Placebo analgesia effects across central nervous system diseases: what do we know and where do we need to go?

Susan Tomczak Matthiesen[a,*], Sigrid Juhl Lunde[a], Sophie Wohlert Kjær[a], Elisa Carlino[b], Lene Vase[a]

Abstract

Placebo effects are well established in healthy participants experiencing experimental or acute pain. Yet, little is known about the mechanisms of placebo analgesia effects in patients with chronic pain and even less is known in patients suffering from central nervous system (CNS) diseases where pain is prevalent, difficult to manage, and often undertreated. This article briefly reviews the current knowledge of placebo analgesia effects in healthy participants with the aim of discussing how the mechanisms in placebo analgesia differ between healthy participants and patients. The focus will be on placebo analgesia effects in chronic pain conditions as well as in 2 CNS diseases: Alzheimer disease and Parkinson disease. Finally, strengths and weaknesses of the current knowledge will be discussed and it will be demonstrated how insights from the placebo literature may point to new ways of improving treatments among patients experiencing pain in relation to CNS diseases.

Keywords: Placebo analgesia effects, Chronic pain, Central nervous system diseases, Open/hidden design

1. Introduction

1.1. Definition of placebo analgesia effects

Placebo analgesia effects are related to healthy participants or patients' *perception* of the therapeutic intervention[90] and they are likely to contribute to the magnitude of various types of analgesic treatments across different diseases. Traditionally, placebo effects have been investigated through administration of inert agents; however, recent designs use active treatments and simply manipulate participants' perception of whether they receive the treatment or not.[2,14,45,58,59] The so-called open/hidden design exemplifies how participant's perception can be manipulated. In the "open" condition, the active treatment is given in full view of the patient, so the patient perceives that a treatment is given, whereas in the "hidden" condition, the same active treatment is delivered unknown to the patient.[11,71] To calculate the placebo analgesia effect, it is important to control for the natural history of the pain[34] so that the changes in pain between the open and hidden conditions should be compared with a no treatment control condition.[70,71]

1.2. Placebo analgesia effect in healthy participants and patients with chronic pain

Placebo analgesia is well studied in healthy participants exposed to experimentally induced painful stimulations.[5,38,62,76] Different psychological factors trigger this phenomenon, for instance, expectations, verbal information, emotions, and learning mechanisms. The neurobiological underpinnings accompanying placebo analgesic effects in healthy participants have been extensively documented, and a complex interplay of biological events has been identified.[21,39,96] However, the question is whether it is possible to transfer the knowledge obtained in healthy participants to populations for whom it is highly relevant, namely *patients* experiencing pain. Relatively few studies have examined placebo analgesia effects in patients with chronic pain. Comparing the placebo analgesia effect in healthy participants and patients with chronic pain, there seems to be some overlap in the psychological mechanisms, but not necessarily in the neurobiological mechanisms. Although central nervous system (CNS) diseases are frequently accompanied by pain conditions, pain is often undertreated in these patient populations[66] and very few studies have examined the possible contribution from placebo analgesia effects.

The aim of this article is to illustrate that knowledge of placebo analgesia effects obtained from studies on healthy participants

cannot necessarily be transferred to patients experiencing pain either as the main disease or as part of a CNS disease. This suggests that placebo analgesia should be examined more stringently across CNS diseases to specify the underlying mechanisms and to clarify whether these patient populations actually benefit from placebo analgesia effects in clinical practice. Central nervous system diseases include various specific conditions such as Alzheimer disease (AD), Parkinson disease (PD), multiple sclerosis, autism, epilepsy, and attention-deficit/hyperactivity disorder, and several of these conditions are accompanied by frequent pain symptoms.[27] Although pain treatment has been studied, eg, in multiple sclerosis[18,80] and in poststroke spasticity,[96] these studies only include a placebo condition and not a no-treatment control condition, which makes it impossible to separate the changes in the placebo condition from confounding factors such as spontaneous remission and regression to the mean.[34] To the best of our knowledge, only studies on AD and PD have included sufficient control conditions to allow for an estimation of the actual placebo effect and therefore, only these studies are reviewed here.

