ISSN: 2474-9206

Review Article

Journal of Anesthesia & Pain Medicine

The Importance of Harnessing Neurophysiological Placebo Analgesic Mechanisms Through Therapeutic Contextual Factors When Treating Patients with Chronic Pain

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Submitted:23 Jan 2023; **Accepted:**26 Jan 2023; **Published:**31 Jan 2023

Citation: Romm, M. J. (2023). The Importance of Harnessing Neurophysiological Placebo Analgesic Mechanisms Through Therapeutic Contextual Factors When Treating Patients with Chronic Pain. *J Anesth Pain Med,* 8(1), 20-25.

Abstract

Chronic pain (CP) is a multifaceted experience that has significant effects on the patients themselves, in addition to their families, social and professional situations. Therapeutic contextual factors (TCFs) are essential components of both psychological and physical interventions, and are understood to be core variables underlying the development of the analgesic placebo effect. With the emergence of imaging studies and other high-resolution medical technology in recent years, these tools have been able to highlight key cortical regions and neuroscientific mechanisms that play a part in the placebo response. The following review dissects what makes-up TCFs. In turn, the review describes various neuroscientific mechanisms that catalyze placebo analgesic responses that are triggered due to of these TCFs. Ultimately, this paper empasizes the need to use these TCFs within clinical situations, as made evidenced through current neuroscientific research, in order to provide patients with CP with the best possible outcomes and overall quality of life.

Keywords: Therapeutic Contextual Factors (TCFs)
Placebo Analgesic Responses (PARs) Chronic Pain (CP)

Introduction

The Global Burden of Disease study, published at the end of 2012, suggests that chronic low back pain (CLBP) is the foremost contributor to disability worldwide [1]. Roughly 20% of Americans live with chronic pain (CP) [2,3] and as a result have serious medical and non-medical consequences [2-4]. Pain severity, psychological health associated with chronic pain (CP) and pain beliefs (such as fear-avoidant behavioral patterns) are correlated with disability in patients whom experience on-going pain [5]. CP a multifaceted experience, has substantial consequences on patients themselves, as well as on their families and social and professional situations, which ultimately causes a decline on the patients` and their families` quality of life [5, 6]. The pain experience is complex and subjective, and is marked by factors such as cognition, mood, beliefs and genetics [7]. Therapeutic contextual factors (TCFs) are essential part of both psychological and physical treatments, and are key contributors to the placebo effect [8]. Many functional Magnetic Resonance Imaging (fMRI) and Positron Emission Tomography (PET) studies have revealed that the placebo analgesic effects take place in the same brain regions as those stimulated by non-sham analgesic treatments [9-13]. A healthy body of literature, specifically gained in the field of pain science, has identified neural networks, as will be described through this paper, stimulated by TCFs [14]. Importantly, when understanding the mechanisms underlying CP pathologies and thus treating such conditions, the concept of the 'pain matrix' and therefore pain perception should not be understood in isolation; ie 'top-down` versus 'bottom-up'. The following condensed review, through an integration of cognitive neuroscientific mechanisms and theories, will focus on TCF`s that contribute to and act as catalysts for placebo analgesic effects. In turn, the paper aims to promote the implementation and enhancement of such therapeutic factors to achieve the best outcomes for patients suffering from CP.

Understanding brain mechanisms may be critical for a broad array of therapeutic approaches,[11] including those concentrating on the therapeutic context [11, 15]. Schafer assert that "the context surrounding a treatment is rich, and includes a variety of factors that can influence placebo effects" [16]. In the past, placebo was viewed as an `inactive` agent within a treatment, however, pla-

cebo is now understood as an active mechanism/s, based on the patient`s perception/s of the intervention during treatment [17]. Placebo analgesic research has revealed that patients` perceptions of a treatment are shaped by, for example, previous experiences with pain treatment, the *patient-clinician relationship* as well as by expectations and emotions. Simply stated, Edvon Koshi (2017, p.6) describes placebo effect as an advantageous "…complex psychophysiological response that involves motor cognitive-verbal and physiochemical responses" [18]. Expanding upon the above description, placebo effects are valuable effects that are a result of the brain-mind responses to the context in which treatment is distributed, rather than to the specific intervention itself [19]. These beneficial effects are facilitated by a conglomeration of varied processes and can influence various clinical and physiological outcomes related to health, such as the experience of CP [17, 19]. The discovery of numerous influential psychological and neurobiological mechanisms involved in placebo hypoalgesia has already transpired and continues to do so, indicating that placebo analgesia has a psycho-neurobiological basis [17, 20-26].

