CHAPTER SIX

Optimizing Placebo and Minimizing Nocebo to Reduce Pain, Catastrophizing, and Opioid Use: A Review of the Science and an Evidence-Informed Clinical Toolkit

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Abstract

Pain, a noxious psychosensory experience, motivates escape behavior to assure protection and survival. Psychological factors alter the experience and trajectory of pain, as well as behavior and treatment response. In the context of pain, the placebo effect (expectation for pain relief) releases endogenous opioids and facilitates analgesia from exogenously administered opioids. Nocebo hyperalgesia (expectation for persistent or worsening pain) opposes endogenous opioid analgesia and patient engagement in prescription opioid tapering. Reductions in nocebo hyperalgesia and pain catastrophizing may enhance descending modulation of pain, mediate adaptive structural brain changes and promote patient engagement in opioid tapering. Interventions that minimize nocebo and optimize placebo may adaptively shape the central nervous system toward pain relief and potentially opioid reduction. Here we provide a critical description of catastrophizing and its impact on pain, placebo and nocebo effects. We also consider the importance of minimizing nocebo and optimizing placebo effects during prescription opioid tapering, and offer a clinical toolkit of resources to accomplish these goals clinically.

1. INTRODUCTION

1.1 The Problem of Pain

Pain is a global health problem with broad negative impacts on physical (Sturgeon, Darnall, Kao, & Mackey, 2015; Sturgeon, Dixon, Darnall, & Mackey, 2015), mental (Bair, Robinson, Katon, & Kroenke, 2003; Feinstein et al., 2017; Ziadni, Sturgeon, & Darnall, 2018), spiritual (Halawa, Al-Diri, McLean, & Darnall, 2015), psychosocial (Karos, Meulders, Goubert, & Vlaeyen, 2018; Karos, Williams, Meulders, & Vlaeyen, 2018; Sturgeon et al., 2016; Ziadni, You, Wilson, & Darnall, 2018), and economic domains (Groenewald, Essner, Wright, Fesinmeyer, & Palermo, 2014; Gustavsson et al., 2012). The 2016 Institute of Medicine report on *Relieving Pain in America* estimated that roughly one-third of the world population is living with ongoing pain of some type (IOM Committee on Advancing Pain Research, 2011). Pain is more costly than diabetes, heart disease, and cancer combined, with combined estimates reaching up to $635 billion each year for medical costs and lost productivity in the United States alone (IOM Committee on Advancing Pain Research, 2011). Effective, scalable, and low-risk pain treatment strategies are urgently needed, particularly in light of calls to reduce opioid prescribing as a pathway to mitigate opioid-related morbidity and mortality in the United States·(CDC, 2016; Hoffman, 2018), Australia, Canada, and elsewhere. Indeed, opioid de-prescribing practices have

rapidly taken effect across the United States with scant attention given to the potential patient harms caused by aggressive tapering approaches, including clear nocebo effects (Hoffman, 2018; Langreth, 2017). Treating pain effectively and compassionately—and at lowest-risk—requires careful attention to the psychological dimensions of pain and, when relevant, opioid reduction (Darnall, 2014a, 2014b).

Pain is a psychosensory experience wherein the brain perceives and interprets pain signaling (Darnall, 2018b). Indeed, by definition pain comprises psychological elements (IASP, 1994), thereby suggesting that, in part, analgesia depends on them. The extant literature demonstrates that psychopathology is both an antecedent (Gerrits, van Marwijk, van Oppen, van der Horst, & Penninx, 2015) and a consequence of persistent pain (Archer et al., 2016). Extending the scope beyond formal psychopathology, psychological factors that are known to influence pain and analgesia include cognition (Burns, Glenn, Bruehl, Harden, & Lofland, 2003; Darnall et al., 2017; Salomons, Moayedi, Erpelding, & Davis, 2014; Seminowicz & Davis, 2006; Seminowicz et al., 2013; Ziadni, Sturgeon, et al., 2018), emotion (Burns et al., 2015; McCracken & Keogh, 2009; Vlaeyen, Crombez, & Linton, 2016), appraisal (Ziadni, Sturgeon, et al., 2018), expectations (Atlas et al., 2012; Colloca & Miller, 2011b; Palermo & Drotar, 1996; Wager, Atlas, Leotti, & Rilling, 2011), attention (Kucyi, Salomons, & Davis, 2013; Seminowicz & Davis, 2006), beliefs about pain and its treatment (Carriere, Martel, Kao, Sullivan, & Darnall, 2017; Carriere et al., 2018). Mechanisms of psychological effects on pain and analgesia include behavioral factors (Linton, Flink, & Vlaeyen, 2018; Vlaeyen et al., 2016), conditioning, and neurochemical pathways. Neurally, psychological factors can influence pain and analgesia through descending modulation of pain wherein pain is either facilitated or impeded depending on one's adaptive capacities. As such, low-risk analgesia may be achieved by targeting psychological factors known to amplify pain (Darnall, 2014a, 2014b). While adaptively engaging descending modulation confers in vivo analgesia, longitudinal clinical research in chronic pain has shown that a pattern of engaging descending modulation over a period of weeks is associated with structural changes in the brain that appear to prime the central nervous system for future analgesia, thereby altering the trajectory of pain (Seminowicz et al., 2013). We review the relevance of placebo and nocebo processing in shaping the central nervous system either toward relief or pain exacerbation, and provide an evidence-based clinical toolkit to enhance placebo and pain relief.

