVA

DEPARTMENT OF NEUROSCIENCE, REHABILITATION, OPHTHALMOLOGY,
GENETICS, MATERNAL AND CHILD HEALTH

**CONTEXTUAL FACTORS, PLACEBO AND
NOCEBO EFFECTS IN PHYSICAL THERAPY:
CLINICAL RELEVANCE AND IMPACT ON RESEARCH.**

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Promotor: MARCO TESTA

“He cures most successfully in whom the people have the most confidence”

(Galen; 131-201 d.C)

To my family who sustained me during this PhD and
to Elisa who holds my hands showing me the best of life.

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CANDIDATE PROFILE

Giacomo Rossettini was born in Arzignano (Vicenza), Italy, June 13th, 1986.

He has a Bachelor's degree in Physiotherapy (2008), a Master's degree in Rehabilitation of Musculoskeletal Disorders (2010) and a Master's degree in Science Rehabilitation (2014).

He has been working as a physiotherapist since 2009 specializing in Rehabilitation of Musculoskeletal Disorders.

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His didactic, clinical and scientific interests concern the field of musculoskeletal rehabilitation, with special emphasis on:

- placebo, nocebo effects and contextual factors;
- cervical disorders;
- cognitive facilitations of therapeutic exercise;
- development of student learning skills.

SCIENTIFIC ACTIVITIES: PHD (2015-2018)

Honours and awards

- **Invited blogpost offered by Pain in motion** (15/03/2017). Context effect in physiotherapy: is it time to potentiate our clinical practice by integration of placebo responses? Testa M, **Rossettini G**. <http://www.paininmotion.be/blog/detail/context-effect-physiotherapy-it-time-potentiate-our-clinical-practice-integration-placebo-responses>
- **Winner of the National Scientific Project (mentor role)**: Concorso nazionale migliore tesi di laurea in fisioterapia. Roma (12/10/2017). Ciolan F, Turcato G, **Rossettini G**. La gestione del paziente con colpo di frusta presso il Pronto Soccorso in Italia: uno studio retrospettivo sul percorso di diagnosi e cura.
- **Winner of Triveneto Scientific Project (mentor role)**: Tesi verso il futuro, il contributo dei giovani fisioterapisti per lo sviluppo della professione. Udine (24/02/2018). Piccoli A, **Rossettini G**, Cecchetto S. Effetti del focus attentivo, indotto da istruzioni verbali, sulle performance e sull'apprendimento motorio in pazienti con disfunzioni muscoloscheletriche e del sistema nervoso centrale: una revisione sistematica.

Articles

- **Rossettini G**, Emadi Andani M, Dalla Negra F, Testa M, Tinazzi M, Fiorio M. The placebo effect in motor performance is differently modulated by external and internal focus of attention. Under review to Scientific Reports.
- **Rossettini G**, Testa M, de Filippis C, Lovato A. Acute vertigo after CrossFit workout in a young woman with Chiari I malformation. Under review to Clinical Journal of Sport Medicine.
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- Ristori D, Miele S, **Rossettini G**, Monaldi E, Arceri D, Testa M. An integrated Clinical Framework for patient with shoulder pain. Under review to Archives of Physiotherapy.
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 - **Podcast of Medical Education Journal:** Effective teaching of manual skills to physiotherapy students. <https://itunes.apple.com/gb/podcast/medical-education-podcasts/id784455563>
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therapy. Clin Exp Rheumatol 2018.36(1) Suppl.109-S59.PT03:021. Oral presentation accepted at Effects of the diet and the climate in rheumatic and musculoskeletal diseases – XVII° Mediterranean Congress of Rheumatology. Genova (13/04/2018)

- **Rossettini G**, Testa M, Vicentin M, Manganotti P. L'effetto delle diverse istruzioni con focus attentivo durante l'esecuzione di movimenti delle dita in soggetti sani: uno studio esplorativo. Oral presentation accepted at XVIII Congresso Nazionale Sirm. Trieste (5-7/04/2018)
- **Rossettini G**, Camerone E, Vicentini A, Carlino E, Palese A, Testa M. Il ruolo dei fattori di contesto come triggers di effetti placebo e nocebo in ambito neurologico: una revisione narrativa. Poster presentation accepted at XVIII Congresso Nazionale Sirm. Trieste (5-7/04/2018)
- Palese A, Cadorin L, Geri T, Testa M, **Rossettini G**. Utilizzo e conoscenza dei fattori di contesto negli infermieri italiani: risultati di una survey nazionale. Poster presentation accepted at XVIII Congresso Nazionale IPASVI: Noi Infermieri – la nostra impronta sul sistema salute. Roma (5-7/03/2018)
- Piccoli A, **Rossettini G**, Cecchetto S. Effetti del focus attentivo, indotto da istruzioni verbali, sulle performance e sull'apprendimento motorio in pazienti con disfunzioni muscoloscheletriche e del sistema nervoso centrale: una revisione sistematica. Poster presentation accepted at X° Convegno: Tesi verso il futuro: il contributo dei giovani fisioterapisti per lo sviluppo della professione. Udine (24/02/2018)
- Ciolan F, Turcato G, **Rossettini G**. La gestione del paziente con colpo di frusta presso il Pronto Soccorso in Italia: uno studio retrospettivo sul percorso di diagnosi e cura. Concorso nazionale migliore tesi di laurea in fisioterapia. Poster presentation accepted at X° Convegno: Tesi verso il futuro: il contributo dei giovani fisioterapisti per lo sviluppo della professione. Udine (24/02/2018)
- **Rossettini G**, Edami Andani M, Dalla Negra F, Testa M, Tinazzi M, Fiorio M. Placebo effect and focus of attention as a new strategy to modulate the motor performance. Poster presentation at XXV Congresso Società Italiana di Psicofisiologia e Neuroscienze Cognitive - SIPF. Roma (16-18/11/2017)
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- Testa M, **Rossettini G**, Geri T, Viceconti A, Colloca L, Palese A. AB1223-HPR Beliefs and attitudes of italian nurses towards placebo and nocebo responses induced by contextual factors in clinical practice. *Ann Rheum Dis.* Jun 2017. 76 (Suppl 2) 1539-1540 Abstract at EULAR Congress. Madrid (14-17/06/2017)
- **Rossettini G**, Palese A, Testa M. Placebo, nocebo and contextual effect in nursing: do we need to rethink clinical care? Poster presentation at 1st official Society for Interdisciplinary Placebo Studies (SIPS) conference on placebo studies. Leiden (2-4/04/2017)
- **Rossettini G**, Dalla Negra F, Edami Andani M, Testa M, Fiorio M. Placebo effect and focus of attention as a new strategy to modulate the motor performance. Poster presentation at 1st official Society for Interdisciplinary Placebo Studies (SIPS) conference on placebo studies. Leiden (2-4/04/2017)
- **Rossettini G**, Testa M. Placebo, Nocebo and Contextual Effect in Physiotherapy: Do We Need to Rethink Clinical Practice? Poster presentation at Pain Science in Motion – Stoccolma (24-25/03/2017)
- **Rossettini G**, Testa M, Vicentini M, Manganotti P Effect of attentional focus on the motor system excitability assessed by single pulsed transcranial magnetic stimulation in healthy subjects: a pilot study. *Man Ther.* 25 (2016) e57-e169. Poster presentation at International Federation of Orthopaedic Manipulative Physical Therapists Congress – Glasgow (08/06/2016)
- Tezza S, **Rossettini G**. A. Prevalenza e fattori di rischio del dolore al pollice nei terapisti manuali italiani: uno studio osservazionale. Poster presentation at VI° Convegno: Tesi verso il futuro: il contributo dei giovani fisioterapisti per lo sviluppo della professione. Venezia (28/02/2015)

Invited speaker: Verona University Workshops

- #takeyourownopportunity: quali opportunità lavorative dopo la laurea? (20/09/2017)
- Il rapporto di lavoro e le incompatibilità del pubblico impiego – possibilità occupazionali del fisioterapista nel settore privato. (12/09/2017)
- Il mondo del lavoro 2016: la libera professione. (21/09/2016)
- Time management: come imparare a gestire meglio il nostro tempo e a focalizzare efficacemente le nostre risorse ed energie. (11/06/2016)
- Cervicalgia aspecifica: introduzione alla valutazione e al trattamento evidence based. (4-5/03/2016)
- Conoscenza e gestione dell'effetto nocebo in fisioterapia. (16/03/2016)
- L'effetto placebo in fisioterapia: uno strumento per incrementare l'outcome terapeutico. (24/02/2016)
- Il ruolo dei fattori di contesto nella fisioterapia dei disordini muscoloscheletrici. (23/10/2015);
- Il mondo del lavoro: la libera professione. (15/09/2015)
- Come strutturare una tesi di laurea: disegno di studio e quesiti. (08/09/2015)
- Il controllo motorio e posturale: interdipendenza regionale spinale. (1/04/2015)
- L'esercizio terapeutico nelle disfunzioni cervico scapolari. (24/03/2015)

Invited speaker: Scientific Conferences

- Fattori di contesto, effetti placebo e nocebo in fisioterapia: rilevanza clinica e impatto sulla ricerca - 2° Forum delle eccellenze in Fisioterapia Muscoloscheletrica e Terapia Manuale - Convegno GTM Bologna (23/06/2018)
- Tell a story: "Esperienza di un dottorato di ricerca" – Studiare dopo la laurea? Attualità e prospettive nella formazione universitaria avanzata in fisioterapia – Congresso Scientifico Regionale AIFI Veneto. Verona (05/05/2018)
- Il ruolo dei Fattori di Contesto in fisioterapia: implicazioni cliniche - X° Congresso Fisiobrain. Rimini (24/03/2018)
- I fattori di contesto in fisioterapia: uno strumento utile per il clinico? – Congresso Scientifico Regionale AIFI Liguria. Genova (20/05/2017)

- Effetto placebo e nocebo in fisioterapia: è tempo di ripensare la pratica clinica? – Congresso Nazionale GIS Terapie fisiche e tecnologie riabilitative – AIFI, Bologna (12/11/2016)
- L'ICF: uno strumento di conoscenza, condivisione ed azione nei contesti di tirocinio – Corso di formazione pedagogica al tutorato clinico per le professioni sanitarie – Ospedale civile di Legnago (14/05/2016)
- Il ruolo del focus attentivo nell'esercizio terapeutico - Congresso Scientifico Regionale AIFI Veneto, Padova (07/05/2016)
- Focus attentivo ed eccitabilità del sistema motorio: facilitazioni cognitive per l'esercizio terapeutico - Congresso Nazionale GIS Neuroscienze – AIFI, Bologna (12/12/2015)
- Controllo motorio e dolore muscoloscheletrico: analisi dei pattern disfunzionali lombari e cervicali – XIII° Congresso Nazionale GTM – AIFI, Savona (27/09/2015)
- Facilitazioni cognitive per l'esercizio terapeutico: come le parole modulano l'attività cerebrale - XIII° Congresso Nazionale GTM – AIFI, Savona (26/09/2015)

FOREWORD

This PhD project represents the end point of my first 10-year journey in the world of physiotherapy. During the first decade of clinical practice the central questions that have continued to motivate my work were: “Why does the patient sometimes improve, independently of the specificity of my treatment?”, “Why does the patient sometimes get worse even if the evidence-based guidelines have been followed?”, “Why does the patient choose a specific clinician instead of another clinician?”.

The healthcare context provides answers to these professional doubts. The features of patient and clinician, the patient-clinician relationship, the feature of the treatment and healthcare setting, represent the context. It pervades all clinical actions: its positive use can trigger placebo effects, while its negative use can generate nocebo effects, thus directly influencing the therapeutic outcome.

The research performed during these last three years has provided insights into the role of the healthcare context as a trigger of placebo and nocebo effects, which contributed to improving my clinical reasoning and expertise. Moreover, the results of the project leave the door open for future studies and didactic activities concerning placebo, nocebo and contextual factors effects.

Heartfelt thanks to my mentor Marco Testa for helping and guiding me during the realization of this PhD project. I cannot forget our walk in Savona when we discussed placebo and nocebo effects for the first time; sowing the seeds of inspiration.

I'm grateful to Prof. Alvisa Palese for her support. Her continuous encouragement to strive for excellence has been an example and source of motivation for my research and personal growth.

Special gratitude goes to my colleagues and friends Angie Rondoni, Tommaso Geri, Marco Minacci, Antonello Viceconti, Simone Cecchetto and Diego Ristori for their constructive feedback, which allowed me to compare and contrast my ideas with different viewpoints.

Finally, I would like to thank all the researchers who have supported me during my PhD: Marco Vicentini, Elisa Carlino, Prof.ssa Luana Colloca, Prof.ssa Mirta Fiorio, Prof. Mehran Edami Andani, Prof. Paolo Manganotti and Prof.ssa Susan Jack.

GENERAL INTRODUCTION

A brief overview on placebo and nocebo effects

Placebo and nocebo effects represent one of the most fascinating topics in the healthcare field. They represent complex and distinct psychoneurobiological phenomena where behavioural and neurophysiological changes occur during an interaction between the patient and the healthcare context (1). Placebo effects (Latin “I shall please”) are produced by a psychosocial context that is capable of positively affecting the patient's brain and therapeutic outcomes (2-4). On the contrary, nocebo effects (Latin “I shall harm”) are consequences of the negative perception of the ritual and therapeutic act on the patient's mind and body, so much so that it generates unwanted effects and side effects (5-7).

Throughout the history of medicine, placebo and nocebo have been traditionally viewed as bothersome variables to check for in a clinical trial. In the last four decades, in light of some significant clinical and laboratory findings, they have become a source of research interest. Indeed, placebo and nocebo have been adopted as a conceptual model to examine the body-mind interaction and the human body systems, exploring their connection with different systems, mechanisms, diseases and therapeutic interventions (8, 9). In particular, placebo and nocebo effects have been studied in mood (10), cardiovascular, respiratory (11), gastrointestinal (12, 13), motor (14), immune and endocrine (15), and pain systems (16-18).

Clinically, not all improvement or aggravation of patients' symptoms is due to placebo and nocebo effects. It is necessary to rule out the patients' modifications created by placebo and nocebo effects from the changes of outcomes related to other

confounding elements. The elements which could create misinterpretations of the patients' clinical picture are: the spontaneous remission of the disease and symptom fluctuation (also called the natural history), the regression to the mean (a statistical phenomenon caused by selection biases), the patient's and clinician's biases during the reports of clinical conditions, and unidentified effects of concomitant co-interventions (8, 9).

Different psychoneurobiological findings allowed the scientific community to begin to understand the underlying mechanisms of placebo and nocebo effects. From a theoretical perspective, two main psychological subjective constructs have been suggested to explain how placebo or nocebo effects act: the expectation and the conditioning. The social learning, reward, anxiety reduction, desire, motivation, memory, somatic focus, genetic and personality traits also represent alternative theories (19-25). "Alternative" however does not mean that these psychological mechanisms are mutually exclusive: they can interact simultaneously (26).

Regarding the actual findings, placebo and nocebo interact with the brain modulatory systems at a neurochemical level, through the release of specific neurotransmitters. For instance, considering pain outcome as a model, the endogenous opioids, dopamine, cannabinoids, oxytocin and vasopressin are involved in placebo analgesia, while cholecystokinin, dopamine, opioid deactivation and cyclooxygenase-prostaglandins activation are implicated in nocebo hyperalgesia (27-29).

Furthermore, recent advances in neuroimaging techniques, such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), suggest an involvement of specific neural correlates during placebo and nocebo effects, mainly the pain one. In fact, placebo and nocebo are able to activate or deactivate the four key

brain regions commonly associated with the descending pain processing pathway: the dorsolateral prefrontal cortex, the rostral anterior cingulate cortex, the periaqueductal gray and the dorsal horn of spine (16). Nevertheless, they represent only a part of brain areas showing a change in their activity during placebo or nocebo (30-32).

Therefore, the previously described evidence suggests that placebo and nocebo effects are concrete and genuine phenomena, triggered by different contexts, and capable of impacting the patients' brain. It is necessary to define what the context is, and why its parts are important from a clinical perspective (33).

The healthcare context as a trigger of placebo and nocebo effects

In 1955 Balint described the context as the “whole atmosphere around the therapy” (34). The context is not a vacuum, but it embodies a healing space composed by internal, external and relational elements capable of interacting with the patient's disease (35). The internal elements consist of memories, emotions, expectations and psychological characteristics of the patient. The external elements include the physical aspects of therapy, such as the kind of treatment (pharmacological or manual) and the place in which the treatment is delivered. Relational elements are represented by all the social cues that characterize the patient-clinician relationship, such as the verbal information that the clinicians give to the patient, the communication style or the body language (36).

In 2001, Di Blasi et al. defined these elements as “contextual factors”. These factors have been grouped, from a clinical practice point of view, in five categories: a) clinician features, b) patient features, c) patient-clinician relationship, d) intervention features, and e) healthcare setting features (37). As a whole, contextual factors

constitute the therapeutic ritual and healing symbols surrounding the patient-clinician encounter, capable of producing changes in the patient at perceptual, neurophysiological and cognitive levels (38). Indeed, contextual factors convey a hidden meaning, actively detected and analysed by the patient, which is essential for the perception of care and the interpretation of the therapeutic intervention (39, 40). When these contextual stimuli and cues are filtered by the patient's perspective and mind-set (41), they are translated into a complex cascade of psycho-neuroimmunoendocrine events, thus triggering placebo and nocebo effects and influencing the course of illness (42, 43).

From a clinical perspective, the contextual factors pervade every healthcare action (history taking, physical examination, therapy and prognosis) and directly affect the quality of the health-related outcome (44-46). A positive context, that is characterized by the presence of positive contextual factors, can improve therapeutic outcome by producing placebo effects, while a negative context, characterized by the presence of negative contextual factors, can aggravate therapeutic outcome by creating nocebo effects (47, 48). For example, during the same treatment delivery (e.g. painkillers), the use of positive verbal suggestion (e.g. "This therapy will help you and it will decrease pain") can improve musculoskeletal pain, while the adoption of verbal suggestion of uncertainty (e.g. "This therapy could help you and sometimes it decrease pain") can aggravate patient's pain (49).

The presented studies offer a starting point for reflection about the role of the contextual factors surrounding the administration of a healthcare treatment: they can be a source of improvement of the efficacy of the therapy or implicated in the manifestation of adverse effects. The logical consequence is to wonder whether context,

placebo and nocebo effects have been taken into consideration in a specific healthcare field, such as physical therapy.

The link between placebo, nocebo effects and physical therapy

Throughout the history of physical therapy and rehabilitation, placebo and nocebo effects have been considered as problematic phenomena for two main reasons. From a research point of view, they have represented confounding factors capable of limiting the internal validity of the study design and reducing the external validity of the findings (50). From a clinical point of view, they have embodied troublesome and non-specific variables able to attenuate the therapeutic role of specific therapies such as massage, joint mobilization and therapeutic exercise (51, 52). As a consequence, for many years the role of placebo and nocebo effects was debated worldwide by clinicians and researchers (53-55).

At the end of the first decade of the twenty-first century the scientific community began to investigate the mechanisms of action of joint, soft tissue and neural therapeutic intervention, consequently revaluing the role of placebo and nocebo effects in physiotherapy (56). Recent studies have suggested a mechanical and neurophysiological mechanism (peripheral, spinal and supraspinal) linked to the therapeutic strategies adopted by physical therapists (57). Among the supraspinal mechanisms, the placebo and nocebo effects have assumed an important top-down role in inducing changes in patient's symptoms (58), thus becoming elements that clinicians should adopt in clinical practice (59).

Recently, also the context in which interventions are delivered has been suggested as a moderator of clinical effects (60). A new line of research has indicated the context

as responsible for a larger non-specific component of treatment efficacy in physical therapy (61). Despite these promising advances, the following issues remain unexplored:

- 1) What are the contextual factors?
- 2) How can the contextual factors trigger placebo and nocebo effects?
- 3) Which therapeutic outcomes can be influenced by the contextual factors?
- 4) Are the physical therapists aware of the use of contextual factors in clinical practice?
- 5) What is the role of contextual factors in research?

General organization of the research project

The main goal of this PhD research project is to *investigate the relevance of the contextual factors as triggers of placebo/nocebo effects and their impact on therapeutic outcomes in physiotherapy*. Different studies were conducted during the 3-year period of PhD training (2015-2018). The results, relative discussions and implications are reported in the chapters of the present dissertation as follows:

- **Chapter I:** a conceptual model regarding the role of the contextual factors as triggers of placebo, nocebo responses and influencers of physical therapy outcomes;
- **Chapter II:** the model of contextual factors regarding musculoskeletal pain, which is a common outcome encountered by physical therapists;
- **Chapter III:** the link between the determinants of patient satisfaction in outpatient musculoskeletal physiotherapy clinics and the contextual factors;
- **Chapter IV:** the knowledge, attitude and behaviour of Italian physiotherapists specialized in manual therapy towards contextual factors;

- **Chapter V:** the translational value of contextual factors and their relevance for physical therapy research.

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CHAPTER I

ENHANCE PLACEBO, AVOID NOCEBO: HOW CONTEXTUAL FACTORS AFFECT PHYSIOTHERAPY OUTCOMES.

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Enhance placebo, avoid nocebo: how contextual factors affect physiotherapy outcomes

Abstract

Introduction: Placebo and nocebo represent complex and distinct psychoneurobiological phenomena in which behavioural and neurophysiological modifications occur together with the application of a treatment. Despite a better understanding of this topic in the medical field, little is known about their role in physiotherapy.

Purpose: The aim of this review is: a) to elucidate the neurobiology behind placebo and nocebo effects, b) to describe the role of the contextual factors as modulators of the clinical outcomes in rehabilitation and c) to provide clinical and research guidelines on their uses.

Implications: The physiotherapist's features, the patient's features, the patient-physiotherapist relationship, the characteristics of the treatment and the overall healthcare setting are all contextual factors influencing clinical outcomes. Since every physiotherapy treatment determines a specific and a contextual effect, physiotherapists should manage the contextual factors as boosting elements of any manual therapy to improve placebo effects and avoid detrimental nocebo effects.

Introduction

Every day physiotherapists (PTs) use different tools, such as manual techniques and exercises, to achieve their main professional goals: the improvement of pain, disability and patient's self-perceived health condition. The management of placebo and avoidance of nocebo responses have recently been suggested as promising additional clinical strategies (1), generating a wide debate in manual therapy research (2-4).

Placebo and nocebo represent complex and distinct psychoneurobiological phenomena in which behavioural and neurophysiological modifications occur following application of a treatment. The placebo (Latin "I shall please") is created by the positive psychosocial context that is capable of influencing the patient's brain (5). Instead, the nocebo (Latin "I shall harm") is the result of the negative ritual and therapeutic act on the patient's mind and body (6-8).

From a psychobiological perspective (Figure 1), conscious expectation and the unconscious classical conditioning, reward-learning, observational and social learning, modulation of anxiety, desire, motivation, memory and prior experience, somatic focus, personality traits and genetics work as facilitators of placebo or nocebo (9-11) and modulate different responses across several diseases, illnesses, and treatment methods (12-14).

Although some attempts to identify (15) and to measure (16) the placebo response induced by sham techniques have been reported, to date the role of placebo response seems to be poorly recognized and applied by PTs in clinical setting (17) and nocebo is still scarcely considered as a possible variable negatively influencing rehabilitation outcome.

Agreeing that the conscious reinforcement of placebo strategies could represent an additional opportunity for every PT to improve their clinical outcomes, the present article aims to:

- a) Synthesize the neurobiological mechanisms underlying the placebo and nocebo responses;
- b) Describe the contextual factors as modulators of the clinical outcomes in musculoskeletal rehabilitation;
- c) Provide guidance for the clinical implementation of placebo enhancement and/or nocebo avoidance;
- d) Identify possible new lines of investigation in manual therapy research.

The neurobiological mechanisms behind placebo and nocebo responses

Pain and motor performance are the most frequently used models to describe the neural network involved during the placebo and nocebo responses (18-21).

Pain

Placebo and nocebo engage distinct top-down modulatory systems using different key neurotransmitters. Endogenous opioids, dopamine, cannabinoids, oxytocin and vasopressin are involved in placebo while cholecystokinin, dopamine, opioid deactivation and cyclooxygenase-prostaglandins activation interact with nocebo (22-24). Placebo analgesia and nocebo hyperalgesia largely involve, with opposite activation, numerous brain areas (Table 1).

Among them, placebo analgesia is mostly associated with an increased functional coupling of the dorsolateral prefrontal cortex, the anterior cingulate cortex, the

hypothalamus, the amygdala, the periaqueductal grey and a decreased activity in pain processing area such as the thalamus, insula and the somatosensory cortex (10, 25-27). On the contrary, negative expectations of pain increase the activation of affective-cognitive pain regions like the anterior cingulate cortex, the prefrontal cortex, the insula and the hippocampus. Furthermore, placebo and nocebo are capable of modulating pain processing at the spinal level (6, 7, 14). For a graphical representation see Figures 2a and 2b.

Motor performance

Placebo and nocebo influence the activity of the motor system and the consequent motor performance (28-31). It has been shown that placebo induces an increase of dopamine in the striatum and a change of neural activity in the basal ganglia and in limbic areas of the brain in patients affected by Parkinson disease (32, 33). Enhanced corticospinal system excitability (34) and reduced fatigue by modulating readiness potential during the anticipatory phase of movement (35) were displayed in healthy subjects. Similarly, a nocebo procedure in which the induced expectation decreases force production modulated the corticospinal circuits influencing motor performance (36).

The contextual factors optimize the rehabilitation outcomes

The psychosocial context and the therapeutic ritual around the patient can also influence the patient's brain activity and the therapeutic outcome such as satisfaction and perceived effect (5, 37, 38). As reported in Figure 3, the physiotherapist's and patient's features, the patient-physiotherapist relationship, the characteristics of the

treatment and the overall healthcare setting are the most relevant categories of contextual factors involved in placebo or nocebo effects (39).

Physiotherapist's features

A “physiotherapist’s effect” is present and influences the outcome of treatment in patients with musculoskeletal disorders (40).

Professional reputation and appearance

The perception of expertise, professionalism, qualification, reputation and the level of training of the PTs are important elements for the patient and can contribute to modify the clinical outcome in musculoskeletal disorders (41-43). Moreover the way a therapist dresses is able to influence the patient’s perception of care (44). Recently the results of a study by Mercer, Mackay-Lyons (45) reported that lab coat and tailored clothing were ranked respectively most professional and preferred, by patients with low back pain (LBP). By contrast, patients were less satisfied if the professional appearance was poor and if PTs used jeans during clinical practice (42, 45).

Beliefs and behaviours

Enthusiastic practitioners and their optimism or pessimism regarding the nature of a treatment have an active effect on the outcome (46-48). This is a self-fulfilling prophecy whereby the convincement of a practitioner about the patient’s outcome leads to an improvement (“Pygmalion effect” – “Rosenthal effect”) or a worsening (“Golem effect”) of the outcome itself (49). Recent evidence linked the attitudes and beliefs of patients with LBP with the attitudes and beliefs of the health care professional (included

PTs) they have consulted (50). Patients appreciate PT's aptitude to encourage questions and to answer the patient's requests, to explore disease and illness experience and to trust their opinion. The PT's ability to deliver positive feedback, to give clear prognostic information and explanation about the patient's condition and the treatment can positively interact with the results of therapy (41, 42, 51-54). On the other hand, PTs should avoid to show nervousness, to be uncooperative or in a hurry, to spend too much time reading patient charts and to use too technical words with the patient during the clinical encounter (41, 52).

Patient's feature

The patient's perception and direct experience of care are central elements capable of influencing the placebo analgesia (55).

Expectation, preferences and previous experience

The expectation of a treatment can shape the patient's pain experience (21, 56-58). It was recently demonstrated that the general expectations for pain relief strategies had an important influence on pain and disability, in patients with LBP (59) and neck pain (60). Moreover, expectation is a significant prognostic factor in musculoskeletal pain and is often underestimated by PTs (61-63). Also the patient's prior experience of care is another factor that can affect the outcome of a therapy (64). Indeed, patient's preferences and previous experiences about a physiotherapy treatment are able to tune the magnitude of the therapeutic response in musculoskeletal rehabilitation just because of the way they are paired with prior positive or negative results (42). By contrary,

avoiding or ignoring the patient's preferences, expectations and previous experiences can negatively influence the therapeutic outcome (41).

Musculoskeletal condition, gender and age

The phases of the course of the musculoskeletal disorder can influence the outcomes of care such as the satisfaction of the patient (65). Indeed, acute patients reported higher satisfaction with physical therapy care and were more sensitive to a number of PT's features such as expertise, reputation, level of training and professional behaviour than those with chronic conditions who perceived the organization of care as the most significant element (42). Moreover, the perception of the quality of physiotherapy care is affected differently in males and females as well as in patients of different age (66). In particular, the main predictors of satisfaction for male patients were the therapist and treatment outcome, whereas for female patients the most important elements were organization and the communication component of care. Older patients seem to be more sensitive to particular aspects of physical therapy care such as access to services and the effectiveness of communication (42).

The patient-provider relationship

A good patient-PT relationship positively influences outcomes like pain, disability, satisfaction and strengths of the therapeutic alliance (51, 67). The clinical encounter is modulated by different factors such as verbal and non-verbal skills (68).

Verbal communication

An appropriate verbal communication is a prerequisite of a good therapeutic relationship (69). PTs spent approximately twice the time passed hands-on talking with the patient (70, 71). Active listening and verbal expressions of support and encouragement, humour and sympathy, empathetic and communicative talk, partnership statements, paraphrasing and requests for patient's opinion and the language reciprocity correlated with patients' satisfaction can significantly influence the outcome of the treatment. (41, 42, 52, 53). PTs should avoid negative communication, verbal expressions of anxiety, closed questions to gather information and use of social niceties (52). Patients were dissatisfied when they were interrupted and could not tell their story and when PT lacked empathy, friendliness, was too confident or behaved arrogantly (41). Furthermore, the use of positive messages associated with treatment for pain relief (e.g. "this treatment is a powerful pain killer") produces a large placebo analgesia effect in medicine (72, 73). In manual therapy, conversely, associating hands on techniques with positive verbal instructions changed positive expectation and patients' satisfaction, without affecting pain or disability (74-76). Moreover, the use of negative information during the leg flexion test (e.g. "this procedure could lead to a slight increase in pain") determined an aggravation of pain and poor performance during the test in patients with chronic LBP (77).

Non-verbal communication

Facial expression and eye contact represent important elements in therapeutic interaction (53) from which patients deduce meaning (5). The expression on the face is capable of influencing pain processing (78) and enhance the placebo analgesia (79). In clinical context, PTs use non-verbal behaviour such as eye contact, smiling (70), caring

expressions of support and interest, potentially contributing to affect therapy outcome (52). Also gestures, postures and physical contact along with speech form an integrated message full of meaning during clinical interaction (41, 80). By observing these elements a patient can infer the therapist's intention and adapt his own behaviour unconsciously with modification of neurohormonal substrate of oxytocin system (5, 81, 82). PTs regularly use affirmative head nodding, touch, forward leaning and body orientation to facilitate and involve patients to improve satisfaction of consultation (52, 70). Additionally, the therapist's ability to interpret patients' nonverbal body language expressions is an important element of satisfaction during the clinical encounter (52). Thus, PTs should avoid an inquisitive eye contact, a slanting position (45° or 90° towards the patients), asymmetrical arm postures, crossed legs, backward leaning and neck relaxation (52, 53).

Treatment feature

Different variables of a treatment can influence the outcome perceived by the patient (83).

Clear diagnosis, overt therapy and observational learning

A diagnosis, which gives meaning to the patient's illness, is a form of treatment per se (84). Delivering an exhaustive diagnosis and explanation of musculoskeletal disorders is appreciated by the patients and can influence their satisfaction about the care during the first visit (42, 53, 85). Moreover, showing and telling patients that a treatment is being applied is important for the creation of the placebo response and modulation of therapeutic outcome (86). In a postoperative analgesia study, covert

administration of analgesic resulted in slower onset of pain relief than when patients knew when morphine was administered, implying that the initial rapid relief is largely effected through a placebo response (87). Also in physiotherapy, the administering of an overt treatment by a mirror feedback was proposed as an effective strategy in chronic LBP (88). Indeed, patients that looked at their back when moving during exercises reported less increase in pain and faster resolution of dysfunction (89, 90). Finally, endorsing the positive effects of a therapy in a therapeutic context in which patients could talk to other patients who successfully received the same treatment, or watching videos of other patients, can influence placebo analgesia and avoid nocebo (9). In musculoskeletal rehabilitation, the use of action observation of others' movement improves pain and disability of patients after total knee replacement (91, 92).

Patient-centred approach and global process of care

Personalizing treatment, taking patient's opinions into account and use of a patient-centred care seem to influence the result of the treatment (41, 42, 52, 53, 93). Moreover, organisational and procedural aspects of physiotherapy such as therapy delivered by the same PT, cleanliness, adequate length of consultation, punctuality, flexibility with patient appointments, timely and efficient treatment, adequate frequency, duration and follow-up of therapy affect the patient's satisfaction and therapeutic outcome (41, 42, 52). Instead, the use of a therapist-centred or biomedical approach, a lack of privacy, an expensive treatment, a too long waiting list, a reduction of patient-PT time, being treated by different PTs or an hastened treatment negatively influence the outcome of therapy (41, 42, 52).

Therapeutic touch

In clinical context, PTs apply different form of touch such as assistive touch, touch used to prepare the patient, touch to provide information, caring touch, touch to provide a therapeutic intervention, and touch used to perceive information (94, 95). Touch is a fundamental element of interpersonal interaction (96) that regulates the social bonding in humans. This kind of touch information is conducted by a class of cutaneous unmyelinated, low threshold mechanosensitive nerves, called c-tactile afferents, that process affiliative tactile stimuli (97, 98). Moreover touch in therapeutic setting acts as a useful strategy to relieve musculoskeletal pain (99, 100). When moderate and light pressure massage were compared, only moderate pressure contributed to enhance pain, depression and anxiety (101). Furthermore, moderate pressure massage was capable of modifying neurophysiological parameters such as heart rate, improved vagal activity, decreased cortisol levels, enhanced serotonin and dopamine levels, influence cortical and spinal excitability and inhibit nociceptive responses at a subcortical and cortical level (101-105).

Healthcare setting feature

The healing environment and the use of combined positive distractors in a therapeutic context can influence the patient's outcomes such as pain, stress and anxiety (106).

Environment

Different sensory elements of the environment can modulate the patient's outcome. Environments with natural lighting, monitored low noise levels, with relaxing

and soft music are more desirable (107-114). Moreover, the use of pleasing aromas and an adequate temperature are important factors to be considered in a therapeutic context (112, 113).

Architecture

Structural aspects of the healthcare environment can influence the patient's perception of care and pain perception (115). Environments that integrate windows and skylights in the workplace, comfortable and private therapeutic settings are more appreciated by patients (107, 108, 111-113). Furthermore, it is advisable the use of supportive indications such as highly visible and easy to read signs, parking information, accessible entrances, clear and consistent verbal or written directions, information desks, and accessible electronic information (108). Indeed, a good access to services, particularly convenient clinic hours, location, parking, and an available and approachable support staff are perceived as important elements for the patient (42).

Interior design

Decorations and ornaments can impact the health status of the patient. Nature artworks that include green vegetation, flowers, water and a setting with a view of nature that integrates plants or garden ornaments have a calming effect (107-113). Also colour schemes based on soothing shades seem to modulate the patient's experience of care (107). However, the meaning of colour differs among persons and should be culturally suitable for the patient population it is intended to serve (108, 112).

Implications for clinicians: maximise placebo, minimize nocebo

In therapeutic settings, placebo and nocebo effects are commonly detected. Various systematic reviews observed placebo when continuous subjective measures of disease are adopted, and not when binary subjective or objective measures are applied (116-118). This advocates that placebo does not influence the disease but affects the illness as subjective perceptions of patient experience (119, 120). Indeed placebo and nocebo can positively and negatively impact impairments and disabilities such as pain (72, 73, 121), motor performance (28-31) and satisfaction in musculoskeletal disorder therapy (42). Therefore, PTs should consider it in clinical practice and be aware to maximize placebo and eliminate nocebo (13, 122). Table 2 provides guidelines on the application of placebo.

From a clinical point of view, placebo and nocebo elements are always present during therapeutic intervention. Every healthcare intervention is formed by two factors: a specific/active biological component and a contextual/psycho-social one (5). These contextual elements interact with the specific effect of the therapy by either increasing or decreasing the global effect of treatment (37, 38). Also manual therapy presents a specific biomechanical and neurophysiological mechanism that could be modulated by the context (17, 123-125). For PTs it is essential to transfer this knowledge in clinical practice to improve therapy application and outcome (1, 126). Figure 4 shows the relevance of adding different contextual factors on the specific effect of a treatment.

PTs should remember that patient satisfaction is determined more by interactions with the PT and the process of care instead of the outcome of treatment (Hush, Cameron, 2011). Therefore, it is useful to strengthen the therapeutic relationship, the healing rituals and treatment setting during the clinical encounter (127-129). In the therapeutic arena multiple signs and cues convey a hidden meaning that is essential for

the perception and interpretation of care and that may be just as important as the specific effect of the treatment (130-133).

Beside placebo and nocebo, other conditions such as the natural history of the disease, the regression to the mean, biases by clinicians and patients, unidentified co-interventions or adverse side effects in the placebo group in a randomized controlled clinical trial (RCT) can modify the outcomes of therapy and can disguise recovery or aggravations, (8, 12). Figure 5 provides a graphical synopsis about the different elements that influence the global therapeutic outcome.

While placebo is a real and powerful phenomenon with a supportive evidence of action, it must be clear that the placebo intervention should not be based on unethical principles or deception and should not be a substitute for other more effective treatments (120). It is ethical to use it as a boosting strategy combined with the best available therapy to improve clinical outcomes of patient and avoid nocebo (134, 135).

Implications for research: design placebo and nocebo trials

The creation of an adequate trial design remains a challenge in placebo and nocebo research (136, 137). Researchers should be aware of the fact that the management of the contextual factors is linked to their goals. Limiting the therapeutic relationship and the ritual around the treatment favours emersion of the specific effect of the therapy. (138-140). On the other hand, the administering of an active therapy increasing the therapeutic alliance and healthcare interaction can help to reveal the role of the context in the modulation of the patient's outcome (141, 142). Much of the information presented in this paper does not result from RCT assessing the effectiveness of individual contextual factors, but it is extrapolated from qualitative research and

patient interviews. Therefore, there is a strong need for a translational research with a significant clinical impact (143). Several lines of investigation are a priority such as: the effect of the single and combined contextual factors on the therapeutic outcome, the PTs' knowledge and expertise about placebo and nocebo effect, the patient's point of view about the role of the contextual elements in influencing the outcome, the identification of psychological and genetic traits of placebo responders.

Conclusion

The difference of clinical success between two different PTs, both practicing respectful of the scientific evidence and applying the clinical guidelines lies in the different level of implementation of the “art” component of the profession. This is probably mostly due to behaviours that have relevant effects on the clinical outcome through placebo or nocebo phenomenon. The possibility of adopting knowledgeable, expert and ethical strategies to enhance placebo and avoid nocebo is a great opportunity for every PT to enrich their therapeutic toolbox.

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Table 1. Description of brain areas involved in placebo analgesia and nocebo hyperalgesia

Placebo Analgesia	Nocebo Hyperalgesia
rostral anterior cingulate cortex, hypothalamus, amygdala, periaqueductal gray, rostral ventro-medial medulla, lateral orbitofrontal cortex, nucleus accumbens, dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, dorsal horn of spinal cord, thalamus, anterior insular cortex, primary and secondary somatosensory cortex, putamen, caudate nucleus, striatum, supramarginal gyrus, left inferior parietal lobule. the parabrachial nuclei	hippocampus, dorsal horn of spinal cord, nucleus accumbens, thalamus, second somatosensory cortex, posterior insular cortex , caudal anterior cingulate cortex, head of the caudate, cerebellum, contralateral nucleus cuneiformis, parietal operculum, bilateral dorsal anterior cingulate cortex, left frontal and parietal operculum, orbitofrontal cortex, lateral prefrontal cortex,

Table 2. Strategies to enhance placebo in physiotherapy

Key points
Physiotherapist's and patient's feature
<ul style="list-style-type: none"> • Improve professionalism, reputation, training and expertise; • Use a lab coat or tailored clothing;

-
- Be optimistic during the consultation and regarding the dysfunction;
 - Deliver clear diagnosis, prognosis and explanation of the patient's problem;
 - Explore the patient's disease and illness, request and trust the patient's opinion;
 - Encourage questions, answer requests by the patient, deliver positive feedback;
 - Investigate expectation, preferences and previous experience of the patient;
 - Consider the phase of the musculoskeletal conditions, gender and age of the patient;

Patient-physiotherapist relationship

- Be warm, confident, friendly, relaxed and open during the clinical encounter
- Use verbal expressions of empathy, support, sympathy, language reciprocity;
- Adopt psychosocial talk, partnership statements and paraphrase;
- Use positive messages associated with treatment for pain relief;
- Use eye contact, smiling, caring expressions of support and interest;
- Use affirmative head nodding, forward leaning and open body posture;
- Interpret patient's nonverbal body language expressions;

Treatment feature

- Use open treatment, show and tell the patient that a therapy is applied;
- Boost the patient's willingness to talk to other patients who undergo the same treatment with positive results;
- Use patient-centred care, personalize the treatment;
- Deliver the treatment by the same physiotherapist in a clean and private environment,
- Set appointments with adequate length, punctuality, frequency, follow-up;
- Use touch to assist, prepare, inform, care of, perceive and treat patients;

Healthcare setting feature

- Combine positive distractors as light, music, temperature and aromas,
 - Adopt supportive indications to facilitate access to physiotherapy service;
 - Decorate the therapeutic environment with artworks and ornaments;
-

Figure 1. Placebo and nocebo psychobiological determinants.

