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Efficacy of placebo analgesia treatment in the management of chronic non-cancer pain compared to opioids a review

By

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INTRODUCTION

According to the Centers for Disease Control and Prevention, more than ninety people die each day from opioid overdoses. Opioid overdoses accounted for two-thirds of drug overdose deaths within the United States in 2015. Death rates have also increased steadily since the 1990s across all socioeconomic, ethnic, and age groups despite a nineteen-percent decrease in opioid prescribing rates.[1,2] There are still almost fifty-eight opioid prescriptions written for every one-hundred Americans and an average of 3.4 prescriptions dispensed per patient.[3,4] Chronic pain disorders represented a substantial economic and health burden due to lost productivity and increased health care usage.[1,2]

Possible solutions to the opioid epidemic have shown variable success. These solutions include limiting coverage on prescriptions, increased training and education to providers, required use of pain management contracts, and improved community resources. Solutions have also included the increased use of opioid partial agonists-antagonists, like buprenorphine, and opioid antagonists, like naloxone. There has also been an increase in the use of alternative therapies, such as physical therapy, massage, and chiropractic adjustments. One ethically controversial therapy that is undergoing increased research recently, is the use of placebos in the treatment of chronic pain. While there is a considerable amount of research that corroborates the beneficial effects of placebo analgesia in the treatment of depression and irritable bowel syndrome, few exist for chronic pain.[4] The placebo effect refers to positive clinical results caused by a treatment that is not attributable to its known mechanism of action or physical properties.

It is often explained because of positive expectations instilled in patients derived from outcomes of previous clinical encounters.[5] Placebo analgesia is often used deceptively, without consent, and with little evidence of benefit.[6]

Little is known regarding how the use of placebo analgesia compares to opioids affect long-term treatment efficacy in patients with chronic non-cancer pain over the first two years of treatment. To best answer this question, one must understand the transition from acute to chronic pain along nociceptive signaling pathways. This literature review aims to describe the major nociceptive signaling pathways involved in opioid and placebo analgesia and to discuss how placebo treatment affects chronic pain undergoing central sensitization. It will also review the current understanding of placebo effect and discuss the effects of dose-extending placebo use of opioid tolerance.

NOCICEPTIVE OPIODERGIC PATHWAYS

Pain sensation is evoked through protopathic pathways carrying temperature and pressure input from the skin through the spinal cord to the brain. Nociceptors are excitatory neurons that release glutamate for primary neurotransmission, as well as, other components including peptides, such as substance P, calcitonin gene-related peptide, and somatostatin. Most nociceptors are unmyelinated free nerve endings with small diameter axons (C and Aδ-fibers). Their peripheral afferent innervates the skin and projects to the posterior marginal nucleus and substantia gelatinosa of the posterior horn of the spinal cord. The signal ascends through the contralateral lateral spinothalamic tracts and splits partially going to the ascending reticular activating system and part to the central posterolateral nucleus of the thalamus where crude

pain is conveyed. From the ascending reticular activating system, it is transmitted to the limbic system, as well as, activating the sympathetic nervous system. From the thalamus, it then ascends to the post-central gyrus where location and quality are conveyed.[7]

The descending pathway in pain inhibition appears to primarily descend through the periaqueductal gray to the nucleus raphe magnus and act on the substantia gelatinosa and nucleus proprius through opioidergic signaling induced from the epicritic pathway (i.e., gate control theory) and periaqueductal gray (produces enkephalin) and rostral cingulate cortex.[7,8] Most of the inhibition appears to occur through local excitatory and inhibitory interneurons in the posterior horn and descending pathway due to opposing signaling priority from homeostatic demands and extrasensory perception. These pathways are the serotonergic-noradrenergic and opioidergic pathways which activate GABAergic/glycinergic depolarization of presynaptic terminals leading to the dorsal root reflex and transmission of an action potential resulting in the release of inflammatory mediators in the skin that intensify nociceptor excitability.[9]