1.2 Placebo and Nocebo Are Integral to Pain Experience

Decades of mechanistic research on placebo and nocebo effects is serving to inform the development and integration of placebo optimization strategies into clinical care pathways to treat pain. To understand how placebo and nocebo science may be applied to address the current dual pain and opioid crises, we first review several elemental principles and relevant key research findings. Beginning with nomenclature, placebo and nocebo effects are psychoneurobiological responses that occur in the body as result of positive and negative expectations (Colloca, 2018a, 2018b; Wager & Atlas, 2015). Expectations result in brain events that trigger the release of endogenous neuropeptides and influence behaviors. Placebo effects due to positive expectations have been linked to the release of endogenous opioids for a review, see Eippert et al. (2009) and Pecina and Zubieta (2018) and cannabinoids (Benedetti, Amanzio, Rosato, & Blanchard, 2011). Studies using indirect pharmacological approaches have demonstrated that placebo analgesia is antagonized by the opioid antagonist naloxone, thus, indicating that endogenous opioids crucially involved in placebo analgesic effects. Moreover, pharmacological fMRI and PET studies using an in vivo receptor binding with opioidergic ligands have provided evidence of the anatomical localization of the neuropeptides in the brain (Eippert et al., 2009; Wager, Scott, & Zubieta, 2007; Zubieta et al., 2005). In another evoked pain paradigm, Tor Wager and colleagues illustrated engagement of mu-opioid activity during placebo analgesia (Wager et al., 2007). Participants in the study were told that pills they were given would relieve their pain. Results showed that reports of placebo analgesia following administration of an inert pill was correlated with endogenous release of opioids. As such, the release of endogenous opioids depended on the belief that treatment-related pain relief was imminent.

The cannabinoid receptor 1 (CB1) antagonist SR 141716A (rimonabant) blocks placebo analgesia elicited by placebo given after NSAID ketorolac indicating an involvement of to the release of endogenous cannabinoids (Benedetti et al., 2011). Recently, it has been shown that oxytocin and vasopressin agonists given intranasally enhance behavioral placebo analgesia in men (Kessner, Sprenger, Wrobel, Wiech, & Bingel, 2013) and women (Colloca, Pine, Ernst, Miller, & Grillon, 2016), suggesting that the oxytocinergic and vasopressinergic systems, typically involved in the modulation of social behaviors (Campbell, 2010; Heinrichs & Domes, 2008) can be used as enhancers of placebo analgesic effects. Further research is needed to determine how distinct doses of oxytocin and vasopressin influences outcomes and affect brain mechanisms underlying this potentiation.

On the contrary, nocebo effects have been linked to the release of cholecystokinins that are involved in the modulation of anxiety and hyperalgesia. The block of the CCK A and B receptors with the type A/B receptor antagonist proglumide antagonizes nocebo hyperalgesia (Benedetti, Amanzio, Vighetti, & Asteggiano, 2006).

A noxious stimulus, pain signals threat or harm to an individual, and motivates escape behavior to achieve protection and survival. Viewed in this light, acute or current pain may serve as a direct nocebo reaction. Context information that is derived from one's environment and habitus (i.e., pain itself) interact with an individual's psychological status—consciously or subconsciously—in dynamic fashion. Indeed, pain placebo and nocebo are opposing phenomena existing most likely on a continuum.

Accordingly, optimizing placebo in the clinical setting requires one identify and extinguish any existing nocebo effects. In later sections, we will address the importance and procedures for attempting to extinguish nocebo effects for pain and opioid reduction.

1.3 Conceptualizing Nocebo to Encompass Pain Proper

Expectation for pain elicits a nocebo effect: facilitation of pain, distress and disease. Given that pain triggers a latent appraisal of noxious experience of varying degrees and related components (e.g., sensory, physical, emotional), it could be argued that an individual's positive appraisal regarding their ability to reduce their pain constitutes a viable way to create placebo effects. Whereas, an appraisal that pain will only worsen and there is nothing that can reduce one's pain constitutes a nocebo effect, whether such appraisal is due to poor faith in current treatments or one's ability to effectively self-manage or self-modulate pain. The patient's prior negative experience (memory, learning, priming and conditioning), internal states, and external context cues may interact dynamically to influence her/his brain responses to either inhibit or facilitate pain (Benedetti, Mayberg, Wager, Stohler, & Zubieta, 2005; Di Blasi & Kleijnen, 2003; Mistiaen et al., 2016).

Research suggests that stronger belief in the treatment enhances its effects (Doering, Glombiewski, & Rief, 2018; Kong et al., 2006; Kube, Glombiewski, & Rief, 2018; Seminowicz, 2006). In this case, greater belief in one's ability to self-modulate pain in turns may facilitate the expected analgesic outcome. Whereas, strong belief in a deficiency to self-modulate pain in turn may result in amplified pain.

1.4 Nocebo and Pain Catastrophizing

Accordingly, pain catastrophizing, a psychological construct and potent index of descending modulation of pain, is a particularly useful model for studying placebo and nocebo effects. Pain catastrophizing is a persistent pattern of distressing cognitive and emotional responses to current or anticipated pain. First described by Rosenstiel and Keefe and measured with the catastrophizing subscale of the Coping Skills Questionnaire, pain catastrophizing is comprised of a pattern of rumination on pain and feelings of helplessness about pain (Rosenstiel & Keefe, 1983). This definition of pain catastrophizing was later expanded upon by Michael Sullivan and colleagues to also include a third component: magnification of pain. The expanded definition is assessed with the Pain Catastrophizing Scale (PCS), a lengthier 13-item measure that prompts respondents to reference painful incidents in their life and to rate the degree to which they tend to have various negative thoughts, expectations or emotions about pain when they are experiencing it (Sullivan, 1995). Example items from the PCS include: "I become afraid that the pain will get worse"; "there's nothing I can do to reduce the intensity pain"; and "[my pain] is terrible and I think it's never going to get any better." Each item is rated on a 0–4 scale wherein 0 = "not at all" and 4 = "all the time." The 13 items are summed to arrive at a total PCS score, which reflects an individual's trait disposition toward pain catastrophizing. Pain catastrophizing is a malleable construct that is responsive to both longer course (Cherkin et al., 2016; Seminowicz et al., 2013; Turner et al., 2016) and brief, targeted psychological treatment (Darnall, Sturgeon, Kao, Hah, & Mackey, 2014; Thorn et al., 2007).