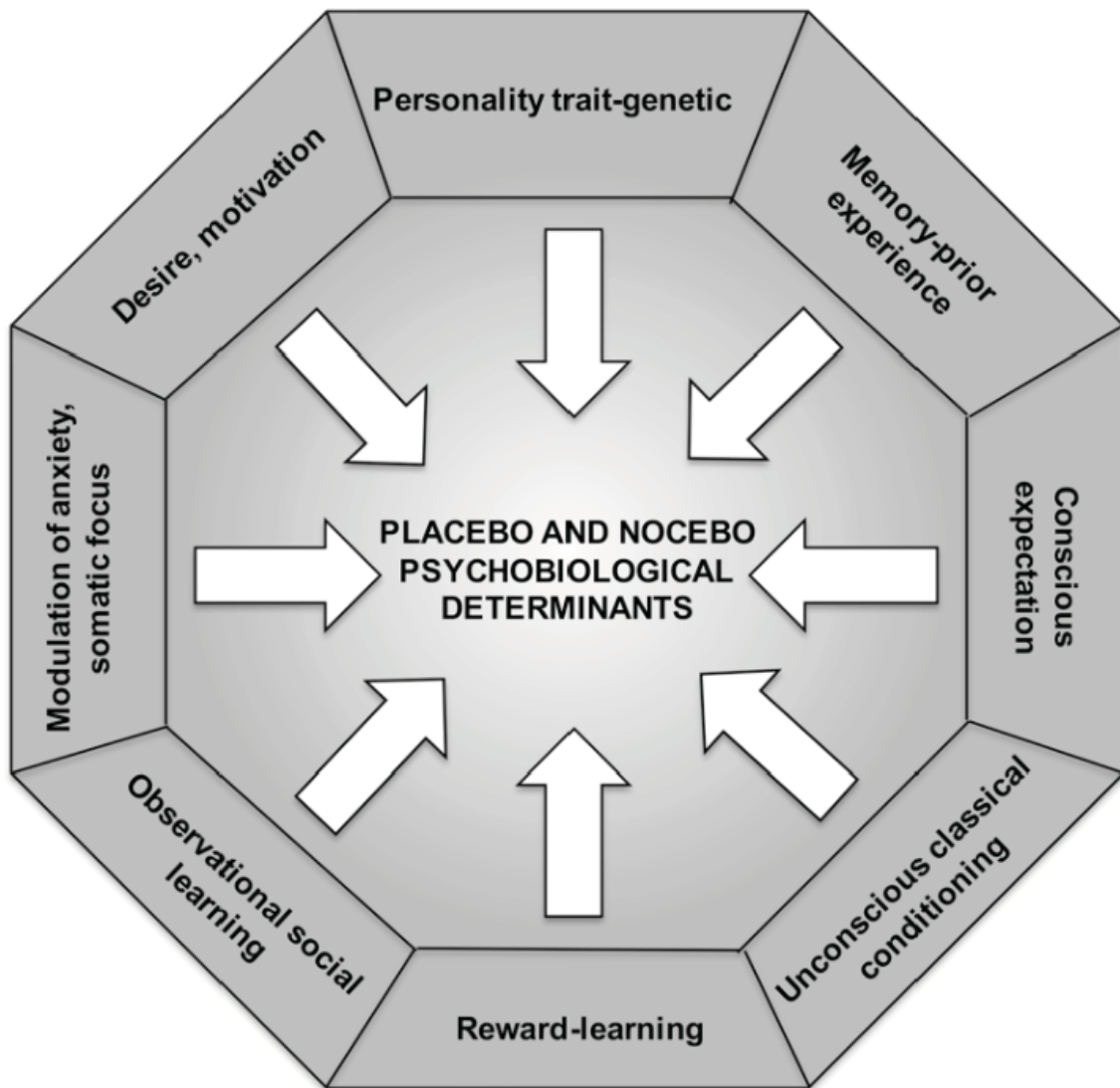
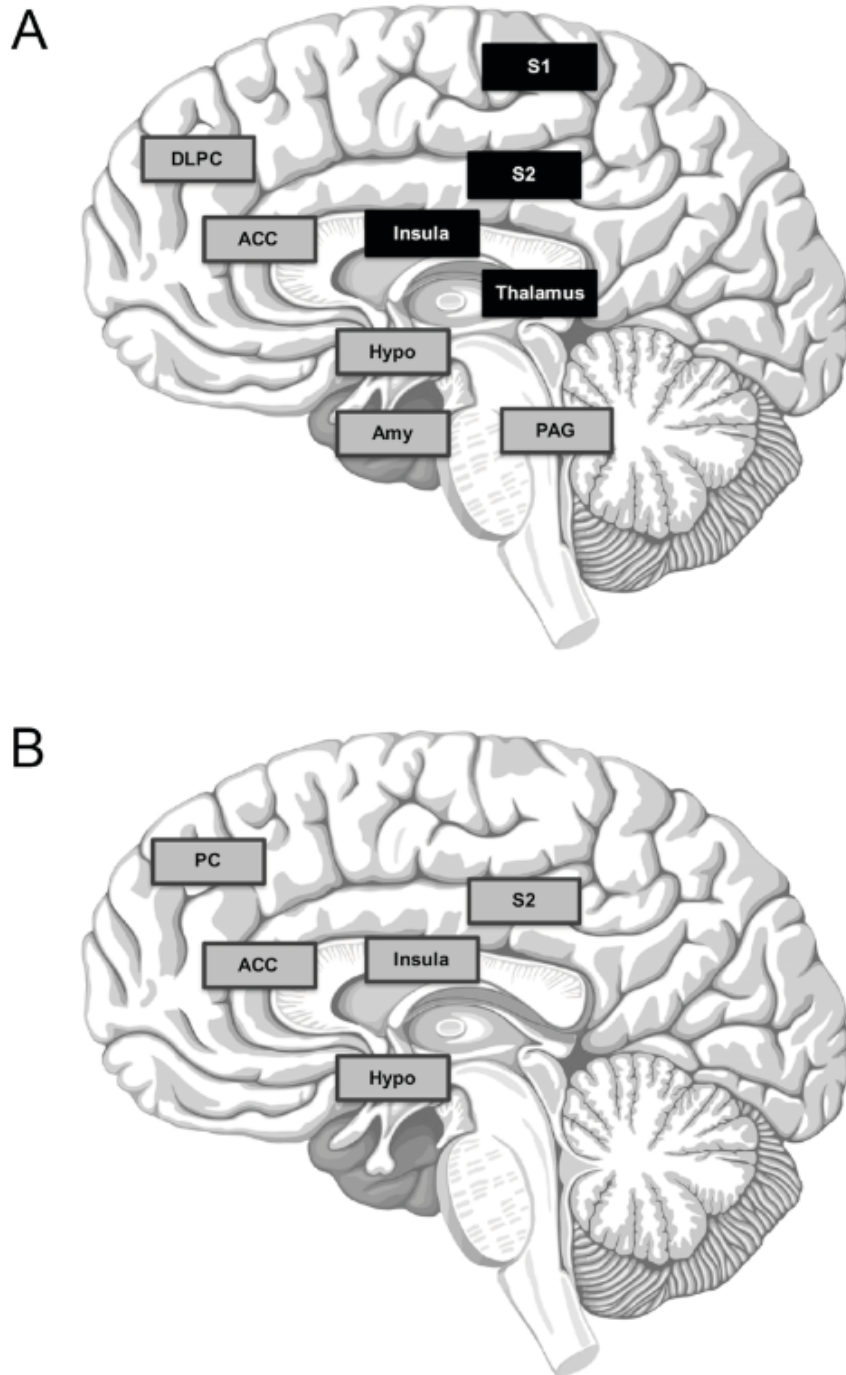


Figure 2. Brain areas most involved in placebo analgesia (a) and nocebo hyperalgesia (b).



For complete listing see Table 1 In grey area activated, in black area deactivated. DLPC: dorsolateral prefrontal cortex, ACC: anterior cingulate cortex; S1: primary somatosensory cortex; Hypo: hypothalamus; Amy: amigdala; PAG: periaqueductal gray; S2: secondary somatosensory cortex; PC: prefrontal cortex.

Figure 3. The contextual factors as modulators of therapeutic outcome.

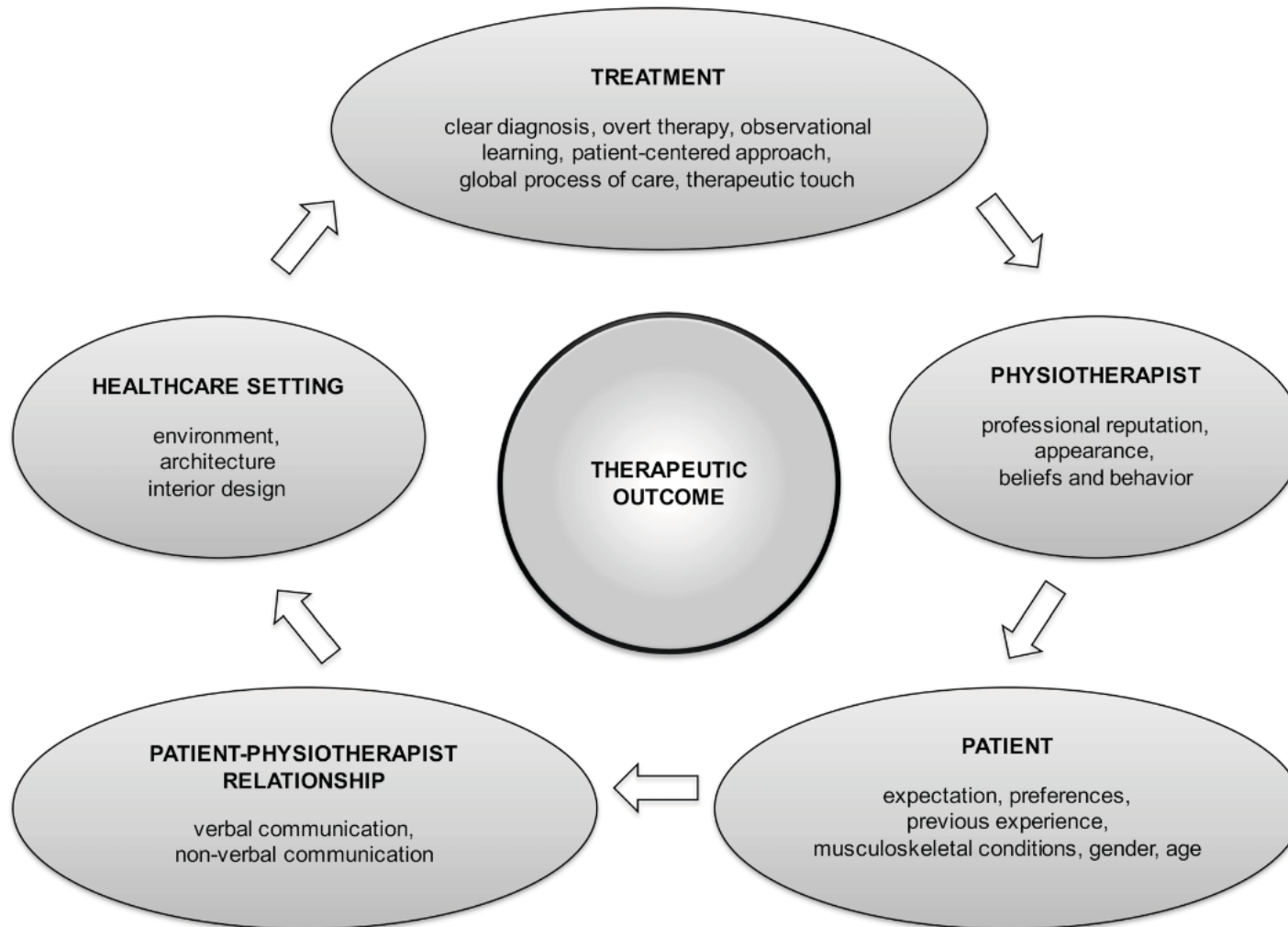


Figure 4. The modulation of the specific effect of therapy by positive and negative context.

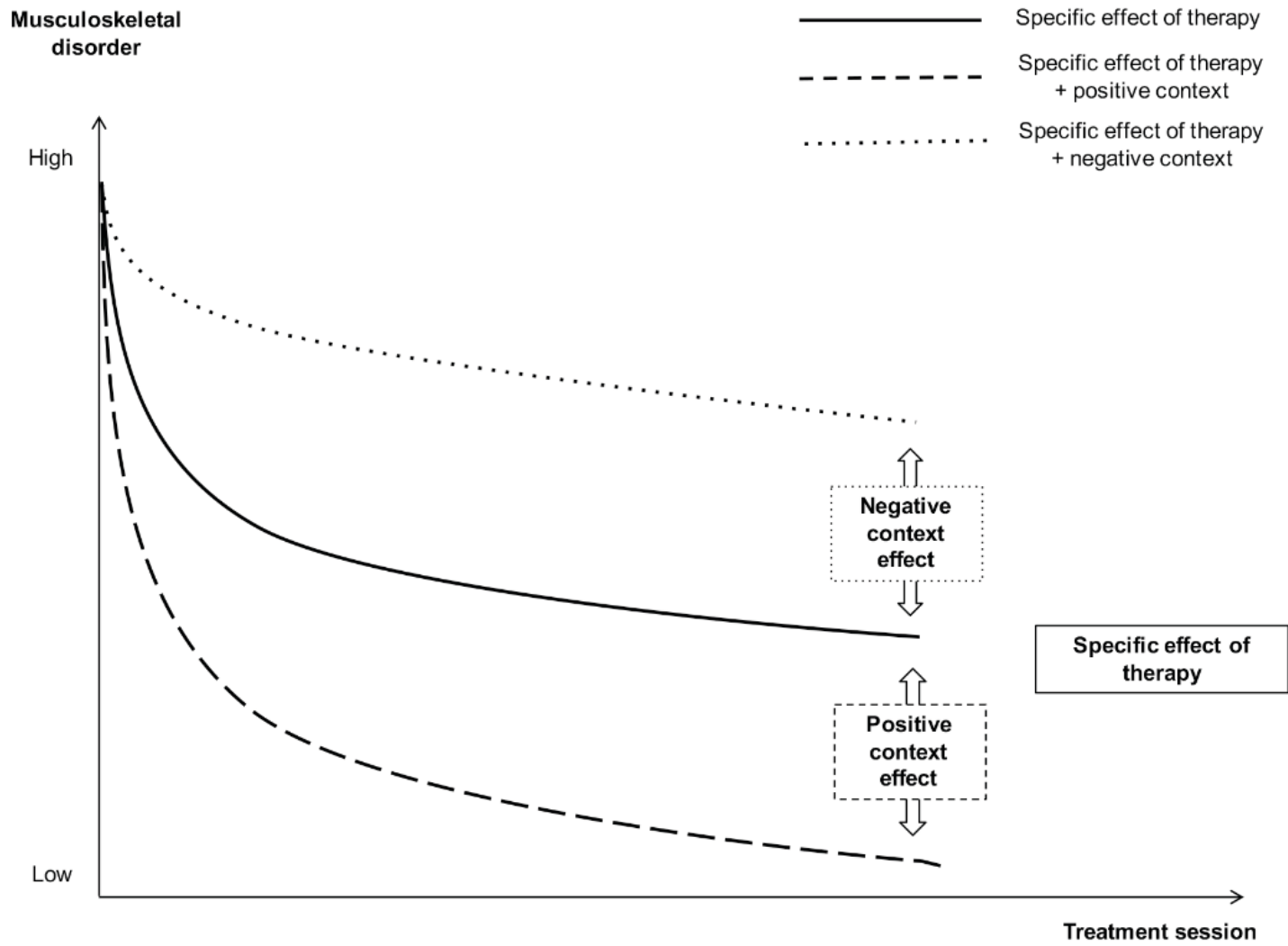
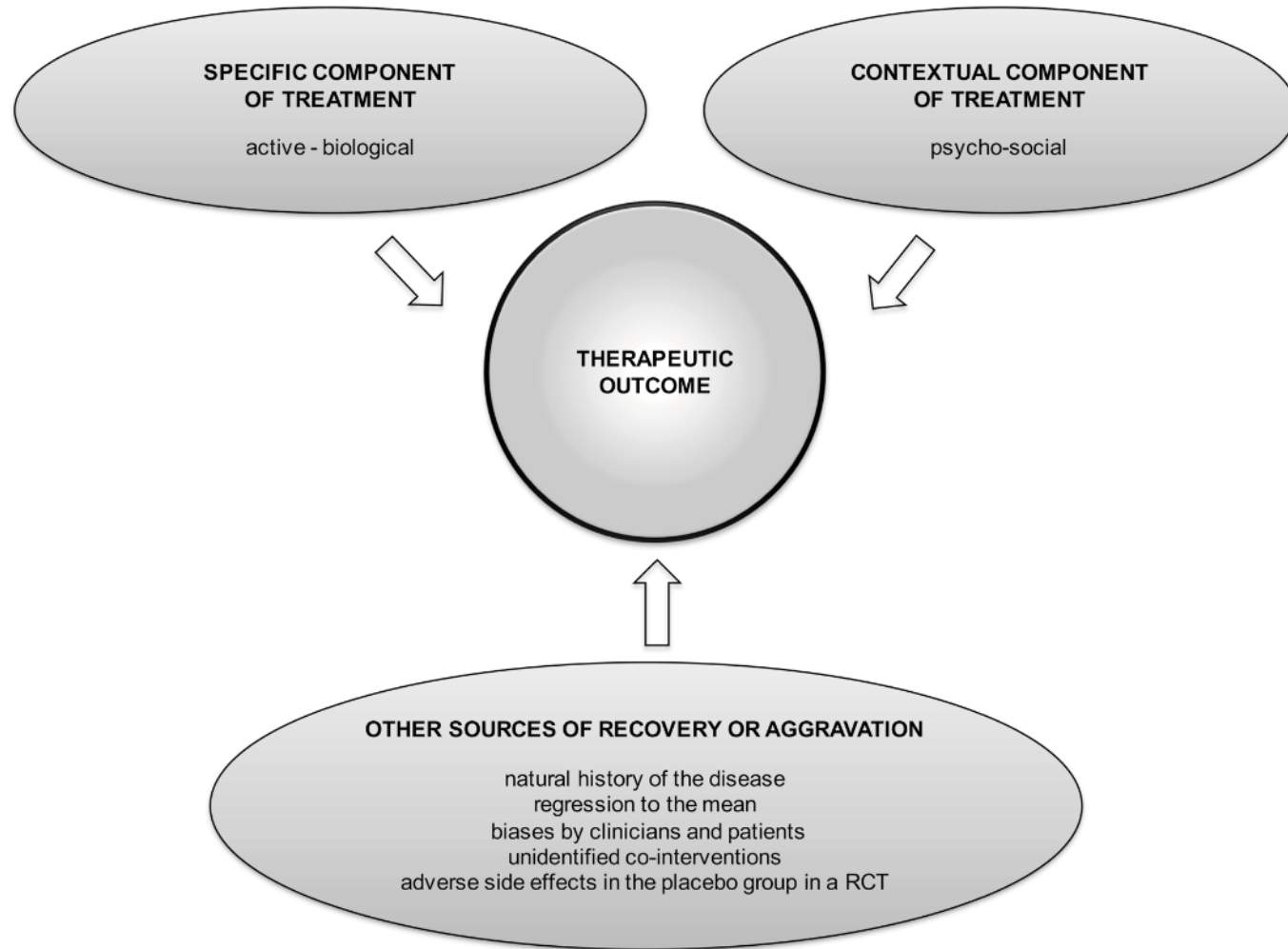


Figure 5. Different determinant of global therapeutic outcome.



CHAPTER II

CLINICAL RELEVANCE OF CONTEXTUAL FACTORS AS TRIGGERS OF PLACEBO AND NOCEBO EFFECTS IN MUSCULOSKELETAL PAIN.

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Clinical relevance of contextual factors as triggers of placebo and nocebo effects in musculoskeletal pain

Abstract

Placebo and nocebo effects are embodied psycho-neurobiological responses capable of modulating pain and producing changes at different neurobiological, body at perceptual and cognitive levels. These modifications are triggered by different contextual factors (CFs) presented in the therapeutic encounter between patient and healthcare providers, such as healing rituals and signs. The CFs directly impact on the quality of the therapeutic outcome: a positive context, that is a context characterized by the presence of positive CFs, can reduce pain by producing placebo effects, while a negative context, characterized by the presence of negative CFs, can aggravate pain by creating nocebo effects. Despite the increasing interest about this topic; the detailed study of CFs as triggers of placebo and nocebo effects is still lacked in the management of musculoskeletal pain.

Increasing evidence suggest a relevant role of CFs in musculoskeletal pain management. CFs are a complex sets of internal, external or relational elements encompassing: patient's expectation, history, baseline characteristics; clinician's behavior, belief, verbal suggestions and therapeutic touch; positive therapeutic encounter, patient-centered approach and social learning; overt therapy, posology of intervention, modality of treatment administration; marketing features of treatment and health care setting. Different explanatory models such as classical conditioning and expectancy can explain how CFs trigger placebo and nocebo effects. CFs act through specific neural networks and neurotransmitters that were described as mediators of placebo and nocebo effects.

Available findings suggest a relevant clinical role and impact of CFs. They should be integrated in the clinical reasoning to increase the number of treatment solutions, boosts their efficacy and improve the quality of the decision-making. From a clinical perspective, the mindful manipulation of CFs represents a useful opportunity to enrich a well-established therapy in therapeutic setting within the ethical border. From a translational perspective, there is a strong need of research studies on CFs close to routine and real-world clinical practice in order to underline the uncertainty of therapy action and help clinicians to implement knowledge in daily practice.

Background

Pain represents a “distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive and social components” (1). Among the different pain conditions, musculoskeletal pain is ubiquitous and multifaceted: it can be the consequence of everyday activities that repeatedly or unusually stress the system, or it can be due to either acute traumatic events or to musculoskeletal diseases (2). It is the most disabling symptom in musculoskeletal disorders, causing a high number of requests for healthcare treatments and rising social costs (3). Moreover, especially in chronic conditions when pain persists beyond the normal healing time, it is influenced by different physical, psychological and social factors (4-6) defined as “contextual factors” (CFs).

The multidimensionality that characterizes pain in musculoskeletal complaints requires an integrative and personalized approach for its treatment. For this reason, the study of the CFs and their conscious use and integration in the clinical practice could represent a novel approach in the management of this complex experience (7-16).

By definition, CFs are physical, psychological and social elements that characterize the therapeutic encounter with the patient (17, 18). CFs are actively interpreted by the patient and are capable of eliciting expectations, memories and emotions that in turn can influence the health-related outcome, producing placebo or nocebo effects (19). In other words, the CFs represent the context that accompany any healthcare treatment: the exposure of a patient to a positive context (positive CFs) very often produces a placebo effect that is the occurrence of symptoms improvement (e.g. analgesia), whereas a negative context (negative CFs) can generate a nocebo effect, with a worsening of the pain condition (e.g. hyperalgesia) (20, 21). In the

following review, we use the term CFs instead of placebo, avoiding the misleading interpretation of placebo as inert treatment given to comfort or please the patient and following the recent conceptualization of the placebo as the psychosocial context that accompanies any medical intervention, be it active or sham (22-31).

As extensively demonstrated by the placebo and nocebo effect literature, the CFs can affect the outcome of a treatment with different mechanisms and in different systems, medical conditions, and therapeutic interventions (32). From a clinical perspective, the study of CFs as triggers of placebo and nocebo effects, is crucial for the management of musculoskeletal pain for several reasons (33). First, even if CFs are embodied in every complex therapeutic interventions in musculoskeletal complaints, they are often considered as incidental factors capable to affect outcomes. For this reason they are not always identified and used intentionally by clinicians (34). Second, CFs can produce a therapeutic effect through the involvement of the same central pathways of pain modulation activated by several hands-on (e.g. manual therapy, therapeutic exercises, acupuncture, injections) and hands-off solutions (e.g. pain neuroscience education) commonly applied in clinical practice (35-37). Third, CFs serve as additional tools for the interpretation of the clinical picture and guide clinicians in managing the complexity behind the patient's musculoskeletal pain (38). Taking into consideration CFs as active influencer of the therapeutic outcomes, can help to explain some unexpected outcomes and variability of symptoms experience (39).

Moving from this vision, the present debate is proposed to all the health professionals (physiotherapists, chiropractors, osteopaths, nurses, occupational therapists, rheumatologists, orthopedics etc.) that work with musculoskeletal pain. In order to support a better and more conscientious therapeutic use of the CFs in

musculoskeletal field, the purposes of this debate are to: 1) briefly define the CFs, how they work and act from a neurophysiological perspective; 2) underline their clinical relevance in pain management; 3) consider their role in clinical reasoning, within the ethical border and 4) suggest how to take them into account in the research field.

Contextual factors

What do the contextual factors represent?

A treatment is never administered in a neutral situation, but rather in a complex set of CFs, that Balint called the “atmosphere around the treatment” (40) and Miller and Kaptchuk called “contextual healing” (41). Following these definitions, it is clear that the CFs can act “independently” by the nature of the treatment: since they represent the context of any medical treatment, they have a role when a sham treatment is administered but also when an active treatment is administered.

CFs were introduced in 2001 by Di Blasi et al. (17) in medical community and recently exploited by Testa & Rossetini in physiotherapy field (33). CFs can be internal, external or relational. The internal factors consist of memories, emotions, expectations and psychological characteristics of the patient; the external factors include the physical aspects of therapy, such as the kind of treatment (pharmacological or manual) and the place in which the treatment is delivered. Relational factors are represented by all the social cues that characterizes the patient-physiotherapist relationship, such as the verbal information that the physiotherapist gives to the patient, the communication style or the body language (19).

A clear identification of the CFs is crucial in clinical practice, in order to enhance the treatment efficacy. In a work targeted to physiotherapy field, CFs have

been grouped in 5 different categories on the base of their sensory and social features (33): physiotherapist characteristics (professional reputation, appearance, beliefs, behaviours); patient characteristics (expectation, preferences, previous experience, musculoskeletal condition, gender, age); patient-physiotherapist relationship (verbal communication, non-verbal communication), treatment (clear diagnosis, overt therapy, observational learning, patient-centered approach, global process of care, therapeutic touch), healthcare setting (environment, architecture, interior design).

During any clinical phase (e.g. consultation, examination and treatment) the CFs “inform” the patient that a healthcare procedure has been delivered and they could positively or negatively affect symptom perception, experience and meaning (20, 21).

The identification of the CFs and the attention to healthcare context is crucial for at least two reasons. First, a treatment delivered in a positive context (positive CFs) produces better outcomes than a treatment delivered in a neutral condition or negative context (negative CFs). The open-hidden approach is one of the best evidence of decreased effectiveness of a medical treatment when a meaningful context is eliminated (42). In the “open” condition, that mimics the routine medical practice, a treatment is delivered in full view of the patient: it means that the patient is aware of receiving a medical treatment and know when the medical treatment is delivered. In the “hidden” condition, the treatment is administered unbeknownst to the patient. Different studies have reported that open treatments are more effective than hidden treatments, because in the hidden condition the surrounding context (healing rituals, therapist-patient interaction, etc.) is absent, thus losing its positive meaning (43-46).

Second, the psychosocial context can influence the patients in different ways since the responsiveness to the context seems to be not a stable trait but a situational

trait (47), and the same patient can sometimes positively respond to the context and sometimes not. Thus, if a patient is not influenced by the therapeutic context (the so called “placebo non-responders”) he/she needs more medical attention because the lower the placebo responsiveness, the lower the treatment responsiveness (48). Indeed, if the total treatment effect is conceptualized as the sum of the CFs effect plus the active treatment effect plus the interaction of the CFs and active treatment effects (49), a patient that is not sensible to the positive influence of the CFs will show a lower treatment response (50).

How do the contextual factors trigger placebo and nocebo effects?

If we aim to implement an aware use of CFs along the clinical routine, the understanding of how they work has a capital importance. The CFs shape placebo and nocebo effects through different sources. Historically, the most important models include classical conditioning and expectation processes.

Following the *classical conditioning*, different external CFs represent an example of conditioned stimuli that evoke a conditioned response (51). In general, as proposed by this model, the repeated contingency between a salient unconditioned stimulus (e.g., sight of food) with a neutral conditioned stimulus (e.g., a bell ringing) can induce the same conditioned response (i.e., salivation) even if the neutral stimulus is presented alone. In the specific contest of healthcare, different aspects of the healthcare setting or physical features of the medical treatment can act as external conditioned stimuli, eliciting a therapeutic response in the absence of an active principle, just because they have been previously associated with it. Recently, other learning mechanisms has been documented, such social learning. In particular,

beyond direct first-hand experience to specific external CFs, it is possible to learn a conditioned response by observing other people that respond to specific CFs (9).

Following the *expectation model*, different external, internal and relational CFs can activate the expectancy of pain relief, triggering neurobiological changes and symptoms' amelioration (52). Verbal suggestions are typical external CFs that trigger positive or negative responses. For example, the administration of an analgesic treatment along with the expectations of pain relief can lead to a positive analgesic response, whereas the administration of an analgesic treatment without specific expectations or with expectations of pain exacerbation can result in a negative response and in the perpetration of pain (53).

Following the Colloca and Miller integrative model (54), conditioning and expectations are not mutually exclusive and can be integrated in a more general learning model, whereby various types of CFs trigger expectancies, memories and emotions that in turn generate behavioral and clinical outcome changes, through the activation of the central nervous system (Fig. 1) (7, 9, 20, 21). In other words, the presence of external CFs, combined with specific internal and relational CFs, is interpreted by the patient and converted into neural input events and behavioral changes (54). This model represents a good conceptualization of the role of the therapeutic context, useful also at the clinical practice level. Indeed, it opens up to the possibility to study the effects and the impacts of every single CF on the outcome of a medical treatment.

How do the contextual factors work at the neurobiological level?

A robust body of knowledge, especially acquired in the field of pain, has identified the neural networks activated by the CFs. Indeed, a crucial question that

catch the attention of neuroscientists and clinicians is whether the subjective changes in the outcome after the exposure to a specific therapeutic context are associated with specific neurobiological activities (10). Pharmacological studies, as well as neuroimaging studies, have address this question using different experimental approaches based on classical conditioning and modulation of expectations. Taken together, these studies demonstrated that different changes in the pain processing network occurs when positive or negative CFs trigger placebo or nocebo effects, respectively. In particular, pain reduction is associated with decreased activity in the classical pain-matrix areas, such as the thalamus, insula, somatosensory cortex, and mid-cingulate regions (55-60). Interestingly, positron emission tomography (PET) studies showed that the analgesic effect induced by the administration of a real mu-agonist, such as remifentanil, and the analgesic effect triggered by verbal suggestions determined similar activation of different brain regions, such as rostral anterior cingulate cortex and the orbital cortex (61, 62). Separating the pain anticipation phase and the pain perception phase, a meta- analysis of brain imaging data using the activation likelihood estimation method, identified the involvement of different brain regions: during expectation, areas of activation are found in the anterior cingulate, precentral and lateral prefrontal cortex, and in the periaqueductal gray, whereas during pain inhibition, deactivations are found in the mid- and posterior cingulate cortex, superior temporal and precentral gyri, in the anterior and posterior insula, in the claustrum and putamen, and in the thalamus and caudate body (63). On the other hand, pain increase is associated with signal increases in several regions including anterior cingulate cortex, insula, left frontal and parietal operculum (64-67). Also, high temporal resolution techniques, such as electroencephalography (EEG), have confirmed that the amplitude of specific evoked potentials, both related to pain

anticipation and to pain perception, are affected by the CFs (68-71). Thus, both early and late sensory components of pain processing are affected by the exposure to positive and negative CFs.

Different studies have also characterized the neurotransmitter systems activated by the CFs. Using a classical conditioning approach, it has been demonstrated that when an opioid drug, such as morphine, is delivered for different days and then it is replaced by a placebo unbeknownst to the patient a placebo analgesic effect occurs (72). This effect can be blocked by the mu opioid antagonist, naloxone, thus indicating that the opioid system plays an important role (57, 73, 74). An indirect evidence of the involvement of the opioid system comes from the study of the anti-opioid action of the cholecystinin (CCK) system. The proglumide, that is a CCK antagonist, enhances placebo analgesia (75, 76), whereas the activation of the CCK type-2 receptors with the agonist pentagastrin disrupts it (77). These pharmacological data have been confirmed by a neuroimaging study, in which the authors proved that naloxone blocked the placebo analgesic response in dorsolateral prefrontal cortex (DLPFC), rostral anterior cingulate cortex (rACC), hypothalamus, periaqueductal gray (PAG), and rostral ventromedial medulla (RVM), and abolished placebo-enhanced coupling between rACC and PAG (57). Using the same conditioning protocol, it has been demonstrated that also the cannabinoid system is activated by the positive therapeutic context: when non-opioid drugs, like ketorolac, are administered for two days in a row and then replaced with a placebo on the third day, the analgesic effect is not reversed by naloxone, whereas the CB1 cannabinoid receptor antagonist, rimonabant, blocks this placebo analgesia completely (78). Also studies in which expectations were manipulated by positive verbal suggestions, showed an activation

of μ -opioid neurotransmission in the dorsolateral prefrontal cortex, the anterior cingulate cortex, the insula, and the nucleus accumbens (79, 80).

A different system activated by the therapeutic context is the dopaminergic system: indeed, the positive effect due to the presence of positive CFs seems to be related to the activation of dopamine in the nucleus accumbens. as assessed using in vivo receptor binding PET with raclopride. Moreover, when expectations of pain reduction were induced, the analgesic effect of the context was associated with activation of opioid neurotransmission in the anterior cingulate, orbitofrontal and insular cortices, nucleus accumbens, amygdala, and periaqueductal gray matter. Dopaminergic activation was observed in the ventral basal ganglia, including the nucleus accumbens. Both dopaminergic and opioid activity were associated with both anticipation and perceived effectiveness of the positive verbal suggestions (81, 82).

Recently, oxytocin (83) and vasopressin (84) have been identified CFs enhancer as they potentiate the analgesic effect due to the presence of positive verbal suggestions. Moreover it has been documented that negative expectations about headache pain led to the enhancement of the cyclooxygenase-prostaglandins pathway, which, in turn, induced pain worsening (85).

Clinical relevance of the contextual factors

What is the magnitude of placebo and nocebo effects induced by CFs in musculoskeletal pain?

The impact of CFs as trigger of placebo and nocebo effects on pain outcome has been quantified in different ways and has been reported in a wide range of musculoskeletal conditions such as low back pain (86-108), neck pain (95, 99, 109-

111), shoulder pain (95, 112, 113), osteoarthritis (38, 91, 99, 100, 114-125), rheumatoid arthritis (126), and fibromyalgia (97, 127-132).

Different studies have measured the magnitude of placebo and nocebo effects induced by CFs in different musculoskeletal pain conditions commonly encounter in daily setting (117, 133). Indeed the clinical effectiveness of placebo analgesia was demonstrated in specific complaints such as fibromyalgia (128) and osteoarthritis (118) with an effect size (ES) over 0.5. Also, nocebo hyperalgesia measured as dropout rate due to adverse event were present in fibromyalgia (9.6%) (134) and osteoarthritis (4.8%) (135). Concerning osteoarthritis, the ES decreased consistently from hand, to knee, to combined hip and knee and then to hip (118, 136).

Moreover, considering the overall treatment efficacy as the sum of the specific component related to the active treatment plus the unspecific component due to the CFs, the impact of the CFs was measured in different conditions and interventions (137). Zou and colleagues showed that 75% of the overall treatment effect in osteoarthritis is attributable to contextual effects rather than the specific effect of treatments (116). In fibromyalgia, the 45% of the response of the active drug is attributable to contextual effect (129) and a relevant contextual effects was shown also in aspecific low back pain (138). Moreover, a recent meta-analysis on spinal manual therapies showed that in acute pain and chronic pain, respectively 81% and 66% of the pain variance were ascribed to CFs (139).

Which kind of CFs influence musculoskeletal pain conditions?

Considering the patient's perspective, *expectations toward the therapy, patient's treatment history and baseline pain severity* are elements capable to predict the outcomes of different musculoskeletal pain treatments.

Expectations of symptoms improvement can be activated by different CFs: for example, the simple act of administering a treatment, the exposure to a clinical setting, the verbal or non-verbal interaction with the physician are capable of triggering patient's expectations. As demonstrated by different studies, boosting patient's expectations toward the therapy significantly increased the chance of pain relief more than delivering a treatment without the expectation of any benefit (86, 90-98, 109, 111, 112, 126, 140).

Patient's treatment history, that is the patient's history of past positive or negative medical treatments, can influence the future response of the patient to new medical treatments. Previous positive experiences obtained by a specific therapy increase the likelihood of future positive experiences with the same therapy, while precedent negative outcomes associated to a particular intervention increase the probability of negative outcomes (99, 141).

Higher pain intensity at baseline (99, 100, 118, 128, 129) and the presence of concomitant diseases and psychosocial elements such as depressions (99, 130) are associated with an augmented placebo analgesia and reduced nocebo hyperalgesia. Long-term dysfunction seems to respond less to placebo analgesia indicating that duration of complaints influence placebo analgesia (128, 132).

From the provider's perspective, *clinician's behavior, belief, verbal suggestions and therapeutic touch* can strongly influence patients' pain perception.

A provider acting as competent, experienced, educated, professional, trustworthy, capable to indicate a diagnosis and prognosis, and to monitor patient with follow up, can moderate pain with his behavior (38, 114, 115, 120, 142). Aligning his/her beliefs with patient's beliefs, a clinician could modulate pain. Indeed, it was demonstrated that the healthcare provider's point of view concerning the clinical pathway, the

therapy and the prognosis influence patient's pain (38, 101-103, 107, 114, 115, 143, 144). Informing the patient that a potent treatment has been delivered enhanced the analgesic effect of the treatment, conversely verbal suggestion concerning the threatening effect of the therapy can compromise the effectiveness of the treatment creating nocebo hyperalgesic effects (108, 121, 122, 141, 145, 146). Non-verbal communication has powerful effects as well. For example, the use of therapeutic touch can positively influence patient's pain (105, 123, 124, 131, 147, 148).

Finally, considering the patient-physician relationship, it appears that a *positive therapeutic encounter* between patient and clinicians can lead to additional clinical benefits. Indeed, an enhanced empathetic interaction comprehensive of therapeutic alliance, active listening, extra time spent with patient, more face-to-face visit, warmth, attention, care, encouragement and support significantly reduced pain more than the same therapy performed with neutral therapeutic interaction (87, 88, 100, 104, 145, 149, 150). Moreover, a *patient-centered approach* can increase the effectiveness of the therapy. Indeed, the patient's involvement in the global process of care has been shown to modulate pain (106, 125). The strategy to favor the *social learning* between patients by the observation of other's pain improvement or reduction is capable to affect the observers' symptomatology (151, 152).

Also the way by which the therapy is administered can influence pain perception. The adoption of an *overt paradigm* that enhances patient's knowledge of being treated modulates the therapeutic outcome (110): a significant pain reduction was observed after the execution of an exercise in an environment that allowed patients to visualize their body (89). Also the *posology of intervention* has an effect as CFs: the placebo effect is higher when therapies are more frequent and repeated a therapy is delivered (e.g. two or more times vs one time) (118). The choice of the

modality of treatment administration can be crucial to modulate patient's pain. In general, the higher is the invasiveness of treatment (e.g. acupuncture, dry needling, injection, surgery), the better is the reduction of pain (116, 118, 119, 153, 154). Moreover, parenteral or subcutaneous administrations (e.g. topical) are more efficient than oral administrations (115, 116, 119).

Even the *marketing features of treatment* should be taken into account. Branded therapy seems to be more effective than unbranded therapy (114, 115). High prize medication produced better pain relief than discounted medication, therapy considered as "new" improved pain more than "usual" therapy (114, 115). The more complex is the procedure including therapeutic rituals, mysterious powers, high technology the larger the placebo effect (114, 115).

Lastly, the *health care setting*, in terms of environment, architecture and interior design should not be overlooked. The use of facilities where evidence-based design such as furnishing, colors, artwork, light, outside views, temperature, soothing sound and music were adopted, positively impacts on patient's pain creating a proper healing setting (127, 155-157).

Clinical applications and translational research

Is it time to implement CFs in our clinical reasoning?

The clinical reasoning adopted by clinicians in musculoskeletal conditions represents a complex procedure that encompasses different dimensions of pain experience in a bio-psycho-social framework (158). Indeed, this multi-factorial thinking process considered biomedical (e.g. tissue pathology, disease), psychological and social elements (e.g. experience of disability, patient's belief, values and perspective) to obtain more complete analyses of the patient's dysfunction (159). The

role and the impact of CFs should be integrated in the clinical reasoning to increase the number of treatment solutions, boosts their efficacy and improve the quality of the decision-making (33). Based on the evidence available, some considerations can be drawn to guide a more conscious use of CFs as activators of placebo analgesia and avoiders of nocebo hyperalgesia.

Considering the *global process of care*, clinicians should be aware that the overall therapeutic outcome is determined by the suitability of the therapy adopted (“what we do”) and by how it is delivered (“how we do”) (33). In this perspective, every musculoskeletal pain treatment is composed by a specific component and by a contextual component (34). These components represent the two faces of the same coin and are capable of influencing pain at multiple levels of the central nervous system (160). The use of the best evidence-based therapy is unquestionable, but clinicians should not forget the role of the CFs, as the context surrounding the specific treatment is capable of generating placebo or nocebo responses and modifying the therapeutic trajectory towards a positive or a negative direction (42).

Because it is a fact that placebo (161-163) and nocebo (164) effects are always present in routine clinical practice and can be triggered by CFs (33), clinicians should be able to use them to optimize the results and reduce failures. Indeed, there are clear evidence that, when placebo was purposely searched as a mechanism, the effect size was about five times greater (Cohen’s d ranging from 0.95 to 1.14) (161-163) than when placebo was used as a control condition (Cohen’s d ranging from 0.15 to 0.27) (165-167). Moreover, clinicians should combine at the same time different CFs to obtain a larger placebo effect and minimize the nocebo effects. Some studies demonstrated that a lower effect size is present when using verbal suggestions alone (placebo - Cohen’s $d = 0.85$; nocebo - Cohen’s $d = 0.65$), while a higher effect size

was observed adopting a combination of verbal suggestions and conditioning procedures (placebo - Cohen's $d = 1.45$; nocebo - Cohen's $d = 1.07$) (161, 164).

Since placebo effects are learning phenomenon (9), during the *history taking*, clinicians should assess the patient's previous experience, expectations and beliefs giving the patient adequate time to tell his/her story (50, 168, 169) (Fig. 2).

Previous successful and unsuccessful experiences of a specific treatment are capable to influence the therapeutic outcome (170). In order to plan a therapeutic intervention, it's important to question about past memories of analgesic and hyperalgesic responses concerning a treatment; reinforcing the positive experiences and devaluating the negative ones (7, 169, 171-173). For example, if a patient had a previous negative experience with a specific treatment, clinician should avoid adopting it. On the contrary, if a patient experienced a positive outcome with a treatment, the use of the very same treatment is recommended in order to "activate" the patient's positive memory of the previous treatment.

Since patients' expectations about the therapeutic benefit influence the effectiveness of the treatment, a clear assessment of patients' expectations toward the therapy is crucial. In particular, it is crucial to identify patients with low expectations in order to work with them with the aim of improving their belief (174). Different scale and semi-standardized questionnaires have been proposed to assess patient's expectations. For example, Younger et al. developed a tool for measuring patient outcome expectancy. The authors found that the final six-item scales, made of two subscales (positive expectancy and negative expectancy), predicted a significant amount of outcome variance in patients receiving surgical and pain intervention (175).

Moreover, clinicians should monitor patient's belief concerning musculoskeletal conditions, therapeutic action, prognosis and ask questions about the meaning they

attribute to symptoms (169, 172, 176-178). In these times of important expansion of healthcare information delivering by Internet, social media and television it is crucial to avoid the misinformation (7). The discussion with the patients can help the clinician to guide them to evidence-based information and avoid that they refer to unproven or fake information (176). Also, asking systematically the patients to summarize the information provided can prevent negative misunderstandings about their complaints (169, 173, 176, 178).