CENTRAL SENSITIZATION

Many quantitative sensory testing studies on pain show that many chronic pain conditions, including migraine headache, osteoarthritis, and chronic visceral conditions can undergo central sensitization.[10] Central sensitization occurs when the nervous system is placed in a persistent state of high reactivity. In this state, the threshold as to what is relayed as pain is lowered and consequently, a state of pain is maintained even after the initial injury has healed. This process seems to occur through temporal and spatial summation. Repeating high-frequency afferent signaling results in increased pain intensity. If a painful stimulus is repeated multiple

times for a set period, the pain will integrate and become more painful toward the end of the stimulus. In addition, pain is increased when the area of painful stimulus is increased.[11] Predisposing factors to central sensitization are likely both biological and psychological. While there is no research linking pre-existing pain tolerance thresholds and development of central sensitization, it is mainly assumed one exists. Also, psychological factors, such as individual stress-responses appear to predispose patients for lowered pain thresholds. There appears to be a correlation between patients with a history of increased anxiety and the development of chronic pain.[12]

PLACEBO EFFECT

Research into placebo analgesia has been divided on whether placebo effects depend on conscious expectancy or learning mechanisms. Several studies have tried to answer this dispute.[13] Popular theories suggest that conditioning is released to both initial expectancies and association-based changes, in other words, the patients' expectations of the treatment and their past experiences with similar treatments. Rescorla and Wagner[14] theorized that conditioning depends on prediction error – discrepancies between expected and observed outcomes. They found that reward prediction errors amount to the difference between received and predicted reward.

It has also been shown that the analgesia benefit in subjects was enhanced when the placebo followed the actual control treatment session. In those subjects that experienced the placebo treatment first, the control treatment's analgesic effects were reduced, or subjects perceived an increased response to the pain stimulus. The analgesic effects were significantly

greater when it followed a successful active session than when the preceding treatment was ineffective, in other words, the subject's expectation appears to affect the treatment efficacy regardless of whether the treatment is active or placebo[15].

In an experiment by Pecina et al[13], it was found that comparisons between expected and observed outcomes are an indicator of sustained placebo effects. They compared the expectation of pain followed by a non-painful condition, which was then followed by a painful condition applied to the masseter muscle. Subjects were told that they would receive a painful stimulus and a non-painful stimulus over a twenty-minute period, but not the order. The subjects also received medication to relieve the painful stimulus. Volunteers would rank their expectation of the medication, rate their perceived pain on a pain visual analog scale at set intervals, and afterward rate the perceived effectiveness of the medication. The results were incongruent with classical theories where the formation of placebo responses was dependent on the development of positive expectations. The largest placebo responses were in those with low expectations and high subjective effectiveness. In other words, the longest lasting and greatest placebo analgesia occurred in subjects that did not expect much from the treatment. They theorized that this correlated with Rescorla and Wagner's theory that prior positive experience may act to condition the procedure inducing an increased analgesic effect following placebo treatment; while an unpleasant previous experience reduced the analgesia active treatment or induces a nocebo effect.

While positive expectations appear to have an unexpected effect on placebo analgesia, outcomes seem to be directly related. In a study by Colloca and Benedetti, [16] participants were given a placebo analgesic treatment and told that they would receive a reduction in pain (thermal

stimulation). Those in the experimental group would receive a lower temperature stimulus to imply effective treatment, while those in the control received the same stimulus. In subsequent stimuli, pain was perceived as reduced in the experimental group, even though the stimulus temperature increased.

A meta-analysis of studies using neuroimaging data on placebo analgesia showed that placebo treatments have modest effects on patient reports of pain, but minimal effects on responses in nociceptive pathways.[17] In the evaluation of the intensity of pain and the response of the nociceptive pathways, they noticed little change in imaging data, but changes in participant response. They concluded that this indicates that there are other processes involved in nociceptive pain response, which they call extra-nociceptive pathways. It is possible that placebo analgesia may affect pain perception along another system. They did note that a limitation to all the studies evaluated was the use of healthy participants and that they may not generalize clinical pain.

