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PREFACE Part II: The Fascinating Mechanisms and Implications of the Placebo Effect

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Neurobiology of the Placebo Effect, Part II is the second part of a two-volume set that examines mechanisms and translational aspects derived from the most recent developments in the area of placebo and nocebo research (Colloca, 2018a, 2018b).

We are seeing a gradual development of placebos and placebo effects from simple tools used to please patients or to validate new drugs to a complex neurobiological phenomenon.

The evaluation of key historical events helps us come to a full appreciation of placebo and its meanings (Finniss, 2018). Moreover, a taxonomy of placebo effects helps us navigate the broadest and narrowest theories by either lumping the most important common features of placebo conceptualizations, or conversely, by splitting their differential elements (Kelley, 2018). Additionally, a linguistic approach by looking at the terms “placebo” and “placebo effects” via Internet-based language corpora helps us discover the impact of placebos not only in medicine but also on our society (Sussex, 2018), while a bibliometric analysis helps us narrow down limitations and gaps in current research (Enck, Horing, Broelz, & Weimer, 2018).

Placebo research started primarily with early 19th century basic clinical and translational studies that are today seen as significant milestones to enhance human health and well-being. These studies include sham surgical interventions such as the skull’s removal by Hildred Carlill to treat a refractory case of insomnia (Cardill, 1919) to Wolffs advocacy for prescribing placebos in accordance with patients’ preferences and choices (Wolff, Dubois, et al., 1946). Pioneering placebo research delved into an exploration of clinical and demographic characteristics of placebo responders (Lasagna, Mosteller, Von Felsinger, & Beecher, 1954). Lasagna and colleagues evaluated patients suffering from postoperative pain who were treated with doses of the opioid morphine interspersed with placebos. Patients were categorized by the frequency at which they responded to the placebo—consistently, intermittently or barely. Translational investigation of placebo continued with the use of “active placebo action” to reduce postoperative pain in patients undergoing major abdominal surgery (Egbert, Battit, Welch, & Bartlett, 1964). Such an active placebo action consisted of interactive preoperative and postoperative visits with increased attention to patients’ expectations and pain coping. As compared to the usual care arm (control), the active

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placebo action resulted in a significant larger reduction of daily morphine intake (30–50% reduction) for postoperative pain (Egbert et al., 1964).

These pioneering studies have paved the way for studying potential factors linked to placebo responsiveness, opening up a set of questions that are timely and ofcurrent interest. These findings are among the first attempts to outline the clinical relevance of shaping patients' expectancies (Darnall & Colloca, 2018; Klinger, Stuhlreyer, Schwartz, Schmitz, & Colloca, 2018) and to use dose-extending placebos along with pharmacological conditioning as a potential pain management tool to taper opioids (Colloca, Enck, & DeGrazia, 2016; Colloca & Howick, 2018).

The United States currently faces an epidemic of opioids (Nahin, 2015; Sullivan & Howe, 2013). Opioid analgesics relieve many types of pain and improve function, but the benefits of opioids when prescribed for chronic pain are questionable (Dowell, Haegerich, & Chou, 2016). Indeed, opioid therapy may actually complicate chronic pain management (Chou, 2016; Chou, Clark, & Helfand, 2003) by causing the development of opioid use disorder (Bohnert et al., 2011) and by increasing the risk of opioid-overdose death (Ray, Chung, Murray, Hall, & Stein, 2016). Placebo research can promote the development and integration of placebos into therapeutic strategies to address both the burden of pain management and the opioid crisis (Darnall & Colloca, 2018).

There is increasing consensus that clinicians can actively set positive patients' expectations (Darnall & Colloca, 2018; Glare, Fridman, & Ashton-James, 2018; Klinger et al., 2018). Educating patients about pain treatments and their effects can strengthen their overall pain reduction, coping, and resilience skills. At the same time, careful attention to negative thoughts, expectations, and beliefs about pain, and pain therapies can help develop strategies for nonpharmacological approaches to be used in conjunction with pharmacological medications. Current understanding of pain management urges us to equip patients and clinicians with "toolkits" (for an example, see Darnall & Colloca, 2018) that can be used to train pain specialists and to strengthen patients' inhibitory endogenous pain modulation (EPM) mechanisms.

A fundamental part of this research is represented by the impact of words and delivered information about treatment responses and their adverse effects (Glare et al., 2018). In clinical research, symptoms and complaints in patient populations, medication nonadherence, and need for additional drug prescriptions, among other topics, are often grouped together into a category called *risk communication and framing effects.* For example, the mere mention of headaches as a common side effect during risk communication for studies on antidepressants and other medications can increase the likelihood that headaches are experienced during the study (Blasini, Corsi, Klinger, & Colloca, 2017; Colloca, 2017a, 2017b; Klinger, Blasini, Schmitz, & Colloca, 2017). Risk communication also leads to an increased rate of withdrawal from the studies, making it difficult to recruit and retain study participants in clinical trials. Communication strategies and framing effects may therefore contribute to the occurrence of side effects and shape decision-making processes, clinical outcomes, and patients' adherence to research protocols and medication (Colloca, 2017a; Colloca & Miller, 2011).