Placebo effects have been linked to a distinct series of psychological factors such as dispositional optimism, hypnotic suggestibility, somatic focus, empathy, neuroticism, altruisms, and the locus of ego-reliance (for a review, see Colloca & Grillon, 2014). Conversely, anxiety (Staats, Staats, & Hekmat, 2001), harm avoidance and persistence (Corsi, Emadi Andani, Tinazzi, & Fiorio, 2016) and anxiety sensitivity and physiological suggestibility (Corsi & Colloca, 2017) have been associated with nocebo effects in healthy subjects. In particular, pain catastrophizing has also been associated to nocebo effects in experimental settings in which nocebo manipulations are performed (Corsi & Colloca, 2017; Swider & Babel, 2013; Vogtle, Barke, & Kroner-Herwig, 2013).

A recent study looked at low scores of pain catastrophizing along with expectation for pain relief, anxiety, depression and the personality trait neuroticism and high levels of positive emotions as predictors of placebo responses in randomized, double-blind, placebo-controlled, crossover study

with the anticonvulsant oxcarbazepine for treatment of peripheral neuropathic pain (Lund et al., 2017). Multiple regression analyses with pain reduction during placebo treatment as the dependent variable and baseline pain, age, sex, and pain duration revealed high significance ($P < 0.001$), while other psychological variables did not reach statistical significance. Further studies are needed exploring the link between placebo and nocebo effects in patients suffering from chronic and acute pain.

Before we discuss the possibility to target psychotherapy to treat catastrophizing thoughts and pain exacerbation = in extinguishing nocebo, we first review its impacts and importance as a therapeutic target.

1.4.1 Experimental Studies

The extent to which a persistent pattern of catastrophizing might sensitize the nervous system has been a recent topic of interest and investigation. Neuroimaging studies conducted on healthy volunteers have shown that pain catastrophizing is associated with amplified activity in areas of the brain associated with the experience of pain, and this directly correlates with report of increased pain (Seminowicz & Davis, 2006).

Our group conducted a controlled pilot study that tested the psychosensory effects of a pain catastrophizing induction in women with chronic pain (evoked pain catastrophizing), and specifically tested whether secondary hyperalgesia was associated with pain catastrophizing during evoked pain (Taub, Sturgeon, Johnson, Mackey, & Darnall, 2017). Study participants assigned to the catastrophizing condition were guided to imagine their pain worsening and to envision great negative consequence resulting from increased pain. The imagined scenario was designed to allow for a personally relevant construction of worsening pain, reduced function, and "worst case scenario" as it pertained to each individual. Quantitative sensory testing conducted before and after the induction was designed to reveal whether greater pain catastrophizing was associated with increased pain intensity (hyperalgesia) as well as spread of pain to non-painful areas (allodynia). Findings revealed that two quantitative sensory tests (weighted pin and mechanical allodynia) were associated with secondary hyperalgesia for women with greater levels of evoked pain catastrophizing. Replication of this work would confirm central sensitization as a mechanism of pain catastrophizing (Taub et al., 2017). Other research provides supporting evidence of catastrophizing having a mechanistic role in central sensitization, though viewed from the other direction. Salomons and colleagues conducted a randomized controlled experiment to test a brief cognitive behavioral

intervention designed to enhance descending modulation of experimental pain could mitigate catastrophizing and pain (Salomons et al., 2014). The intervention included 5-min instructional sessions on cognitive regulation of pain given prior to each of eight sessions of evoked heat pain. The researchers found that the brief cognitive training reduced pain unpleasantness—but not pain intensity—as well as secondary hyperalgesia and pain catastrophizing. The authors stated that their reported association between reduced secondary hyperalgesia and pain catastrophizing suggested that reductions in central sensitization are related to volitional alterations of pain-related cognitions (Salomons et al., 2014).

Longitudinal studies conducted in clinical samples are needed to extend beyond the proximal impacts of nocebo and characterize the mechanisms of pain catastrophizing and placebo and nocebo effects.

1.4.2 Clinical Research

Across different treatment settings spanning outpatient, inpatient, and perioperative environments, pain catastrophizing consistently emerges as one of the strongest predictors of pain treatment outcomes.

A systematic review of pain catastrophizing (total $N = 2269$) found that pain catastrophizing predicted pain intensity and disability, and pain catastrophizing mediated back pain treatment efficacy in outpatients seeking specialty pain care (Wertli et al., 2014). Independent of depression, pain catastrophizing has been associated with an array of negative phenomena including increased affective distress (Picavet, Vlaeyen, & Schouten, 2002; Spinhoven et al., 2004), muscle and joint tenderness (Severeijns, Vlaeyen, van den Hout, & Weber, 2001), muscular tension at rest (Smeets, van Geel, Kester, & Knottnerus, 2007), pain-related disability (Severeijns, Vlaeyen, & van den Hout, 2004; Severeijns et al., 2001), and poor response to various pain treatments including surgery (Abbott, Tyni-Lenne, & Hedlund, 2011; Helmerhorst, Vranceanu, Vrahas, Smith, & Ring, 2014; Jensen, Thomsen, & Hojsted, 2006; Kennedy, Vranceanu, Nunez, & Ring, 2010; Smeets et al., 2007; Spinhoven et al., 2004; Theunissen, Peters, Bruce, Gramke, & Marcus, 2012). Indeed, the perioperative setting is useful for investigating the clinical impacts of pain, nocebo-induced hyperalgesia, particularly with surgery often involving a clear pain stimulus and a defined recovery period. To investigate the impact of pain catastrophizing on post-surgical outcomes, researchers typically measure pain catastrophizing tendencies prior to surgery. Greater pain catastrophizing has been shown to be directly associated with greater use of opioids and pain