2. What do we know

2.1. Placebo analgesia effects in healthy participants

Most of the knowledge of placebo analgesia effects derives from studies on healthy participants[5,38,62,76] exposed to experimental pain through electrical stimulations,[19,67] heat stimulations,[18,20,24,95] visceral pain,[33,73] or ischemic pain.[1,9,15] From these studies, we know that healthy participants can experience large placebo analgesia effects[38,68,83] and that these placebo effects can be mediated by different psychological mechanisms such as expectations, verbal suggestions, emotions, and learning.[14,31,35,51,52,54,63,73]

2.2. Psychological factors

Whereas expectations of receiving low pain are associated with a larger magnitude of the placebo analgesia effect,[14,77] high levels of fear decrease the magnitude of the placebo analgesia effect.[61] Furthermore, it is well established that the information given about the treatment can substantially change the effect of a treatment, producing placebo analgesia effects or nocebo hyperalgesic effects.[2,8,98,99] For example, Bingel et al. have shown that different information about the same potent painkiller can induce different magnitudes of analgesia. In this study, after a no-treatment condition, participants received remifentanil and were tested under 3 different conditions: (1) hidden administration in which participants had no expectations for analgesia, (2) open administration accompanied by verbal suggestions for pain relief (positive expectation condition), and (3) hidden administration accompanied by verbal suggestions for hyperalgesia (negative expectation condition). Using this extended open/hidden design, Bingel et al. demonstrated that positive expectations significantly increased pain relief. This suggests that the overall analgesic treatment effect benefits from the contribution of a placebo effect. In addition, the study also demonstrates the importance of our perception of and expectations toward the treatment by showing that verbal suggestions contributing to negative expectations block the analgesic capacity of remifentanil.[17] Thus, positive and negative expectations may greatly influence the treatment outcome.

Learning also plays a pivotal role in placebo analgesia. It has been extensively documented that after different exposures to active treatments, the administration of a placebo produces robust placebo analgesia effects.[23,25,74] In particular, the longer the conditioning procedure, the higher the analgesic effect is.[23] Negative learning effects have been documented as well. For example, after different ineffective treatments (negative treatment history), the analgesic responses to a new treatment are substantially reduced.[49] Moreover, changing the route of administration inducing positive expectations of treatment efficacy does not counteract the negative carryover effects on treatment efficacy.[98]

2.3. Neurobiological underpinning

Substantiating placebo analgesia at a neurophysiological level, the placebo analgesia effect is associated with an increased activity in the prefrontal cortices during the anticipation phase when participants *expect* to obtain an analgesic effect of the treatment.[4,93,94] This result has been confirmed by Krummenacher et al., who demonstrated that expectation-induced placebo analgesia in healthy participants can be blocked by disruption of prefrontal cortex (PFC) function using repetitive transcranial magnetic stimulation.[56] Furthermore, when participants *experience* analgesia after a placebo treatment, decreased activity can be observed in the so-called pain matrix involving areas such as the thalamus, the insula, the somatosensory cortices, and the anterior cingulate cortex (ACC)[4,96] and even at the level of the spinal cord.[32] These findings suggest that placebo analgesia alters the perception of pain at early levels of pain processing, although a recent meta-analysis questions this finding.[99] Studies using pharmacological manipulations and brain imaging techniques have contributed with knowledge of how neurotransmitter systems modulate placebo analgesia effects in healthy participants. The involvement of the endogenous opioid system and the endocannabinoid system has been substantiated by means of opioid and cannabinoid antagonists (naloxone and rimonabant, respectively). Specifically, these antagonist drugs compete for the opioid and endocannabinoid receptors blocking these systems and, correspondingly, blocking or diminishing the placebo analgesia effect.[1,2,6–8,14,26,32,40,57] More ambiguous is the involvement of the dopaminergic system. Whereas one study using a similar antagonist paradigm has shown that the placebo analgesia effect in healthy participants cannot be blocked or diminished by means of a dopamine antagonist,[87] studies using brain scanning techniques or genetic analysis have supported the involvement of the dopaminergic system.[42,81–83] Even so, the role of these neurotransmitter systems in placebo analgesia effects in patients with chronic pain is less understood, and the neurobiological foundation for placebo analgesia effects may constitute an important argument as to why it is necessary to distinguish between placebo analgesia effects in healthy participants *exposed* to pain and placebo analgesia effects in patients *experiencing* pain.

2.4. Placebo analgesia effects in patients with chronic pain

In pain research, it is important to differentiate chronic pain from experimental and acute pain. Specifically, chronic pain conditions, eg, neuropathic pain, are often characterized by a combination of hyperalgesia (increased pain sensitivity) and allodynia (lowered threshold for pain),[77] reflecting a fundamental change in pain processing and pain perception. Furthermore, studying patients with chronic pain in an experimental setting requires a distinction between ongoing and evoked pain.[78] A few studies have investigated placebo effects in both spontaneous and evoked pain and found large effects for both types of

pain.[20,88] A meta-analysis looking at clinical pain and evoked pain further found that patients with chronic pain are able to experience large placebo analgesic effects, just as healthy participants, and that they may even experience more clinically relevant pain reduction.[38]