TCFs can affect the outcome of an intervention through varying mechanisms and in different physiological systems, diverse medical conditions and different therapeutic treatments [14, 27]. A treatment is never administered in a neutral environment, but rather in a multifaceted composite of TCFs that have cognitive neuroscientific effects [27]. Emerging neuroscientific evidence suggests multiple brain systems and networks (`pain matrix`) involved under the umbrella of pain processing. The *descending pain modulation system*, the major system involved in pain regulation and therefore an individual`s overall pain perception, includes the periaqueductal gray (PAG), the rostral ventromedial medulla (RVM) and the spinal cord (SC); the PAG-RVM-SC system [16]. The descending pain modulation system obtains both direct and indirect input from many cortical and subcortical brain regions that include, but not limited to, the dorsolateral prefrontal cortex (dIPFC), ventromedial prefrontal cortex (vmPFC), rostral anterior cingulate cortex (rACC), anterior insula (aIns), amygdala, nucleus accumbens (NAc) and hypothalamus [16, 28].

TCFs may be divided into internal (eg memories, emotions, expectations, psychological traits of the patient), external (physical aspects of the treatment such as medication based or manual, the setting in which the intervention is given etc) and relational / the therapeutic alliance (factors that depict the patient-clinician relationship such as communication style, body language etc) [14, 15]. The above suggests both bottom-up and top-down processes are at play based on TCF factors. Accordingly, Schafer et al outlines, based on previous literature, that human neuroimaging studies have located placebo induced activations as well as deactivations within PAG-RVM-SC system, as well as in various cortical analgesic input areas [9, 16, 29, 30]. Briefly, there are numerous forebrain areas that show increased activity during placebo analgesia and are understood to reduce pain processing [16,19]. These regions include the dIPFC, rACC, vmPFC, medial orbitofrontal cortex (mOFC) and NAc [16, 29, 30-32]. Each one of the above regions are directly or/and indirectly involved in pain reduction through possible mechanisms such as the ACC being directly involved in the affective and reward component of pain processing through the ability to avoid noxious stimuli [33, 34]. The PFC is indirectly involved through its networking and connections with other areas directly involved in pain processing such as the hippocampus (memory and expectation) and amygdala (emotional relationship with pain behaviors and experiences) [35]. In contrast, while generally exhibiting increased activity during the application of painful stimuli, following placebo analgesic intervention, cortical regions exhibit reduced activity such as the aIns, dorsal anterior cingulate cortex (dACC), amygdala and the somatosensory cortex [9, 15, 30, 33, 37, 38]. Therefore, studies to date, support the idea that top-down activation of endogenous analgesic mechanisms through the descending modulatory system signifies an important mechanisms of placebo analgesia.

Ultimately, the placebo effect is achieved through the relationship between bottom-up and top-down mechanisms, however central to all these factors is the notion of the patient`s *expectancy/ anticipation* [14]. The conditioning model suggests that patients` expectations are greatly learned through patient`s previous contacts and experiences with the medical/health-care system [14, 18, 39]. Structures and systems implicated in the conditioning model such as fear conditioning include the parietal insular cortext, amygdala, hippocampus and the posterior intralaminar nucleus of the thalamus, as well as others [40]. This theory situates the responsibility for placebo response not with the patient per say, but rather in the hands of the medical system [18]. With reference to both positive and negative patient conditioning, research has identified numerous top-down descending pain-modulatory schemes that involve neurochemical mediators such as endogenous opioids, cannabinoids, serotonin, dopamine, norepinephrine, oxytocin, choleycystokinin, galanin and NK1 [16, 41]. Of note, many of these chemicals can act as both facilitators and inhibitors of the pain experience and thus, introducing the notion of the neuroscience pain paradox. Colloca et al (2013) suggests that psychological mechanisms such as verbally tempted expectancies, cued and contextual conditioning and social learning, act as catalysts for the cascade of events leading to the production and release of endogenous opioids and other endogenous analgesic chemicals and hormones [25, 42]. Recent findings have shown that placebo analgesic effects can perfectly emulate the actions of real exogenous pain killers and can enhance the release of endogenous opioids and non-opioids in the human body [25, 43].