in the hospital after surgery (Papaioannou et al., 2009; Wright, Hoang, Sofine, Silva, & Schwarzkopf, 2017), longer hospital stay (Wright et al., 2017), delayed recovery from surgery (Roh et al., 2014), and persistent opioid use (Helmerhorst et al., 2014). Pain catastrophizing also harmful in the context of acute pain and even for individuals who are pain-free. For instance, pain catastrophizing is implicated in the persistence of back pain (Picavet et al., 2002) and researchers found that pain catastrophizing accounted for 47% of the variance in the *development* of chronic back pain following an episode of acute back pain (Burton, Tillotson, Main, & Hollis, 1995). Moreover, a cross-sectional observational population study revealed that among all factors investigated, pain catastrophizing best predicted the acquisition of chronic low back pain 1 year after a pain-free baseline (Linton, 2005). Taken together, these data illustrate the detrimental impacts of pain catastrophizing across settings and populations, and suggest that early treatment for pain catastrophizing may serve as prophylaxis for prevention of chronic pain phenotypes.

Given that pain catastrophizing appears to undermine response to medical pain treatments, it is perhaps unsurprising that *reductions in pain catastrophizing are associated with subsequent* improvements in pain and intervention effectiveness. In a prospective study, Burns et al. used cross-lagged analysis to show that early reductions in pain catastrophizing significantly improved later response to multidisciplinary treatment in terms of pain intensity and pain interference (Burns, Glenn, et al., 2003; Burns, Kubilus, Bruehl, Harden, & Lofland, 2003). Neuroimaging studies conducted on individuals with chronic pain reveal that greater pain catastrophizing is associated with volumetric deficits in key brain regions associated with descending modulation of pain (Seminowicz et al., 2013). While it is unknown whether structural deficits were antecedents or consequences of catastrophizing, their co-occurrence suggests a mutually-reinforcing biobehavioral cycle of pain and potential nocebo-induced hyperalgesia (Blasini, Corsi, Klinger, & Colloca, 2017). Indeed, pain catastrophizing in individuals with chronic pain has been shown to associate with altered neural functioning outside of the context of evoked pain or in vivo catastrophizing (Jiang et al., 2016). Greater pain catastrophizing is associated with altered brain functioning in the default mode network—an over-coupling between the central executive network and the amygdala—that attune the brain to pain (Jiang et al., 2016). These findings suggest that pain catastrophizing is associated with neural alterations in individuals with chronic pain that appear to prime their nervous pain signaling systems for future pain.

1.5 Reducing Pain Catastrophizing: Shaping Patient Expectations Toward Pain Relief

Cognitive behavioral therapy for chronic pain (pain-CBT) effectively reduces pain catastrophizing and increases pain self-efficacy; that is, the belief in one's ability to engage in various life activities despite living with ongoing pain (Cherkin et al., 2016; Stewart et al., 2015; Thorn et al., 2007; Williams, Eccleston, & Morley, 2012). Pain-CBT is typically delivered by a trained psychologist either individually or in group classes. Most often, group pain-CBT is a series of 2-h classes (often 8–11 classes) delivered weekly. Classes include social interaction, didactic content, and experiential exercises. Didactic content includes education about pain and the role of psychology in its treatment, thereby establishing the treatment rationale, as well as remoralization around the notion that personal control over pain may be cultivated. Participants learn about the role of cognition in pain perception, emotional experience, and physiological responses. Importantly, participants learn to identify their maladaptive thought patterns that maintain and amplify pain and distress. Often negative thoughts involve catastrophizing, and pain-related negative thoughts (e.g., "My pain is never going to go away," or "I am at the mercy of my pain."). Acquired skills specifically enhance descending modulation of pain. Cognitive restructuring, relaxation training, and positive distraction are adaptive modulatory skills that may effectively interrupt in vivo catastrophizing. Repeated application and thought interruption weakens the negative neural and behavioral patterns. Volitionally calming the nervous system allows for recoding of physiological responses that oppose pain and nocebo (e.g., relaxation, positive expectation for relief and belief in one's ability to self-soothe) and lead to lasting adaptive changes in the nervous system. Seminowicz and colleagues provided strong evidence in this direction. The research group conducted pre-post treatment neuroimaging on patients with chronic pain who underwent an 11-week course of group pain-CBT (Seminowicz et al., 2013). The authors reported that prior to pain-CBT, patients evidenced volumetric deficits in regions of the brain associated with pain control. However, the pre-treatment volumetric deficits were mitigated substantially in the post-treatment scans, and the pre-frontal gray matter brain volume increases were entirely mediated by reductions in pain catastrophizing. The adaptive structural brain changes and reductions in pain catastrophizing correlated directly with decreased pain intensity.

These findings underscore that descending modulation of pain may be applied to directly impact pain perception and cultivated to shape enduring

brain changes that confer relief. Placebo and patient engagement in pain-CBT may be optimized by sharing these specific neuroscientific findings for treatment research conducted on clinical samples. Indeed, a central goal of pain-CBT is to enhance descending modulation of pain. Colloca and colleagues' work reveals that a reinforced expectancy (e.g., via conditioning) strongly create large pain modulatory effects (Au Yeung, Colagiuri, Lovibond, & Colloca, 2014; Colloca, Jonas, Killen, Miller, & Shurtleff, 2014; Klinger, Colloca, Bingel, & Flor, 2014). The greater one's expectations for pain to improve (or worsen), the greater pain modulation occurs in the expected direction (Corsi & Colloca, 2017). Shaping placebo to enhance descending modulation and facilitate ongoing engagement with adaptive skills may optimize its clinical manifestation (Klinger, Blasini, Schmitz, & Colloca, 2017). A recent meta-analysis of 27 studies showed that how interventions are presented to patients impacts their pain. Basic information about a treatment can serve to reassure patients that they will have a good response to the treatment—they experience greater analgesia, including individuals with chronic pain (Peerdeman et al., 2016). Providing compelling positive results for scientific studies may boost placebo further, in part by enhancing patient preference and engagement in the treatment. Indeed, a common notion is that psychological treatment for pain is "palliative care," something to be administered when all real medical treatment fails. This common flawed perspective that relegates psychological treatment to "learning how to cope with pain" can severely limit engagement in pain-CBT and undermine placebo. Placebo optimization for pain-CBT includes providing patients with the scientific evidence that psychological treatment extends well beyond "pain coping"; rather, pain-CBT alters the pain experience itself, shapes the trajectory of pain, changes the functioning and the structure of the brain so that the nervous system becomes "primed" for relief.