2.4.1. Psychological factors

As shown in relation to healthy participants, expectations of low pain levels as well as high levels of positive emotions and low levels of negative emotions also contribute to the magnitude of placebo effects in patients with chronic pain.[71,89] Furthermore, desire for pain relief has been suggested to play a role in placebo analgesia especially in patients with chronic pain.[70,71,86,89,91]

The role of learning mechanisms in patients with chronic pain has not been systematically investigated. Thus, it is not clear whether the robust placebo conditioning effect observed in healthy volunteers can be reproduced in patients with chronic pain. Only one study investigated the role of negative treatment history in patients with chronic pain, showing that patients with a more negative pain-related treatment history reported significantly larger placebo responses to their own chronic pain,[67] which seems to be in contrast to the findings in healthy volunteers.[98]

2.4.2. Neurobiological underpinning

At a neurophysiological level, neuroimaging studies have demonstrated that placebo analgesia in patients with irritable bowel syndrome is associated with reductions in neural activity in areas of the pain matrix, such as the thalamus, the insula, the somatosensory cortices, and the ACC.[27,78,79] Accordingly, the neurophysiological foundation for placebo analgesia effects in patients with chronic pain seems to be similar to the neurophysiology underlying placebo analgesia effects in healthy participants. In contrast to the findings in healthy participants, however, the few studies examining the involvement of neurotransmitters in placebo analgesia effects have not directly demonstrated the involvement of the endogenous opioid and dopaminergic systems.[55,86,91] At present, no studies have examined the involvement of the endocannabinoid system in placebo analgesia effects in patients with chronic pain. The neurobiological underpinnings for placebo analgesia effects hereby accentuate the necessity to distinguish between placebo analgesia effects in healthy participants and placebo analgesia effects in patients with chronic pain.

Part of this difference in the neurobiological foundation for placebo analgesia may be associated with more fundamental differences in the processing of chronic pain as opposed to acute and experimental pain as previously described. Furthermore, psychological factors such as experience with treatment failure and negative expectations, anxiety, and depression are likely to accompany chronic pain conditions and, accordingly, are also likely to affect the prolonged pain experience[44,77,89,91,92] and potentially treatment outcome, although this awaits further investigations. This accentuates the importance of considering prior treatment history—and accompanying expectancy and emotions embedded in all treatment contexts—when treating patients with chronic pain.[22,36,37,70,71]

2.4.3. The open-hidden design

Petersen et al. have used the open/hidden design to investigate placebo analgesia effects in patients with chronic pain suffering from neuropathic pain.[70,71] Open vs hidden administration of

lidocaine compared with a no treatment control condition showed significant placebo analgesia effects on spontaneous ongoing neuropathic pain[71] as well as on a range of evoked pain measures including area of hyperalgesia.[70,71] The pain reduction in the open administration of lidocaine was related to expectations of lower pain levels and positive emotions.[71]

Recently, Skyt et al[84] have demonstrated that the open/hidden design can also be used to investigate the involvement of neurotransmitter systems in placebo analgesia effects in neuropathic pain patients. Using the open/hidden administration of lidocaine together with administration of a dopamine agonist and a dopamine antagonist on different test days, the study demonstrated that the placebo analgesia effect was not increased or blocked, respectively, by the agonist and the antagonist drugs. In this extended version, the open/hidden design thereby allows us to demonstrate a placebo analgesia effect in patients with chronic pain that relies on the patient's perception of the treatment but not on the underlying dopaminergic activity.

The abovementioned studies point to the open/hidden design as a promising methodological approach for examining placebo analgesia effects and the underlying mechanisms in a clinically relevant setting across patient populations experiencing pain. Similarly, it could profitably be used to explore placebo mechanisms in patients experiencing pain in relation to CNS diseases as well.

2.5. Placebo analgesia effects in central nervous system diseases

At present, relatively few studies have examined placebo analgesia effects in patients with AD and PD. The majority of these studies have, however, used the open/hidden design or related designs.

2.6. Alzheimer disease

To the best of our knowledge, only one study has investigated placebo-related mechanisms in patients with AD. Benedetti et al. studied patients with AD at the initial stage of their disease and after one year and compared them to healthy participants matched for sex and age. Both patients with AD and healthy participants were treated with open and hidden lidocaine following pain, induced via venipuncture. A significant difference in pain levels occurred between the open and hidden application of lidocaine in both patients with AD and healthy volunteers at the initial stage, indicating that both groups obtained a placebo analgesia effect.[11] Yet, at the 1-year retest, when the disease has progressed, only the healthy participants obtained the placebo analgesic effect, whereas the patients with AD no longer experienced a placebo analgesia effect.