In the *waiting, examination, therapeutic and follow-up phases*, the social interaction between patients (179, 180), the therapeutic ritual (181, 182) and the awareness of the ongoing procedure (42, 43) are fundamental elements to consider. While waiting for healthcare encounter, a pleasant and peaceful environment, employing professional, friendly and helpful support staff can help patients to feel comfortable (169). In waiting rooms, clinicians should reduce the social contagion of negative emotions preventing the patient's interaction and/or observation of another patient experiencing a negative outcome (e.g. increased pain) (7, 183). Instead, they should promote the social interaction favoring observation of the positive effects of the therapy (e.g. reduction of pain) also using video clips showing patients coping well with painful condition (50, 176, 179, 180) (Fig. 3).

Before starting the treatment clinicians should read records, thoroughly examine the patients, provide a confident diagnosis and propose, when available, different treatment options encouraging the patient's involvement in the choice of therapy and treatment goals (169, 171, 184-186).

During treatment it is useful to avoid unintentional "hidden administration" of therapy (173). Thus, it is crucial to focus the patient's attention to all the salient sensory elements presented in the therapeutic arena in order to increase the contextual

power of the therapy (169). These elements are: the healthcare environment (e.g. light, color, design of the room), the physical features of the therapy (e.g. shape, size, colour, smell and taste) and the technological features of the device (e.g. novelty, price, invasiveness) (50, 169-173, 187) (Fig. 4).

After the treatment, it is valuable to assess the therapeutic outcome and give to patient a feedback on the clinical course in order to maximize the treatment adherence, encouraging the self-managing of the condition (50, 169).

The clinician's not-verbal and verbal communication represent important element of the *overall clinical interaction* (33). Clinicians should prepare themselves mentally and physically for the clinical encounter (38), acting as experts in their field (169, 172). It is crucial to effectively inform about the efficacy of a specific treatment (169, 172), considering that beliefs and behaviors could influence patients' attitudes in a positive or negative way (7, 169). It is suitable to individualize consultation style according to the patient's preference opting for a personal interaction and seeking for a warm, authentic and empathic style, limiting technical contacts to the minimum (169, 171, 172, 176, 188-190).

Also, the content of the message (what), the modality of delivering (how) and the time of communication (when) represent a great clinical enigma (191) and should be taken into account. It is recommended to enhance the positive expectation toward the treatment and limit the emphasis on contraindications, tell patients about side effects, but associated with positive clinical outcome. Side effects of treatment should be presented in form of probability instead of a mere list and during the informed consent process positive and negative information should be balanced (7, 50, 169, 172, 173, 176, 180, 183, 191, 192).

What is the concern about ethics?

The adoption of placebo strategies seems to be common practice in clinical routine among healthcare providers (193). In musculoskeletal field, orthopedics surgeon, rheumatology physicians and nurses thought that placebo effects are real, have therapeutic benefits, and are permissible within the ethical borders (194-196). Patients with chronic musculoskeletal pain and rheumatologic complaints know what placebo effects are, consider placebo treatments acceptable when adopted as complementary/adjunct treatments and when no other established treatments are available. However, they present a lack of understanding of nocebo effects (196-198). Scientific community is still focusing the debate on the possibility of a transparent disclosure to patients of placebo treatments (199-202). The current researches suggest the possibility to openly prescribe sham medication or sham physical treatments with advanced prior consent (169). Thus, when available the choice of the best evidence-based therapy is mandatory and a patient must be informed about the use of a placebo intervention with an amount of disclosure sufficient to avoid deception (201, 203, 204). Although it is common thought that revealing the use of a placebo inhibits its effect, different studies point out the efficacy of placebo interventions also in “open label” conditions where the use of a placebo was disclosed in patients with chronic low back pain (205, 206). From a clinical perspective, the mindful manipulation of CFs represents a useful opportunity to enrich a well-established therapy that have different ethical implication in comparison with the replacement of real treatment with a potentially ineffective treatment (200).

Is there a place for a translational research on CFs?

There is a strong need of research studies on CFs close to routine and real-world clinical practice (49, 207) in order to underline the uncertainty of therapy action (208) and help clinicians to implement knowledge in daily practice.

The research community should investigate the effect of the different CFs on therapeutic outcome, instead of minimizing or labeling them exclusively as confounders (209, 210). The search for a good placebo control in musculoskeletal pain field (e.g. physical therapy) represents an unresolved challenge (211, 212). Indeed, medical treatments are generally more complex than the mere administration of a drug, involving multiple treatment components that interact with each other and that are difficult to separate (e.g. verbal instruction and education, patient-therapist contact, physical action by the patient or therapist, and sensory feedback) leading to biased estimates of treatment effect (213).

In clinical trial there is a urge to measure patient's expectation before, during, and after the treatment (214) evaluating by standardized and validated scale all the dimensions of expectation (optimism, pain catastrophizing, hope, trust, worry and neuroticism) (215, 216). Also measuring the impact of CFs from the patient's perspective represents a desirable outcome to be implemented in the future researches. Recently, a new item banks (Healing Encounters and Attitudes Lists - HEAL) was proposed as suitable for measuring CFs of the treatment and present promising evidence of predictive and concurrent validity (217).

Despite CFs play a key role in pain (20, 21), there is a still paucity of knowledge on their effects in different musculoskeletal diseases, in young and old participants (218-220), in acute and chronic conditions (141), in different pain mechanism such as nociceptive, neuropathic, central sensitization (221). It is of paramount importance to try to identify psychological, neuroendocrine or genetic

elements that predict the responsiveness to specific CFs (50). Finally, the use of meta-analysis may help to estimate the effects of the CFs (222).

Limitations

This debate presents some limitations. The framework adopted (17, 33) for reviewing the role of the CFs was not preliminarily validated for its specific consistency in the musculoskeletal field and some factors are not related exclusively to musculoskeletal pain literature but refer to pain in general. Examples of primary studies and data offered to sustain each factors of the model were not selected by adopting a systematic review approach and not criticized in depth, given that the main goal was to propose a short synopsis. CFs have been categorized into a conceptual framework by describing each factor involved, therefore interpretations about the relationships between factors and placebo/nocebo effects need additional critical analysis and discussion.

Conclusion

This debate points to a conscious use of the CFs, as supplementary therapeutic strategy for pain management capable to improve analgesia and prevent hyperalgesia. The good news is that pain perception can be positively influenced by an honest and aware use of CFs. The bad news is related to the complexity of the phenomenon, to a certain degree of uncertainty in the individual response and to a risk of patient's deception associated with their use. Nevertheless, clinicians have already enough comprehensive scientific information that allows them to choose the correct behavior wisely and adjust the CFs of the therapeutic setting in an evidence-based and ethically respectful perspective. We think that time has come for clinicians to manage

conscientiously and ethically the CFs to enhance the placebo and avoid nocebo effects for the benefit of their patients.

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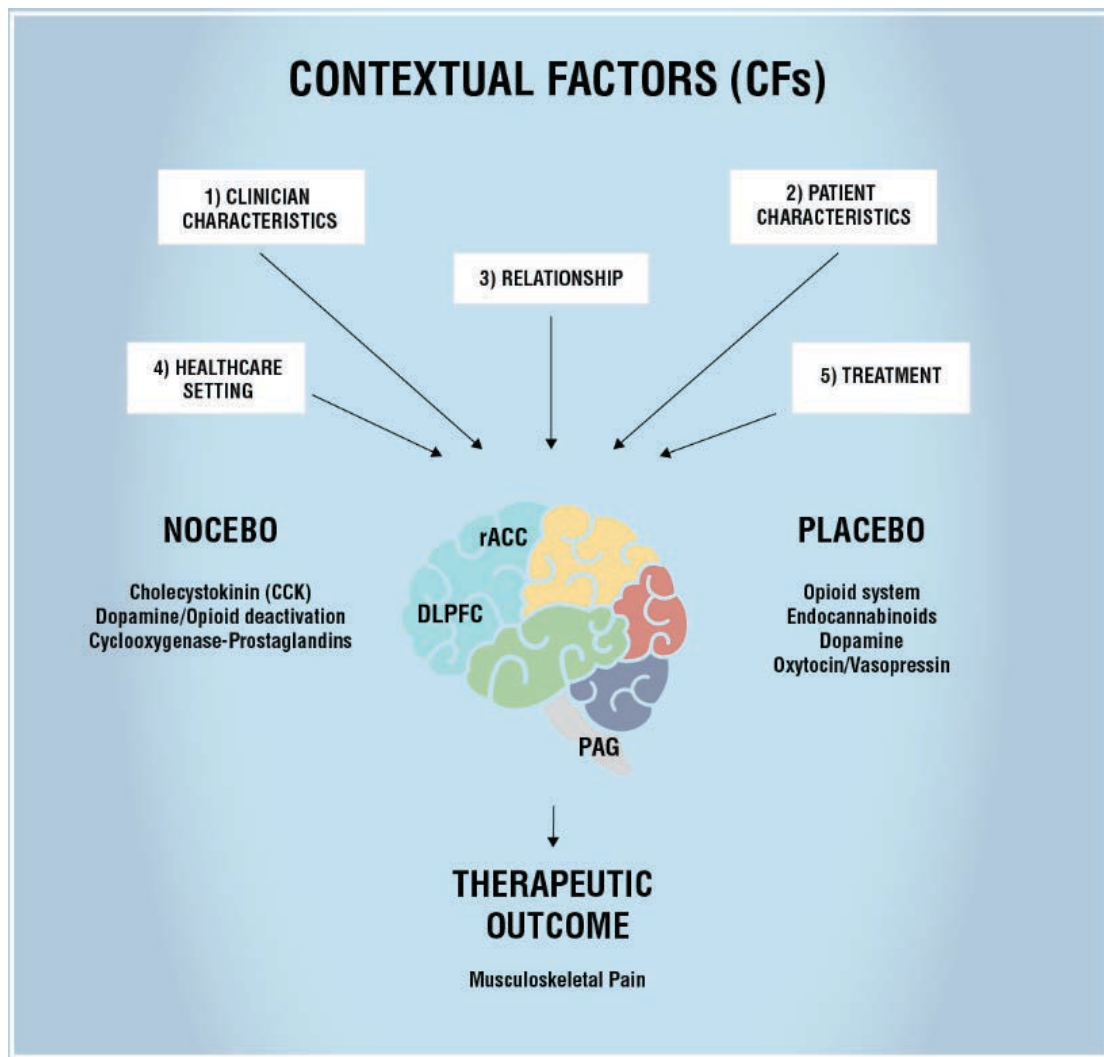
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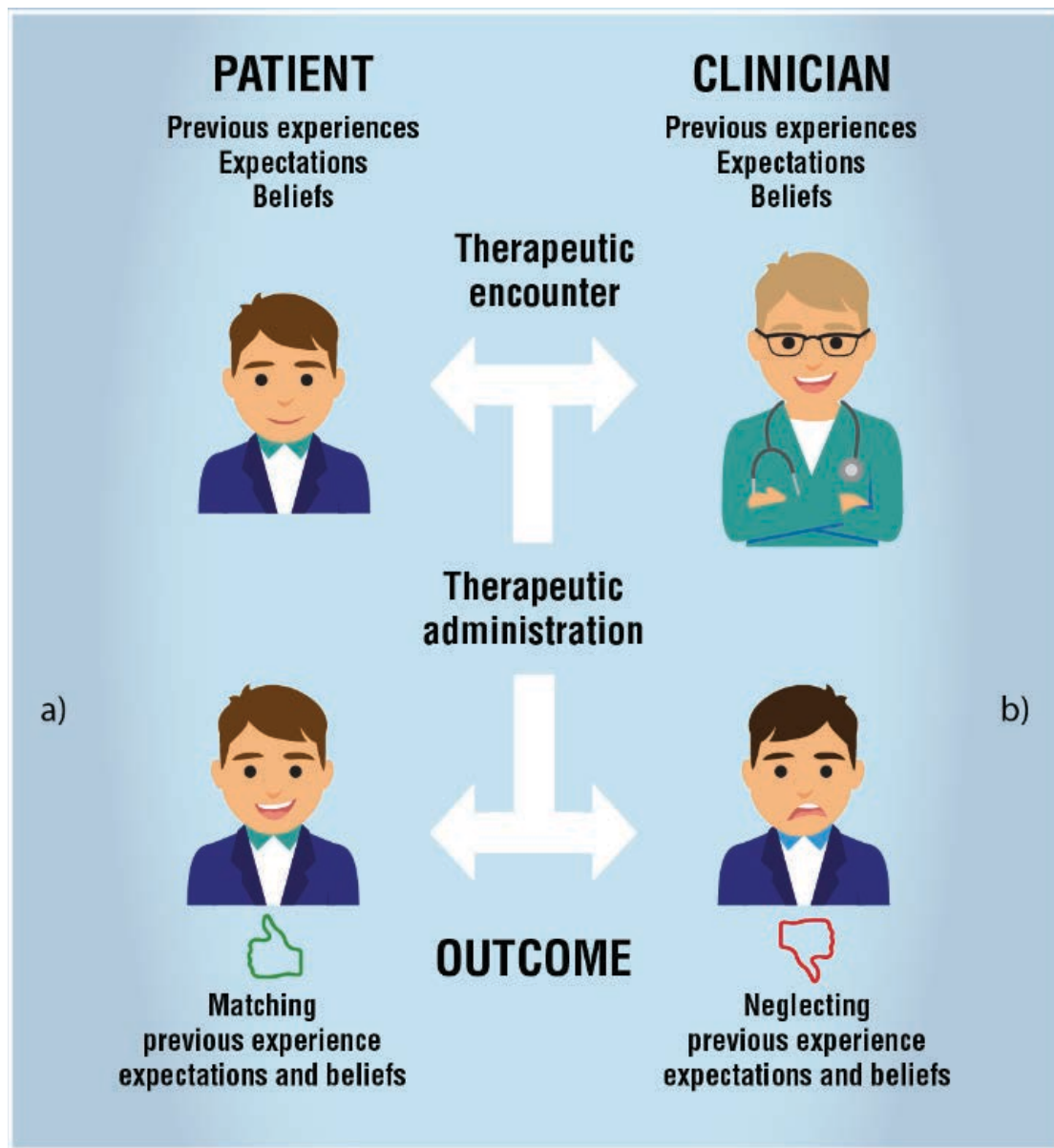
Figure 1. Psycho-neurobiological mechanism of CFs.



The image displays how CFs are capable to influence the brain networks, neurochemistry and therapeutic outcome. The principal neural areas and neurotransmitters involved in placebo and nocebo effects are reported.

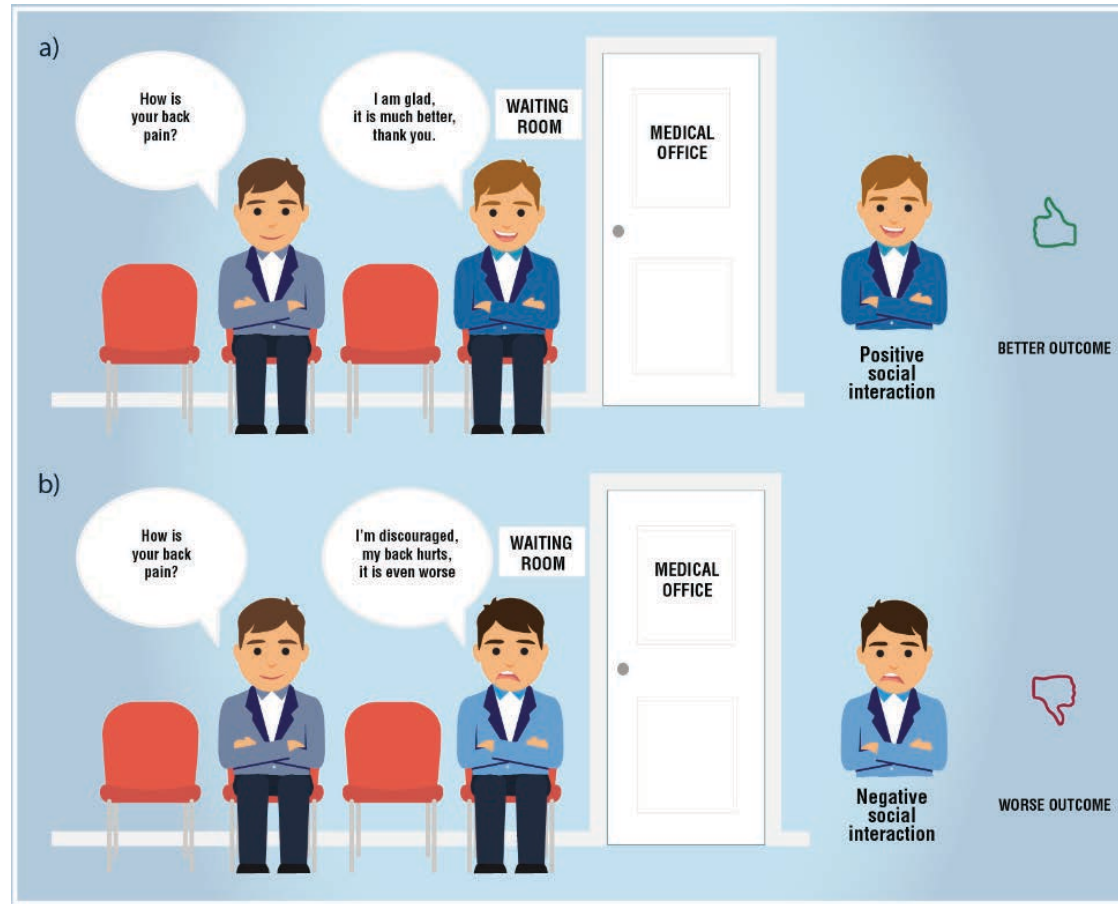
Abbreviation: rACC = Rostral Anterior Cingulate Cortex; DLPFC = Dorsolateral prefrontal cortex; PAG = Periaqueductal gray.

Figure 2. Influencers of decision-making process.



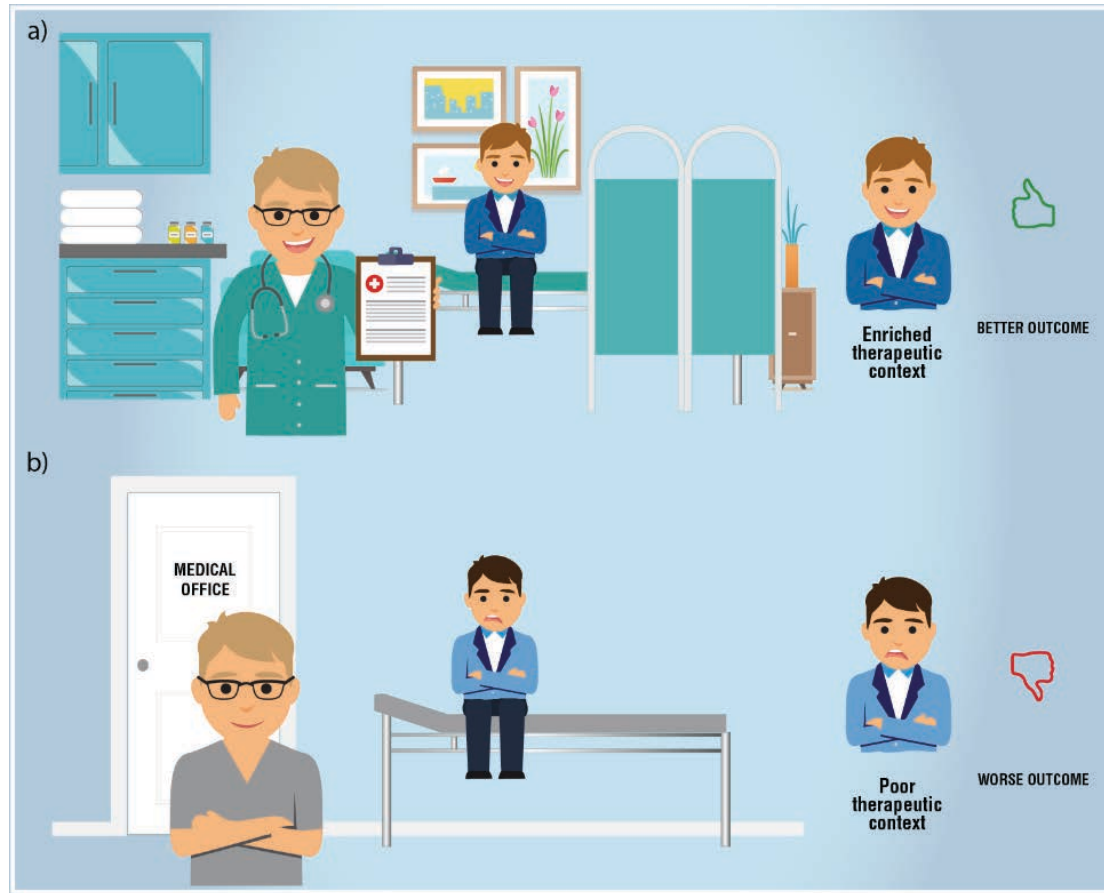
The image presents: a) the clinical situation in which meeting patient's expectation, previous experience and beliefs creates positive therapeutic outcomes; b) the clinical situation in which ignoring patient's expectation, previous experience and beliefs creates negative therapeutic outcomes

Figure 3. Social interaction and learning.



The image displays: a) a positive social interaction between patients in waiting room capable to produce positive therapeutic outcome; b) a negative social interaction between patients in waiting room capable to produce negative therapeutic outcome.

Figure 4. Therapeutic rituals and overt therapeutic administration.



The image displays: a) an enrich therapeutic context capable to produce positive therapeutic outcome; b) a poor therapeutic context capable to produce negative therapeutic outcome.

CHAPTER III

**THE DETERMINANTS OF PATIENTS’
SATISFACTION IN OUTPATIENT
MUSCULOSKELETAL PHYSIOTHERAPY: A
SYSTEMATIC REVIEW WITH A METASUMMARY
AND METASYNTHESIS.**

Submitted as:

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The determinants of patients' satisfaction in outpatient musculoskeletal physiotherapy: a systematic review with a metasummary and metasynthesis

Abstract

Purpose: To identify and synthesize patient-identified factors that influence satisfaction with outpatient musculoskeletal physiotherapy (O-MSK).

Methods: A systematic literature search was conducted using six electronic databases: CINAHL, Embase, MEDLINE, Scopus, Web of Science, Wiley Online Library from inception to March 2017. Additional articles were identified using a “berry-picking” method. Search limits were: primary studies; English language, human subject. Qualitative peer reviewed articles describing patient satisfaction in O-MSK were selected for inclusion. After a process of exclusion, 11 publications were included in the synthesis. Two reviewers critically appraised studies independently using the Critical Appraisal of Skills Program (CASP) tool for qualitative studies. All text identified in the findings sections of the selected studies were extracted verbatim for analysis using a purpose-designed form.

Results: Extracted data were synthesized using the metasummary and metasynthesis approach. Factors influencing patient satisfaction were grouped into six broad themes: 1) clinical outcome; 2) physiotherapist features; 3) patient features; 4) physiotherapist-patient relationship; 5) treatment features and 6) healthcare setting features.

Conclusions: These findings suggest that patient satisfaction towards O-MSK is a multidimensional construct influenced by individual patient/provider, clinical and contextual factors. Further research is required to investigate the relationships between these factors.

Introduction

Within healthcare, there is an increased emphasis on identifying and understanding patient-reported outcomes (PRO) (1). PRO are important because they offer constructs capable of depicting the patient's health status (2). In order to identify PRO, and then subsequently deliver patient-centered care, it is essential to gather information directly from patients or the users of health care services. The inclusion of patient perspectives is aimed at better understanding structures, processes and outcomes of care based upon their personal experiences within the system (3). Within this process of identifying PRO, patient satisfaction has been considered a milestone to be examined due to its adequateness of measure the quality of care (4).

Patient satisfaction represents a complex, implicit, subjective and multidimensional construct (5). It involves cognitive, affective and emotional processes (5) through which the patient evaluates the congruence between the actual healthcare experience and his/her needs, values, desires and expectations (6). The higher the congruence between the actual experience and the patient's expectations, the greater reported level of patient satisfaction (7). Overall, various factors contribute to patient satisfaction including technical and interpersonal care, the physical environment, the access of care, organizational features, the continuity of care and the clinical outcomes (8-12).

At multiple levels, stakeholders, organizations and governments have adopted patient satisfaction as a proxy of care appropriateness, efficacy, quality and feasibility (1, 13). This proxy helps to identify problems, to improve quality of healthcare services, to ameliorate health professionals' behaviors, to define appropriate policies and to allocate resources (4, 14). Satisfaction enhances also the attractiveness of a healthcare

service, guiding the patient to choose, return and recommend it and to improve the compliance towards treatment and follow-up (15, 16).

Patient satisfaction (17) and their perceptions of their health care experiences (18, 19) have been identified as a health service research priority (20) among inpatient and outpatient rehabilitation settings (21). Specifically, the outpatient musculoskeletal physiotherapy (O-MSK) represents an ideal setting for patient satisfaction research (6). O-MSK is an increasingly used service capable of responding faster to the patient's health needs thus reducing costs within the public health system (22). O-MSK differs from inpatient physiotherapy among a variety of constructs including the musculoskeletal disorders addressed, patients' expectations, recovery times and treatment goals (23). Generally O-MSK patients are exclusively managed by a physiotherapist and, therefore, their evaluations of the received care can directly be attributable to the physiotherapy instead of to other healthcare interventions (6).

A systematic review with meta-analysis revealed that the level of satisfaction with O-MSK was high with a pooled estimate of 4.44 (95% confidence interval = 4.41–4.46) on a scale of 1 (very dissatisfied) to 5 (very satisfied) (17). This review is a decade old, included only studies until 2009 by searching three databases; although some qualitative findings were reported by identifying the physiotherapist's interpersonal attributes and the process of care as key determinants of patient satisfaction, these were not synthesized through a declared method of analysis. Therefore, there is a need to advance the synthesis of the knowledge available in the field and more comprehensively understand the concept of patient satisfaction in O-MSK focussing only on data collected through qualitative methods, such as in-depth, semi-structured interviews. This type of qualitative data allows for a holistic understanding of specific patient

perceptions and experiences that is not typically expressed when satisfaction is measured with surveys based upon quantitative methods (24, 25).

Therefore, the aim of qualitative metasummary and metasynthesis is to identify the determinants of patient satisfaction with O-MSK. This approach is commonly used to understand experiences of healthcare and has been documented of being used to specifically explore services to address musculoskeletal issues (26, 27). It represents an adequate design for the interpretation of findings across multiple studies enhancing our understanding of the phenomenon of interest (28), it provides a mechanism to understand from the service user's perspective the factors that contribute to patient satisfaction (21), and findings from metasynthesis are then better positioned to inform policies that offer direction for clinical practice (29).

Materials and methods

Design

A systematic, qualitative metasummary and metasynthesis was performed using the methods outlined by Sandelowsky and Barroso (30) which include: 1) developing the research question, 2) searching and extracting systematically studies to be analyzed, 3) appraising the quality of the studies retrieved, 4) classifying the studies that emerged and 5) synthesizing data into metasummary and metasynthesis (30). A metasummary refers to the quantitative summation of qualitative research findings, while a metasynthesis involves the integration of the qualitative results through a new interpretation of findings (31). This systematic qualitative synthesis was registered in the Prospero database (CRD42016049124) in November 2016 and it is reported here in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-

Analyses (PRISMA) statement (32) and with the Enhancing transparency in reporting the synthesis of qualitative research (ENTREQ) (33).

Research question and systematic search

The research question established was: “What are the determinants of patient satisfaction towards O-MSK?” A pre-planned search was performed in six electronic databases (CINAHL, Embase, MEDLINE -via PUBMED-, Scopus, Web of Science, Wiley Online Library) from inception until March 2017. Study limitations applied to the search included searching only for studies published in the English language, included human subjects and primary studies. The search strategies adopted are reported in Appendix 1. The keywords used were: patient satisfaction, outpatient setting, and physiotherapy treatment. A combination of free text terms and thesaurus or subject headings was adopted due to challenges with methodological indexing of qualitative research (34). As suggested by Sandelowsky and Barroso (35), a “berry-picking” method was used to ensure a comprehensive search and location of published qualitative studies that met our inclusion criteria including: footnote chasing, citation searching, hand searching, journal run, author searching and fugitive literature (e.g Master’s theses and doctoral dissertations). A medical library health information specialist was consulted throughout the systematic search of the databases (36).

Eligibility criteria and study selection

The eligibility criteria for study inclusion in the synthesis included: 1) study used a qualitative design or a mixed methods design where the qualitative and quantitative data analyses were conducted and presented separately; 2) included study participants >18 years of age, 3) presenting with musculoskeletal complaints, 3) who received

physiotherapy treatment in an outpatient service; and 4) where the authors examined factors related to patient satisfaction. Studies were excluded if they were: 1) quantitative in nature or a mixed-method study that did not separate the qualitative and quantitative data analysis; 2) included patients with a specific diagnosis of pain not attributed to musculoskeletal complaints; 3) performed a treatment not delivered by a physiotherapist, and 4) treated in an inpatient service setting. Two authors (TL, SG) independently reviewed the articles. Titles, abstracts and then the full text of all articles (manuscript, figures and tables) were screened using Sandelowsky and Barroso's reading guide (37). When both reviewers individually agreed, a study was included. In case of uncertain eligibility, any disagreement was resolved through a discussion with the research group.

Critical appraisal

Despite debate (38-40) around the value and need to critically appraise qualitative studies included in a metasynthesis, and the lack of recommendations around the most appropriate tools for appraising qualitative studies, our research team made the decision to appraise all included studies with a goal to provide commentary on the overall quality of the qualitative evidence conducted in this field. However, overall quality of the individual studies was not used as a criteria for inclusion or exclusion within this review (36). The Critical Appraisal Screening Programme (CASP) tool for appraising qualitative research was used (41), due to its extensive adoption in other systematic reviews in musculoskeletal field (26, 42). The CASP is a 10-question tool useful to examine: the aim of research, the appropriateness of qualitative methodology, the research design, the recruitment strategy, the data collection, the researcher and participant relationship, the research ethics, the data analysis, the findings, and the

contribution to knowledge. Each item was scored as “yes” (Y) or “no” (N), depending on whether the topic was described sufficiently. An additional score of “Unclear” (U) was added to differentiate between sufficiently and insufficiently (43). This resulted in 3 options: 1, 1/2, and 0 (43). The higher the total score, the better the methodological quality was, with a maximum score of 10. Because the CASP does not offer a scoring matrix for the overall method rating, we decided *a priori* to identify cut-off point for low (CASP 0-5), medium (CASP 6-8) and high levels of quality (CASP 9-10). Two authors (GR, SJ) determined the quality of the studies independently, with any disagreements resolved by consensus and consultation with a research group.

Data extraction and study classification

Data extraction was performed by using a purpose-designed form by one author (DR); the form was populated and cross-checked by another author (MT) (26, 27). Extracted data included: description of the setting, study population, sample size, gender and age, aims of the study, methods of data collection and analysis and key findings about patient satisfaction. The research group overcame any disagreement between the two researchers. Moreover, we classified the findings of the included studies based upon the degree of researcher transformation of the raw data, thus to guide the subsequent analysis and synthesis of findings (36). The classification system included: thematic surveys (e.g. latent pattern of themes discerned from data), conceptual/thematic descriptions (e.g. concepts or themes developed *in situ*), or interpretive explanations (e.g. fully integrated explanations of phenomenon) (44).

Data analysis and synthesis

Three independent authors (TL, GR, AP), through an inductive approach performed the analysis of the included studies, following these steps simultaneously rather than subsequently (30): 1) the articles were read multiple times, line-by-line to obtain an idea of the topics; 2) the target findings of each report were extracted from the “Result” section and separated from not-relevant data; then copied and pasted into a Microsoft Word (Microsoft Corp, Redmond, Washington) document; 3) the findings were edited to make them as accessible as possible to any reader and to ensure that the original wording was captured and to preserve the authors’ original intentions; 4) similar findings were grouped according to their topical similarity to determine, when compared, if findings across studies confirm, extend, or refute findings with the dataset; 5) the grouped findings were abstracted by elimination of redundancies, refinement of statements and preservation of contradictions and ambiguities; 6) the final findings were coded through a highly iterative and collaborative process and reduced into categories and themes, then findings were evaluated for similarities and differences within and between studies and synthesized using a constant target comparison; 7) the manifest inter-study frequency effect sizes (e.g. prevalence rate of findings) and intra-study intensity effect sizes (e.g. concentration of findings in each report) were then calculated (45).

Validity, rigor and trustworthiness of metasynthesis

The validity, rigor and trustworthiness of this metasynthesis was ensured by several strategies (30). A multidisciplinary panel of experts were involved. Authors were clinicians and academic researchers with a range of different professional backgrounds and experiences evaluating qualitative research (physiotherapy, nursing and marketing). This strategy helps to continually scrutinize and criticize the study

procedures and outcomes (30). Moreover, an audit trail was adopted to document every phase of the project, the rationale behind the choice, adoption, creation or leaving of specific strategies (46). This solution helped to enhance the transparency of reporting and reflexivity process of the panel (47). Finally, a debriefing session and a negotiated process to achieve consensual validity was performed (48). Authors discussed their methodological choices, data analysis, procedures and interpretations by using a “think aloud” strategy (49). Any discrepancy was negotiated and resolved by a consensus process.

Results

Study selection

The search resulted in 21,972 records. After the removal of duplicates, 20,068 records remained. Once the study inclusion and exclusion criteria were applied to a reading of titles of abstracts, 19,537 studies were eliminated. Out of the remaining 531-screened articles, 69 were considered potentially relevant and the full texts were retrieved. Then, 58 studies were excluded as reported in appendix 2. Finally, 11 articles (50-60) describing findings from 9 unique studies were included in the qualitative metasynthesis. Two of the studies each produced two unique articles (53, 54, 56, 57), presenting findings on the same samples yet for different study objectives. The selection process is shown in figure 1.

Characteristic of the studies

A total of 362 participants (169 males; 193 females) were included in the studies ranging from 10 (60) to 57 (52, 56, 57) per study, with a range of age between 18 (51) and 82 (53, 54, 60) years. Globally, patients presented non-specific low back pain (50,

51, 55, 59), or not specified musculoskeletal complaints (52-54, 56-58, 60). Two studies analyzed acute and chronically ill patients (53, 54), two investigated chronic conditions (51, 59), two focused on post-acute care (52, 57), one on a non-acute condition (60), and the remaining studies did not clarify the condition type (50, 55, 56, 58).

The included studies were informed by a range of qualitative designs which included thematic surveys (54, 58, 60), conceptual/thematic description (50, 52, 55-57) and interpretive explanations (51, 53, 59). The data collection methods reported in the included papers were focus groups (52-54, 56, 59), semi-structured interviews (51, 55), focus groups and semi-structured interviews (50, 57, 60), and the nominal group technique (58). Clinical outpatient settings were located in Spain (52, 56, 57), Australia (58-60), England (53-55), Scotland (51) and Egypt (50). A summary of the data is reported in table 1.

Quality appraisal

Using the CASP tool for the appraisal of qualitative studies, all of the included studies (50-60) were satisfactory with regards to the items: 1 (Clear research statement), 2 (Qualitative methodology), 7 (Ethical considerations), 9 (Clear statement of findings) and 10 (Value of the research). Globally, item 3 (Research question appropriate) was considered as “Unclear” in all the studies. The assessment “No” was presented in nine studies (51-59) for item 6 (Relationship researcher-participants described adequately) and in one study (50) for item 5 (Data collection). Three studies (53, 54, 59) considered the item 8 (Data analysis) as “Unclear”. Item 4 (Recruitment strategy) was appraised as “No” in two studies (55, 59) and as “Unclear” in one study (58). The overall quality appraisal (table 2) ranged from 7 to 9.5 with a mean of 8.2. Only one study (60) was assessed as high quality, the others (50-59) presented a medium quality.

Synthesis

The metasummary and metasynthesis processes of included studies (appendix 3) resulted in 123 statements, 66 codes, which were condensed in 13 categories and lastly systematized into 6 themes: 1) clinical outcome; 2) physiotherapist features; 3) patient features; 4) physiotherapist-patient relationship; 5) treatment features and 6) healthcare setting features (figure 2).

The most frequent categories were: organization of care (82%), education (82%) and attitude of the physiotherapist (73%). The studies of Ali & May (69%) (50), Cooper et al. (69%) (51) and Hills & Kitchen (64%) (53, 54) reported the highest level of intensity, while Del Baño-Aledo et al. (52) and Medina-Mirapeix et al. (57) revealed the lowest (23%) (table 3).

Theme 1: Clinical outcome

Result of treatment

For some patients the desired outcomes were complete recovery and the control of pain (50, 53). For others, it was important to develop and learn helpful coping strategies for the self-management of the problem over the long-term (50, 54, 55). In general, patients were satisfied by any effective therapy capable of achieving their desired outcome(s) (50, 54). Moreover, the presenting clinical conditions were reported to influence the desired outcome (53). Patients with an acute injury identified the following as factors influencing satisfaction: the continuity of treatment and the progressive improvement of daily activities between physiotherapy sessions, compared to patients with a chronic complaint/injury who were satisfied from an improvement in range of motion or pain relief (54).

Theme 2: Physiotherapist features

Attitude

In general, patients described high levels of satisfaction in working with physiotherapists who had the following aptitudes: friendly, respectful, confident, clean, and capable of creating a pleasant and welcoming environment in clinical practice (50-53, 55, 58). Moreover, patients appreciated an empathetic, good listener, as well as a physiotherapist who expressed a genuine interest in the patient's concerns and disease (50-52, 54, 55, 58, 60). They valued engaging with physiotherapists who were non-judgmental, not egoistical, and who provided emotional support during the rehabilitation process (52, 58). Within two of the studies, participants also identified valuing physiotherapists who demonstrated sensitivity to patients' functional and emotional status changes, who were capable of identifying patient-specific modifications and then who could quickly revise the plan of care to adopt new therapeutic strategies tailored to patient needs (52, 55).

Professionalism

Overall, patients appreciated competent and skilled physiotherapists who were knowledgeable on the most effective treatment, aware of current best practices and capable of prioritizing the patient's needs and identifying the most appropriate therapies for each individual patient (50-52, 55, 58). Furthermore, patients desired a physiotherapist who used detailed notes, who was reliable, punctual and who demonstrated strong organizational abilities (58). They further appreciated physiotherapists who demonstrated the capacity to work as a part of a larger interdisciplinary health care team, those who were able to establish and maintain

professional-client boundaries during the rehabilitation sessions and those who treated the patient as an individual (50, 58). Moreover, patients were satisfied with physiotherapists who were passionate about their work, honest and aware of their limits (50, 58).

Gender

Physiotherapist's gender was reported as impacting patient satisfaction only in Egyptian patients (50). These patients felt comfortable with physiotherapists of the same gender, but if there was the opportunity to be treated by an expert physiotherapist, they preferred a more competent provider from the opposite gender rather than a less experienced colleague of the same gender (50).

Theme 3: Patient features

Expectations

The assessment of patients' expectations represented a key factor of satisfaction towards O-MSK (51). These expectations were frequently established based upon the nature of the information shared by the referring physician (60), patients' previous positive or negative experiences with physiotherapy and their presenting clinical condition (53). Indeed, patient satisfaction arose when physiotherapists were able to meet patients' expectations formed by the referring physician (60). The symptom relief, the adequate education on management and prognosis of patients' disorder, and previous positive treatment experiences, were all elements capable of modifying patients' expectations, especially when they were unrealistic to more realistic ones (54). Acute patients usually were naïve of physiotherapy and optimistic about a positive resolution of their problem, while chronic patients were not always optimistic because

they had previous experience with physiotherapy, and they were interested in the amount of problem reduction they could obtain (54). In general, patients were satisfied when their expectations to be helped were met or exceeded by the treatment (53). Sometimes patients' expectations of recovery were excessive, but they could be modified during the course of treatment, thus influencing the outcome, through a careful explanation to the patients of their conditions and how to cope with the problem (50, 54).

Theme 4: Physiotherapist-patient relationship

Communication

Patients considered tailored communication that addressed specific, individual needs and feelings as an important dimension of satisfaction (51, 53, 54, 60). Effective communication requires adequate time spent with a patient, specific interpersonal communication skills including the ability to actively listen and be receptive to patient's input, and being respectful of the patient's point of view (51, 58, 59). Patients also appreciated non-verbal communication elements that contributed to the establishment of trust between the provider and the patient, including: open body language, direct eye contact and orientation of the provider's body and face towards the patient (58). Moreover, they appreciated the use of verbal communication that provided adequate explanations, that included the use of language that accurately reflected the health condition, that was understandable to a lay person, as well as the encouragement of the patient's participation in the communication process from both parties, and the use of simple and clear questions (51, 58, 60).

Partnership of care

From the perception of the patients, one of the most important elements was the establishment of a therapeutic alliance with the physiotherapist, where the patient felt that the physiotherapist was genuinely engaged and viewed the patient as a partner in the care provision (56, 59). Specifically, patients appreciated when physiotherapists took the time to holistically learn about their patient, including the individual's values, preferences and lifestyle and consider the patients' experiences, abilities and life circumstances in developing a plan of care (51, 59). Ultimately, patients wanted to be respected as individuals (60). They expressed a need for mutuality and appreciated the development of symmetrical and consultative relationships that enhanced the patients' sense of connection with care, their efforts in the care plan and the trust in their physiotherapist (51, 54, 56, 59, 60).

Theme 5: Treatment features

Education

Education was considered as an influencer of satisfaction (50-52, 55, 59). Education was not a passive transmission of knowledge from physiotherapist to patients, but it represented an active process through which patients obtained a deeper understanding and reassurance about their dysfunction, thus influencing their mindset and increasing their self-management, motivation and responsibility in the long-term (50, 54, 55). Patients appreciated information received in the beginning of the treatment (52, 54), in form of accurate, understandable, free of jargon-free explanations (59) or charts, drawings, written information and models (55, 58, 59). They desired to know the cause of their problem (50, 52-54, 58, 59), and they appreciated getting anatomical and biomechanical explanations (50, 55). Patients were satisfied with specific advice on movement, position, ergonomics, activities of daily living to follow or avoid, and

information about the treatment plan, its rationale, positive effects and side-effects (50, 53-56, 58). Moreover, they appreciated information regarding patients' active role in the management of the dysfunction as well as regarding the prognosis of the condition, the long-term consequences and the limitations (50, 53, 55, 56).

Organization of care

Patients most appreciated a positive service organization that was conveniently located with easy access for injured or disabled individuals, flexible payment plans, precision in data management and the ability to schedule appointments through a simple booking system (50, 51, 53-55, 58). Also, patient satisfaction with the care delivery organization was increased when treatment sessions were scheduled so they started on time, when there was a short waiting list to access services, when they could directly access an appointment to manage a "flare-up," a wait time not longer than 5-10 minutes, and the consistent offer of an appointment to follow up or contact to the service again if problems occurred (50, 51, 53-55, 57, 58, 60). Moreover, patients were pleased to be treated by the same physiotherapist in one-to-one individualized sessions and to be re-evaluated by experienced physiotherapists (50, 51). A proper clinical contact time with a physiotherapist, an adequate amount of time spent with the physiotherapist and a reasonable frequency of sessions were elements identified to influence patient satisfaction (50, 51, 55, 57, 60). Moreover the absence of interruption, to be guided and supervised during manual therapy and exercises contributed to overall patient satisfaction (57). Also, when treatments were provided as a part of a multi-professional rehabilitation team, the consistency of information and care among providers, enhanced the satisfaction with the overall rehabilitation process (56).