1.6 The "Actual" Effect of a Treatment: A Mythical Pursuit in Chronic Pain?

To date, research has mainly focused on controlling for placebo effects and minimizing them for the purpose of elucidating the "actual" effect of a therapy in the context of clinical trials. However, the recent research suggests that it is challenging to isolate the so-called "actual" treatment effect in real-world clinical settings (emerging uncertainty principle, see Colloca & Benedetti, 2005) wherein treatments are applied to patients who bring their entire psychology with them—including their cognition, emotion, beliefs

and expectations about the treatment they are about to receive—the very factors that profoundly influence pain and treatment response. Furthermore, the success of behavioral treatment such as pain psychology treatment is dependent on patient engagement and a belief that the treatment will benefit them (placebo). As such, the notion of a static pain treatment effect existing in the absence of placebo/nocebo may have questionable value in everyday clinical settings. Pain is an individual experience, as is treatment response, and both interact dynamically with psychological factors. As such, perhaps the most useful clinical pathway is to phenotype patients prior to treatments, identify therapeutic targets for minimizing nocebo and optimizing placebo, and direct resources to enhance pain treatment outcomes (Darnall, 2018a). Owing to its impacts and relationship to nocebo and treatment outcomes, pain catastrophizing remains a primary, high-yield therapeutic target.

1.7 Patient Preference: A Fly in the Ointment

The potential mechanisms of placebo effects are manifold and in addition to neural and pharmacological pathways include behavioral factors that impact engagement and adherence to the treatment regimen, including patient preference for a particular treatment. Patient preference may partially index a belief that the treatment will be beneficial, although various other factors are known to influence patient preferences (Enck, Grundy, & Klosterhalfen, 2012), such as burdens related to actively engaging in a treatment, associated costs, and potential side effects.

Above we briefly touched on the importance of placebo optimization for pain-CBT as a pathway to enhance patient preference and engagement in this clinical treatment pathway. The goal is to provide compelling contextual information that makes the patient *want* the treatment, then boost their engagement in the treatment (behavior change). Combined, this creates a powerful cycle of cognitive, emotional, and behavioral reinforcement related to the treatment. Despite its strong influence on placebo and treatment response, patient preference for treatment type is often ignored in pain research, thereby confounding study findings. Indeed, similar to the placebo studies, in the "gold standard" of clinical trials designs, the randomized controlled clinical trial, patient participant treatment preference is often "subtracted out" as if real-world treatment response does not depend on it. Admittedly, controlling for patient preference in analytic models does

inform its predictive value. However, assigning a patient to a treatment group they do not believe will benefit them reduces the likelihood of positive treatment response. In the absence of patient choice, treatment research results likely underestimate true treatment effects (Bingel et al., 2011), particularly in psychological treatment studies that require a high degree of active engagement compared to relatively passive pharmacologic treatments. Recognizing that clinical care does not exist in blinded fashion, research that aims study treatment effects should consider allowing patient choice in the treatment (Enck et al., 2012) whenever possible (equipoise randomized stratification is one statistical method that can be applied for this purpose (Lavori et al., 2001)), as well as include strategies to further enhance preference. The rationale is that the true *available* treatment effect is:

Treatment applied in an engaged patient who chooses the treatment pathway based on a belief that the treatment will be of benefit:

- With treatment = x and placebo = y, the true available treatment effect is x + y.

While the treatment (x) is relatively static, (y) is malleable and dependent on a variety of contextual factors, including the patient-provider dynamics, careful education and patient comprehension about treatment benefits and why they are important to the patient. A new era of patient-centered care and precision medicine stands to improve the effectiveness of various treatments both because the treatment has greater precision and because patient receptivity is enhanced by clear understanding of the personal relevance and importance of the treatment. Placebo optimization strategies may also be applied within the context of any type of analgesic treatment, including psychological treatment, physical therapy, as well as strategies individuals use in their daily lives to self-manage their pain.

1.8 Minimizing Nocebo and Optimizing Placebo for Opioid Reduction

Klinger and colleagues discussed several approaches to optimize placebo response for prescribed analgesic medications (Klinger et al., 2017, 2014). Two examples of strategies designed to enhance positive patient expectations include emphasizing the drug's positive value while minimizing side effects, as well as carefully explaining the drug's mechanisms of actions to the patient (Klinger et al., 2017, 2014). Here, through the lens of prescription opioids, we extend the discussion of placebo optimization beyond the

medication to include medication prescribing procedures (e.g., patient engagement), medication titration procedures and specifically symptom management in regards to prescription opioid tapering.