As alluded to above, these neurobiological processes may be activated by the subject`s expectations which are the consequence of the interplay between various psychological perceptual mechanisms such as emotions and motivations (e.g., anxiety, stress, desire for pain relief), somatic focus and cognitions (e.g., thoughts and attitudes towards the treatment and or treating clinician) [10, 20, 42, 44-46]. Therefore, current laboratory-based and clinical re-

search highlights the clinical relevance of placebo hypoalgesia in order to advance improved treatment outcomes [10, 20, 24]. In addition, treating clinicians also need to be fully aware of the above mechanisms when treating patients with CP in order to further enhance the overall success of the patients` management

Expanding upon the topic of patient expectations, anticipation may be facilitated by a variety of psychological and cognitive mechanisms including learning by instructions, learning through experience and social and observational learning [25, 42]. Bassett and Mattar (2017) suggest that there are multiple dynamic cortical networks in operation during any learning activity and highlights moving forward towards a network based model underlying learning theory [46]. Of particular interest to this paper, neural correlates pertaining to direct observational learning on the pain experience and placebo analgesia have not been systematically researched to date [47]. However, past studies outline that the anterior insula (AI) and ACC light up during the processing of both experienced and observed pain, in addition to pain prediction and anticipation [47, 48]. Therefore, these brain regions, and feasibly others, may be involved in placebo effects encouraged by social observational learning [47, 48]. According to the social observational learning theory model, placebo effects can be learned through observations of other patients having an analgesic response to a particular treatment, such as medication, invasive treatment, manual treatment, exercise, cognitive behavioral treatment, other psychoeducational treatments for CP and other conditions [22, 42, 47, 49]. Based on previous social learning theory work by Albert Bandura, Bajcar and Babel outline a model of social observational learning (see figure 1) that explains the mechanisms and factors, relating to observational learning, that contribute to placebo analgesic effects [47]. The model includes three ways in which information is conveyed from one subject to another subject (observer): (1) through physical demonstration of pain behavior (behavior modeling), (2) through verbal report of pain (verbal modeling) and (3) via indirect pictorial representation (symbolic modeling) [47]. In addition, the model, importantly, includes the role of expectancies and the individual characteristics of the observing subject in the production of placebo analgesia as well as nocebo hyperalgesia brought on by social observational learning [47]. Thus, the notion to enhance the social learning effect in treatment through the witnessing of other patients having improvement in their pain symptomology and in turn a reduction in the observer`s symptomology, should stimulate the topic around the effects and further use of group-based pain management intervention [10, 20 42, 23, 47, 49, 50].

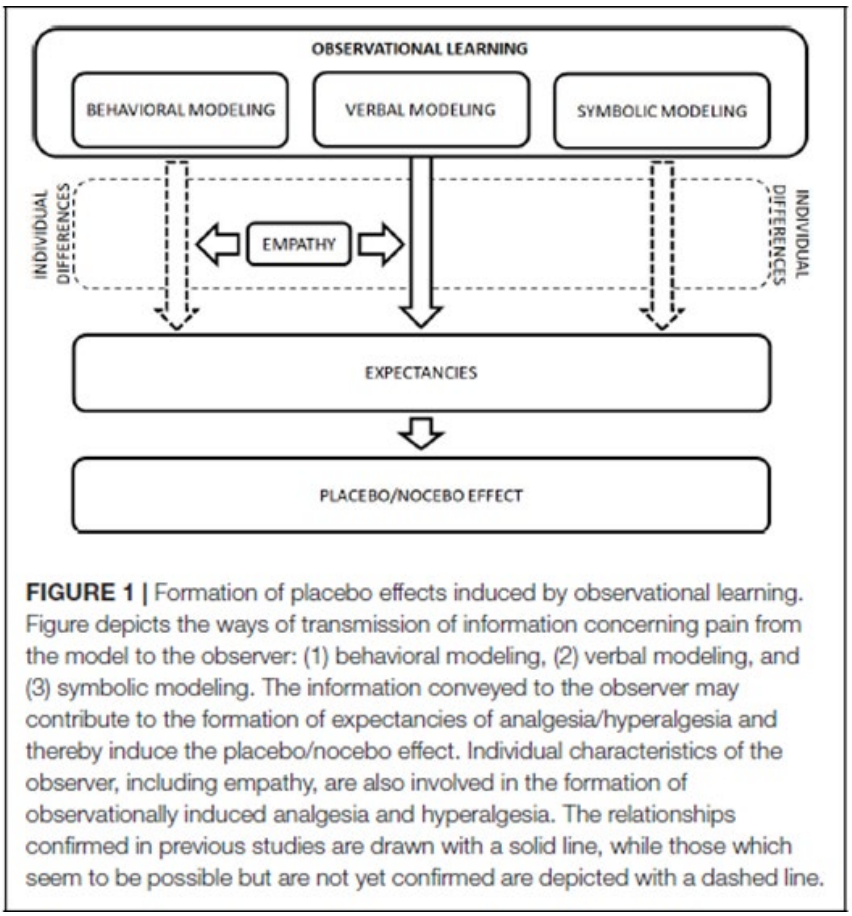

FIGURE 1 | Formation of placebo effects induced by observational learning. Figure depicts the ways of transmission of information concerning pain from the model to the observer: (1) behavioral modeling, (2) verbal modeling, and (3) symbolic modeling. The information conveyed to the observer may contribute to the formation of expectancies of analgesia/hyperalgesia and thereby induce the placebo/nocebo effect. Individual characteristics of the observer, including empathy, are also involved in the formation of observationally induced analgesia and hyperalgesia. The relationships confirmed in previous studies are drawn with a solid line, while those which seem to be possible but are not yet confirmed are depicted with a dashed line.