Typology

Patients appreciated a treatment derived from an adequate clinical evaluation and imaging view (51, 54). Some patients did not have a specific preference between passive (e.g. manual therapy, physical therapy modalities) or active (e.g. therapeutic exercises) treatment strategies (53), others gave great emphasis to exercise (51, 59). Exercise was considered an element of active self-help management and involvement (58), through which patients improved their feeling of empowerment, their knowledge of their body's functioning and their response to pain and activities (59). To increase compliance with a prescribed treatment plan, patients appreciated receiving exercises tailored to their preferences and lifestyle (51, 58). Moreover, a physiotherapist's flexibility in adapting treatment to patients' functional needs (56), and the creation of an individual strategy of care seem to be important elements that ultimately increase patient satisfaction in O-MSK (51).

Decision-making

An individualized approach to decision-making about treatment represented the best strategy to increase patient satisfaction (51). Patients desired to be listened to, and asked about, their involvement in the plan of care through a democratic-participatory rather than a prescriptive process (50, 55, 56). Some patients expressed the desire to participate in the plan of treatment after the physiotherapist's explanation about the importance of their input to develop a customized therapy for their needs (50). Others preferred that their physiotherapist did not seek collaboration or explicitly request it (56), thus it is important to consider and explore the patient's expectations about his/her level of involvement in decision-making (51). Several patients preferred to not

participate or to delegate the choice to the expert physiotherapists, but every decision had to be explained and justified to patients during the process (50, 51).

Theme 6: Healthcare setting

Physical environment

The physical environment where the treatment was provided was important for patient comfort and safety. Patients valued being treated in a facility where the office design and ambient conditions created a healing environment (50). It is essential to provide single or private rooms both for changing clothes and for the receipt of therapy (57). Moreover, the control of nonvisual aspects such as the temperature and the smell represented additional important elements related to overall satisfaction (57).

Social context

A social environment that facilitated positive interactions with other patients, especially during group therapy, increased patient satisfaction (57). This positive environment was perceived as motivational because patients could support each other in their efforts and share similar stories concerning their disability (57).

Discussion

Summary of evidence

This metasummary and metasynthesis informed by 11 reports informed by 9 primary qualitative studies offers a thorough understanding of patient-identified factors that influence satisfaction in O- MSK. The clinical outcome, patient and physiotherapist features, the treatment features, the patient and physiotherapist relationship, and the

healthcare setting were identified as overall determinants of patient satisfaction in O-MSK.

According to the contextual factors theory (61), findings from this review emphasize the multidimensionality of the phenomenon of patient satisfaction in physiotherapy and how clinical and contextual determinants both, inseparably, influence its manifestation. Indeed, improving the clinical outcome (e.g. range of motion) only (10, 11, 17) or meeting a singular contextual factor (51, 52, 55, 57) (e.g. healthcare setting) represents a useful condition, but it is not sufficient to completely reach patient satisfaction, thus indicating that the global outcome of therapeutic intervention is strongly linked to the interdependence between the different determinants of patient satisfaction (5). From a translational perspective, our review suggests to physiotherapists a conscious adoption of contextual factors during the administration of specific evidence-based physiotherapy treatment to improve the overall patient satisfaction in O-MSK (61).

According to the findings, the active role of the patient in the process of care at multiple levels is strengthened as influencing the patient satisfaction (17). Indeed, considering the expectations of patients about what should occur during physiotherapy sessions is an important element of the clinical assessment in order to orient the treatment (62) and to meet patient satisfaction (9, 17). During the decision-making process, patients desired to be questioned to choose freely their direct involvement or delegation in the healthcare decision, thus highlighting the importance of a patient-centered approach in O-MSK (10, 11, 63, 64).

This systematic metasynthesis also confirmed the role of physiotherapist as a moderator of patient satisfaction (17). Patients were satisfied by different physiotherapist's traits such as personality, leadership, competence, flexibility and

critical thinking, thus supporting the key role of the provider's interpersonal (8-12) and technical care (8, 10, 11) in influencing patient satisfaction. Moreover, patient appreciated physiotherapist's education and information (9, 10, 17, 63) as strategies for a better understanding of pain experience and modification of misleading behaviors (65).

Our findings further corroborate the function of effective, efficient, well organized and coordinated O-MSK services as mediators of patient satisfaction (17). In accordance with previous systematic reviews (8-12), different elements of caring process such as continuity, accessibility, availability and affordability of the services were positively associated with patient satisfaction and contribute to increase their attractiveness and magnetism in the contemporary competitive healthcare context.

Moving away from a previous systematic review in O-MSK (17), this qualitative metasummary and metasynthesis adds innovative findings. In only one study (50), we have found that physiotherapist's gender can put the patient at ease differently, thus influencing patient satisfaction and patient's engagement directly during the plan of care (66, 67). Moreover, our findings highlights the importance of the therapeutic alliance and the partnership of care (68, 69), the verbal and non-verbal elements of communication (8, 10, 70, 71) as determinants of patient satisfaction capable to affect the quality of interaction between physiotherapist and patient.

Another interesting novel findings concerns patients' desires to acquire coping strategies and self-treatment tools (e.g. therapeutic exercises) (72) to better manage their problems in daily life, thus strengthening their resilience and affecting their well-being (73). Moreover, this qualitative metasynthesis emphasizes the relevance of a pleasant atmosphere, room comfort, noise level, temperature and lighting as physical environmental determinants capable of influencing overall patient satisfaction (10).

Patients also valued the social context as a space that enhances supportive relationships between patients, offers an opportunity for reflection and increases the sharing of individual experiences (74).

Strength and limitations

To our knowledge, this is the first metasummary and metasynthesis that summarizes the determinants of patient satisfaction with O-MSK (30), thus responding to a recent call to action concerning the need for health service research in rehabilitation (20). Despite we have performed an extensive search in six databases using the “berry-picking” method to improve the investigation (35), some relevant studies could be missed and publication bias could be occurred. This review obtained studies regarding patient satisfaction only in O-MSK reported in English, performed prevalently in Europe, therefore our findings cannot be generalized across patients with other health problems, in different settings (inpatient), in other continents with different cultural and language references (29). Moreover, the interpretation of findings may have been influenced by some of the authors’ experiences as physiotherapists. However, the methodological approach combining a multidisciplinary team of experts served to reduce this potential bias (30). Finally, during the critical appraisal process, we used the CASP tool (43) with a scoring matrix to classify the overall quality of the included papers. This *a priori* decision was made because no cut-off point systems were presented in the literature for the categorization of methodological quality of the studies (42). Overall the included papers reported a critical appraisal ranged from medium to high quality. We have also commented on all of the included CASP items thus identifying any possible weaknesses in the included study, including: the appropriateness of the research question; the description of the relationship between

researcher and participants; the collection and the analysis of data; the strategy of recruitment.

Conclusion

This qualitative metasummary and metasynthesis contributes to extend the knowledge concerning patient satisfaction in O-MSK and identified this proxy as composed both by clinical and contextual factors. Policies of healthcare services should take in account patient satisfaction as a fundamental indicator of quality care, thus stimulating its assessment and analysis in clinical settings. Future qualitative research should investigate the relationships between the determinants of patient satisfaction and expand the investigation in other settings to provide a depth understanding about this topic.

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Table 1. Characteristic of the included studies.

Study (year)	Country (setting)	Diagnosis	Participant	Aim	Data analysis (as reported by authors)	Data collection (as reported by authors)	Determinants of patient satisfaction
Ali & May (2015) (50)	Egypt (outpatient)	Non-specific low back pain	N = 18 M/F = 9/9 Age = 19-81	Explore patients' expectation and satisfaction with physiotherapy in Egyptian patients attending for low back pain	Framework analysis	Focus group Semi-structured interviews	outcome patient education the therapist service provision decision making
Cooper et al. (2008) (51)	Scotland (outpatient)	Chronic low back pain	N = 25 M/F = 5/20 Age = 18-65	Define patients' perspectives about patient-centeredness in the context of	Framework analysis	Semi-structured interviews	communication individual care decision-making information sharing the physiotherapist

				physiotherapy for chronic low back pain			organisation of care
Del Baño-Aledo et al. (2014) (52)	Spain (outpatient)	Musculo-skeletal disorders (fractures, soft tissue injuries, amputation)	N = 57 M/F = 33/24 Age = > 18	Identify elements of the physiotherapist-patient interaction considered by patient when evaluating the quality of care	Modified grounded theory approach	Focus group	interpersonal manners providing information and education technical expertise
Hills & Kitchen (2007a) (53)	England (outpatient)	Acute and chronic musculoskeletal disorders (fracture,	N = 30 (acute n=14; chronic n=16) M/F = 9/21 Age = 36-82	Identify factors leading to satisfaction Provide explanation for	Interactive model of analysis	Focus group	expectations of physiotherapy communication/information/explanation perceptions of the therapist process/content of treatment result of treatment

trauma, degenerative spinal or peripheral joint disease)	relationship between expectations and satisfaction as a basis for patients' evaluation of physiotherapy care
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Hills & Kitchen (2007b) (54)	England (outpatient)	Acute and chronic musculoskeletal disorders (fracture, trauma, degenerative)	N = 30 (acute n=14; chronic n=16) M/F = 9/21 Age = 36-82	Explore the factors that affect patients' satisfaction with musculoskeletal outpatient physiotherapy	Interactive model of analysis	Focus group	expectations of treatment communication/information/explanation perception of the therapist process /content of treatment treatment outcome
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May (2001) (55)	England (outpatient)	Low back pain	N = 34 M/F = 14/20 Age = 29-77	Describe the aspects of physiotherapy care that patients considered important	Framework analysis	Semi-structured interviews	personal manner and professional manner of the therapist therapist's role in providing information treatment as a consultive process structure of service provision outcome of treatment episode
Medina- Mirapeix et al. (2011) (56)	Spain (outpatient)	Musculoskeletal disorders (fractures, soft tissue injuries, amputation)	N = 57 M/F = 33/24 Age = > 18	Explore ambulatory outpatient experiences and perceptions in post-acute care settings Determine if there	Modified grounded theory approach	Focus group	relational continuity (consistency of multi- professional rehabilitation team; established provider- patient relationship) informational continuity (transfer of information among providers; accumulated knowledge of

				are any perceived gap in continuity of rehabilitation care			patients' disability experience) management continuity (consistency of care among providers; flexibility of the team in adapting care to functional changes or needs; involvement in achieving patient collaboration)
Medina- Mirapeix et al. (2013) (57)	Spain (outpatient)	Musculoskeletal disorders (fractures, soft tissue injuries, amputation)	N = 57 M/F = 33/24 Age = > 18	Identify elements of the environment that patient consider when evaluating the quality of care experience	Modified grounded theory approach	Semi-structured interviewing during focus group	physical environment (facility design; ambient conditions; social factors) organizational environment (duration; interruptions; waiting times in the sequence of treatment; patient safety)
Potter et	Australia	Musculoskeletal	N = 26	Explore patients'	Analyst	Nominal group	communication ability

al. (2003) [58]	(outpatient)	mental disorders	M/F = 10/16 Age = 20-79	perspectives regarding the qualities of a good physiotherapist Identify the characteristics of good and bad experience in private practice physiotherapy	triangulation with two independent researchers	technique	(interpersonal skills, physiotherapist's manner, teaching/education) other attributes (professional behaviour; organisational ability) service provided (diagnostic and treatment expertise, the environment, convenience and accessibility)
Slade et al. (2009) [59]	Australia (outpatient)	Non-specific chronic	N = 18 M/F = 6/12 Age = mean	Determine patients' experience of	Grounded Theory	Focus group	Engagement with the health care process listen to me, I know my body

		low back pain	51.2 ± 9.5	exercise programmes			tell me: explain it to me can understand
Waters et al. (2016) [60]	Australia (outpatient)	Musculoskeletal disorders	N = 10 M/F = 4/6 Age = 22-82	Identify the factors influencing patient satisfaction with orthopaedic outpatient clinic services	Thematic analysis	Focus group 1-1 interviews	clinic waiting time clinical contact time empathy communication expectation trust relatedness




Legend: N = number of participants; M = male; F = female; ± = + or – standard deviation;


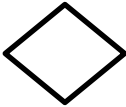

Item 6. Has the relationship between researcher and participants been adequately considered?	Y	N	N	N	N	N	N	N	N	N	Y
Item 7. Have ethical issues been taken into consideration?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Item 8. Was the data analysis sufficiently rigorous?	Y	Y	Y	U	U	Y	Y	Y	Y	U	Y
Item 9. Is there a clear statement of findings?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Item 10. How valuable is the research?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Overall score	8.5	8.5	8.5	8	8	7.5	8.5	8.5	8	7	9.5

Legend:

Y = yes; N = No; U = Unclear.

Table 3. Metasummary.

THEMES	Categories	First author (year)										INTERSTUDY FREQUENCY	
		Ali & May (2015) (50)	Cooper (2008) (51)	Del Baño-Aledo (2014) (52)	Hills & Kitchen (2007 a) (53)	Hills & Kitchen (2007 b) (54)	May (2001) (55)	Medina-Mirapeix (2011) (56)	Medina-Mirapeix (2013) (57)	Potter (2003) (58)	Slade (2009) (59)		Waters (2016) (60)
CLINICAL OUTCOME 	Results of treatment	X			X	X	X						36%
PHYSIOTHERAPIST FEATURE 	Attitude	X	X	X	X	X	X			X		X	73%
	Professionalism	X	X	X	X		X		X				54%
	Gender	X											9%
PATIENT FEATURE 	Expectation	X	X		X	X						X	45%

PHYSIOTHERAPIST/PATIENT RELATIONSHIP 	Communication	X	X	X					X	X	X	54%
	Partnership of care	X		X		X				X	X	45%
TREATMENT FEATURE 	Education	X	X	X	X	X	X	X	X	X		82%
	Organization of care	X	X		X	X	X	X	X		X	82%
	Typology		X	X	X		X		X	X		54%
	Decision making	X	X				X	X				36%
HEALTHCARE SETTING FEATURE 	Physical environment	X							X			18%
	Social context								X			9%
INTRASTUDY INTENSITY		69%	69%	23%	62%	62%	46%	38%	23%	46%	31%	38%

Interstudy Frequency = (number of study containing a finding / total number of study) * 100

Intrastudy Intensity = (number of findings in the study / total number of findings) * 100

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Chart (31).

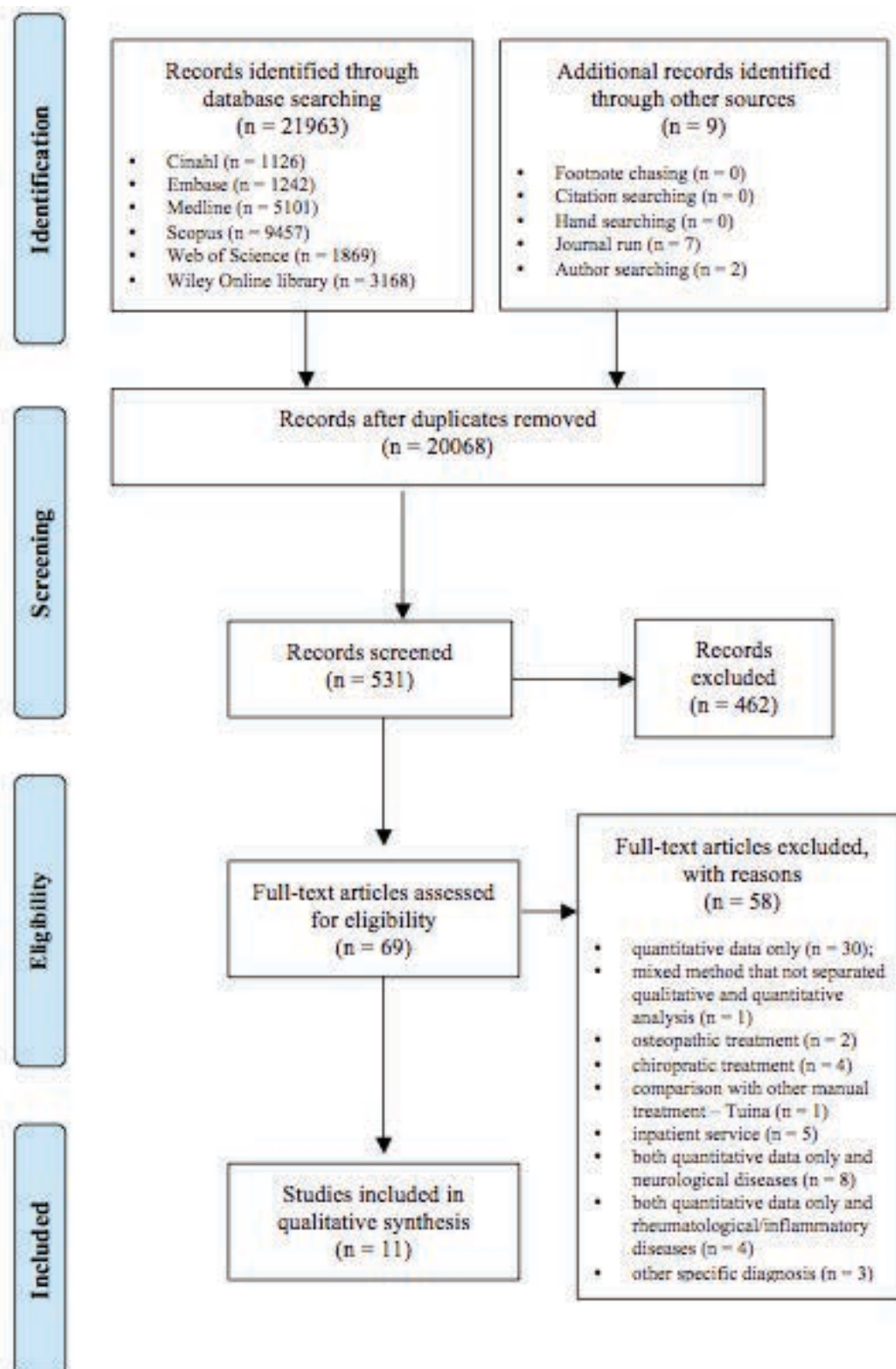
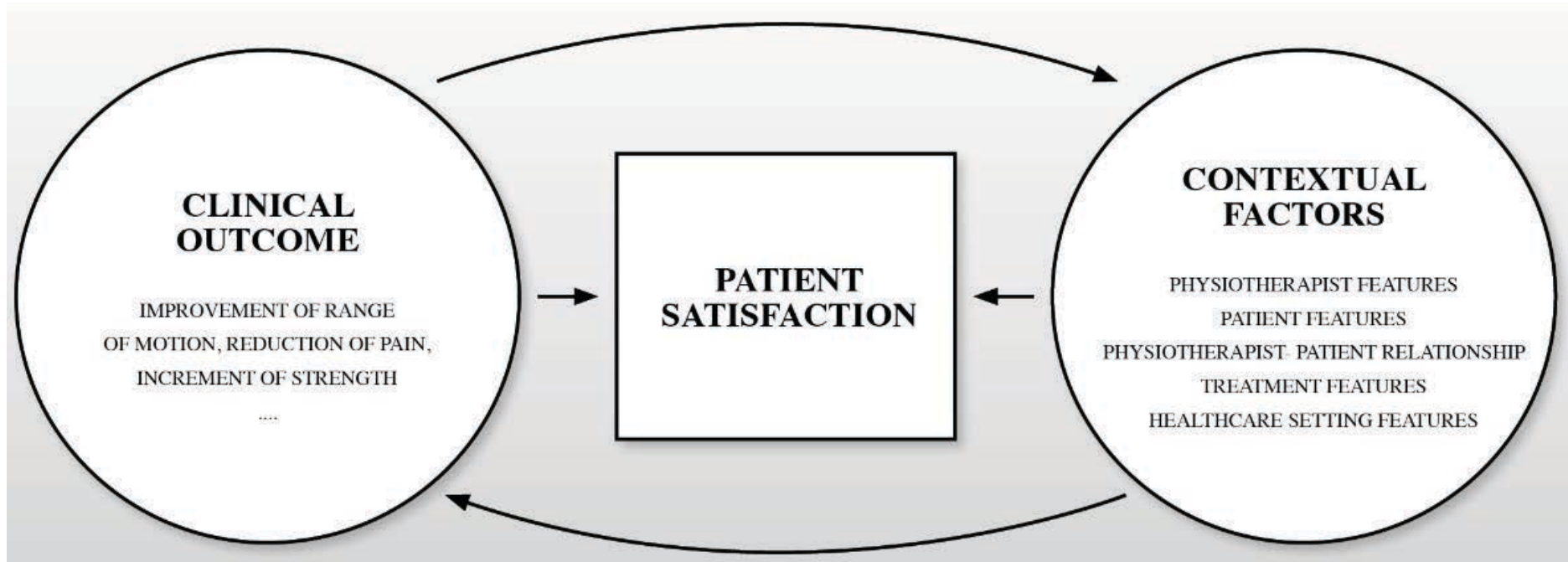


Figure 2. The determinants of patient satisfaction towards O-MSK



Appendix 1. Search strategy for different database.

DATABASE	SEARCH STRATEGY
MEDLINE (VIA PUBMED)	<p>("Patient Satisfaction"[Mesh] OR "patient satisfaction" OR "Consumer Behavior"[Mesh] OR "consumer satisfaction" OR "client satisfaction" OR "patient experience" OR "client experience") AND ("physiotherapy" OR "physical therapy" OR "Physical Therapy Modalities"[Mesh] OR "Musculoskeletal Manipulations"[Mesh] OR "allied health" OR "outpatient")</p> <p>LIMITS: English, humans, full text</p>
CINAHL	<p>("patient satisfaction" OR "consumer satisfaction" OR "client satisfaction" OR "patient experience" OR "client experience" OR "customer experience" OR "consumer experience" OR "patient behavior" OR "client behavior" OR "consumer behaviour" OR "customer behavior") AND ("physiotherapy" OR "physical therapy" OR "physical therapy modality" OR "physical therapy modalities" OR "physical therapy technique" OR "physical therapy techniques" OR "musculoskeletal manipulations" OR "manual therapy" OR "manual therapies" OR "manipulation therapy" OR "manipulation therapies" OR "manipulative therapy" OR "manipulative therapies" OR "allied health" OR "outpatient")</p> <p>LIMITS: English, humans, full text</p>
SCOPUS	<p>TITLE-ABS-KEY(("patient satisfaction" OR "consumer satisfaction" OR "client satisfaction" OR "patient experience" OR "client experience" OR "customer experience" OR "consumer experience" OR "patient behavior" OR "client behavior" OR "consumer behaviour" OR "customer behavior") AND ("physiotherapy" OR "physical therapy" OR "physical therapy modality" OR "physical therapy technique" OR "musculoskeletal manipulations" OR "manual therapy" OR "manipulation therapy" OR "manipulative therapy" OR "allied health" OR "outpatient")) AND (LIMIT-TO(DOCTYPE,"ar")) AND (LIMIT-TO(LANGUAGE,"English")) AND (LIMIT-TO(SRCTYPE,"j")) AND (LIMIT-TO(SUBJAREA,"HEAL"))</p> <p>LIMITS: English, type of document (article), area (professional health), source (documents from journal sources)</p>
Web of science	<p>("patient satisfaction" OR "consumer satisfaction" OR "client satisfaction" OR "patient experience" OR "client experience" OR "customer experience" OR "consumer experience" OR "patient behavior" OR "client behavior" OR "consumer behaviour" OR</p>

(core collection) “customer behavior”) AND (“physiotherapy” OR “physical therapy” OR “physical therapy modality” OR “physical therapy modalities” OR “physical therapy technique” OR “physical therapy techniques” OR “musculoskeletal manipulations” OR “manual therapy” OR “manual therapies” OR “manipulation therapy” OR “manipulation therapies” OR “manipulative therapy” OR “manipulative therapies” OR “allied health” OR “outpatient”)

LIMITS: English, type of document (article)

Wiley Online library (“patient satisfaction” OR “consumer satisfaction” OR “client satisfaction” OR “patient experience” OR “client experience” OR “customer experience” OR “consumer experience” OR “patient behavior” OR “client behavior” OR “consumer behaviour” OR “customer behavior”) AND (“physiotherapy” OR “physical therapy” OR “physical therapy modality” OR “physical therapy technique” OR “musculoskeletal manipulations” OR “manual therapy” OR “manipulation therapy” OR “manipulative therapy” OR “allied health” OR “outpatient”)

LIMITS: type of source (journal), entry terms present in abstract

EMBASE (‘patient satisfaction’/exp OR ‘patient satisfaction’ OR ‘consumer experience’/exp OR ‘consumer satisfaction’ OR ‘client satisfaction’ OR ‘patient experience’/exp OR ‘patient experience’ OR ‘client experience’ OR ‘customer experience’ OR ‘consumer experience’ OR ‘patient behavior’/exp OR ‘patient behavior’ OR ‘client behavior’ OR ‘consumer behavior’/exp OR ‘consumer behavior’ OR ‘customer behavior’) AND (‘physiotherapy’/exp OR ‘physiotherapy’ OR ‘physical therapy’/exp OR ‘physical therapy’ OR ‘physical therapy modality’ OR ‘physical therapy modalities’/exp OR ‘physical therapy modalities’ OR ‘physical therapy technique’ OR ‘physical therapy techniques’/exp OR ‘physical therapy techniques’ OR ‘musculoskeletal manipulations’/exp OR ‘musculoskeletal manipulations’ OR ‘manual therapy’/exp OR ‘manual therapy’ OR ‘manual therapies’ OR ‘manipulation therapy’/exp OR ‘manipulation therapy’ OR ‘manipulation therapies’ OR ‘manipulative therapy’/exp OR ‘manipulative therapy’ OR ‘manipulative therapies’ OR ‘allied health’ OR ‘outpatient’/exp OR ‘outpatient’)

LIMITS: English, type of document (primary studies), human subjects

Appendix 2. Excluded studies with motivations.

References	Motivations
Carlesso LC, MacDermid JC, Santaguida PL, Thabane L. A survey of patient's perceptions of what is adverse in manual physiotherapy and predicting who is likely to say so. <i>J Clin Epidemiol.</i> 2013 Oct;66(10):1184-91.	Quantitative method
Abtahi AM, Presson AP, Zhang Z, Saltzman CL, Tyser AR. Association Between Orthopaedic Outpatient Satisfaction and Non-Modifiable Patient Factors. <i>J Bone Joint Surg Am.</i> 2015 Jul 1;97(13):1041-8.	Quantitative method
McKinnon AL. Client Satisfaction with Physical Therapy Services does age make a difference. <i>Physical and Occupational Therapy in Geriatrics</i> 2001 19:2 (23-37)	Quantitative method
Solomon DH, Bates DW, Horsky J, Burdick E, Schaffer JL, Katz JN. Development and validation of a patient satisfaction scale for musculoskeletal care. <i>Arthritis Care Res.</i> 1999 Apr;12(2):96-100.	Quantitative method
Roush SE, Sonstroem RJ. Development of the Physical Therapy Outpatient Satisfaction Survey (PTOPS). <i>Phys Ther.</i> 1999 Feb;79(2):159-70.	Quantitative method
Diògenes TPM, Mendinca KMPP, Guerra RO. Dimension of satisfaction of older adult brazilian outpatients with physical therapy. <i>Rev Bras Fisioter.</i> 2009 Jul;13(4).	Quantitative method
Metcalfe CJ, Klaber Moffett JA. Do patients' expectations of physiotherapy affect treatment outcome Part 1 Baseline data International. <i>International Journal Of Therapy & Rehabilitation</i> 2005 Feb;12(2):55-62.	Quantitative method
Schafer DS. Environmental-scanning behavior among private-practice physical therapy firms. <i>Phys Ther.</i> 1991 Jun;71(6):482-90.	Quantitative method
Sephton R, Hough E, Roberts SA, Oldham J. Evaluation of a primary care musculoskeletal clinical assessment	Quantitative method

service a preliminary study. *Physiotherapy*. 2010 Dec;96(4):296-30.

Roberts L. Improving quality, service delivery and patient experience in a musculoskeletal service. *Man Ther*. 2013 Feb;18(1):77-82. Quantitative method

Hush JM, Lee H, Yung V, Adams R, Mackey M, Wand BM, Nelson R, Beattie P. Intercultural comparison of patient satisfaction with physiotherapy care in Australia and Korea an exploratory factor analysis. *J Man Manip Ther*. 2013 May;21(2):103-12. Quantitative method

Larsson MEH, Kreuter M. Is patient responsibility for managing musculoskeletal disorders related to self-reported better outcome of physiotherapy treatment. *Physiother Theory Pract*. 2010 Jul;26(5):308-17. Quantitative method

Medina-Mirapeix F, Jimeno-Serrano FJ, Escolar-Reina P, Del Baño-Aledo ME. Is patient satisfaction and perceived service quality with musculoskeletal rehabilitation determined by patient experiences. *Clin Rehabil*. 2013 Jun;27(6):555-64. Quantitative method

Beattie P, Dowda M, Turner C, Michener L, Nelson R. Longitudinal continuity of care is associated with high patient satisfaction with physical therapy. *Phys Ther*. 2005 Oct;85(10):1046-52. Quantitative method

Durant TL, Lord LJ, Domholdt E. Outpatient views on direct access to physical therapy in Indiana. *Phys Ther*. 1989 Oct;69(10):850-7. Quantitative method

Medina-Mirapeix F, Jimeno-Serrano FJ, Escolar-Reina P, Del Baño-Aledo ME, Montilla-Herrador J, Lomas_Vega R, Franco-Sierra MA. Outpatients' perceptions of their experiences in musculoskeletal rehabilitation care. *Eur J Phys Rehabil Med*. 2012 Sep;48(3):475-82. Quantitative method

Licciardone J, Gamber R, Cardarelli K. Patient satisfaction and clinical outcomes associated with osteopathic manipulative treatment. *J Am Osteopath Assoc*. 2002 Jan;102(1):13-20. No physiotherapy treatment (osteopathic)

Hush JM, Kirsten Cameron K, Mackey M. Patient satisfaction with musculoskeletal physiotherapy care in Australia an international comparison. <i>J Man Manip Ther.</i> 2012 Nov;20(4):201-8.	Quantitative method
Miao EY. Perception of patients, physiotherapists and traditional Chinese medicine practitioners towards manual physiotherapy and Tuina (Chinese manipulative therapy) in Australia a qualitative. <i>Zhong Xi Yi Jie He Xue Bao.</i> 2011 Jul;9(7):737-45.	Comparison with other manual treatment treatment (Tuina)
Scholte M, Calsbeek H, Nijhuis-van der Sanden MW, Braspenning J. Quality of physical therapy from a patient's perspective factor analysis on web-based survey data revealed three dimensions on patient experiences with physical therapy. <i>BMC Health Serv Res.</i> 2014 Jun 18;14:266.	Quantitative method
Knight PK, Cheng AN, Lee GM. Results of a survey of client satisfaction with outpatient physiotherapy care. <i>Physiother Theory Pract.</i> 2010 Jul;26(5):297-307.	Quantitative method
Candy E, Haworth-Booth S, Knight-Davis M. Review of the Effectiveness of a Consultant physiotherapy led musculoskeletal interface team. <i>Musculoskeletal Care.</i> 2016 Sep;14(3):185-91.	Quantitative method
Hills R, Kitchen S. Satisfaction with outpatient physiotherapy a survey comparing the views of patients with acute and chronic musculoskeletal conditions. <i>Physiother Theory Pract.</i> 2007 Jan-Feb;23(1):21-36.	Quantitative method
Monnin D, Perneger TV. Scale to measure patient satisfaction with physical therapy. <i>Phys Ther.</i> 2002 Jul;82(7):682-91.	Quantitative method
Beattie PF, Nleson RM, Heintzelman M. The relationship between patient satisfaction with physical therapy care and global rating of change reported by patients receiving worker's compensation. <i>Physiother Theory Pract.</i> 2011 May;27(4):310-8.	Quantitative method
Medina-Mirapeix F, Oliveira-Sousa SL, Sobral-Ferreira M, Montilla-Herrador J, Jimeno-Serrano FJ, Escolar-	Quantitative method

Reina P. What elements of the informational, management, and relational continuity are associated with patient satisfaction with rehabilitation care and global rating change. *Arch Phys Med Rehabil.* 2013 Nov;94(11):2248-54.

Overmeer T, Boersma K. What Messages Do Patients Remember Relationships Among Patients' Perceptions of Physical Therapists' Messages, Patient Characteristics, Satisfaction, and Outcome. *Phys Ther.* 2016 Mar;96(3):275-83.

Rajendran D, Bright P, Bettles S, Carnes D, Mullinger B. What puts the adverse in 'adverse events' Patients' perceptions of post treatment experiences in osteopathy qualitative study using focus groups. *Man Ther.* 2012 Aug;17(4):305-11.

Vanti C, Pillastrini P, Monticone M, Ceron D, Bonetti F, Piccarreta R, Guccione A, Violante FS. The Italian version of the physical therapy patient satisfaction questionnaire - [PTPSQ-I(15)]: Psychometric properties in a sample of inpatients. *BMC Musculoskeletal Disorders.* 2014 Apr 23;15:135.

Peiris CL, Taylor NF, Shield N. Patients value patient-therapist interactions more than the amount or content of therapy during inpatient rehabilitation: A qualitative study. *J Physiother.* 2012;58(4):261-8.

Berghofer G, Lang A, Henkel H, Schmidl F, Rudas S. Satisfaction of inpatients and outpatients with staff, environment and other patients. *Psychiatr Serv.* 2001 Jan;52(1):104-6.

Stiller K, Cains G, Drury C. Evaluating inpatient satisfaction with a physiotherapy service: A rehabilitation centre survey. *Int J Ther Rehabil.* 2016;96(3):275-83.

Grønhaug G, Hagfors J, Borch I, Østerås N, Hagen KB. Perceived quality of health care services among people with osteoarthritis – Results from a nationwide survey. *Patient Prefer Adherence.* 2015 Sep 3;9:1255-61.

<p>Ku JH, Danve A, Pang H, Choi D, Rosenbaum JT. Determinants of patient satisfaction in an academic rheumatology practice. <i>J Clin Rheumatol</i>. 2015 Aug;21(5):256-6.</p>	<p>disease (osteoarthritis) Quantitative method; rheumatological/inflammatory diseases</p>
<p>Kim KW, Cho KJ, Kim SW, et al. A nation-wide, outpatient-based survey on the pain, disability, and satisfaction of patients with osteoporotic vertebral compression fractures. <i>Asian Spine J</i>. 2013 Dec;7(4):301-7.</p>	<p>Quantitative method; specific diagnosis (osteoporotic vertebral compression fractures)</p>
<p>Normann B, Moe S, Salvesen R, Sørgaard KW. Patient satisfaction and perception of change following single physiotherapy consultations in a hospital's outpatient clinic for people with multiple sclerosis. <i>Physiother Theory Pract</i>. 2012 Feb;28(2):108-18.</p>	<p>Quantitative method; neurological disease (Multiple sclerosis)</p>
<p>French HP, Keogan F, Gilsenan C, Waldron L, O'Connell P. Measuring patient satisfaction with exercise therapy for knee osteoarthritis: evaluating the utility of the physiotherapy outpatient survey. <i>Musculoskeletal Care</i>. 2010 Jun;8(2):61-7.</p>	<p>Quantitative method; rheumatological/inflammatory disease (osteoarthritis)</p>
<p>Juby AG, Skeith K, Davis P. Patients' awareness, utilization, and satisfaction with treatment modalities for the management of their osteoarthritis. <i>Clin Rheumatol</i>. 2005 Sep;24(5):535-8.</p>	<p>Quantitative method; rheumatological/inflammatory (osteoarthritis)</p>
<p>Smith DL. Does type of disability and participation in rehabilitation affect satisfaction of stroke survivors? Results from the 2013 Behavioral Risk Surveillance System (BRFSS). <i>Disabil Health J</i>. 2015 Oct;8(4):557-63.</p>	<p>Quantitative method; neurological disease (stroke)</p>
<p>Ytterberg C, Johansson S, Gottberg K, Holmqvist LW, von Koch L. Perceived needs and satisfaction with care</p>	<p>Quantitative method;</p>

in people with multiple sclerosis: A two-year prospective study. BMC Neurol. 2008 Sep 29;8:36.	neurological disease (Multiple sclerosis)
Forsberg A, de Pedro-Cuesta J, Widén Holmqvist L. Use of healthcare, patient satisfaction and burden of care in Guillain-Barré syndrome. J Rehabil Med. 2006 Jul;38(4):230-6.	Quantitative method; neurological disease (Guillain-Barré)
Byrne NM, Hardy L. Community physiotherapy for children with cystic fibrosis: A family satisfaction survey. J Cyst Fibros. 2005 May;4(2):123-7.	Quantitative method; specific diagnosis (cystic fibrosis)
Keus SH, Bloem BR, Verbaan D, et al. Physiotherapy in Parkinson's disease: Utilisation and patient satisfaction. J Neurol. 2004 Jun;251(6):680-7.	Quantitative method; neurological disease (Parkinson's disease)
Roush SE. The satisfaction of patients with multiple sclerosis regarding services received from physical and occupational therapists. J Inter of Rehabilitation and Health. 1995 Jul; 1(3):155-166.	Quantitative method; neurological disease (Multiple sclerosis)
Wittmer M, Volpatti M, Piazzalonga S, Hoffmann A. Expectation, satisfaction, and predictors of dropout in cardiac rehabilitation. Eur J Prev Cardiol. 2012 Oct;19(5):1082-8.	Quantitative method; specific diagnosis (coronary heart disease, valvular heart disease)
Geberemichael SG, Metaferia GZ, Takele GM, Johnston JC. Patient satisfaction with outpatient neurology services: a momentum for improvement. J Neurol Sci. 2011 Apr 15;303(1-2):128-32.	Quantitative method; neurological disease (cerebral palsy; nerve root-cord compression disorders;

extrapyramidal movement disorders)

Dennis D, Mullins R. Guillain-Barre syndrome patient's satisfaction with physiotherapy: A two-part observational study. <i>Physiother Theory Pract.</i> 2013 May;29(4):301-8.	Quantitative method: neurological disease (Guillain-Barré)
Stiller K, Cains G, Drury C. Evaluating inpatient satisfaction with a physiotherapy service: a rehabilitation centre survey. <i>J Inter of Theory & Rehabilitation.</i> 2009 Jul; 16(7):376-384.	Inpatient
McCarthy CJ, Oldham JA, Sephton R. Expectations and satisfaction of patients with low back pain attending a multidisciplinary rehabilitation service. <i>Physiother Res Int.</i> 2005;10(1):23-31.	Quantitative method
Leininger BD, Evans R, Bronfort G. Exploring Patient Satisfaction: A Secondary Analysis of a Randomized Clinical Trial of Spinal Manipulation, Home Exercise, and Medication for Acute and Subacute. <i>J Manipulative Physiol Ther.</i> 2014 Oct;37(8):593-601.	Quantitative method
Rowell RM, Polipnick J. A Pilot Mixed Methods Study of Patient Satisfaction With Chiropractic Care for Back Pain. <i>J Manipulative Physiol Ther.</i> 2008 Oct;31(8):602-10.	No physiotherapy treatment (chiropratic)
Gemmell HA, Hayes BM. Patient satisfaction with chiropractic physicians in an independent physicians' association. <i>J Manipulative Physiol Ther.</i> 2001 Nov-Dec;24(9):556-9.	No physiotherapy treatment (chiropratic)
Nyiendo J, Haas M, Goldberg B, Sexton G. Pain, disability, and satisfaction outcomes and predictors of outcomes: A practice-based study of chronic low back pain patients attending primary care and chiropractic physicians. <i>J Manipulative Physiol Ther.</i> 2001 Sep;24(7):433-9.	No physiotherapy treatment (chiropratic)
Silvis WL, Lakke SE, Stegeman P, et al. Can patients with low back pain be satisfied with less than expected?.	Quantitative method

Spine (Phila Pa 1976). 2016 Oct 15;41(20):1606-1612.

Greig A, Bainbridge L, Bedard-Gautrais C, et al. An evaluation of patient-centred care elements that influence patient satisfaction in physiotherapy practice: a systematic review. *Physiother*. 2015 May;101(1):104. Quantitative method

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Evans RL, Maiers MJ, Bronfort G. What do the patients think? Results of a mixed method pilot study assessing sciatica patients' interpretations of satisfaction and improvement. *J Manipulative Physiol Ther*. 2003;26(8):502-9. No physiotherapy treatment (chiropractic)

Peersman W, Rooms T, Bracke N, et al. Patients' priorities regarding outpatient physiotherapy care: a qualitative and quantitative study. *Man Ther*. 2013;18(2):155-64. Mixed method that not separate qualitative and quantitative analysis

Appendix 3. The metasynthesis process.

EXAMPLE OF ILLUSTRATIVE QUOTES	CODES	CATEGORIES	THEMES
<p>After physiotherapy some patients perceived that the outcome was to develop coping strategies. Patients appreciated any effective therapy, which could help them achieve the desired/expected outcome.</p> <p>Most participants considered complete recovery an important determinant of satisfaction, immediately or over time. (50)</p>	<p>Outcome, result of treatment, recovery</p>	<p>Result of treatment</p>	<p>CLINICAL OUTCOME</p>
<p>Patients were satisfied by physiotherapist's personal manner such as: friendliness and bedside manner; sensitivity to patients' needs; friendliness and empathy.</p> <p>Generally, the respondents liked the physiotherapists' friendly attitude, their ability to put people at ease, and their helpfulness.</p> <p>The characteristic of empathy involved a range of skills, which allowed patients to feel they were being dealt with in a sympathetic and respectful</p>	<p>Interpersonal manners, attitude, empathy, support, physiotherapist's personality, personal and professional manner, professional behaviour, organisational ability, perception of the therapist</p>	<p>Attitude</p>	<p>PHYSIOTHERAPIST FEATURE</p>

way. Listening to the patients' concerns and being understanding of their situation. (55)

Physiotherapists' technical expertise impacted patients' perceptions.

The impact was based on patients' feeling about physiotherapists' ability to provide good assessments and early improvement of functioning.

These feelings were reported based on comparing outcomes or qualifications of knowledge among physiotherapists. (52)

Technical expertise, competence

Professionalism

Most patients felt comfortable with therapist of the same sex, but working with an expert from the opposite gender was some time favoured over less experienced therapist of the same gender. (50)

Gender

Gender

Patients with acute problems did not know what to expect, expect specific treatment modality, and expect to make a full recovery, expect a good recovery, not expect full recovery, and expect treatment to be painful.

Patients with chronic problems expect symptomatic

Patient's wishes, expectation about physiotherapy, treatment, recovery

Patient expectation

PATIENT FEATURE

relief, specific treatment modality, and resolution of the problem “cure”, expect no treatment to help.

Subjects with positive expectations of being helped tended to report a positive outcome to the encounter if the treatment met or exceeded their expectations.

(53)

Patients were appreciative explanations they were given about their problem and what improvements they were likely to make with treatment.

Patients in the acute group needed reassurance that by the time they came for treatment their fracture had healed. An explanation that there is no danger in moving the limb will reduce apprehension and facilitate more effective treatment.