1.9 Avoiding the Nocebo Pitfall of Opioid Tapering

Human physiology fairly rapidly adapts to daily administration of opioids. Over the course of weeks of daily opioid use, most people will develop a degree of physical dependence; that is, if the drug is suddenly withdrawn, noxious symptoms arise (e.g., withdrawal symptoms). Withdrawal symptoms may include increased pain, nausea, anxiety, restlessness, opioid craving, muscle aches, and stomach cramps. While not dangerous, the severity of withdrawal symptoms and related discomfort may range from mild to intolerable. Most patients taking long-term opioids understand withdrawal symptoms through prior experience: they may have accidentally missed a dose of medication, or may have tried to taper or stop opioids and experienced withdrawal symptoms. The experience of opioid withdrawal symptoms may lead patients to encode a false belief that they are unable to taper their opioids and must maintain their current dose. In fact, withdrawal symptoms do not index an individual's capacity to reduce prescription opioid dose; rather, withdrawal symptoms index a need for better tapering methods. Moreover, increased pain is a common opioid withdrawal symptom; however, many patients may encode the false belief that this amplified withdrawal-related pain is their "baseline pain level," thereby leading them to conclude that opioids are the only way to maintain a tolerable level of pain. These common false beliefs are may be powerfully anchored with negative reinforcement in that re-administration of opioids eliminates noxious symptoms, including amplified pain. Unfortunately, current guidelines may be in some clinical cases too aggressive for chronic pain patients who often have been taking opioids for years or decades (Berna, Kulich, & Rathmell, 2015). Aggressive tapers may trigger withdrawal symptoms and unintended nocebo effects, thereby perpetuating the false beliefs that can maintain patients on opioids when they otherwise would have been interested in reducing or stopping opioids if offered a successful pathway forward.

Even in the absence of prior experience with opioid withdrawal symptoms, it is intuitive for patients to assume that their pain will increase in the absence of their pain medication. However, data from opioid tapering studies demonstrate that opioid reduction is more often associated with *reduced* pain when they are tapered the right way (Baron & McDonald, 2006;

Crisostomo et al., 2008; Murphy, Clark, & Banou, 2013). While these studies involved resource-intense methods to achieve opioid cessation (e.g., inpatient interdisciplinary treatment delivered over the course of weeks), intensive and costly treatment may not be requisite. For instance, Darnall and colleagues' findings suggested that patient-centered opioid tapering methods may help community-based outpatients achieve opioid reduction without costly resources, and without increased pain (Darnall et al., 2018). A key aspect of patient-centered opioid tapering methods involves identifying and addressing opioid tapering negative expectations and related-nocebo effects as a pathway to patient engagement in the taper process. A second key aspect is reducing the pace of the taper to allow ample time for physiologic and psychologic adaptive to occur; this serves to obviate nocebo effects, as well as contextually cultivate placebo and a belief that successful tapering is possible.

To set the stage for placebo optimization and patient-centered opioid tapering, we administered an online survey to 1561 patients with chronic pain taking long term opioids to understand their opinions and concerns regarding potential opioid reduction. Surveys were completed by 248 patients (16% response rate). Results were perhaps unsurprising: patients reported that their primary concerns about opioid reduction were increased pain and withdrawal symptoms—negative thoughts and nocebo effects about opioid reduction. Results also revealed that respondents were unaware that opioid reduction could be associated with reduced pain. Seventy percent of patients reported that they would be interested in trying to reduce their opioids if they knew first about the positive results for prior opioid tapering studies (unpublished data). These findings dovetail with work conducted by Darnall, Colloca and others showing that patient concerns and fears about opioid tapering must be addressed first to minimize nocebo effects, empowering positive expectations by optimizing patients' education and patient–clinician communication (Colloca & Finniss, 2012) including amplified pain and poor taper result, and to best ensure patient engagement in the opioid tapering process and clinically-relevant outcomes (Benedetti, Lanotte, Lopiano, & Colloca, 2007; Colasanti, Rabiner, Lingford-Hughes, & Nutt, 2011; Colloca & Benedetti, 2007; Colloca, Klinger, Flor, & Bingel, 2013; Colloca & Miller, 2011a, 2011b; Darnall et al., 2018; Horin, Lee, & Colloca, 2014). Brief education from the prescribing physician can reassure, soften or eliminate negative expectations and enhance patient receptivity and actual analgesic response to the intervention (Benedetti et al., 2007; Colasanti et al., 2011; Colloca & Benedetti, 2007; Colloca & Finniss, 2012;

Colloca et al., 2013), a particularly crucial strategy when opioids are being reduced (Colloca & Miller, 2011b; Darnall et al., 2018; Horin et al., 2014). Indeed, positive patient expectations can enhance response to opioids, reduce pain, and help opioids work better at lower doses.

Assessment of patient expectations and readiness to taper opioids is vitally important for clinical outcomes as well as empirical study on the topic. Scant research exists on prescription opioid tapering, and few studies that have assessed patient expectations prior to the taper. To address this unmet need, our national clinical trial on patient-centered prescription opioid tapering will be carefully assessing patient expectations for opioid tapering (https://www.pcori.org/research-results/2017/comparative-effectiveness-pain-cognitive-behavioral-therapy-and-chronic-pain, 2017). Further, it includes methods to enhance placebo and patient readiness to engage in opioid tapering process. This pragmatic study will allow us to conduct a large scale test of placebo/nocebo on opioid tapering, as well as methods to optimize placebo effects and taper response.

An additional strategy can be employed to challenge patient expectation that they will experience withdrawal symptoms and pain as a consequence of prescription opioid tapering: micro-dose decrements. Anxiety regarding opioid reduction is likely to be highest at the outset of a taper. As such, making tiny reductions in dose can obviate withdrawal symptoms and allow patients to remain comfortable and gain confidence in their ability to reduce their opioids very slowly without experiencing noxious symptoms (Darnall et al., 2018). As such, preventing noxious symptoms at the outset of a taper—and providing sufficient time for physiologic and psychologic adaptation to opioid dose reductions—may minimize attrition and improve taper response (Darnall et al., 2018).