Figure 1: Model of social observational learning mechanisms and factors, that contribute to placebo analgesi

Research has revealed, that the most vital therapeutic contextual expectancies related to placebo analgesia are most likely correlated to the patient-healthcare relationship (the therapeutic alliance, as I refer to it), the healthcare provider`s attitudes and behaviors towards the patient and the passion for the suggested mode of treatment [18, 52]. A clinician`s behavior, belief, verbal and non-verbal suggestions can powerfully influence patients` pain perceptions [14]. Referring to the notion of the therapeutic alliance (TA), it is widely considered crucial that the interaction between health care providers and their chronic pain patients, portray understanding and empathy, the knowledge to highlight self-management, empowerment and combined decision making; a feeling of partnership [53]. Strong evidence suggests that a strong patient-clinician relationship and positive therapeutic encounter between the patient and clinician leads to further clinical benefits. Finniss and Benedetti (2005), for example, note how aspects within the therapeutic relationship such the clinician`s use of appropriate words may activate the endogenous opioids and/or dopamine systems, hence improving the patient`s pain outcomes [18, 54]. Therefore, the mere use of a regulatory top-down mechanism such as the use of language (suitable words) by a treating clinician has been shown to have a powerful effect on the patient`s expectations and the meaning of treatment [18, 54]. The above highlights an extremely useful top-down mechanism which stimulates neurobiological alterations in the human body that could promote improved pain outcomes; further highlighting the importance of positive neurophysiological mechanisms at play within a strong TA [18, 54]. Non-verbal communication has also been shown to have very strong positive effects on the pain experience such as the notion of the therapeutic touch [18, 55-58]. Other key TA factors that facilitate placebo analgesia mechanisms include a clinician`s empathetic interaction, active listening, increased time spent with the patient, more face-to-face consultations, warmth, attention, care, encouragement and support [18, 59-65]. All the above elements have been shown to significantly decrease pain more so than the same treatment completed with neutral therapeutic interaction [18, 59-65]. Ultimately, a close interaction between clinicians and their patients is possibly one of the most beneficial ways in which to positively engage a patient`s perception of the treatment that is being supplied and therefore progress the results of treatment [18]. Paying little to no attention to the above components of health-care treatment can be seen as a scientific error. Although it has been identified as crucial to CP outcomes, there is still plenty of space for cognitive neuroscientific research to further dissect the specific mechanisms underlying the positive impact that a strong TA has on the subject matter of placebo analgesia.

Conclusion

In conclusion, novel theories on placebo analgesic mechanisms, have revealed that placebo analgesia largely represents the psychosocial dimension of every intervention and therefore its study should include the psychosocial context that surrounds the patient [18]. To note, every time a patient encounters the medical or health-care system, the placebo response or "context effect" is being molded [18]. TCFs must be understood as active influencers of the therapeutic outcome and in turn may assist in explaining some unanticipated results and fluctuations in the experience of CP symptomology [14, 66]. *Importantly, it is the responsibility and obligation of all staff working in the populating field of pain management and pain neuroscience, whether it being administrative staff, clinical and/or research staff etc, to pay attention to feasible TCFs in the working environment, in order to assist in harnessing and potentiating potential placebo analgesic effects for patients with CP* Thus, the study and practice of placebo analgesia, specifically in relation to TCFs, should be critical for all researchers and clinicians whom research and treat patients with CP [18]. There is cumulative placebo analgesic evidence suggesting that expectations can be activated by verbal suggestions, learning processes and social catalysts amongst other TCFs [43]. Knowledge of the psychological activities involved in placebo analgesic mechanisms and its effects should provide clinicians involved in pain management with tools to better navigate placebo effects within their interventions [43]. Through understanding an individual`s CP experience as an integration between bottom-up and top-down processes, this paper has attempted through a magnifying glass, to provide an abbreviated scope of relevant literature, in order to advocate for a translational understanding of placebo analgesia TCFs and in turn steer in the direction towards their optimal usage in clinical settings. Noteworthy, as with all scientific research, there is still plenty room for further investigation into this crucial subject matter that surrounds the management of patients with CP. Ongoing and future cognitive neuroscientific research should further cement and expand upon the content presented within this paper.

Acknowledgements

There are no conflicts of interest for any of the authors of this manuscript.

No sources of external support or funding. There are no additional acknowledgements to be made.

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