Devising home exercise regimens that incorporate functional activities rather than those which may appear divorced from everyday life is a way of improving compliance and ensuring continued improvement. (54)

Interpersonal skills, communication, explanation, information sharing

Communication

PHYSIOTHERAPIST/
PATIENT
RELATIONSHIP

Listening, understanding and getting to know the

Partnership with practitioner,

Partnership of care

<p>patient and allowing the patient to explain their problem and to question the physiotherapist were recurrently cited in relation to this dimension. (51)</p>	<p>engagement with the health care process, individual care, trust, relatedness, relationship with the therapist, knowledge of patients' disability experience</p>		
<p>All the patients reported a strong motivation to understand and explain their situation and to be given educational materials and resources. They reported that explanations should be accurate, understandable and free of jargon, they agreed that this facilitated positive therapeutic experiences. (59)</p>	<p>Patient education, teaching, therapist's role in providing information</p>	<p>Education</p>	<p>TREATMENT FEATURE</p>
<p>Patients were satisfied by different elements of the treatment process such as: the clinic waiting time, the patient awareness of clinic efficiency as a factor influencing waiting times and the clinical contact time. Patient awareness of time spent within clinic was also acknowledge by front desk reception staff. (60)</p>	<p>Organization, time, consistency of care, value for money, convenience, accessibility, organizational environment, organization of care, service provision, duration of attendance, interruptions, patient safety, management continuity, informational continuity, consistency</p>	<p>Organization of care</p>	

	<p>of team, clinical contact time, clinic waiting time, treatment process, relational continuity, informational continuity, management continuity</p>	
<p>Participants liked or wanted both treatment and the delivery of treatment to be individualised.</p> <p>Patients who felt that their exercises made sense to them and were well explained also felt that their individual needs were addressed, in contrast to those who felt that their exercises did not make sense or did not push them hard enough.</p> <p>Patients described the type of exercise as affecting compliance, only doing the exercises that fitted in with their lifestyle, suggesting the physiotherapists need to take this into account when prescribing exercise for chronic low back pain patients.</p> <p>Many placed importance on a thorough assessment, feeling that it enabled their treatment to better relate to their needs and emphasizing the importance that patients seem to place on this aspect of</p>	<p>Diagnostic and treatment expertise, individual treatment, content of treatment, flexibility in adapting care to functional change or needs</p>	<p>Typology</p>

physiotherapy. (51)

Patients needs to be listened to and involved in the treatment; so that it is seen as a consultive, rather than a prescriptive, process. (55)

Participation in decision making, involvement in the process, consultive process, involvement in achieving patient's collaboration

Decision-making

Patients felt low visual privacy to move to one room to another and when they were attended by therapists or performed exercise in a large room that was used by other people.

They feel high service quality when having private rooms when they needed to change clothes for receiving therapy. (57)

Standard of premises, facility design, ambient condition

Physical environment

HEALTH CARE

SETTING FEATURE

Positive influence on quality environment when the patients were supportive of each other in their efforts to improve health status. When this happened, they rated the environment as motivational (mutual help, similar stories and disability). (57)

Social factors

Social context

CHAPTER IV

**PHYSICAL THERAPISTS' PERSPECTIVES
TOWARDS EXPLOITING CONTEXTUAL FACTORS
IN CLINICAL PRACTICE: FINDINGS FROM AN
ITALIAN NATIONAL SURVEY**

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Physical therapists' perspectives towards exploiting contextual factors in clinical practice: findings from an Italian national survey

Abstract

Background: Contextual factors (CFs) represent a potential therapeutic tool to boost physiotherapy outcomes, triggering placebo effects. Nevertheless, no evidence about the use of CFs among physical therapists is currently available.

Objective: To investigate the perspective of Italian physical therapists specialized in Orthopaedic Manual Therapy (OMTs) towards CFs.

Design: A cross-sectional online survey.

Methods: A 17-item questionnaire and two clinical vignettes assessed the perspective of OMTs about the adoption of CFs in daily clinical practice. The target population was composed of 906 OMTs. An online survey was performed in 2016 using SurveyMonkey Software®. Data were analyzed by descriptive and inferential statistics.

Results: A total of 558 volunteers (61.6% of the target OMT population) participated in the study. Half of the participants (52.0%) claimed to use CFs frequently in their practice. More of 50% of OMTs valued the therapeutic significance of CFs for different health problems as determined by a combined psychological and physiological effect. OMTs considered the use of CFs ethically acceptable when they exert beneficial therapeutic effects and their effectiveness has emerged in previous clinical experience (30.6%). They disagreed on the adoption of CFs when they are deceptive (14.1%). Moreover, OMTs did not communicate the adoption of CFs to patients (38.2%), and CFs were usually used in addition to other interventions to

optimize clinical responses (19.9%). Psychological mechanisms, patient's expectation and conditioning were believed to be the main components behind CFs (7.9%).

Limitations: Considering that the data collected were self-reported and retrospective, recall and response biases may limit the internal and external validity of the findings.

Conclusions: The use and beliefs of CFs among Italian OMTs depends on the specific type of CFs considered. The findings of this study suggest the need for an educational course about CFs and placebo effects.

Introduction

Contextual factors (CFs) have been proposed in the scientific literature as an emerging topic (1). These are multidimensional aspects of the therapeutic encounter (provider, patient, patient-provider relationship, treatment and setting) (2) capable to enact psycho-neuro-immuno-endocrine responses that can trigger positive or negative clinical outcomes by placebo and nocebo effects (3). Placebo effects have been associated to the optimal use of CFs, whereas nocebo has been associated with a negative context surrounding the clinical encounter (4). Different psychological theories based upon expectations and learning processes have been established as the fundamentals mechanisms of CFs effects, whilst specific neurotransmitters such as endogenous cholecystokinin, opioid, endocannabinoid, vasopressin, and dopamine have been documented as orchestrating the neurobiology behind their clinical effect (5).

Although the use of CFs as triggers of placebo and nocebo effects has been studied for many years in medicine discipline, only recently they have only recently been introduced in physical therapy discipline (6). Clinically, CFs are considered not eliminable components (7) of a specific physiotherapy treatment (8), thus capable of modulating symptoms. Available randomized controlled trials have reported the positive effect of CFs on musculoskeletal conditions such as low back pain (9-12), neck pain (13) and shoulder pain (14). Patients' expectations with regard to a treatment (10, 13), the physical therapist's verbal suggestions associated with treatment (9, 14), and the enhanced therapeutic alliance between the patient and the physical therapist (11, 12) all have been documented as improving outcomes in different domains such as pain, disability, expectation and satisfaction (15-17).

Despite the increased interest concerning the use of CFs also in some clinical trials (9-14), no data have been published on physical therapists' perspectives harnessing CFs in routine clinical practice. On the contrary, available surveys have investigated the use of placebos in specific groups of healthcare providers (18) documenting an overall use of them ranging from 17.0% to 80.0% among physicians (19-36), and from 51.0% to 100.0% among nurses (22, 37-39) in Canada (29, 32), Denmark (21), England (28, 31), France (38), Germany (23, 24, 36), India (34), Iran (37), Israel (22), Poland (27), Saudi Arabia (35), Switzerland (19), Turkey (39), the United Kingdom (20) and the United States (25, 26, 30, 33).

Clinical implementation and perspectives about CFs use have been suggested as a priority field of investigation (18), in different professional healthcare groups, such as physical therapists (6). In fact, physical therapists establish a one-to-one relationship with the patient, following alongside the clinical pathway and, more directly, influencing his/her experience and degree of satisfaction (40). Among these professionals, physical therapists specialized in Orthopaedic Manual Therapy (OMTs) represent a professional group to be investigated because their clinical practice is widely pervaded by CFs (41). Therefore, we decided to explore within this area of medicine the frequency of use, beliefs, behaviors, attitudes, and knowledge with regard to CFs in a nationwide sample of Italian OMTs.

Materials and Methods

Design

A quantitative web-based cross-sectional survey herein reported according to the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) guidelines (42) was performed at the University of Genoa (Italy) between October and December

2016. Ethical approval was obtained from the Liguria Clinical Experimental Ethics Committee (P.R.236REG2016, approved on 19/07/2016).

Participants and setting

A nationwide sample of Italian physical therapists specialized in OMTs was the target population identified from the complete email database of Master in Rehabilitation of Musculoskeletal Disorders (MRDM) of Genoa University (n=906). This advanced educational program captures almost the totality of the Italian physical therapists specialized as OMTs (43); moreover it represents the oldest academic post-graduation program in manual therapy in Italy (44), based upon the standards established by the International Federation of Orthopaedic Manipulative Physical Therapists (45).

Within the established population, we included those OMTs who: a) had a valid e-mail account, b) understood the Italian language; and c) were working as clinicians at the time of the survey. Considering previous surveys on placebos (19-21, 25, 26, 36) that a likely response rate would range from 40.0% to 60.0%, we expected approximately 363 to 544 overall responses from the population of 906 OMTs. The application of these predicted values to the formula for estimating the sample size for a single population proportion with the population proportion set at 50.0%, which is the most conservative value to apply, produced a two-sided 95.0% confidence level within three to four percentage points of the true value and a relative standard error ranging from 2.7 to 4.1 (46).

Questionnaire development and pre-testing

A survey instrument, composed of questions and clinical vignettes, was developed using distinct and iterative steps (47). Items from the existing surveys on placebo were extracted from the literature (19-39). Moreover two clinical vignettes were derived and adapted from a recent survey on placebo (20). Clinical vignettes represent written case scenarios presenting fictitious patients: they are adopted for measuring health providers' clinical behavior (48) by asking participants to report what their behavior would be (49).

The initial list was composed of 17 questions and two clinical vignettes that were critically evaluated for face and content validity(47) by a panel of six experts with extensive experience in placebo and survey design (a physician, a psychologist, a nurse, and three physical therapists). These experts worked independently and then agreed upon the final list by providing feedback on content accuracy, wording clarity, and survey structure. Adjustments were progressively included by considering the feedback that emerged. When full agreement among experts was achieved, a preliminary version of the survey composed of 17 questions and two clinical vignettes was piloted in a convenience sample of 10 OMTs. The outcome of the pilot phase was satisfactory; therefore, no changes or comments were necessary.

Questionnaire implementation

A self-administered questionnaire (translated into English, S1 Appendix and in original language S2 Appendix) composed of three sections (A, B and C) was used. The socio-demographic variables were investigated by two open-ended questions (e.g. age) and five closed multiple-choice questions (e.g. gender, geographic region) in section A. Two clinical vignettes structured as closed multiple-choice questions were included in section B:

- a) the first vignette regarded the use of transcutaneous electrical nerve stimulation (TENS) in a patient with low back pain and high positive expectation towards this treatment based on previous encouraging experience. OMTs were asked to undertake a decision in this situation in which the use of TENS did not present contraindications and in absence of any evidence of efficacy;
- b) the second vignette was focused on an in-patient clinical case with shoulder pain positively responding when the active TENS was replaced by a sham TENS. Additionally, OMTs were asked to draw a conclusion about the efficacy and effectiveness of sham TENS.

The last section (section C) lists 10 closed questions. Six questions were single-choice questions exploring the knowledge of CFs, including the definition (e.g. ‘How would you define the therapeutic role of CFs?’), the frequency of CF use (answers from ‘never’ to ‘many times’) and the case-by-case frequency of CF use (Likert from 0 ‘never’ to 4 ‘daily’, and ‘I was not aware of it was a CF capable to influence therapeutic outcome’). The section explored also participants’ CFs belief (Likert from 0 ‘not at all’ to 4 ‘a lot of’) and the potential beneficial effects of CFs (e.g. ‘What are the potential effects of CFs in the following health problems?’). In the remaining 4 questions multiple responses were allowed to describe the ethical implications perceived in using CFs (e.g. ‘The use of CFs for therapeutic purposes can be considered ethically acceptable when....’), communication implications about CFs (e.g. ‘How do you communicate to the patient the use of CFs at the end of treatment?’), the circumstances under which they are applied (e.g. ‘Under what circumstances would you use CFs?’), and the possible mechanisms of action (e.g. ‘What mechanism of action can explain the effect of CFs?’). Overall, the term

‘contextual factor’ was preferred to ‘placebos’, as suggested in previous studies (26, 50).

Data collection procedure

The Survey Monkey (Survey-Monkey, Palo Alto, California, www.surveymonkey.com) online survey tool was used. The survey was administered over an eight-week period between 14th October 2016 and 14th December 2016. After permission was obtained from MRDM of Genova University, all OMTs were contacted by using the blast email method (51). An email containing the survey and a brief note outlining (a) the aim of the study, (b) data handling (anonymity), (c) the informed consent statement, and (d) the invitation to complete the survey was delivered. Specifically, the statement within the email informed that by clicking the survey link the respondents were providing their consent to participate in the study (52).

Two email reminders were sent two and four weeks after the initial contact to encourage those who did not participate in the survey. Ten to 15 minutes were needed to complete the survey, corresponding to the completion time found to optimize response rates in online surveys (53). Participation was voluntary and no incentives were offered to participants; there was the option to decline to answer specific questions or to leave the entire questionnaire blank (52). The order of questions was randomized. Participants were able to review or change responses using a back button until the end of the questionnaire.

Data were downloaded and stored in an encrypted computer, and only the project manager could access to the information involved in all the stages of the study. Participants were ensured that their identities would not be disclosed to

investigators. All data were de-identified (name and email address) to maintain confidentiality and data protection (52).

Data Analysis

Survey data were downloaded from the SurveyMonkey into Excel spreadsheets and reviewed for accuracy and missing values. A questionnaire was considered incomplete if there were more than 20.0% of missing data (54). For questions allowing only one choice, descriptive statistics (mean, standard deviation \pm SD) were used for continuous variables by calculating also confidence intervals (CI) at 95%, while absolute frequencies and percentages were applied to dichotomous, nominal, and ordinal variables. The variables age and years of practice were transformed into ordinal variables considering a decade as variable levels for the analysis of correlations, as described below. For questions allowing more than one choice, the absolute frequency and percentages were calculated for every combination of responses given by each participant. For example, considering that the fields (n) asked in the domain 'Ethic' were four with dichotomous responses (r), we did not calculate the absolute frequency of the four possible fields but of their 16 combinations, given by the formula r^n , to better describe the responses given by each participant.

The presence of any relationship between the individual characteristics (section A of the survey) and the responses given (sections B and C of the survey) was investigated with the Cramer's V which is a measure of strength and direction of association derived from the chi-square statistics. Only correlation values higher $>$ 0.60 were deemed acceptable and, therefore, here reported.

The five response options for the domains of frequency of use ('never', 'around once per year', 'around once per month', 'around once per week', 'daily') and beliefs

about CFs ('not at all', 'few', 'enough', 'much', 'a lot of') were converted into a five-point Likert scale ranging from 0 ('never' and 'not at all') to 4 ('daily' and 'very much') in order to have an average distribution of the two domains and to analyze the relationship between the frequency of use and the associated beliefs about CFs using the Spearman's rho. The R software was used for data analysis (55) with the packages psych (56) and ggplot2 (57).

Results

Participant's characteristics

Out of the 906 invited OMTs, a total of 571 responded (63.0%). Thirteen incomplete surveys were excluded from data analysis, leaving 558 questionnaires to be considered as valid (61.6%) for the analysis. The majority of OMTs (n=329; 59.0%; 95%CI 54.7–63.0) were male, and their average age was 30.5 ± 6.5 years. Seventy-two percent of the participants (n=400; 95%CI 67.7–75.3) were living in the north of Italy.

The participants reported an average of 6.8 ± 5.7 years of clinical experience. A high proportion was working 31–45 hours/week (n=316; 56.6%; 95%CI 52.4–60.8) as private practitioners (n=433; 77.6%; 95%CI 73.9–80.9) in the musculoskeletal field (n=472; 84.6%; 95%CI 81.3–87.4). The respondents' demographics are described in Table 1.

Definition of CF

The majority of participants defined CFs as 'an intervention without a specific effect for the condition being treated, but with a possible aspecific effect' (n=407; 72.9%; 95%CI 69.0–76.5). The remaining considered CFs as 'an intervention that has

a special effect through known physiological mechanisms' (n=112; 20.1%; 95%CI 16.9–23.7), 'a sham treatment used as control tests for safety and efficacy of active treatment' (n=20; 3.6%; 95%CI 2.3–5.6), and in minor frequency, as 'a harmless or inert intervention' (n=19; 3.4%; 95%CI 2.1–5.4).

Clinical vignette 1

Concerning the first vignette, the two most frequently chosen solutions were 'to deliver TENS' (n=169; 30.3%; 95%CI 26.5–34.3) and 'to suggest the possibility of delivering the TENS if the clinical condition fails to improve' (n=157; 28.1%; 95%CI 24.5–32.1). The remaining responders selected the following answers: 'to convince the patient of the futility of TENS' (n=104; 18.6%; 95%CI 15.5–22.2), 'to advise a different treatment commonly used for low back pain' (n=103; 18.5%; 95%CI 15.4–22.0), and 'to advise a follow-up appointment in the following days' (n=21; 3.8%; 95%CI 2.4–5.8). Only four OMTs (0.7%; 95%CI 0.2–1.9) chose 'to tell the patient that low back pain would resolve itself in a few days'.

Clinical vignette 2

With regard to the second vignette, the most frequent answers were: 'the positive attention of the healthcare team leads to decreased pain' (n=114; 20.4%; 95%CI 17.2–24.1), 'the pain as non-organic but psychological' (n=71; 12.7%; 95%CI 10.1–15.8), 'the patient as very suggestible' (n=46; 8.6%; 95%CI 6.2–10.9), 'the natural decrease of pain intensity' (n=44; 7.9%; 95%CI 5.8–10.5) and their combinations (Fig 1). The least frequent answers were 'the patient provides the expected response by the physical therapist' (n=5; 0.9%; 95%CI 0.3–2.2) and this option combined with the others (Fig 1).

Frequency of use

The frequency of use presented an average of 3.04 (95%CI 3.00–3.07) on a four-point Likert scale, indicating a higher adoption of CFs among OMTs. Fifty-two percent of OMTs (n=290; 95%CI 47.7–56.2) claimed to use the CFs ‘many times’ in their clinical practice. The remaining participants reported the use as ‘often’ (n=112; 20.1%; 95%CI 16.9–23.7), ‘at least once’ (n=126; 22.6%; 95%CI 19.2–26.3), and ‘never’ (n=30; 5.4%; 95%CI 3.7–7.7). Regarding the specific adoption of CFs, the most used CFs selected as ‘daily’ and ‘around once per week’ were (in descending order): the verbal communication (n=465; 83.3%; 95%CI 79.9-86.3), the patient-centered approach (n= 451; 80.8%; 95%CI 77.3-84.0), the empathetic therapeutic alliance with the patient (n= 437; 78.3%; 95%CI 74.6-81.6), the positive attitudes and the optimistic behavior (n= 416; 74.5%; 95%CI 70.7-78.1), the physical contact with the patient (n= 414; 74.2%; 95%CI 70.3-77.7), the professional approach to the patient (n=385; 69.0%; 95%CI 65.0-72.8), the not verbal communication (n=374; 67.0%; 95%CI 62.9-70.9), the creation of a comfortable setting (n= 327; 58.6%; 95%CI 54.4-62.7), an overt therapy (n= 288; 51.6%; 95%CI 47.4-55.8), the patient’s expectations and preferences (n=277; 49.6%; 95%CI 45.4-53.9) and the previous experiences of the patient (n=197; 35.3%; 95%CI 31.4-39.4).

The less used CFs, selected as ‘never’, was the professional reputation (n=188; 33.7%; 95%CI 29.8-37.8).

Three CFs presented opposite frequencies as ‘daily’ (the uniform: n=215; 38.5%; 95%CI 34.5-42.7; an adequate environmental architecture: n=219; 39.2%; 95%CI 35.2-43.4; an adequate design: n=207; 37.1%; 95%CI 33.1-41.3) and ‘never’ (the uniform: n=180; 32.3%; 95%CI 28.4-36.3; an adequate environmental

architecture: n=147; 26.3%; 95%CI 22.8-30.2; an adequate design: n=167; 29.9%; 95%CI 26.2-33.9). A complete reporting of CF use is presented in Table 2.

Beliefs

Concerning the beliefs, the average score was 2.79 (95%CI 2.77–2.82) out of 4, thus denoting a substantial level of conviction towards CFs among the OMTs.

In detail, the most believed CFs selected as ‘much and ‘a lot of’ were (in descending order): the empathetic therapeutic alliance with the patient (n=332; 59.5%; 95%CI 55.3-63.6), the patient-centered approach (n=312; 55.9%; 95%CI 51.7-60.1), the physical contact with the patient (n=274; 49.1%; 95%CI 44.9-53.3), the verbal communication (n=266; 47.7%; 95%CI 43.5-51.9), the patient’s previous experience (n=244; 43.7%; 95%CI 39.6-48.0), the patient’s expectations and preferences (n=240; 43.0%; 95%CI 38.9-47.2), the professional approach with the patient (n=239; 42.8%; 95%CI 38.7-47.1), the positive attitudes and the optimistic behavior (n=238; 42.6%; 95%CI 38.5-46.9), the not verbal communication (n=236; 42.3%; 38.2-46.5 95%CI), the comfortable setting (n=230; 41.2%; 95%CI 37.1-45.4) and the overt therapy (n=213; 38.2%; 95%CI 34.1-42.4).

The least believed CF selected as ‘enough’ were (in descending order): the adequate design (n=236; 42.3%; 95%CI 38.2-46.5), the professional reputation (n=222; 39.8%; 95%CI 35.7-44.0) and the adequate environmental architecture (n=217; 38.9%; 95%CI 34.8-43.1).

Moreover, the uniform divided the group between those who believed ‘enough’ (n=199; 35.7%; 95%CI 31.7-39.8) and those who believed ‘few’ (n=203; 36.4%; 95%CI 32.4-40.5). An overall description of beliefs towards CFs is presented in Table 3.

Therapeutic effect

‘Physiological and psychological’ effects were the most often therapeutic effects chosen by OMTs in caring for the following health problems (in order): chronic pain (n=436, 78.1%; 95%CI 74.4–81.4), insomnia (n=345; 61.8%; 95%CI 57.6–65.8) and acute pain (n=317, 56.8%; 95%CI 52.6–60.9); as well as in the case of cognitive (n=317; 56.8%; 95%CI 52.6-60.9), rheumatologic (n=313; 56.1%; 95%CI 51.9– 60.2), gastrointestinal (n=307; 55%; 95%CI 50.8-59.2), emotional (n=303; 54.3%; 95%CI 50.1-58.5), sexual (n=295; 52.9%; 95%CI 48.6-57.1) and neurological disorders (n=295; 52.9%; 95%CI 48.6-57.1).

Drug and medication addictions, immune/allergic and cardiovascular problems were considered as sensitive to therapeutic effects due to ‘Physiological and psychological’ (n=238; 42.6%; 95%CI 38.5-46.9; n=204; 36.6%; 95%CI 32.6-40.7; n=253; 45.3%; 95%CI 41.2-49.6 respectively) and ‘Psychological’ (n=187; 33.5%; 95%CI 29.6-37.6; n=170; 30.5%; 95%CI 26.7-34.5; n=156; 28.0%; 95%CI 24.3-31.9). However, about a quarter of OMTs reported that these clinical conditions have ‘No benefit’ from CFs (n=126; 22.6%; 95%CI 19.2-26.3; n=167; 29.9%; 95%CI 26.2-33.9; n=129; 23.1%; 95%CI 19.7-26.9 respectively).

Finally, OMTs indicated the therapeutic effect for oncological problems as predominantly ‘Psychological’ (n=274; 49.1%; 95%CI 44.9-53.3), while they believed mainly in ‘No benefit’ for infectious problems (n=229; 41.0%; 95%CI 36.9-45.3). An overall report of therapeutic effects is presented in Table 4.

Ethical implications

Concerning the ethical use of CFs, the most frequent response was the combination: ‘it exerts beneficial psychological effects’ and ‘clinical experience has

shown the effectiveness' (n=171; 30.6%; 95%CI 26.9-34.7). Moreover, both of these answers particularly, resulted among the most often selected (Fig 2). The least selected items were 'the patient wants or expects this treatment' (n=13; 2.3%; 95%CI 1.3-4.1), 'the other therapies are over' (n=8; 1.4%; 95%CI 0.7-2.9) and their combinations (Fig 2).

With regard to the non-ethical adoption of CFs, the most frequently chosen item was when 'It is based on deception' (n=79; 14.1%; 95%CI 11.4–17.4). Among the answers mostly selected with the higher frequencies there were the six first combinations of multiple items that encompassed more than 50% of our sample (Fig 3).

Differently, the least frequent selected answers were 'it can create adverse effects' (n=20; 3.6%; 95%CI 2.3-5.6), 'it undermines trust between patient and physiotherapist' (n=19; 3.4%; 95%CI 2.1-5.4), 'the evidence is insufficient' (n=11; 2.0%; 95%CI 1.0-3.6), 'legal problems arise' (n=4; 0.7%; 95%CI 0.2-1.9) and their combinations (Fig 3).

Communication

Participants reported higher frequency to 'do not say anything' (n=213; 38.2%; 95%CI 34.1– 42.4) when they were asked about communication and CFs. However, they reported to communicate CFs adoption when 'it is a treatment that can help and will not hurt' (n=114; 20.4%; 95%CI 17.2–24.1), 'it is an effective treatment' (n=36; 6.4%; 95%CI 4.6-8.9). Some combinations indicating the complexity of communication regarding the CFs use also emerged, such as 'do not say anything' plus 'it is a treatment that can help and will not hurt' and 'it is a treatment that can help and will not hurt' plus 'it is an effective treatment' (Fig 4).

The least frequent chosen items with regard to the communication implications of CFs were: ‘it is a treatment that induces a psychological change’ (n=11; 2.0%; 95%CI 1.0-3.6), ‘it can help but you are not sure about its effect’ (n=3; 0.5%; 95%CI 0.1-1.7), ‘it is a treatment without a specific effect’ (n=2; 0.4%; 95%CI 0.1-1.4) and the combinations with other responses (Fig 4).

Circumstances of CFs application and mechanism of action

Regarding the circumstances of CFs application, the most frequent item was ‘as an adjunct to other physical therapy interventions to optimize the clinical responses’ (n=111; 19.9%; 95%CI 16.7–23.5) and the combinations ‘to calm the patient’ plus ‘as an adjunct to other physical therapy interventions to optimize the clinical responses’ (n=105; 18.8%; 95%CI 15.7-22.4). The least frequent answers were ‘to calm the patient’ (n=18; 3.2%; 95%CI 2.0-5.1), ‘for non-specific problems’ (n=5; 0.9%; 95%CI 0.3-2.2), ‘as a result of unjustified and constant demands for physiotherapy interventions’ (n=1; 0.2%; 95%CI 0.0-1.2), ‘when all other therapies are over’ (n=1; 0.2%; 95%CI 0.0-1.2), ‘as a diagnostic tool to differentiate between psychological and physiological problems’ (n=1; 0.2%; 95%CI 0.0-1.2), ‘to control pain’ (n=1; 0.2%; 95%CI 0.0-1.2) and their combinations (Fig 5).

Concerning the mechanism of action behind CFs, OMTs selected heterogeneous responses. The most frequent option was the combination ‘the patient’s expectation’ plus ‘conditioning’ and ‘psychological factors’ (n=44; 7.9%; 95%CI 5.8–10.5) as reported in Fig 6.

Correlation between variables

The correlation between the frequency of use and the beliefs of each CF was poor with a Spearman's $\rho \leq 0.4$ for the following items (in descending order): physical contact with the patient ($\rho=0.39$), overt therapy ($\rho=0.39$), patient's previous experience ($\rho=0.38$), professional reputation ($\rho=0.37$), professional approach to the patient ($\rho=0.36$), patient-centered approach ($\rho=0.36$), verbal communication ($\rho=0.33$), empathetic therapeutic alliance with the patient ($\rho=0.32$), adequate design ($\rho=0.32$), adequate environmental architecture ($\rho=0.29$), and comfortable setting ($\rho=0.26$). Positive weak associations with Spearman's $\rho > 0.40$ were found for the following items: uniform ($\rho=0.48$), patient's expectation and preference ($\rho=0.44$), positive attitudes and optimistic behavior ($\rho=0.43$), and non-verbal communication ($\rho=0.40$). No significant correlations were found between demographic characteristics and responses in all domains.

Discussion

To the best of our knowledge, this is the first study evaluating awareness regarding CFs among physical therapists specialized in OMTs. The findings suggest that the use and the belief about the effectiveness of CFs are related to the specific type of CFs under consideration. Their adoption is in general decided based on clinical circumstance and perception of ethical as a component of the treatment capable of enhancing the effect of the physiotherapy intervention. The underlying mechanism of CFs action is still thought to be a combination of psychological and physiological effects.

Although previous studies have not been conducted in the field, some considerations are possible when comparing our results with a similar survey

performed among other healthcare professions (19-39). In accordance with previous surveys among physicians (25, 28, 29, 32), almost 70.0% of OMTs defined CFs as an intervention without a specific effect, but with a possible non-specific effect. These findings reveal that physical therapists conceptualize the context around the treatment as an incidental element that can occur during treatment (58) instead of a powerful therapeutic tool capable of influencing patients' outcome (59), thus reflecting a lack of knowledge in the field (6).

As emerged from clinical vignette 1, only 40% of Italian OMTs refused TENS or offered an alternative treatment in accordance with the national guidelines for acute low back pain (60). Instead, a 60% of participants valued patients' expectations during the choice of treatment immediately or after a few days, which have been recognized as a CFs capable of increasing the likelihood of clinical success (10, 13). Globally, these findings suggest that both external evidence and patient's expectations influence the OMTs' decision-making, thus embracing the principles of evidence-based practice in physiotherapy (61).

Various responses in term of frequency emerged from clinical vignette 2. Around two out ten OMTs identified the positive healthcare attention as an element capable of reducing pain, remarking the importance of the humanity in clinical practice (11). Others participants reported instead that the decrease of symptom could be explained considering the pain as non-organic but psychological, the patient's suggestibility, the natural course of pathology and their combinations. The psychological nature of some symptoms should be taken into consideration as a source of some unexplained musculoskeletal disorders (62). The suggestibility also represents a psychological trait capable of enhancing placebo effects, thus influencing

the patient's conditions (63); moreover, the natural course of pathology (e.g. spontaneous fluctuations of symptoms) can mask the therapeutic effects of CFs (64).

At overall levels, around seven out ten OMTs reported a high frequency of application of CFs in their daily practice, in line with previous studies among physicians (19-34) and nurses (22, 37-39). Globally, the professional reputation resulted in the least adopted CFs, identifying it as an undiscovered variable enclosed behind the complex concept of professional identity in physiotherapy discipline (65). The dichotomy frequency of use ('daily' vs 'never') reported in some CFs (e.g. uniform, adequate design and adequate environmental architecture) was unexpected. Speculating, the uniform (e.g. white coat) is often imposed in workplaces, thus becoming a CFs not always chosen independently by a physical therapist to influence patient's perception (66). Moreover, the design (e.g. colors of the room) and the environmental architecture (e.g. windows and skylights) are not modifiable infrastructural elements as compared to music, fragrances or temperature (67).

According to physicians' (21, 22, 25, 27-35) and nurses' (22, 37, 38) perspectives, our participating OMTs strongly believed in the actual therapeutic value of CFs. Also in this case, the least believed CFs concerned specific elements of a physical therapist (e.g. professional reputation, uniform) and of healthcare setting (e.g. architecture and design) and this may be associated with a lack of knowledge. In fact these specific CFs have not been included in the national academic curriculum as compared to other elements (e.g. verbal and not verbal communication) (68) and this can have threatened their knowledge. As already documented, the clinician's leadership and the healthcare environment represent all emerging elements of personal branding (69) and marketing position (70) capable of influencing also the therapeutic outcome.

Regarding the therapeutic effect of CFs, OMTs believed in psychological and physiological effects for most of the health problems (e.g. pain conditions). This trend is similar to that reported previously by nurses and physicians who believed in predominantly subjective or a mixture of subjective and objective effects (21, 25, 27, 29, 32-35, 37), depending upon the specific health problems considered (18). Moreover, OMTs reported a variety of responses for some specific clinical conditions: ‘psychological and physiological effects’ combined with ‘psychological’ and ‘no benefit’ (e.g. drug and medication addiction, immune/allergic and cardiovascular); as well as mainly ‘psychological’ (e.g. oncological problems) and ‘no benefit’ (e.g. infectious problems), thus reflecting a possible lack of direct clinical experience in managing these conditions (18).

Concerning the ethical implications of CFs, OMTs considered their use acceptable to enhance positive psychological effects when the clinical experience has shown their effectiveness. However, when CFs are based upon deception, they should be avoided, thus remarking the importance of an ethical application of CFs in the patient-physical therapist encounter (71). As reported in previous surveys (18), nurses (22, 37) and physicians (19-22, 24-29, 31-35) were also in favor towards the use of placebos, and they rarely considered placebos as not allowed or as a treatment that is never permissible.

Furthermore, as previously documented (19, 20, 22, 24-26, 29, 32-35, 37, 39), our participants were not used to communicate the adoption of CFs to their patients or to inform them that the context is an effective addition to the treatment, capable of helping without hurting. The need to disclose to the patient the use of a placebo intervention during the informed consent process is still under debate among clinicians and researchers (72); however, open-label adoption of a placebo is capable

of positively influencing therapeutic outcomes in chronic low back pain (73) and it is appreciated by the patients (74).

As clinical indications, OMTs attributed to CFs a therapeutic role in calming patients and as an adjunctive strategy to physical therapy interventions, thus remarking the value of the contextual component in influencing patient's therapeutic outcomes (6, 59). Instead, reasons reported among other health professions are variable (18) where physician (19, 21, 22, 25, 32) (20, 24, 27, 31, 33-35) and nurses (22, 37) embraced placebos predominantly to gain therapeutic advantage, to calm the patient, to satisfy the patient's request, to avoid conflicts, to distinguish organic from psychogenic problems, to supplement the therapy, to control pain, to treat non-specific symptoms, or use when all other interventions have been ineffective.

Moreover, OMTs presented a multifaceted point of views concerning the mechanisms of action, reporting as most frequent the combination of patient's expectations, conditioning and psychological factors. This heterogeneity can reflect a lack of knowledge toward the topic as already reported by other healthcare providers (22, 24, 25, 27, 28, 31, 32, 34, 35), thus suggesting the need of educational efforts on CFs and on placebo effects (6).

Strengths and weaknesses of the study

A high response rate was achieved (61.6%) as compared to previous studies on placebos (from 40.0% to 60.0%) (19-21, 25, 26), confirming the willingness of Italian OMTs to participate in the web-based cross-sectional survey (43). It was surveyed a specific group of Italian physical therapists with OMT specializations (n= 906) who are educated to manage mainly musculoskeletal disorders in the private healthcare

sector (75). Therefore, their responses may differ from those of non-specialized physical therapists or from those of other physical therapy specialists (33, 75).

A survey instrument was adopted instead of focus groups or interviews to ensure data were collected at the national level, thus reflecting the perspectives of the target population (76). The questionnaire was composed of different items (e.g. closed-ended questions) to increase the likelihood to capture the complexity of the phenomena under study (77). Moreover, clinical vignettes were used despite the fact their validity has been recently questioned (78-80).

Given that data were self-reported and retrospective in nature, recall bias can threaten the validity of the findings (20). Despite the assurance of anonymity, some participants may have misreported their use of CFs (25).

Conclusions

Implications for clinicians, policymakers and researchers

A wide use of CFs in physical therapy practice has emerged among Italian OMTs. To ensure appropriate competence, awareness, and the ethical use of the context, this issue should be included in physical therapy graduate and postgraduate study programs and in professional lifelong learning courses. The research on CFs in physical therapy has to be considered in its early stages. Therefore, further quantitative studies evaluating knowledge, uses, and aptitudes on CFs among non-specialized physical therapists across different countries, are strongly recommended. Moreover, studies comparing CFs beliefs, perspectives, and use among healthcare workers are also suggested. To develop a more comprehensive understanding of the phenomena, there is also a need to investigate patients' perceptions towards CFs in

physical therapy practice as well as clinicians' subjective experience of placebo and nocebo effects.

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Table 1. Participant characteristics (n=558)

Demographic	Values	95%CI
Gender		
Male, n (%)	329 (59.0)	54.7-63.0
Female, n (%)	229 (41.0)	36.9-45.3
Years, average (SD)		
	30.5 (6.5)	30.0-31.1
Italian Region		
North, n (%)	400 (71.7)	67.7-75.3
Centre, n (%)	120 (21.5)	18.2-25.2
South, n (%)	38 (6.8)	4.9-9.3
Years of practice, average (SD)		
	6.8 (5.7)	6.3-7.3
Workplace, n (%)		
Private practice	433 (77.6)	73.9-80.9
Hospital	87 (15.6)	12.7-18.9
Residential care (nursing home)	38 (6.8)	4.9-9.3
Field of work, n (%)		
Musculoskeletal	472 (84.6)	81.3-87.4
Geriatric	45 (8.1)	6.0-10.7
Neurological	36 (6.4)	4.6-8.9
Hearth, Respiratory, Pediatric	5 (0.9)	0.3-2.2
Hours of work per week, n (%)		
0-15	26 (4.7)	3.1-6.8
16-30	102 (18.3)	15.2-21.8
31-45	316 (56.6)	52.4-60.8
46-60	102 (18.3)	15.2-21.8
> 60	12 (2.1)	1.2-3.8

N, number of participants; %, percentage; SD, standard deviation; 95%CI, 95% confidence interval; > ,

more

Table 2. Contextual factors use in clinical practice (n=558)

Contextual factors items ^a	Likert Score	4	3	2	1	0	Unaware
	average	n (%);	n (%);	n (%);	n (%);	n (%);	n (%);
	(95%CI)	95%CI	95%CI	95%CI	95%CI	95%CI	95%CI
A: Professional reputation (e.g. qualification, expertise)	1.7 (1.6-1.9)	90 (16.1); 13.2-19.5	98 (17.6); 14.5-21.0	104 (18.6); 15.5-22.2	42 (7.5); 5.5-10.1	188 (33.7); 29.8-37.8	36 (6.4); 4.6-8.9
A: Uniform (e.g. white coat)	2.2 (2.0-2.3)	215 (38.5); 34.5-42.7	47 (8.4); 6.3-11.1	33 (5.9); 4.2-8.3	30 (5.4); 3.7-5.7	180 (32.3); 28.4-36.3	53 (9.5); 7.3-12.3
A: Positive attitudes and optimistic behavior (e.g. towards a patient's dysfunctions)	3.5 (3.4-3.6)	416 (74.5); 70.7-78.1	80 (14.3); 11.6-17.6	19 (3.4); 2.1-5.4	9 (1.6); 0.8-3.1	32 (5.7); 4.0-8.1	2 (0.4); 0.1-1.4
B: Patient's expectation and preference (e.g. towards a physiotherapy treatment)	3.1 (3.0-3.2)	277 (49.6); 45.4-53.9	173 (31.0); 27.2-35.0	55 (9.9); 7.6-12.7	15 (2.7); 1.6-4.5	37 (6.6); 4.8-9.1	1 (0.2); 0.0-1.2
B: Patient's previous experience (e.g. towards a physiotherapy treatment)	2.8 (2.7-2.9)	183 (32.8); 28.9-36.9	197 (35.3); 31.4-39.4	93 (16.7); 13.7-20.1	31 (5.6); 3.9-7.9	48 (8.6); 6.5-11.3	6 (1.1); 0.4-2.4
C: Verbal communication (e.g. positive messages associated with the treatment)	3.6 (3.5-3.7)	465 (83.3); 79.9-86.3	44 (7.9); 5.8-10.5	15 (2.7); 1.6-4.5	1 (0.2); 0.0-1.2	32 (5.7); 4.0-8.1	1 (0.2); 0.0-1.2
C: Not verbal communication (e.g. posture, gestures, eye contact, facial expressions)	3.4 (3.3-3.5)	374 (67.0); 62.9-70.9	107 (19.2); 16.0-22.7	20 (3.6); 2.3-5.6	11 (2.0); 1.0-3.6	42 (7.5); 5.5-10.1	4 (0.7); 0.2-2.0
C: Empathetic therapeutic alliance with the patient (e.g. active listening)	3.6 (3.5-3.7)	437 (78.3); 74.6-81.6	69 (12.4); 9.8-15.4	19 (3.4); 2.1-5.4	1 (0.2); 0.0-1.2	31 (5.6); 3.9-7.9	1 (0.2); 0.0-1.2
D: Overt therapy (e.g. possibility for the patient to see	3.0	288 (51.6);	128 (22.9);	50 (9.0);	17 (3.0);	59 (10.6);	16 (2.9);

the therapy using a mirror)	(2.9-3.2)	47.4-55.8	19.6-26.7	6.8-11.7	1.8-4.9	8.2-13.5	1.7-4.7
D: Patient-centered approach (e.g. shared-decision of physiotherapy treatment)	3.6 (3.5-3.7)	451 (80.8); 77.3-84.0	59 (10.6); 8.2-13.5	14 (2.5); 1.4-4.3	2 (0.4); 0.1-1.4	32 (5.7); 4.0-8.1	0 (0.0); 0.0-0.0
D: Professional approach to patient (e.g. privacy, punctuality)	3.4 (3.4-3.5)	385 (69.0); 65.0-72.8	103 (18.5); 15.4-22.0	25 (4.5); 3.0-6.6	11 (2.0); 1.0-3.6	30 (5.4); 3.7-7.7	4 (0.7); 0.2-2.0
D: Physical contact with the patient (e.g. touch to inform, assist, prepare, take care)	3.5 (3.4-3.6)	414 (74.2); 70.3-77.7	82 (14.7); 11.9-18.0	16 (2.9); 1.7-4.7	7 (1.2); 0.5-2.7	31 (5.6); 3.9-7.9	8 (1.4); 0.7-2.9
E: Comfortable setting (e.g. little noise, music, fragrances, temperature)	3.1 (3.0-3.2)	327 (58.6); 54.4-62.7	99 (17.7); 14.7-21.2	44 (7.9); 5.8-10.5	15 (2.7); 1.6-4.5	64 (11.5); 9.0-14.5	9 (1.6); 0.8-3.2
E: Adequate environmental architecture (e.g. windows and skylights, supportive indicators)	2.4 (2.2-2.5)	219 (39.2); 35.2-43.4	75 (13.4); 10.8-16.6	56 (10.0); 7.7-12.9	22 (3.9); 2.5-6.0	147 (26.3); 22.8-30.2	39 (7.0); 5.1-9.5
E: Adequate design (e.g. decorations, ornaments and colors)	2.2 (2.1-2.4)	207 (37.1); 33.1-41.3	74 (13.3); 10.6-16.4	52 (9.3); 7.1-12.1	26 (4.7); 3.1-6.8	167 (29.9); 26.2-33.9	32 (5.7); 4.0-8.1

%, percentage; n, number of participants; 95%CI, 95% confidence interval; 0, never; 1, around once per year; 2, around once per month; 3,

around once per week; 4, daily; A: physical therapist domain; B: patient domain; C: physical therapist - patient relationship domain; D: therapy domain; E: healthcare setting domain.