Finally, whenever possible, helping patients have choice and control in the process will best support successful outcomes. As discussed earlier, patient preference *for the intervention*—in this case choosing to reduce opioids because they are convinced of its benefits—enhances treatment outcomes. Going one step further, accounting for patient preferences *during the tapering process* may be equally important. Allowing patients to control over the pace of their taper—pausing their taper or go more slowly when desired—can provide added reassurance during critical time points that are likely to be laden with emotional distress. Continuing the taper process when the patient has confidence in their own readiness signals optimized placebo and increased likelihood for successful outcome.

1.10 Clinical Implications of Placebo and Nocebo Effects and Endogenous Mediated-Opioid Analgesia

As discussed earlier, evidence reveals that placebo/nocebo expectations influence the endogenous release of opioids, suggesting influence on analgesic response to exogenously administered opioids. Bingel et al. investigated the impacts of opioid analgesia on 22 healthy volunteers who were exposed to a heat pain stimulus while simultaneously being administered IV remifentanil in each of three conditions (Bingel et al., 2011). Pain intensity was individually determined to a self-reported moderate intensity, and was applied to participants during in all three conditions. In the first condition, participants were told they were receiving a powerful painkiller during the pain experiment. In the second condition, participants were told they were receiving only saline through the IV, and therefore they would experience the moderate amount of pain that had been individually determine. In the third condition, participants were told they would receive something that would amplify their experience of the heat pain. As such, the researchers only altered participant expectations for pain and relief thusly: (1) placebo, (2) neutral, (3) nocebo. Positive expectations for pain relief due to opioids (opioid placebo) were found to double the analgesic effect of remifentanil relative to the neutral condition. Conversely, nocebo expectations that were induced in the third condition effectively abolished the analgesic effect of remifentanil. Moreover, pain and analgesia findings correlated with functional neuroimaging data supporting modulation of pain processing in the brain based on the condition group. Finally, across the conditions, modulation of anxiety directly aligned with expectations for pain. The findings from this study suggest profound influence of placebo and nocebo effects on exogenously administered opioid analgesia with implications for real-world patients receiving prescription opioids for acute and chronic pain.

To summarize, findings for nocebo/placebo suggest that: (1) treatment beliefs (placebo) are sufficient to release endogenous opioids; (2) opioid analgesia was doubled when coupled with placebo relative to when opioids are administered without knowledge of receipt; (3) nocebo can block analgesia from exogenously administered opioids. Given that placebo/nocebo profoundly influence opioid analgesia it is somewhat surprising that there are no widely used interventions to that target placebo as a pathway to boost opioid analgesia. Moreso, it is clear that opioid reduction nocebo is a timely and urgent issue given its potential iatrogenic harms.

In the United States multiple government agencies and leaders, including the Centers for Disease Control, the U.S. surgeon general, the Institute of

Medicine, and the Department of Health and Human Services have called for reduced opioid prescribing. Such calls have led to local, state, and federal guidelines and policies that recommend or enforce prescribing limits, regardless of patient readiness or willingness, two indices of potential nocebo for opioid reduction (Hoffman, 2018; Langreth, 2017; McCoy, 2018). Overlooking these key patient factors may greatly undermine patient response to opioid tapering because (1) nocebo increases distress and amplifies pain; (2) nocebo opposes opioid analgesia; and (3) forced tapers may contaminate the doctor-patient bond and its positive influence on treatment outcomes; (4) the placebo context of the medical environment can quickly shift to a nocebo context with detrimental effects. Forced tapers have questionable clinical value, amplify patient suffering and may contribute to self-harm and suicide (Demidenko et al., 2017). Compassionate opioid tapering requires attention to patient preference and willingness to taper and applying placebo optimization to cultivate patient engagement, placebo effects, and enhanced outcomes. Outside the context of opioid tapering and considering new or existing opioid prescriptions, such findings underscore the importance of minimizing nocebo effects to potentially prevent risky dose escalation, and optimizing placebo as a pathway to either enhance opioid analgesia or obviate the need for opioids. The question then becomes how might we help patients cultivate placebo effects for improved outcomes?

As outlined in Table 1, we argue that it is possible to minimize nocebo effects and optimize placebo for pain relief and opioid reduction and summarize the clinical strategies as follows.

(1) *Set positive expectations*. Placebo effects and positive expectations for treatments are strengthened when patients are educated about the treatments and their analgesic effects. In the case of pain being the contextual cue, the discussion centers around the potential *placebo cultivation* by facilitating belief in one's ability to shape adaptive brain responses toward pain relief and wellbeing.

(2) *Identify and Extinguish Nocebo*. Assess cognition negative thoughts, expectations and beliefs about pain and opioid use/reduction, self-efficacy to self-manage pain, and treatments.

(3) *Equip individuals with skills to enhance descending modulation of pain and distress reduction*. Enhanced descending modulation of pain dually promotes awareness of pain control and therefore placebo proper. While the Clinical Toolkit (Table 1) is not exclusive to psychologists several of the skillsets are specific to trained pain psychologists, including cognitive behavioral therapy (CBT) for pain.