It is still possible that the intensity of the placebo intervention used could have a variable effect on analgesia; however, in a systemic review by Fassler et al[18] found no significant difference in interventions – whether there was a difference in intensity or invasiveness. They looked at twelve studies with 1,059 participants utilizing various routes of placebo. Their study was limited due to the heterogeneity of the studies lengths, and there was no statistical difference between groups regarding placebo dose. To account for these differences, they limited their analysis to patient outcomes. Their data were also limited by the small number of studies involved and the variability of disorders evaluated (e.g., chronic pain, irritable bowel syndrome,

vaginal pain, and anxiety). It is notable that their data reflect what Zunhammer and his colleagues[17] found regarding little changes in nociceptive pain response.

TOLERANCE AND PLACEBO DOSE-EXTENSION

A new area of research is the congruent use of placebo with active medication treatment in which the placebo is given after an effective treatment in a repetitive manner. The placebo mimics the psychologic and biologic responses that are associated with the effectiveness of the medications and reducing the side effects, overall costs and reducing tolerance.[19] Dose-extending placebo could be used to exploit endogenous pain modulatory processes. Colloca and colleagues[5] concluded that placebo could be used therapeutically by integrating it into the therapeutic schedule. They conducted a systematic review of twenty-two studies (consisting of animal and human studies) and found that placebo integration reduces total drug intake and limits dose escalation over time. They found that placebos that were given after scheduled active treatment mimic pain reduction in both animals and humans. Their research corroborated a study by Ader and colleagues[20]; it was shown that the relapse of psoriasis following a full dose of corticosteroids, a half-dose with congruent placebo, and placebo alone was 22.2%, 26.7%, and 61.5%, respectively. While research into dose-extension in analgesia is developing and limited by small sample sizes, there could be possible therapeutic strategies in some patients.

FUTURE DIRECTIONS

While the physiology of placebo analgesia is still not well understood, there is evidence that it has a place in the treatment of chronic non-cancer pain. Placebo effect can contribute to positive clinical outcomes. There is also growing evidence that it can modulate the course of

concurrent opioid therapy through dose-extension. Placebo effect appears to benefit from learned mechanisms, as well as, subconscious expectations as the outcomes of placebo analgesia are altered by clinician-patient social interactions, classical conditioning, and how the information regarding the treatment and its outcome is framed.[6,7,21]

It is unclear whether placebo analgesia is acceptable in clinical use. There still many questions regarding the ethics of using placebo treatments.[14,19] While a 2008 survey by Tilburt and colleagues[22] of US internists and rheumatologists found that about half of respondents admitted that they have prescribed a placebo to patients, there is still no consensus on whether it is acceptable. There are currently few studies on the use of open-labeled placebo (placebo without deception), and most lack large sample sizes. The studies also appear to suffer some level of bias due to the Hawthorne effect, which may be unavoidable due to the inability to blind the subjects.[21,23,24] There are still other ethical concerns to consider. While open-label placebo removes the need to deceive the patient, it is questionable there are no harms in prescribing an inactive agent.

Further inquiry into the relationship between placebo and pain processing is necessary to verify the current understanding of neurophysiologic effects on pain response[21]. In addition, longitudinal studies with larger sample sizes utilizing open-label placebo are needed to help alleviate current limitations of sample size and bias from lack of blinding researchers and subjects. Current research into dose-extension and open-label placebo all include small samples and short durations. In addition, further analysis of biological variables, including twin studies, are needed to explain interindividual variability in response to placebo[25].

This review set out to describe the major nociceptive pain pathways involved in placebo analgesia, as well as, the current understanding of placebo effect on concurrent opioid use. After reviewing the literature, one can be cautiously optimistic on the future clinical use of placebo analgesia as a tool in the treatment of chronic non-cancer pain, especially in the presence of opioid dependence as a possible adjunct in decreasing opioid dosage. The current use of placebo in the treatment of chronic non-cancer pain; however, should include a thorough discussion and mutual consensus between provider and patient.

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