^a The items were reported from: Testa M, Rossetini G. Enhance placebo, avoid nocebo: How contextual factors affect physiotherapy outcomes.

Man Ther. 2016;24:65-74.

Table 3. Beliefs regarding contextual factors (n=558)

Contextual factors items^a	Likert Score average (95%CI)	4 n (%); 95%CI	3 n (%); 95%CI	2 n (%); 95%CI	1 n (%); 95%CI	0 n (%); 95%CI	Unknown n (%); 95%CI
A: Professional reputation (e.g. qualification, expertise)	2.4 (2.3-2.5)	79 (14.2); 11.4-17.4	171 (30.6); 26.9-34.7	222 (39.8); 35.7-44.0	66 (11.8); 9.3-14.9	8 (1.4); 0.7-2.9	12 (2.1); 1.2-3.8
A: Uniform (e.g. white coat)	1.6 (1.5-1.7)	10 (1.8); 0.9-3.4	76 (13.6); 10.9-16.8	199 (35.7); 31.7-39.8	203 (36.4); 32.4-40.5	58 (10.4); 8.0-13.3	12 (2.1); 1.2-3.8
A: Positive attitudes and optimistic behavior (e.g. towards a patient's dysfunctions)	3.1 (3.1-3.2)	203 (36.4); 32.4-40.5	238 (42.6); 38.5-46.9	97 (17.4); 14.4-20.8	18 (3.2); 2.0-5.1	0 (0); 0.0-0.8	2 (0.4); 0.1-1.4
B: Patient's expectation and preference (e.g. towards a physiotherapy treatment)	3.1 (3.0-3.1)	189 (33.9); 30.0-38.0	240 (43.0); 38.9-47.2	107 (19.2); 16.0-22.7	18 (3.2); 2.0-5.1	2 (0.4); 0.1-1.4	2 (0.4); 0.1-1.4
B: Patient's previous experience (e.g. towards a physiotherapy treatment)	2.8 (2.7-2.9)	122 (21.9); 18.5-25.6	244 (43.7); 39.6-48.0	147 (26.3); 22.8-30.2	36 (6.4); 4.6-8.9	3 (0.5); 0.1-1.7	6 (1.1); 0.4-2.4
C: Verbal communication (e.g. positive messages associated with the treatment)	3.3 (3.3-3.4)	266 (47.7); 43.5-51.9	219 (39.2); 35.2-43.4	54 (9.7); 7.4-12.5	11 (2.0); 1.0-3.6	1 (0.2); 0.0-1.2	7 (1.2); 0.5-2.7
C: Not verbal communication (e.g. posture, gestures, eye contact, facial expressions)	3.1 (3.1-3.2)	205 (36.7); 32.7-40.9	236 (42.3); 38.2-46.5	85 (15.2); 12.4-18.5	19 (3.4); 2.1-5.4	2 (0.4); 0.1-1.4	11 (2.0); 1.0-3.6
C: Empathetic therapeutic alliance with the patient (e.g. active listening)	3.5 (3.4-3.6)	332 (59.5); 55.3-63.6	175 (31.4); 27.6-35.4	36 (6.4); 4.6-8.9	10 (1.8); 0.9-3.4	0 (0); 0.0-0.8	5 (0.9); 0.3-2.2
D: Overt therapy (e.g. possibility for the patient to	2.6	102 (18.3);	213 (38.2);	161 (28.8);	38 (6.8);	20 (3.6);	24 (4.3);

see the therapy using a mirror)	(2.5-2.7)	15.2-21.8	34.1-42.4	25.2-32.8	4.9-9.3	2.3-5.6	2.8-6.4
D: Patient-centered approach (e.g. shared-decision of physiotherapy treatment)	3.4 (3.4-3.5)	312 (55.9); 51.7-60.1	194 (34.8); 30.8-38.9	40 (7.2); 5.2-9-7	10 (1.8); 0.9-3.4	0 (0); 0.0-0.8	2 (0.4); 0.1-1.4
D: Professional approach to patient (e.g. privacy, punctuality)	2.7 (2.6-2.8)	108 (19.3); 16.2-22.9	239 (42.8); 38.7-47.1	157 (28.1); 24.5-32.1	41 (7.3); 5.4-9.9	6 (1.1); 0.4-2.4	7 (1.2); 0.5-2.7
D: Physical contact with the patient (e.g. touch to inform, assist, prepare, take care)	3.0 (3.0-3.1)	158 (28.3); 24.6-32.3	274 (49.1); 44.9-53.3	75 (13.4); 10.8-16.6	26 (4.7); 3.1-6.8	1 (0.2); 0.0-1.2	24 (4.3); 2.8-6.4
E: Comfortable setting (e.g. little noise, music, fragrances, temperature)	2.6 (2.5-2.6)	65 (11.6); 9.2-14.7	230 (41.2); 37.1-45.4	201 (36.0); 32.1-40.2	33 (5.9); 4.2-8.3	10 (1.8); 0.9-3.4	19 (3.4); 2.1-5.4
E: Adequate environmental architecture (e.g. windows and skylights, supportive indicators)	2.2 (2.1-2.3)	38 (6.8); 4.9-9.3	162 (29.0); 25.3-33.0	217 (38.9); 34.8-43.1	92 (16.5); 13.6-19.9	15 (2.7); 1.6-4.5	34 (6.1); 4.3-8.5
E: Adequate design (e.g. decorations, ornaments and colors)	2.1 (2.0-2.2)	35 (6.3); 4.5-8.7	134 (24.0); 20.6-27.8	236 (42.3); 38.2-46.5	101 (18.1); 15.0-21.6	18 (3.2); 2.0-5.1	34 (6.1); 4.3-8.5

%, percentage; n, number of participants; 95%CI, 95% confidence interval; 0, not at all; 1, few; 2, enough; 3, much; 4, a lot of; A: physical therapist domain; B: patient domain; C: physical therapist - patient relationship domain; D: therapy domain; E: healthcare setting domain.

^a The items were reported from: Testa M, Rossetini G. Enhance placebo, avoid nocebo: How contextual factors affect physiotherapy outcomes.

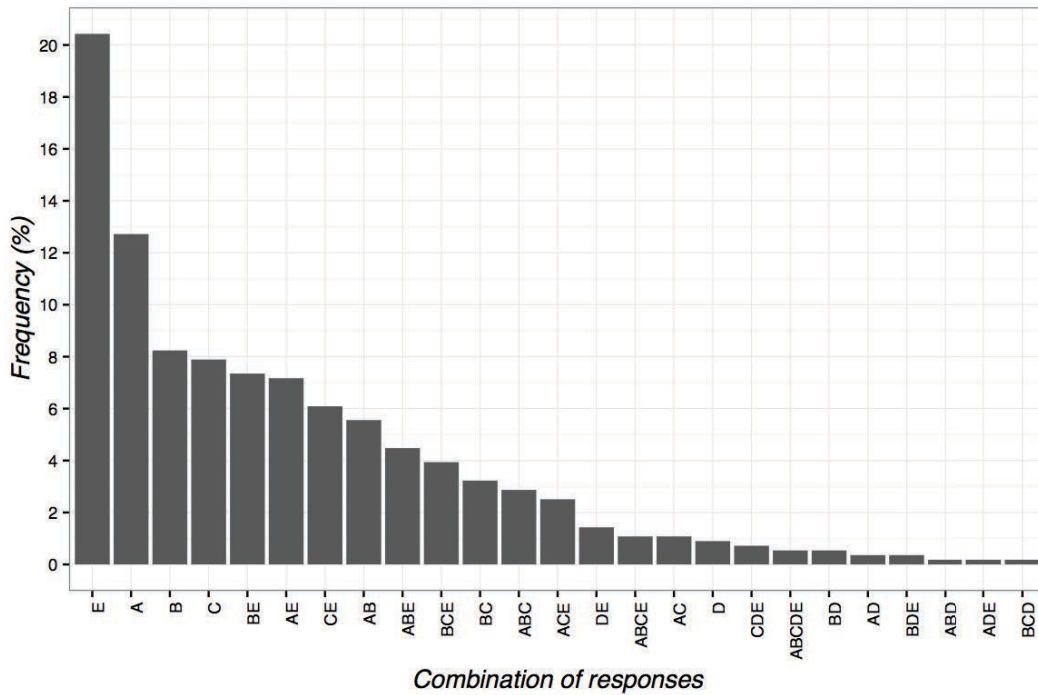
Man Ther. 2016;24:65-74.

Table 4. Therapeutic effect(s) of contextual factors (n=558)

Clinical conditions	Psychological and Physiological n (%); 95%CI	Physiological n (%); 95%CI	Psychological n (%); 95%CI	No benefit n (%); 95%CI
Chronic pain	436 (78.1); 74.4-81.4	12 (2.1); 1.2-3.8	104 (18.6); 15.5-22.2	6 (1.1); 0.4-2.4
Insomnia	345 (61.8); 57.6-65.8	4 (0.7); 0.2-1.9	167 (29.9); 26.2-33.9	42 (7.5); 5.5-10.1
Acute pain	317 (56.8); 52.6-60.9	26 (4.7); 3.1-6.8	164 (29.4); 25.7-33.4	51 (9.1); 6.9-11.9
Cognitive disorder	317 (56.8); 52.6-60.9	8 (1.4); 0.7-2.9	230 (41.2); 37.1-45.4	3 (0.5); 0.1-1.7
Rheumatologic problem	313 (56.1); 51.9-60.2	19 (3.4); 2.1-5.4	170 (30.5); 26.7-34.5	56 (10.3); 7.7-12.9
Gastrointestinal problem	307 (55); 50.8-59.2	21 (3.8); 2.4-5.8	112 (20.1); 16.9-23.7	118 (21.1); 17.9-24.8
Emotional disorder	303 (54.3); 50.1-58.5	10 (1.8); 0.9-3.4	232 (41.6); 37.5-45.8	13 (2.3); 1.3-4.1
Sexual problem	295 (52.9); 48.6-57.1	9 (1.6); 0.8-3.1	151 (27.1); 23.5-31.0	103 (18.5); 15.4-22.0
Neurological problem	289 (51.8); 47.6-56.0	10 (1.8); 0.9-3.4	155 (27.8); 24.1-31.7	104 (18.6); 15.5-22.2
Cardiovascular problem	253 (45.3); 41.2-49.6	20 (3.6); 2.3-5.6	156 (28.0); 24.3-31.9	129 (23.1); 19.7-26.9
Drug and medication addiction	238 (42.6); 38.5-46.9	7 (1.2); 0.5-2.7	187 (33.5); 29.6-37.6	126 (22.6); 19.2-26.3
Immune/allergic problem	204 (36.6); 32.6-40.7	17 (3.0); 1.8-4.9	170 (30.5); 26.7-34.5	167 (29.9); 26.2-33.9
Oncological problem	195 (34.9); 31.0-39.1	7 (1.2); 0.5-2.7	274 (49.1); 44.9-53.3	82 (14.7); 11.9-17.8
Infectious problem	123 (22.0); 18.7-25.8	17 (3.0); 1.8-4.9	189 (33.9); 30.0-38.0	229 (41.0); 36.9-45.3

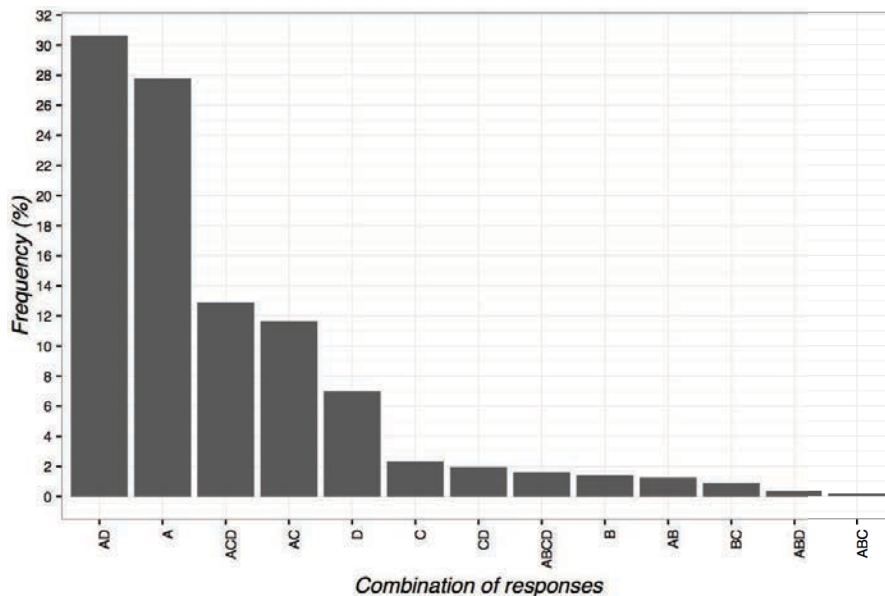
- %, percentage; n, number of participant; 95%CI, 95% confidence interval

Fig 1. Percentages of responses for clinical vignette 2.



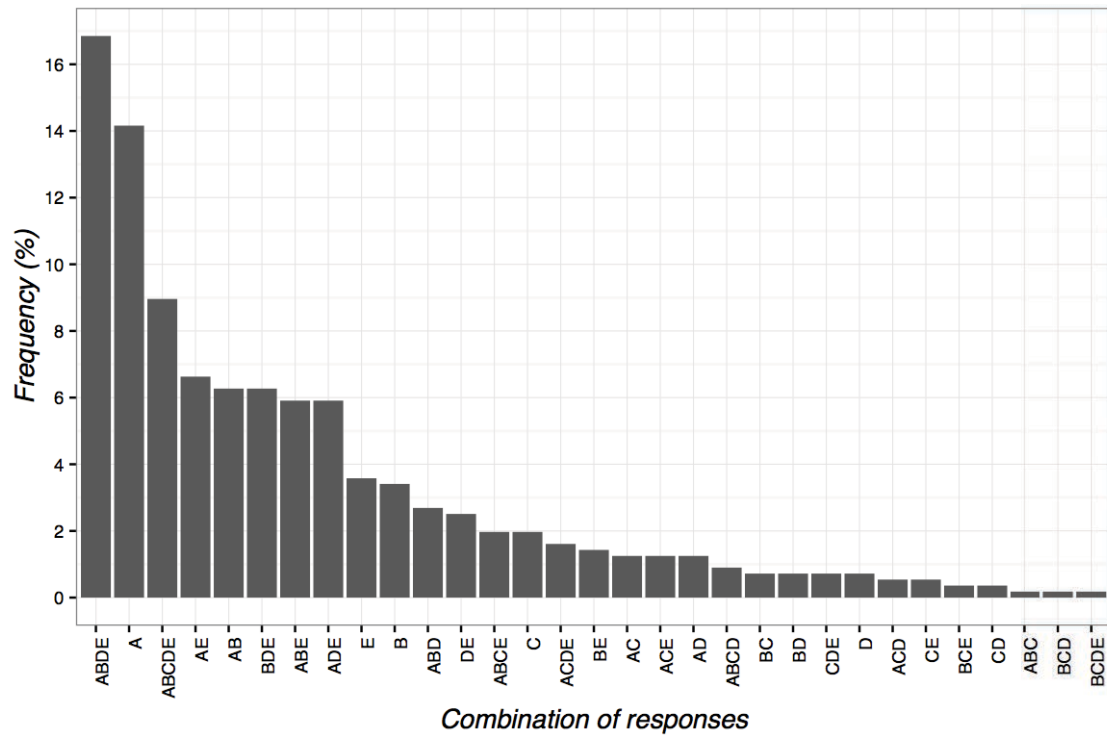
A: the pain as non-organic but psychological, B: the patient as very suggestible, C: the natural decrease of pain intensity, D: the patient provides the expected response by the physical therapist, E: the positive attention of the healthcare team leads to decreased pain.

Fig 2. Percentages of responses for ethical use of contextual factors.



A: it exerts beneficial psychological effects, B: the other therapies are over, C: The patient wants or expects this treatment, D: Clinical experience has shown the effectiveness.

Fig 3. Percentages of responses for not-ethical use of contextual factors.



A: it is based on deception, B: it undermines trust between patient and physical therapist, C: the evidence is insufficient, D: legal problems arise, E: it can create adverse effects.

Fig 4. Percentages of responses for communication to patients implications of contextual factors.

S1 Appendix. The questionnaire: “Knowledge about contextual factors among Italian physical therapists specialized in manual therapy (OMTs).”

Welcome to this survey!

Dear colleague thank you for taking part in this survey.

This survey aims to clarify the use of *contextual factors* in enhancing the therapeutic outcome in physiotherapy.

The contextual factors consist of a series of relational or environmental situations that may affect the perception of patients' suffer and functional impairment. Examples of the main contextual factors are: the words and posture used by the physical therapist, the smells, the sounds and the decor of the therapeutic setting to enhance the effectiveness of physiotherapy.

We consider important to study them in their spread within physiotherapy practice.

Kindly answer the following questions based on your personal clinical experience.

The compilation of the entire questionnaire is voluntary and requires 10 to 15 minutes. Your answers are completely anonymous and will only be used for the purposes of this research.

By clicking on the link to the survey, you provide your consent to participate in the study. Whenever you complete the page, click on "Next" to save your answer. If you decide to abandon the survey, select "Exit".

Socio-demographic characteristics

What is your gender? [select]

- Male
- Female

How old are you? [complete]

.....

How long have you licensed as physical therapist? [complete]

.....

In which region of Italy do you work? [select]

- North
- Center
- South

What is your clinical workplace? [select]

- Hospital
- Residential care (nursing home, RSA)
- Private practice

What is your field of intervention? [select]

- Geriatric
- Neurological
- Musculoskeletal

- Hearth, Respiratory, Pediatric

How many hours do you work for each week? [select]

- 0-15
- 16-30
- 31-45
- 46-60
- > 60

Clinical vignettes

Clinical vignette 1

A man of 40 years, freelancer, visits your clinic complaining low back pain. He requests a TENS therapy to return to work more quickly. Based on clinical examination, you don't find contraindications for the use of TENS, but you know that in this case there is no indication to use this therapy. The patient insists to require TENS, on the grounds that this therapy helped him in the past during a previous episode of low back pain.

What would you do in this situation? [select]

- deliver TENS
- suggest the possibility of delivering the TENS if the clinical condition fails to improve
- try to convince the patient of the futility of TENS
- advise a different treatment commonly used for low back pain
- advise a follow-up appointment on the following days

- tell the patient that low back pain would resolve itself in a few days

Clinical vignette 2

In a hospital, a patient with important shoulder pain receives TENS therapy several times a day on demand. For frequent requests occasionally therapy is replaced with sham T.E.N.S. (with power-off). The patient reports that in each case the TENS (whether active or sham) improve the clinical condition.

What conclusion can be drawn about the effectiveness of TENS sham? [More answers are possible]

- the positive attention of the healthcare team leads to decreased pain
- the pain is non-organic but psychological
- the patient is very suggestible
- the natural decrease of pain intensity
- the patient provides the expected response by the physical therapist

Frequency of use (1/2)

How often in your career do you INTENTIONALLY used the contextual factors to enhance the result of physiotherapy? [select]

- many times
- often
- at least once
- never

Frequency of use (2/2)

Indicate how often do have you INTENTIONALLY used the following contextual factors with the patient to enhance the physiotherapy

outcome: [select]

	Every day	Around once a week	Around once a month	Around once a year	Never	I did not aware it was a contextual factor capable to influence therapeutic outcome
Professional reputation						
Uniform						
Positive attitudes and optimistic behavior						
Patient's expectation and preference						
Patient's previous experience						
Verbal communication						
Not verbal communication						
Empathetic therapeutic alliance with the patient						
Overt therapy						
Patient-centered approach						
Professional approach to patient						
Physical contact with the patient						
Comfortable setting						
Adequate environmental architecture						
Adequate design						

Beliefs

How do you BELIEVE that your therapeutic outcome can be influenced by ...? [select]

	Very Much	Much	Enough	Few	None	I don't know
Professional reputation						
Uniform						
Positive attitudes and optimistic behavior						
Patient's expectation and preference						
Patient's previous experience						
Verbal communication						
Not verbal communication						
Empathetic therapeutic alliance with the patient						
Overt therapy						
Patient-centered approach						
Professional approach to patient						
Physical contact with the patient						
Comfortable setting						
Adequate environmental architecture						
Adequate design						

Ethical issues

The use of contextual factors for therapeutic purposes can be considered

ETHICALLY ACCEPTABLE when ... [you can select more than one answer]

- it exerts beneficial psychological effects
- the other therapies are over
- the patient wants or expects this treatment
- clinical experience has shown the effectiveness

The use of contextual factors for therapeutic purposes can be considered

ETHICALLY NOT ACCEPTABLE when ... [you can select more than one answer]

- it is based on deception
- it undermines trust between patient and physical therapist
- the evidence is insufficient
- legal problems arise
- it can create adverse effects

Communication and application

How do you COMMUNICATE to the patient the use of contextual factors at the

end of treatment? The notified its ... [you can select multiple possibilities]

- it is a treatment that can help and will not hurt
- it is an effective treatment
- do not say anything
- it is a treatment without a specific effect
- it is a treatment that induces a psychological change
- it can help but you are not sure about its effect.

Under what CIRCUMSTANCES would you use contextual factors? [you can select multiple possibilities]

- as a result of unjustified and constant demands for physiotherapy interventions
- to calm the patient
- when all other therapies are over
- as an adjunct to other physical therapy interventions to optimize the clinical responses
- for non-specific problems
- to stop the patient's complaints
- as a diagnostic tool to differentiate between psychological and physiological problems
- to control pain
- to gain time

Mechanism of action, therapeutic effect and definition

What MECHANISMS OF ACTION can explain the effect of contextual factors?

[you can select multiple possibilities]

- patient's expectation
- conditioning
- suggestibility
- natural history of disease
- psychological factors
- unexplained
- physiological/biological factors
- spiritual energies

- mind-body connections

*What are, in your opinion, the **POTENTIAL EFFECTS** of contextual factors in the following health problems? [select]*

	Psychological	Physiological	Psychological and Physiological	No benefit
acute pain				
chronic pain				
cognitive disorder				
emotional disorder				
gastrointestinal disorder				
sexual disorder				
drug and medication addiction				
neurological disorder				
rheumatologic disorder				
immune/allergic disorder				
oncological disorder				
cardiovascular disorder				
infectious				
insomnia				

How would you define, in the light of this survey, the therapeutic role of contextual factors? [select]

- an intervention without a specific effect for the condition being treated, but with a possible aspecific effect
- an intervention that has a special effect through known physiological mechanisms
- sham treatment used as control tests for safety and efficacy of active treatment
- a harmless or inert intervention

Dear colleague thanks for spending your precious time in completing this survey!

CHAPTER V

MANUAL THERAPY RCTS: SHOULD WE CONTROL PLACEBO IN PLACEBO CONTROL?

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Manual therapy RCTs: should we control placebo in placebo control?

Dear Editor,

We have read with interest the paper by Bautista-Aguirre and colleagues recently published in the European Journal of Physical and Rehabilitation Medicine (1).

The authors in their randomized controlled trial (RCT) have compared, in patients with chronic mechanical neck pain, the efficacy of the high-velocity low-amplitude thrust technique directed to the cervical or the thoracic spine with a *placebo* control. The placebo intervention consisted in a sham-manual contact applied over the lateral sides of the cranium, with a “five-finger hold” and with no movement or therapeutic intention. Interestingly, their findings have revealed a lack of clinically relevant differences on neural mechanosensitivity of upper limb nerve trunks and grip strength between groups, thus suggesting a role of *placebo* in the modulation of outcomes. This valuable study offers the research community a starting point of reflection about three main features associated with *placebo* intervention when adopted as control in manual therapy and stimulates considerations of possible strategies to go beyond the limits.

Firstly, conceptualising the *placebo* control as inactive, inert or false could be not adequate. Despite the lack of a specific therapeutic action, *placebo* control can elicit real psychobiological responses. These responses, that are the result of well-known mechanisms, involving neurotransmitters (endogenous opioids, dopamine, cannabinoids, oxytocin and vasopressin) and key brain areas (the dorsolateral prefrontal cortex, the rostral anterior cingulate cortex, the periaqueductal grey and the spinal cord), are able to influence the patient’s symptoms, such as pain, anxiety and motor performance (2).

Secondly, continuing to discretionarily choose a *placebo* control could hide a pitfall. Although up-to-date systematic review recognized the use of heterogeneous typology of *placebo* control in manual therapy such as hands-on techniques (e.g. light touch, gentle touch), physical modalities (e.g. ultrasound, laser) and mixed procedures (3), researchers should choose a sham comparator as much as possible indistinguishable from the active treatment. Aspects like patient and provider positioning and contact, movement induced on the patient's body, mechanical thrusting applied to the patient and sound of cavitation should be carefully balanced between experimental and control groups (4).

Thirdly, considering the clinical modifications induced in patients as exclusively dependent on the so-called "intervention" (both inactive or active), and neglecting the contextual factors surrounding the setting of the intervention could be a fault. Indeed, every intervention is administered in a psychosocial arena that is composed also by contextual factors, such as therapeutic signs and rituals, the encounter between patient and provider, the verbal and non-verbal interaction, the behaviour and appearance of provider and the expectation of patient. *Placebo* control includes a contact between provider and patient, it is administered in an environment created for the active intervention and is, therefore, similarly influenced by contextual factors (5).

The designing of the administration of a *placebo* control in RCTs on manual therapy efficacy is far more complex than administration of *placebo* control in RCT assessing drugs efficacy (3). Manual treatment presents specific and contextual elements intimately encapsulated that interact with each other, and are difficult to separate when planning a RCT (4). From a research perspective, to neglect the contextual factors component of the *placebo* control and its capacity to influence the therapeutic outcome could bias the results, underestimating or overestimating the differences between the

treatment and *placebo* conditions and reducing the possibility to highlight the real weight of the specific intervention (5) (figure 1).

To manage these challenges when designing an RCT on manual therapy, investigators could:

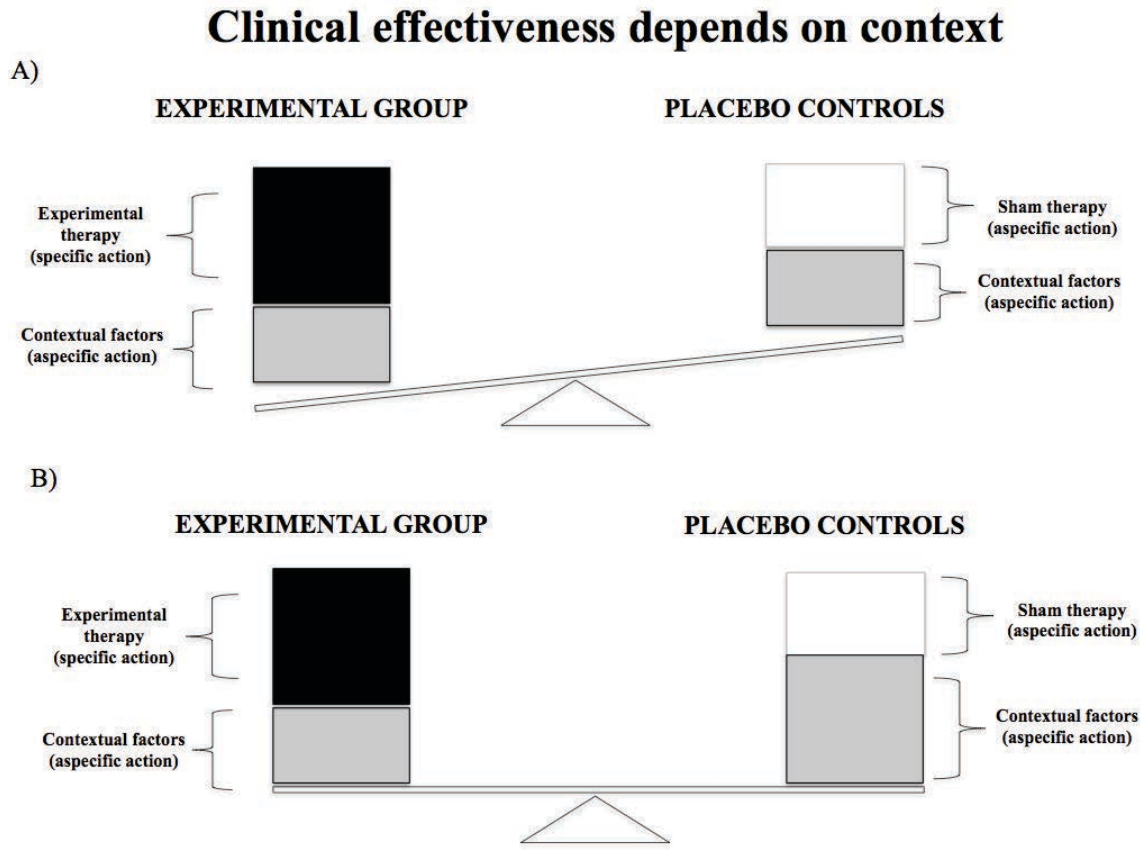
- a) balance the contextual factors across the intervention and control groups (4). For example, the modality of administration, the feature of the healthcare settings, the behaviour and presence of the clinicians, the verbal instruction given to the patient. The social interaction of patients and the amount of contact time should be controlled as much as possible to be structurally equivalent and comparable in order to offer similar context between experimental and control groups (3).
- b) improve the details of a sham procedure in the control group (4). For example, the sham dosage (i.e., duration, session, period); the sham procedures (i.e., protocol-based or personalised, type of approach); and sham operator (type of practitioner, number of operators, operator's years of experience, training for practitioner, operator background, supervision/tutoring) should be reported similarly between experimental and control groups (5).

Placebo control in physical and rehabilitation medicine continues to represent an intriguing topic still debated from both, theoretical and practical perspective. Even more than in other research fields, manual therapy researchers should change their mind about *placebo* as inert treatment, start to consider *placebo* as therapeutically active treatment and take care of all the aspects that determine its influence on clinical outcomes, such as contextual factors. We think that time has come to reconsider the design of RCTs in physiotherapy and manual therapy to better measure the power of our therapeutic solutions and increase the internal and external validity of our findings.

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Figure 1. Clinical effectiveness depends on context.



A) Balanced use of contextual factors. When contextual factors were adequate controlled among experimental and control groups, is it possible to observe the specific action of the experimental therapy.

B): Unbalanced use of contextual factors. When contextual factors were overbalanced among experimental and control groups, a bias could occur limiting the specific action of the experimental therapy.

GENERAL DISCUSSION

Every chapter of this thesis contains a thorough discussion concerning the specific topic investigated. In this last section some critical points, which emerged from the discussions of each chapter, are analysed, offering some suggestions that may be helpful for future developments and implementation of the contextual factors model in clinical practice and research in physical therapy.

Implication for physical therapy discipline

As demonstrated in this PhD project, the contextual factors may represent useful therapeutic tools capable, in their entirety, of affecting the physical therapy discipline. From a *clinical perspective*, the use of the contextual factors with the best evidence-based therapy represents an opportunity to enhance placebo effects and to avoid nocebo effects, influencing the whole therapeutic outcome in full compliance with ethical code and conduct (1, 2). The contextual factors help clinicians to interpret the patients' clinical picture and to unravel the conundrum of underlying complaints, thus explaining some unexpected outcomes and variability of symptoms (3, 4). Moreover, physical therapists who consider the context as an influencer of therapeutic outcome can critically evaluate their therapeutic solutions and also accept potentiality and limits of their profession (5).

From a *policy perspective*, contextual factors represent important elements to be considered to understand the complexity of modern health systems (6). At multiple levels, stakeholders, organizations and governments should take into account the context around the healthcare as an element that can affect effectiveness and quality of

care, to encourage its assessment and analysis in clinical settings (7). For example, the context around the treatment can impact the overall patients' satisfaction and their perceptions of their health care experiences, so as to enhance the attractiveness of a specific healthcare service, guiding the patient to choose, return to and recommend it, and to improve the compliance towards treatments and follow-up (8). Moreover, the investigation of the dynamic interactions among health, personal, organizational and contextual variables can help to identify problems, to improve healthcare processes, to define appropriate policies and to allocate resources (9, 10).

From an *academic perspective*, contextual factors (e.g. patient-clinician relationship) embody useful elements, the awareness and the practice of which have to be strengthened in the teaching programs and activities during the university training, in order to prepare the students for a better management of the psychosocial component of disease during internships (11). In medical education, contextual factors help student to consider the therapeutic outcome as a product of the interactions between clinicians, patients and setting as a complex, not predictable and nonlinear system that evolves over time (12). In addition, recent findings have proposed the contextual factors as capable to impact the clinician's clinical reasoning performance during diagnostic and therapeutic process (13-15), thus offering to mentors and teachers a further didactic topic for the improvement of students' clinical competences (16).

Implication for future studies

The results of the present PhD project represent a starting point for future researches in physical therapy, part of which has already been initiated in the scientific world. The possibility to study the contextual factors, placebo and nocebo effects allows

the scientific community to measure their impact on different outcomes and in different musculoskeletal conditions, through primary studies.

A first line of research aims to identify the best placebo comparator for different manual therapy treatments. Various studies tried to develop (17, 18) and validate (19-21) a sham placebo procedure, however many complications challenged this research, due to the difficulty of controlling the subjects' blinding, the expectations and the a priori inertness of the sham procedure (22-24). Recently a novel sham procedure had been validated (25) and applied in clinical setting in patients with migraine (26) and cervicogenic headache (27), thus opening the possibility of investigations, the results of which are expected in the following 3 years.

A second line of research should analyse the active mechanism of action of contextual factors. Despite the creation of an adequate trial design remains a challenge in placebo and nocebo research (28, 29), randomized clinical trials are planned in the next years to measure the impact of contextual factors on different therapeutic outcomes in various musculoskeletal conditions (30). This research approach could be developed through the comparison of the same physical therapy treatment performed in a neutral and enriched context, to measure the change of subjective (e.g. pain and disability) and objective (e.g. strength) outcomes (31, 32).

A third line of research can explore the patient's point of view concerning the contextual factors. Indeed, survey (33-35) and qualitative interview (36-39) have been adopted to study the patient's perspective regarding the ethics and the acceptability of placebo treatments. To date, no studies of that kind have been performed in Italy, thus opening a window of opportunity for similar investigations there. Furthermore, an item bank of contextual factors has been proposed to assess the healthcare experience and attitudes from the patient's perspective (40). This recent finding offers a starting point

for the creation of a questionnaire, to classify the patients on the basis of their preferences about contextual factors, to guide clinicians on enriching the physical therapy treatment with a specific contextual element.

Strength and limitations of the PhD project

The use of different study designs represents the strength of this PhD project. The contextual factors have been investigated using a clear and defined methodology as reported in chapter III (systematic review of qualitative studies using a metasynthesis and metasummary approach) and chapter IV (national online survey), thus reducing the possible source of bias and improving the overall quality of the project (41, 42). Moreover, the topic has been discussed using a multidisciplinary broad-spectrum analysis ranging from clinical to research points of view, helping the reader to understand the topic from different perspectives and increasing the PhD student's reflective process (43).

The creation of the conceptual model of contextual factors through non systematic-review methods for physiotherapy outcomes (chapter I), for musculoskeletal pain (chapter II), and for clinical trial research (chapter V) could represent a possible weakness of this PhD project. However, narrative review, debate and letter to the editor have been considered an accepted method for discussion (42) and have been previously adopted as a model in placebo, nocebo and contextual factors research (44-47).

Conclusion

The aim of this PhD project has been to investigate the relevance of contextual factors as triggers of placebo, nocebo effects and their impact on therapeutic outcome in

physical therapy. This goal has been achieved through different study designs, in order to present the contextual factors as a general conceptual model for physical therapy practice.

Three main findings emerged:

- 1) The contextual factors affect the different physical therapy outcomes such as pain and patients' satisfaction;
- 2) Italian physiotherapists deliberately use contextual factors in their daily practice, and believe they have therapeutic effects;
- 3) The contextual factors represent elements to be carefully considered while designing clinical trials.

In summary, the research on contextual factors as triggers of placebo and nocebo effects is at an early stage, and it represents a vast area for further investigation.

This translational approach includes an opportunity of growth for the whole physical therapy profession.

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APPENDIX

In the Appendix, different corollary papers, conducted during the three years of this PhD are presented. The contextual factors model was adapted in the nursing field. After this, the knowledge, attitude and behaviour of Italian nurses regarding contextual factors were examined. Finally, the context effect was investigated in motor performance. All the presented research has been reported in abstracts or full-text papers.

APPENDIX I

THE IMPACT OF CONTEXTUAL FACTORS ON NURSING OUTCOMES AND THE ROLE OF PLACEBO/NOCEBO RESPONSES: A DISCUSSION PAPER

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The impact of contextual factors on nursing outcomes and the role of placebo/nocebo responses: a discussion paper

Abstract

Placebo and nocebo responses represent one of the most fascinating topics in the healthcare field. The placebo response (from Latin “I shall please”) is a beneficial outcome(s) triggered by a positive context. The opposite is the nocebo response (from Latin “I shall harm”), which indicates an undesirable outcome(s) triggered by a negative context. Both are complex and distinct psycho-neurobiological phenomena in which behavioural and neurophysiological changes arise subsequent to an interaction between the patient and the healthcare context. Placebo and nocebo concepts have been recently introduced in the nursing discipline, generating a wide debate on ethical issues; however, nursing implications of education, clinical practice, nursing administration and research regarding contextual factors triggering nocebo and placebo effects, have not been debated to date. Therefore, the aims of this discussion paper were: (a) to briefly introduce the placebo and nocebo mechanisms and responses, (b) to elucidate the contextual factors capable of triggering placebo and nocebo responses in the nursing field, and (c) to debate implications of contextual factors at the nursing education, practice, organisational and research levels.

Introduction

Placebo and nocebo responses represent one of the most fascinating topics in the healthcare field. They constitute two multifaceted phenomena in which psychoneurobiological modifications arise after an interaction between the patient and the context. While the placebo response (from Latin placēbō, “I shall please”) represents a beneficial outcome(s) produced by a positive context (1), the nocebo response (from Latin nocēbō, “I shall harm”) expresses an undesirable outcome(s) produced by a negative context (2).

In the medical literature, the concept of placebo has been debated since 1941 (3), specifically in the field of medication administration, and was introduced as a Medical Subject Heading (MeSH) in 1990. On the other hand, the concept of nocebo was introduced by Kennedy in 1961 and recognised as a MeSH only in 2014. In the nursing discipline, while placebo was introduced in 1966 (4), nocebo was formally introduced in the literature only eight years ago (5).

Moreover, both concepts have generated a wide debate mainly regarding ethical issues (6, 7) despite that they have been proposed as promising clinical tools useful in modulating nursing outcomes (8, 9). According to the most recent review in the field, primary studies on nocebo effects have not been summarised to date (8, 9).

In recent years, the investigation of placebo and nocebo responses have been included the evaluation of the context supporting the patient in achieving (or not) the desired health outcomes (10). As a consequence, the misleading interpretation of placebo as inert treatment given to comfort or please the patient have been overcome; differently, the modern conceptualization of the placebo and nocebo responses as the psychosocial context that accompanies any healthcare intervention, be it active or sham, have been embraced (11-13).

The context is composed by the “*whole atmosphere around the therapy*” (14) created by the health-care team, technologies and settings. Recently, specific contextual factors have been proposed in the literature as potential triggers of placebo and nocebo responses (11, 15). As suggested by Di Blasi, Harkness, Ernst, Georgiou, and Kleijnen (16) these factors are embodied at different levels: a) provider and patient features, b) patient-provider relationship (e.g. empathy), c) intervention (e.g. colour and shape of a medication), and d) healthcare setting (e.g. home or hospital, room layout). These factors constitute the therapeutic ritual and healing symbols surrounding the encounter capable of triggering placebo and nocebo responses, impacting the patient’s physiology and psychology and, ultimately, influencing the expected clinical outcome (17, 18).

Since a boost of placebo and prevention of nocebo would be valuable for nursing practice, this discussion paper aimed to: (a) briefly introduce the placebo and nocebo mechanisms and responses, (b) elucidate the contextual factors capable of triggering placebo and nocebo responses in the nursing field, and (c) debate implications at the nursing education, practice, organisational and research levels.

Placebo and nocebo mechanisms and responses

Placebo and nocebo responses have been used as a model to investigate the human body systems, analysing their interaction with different systems, mechanisms, diseases and therapeutic interventions (19). Specifically, placebo and nocebo responses have been studied in mood, cardiovascular, respiratory, gastrointestinal, motor, immune and endocrine systems (20-22). However, pain represents the most investigated symptom of placebo and nocebo responses (2, 23) as reported in Figure 1. The factors explaining placebo and nocebo responses, have been identified at the individual levels and at the context levels.

Individual and psychological factors

At the individual level, early stages of the research aimed at evaluating the role of some genetic variants were established as relevant in placebo and nocebo responses but the available findings are not conclusive (24). Preliminary evidence regarding that goal-seeking, self-efficacy/esteem, the locus of control, optimism, fun seeking, sensation seeking, neuroticism, suggestibility, beliefs and body consciousness, can all act as trait predictors of placebo responses (25), differently, anxiety, panic disorder or pessimism can exacerbate nocebo responses (9). However, more evidence is available regarding the role of psychological determinants such as expectations and learning (26, 27).

An expectation represents a conscious element through which the patient expects a beneficial or harmful outcome based upon the evaluation of contextual factors such as verbal instructions (e.g. communication associated with interventions provided by the nurse) or past experiences (e.g. previous interaction with a nurse) (26). The expectations are capable of creating modifications through the influence of the reward mechanism and anxiety and can be further influenced by emotional and cognitive factors, such as self-efficacy, self-reinforcing feedback, memory, attention and motivation (19, 20, 28).

Learning encompasses associative, social and reinforced expectation mechanisms (27). Associative learning emerges when a conditioned neutral stimulus such as a contextual factor (e.g. the colour of a medication) is associated with an unconditioned stimulus (e.g. the active molecules contained in the medication), and it is capable of modulating the symptom even when the active principle is not administered (29). Social learning occurs, for example, when a patient following a specific treatment learns to modulate symptoms by appreciating the responses reported by other patients (27). Moreover, in accordance with Colloca (27) expectations and learning represent an

interactive phenomenon, given that learning can increase expectations or develop new expectations.

Neurobiological factors

From a neurobiological perspective, placebo and nocebo responses have been documented to be developed by a specific neurochemistry and neural network (21). Placebo and nocebo interact with the brain modulatory systems at a neurochemical level, through the release of specific neurotransmitters (21). For instance, considering pain outcome as a model, the endogenous opioids, dopamine, cannabinoids, oxytocin and vasopressin are involved in the reduction of pain (e.g. placebo analgesia) whenever the patient interact with positive contextual factors (1, 30). Opposite, cholecystikinin, dopamine, opioid deactivation and cyclooxygenase-prostaglandins activation are implicated in the amplification of pain (e.g. nocebo hyperalgesia) during healthcare-patient encounter surrounded by negative contextual factors (2, 30).