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Preventing harmful communication while still protecting patients' rights and preferences is critical. A potential area of clinical relevance for its applicability is the use of message framing to remodel and retain expectations of patients in clinical contexts (Glare et al., 2018). In the era of automation of health care and telemedicine, message framing can be powerfully used to engage patients during the delivery of treatment and long-term follow-ups (Darnall & Colloca, 2018; Glare et al., 2018). The implementation of such toolkits, automation of health care, and telemedicine should occur in clinical settings in which the patient-clinician interaction and the overall encounter around the patient are optimized. For example, research has linked the relationship between health care providers and outcomes to placebo and nocebo effects (Wampold, 2018). Rooted in ancient medicine, the patient-clinician interaction and its anthropological elements can meaningfully contribute to the overall improvement of outcomes (Blasini, Peiris, Wright, & Colloca, 2018).

Outcome changes do not occur in a vacuum; rather, they can shape brain responses favoring pain relief and well-being. Brain responses and perceptions generate predictions that can in turn affect the process of interpreting pain-related sensory inputs received from the periphery (Hashmi, 2018), further raising the interest in investigating the EPM mechanisms in physiological conditions and pathological disorders. How does the central nervous system (CNS) inhibit pain signaling? Which are the CNS mechanisms that are in common between placebo effects and other forms of pain modulation such as conditioned pain modulation (CPM) and the diffuse noxious inhibitory control (DNIC)? These and other questions are addressed in a comprehensive overview of the CPM mechanisms and their clinical relevance (Damien, Colloca, Belleï-Rodriguez, & Marchand, 2018). It has been speculated that patients who present less efficient CPM might need treatments that restore central and peripheral pain inhibitory processes (Colloca et al., 2017). The prospect of using individual patterns of pain modulation may lead the way to a form of personalized pain management.

Indeed, EPM profiles might predict the development of neuropathic and chronic pain components, the responsiveness to specific classes of pain treatments, and the ability to harness self-healing pain processes.

Placebo effects are observed not only in pain processes but also in other systems. For example, placebo effects and related analyses of patterns of responsiveness have been described in the motor system (Fiorio, 2018; Pollo, Carlino, & Benedetti, 2011) and other neurological disorders (Panagiotis & Mitsikostas, 2018). Also, placebo effects are likely influenced by sleep patterns whereby sleep deprivation may improve expectations and placebo-induced pain reduction (Chouchou, Thien Thanh, Rainville, & Gilles, 2018).

Factors that are external to the patient can also be relevant in triggering placebo and nocebo effects. These factors can range from manufacturing characteristics (e.g., blue versus green pills) to marketing features (Faasse & Martin, 2018; Meissner & Linde, 2018). Generic, as opposed to brand labelling, is one of the most common marketing factors that influence placebo and nocebo effects. Generic medicines that are pharmaceutically equivalent to their branded medicines are often met with distrust and perceived as less effective than branded medicines. Negative perceptions of generic pharmaceuticals may contribute to reduced

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treatment efficacy via enhanced nocebo effects (Faasse & Martin, 2018). These effects are relevant when medications are released on the market.

Depending on the medication and its mechanisms of action, placebo and treatment effects can be additive, subadditive, or superadditive (Coleshill, Sharpe, Colloca, Zachariae, & Colagiuri, 2018). Additivity implies that the treatment effect and the placebo component do not interact; that is, the placebo component is identical for both the placebo and the treatment arms and the overall outcome is the sum of the treatment plus the placebo component. As such, additivity cannot explain the variety of results observed in clinical trials. Subadditivity, the combined placebo and treatment effects that are less than the summed size of the isolated active treatment and isolated placebo effect, can result in considering as ineffective a treatment that is effective. On the other hand, superadditivity, a synergistic interaction between the active treatment and placebo effects, can overestimate the efficacy of the treatment in a randomized clinical trial (Coleshill et al., 2018).

The attentive consideration of the variety of additive- versus nonadditive-related placebo mechanisms, the use of ethical approaches (Annoni, 2018), the development of toolkits (Darnall & Colloca, 2018), and automation of message framing to engage patients (Glare et al., 2018) can maximize placebo effects in medical practice and help implement novel strategies to improve patients' well-being and drug validation and contribute to clinically relevant health outcomes.

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