Table 1 Placebo Optimization Clinical Toolkit

	Placebo Optimization Toolkit	
Clinical Goal	**The Clinician Toolkit**[b]	**The Patient Toolkit**
Enhance positive expectation for the cultivation of pain relief skills[a]	• Establish the basic treatment rationale by explaining the role of psychology in the experience of pain • Establish psychological treatment and enhanced descending modulation of pain as *primary* pain treatment • Summarize results of psychology treatment research as evidence-informed medicine • Provide education on psychological treatment and self-treatment yielding some of the largest effects • Provide education regarding psychological treatment's ability to "boost" medical treatments for pain • To ensure comprehension, answer questions, ask patients to tell you their understanding of the information you provided	• Acquire a fundamental understanding of the importance of psychoneurobiological processes on pain experience Understand that there are many evidence-informed simple skills that can be learned, that, when used over time, shape brain changes toward the experience of pain relief
Extinguish pain nocebo. Part 1	• Assess nocebo/catastrophizing using the Pain Catastrophizing Scale or other relevant measure • Review the patient's findings with them. (e.g., "Your score tells me that we can help you learn to reduce your distress around pain, and even the pain itself.") • Validate their distress, and connect their distress to being a pain amplifier • Using patient-friendly language, such as "negative pain mindset" in lieu of the term pain catastrophizing may enhance receptivity to the concepts and the treatment plan • Use imagery and narrative: "Nobody want more pain, but having a negative pain mindset is like picking up the can of gasoline and pouring it on a fire. You can learn to put the can of gasoline down, and by doing so it changes your pain in the moment, and steers your nervous away from pain in the future"	• Acquire a personal understanding the relevance of psychoneurobiological processes (e.g., one's score on the measure) • Understand that negative thought patterns amplify pain processing and oppose relief • Receive reassurance that while it's not "all in your head," there is much you can do to impact brain-pain experience • Become re-moralized that while a "negative pain mindset" amplifies pain, mindset is under your control. "I can learn to put the can of gasoline down so that I am not unwittingly contributing to my pain and distress"

Continued

Table 1 Placebo Optimization Clinical Toolkit—cont'd

	Placebo Optimization Toolkit	
Clinical Goal	**The Clinician Toolkit**	**The Patient Toolkit**
Part 2. Entrain descending modulation with frequent application of acquired skills	• Cognitive restructuring (reframing negative/nocebo thoughts) • Positive self-talk; learning to "talk back" to the automatic negative thoughts • Demonstrate the relaxation response and discuss its utility for comfort and control over physiological processes and self-treatment of pain • Mindfulness observing • Learn to identify pain-related distress and apply self-soothing techniques (e.g., relaxation response, mindfulness meditation, diaphragmatic breathing) • Utilize distraction	• Acquire ability to identify negative thoughts and reactions (physical, emotional) and apply adaptive strategies to interrupt pain nocebo: ✓ Cognitive reframing ✓ Positive self-talk ✓ Relaxation response ✓ Mindfulness observing ✓ Distraction ✓ Self-soothing actions • Practice the relaxation response as a self-treatment tool to reduce pain, distress and adaptive conditioning. Positive biofeedback enhances placebo—a belief that one can modulate pain and distress
Enhancements: Behavioral engagement and reinforcements	• Provide visual material, handouts and video-clips • Provide clinical worksheets • Prescribe exercises that cultivate a pain-relief mindset • Review progress in follow-up; acknowledge any challenges that arise, provide supportive encouragement, and highlight small successes • Remind patients that structural brain changes are shown after 11 weeks of skills use • Encourage a focus on skills use and behavior change vs change in pain intensity—which typically follows later	• Review visual material, handouts and video-clips • Complete worksheets and apply information • Set goals • Review progress in follow-up • Adopt an approach to skills use that is not pain contingent but rather focuses on long-range adaptation with an eye to achieving adaptive structural changes of the nervous system

Extinguish opioid reduction nocebo	• "Tell me your concerns about reducing opioids." Listen and address their fears • Discuss the data for patient-centered opioid tapering • Review the physiology of opioid reduction and how very slow tapering will allow for comfortable adaptation • Prescribers may use adjuvant medications to address discomfort and optimize placebo with a non-opioid medication • Withdrawal symptoms are just a sign that the taper is going too fast. Remind them you have a plan to prevent withdrawals, and you will work with them to adjust the taper if any discomfort arises • Keep the process very simple, avoid making any other changes during an opioid taper to obviate confounding, patient anxiety, and negative effects • Maintain very small dose reduction for the first month (see Darnall et al., 2018) • Partner with your patient. As much as possible, allow them to feel and be in control (e.g., allow them to go slower or pause the taper) • Follow-ups every 3 weeks for the first few months for close monitoring, to address any discomfort or concerns quickly, and to solidify therapeutic trust and placebo • Provide access to descending modulatory skills	• Understand the science behind endogenous pain modulation and opioid tapering: most patients experience the same or less pain when opioids are tapering the right way—very slowly so that brain and body have time to adjust • Encode that withdrawals are not harmful; they are uncomfortable and mostly preventable. My doctor will help me stay comfortable and will track me closely to make sure I'm doing ok • My doctor and I created a plan that helps me be in control. I can pause my taper if I need to during a difficult time • Understand that there's much I can do during my taper to help manage my pain (see above Patient Toolkit for the clinical goal, "Entrain descending modulation with frequent application of acquired skills" • Additional targeted reading and skills application specific to opioid reduction may be useful (Darnall, 2014a, 2014b, 2016)

[a]Enhancing placebo may dually optimize patient preference for the treatment.
[b]To assure comprehension, use simple lay language to explain complex concepts. Ask patients to explain their understanding of the concepts you describe to (1) facilitate learning through verbal recall; and allow you to (2) positively reinforce their accurate comprehension, (3) correct any misunderstandings, and (4) identify and address any concerns they raise.

2. CONCLUSION

Historically, pain-related placebo and nocebo effects have been viewed as psychological responses to external contextual information, often involving aspects of treatment. Considering the role of the patient in self-modulating, self-managing, and self-treating chronic pain, we argue for an expanded therapeutic exploitation of placebo and nocebo effects to include strategies immediately feeding back to either amplify the analgesic experience or diminish the pain experience. Pain catastrophizing illustrates the concept of pain amplification and related nocebo effects, with supporting experimental and clinical data suggesting that it may contribute inhibiting descending pain modulation. Therefore, it is necessary to face the burden of pain and the epidemic of opioids with novel approaches including psychological interventions to manage catastrophizing thoughts and other psychological factors known to amplify pain and undermine pain treatment outcomes. Clinical toolkits are needed, and we have provided a resource that may facilitate these goals of patient-centered pain management and successful tapering of prescription opioids by minimizing and optimizing placebo effects and descending pain control.

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