Furthermore, recent advances in neuroimaging techniques, such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), suggest an involvement of specific neural correlates during placebo and nocebo responses of pain (21). The positive and negative use of contextual factors are capable of acting or de-acting the four key brain regions commonly associated with the descending pain processing pathway: the dorsolateral prefrontal cortex, the rostral anterior cingulate cortex, the periaqueductal grey and the dorsal horn of spine (30, 31) Nevertheless, other classical pain-matrix areas have been reported to change in their activity during placebo or nocebo responses such as thalamus, insula, somatosensory cortex, and mid-cingulate regions (12, 13).

The trigger role of contextual factors

Contextual factors have been documented as triggering placebo and nocebo responses. Specifically, all clinical interventions have been defined as composed by two inseparable elements: (a) the first is the intervention itself (e.g. the medication, the treatments) mainly based upon biological elements, while the (b) second is based upon the context (1). The context is not a vacuum but it represents a powerful healing space enriched by emotional, cognitive, affective, social and relational factors, and is capable of interacting with the patient's clinical condition (12). These contextual factors convey a hidden meaning, detected and actively analysed by the patient, which are essential for the perception of care and the interpretation of the therapeutic intervention (29). When these factors are filtered by the patient's perspective, they are translated into a complex cascade of psycho-neuroimmunoendocrine events capable of generating placebo/nocebo responses and eliciting expectations, memories and emotions that in turn can influence the patient's health-related outcome (12, 29).

To date the contextual factors relevant in triggering placebo and nocebo responses have been identified by Di Blasi, Harkness, Ernst, Georgiou, and Kleijnen (16) and recently translated by Testa and Rossettini (15) in the physiotherapist field and by Rossettini, Carlino and Testa (11) in musculoskeletal pain. These contextual factors, which are capable of influencing the clinical outcomes, have been identified as: professional reputation, appearance, beliefs and behaviours of healthcare providers; expectations, preferences, previous experience, clinical conditions, gender and age of the patient; verbal and non-verbal elements of communication characterising the patient-healthcare provider relationship; the environment, architecture and internal design of the healthcare setting; specific aspects of treatment such as a clear diagnosis,

an overt therapy, observational learning and patient-centred approach, a global process of care and the therapeutic touch.

Nursing outcomes can be modulated by contextual factors

Nursing outcomes are considered those changes subjectively or objectively reported by patients or by their caregivers and/or family members, as a result of the nursing care received. Safety and effectiveness outcomes have been categorised and specific indicators have been established (32). Among safety outcomes, falls, pressure sores, hospital acquired infections (e.g. pneumonia, surgical site infections) and medication errors leading to mortality have been described (32). Among effectiveness outcomes, activity daily living independence, as well as patient or family self-management competence, coping, comfort and satisfaction with nursing care have been established and included in several national and international quality indicators and research projects (32).

With the goal of preventing negative outcomes as those associated to safety, and achieving positive outcomes as those associated with effectiveness, clinical nurses develop the plan of care after identifying actual or at-risk problems. On the basis of patient and caregiver preferences, values and resources, clinical nurses identify the nursing interventions required. These interventions should be based upon the evidence available and can be composed of simple interventions (patient mobilisation), bundle interventions (such as the prevention of infections associated with care) or complex interventions (such as those performed for improving independence in nursing homes or in mental health care). All of these interventions can be performed by the same nurse (as in the case of a family nurse or primary nurse) or by a team (as in the case of hospital nursing care).

Although evidence emerging from research can suggest the likelihood of preventing a certain negative outcome, or achieving a positive outcome thanks to an intervention, there is a need to consider the “uncertainty principle” (10). Paraphrasing Colloca and Benedetti (10) it is a challenge to measure with a certain degree of accuracy the contribution of each intervention (e.g. the effect of an educational session) on outcomes because the intervention itself is influenced by contextual factors. Effects determined by interventions have been conceptualized as the sum of the contextual factors effect plus the active intervention effect plus the interaction of the contextual factors and active intervention effects (33). The contextual factors surrounding the patient has the power to interact with the intervention, modulating its effect and outcomes (12, 30, 31). Positive contextual factors can increase the effectiveness of the nursing intervention, while negative contextual factors can decrease it (22). Thus, the contextual factors embody a non-eliminable component of nursing care capable of influencing the overall patients’ outcomes (34) such as (a) the positive patient’s experience with care (e.g. satisfaction, involvement, perception of quality, empowerment, adherence and compliance to treatments, motivation, willingness, hope, safety); (b) the occurrence of adverse events (e.g. patient mortality, medication errors, restraint use and hospital-acquired infections); and (c) symptoms (e.g. pain, discomfort, anxiety, nausea, stress, fatigue, social, psychological, physical and spiritual wellness) (35-85).

To our knowledge, no attempt has been established to develop conceptual models aimed at summarising the contextual factors relevant for placebo and nocebo responses among the nursing discipline. Thus, the conceptual models available in the field and developed by Di Blasi, Harkness, Ernst, Georgiou, and Kleijnen (16), Testa and Rossettini (15) and by Rossettini, Carlino and Testa (11) have been considered and

translated in the nursing field by categorising contextual factors in: a) nurse and patient features, b) the patient-nurse relationship, c) intervention features, and d) the characteristics of the healthcare setting, as reported in Figure 2. Table 1 reports a summary of contextual factors triggering placebo and nocebo responses that clinical nurses should consider in their daily care.

Nurse features

Nurses embody a specific “effect” because they convey information to the patient through appearance and behaviour that communicate the essence of nursing care (35). As the first impact, a nurse’s uniform is capable of influencing the perception of nursing professionalism and competence by patients (36, 37).

The professional qualifications, expertise, competences and technical skills of nurses can influence patient satisfaction and compliance with care (38-41). Moreover, personal qualities such as leadership, attitudes and beliefs are components capable of influencing patient satisfaction and the occurrence of adverse events such as patient mortality, medication errors, restraint use and hospital- acquired infections (42). Other personal qualities include honesty, openness, trustworthiness, empathy, compassion, confidentiality and commitment to providing the best care. Authenticity, assertiveness, humility and the ability to provide holistic care have also been associated with patient satisfaction and perception of quality with nursing care (43, 44). Moreover, awareness of unvoiced needs by encouraging patients to share their concerns, have also been documented as capable of influencing outcomes. When caring for patients and caregivers, demonstrating care, tolerance and respect, accepting patient preferences and decisions, and providing information regarding illness and health processes all influence nursing outcomes (38-41, 43, 44).

On the other hand, failure to anticipate or recognise patient needs, depersonalising the patient by referring to him or her by the medical diagnosis or bed number, neglecting care responsibilities, in which patients feel abandoned, vulnerable, ashamed, ignored or insecure can negatively affect nursing outcomes by increasing the occurrence of adverse events (38, 43, 45-47).

Patient features

The patient's previous experiences, preferences, and expectations are significant elements capable of influencing both placebo and nocebo responses.

The expectations regarding an intervention can influence the patient's involvement, satisfaction and experience as well as the outcomes regarding pain control (48-50). Positive expectations, desires and hopes may increase nursing outcomes (48, 49), while, as reported recently by Woo (50) negative expectations of discomfort during wound dressing changes have been associated with an increased occurrence of pain (also known as nocebo hyperalgesia), wound exudate and occurrence of necrotic tissues.

Moreover, previous experience of care and preferences can also influence outcomes. According to a recent systematic review, the likelihood of a nocebo response is increased when prior negative knowledge or expectations exist. In addition, pre-existing psychological traits (e.g. anxiety) may exacerbate the nocebo influence (9).

Finally, the socio-demographic backgrounds of patients such as age and gender have also been documented as nursing outcome triggers. Elderly patients have been reported to be more satisfied with nursing care; moreover, men have been documented to report a higher level of satisfaction with nursing care compared to women, similarly to patients with lower education levels (51). Differently, the nocebo effect has been reported more often among women (9).

The patient-nurse relationship

A patient-centred communication based upon verbal and non-verbal strategies positively influences the clinical encounter between the nurse and the patient, improving satisfaction, empowerment, adherence to care treatments and symptom resolution (52, 53). Differently, as documented recently by Doyle, Hungerford and Cruickshank (54) poor patient outcomes occur when the nurse's behaviour is callous and lacks empathy.

Verbal communication is emphasised by open-ended and affective questions and the ability to listen actively, as well as by techniques aimed at increasing understanding of the patient's concerns such as communicating with empathy, paraphrasing, and following-up cues (5, 55). Verbal communication used by nurses during medication administration has been documented to influence the patient's satisfaction and symptoms: pain is influenced positively by verbal suggestion of amelioration and negatively by verbal sentences of aggravation (55-57).

Non-verbal communication is also considered a key factor influencing nursing outcomes. Additionally, the nurse's ability to interpret non-verbal body language expressions of emotion and/or distress may affect patient satisfaction (55). Tailoring non-verbal communication to patients' sensory deficits is also crucial: deaf patients report an increased sense of vulnerability, a risk of delayed recognition of their symptoms and needs and in receiving appropriate interventions (58).

Intervention features

Several elements of nursing interventions can affect patient outcome(s). Showing or telling a patient that an intervention is being applied can stimulate placebo responses

(59). Moreover, presenting information about side effects of treatment in form of probability instead of a mere list, as well as balancing positive and negative information during care, can reduce the nocebo responses (60).

Creating a therapeutic context in which patients can share their experiences with other patients or can watch videos where patients report their positive experience with the same intervention may increase the likelihood of positive effects of the treatment (61). Similarly, reducing exposure to patients experiencing side effects of the medication can reduce nocebo (60). In addition, in the field of educational interventions, offering in-group sessions by nurses instead of individual interventions can trigger some effects (62): according to the literature available, patients who receive education sessions in a group have increased motivation, willingness, compliance and hope, and also interact with other participants (63).

The patient-centred approach is also capable of modulating nursing care effects (64). Tailoring nursing interventions by considering patient preferences and needs, empowering patients in self-care management and ensuring continuity along care transitions, as well as offering visits by the same nurse, can all positively influence nursing outcomes such as patient's satisfaction, compliance and experience with care (38-41, 43, 65-68). On the other hand, higher workloads, long waiting times, the use of medical and sophisticated language, or the adoption of nurse-centred approaches with a lack of patient understanding and proximity can hamper patient satisfaction (38, 40, 43, 45, 66, 67). In addition, the above-mentioned factors may reduce consistency between patients and nurses regarding the care plan, thus threatening its quality (69).

The comfort touch adopted by nurses has also been recognised as a contextual factor. Touch represents the basis of social interaction conveying information about the emotional and mental state of individuals involved in the relationship (70). In nursing

care, touching has been documented as a useful intervention that alleviates pain, anxiety, nausea and fatigue, thus increasing the quality of life (71-75). While touching patients, nurses communicate empathy, caring, affection, concern and security, thus facilitating the achievement of the expected outcomes (70).

Healthcare setting features

Sensory cues, structural aspects, decorations and ornaments are the most influential elements of the healing environment that should be considered when planning and designing the care settings (76, 77).

In general, clear indication of health-care settings can improve healthcare accessibility (78). Specifically, environments with natural lighting (e.g. full spectrum lighting), low noise levels (e.g. adoption of sound-absorbing ceilings or earplugs/earmuffs) and relaxing and soft sound (e.g. music, bird songs, rain showers, ocean waves) have been documented as greatly appreciated by patients (79-81). Also the adoption of pleasant aromas and an adequate temperature and microclimate (e.g. filters, airflow control and ventilation systems) all generate a positive therapeutic setting (82).

Moreover, environments that integrate windows and skylights, with comfortable and private settings (e.g. single-bed or private patient rooms) have also been documented as greatly appreciated by patients (78). Nature artwork, such as flowers or green vegetation in nursing homes, can have a calming effect (78, 82). The adoption of healing gardens close to wards (e.g. plants, water) and social spaces (e.g. lounge, day rooms and waiting rooms) have been documented as increasing connections between patients and their caregivers, thus reducing stress and promoting wellbeing (82). Colour

frames based on calming tones also mitigate patient involvement in nursing care, however the meaning of colour is culturally based and can differ between patients (78).

Finally, combining positive distractors have been documented as modulating pain, stress, anxiety and safety, promoting social, psychological, physical and spiritual wellness (83). However, uncomfortable, frightening, oppressive, claustrophobic and dirty rooms have been associated with patient dissatisfaction and negative outcomes (84, 85).

Implications for the nursing discipline

While the placebo has a longer history in the nursing literature, the recent introduction of the nocebo concept suggests that these concepts require complete consideration at different levels of the nursing discipline, e.g. from education to clinical practice, nursing administration and research. Because of the relationship with patient clinical outcome, it is necessary to identify future directions for inquiry and application starting with a critical evaluation of current nursing practices.

Nursing education

Although the concept of caring as acquired during nursing education embodies several of the above-mentioned factors (86), these are not always clearly described in nursing programs (87). The nursing curriculum should consider the relevance of contextual factors by including these in their programs. Specifically, if these factors are ignored, that may communicate to students and faculty members that they are irrelevant in nursing care.

Students at different levels of education (from bachelor's and master's nursing degrees) with different degrees of nursing competence should be coached to analyse and

consider the relevance of contextual factors in triggering nursing outcomes. They should be accompanied to progressively increase their awareness of their own attitudes and traits. In addition, they should be accompanied to develop complex competences in assessing patient and caregiver needs and preferences, also taking into consideration cultural patterns.

Students should have the opportunity to reflect on how their personal qualities evolve by reflecting on clinical experiences. On the other hand, supervisors at both the faculty and clinical levels should consider student aptitudes and qualities (such as openness and honesty) as specific traits on which students need to receive feedback aimed at promoting their growth. Students should also have the opportunity to reflect with experienced nurses on unexpected negative patient outcomes, by identifying the relevant contribution of some contextual factors in addition to other well-known mechanisms such as the nurse-to-patient ratio or physiopathology mechanisms.

Moreover, the clinical context in which students undertake their clinical experience should be qualitatively adequate. Contextual elements triggering placebo and nocebo responses may also have a role in student learning outcomes, preventing or facilitating their achievements, an area that has not attracted the attention of researchers to date.

Nursing clinical practice

How clinical nurses consider the contextual factors triggering nocebo/placebo responses in their daily practice has been not documented to date. However, in those contexts in which nurses work in groups as in the hospital, the inter-nurse variability with regard to the consideration of contextual factors may offset the positive effects obtained or reinforce negative ones. Patients switching from one nursing team to

another at the end of shifts, or transiting from one context to another (the medical unit to rehabilitation unit), can experience uncertainty or confusion even if nursing interventions are similar. These effects can be different due to different contextual factors.

Moreover, experienced clinical nurses may identify other factors not clearly included in the available frameworks (88) by their clinical wisdom and expertise, as well as their close relationship with patients, and may develop an in-depth knowledge of other factors that may modulate the relationship between nursing care and patient outcomes. Therefore, it is ideal to ensure continuity in care by providing the same nurse (e.g. primary nursing models). When this is not possible, it is suggested that care plans contain documentation regarding relevant contextual factors and their clinical effects, aiming at ensuring consistency across shifts and contexts in order to increase the likelihood of a positive nursing outcome.

Clinical nurses should also be supported in developing and maintaining their competences through continuing education strategies that should not only concern interventions, but also the context in which they are implemented. Moreover, with regard to the ethical implications of the contextual factors, clinical nurses have been documented to consider placebo responses as real, with therapeutic benefits, and permissible within the ethical borders in daily practice (89). Therefore, the elicitation of placebo and the avoidance of nocebo responses by contextual factors have been reported as ethical (11, 15). In fact, the conscious adoption of contextual factors symbolises a useful chance to improve evidence-based nursing care without threatening the principle of non-maleficence, the patient autonomy and informed consent. Therefore this approach is profound different with that replacing the required treatment with a potentially ineffective treatment (20, 22, 90).

Nursing care organization

The ward atmosphere and environment have received increased attention in recent years as mediators of the quality of nursing care. Examples may be detected in recent studies where the organisational support perceived by clinical nurses may modulate patient outcomes by increasing or decreasing their occurrence (91, 92). Differently, in light of nocebo/placebo mechanisms, contextual factors may directly influence patients and promote (or hamper) the achievement of expected outcomes. Therefore, the role of the environment should be considered not only as affecting the performance of the nursing workforce, but also as triggering patient outcomes with direct effects.

Nurse leaders should be prepared to continually assess, design and promote interventions to improve the quality of the environment while working with other leaders both at the hospital and at the residential levels. There is also a need to develop and validate instruments capable of measuring the quality of factors implied in nocebo/placebo mechanisms, aiming at monitoring the amelioration of the contextual factors over time.

Any form of nursing care standardisation, addressing patients' needs without considering preferences, expectations and unique needs, should be detected early and prevented. Specifically, some models of nursing care delivery (e.g. functional models), should be immediately replaced with person-centred models where evidence-based approaches, capable of identifying the best interventions within those documented in the literature, are implemented in an appropriate environment, capable of maximising the effects of the intervention delivered.

Nursing research

While placebo and nocebo responses are well documented, there has been minimal research in the nursing field (8, 9).

Designing and implementing a trial for placebo and nocebo investigation represents a challenge (33) and several confounding factors should be controlled. The history of disease, the influence of uncontrolled biases, unidentified co-interventions and adverse side effects can all modulate nursing care outcomes (93). Research on placebo and nocebo should adopt placebo ethically as an enhancing strategy associated with the best evidence-based available interventions to prevent nocebo and improve nursing outcomes (20, 90). Moreover, research on placebo and nocebo responses should be moved on contextual factors effect (11, 15). Limiting the influence of the contextual factors around the intervention can help to identify the specific effect of the intervention itself. On the other hand, boosting the context around an active intervention can disclose the role of contextual factors in modulating clinical outcomes (59).

Different lines of research can be designed and promoted in specialist areas (e.g. critical care nursing, oncology care, mental health or chronic care) or in general areas, at national and international levels, also considering the cultural differences that may affect placebo and nocebo effects. Firstly, there is a need to explore the knowledge and expertise on placebo and nocebo responses both among undergraduates and registered nurses, aiming at assessing their awareness in the field and promoting improvements to increase their awareness. There is also a need to discover the effect of single and/or combined contextual factors affecting nursing care outcomes, possibly through incremental study designs to weigh the effect of each component. Lastly, exploring patient perceptions regarding the contextual elements capable of positively or negatively influencing expected nursing outcomes, as well as researching psychological

and genetic traits of placebo and nocebo responders given the documented variability across patients (15), are recommended.

Limitations

This discussion paper is affected by several limitations. First, the model selected (11, 15, 16) for summarizing the role of the contextual factors was not preliminarily validated for its consistency in the nursing discipline. However, some elements are not tied to individual disciplines but are common frameworks for all health disciplines. Second, examples of primary studies and data provided in supporting each element of the model were not selected by using a systematic approach (e.g. a systematic review of the literature) and not criticized in depth given that the priority was to offer a brief overview. Third, contextual factors have been categorized into a conceptual model by describing each factor involved; interpretations with regard the relationships between factors and placebo require further critical analysis and discussion. Fourth, in this discussion paper we emphasize the need of continuing scrutiny and reflection on daily practice aiming at potentiating positive and at preventing negative outcomes by modulating the contextual factors. However, reflective professional processes are important above the placebo and nocebo effects, given that allow nurses, and all clinicians, to continuing understand and learn how their behavior, and attitudes and the environment of care contribute to improve patients' experience. Finally, according to the aims of the study, the use placebos as controls in clinical trials was not considered in the development of the discussion paper.

Conclusions

To our knowledge, this is the first paper discussing the implications of nocebo/placebo mechanisms in the nursing field. Paradoxically, Florence Nightingale, in defining the role of the nursing over 100 years ago, was the first theorist who expressed nursing as “*the act of utilizing the environment of the patient to assist him in his recovery (Nightingale, 1860)*”. Contextual factors have a trigger effect on nursing outcomes. Therefore, besides appropriate evidence-based interventions, nurse educators, clinicians, leaders and researchers, in their different fields of competence, should pay specific attention to contextual factors in order to develop their awareness, unveil their mechanisms of action by considering them in their implementation in daily practice.

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Table 1. Contextual factors increasing placebo responses and contrasting nocebo responses: a summary for clinical practice (adapted by Testa and Rossetini 2016)

Nurse and patient features

Develop qualification, knowledge, competence and expertise;

Adopt a professional uniform;

Be genuine, respectful, tolerant, honest and trustworthy during nursing care;

Provide clear information, prompts and explanations of patients' problem(s);

Explore each patient's disease and illness, expectations, preferences, desires, hopes and previous experience;

Stimulate enquires and answers to patient requests by offering advice and reassurance;

Consider patient's gender, age and educational background

Patient-nurse relationship

Be warm, confident, compassionate, assertive and open with patient;

Adopt empathetic speech pattern, language mutuality, open-ended and affective questions;

Adopt a patient-centered communication style and active listening;

Offer positive messages associated with nursing intervention implementation;

Make eye contact, smile, adopt facial expressiveness of concern, assistance and engagement;

Use affirmative head nodding, gestures and postures orientated towards the patient;

Interpret the patient's non-verbal body language expressions of emotion and distress.

Intervention features

Demonstrate and communicate to the patient that the intervention is going to be delivered;

Stimulate patient to discuss with other patients who have undertaken similar interventions with positive results;

Adopt a holistic approach, tailoring interventions to patient preferences and values;

Ensure continuity by offering nursing care by the same nurse (e.g. primary nursing model);

Offer easy accessibility, adequate time and continuity of nursing care;

Inform, facilitate, help, assist, comprehend and take care of patients through the adoption of touch.

Health-care setting features

Ensure indications to facilitate nursing care accessibility;

Offer a pleasant caring environment by decorating with artwork and ornaments;

Modulate light, sound, climatic characteristics and fragrance as beneficial sensory clues.

Fig.1 Overview of placebo and nocebo effects

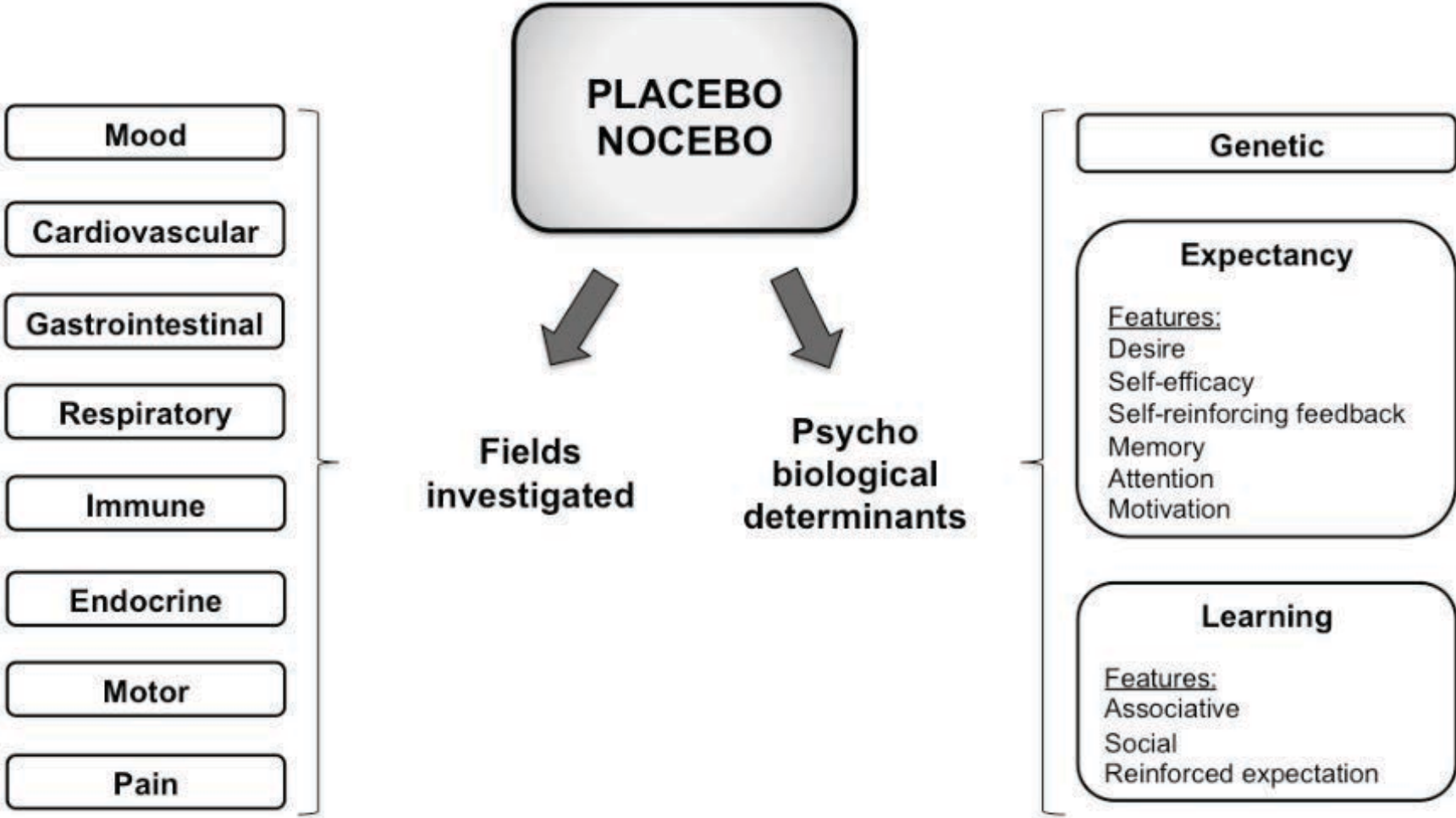
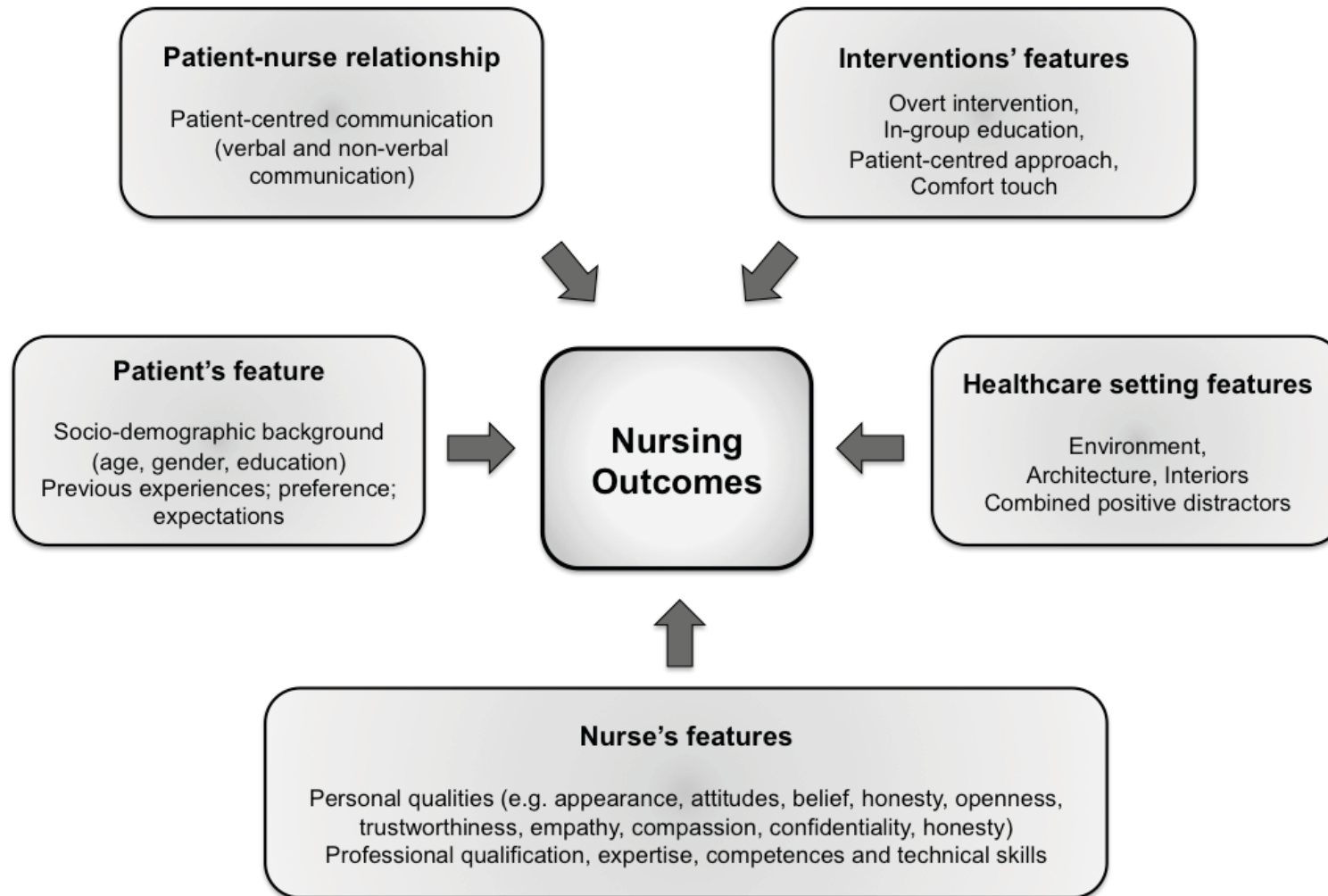


Fig.2 Contextual factors as modulators of the nursing outcomes



APPENDIX II

CONTEXTUAL FACTORS TRIGGERING PLACEBO/NOCEBO EFFECTS IN NURSING DAILY PRACTICE: FINDINGS FROM A NATIONAL CROSS-SECTION STUDY

Submitted as:

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Contextual factors triggering placebo/nocebo effects in nursing daily practice: findings from a national cross-section study

ABSTRACT

Background: The placebo phenomenon has been studied in nursing discipline while the nocebo effect remains unexplored. Recently a set of contextual factors functioning as potential triggers of placebo and nocebo effects has been described; however, their use in daily nursing clinical practice have never been reported.

Objectives: To describe beliefs and daily use of the contextual factors aiming at increasing the placebo effects and at preventing nocebo effects in nursing practice.

Design: A national web-based cross-sectional survey on 2016.

Settings: National nurses' associations specialized on medical, diabetic, geriatric and neuroscience care.

Participants: A national wide sample of Italian nurses appertaining to four national associations. There were included those nurses who: a) had a valid e-mail account, and b) were working as clinicians at the time of the survey.

Methods: A questionnaire self-administered through SurveyMonkey Software® developed upon the literature and conceptual frameworks available on contextual factors. There were explored: 1) contextual factors definition; 2) beliefs (from 0 'not at all' to 4 'a lot of'), 3) their case-by-case frequency of use (from 0 'never' to 4 'daily'); 4) the circumstances under which they are applied in daily care, 5) the clinical conditions where participants have perceived their potential beneficial effects, 6) the ethical implications in using the contextual factors, and 7) the communication to the patient about their use.

Results: Out of 1,411 eligible nurses, a total of 455 responded (32.2%) and 425 questionnaires (30.1%) were valid for the analysis. The majority of participants (n=211; 49.6%) defined the contextual factors as ‘an intervention without a specific effect for the condition being treated, but with a possible aspecific effect’. They have reported to belief on the contextual factors (2.91; 95%CI 2.88–2.94) and to use them > 2 times/month mainly in addition to a nursing intervention to optimize clinical outcomes’ (n=79; 18.6%). The psychological and physiological therapeutic effects have been perceived mainly in chronic pain (n=259, 60.9%), insomnia (n=243; 57.2%), and emotional disorders (n=230; 54.1%). Contextual factors have been reported as ethically acceptable when ‘It exerts beneficial psychological effects’ (n=148; 34.8%). Around a quarter of nurses have reported to ‘Say anything’ to the patient when the contextual factors are used.

Conclusions: Behind those evidence-based interventions appropriate to the condition(s) of the patient, clinical nurses believe and use other factors aimed at increasing the effects of the interventions.

What is already known about the topic?

Placebo unlike nocebo has been largely studied in the nursing discipline and it reflects all benefits in a patient's health ascribable to the symbolic impact of medical treatment/nursing intervention or the setting.

A set of contextual factors have been identified to function as triggers of placebo/nocebo responses capable of increasing the positive outcomes or to preventing those negative by enacting different psychological and neurobiological mechanisms.

What this paper adds:

Nurses are aware on CFs in their capability of increasing the placebo effects and in preventing the nocebo effects of nursing interventions.

They belief in the value of the CFs which are implemented around two times/month in several different clinical conditions where psychological and physiological mechanism explain their effectiveness.

Nurses are not use to communicate the implementation of CFs to the patients, therefore their use remain silent. Moreover, nurses consider the use of CFs as ethically acceptable when capable of producing benefits for the patient.

Introduction

In recent years placebo has been largely studied in the nursing discipline (1, 2), while less often nocebo effects have been considered to date (3). Specifically, placebo (Latin "*I shall please*") represents "all benefit in a patient's health ascribable to the symbolic impact of medical treatment/nursing intervention or the setting" (4); differently, nocebo (Latin "I shall harm") describes the "ill effect caused by the suggestion or belief that something is harmful" and reflects new or worsened symptoms occurring during a medical treatment or a nursing intervention (4).

Several researchers (5, 6) have studied the rationale mechanisms explaining the occurrence of placebo or nocebo effects in certain circumstances and recently a set of contextual factors (CFs) functioning as a mediators or triggers of placebo/nocebo responses capable of influencing the clinical outcomes, has been described (7, 8). The CFs have been documented to enhance the clinical outcomes of evidence-based interventions, by enacting various psychological and neurobiological mechanisms increasing placebo and preventing or reducing nocebo effects (4). For example, clinical nurses can improve patient's symptoms and well-being through the activation of some CFs capable of stimulating placebo responses e.g., by creating a comfortable environment or by using the therapeutic approach; on the contrary, some CFs can trigger nocebo effects, stimulating adverse effects of interventions (4) e.g., by negatively use verbal or non-verbal body language (9) when, nurses are work to increased work pressure and therefore less work-engaged and burned-out (10). Recently the term 'CFs' has been preferred instead to 'placebo' (11) specifically while conducting research aiming at preventing bias in responses (12, 13).

In accordance to the available conceptual frameworks (7, 8, 14) the CFs relevant for placebo and nocebo responses have been recognized in health-care

professional features (professional reputation, appearance [e.g., uniform], positive attitudes and optimistic behaviour); patient's features (expectations, preferences, previous experience, clinical conditions, gender and age); health-care-patient relationship (verbal, non-verbal communication, empathetic therapeutic alliance); specific aspects of the interventions (over therapy, patient-centered approach, professional approach, and therapeutic touch); and in the healthcare setting (comfortable setting, environment, architecture and internal design). Translating the framework in the clinical practice, the manner in which health-care professionals implement an intervention (e.g., by manifesting an optimistic approach), the patients' expectations (e.g., to ameliorate the symptoms), as well as the verbal, non-verbal communication and the patient-centered approach enacted by professionals and the environment feature where the process happens, can trigger positive or negative outcomes.

In the nursing discipline, available studies have been measured mainly the perceived effectiveness of placebo medication among rheumatology, hemodialysis and non-hemodialysis nurses (1, 15, 16) as well as the general aptitudes of head nurses (17) and clinical nurses (2) regarding the adoption of placebo, by involving monocentric cross-sectional surveys. Therefore, no large-scale data with regard to the daily use of different CFs by nurses have been reported to date as well as their process of implementation, e.g., in which clinical conditions they are mostly effective, to the patient's information and ethical implications. Moreover, while some CFs can be considered as background of each intervention (e.g., comforting environment), others are themselves evidence-based interventions in nursing discipline: for example, therapeutic touch, patient-center care and developing an empathic relationship with the patient (18) are all considered themselves evidence-based nursing interventions.

Therefore, understanding whether these interventions are used by nurses to enhance the effects of other interventions or not in their daily practice, is essential in order of: a) describing the awareness of nurses in daily use of factors modulating placebo/nocebo responses; b) understanding research implications e.g., the need to describe and evaluate also the use of these factors when the effectiveness of other nursing interventions are tested; and c) reflecting on nursing education and managerial implications. Therefore, with the intent to describe beliefs and daily use of CFs as triggers factors of placebo/nocebo effects in daily practice, a national study design was performed.

Methods

Design

A web-based cross-sectional survey herein reported according to the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) guidelines (19) and STrengthening the Reporting of OBServational studies in Epidemiology (STROBE) (20) was performed after having obtained the ethical approval from the Liguria Clinical Experimental Ethics Committee (P.R.236REG2016, July 7, 2016).

Participants and setting

A nationwide sample of Italian nurses was the target population identified from the email database of nurses' associations specialized on medical (A.N.I.M.O. - Associazione Nazionale Infermieri Medicina Ospedaliera; n=931), diabetic (O.S.D.I. - Operatori Sanitari di Diabetologia Italiani; n=910), geriatric (G.R.G. - Gruppo di Ricerca Geriatrica; n=123), and neuroscience care (A.N.I.N. - Associazione Nazionale Infermieri di Neuroscienze; n=50).

Within the target population, there were included those nurses who: a) had a valid e-mail account, and b) were working as clinicians at the time of the survey. Taking into consideration previous surveys in the field (12, 21-25) where the response rate was from 30% to 60%, there were expected approximately 423 to 847 responses from the population of 1,411 nurses. The application of these predicted values to the formula for estimating the sample size for a single population proportion with the population proportion set at 50.0%, which is the most conservative value to apply, produced a two-sided 95% confidence level within two to four percentage points of the true value and a relative standard error ranging from 2.17 to 4.08 (26).

Questionnaire development

A survey instrument was developed using distinct and iterative steps (27). Items from existing surveys on placebo were extracted from the literature (2, 12, 15-17, 21-25, 28-38). The initial list was composed of 17 items that were critically evaluated for face and content validity (27) by a panel of six experts with extensive experience in placebo and survey design (nurses, physicians, psychologists and physical therapists). These experts worked independently and then agreed upon the final list of items by providing feedback on content accuracy, wording clarity, and survey structure. Those questions regarding the beliefs and the use of CFs were organized according to the available framework (7, 14) [ENREF 26](#) thus evaluating each specific aspect (e.g., verbal communication). Adjustments were progressively included by considering the feedback emerged. When full agreement among experts was achieved, a preliminary version of the survey composed of 14 items was pilot tested in a convenience sample of 10 registered nurses (RNs).

Thus, a self-administered questionnaire (translated in English, available as Supplementary File 1 composed by two sections (A-B) was used: the first was aimed at investigating the socio-demographic variables by two open-ended questions (experience as a nurse, gender) and five closed multiple-choice questions (e.g. nursing education) (seven items).

The section B was composed by seven closed multiple-choice questions exploring: 1) CFs definition; 2) participants' beliefs regarding each CF (from 0 'not at all' to 4 'a lot of'), 3) the case-by-case frequency of use of each CF (Likert from 0 'never' to 4 'daily'); 4) the circumstances under which they are applied, 5) the clinical conditions where participants have perceived the potential beneficial effect of CFs, 6) the ethical implications perceived in using CFs, and 7) the communication to the patient about CFs use.

Data collection procedure

The Survey Monkey (Survey-Monkey, Palo Alto, California, www.surveymonkey.com) online survey tool was used. The survey was administered over an eight-week period between September 2016 and November 2016. After permission was obtained from the Nurses Associations, all nurses were contacted using the blast email method (39). An email containing the survey and a brief note outlining the aim of the study, data handling (anonymity), the informed consent statement, and the invitation to complete the survey, was delivered (39). Two reminder emails were sent two and four weeks after the initial contact to encourage those who did not participate to complete the survey (40).

Ten to 15 minutes were needed to complete the survey, in line with the completion time documented as optimizing response rates in online surveys (41).

Participation was voluntary and no incentives were offered to participants; there was the option to decline to answer specific questions or to leave the entire questionnaire blank (40). The order of questions was randomized. Participants were able to review or change responses using a back button until the end of the questionnaire.

Data were downloaded and stored in an encrypted computer, and only the project manager could access the information at all study stages. All data were de-identified (name and email address) to maintain confidentiality and data protection (39).

Data Analysis

A questionnaire was considered incomplete if there were more than 20% of missing. Descriptive statistics were used to calculate frequencies, percentages, averages and confidence of intervals (CI) at 95%. Specifically, in the case of CFs frequency of use and beliefs, the five response categories were collapsed into three categories ('very often' and 'never'; 'very much' and 'nothing', respectively) leaving unaltered the central categories ('occasionally' and 'enough'). For those questions allowing more than one choice, the absolute frequency and percentages were calculated for every combination of responses given by each participant, e.g. to better describe the responses given by each participant in the item regarding 'Ethics' we did not calculate the absolute frequency of the four possible responses (r) but their 16 combinations, given by the formula r^n .

In those response options of CFs frequency of use (from "never" to "daily") and beliefs (from "not at all" to "a lot of") there were then converted in continuous variable aiming at describing the averages and the correlations by using the Spearman's (rho, ρ). Relationship between the individual characteristics and the

responses given was investigated with the Eta squared and the Cramer's V according to the variable nature (continuous and nominal). The R software was used for data analysis (42) with the packages "psych" and "ggplot2".

Results

Participant's characteristics

There were invited to participate 2,014 Italian nurses; 603 of them were bounced because their addresses were unknown or not up-to-date, thus leaving a sample of 1,411 nurses that it was set as 100%. A total of 455 responded (32.2%); among these 30 RNs provided incomplete surveys, leaving 425 (30.1%) questionnaires valid for the analysis.

The majority of RNs (361; 84.9%; 95%CI 81.1-88.1) were female, and their average age was 46.6 years (95%CI 45.7-47.4). Fifty-nine percent (n=251; 95%CI 54.2-63.7) were living and working in the north of Italy.

The majority of participants were educated at the bachelor levels (n=194; 45.6%; 95%CI) and reported an average of 23.7 years (95%CI 22.7-24.7) of clinical experience; at the moment of the survey the majority were working in the hospital (n=348; 81.8%; 95%CI 77.8-85.4) and belonged to Medical Nurses Association (n=263; 61.8%; 95%CI 57.1-66.5) as reported in Table 1.

Definition of CFs

The majority of participants defined CFs as 'an intervention without a specific effect for the condition being treated, but with a possible aspecific effect' (n=211; 49.6%; 95%CI 44.8–54.5). The remaining considered CFs as 'an intervention that has a special effect through known physiological mechanisms' (n=138; 32.5%; 95%CI

28.1–37.2), ‘a sham treatment used as control tests for safety and efficacy of active treatment’ (n=46; 10.8%; 95%CI 8.1–14.3), and in minor frequency, as ‘a harmless or inert intervention’ (n=30; 7.1%; 95%CI 4.9–10.0).

Beliefs

Participants have reported a substantial level of conviction towards CFs (average 2.91; 95%CI 2.88–2.94). As reported in Table 2, the highest trusted factor was the ‘verbal communication’ (n=353; 83.1%, 95%CI 79.1-86.4) and the ‘patient-centered approach’ (n=353; 83.1%; 95%CI 79.1-86.4%) while those lowest factors were, in order, the ‘professional reputation’ (n=199; 46.8%; 95%CI 42.0-51.7), the ‘uniform’ (n=196; 46.1%; 95%CI 41.3-50.9), the adequate ‘architecture’ (=157, 36.9%; 95%CI 32.4-41.7) and ‘environmental design’ (n=124, 29.2%; 95%CI 24.9-33.7).

Frequency of use

As reported in Table 3, RNs have reported to use the CFs more than 2 times/month (average 2.56; 95%CI 2.52–2.60). The majority (n=180; 42%; 95%CI 37.6–47.2) has reported to use the CFs ‘many times’ in their clinical practice while the remaining ‘often’ (n=92; 21.7%; 95%CI 17.9–25.93) and ‘at least once’ (n=50; 11.7%; 95%CI 8.9–15.3). A total of 103 RNs has instead reported to use CFs ‘never’ (24.2%; 95%CI 20.3–28.7); specifically, there were reported ‘never’ use an ‘adequate design’ (n=183; 43.1%; 95%CI 38.3-47.9), an ‘adequate environmental architecture’ (n=156; 36.7%; 95%CI 32.2-41.5), the ‘professional reputation’ (n=159; 37.4%; 95%CI 32.8-42.2), the ‘uniform’ (n=150; 35.3%; 95%CI 30.8-40.1), and a ‘comfortable setting’ (n=127; 29.8%; 95%CI 25.6-34.5).

Circumstances of application

As reported in Figure 1, participants were divided among those providing a unique reason such as ‘in ad addition to a nursing intervention to optimize clinical outcomes’ (n=79; 18.6%; 95%CI 15.1-22.7%) and ‘to calm the patient’ (n=22; 5.18% 95%CI 3.35-7.85) and more options, mostly combining ‘to calm the patient’ and ‘in addition to a nursing intervention to optimize clinical outcomes’ (n=63; 14.8%; 95%CI 11.6-18.6), followed by ‘to calm the patient’, ‘in addition to a nursing intervention to optimize clinical outcomes’ and ‘to control pain’ (n=31; 7.3%; 95%CI 5.1-10.3).

Therapeutic effects

Nurses have reported ‘no effects’ in some clinical conditions such as infections (n=181; 42.6%; 95%CI 37.9-47.5), immunological problems and allergies (n=158; 37.2%; 95%CI 32.6-41.9), and in drug/medication addictions (n=134; 31.5%; 95%CI 27.2-36.2). Moreover, the therapeutic effects of CFs has been identified mainly as ‘psychological and physiological’ in chronic pain (n=259, 60.9%; 95%CI 56.1-65.6), insomnia (n=243; 57.2%; 95%CI 52.3-61.9), emotional (n=230; 54.1%; 95%CI 49.3-58.9), acute pain (n=202, 47.5%; 95%CI 42.7-52.4), oncological (n=190; 44.7%; 95%CI 39.9-49.6), cardiovascular (n=187; 44.0%; 95%CI 39.2-48.8), neurological (n=182; 42.8%; 95%CI 38.1-47.7) and in rheumatologic problems (n=179; 42.1%; 95%CI 37.4-46.9) (Supplementary File 2).

Differently, participants have reported only ‘psychological’ effects in cognitive disorders (n=177; 41.6%; 95%CI 36.9-46.5) and sexual conditions (n=136; 32.0%;

95%CI 27.6-36.7) while only 'physiological' effects were reported more often in gastrointestinal problems (n=86; 20.2%; 95%CI 16.6-24.4).

Ethical implications

Participants have reported that CF use is ethically acceptable when 'It exerts beneficial psychological effects' (n=148; 34.8%; 95%CI 30.3-39.6), 'It exerts beneficial psychological effects' and the 'Clinical experience has shown the effectiveness' (n=81; 19.1%; 95%CI 15.5-23.2) as well as when 'It exerts beneficial psychological effects' and 'The patient desire or expects this intervention (n=46; 10.8%; 95%CI 8.1-14.3) as reported in Figure 2.

However, participants have considered non-ethical when CFs use 'It is based on deception', 'Threatens trust between the patient and the nurse' (n=66; 15.5%; 95%CI 12.3-19.4), or simply 'Threatens trust between the patient and the nurse' (n=63; 14.8%; 95%CI 11.7-18.6), 'It is based on deception' (n=49; 11.5%; 95%CI 8.7-15.0) or 'It is based on deception', 'Threatens trust between the patient and the nurse' and 'It can create adverse effects' (n=30; 7.1%; 95%CI 4.9-10.0) as also reported in Figure 2.

Communication

The 24.2% of nurses reported to 'Say anything' to the patient (n=103; 95%CI 20.3-28.7); another 20.7% (n=88; 95%CI 17.0-24.9) informed the patients that CFs 'Is a treatment that can help and will not hurt'; the 15.5% communicated to the patients that the CFs 'Is an effective treatment' (n=66; 95%CI 12.3-19.4) and in similar proportion (n=65; 15.3%; 95%CI 12.1-19.2) is used to communicate that 'The treatment can help and will not hurt' and 'It is effective'.

Correlations

A moderate correlation ($\rho=0.47$) emerged between overall beliefs and the overall frequency of use; specifically, moderate positive associations (Supplementary Figure 1) were found between the frequency and the use of ‘patient’s expectation and preference’ ($\rho=0.57$), ‘uniform’ ($\rho=0.56$), ‘professional reputation’ ($\rho=0.51$), ‘patient-centered approach’ ($\rho=0.46$), ‘non-verbal communication’ ($\rho=0.45$), ‘positive attitudes and optimistic behavior’ ($\rho=0.44$), ‘physical contact with the patient’ ($\rho=0.44$), ‘verbal communication’ ($\rho=0.44$), ‘patient’s previous experience’ ($\rho=0.42$), and ‘over therapy’ ($\rho=0.41$). Correlations were not emerged between individual characteristics of participants and responses in all domains of the questionnaire.

Discussion

To our best knowledge this is the first national study aimed at examining the attitudes of nurses towards the implementation of CFs to promote placebo effects and minimize nocebo effects in daily practice.

CFs are considered interventions capable of enhancing the effectiveness of other nursing interventions. Findings reflect those emerged in previous nurse (2, 15-17) and physician surveys (31, 35) suggesting that nurses are aware not only of the use of placebos in clinical settings, but also they value factors that can optimize clinical outcomes.

Nurses have reported to take in consideration CFs, on average from ‘enough’ to ‘much’, specifically with regard to (in order) verbal and non-verbal communication, patient-centered approach, physical contact and the empathetic therapeutic alliance which represent all core concepts of caring (43). An inferior degree of trust has been

reported, in order, on professional reputation, uniform, adequate environment and design, which represent factors capable of increasing care humanization as emphasized recently in the literature (44) thus likelihood not included yet in undergraduate and continuing education programs. However, health care professional's reputation and environment (23) represent important CFs and milestones of personal branding as "*introspective process by which you define yourself professionally*" capable of influencing clinical outcomes and to increase professional realization and reputation (45).

The adoption of CFs in the clinical practice occurs more often than two times per month, with a consistent variation across factors: for example, higher use has been reported during verbal and non-verbal communication, positive attitudes and optimistic behavior, and in professional approach with patients in line with the nurses' beliefs. On the contrary, nurses have reported to use less often (around at least one per year) the adequate setting design, the environmental architectures and the professional reputation which have been also reported as those factors 'never' used. Italian nurses are used to work mainly at the National Health Service public sector, where the architecture features are in general old (46) and unmodifiable; in addition, the professional reputation as a single nurse is not used given that nurses work as a team and patients cannot decide to be cared for by a specific nurse. Therefore, the adoption of these CFs is more challenging for NHS nurses, and exploring their value among those nurses working in the private sector is suggested.

Nurses have reported to apply CFs in different circumstances mainly in addition to nursing interventions required by the clinical condition to obtain therapeutic effects, such as to relaxing or controlling pain, as already documented among nurses (2, 15-17) and physicians (17, 21-23, 35). On the contrary, the CFs adoption is rarely

used when patients required continuously unjustifiable interventions, to prevent their complaints or when evidence-based interventions are ineffective, thus suggesting that CFs are not used alone in high demanding and in high complex patients. Moreover, CFs are never used to gain time (e.g., waiting for physician consultation) indicating that no other factors (e.g. organizational factors) than those strictly clinical play a role in the decision to stimulate placebo and to avoid nocebo effects.

From the experience of participants, different clinical conditions can be benefited by CFs. Above all, emotional disorders, chronic pain, cognitive disorders, insomnia and acute pain. With regard to pain, previous studies have already documented nurses' attitudes towards the use placebo of medication (1, 15, 16); while the adoption of other strategies aimed at reducing pain have never been documented before. The remaining clinical conditions, suggest that nurses have experienced positive effects in the majority of health issues with the exception of infections, immune problems/allergies, drug/medication addictions, and sexual problems. The specificity mission of the nursing associations approached can explain these findings considered that nurses included do not dealt on a daily basis these clinical conditions. Moreover, the therapeutic effects of CFs have identified mainly among 'psychological and physiological' thus suggesting a mixed effect in the majority of health conditions; also in previous studies subjective mechanisms or a mix of subjective and objective mechanisms (2, 17, 30) have been reported.

Nurses considered the use of CFs as ethically acceptable when the benefits are evident from the side of patients and the nurses: in other words, when the intervention is not harmful. In performing this evaluation, the amount of clinical experience of nurses (e.g., newly graduates or experts), as well as their capability to detect psychological benefits or to diagnose patients desires or expectations can play a great

role in defining the ethical acceptability of the intervention. Otherwise, the use of CFs has been considered non-ethical when negative effects at different levels can emerge as documented in previous studies (2, 17) confirming that caring is based upon non-maleficence (2, 47).

Around a quarter of nurses have reported to do not inform the patient on the CF use, thus jeopardizing the principles of the autonomy (48); the remaining are used to communicate in general the benefits, as previously documented (21, 34). The lack of information can denote a paternalistic approach towards patients that has been documented among Italian health care professionals (49). Moreover, the informed consent can influence the effects of the CFs implementation and, therefore, their clinical outcomes (50) perceived by nurses that can turn in increased or decreased use of CFs. However, it can be difficult for nurses to inform patients regarding the use of some specific CFs, e.g. the empathetic relationship, because they are embodied in the concept of caring (47). Furthermore, while no individual factors (e.g., age, gender, education) were correlated both with beliefs and CFs use, a moderate correlation emerged between beliefs and the occurrence of some specific factors. Some CFs (e.g. professional approach) are fundamentals elements of caring (47) and, therefore, routinely adopted in daily nursing care.

Strengths and weaknesses of the study

Although the study novelty, several limitations affect its findings. Firstly, the RNs involved appertained to four different national associations developing nursing care in specific groups of patients whom reflect the main issues of the Italian population (51); however, they cannot reflect the entire population of RNs composed by 441,000 nurses (52). Secondly, in developing the questionnaire, not all

factors included in the available frameworks (e.g., patient age, gender) (14) have been considered. Thirdly, although the participant rate was in line with previous studies (12, 21-25), only those interested on the topic may have answered to the survey, thus introducing a selection bias. Social desirability (53) or memory bias with regarding some specific items (e.g., the frequency of use of CFs in daily practice) can have all affected the findings. Finally, although the participants' profile was in line with that documented at the Italian level where nurses have been documented predominantly to be female, in the middle age, educated mainly in university settings, and working in hospitals (54) the sample of responders may not be representative of the overall Italian nurse population therefore limiting the generalizability of the results.

Educational, research and managerial implications

The CFs valued by nurses and experienced as effective are based upon the internal quality of the nurse and the quality of the relationship between the nurse and the patient. These qualities require a large personal investment: therefore, nurses should be supported in developing these qualities since their nursing graduation. With regard to those neglected CFs, e.g. the quality of the setting where the care is offered, increasing awareness among nurses since nursing education and after, during their clinical experience.

From the point of view of the research and managerial implications, according to the current debate, nursing practice is considered of poor quality when missed nursing care or unfinished nursing interventions occur and this can increase the likelihood of adverse events (55). In this light, different tools are used of measuring the process of nursing care and whether or not interventions are missed or undone, as well as if some implicit rationing of nursing care occur. However, an evidence-based

intervention can be implemented in the expected time and manner, but not accompanied by appropriate CFs, which can reduce its effectiveness.

Moreover, research has already defined how important are the organizational environments and the nursing leadership styles in supporting nurses to be engaged and committed (10); in a poor environment, nurses can be constrained in enacting their compassionate care, thus paradoxically apply all interventions required by patients by neglecting other factors (e.g., verbal communication) that can trigger negative outcomes. Therefore, future research and nurse managers actions focused on safety and adverse effects, should also consider the role of CFs as modulators.

Finally, in designing studies aimed at measuring the effectiveness of nursing interventions, assessing the presence of CFs, for example measuring beliefs or the frequency of their use at the baseline, can help to (a) compare the homogeneity of different contexts, (b) identify groups to compare, or (c) define the contribution of factor(s) other than the intervention under study in the expected outcomes.

Conclusion

Nurses are aware of the CFs as elements to increase the placebo effects and prevent the occurrence of nocebo effects in concomitance with nursing interventions. Nurses believe in the value of the CFs which are implemented around two times per month in several different clinical conditions where psychological and physiological mechanisms might explain their effectiveness. Nurses are not used to communicate the implementation of CFs to the patients, therefore their adoption remains as part of the optimization of the routine clinical practice. Moreover, nurses consider the use of CFs as ethically acceptable when capable of producing benefits for the patient.

Nurses like and use mainly verbal and non-verbal communication, patient-centered approaches, psychical contact and the empathetic therapeutic alliance; differently, those who dislike contextual factors are concerned about professional reputation, uniform, adequate environment and design.

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Table 1. Participant characteristics (n=425)

Variables	Frequency (%)	95%CI
	Average (SD)	
Gender		
Female	361 (84.9)	81.1-88.1
Male	64 (15.1)	11.8-18.9
Age, years		
	46.60 (8.6)	45.7-47.4
Italian Region		
North	251 (59.1)	54.2-63.7
Centre	93 (21.8)	18.1-26.2
South	81 (19.1)	15.5-23.2
Nursing Education		
Bachelor	194 (45.6)	40.8-50.5
Bachelor + E-learn	58 (13.6)	10.6-17.4
Bachelor + MNS	21 (4.9)	3.2-7.6
Bachelor + MNS + E-learn	8 (1.8)	0.8-3.8
Bachelor + MSN + Post grad dip	22 (5.2)	3.4-7.8
Bachelor + MSN + Post grad dip + E-learn	11 (2.6)	1.4-4.7
Bachelor + Post grad dip	11 (2.6)	1.4-4.7
Bachelor + Post grad dip + E-learn	100 (23.5)	19.6-27.9
Years of professional practice		
	23.7 (10.1)	22.7-24.7
Setting		
Hospital	348 (81.8)	77.8-85.4
Nursing home	19 (4.5)	2.8-7.0
Community care	40 (9.4)	6.8-12.7
Other	18 (4.2)	2.6-6.7
Nursing Association		
Medical Nurses	263 (61.8)	57.1-66.5
Diabetic care Nurses	119 (28.0)	23.8-32.6
Geriatric Nurses	23 (5.4)	3.5-8.1
Neuroscience Nurses	20 (4.7)	2.9-7.3

Legend: N, number of participants; %, percentage; SD, standard deviation; 95%CI, 95% confidence interval; E-learn, e-learning; MNS, master of nursing science; Post grad dip, post graduated diploma

Table 2. Beliefs regarding contextual factors as reported by participants (n=425)

Domains	Item	Likert Score average [†] (95%CI)	Very Much n (%); 95%CI	Enough n (%); 95%CI	Nothing n (%); 95%CI	Unknown n (%); 95%CI
Nurse	Professional reputation	2.35 (2.24-2.46)	191 (44.9); 40.2-49.8	199 (46.8); 42.0-51.7	17 (4.0); 2.4-6.4	18 (4.2); 2.6-6.7
	Uniform	2.01 (1.89-2.12)	164 (38.6); 33.9-43.4	196 (46.1); 41.3-50.9	55 (12.9); 9.9-16.6	10 (2.4); 1.2-4.4
	Positive attitudes/optimistic behavior	3.14 (3.04-3.23)	334 (78.6); 74.3-82.3	82 (19.3); 15.7-23.4	7 (1.6); 0.7-3.5	2 (0.5); 0.1-1.8
Patient	Patient's expectation and preference	3.06 (2.97-3.15)	311 (73.2); 68.7-77.3	108 (25.4); 21.4-29.8	3 (0.7); 0.2-2.2	3 (0.7); 0.2-2.2
	Patient's previous experience	2.94 (2.85-3.03)	298 (70.1); 65.5-74.4	120 (28.2); 24.1-32.8	2 (0.5); 0.1-1.8	5 (1.2); 0.4-2.9
Nurse Patient Relationship	Verbal communication	3.30 (3.22-3.39)	353 (83.1); 79.1-86.4	62 (14.6); 11.4-18.4	2 (0.5); 0.1-1.8	8 (1.8); 0.4-2.9
	Not verbal communication	3.29 (3.20-3.38)	351 (82.6); 78.6-86.0	62 (14.6); 11.4-18.4	3 (0.7); 0.2-2.2	9 (2.1); 1.0-4.1
	Empathetic therapeutic alliance	3.34 (3.25-3.43)	349 (82.1); 78.1-85.6	64 (15.1); 11.8-18.9	2 (0.5); 0.1-1.8	10 (2.4); 1.2-4.4
Intervention	Over therapy	3.02 (2.92-3.13)	307 (72.2); 67.7-76.4	74 (17.4); 14.0-21.4	20 (4.7); 2.9-7.3	24 (5.6); 3.7-8.4
	Patient-centered approach	3.32 (3.22-3.42)	353 (83.1); 79.1-86.4	49 (11.5); 8.7-15.1	9 (2.1); 1.0-4.1	14 (3.3); 1.8-5.6
	Professional approach with patient	3.15 (3.06-3.24)	324 (76.24); 71.8-80.1	68 (16.0); 12.7-19.9	5 (1.2); 0.4-2.9	28 (6.6); 4.5-9.5
	Physical contact with patient	3.19 (3.10-3.28)	331 (77.88); 73.6-81.7	57 (13.4); 10.4-17.1	11 (2.6); 1.4-4.7	26 (6.1); 4.1-8.9
Healthcare setting	Comfortable setting	2.68 (2.56-2.79)	279 (65.65); 60.9-70.1	88 (20.7); 17.0-24.9	44 (10.4); 7.7-13.7	14 (3.3); 1.8-5.6
	Adequate environmental architecture	2.52 (2.41-2.63)	244 (57.41); 52.6-62.1	124 (29.2); 24.9-33.8	42 (9.8); 7.3-13.2	15 (3.5); 2.1-5.8
	Adequate design	2.32 (2.21-2.44)	205 (48.24); 43.4-53.1	157 (36.9); 32.4-41.8	48 (11.3); 8.5-14.8	15 (3.5); 2.1-5.8

Legend: %, percentage; n, number of participants; 95%CI, 95% confidence interval

[†] Likert scale: 0, not at all; 1, few; 2, enough; 3, much; 4, a lot of.

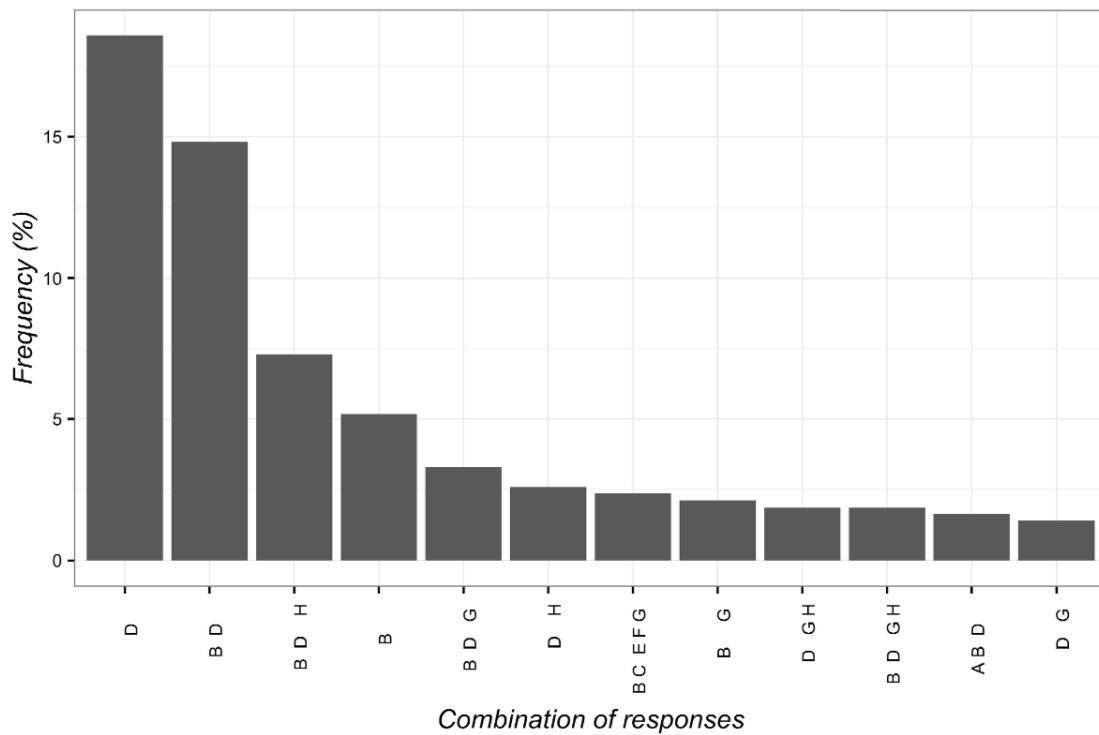
Table 3. Contextual factors use in clinical practice as reported by participants (n=425)

Domains	Item	Likert Score average† (95%CI)	Very Much n (%); 95%CI	Enough n (%); 95%CI	Nothing n (%); 95%CI	Unknown n (%); 95%CI
Nurse	Professional reputation	1.95 (1.76-2.14)	174 (40.9); 36.3-45.8	35 (8.2); 5.8-11.4	159 (37.4); 32.8-42.2	57 (13.4); 10.4-17.1
	Uniform	2.21 (2.03-2.39)	218 (51.3); 46.4-56.1	31 (7.3); 5.1-10.3	150 (35.3); 30.8-40.1	26 (6.1); 4.1-8.9
	Positive attitudes/optimistic behavior	2.90 (2.73-3.06)	307 (72.2); 67.7-76.4	13 (3.1); 1.7-5.3	103 (24.3); 20.3-28.6	2 (0.5); 0.1-1.8
Patient	Patient's expectation and preference	2.76 (2.60-2.92)	306 (72.0); 67.4-76.2	14 (3.3); 1.8-5.6	103 (24.3); 20.3-28.6	2 (0.5); 0.1-1.8
	Patient's previous experience	2.49 (2.34-2.65)	273 (64.2); 59.5-68.7	40 (9.4); 6.9-12.7	108 (25.4); 21.4-29.8	4 (0.9); 0.3-2.6
Nurse Patient Relationship	Verbal communication	2.96 (2.80-3.12)	317 (74.6); 70.1-78.6	5 (1.2); 0.4-2.9	101 (23.7); 19.8-28.2	2 (0.5); 0.1-1.8
	Not verbal communication	2.91 (2.75-3.08)	316 (74.4); 69.8-78.4	5 (1.2); 0.4-2.9	102 (24.0); 20.1-28.4	2 (0.5); 0.1-1.8
	Empathetic therapeutic alliance	2.80 (2.64-2.95)	308 (72.5); 67.9-76.6	13 (3.1); 1.7-5.3	102 (24.0); 20.1-28.4	2 (0.5); 0.1-1.8
Intervention	Over therapy	2.64 (2.49-2.80)	287 (67.5); 62.8-71.9	28 (6.6); 4.5-9.5	104 (24.5); 20.5-28.9	6 (1.4); 0.6-3.2
	Patient-centered approach	2.86 (2.70-3.02)	306 (72.0); 67.4-76.2	14 (3.3); 1.8-5.6	102 (24.0); 20.1-28.4	3 (0.7); 0.2-2.2
	Professional approach with patient	2.91 (2.75-3.08)	313 (73.7); 69.1-77.7	6 (1.4); 0.6-3.20	102 (24.0); 20.1-28.4	4 (0.9); 0.3-2.6
	Physical contact with patient	2.88 (2.72-3.04)	311 (73.2); 68.6-77.3	8 (1.8); 0.8-3.82	102 (24.0); 20.1-28.4	4 (0.9); 0.3-2.6
Healthcare setting	Comfortable setting	2.38 (2.22-2.55)	258 (60.7); 55.8-65.4	30 (7.1); 4.9-10.0	127 (29.8); 25.6-34.5	10 (2.4); 1.20-4.43
	Adequate environmental architecture	1.99 (1.82-2.16)	202 (47.5); 42.7-52.4	45 (10.6); 7.9-14.0	156 (36.7); 32.2-41.5	22 (5.2); 3.35-7.85
	Adequate design	1.57 (1.41-1.76)	145 (34.1); 29.7-38.8	74 (17.4); 14.0-21.4	183 (43.1); 38.3-47.1	23 (5.4); 3.54-8.13

Legend: %, percentage; n, number of participants; 95%CI, 95% confidence interval

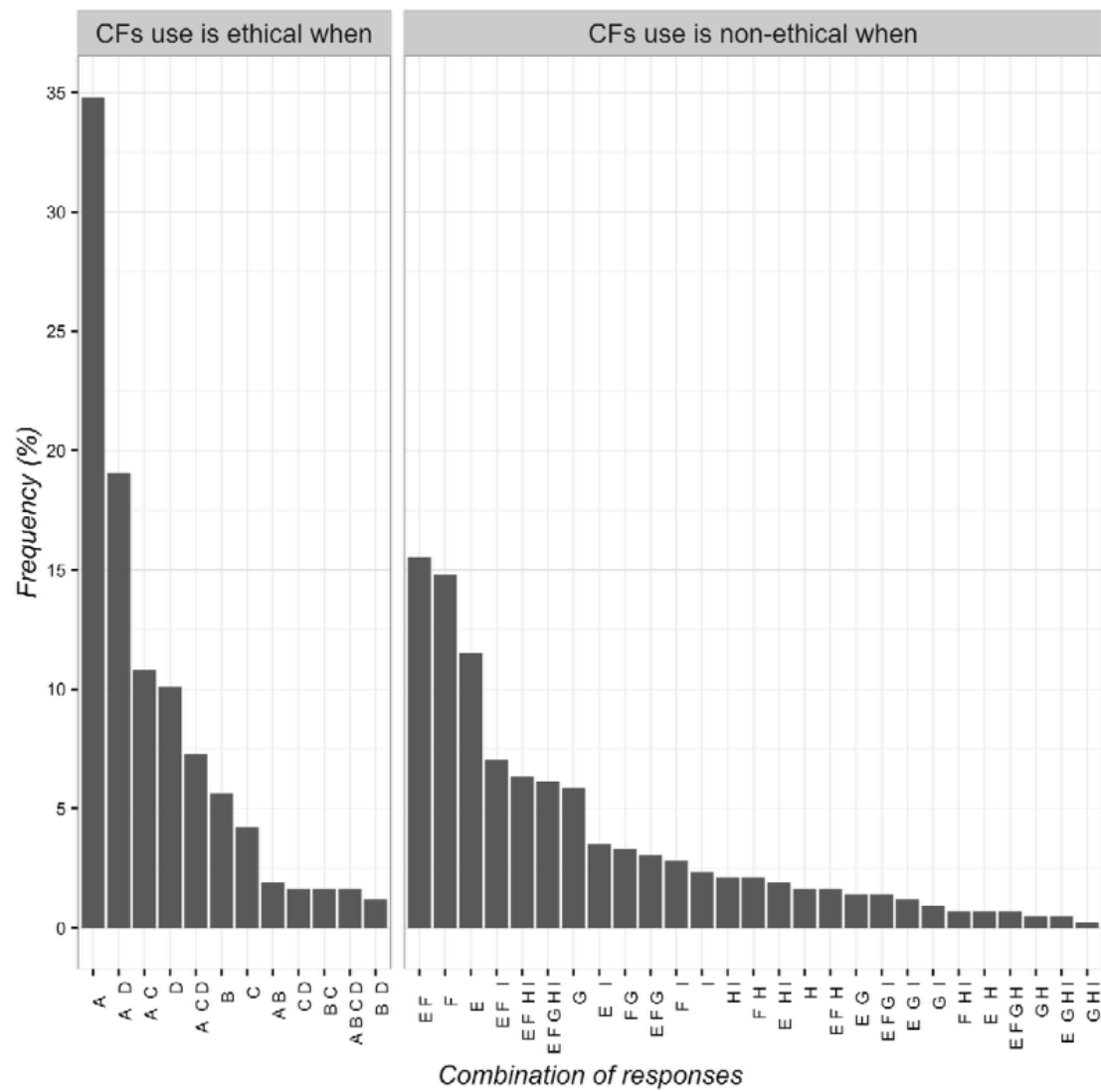
† Likert scale: 0, never; 1, at least once per year; 2, at least once per month; 3, at least once per week; 4, daily.

Figure 1. Contextual Factors circumstances of application



A: 'As a result of unjustified and continuing demand of nursing interventions by the patient', B: 'To calm the patient', C: 'when all other interventions are over', D: 'As an adjunct to other nursing intervention to optimize clinical outcomes', E: 'For non-specific problems, F: 'To stop the patient's complaints', G: 'As a diagnostic tool to differentiate between psychological and physiological problems', H: 'To control pain', I: 'To gain time' (e.g., physician arrival or consultation).

Figure 2. Contextual factors use and ethical implications



CFs use is ethical when. A: ‘It exerts beneficial psychological effects’, B: ‘Other interventions are over’, C: ‘The patient desire or expects this intervention, D: ‘My clinical experience has shown the effectiveness’.

CFs use is not-ethical when. E: ‘It is based on deception’, F: ‘Threatens trust between the patient and the nurse’, G: ‘The evidences available are insufficient’, H: ‘Some legal problems can arise’, I: ‘It can develop adverse effects’.

Supplementary file 1. The questionnaire: “Knowledge about contextual factors among Italian nurses.”

Welcome to this survey!

Dear colleague thank you for take part in this survey.

This survey aims to clarify the use of *contextual factors* in enhancing the therapeutic outcome in nursing care.

The contextual factors consist of a series of relational or environmental situations that may affect the perception of patients’ suffer and functional impairment. Examples of the main contextual factors are: the words and posture used by the nurse, the smells, the sounds and the decor of the therapeutic setting to enhance the effectiveness of nursing care.

We consider important to study them in their spread within nursing care.

Kindly answer the following questions based on your personal clinical experience. The compilation of the entire questionnaire takes a maximum of 10 minutes. Your answers are completely anonymous and will only be used for the purposes of this research.

Whenever you complete the page, click on "Next" to save your answer. If you decide to abandon the survey, select "Exit".

Socio-demographic characteristics

What is your gender? [select]

- Male
- Female

How old are you? [complete]

.....

How long have you licensed as nurse? [complete]

.....

In which region of Italy do you work? [select]

- North
- Center
- South

What is your clinical workplace? [select]

- Hospital
- Nursing home
- Community care
- Other

What is your reference association? [select]

- A.N.I.N. (Associazione Nazionale Infermieri Neuroscienze)
- A.N.I.M.O. (Associazione Nazionale Infermieri Medicina Ospedaliera)
- G.R.G (Gruppo di Ricerca Geriatrica)
- O.S.D.I. (Operatori Sanitari di Diabetologia Italiani)

Which training path did you experience? [you can select more than one answer]

- Bachelor of nursing
- Master of nursing science
- Post graduated diploma
- E-learning

Definition

How would you define the therapeutic role of contextual factors? [select]

- an intervention without a specific effect for the condition being treated, but with a possible aspecific effect
- an intervention that has a special effect through known physiological mechanisms
- sham treatment used as control tests for safety and efficacy of active treatment
- a harmless or inert intervention

Beliefs

How do you BELIEVE that your therapeutic outcome can be influenced by ...? [select]

	Very Much	Much	Enough	Few	None	I don't know
Professional reputation						
Uniform						
Positive attitudes and optimistic behaviour						
Patient's expectation and preference						
Patient's previous experience						
Verbal communication						
Not verbal communication						
Empathetic therapeutic alliance with patient						
Over therapy						
Patient-centered approach						
Professional approach with patient						
Physical contact with patient						
Comfortable setting						
Adequate environmental architecture						
Adequate design						

Frequency of use (1/2)

How often in your career do you INTENTIONALLY used the contextual factors to enhance the result of nursing care? [select]

- many times
- often
- at least once
- never

Frequency of use (2/2)

Indicate how often do have you INTENTIONALLY used the following contextual factors with the patient to enhance the nursing outcome:

[select]

	Every day	At least once a week	At least once a month	At least once a year	Never	I did not think it was a contextual factor capable to influence therapeutic outcome
Professional reputation						
Uniform						
Positive attitudes and optimistic behaviour						
Patient's expectation and preference						
Patient's previous experience						
Verbal communication						
Not verbal communication						
Empathetic therapeutic alliance with patient						
Over therapy						
Patient-centered approach						
Professional approach with patient						
Physical contact with patient						
Comfortable setting						
Adequate environmental architecture						
Adequate design						

Application

Under what CIRCUMSTANCES would you use contextual factors? [you can select multiple possibilities]

- as a result of unjustified and constant demands for nursing interventions
- to calm the patient
- when all other therapies are over
- as an adjunct to other nursing interventions to optimize the clinical responses
- for non-specific problems
- to stop the patient's complaints
- as a diagnostic tool to differentiate between psychological and physiological problems
- to control pain
- to gain time

Therapeutic effect

What are, in your opinion, the POTENTIAL EFFECTS of contextual factors in the following health problems? [select]

	Psychological	Physiological	Psychological and Physiological	No benefit
acute pain				
chronic pain				
cognitive disorder				
emotional disorder				
gastrointestinal disorder				
sexual disorder				
drug and medication addiction				
neurological disorder				
rheumatologic disorder				
immune and allergic disorder				
oncological disorder				
cardiovascular disorder				
infectious				
insomnia				

Communication

How do you COMMUNICATE to the patient the use of contextual factors at the end of treatment? The notified its ... [you can select multiple possibilities]

- it is a treatment that can help and will not hurt
- it is an effective treatment
- do not say anything
- it is a treatment without a specific effect
- it is a treatment that induces a psychological change
- it can help but you are not sure about its effect.

Ethical issues

The use of contextual factors for therapeutic purposes can be considered

ETHICALLY ACCEPTABLE when ... [you can select more than one answer]

- it exerts beneficial psychological effects
- the other therapies are over
- the patient wants or expects this treatment
- clinical experience has shown the effectiveness

The use of contextual factors for therapeutic purposes can be considered

ETHICALLY NOT ACCEPTABLE when ... [you can select more than one answer]

- it is based on deception
- it undermines trust between patient and nurse
- the evidences are insufficient
- legal problems arise
- it can create adverse effects

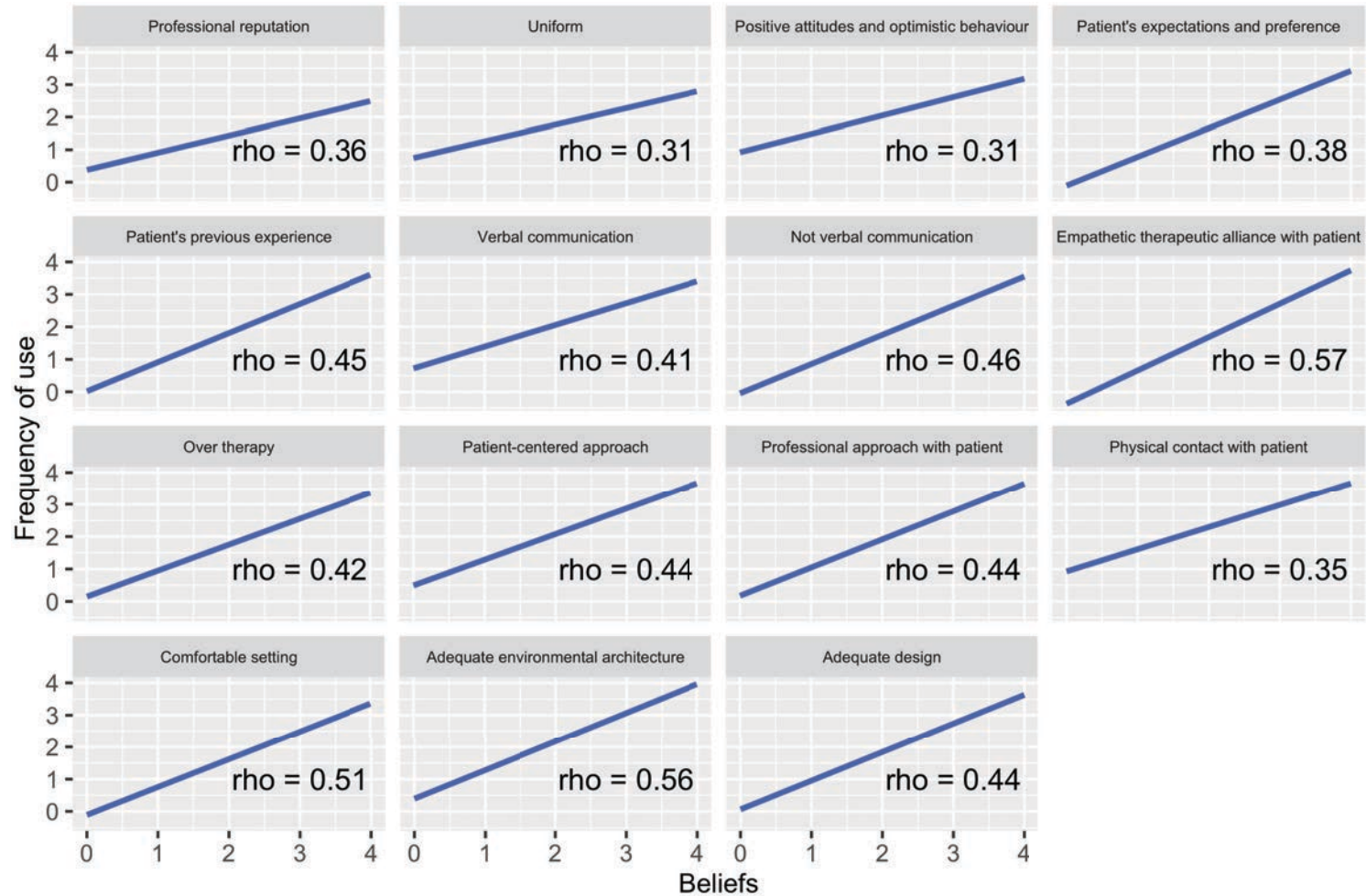
Dear colleague thanks for spending your precious time in completing this survey!

Supplementary File 2. Therapeutic effects of contextual factors as reported by participants (n=425)

Clinical conditions	Psychological and Physiological n (%); 95%CI	Psychological n (%); 95%CI	Physiological n (%); 95%CI	No effects n (%);95%CI
Emotional disorders	230 (54.1); 49.2-58.9	172 (40.5); 35.8-45.3	15 (3.5); 2.1-5.8	8 (1.8); 0.8-3.8
Chronic pain	259 (60.9); 56.1-65.6	108 (25.4); 21.4-29.8	35 (8.2); 5.8-11.4	23 (5.4); 3.5-8.1
Cognitive disorders	199 (46.8); 42.0-51.7	177 (41.6); 36.9-46.5	22 (5.2); 3.4-7.8	27 (6.4); 4.3-9.2
Insomnia	243 (57.2); 52.3-61.9	144 (33.8); 29.4-38.6	5 (1.2); 0.4-2.9	33 (7.7); 5.5-10.8
Acute pain	202 (47.5); 42.7-52.4	140 (32.9); 28.5-37.6	39 (9.2); 6.7-12.4	44 (10.4); 7.7-13.7
Oncological problems	190 (44.7); 39.9-49.6	134 (31.5); 27.2-36.2	43 (10.1); 7.5-13.5	58 (13.6); 10.6-17.4
Rheumatologic problems	179 (42.1); 37.4-46.9	99 (23.3); 19.4-27.6	70 (16.5); 13.1-20.4	77 (18.1); 14.6-22.2
Cardiovascular problems	187 (44.0); 39.2-48.8	90 (21.2); 17.5-25.4	68 (16.0); 12.7-19.9	80 (18.8); 15.3-22.9
Gastrointestinal problems	190 (44.7); 39.9-49.6	61 (14.4); 11.2-18.1	86 (20.2); 16.6-24.4	88 (20.7); 17.0-24.9
Neurological problems	182 (42.8); 38.1-47.7	84 (19.7); 16.2-23.9	67 (15.7); 12.5-19.6	92 (21.6); 17.9-25.9
Sexual problems	163 (38.4); 33.7-43.2	136 (32.0); 27.6-36.7	23 (5.4); 3.5-8.1	103 (24.2); 20.3-28.6
Drug/medication addiction	140 (32.9); 28.5-37.6	125 (29.4); 25.2-34.0	26 (6.1); 4.1-8.9	134 (31.5); 27.2-36.2
Immunological problems/allergies	136 (32.0); 27.6-36.7	88 (20.7); 17.0-24.9	43 (10.1); 7.50-13.48	158 (37.2); 32.6-41.9
Infections	92 (21.6); 17.8-25.9	122 (28.7); 24.5-33.3	30 (7.1); 4.89-10.03	181 (42.6); 37.8-47.5

Legend: %, percentage; n, number of participants; 95%CI, 95% confidence interval

Supplement Figure 1. Correlation between the frequency of use and beliefs for each Contextual factor under study.



APPENDIX III

THE PLACEBO EFFECT IN MOTOR PERFORMANCE IS DIFFERENTLY MODULATED BY EXTERNAL AND INTERNAL FOCUS OF ATTENTION

In preparation:

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The placebo effect in motor performance is differently modulated by external and internal focus of attention.

Abstract

Background: The placebo effect is a beneficial outcome that follows the application of an inert treatment. It can influence not only perception (like pain), but also behaviour, for example by improving motor performance. Motor control can be modulated in many ways. One of the most powerful is the focus of attention. In this context, directing attention to the movements of the body (internal focus) or to the goal of the action (external focus) can have different effect on motor performance. The aim of our study was to investigate whether attentional focus and placebo procedures interact in modulating motor performance.

Methods: 60 healthy subjects (25 women; mean age, 23.2 ± 3.3 years) were randomized in 4 groups: placebo group with internal focus of attention (PI), placebo group with external focus of attention (PE), control group with internal focus of attention (CI) and control group with external focus of attention (CE). Subjects performed a motor task by pressing a piston as strongly as possible with the right index finger. The PE and CE groups were instructed to “concentrate on the piston’s movement”; the PI and CI groups were instructed to “concentrate on the finger’s movement”. The PE/PI groups were verbally informed that treatment with peripheral low-frequency transcutaneous electrical nerve stimulation (TENS) applied on the first dorsal interosseus would induce force enhancement. These groups were also conditioned after TENS application, with a surreptitious amplification of the visual feedback signalling the force level; the CE/CI groups instead, were told that TENS was not effective and they did not undergo the conditioning phase.

Results: The PE and PI groups believed that TENS had been effective and expected to perform better compared with the CE and CI groups. Moreover, the PI group presented higher force levels than the PE group, suggesting that the placebo effect in motor performance can be enhanced with an internal focus of attention.

Conclusion: These findings show for the first time that the placebo effect in motor performance can be influenced by the subject's attentional focus.