2.6.1. Psychological factors

The literature on placebo analgesia effects in healthy participants has demonstrated that factors such as verbal suggestions and expectations are involved in obtaining placebo analgesia effects. Although the study by Benedetti et al. suggests a disruption of placebo analgesic effect in patients with AD at their late stage of disease, this phenomenon still needs to be examined more systematically. For example, it will be important to directly measure AD patients' level of expectations, apply standardized pain measurement, and control for the natural history of pain to fully understand how these factors influence the placebo effect.

Still, the study by Benedetti et al.[11] indicates that the potential loss of expectancy-related mechanisms may make analgesic treatments less effective. Therefore, one could argue that the analgesic treatment should be increased progressively to compensate for the loss of placebo- and expectation-related mechanisms.[11]

2.6.2. Neurobiological underpinning

The study by Benedetti et al. also investigated the relationship between placebo mechanisms and frontal lobe connectivity by recording electrical activity of the brain with an electroencephalogram. Interestingly, patients with AD showed reduced connectivity between the prefrontal lobes and the rest of the brain at the 1-year retest, thereby indicating that the disruption of the placebo mechanisms co-occurred with reduced connectivity. It was therefore suggested that the impaired prefrontal connectivity reduces the communication between the prefrontal lobes and the rest of the brain, thereby obstructing placebo mechanisms such as expectancy to evolve.[11] In light of the findings previously mentioned by Krummenacher et al. demonstrating that expectation-induced placebo analgesia in healthy participants can be blocked by disruption of PFC function, the reduced connectivity of the prefrontal lobes may at least in part explain why patients with AD do not experience placebo analgesia effects as the disease progresses.[56]

2.7. Parkinson disease

Studies of placebo effects in patients with PD have shown prominent effects.[28] The studies have primarily been conducted in relation to motor symptoms and several have been conducted in patients implanted with electrodes in the subthalamic nuclei for deep brain stimulation (DBS).[46,48,75] On this basis, placebo effects have been observed on motor symptoms when modulating expectations related to the subthalamic stimulation.[46,57,64,75]

2.7.1. Psychological factors

Pollo et al. have investigated how verbal suggestions for either good or bad motor performance influence the velocity of hand movement. A significant change in motor performance occurred when patients with PD expected a good motor performance, thereby suggesting that expectations induce neural changes within a very short time.[75]

In another study by Benedetti et al., patients with PD were tested for the velocity hand movement according to a double-blind experimental design in which neither the patient nor the experimenter knew whether the stimulator was turned on or off. On the day of the experimental session, the stimulator was kept on but the patients were told it had been turned off to induce negative expectations of motor performance. Although the stimulator was on, the patients' motor performance worsened.[9]

Both studies thereby demonstrate that motor performance in patients with PD, as has been seen with pain in other populations, can be modulated in 2 opposite directions by placebo and nocebo effects, and this modulation occurs on the basis of positive and negative verbal suggestions about motor performance.[8,71] Recently, the role of learning mechanisms has been documented in patients with PD, showing promising results. In particular, it has for the first time been demonstrated that placebo administration induces neither clinical nor neuronal improvement in patients with PD who undergo DBS implantation without prior conditioning.[16] However, substantial placebo responses occurred after repeated administrations of the anti-Parkinson agent apomorphine. As the number of apomorphine administrations increased from 1 to 4, both the clinical motor response and the neuronal activity in the ventral anterior and anterior ventrolateral thalamus increased.[16] Importantly, beyond motor symptoms, DBS has shown potential for significant pain alleviation.[43,44,50,60,68] These findings suggest that it is possible to investigate placebo analgesia effects in patients with PD using the open/hidden design either in relation to nonpharmacological treatments such as DBS and/or in relation to pharmacological analgesic treatment.

2.7.2. Neurobiological underpinning

As for the neurobiological mechanisms underlying placebo effects in patients with PD, neuroimaging studies have demonstrated that placebo effects in patients with PD are associated with dopamine release in the striatum.[29,30,59] Specifically, de la Fuente-Fernández et al. conducted a neuroimaging study of placebo effects with a positron emission tomography. In the study, patients were aware that they would either receive an injection of an active drug or a placebo. The results suggested that the dopamine released in the ventral striatum was associated with the patient's expectation of improvement in motor symptoms. de la Fuente-Fernández et al.[28] were the first to relate placebo effects to reward mechanisms and dopamine release in the nucleus accumbens, but other studies have later confirmed these findings.[28,29,61,75] These reward mechanisms could also be expected to be central to analgesia effects of DBS.[46,50] It would therefore be important to test whether dopamine is involved in placebo analgesia effects in patients with PD and especially investigate whether dopamine has a central role in the anticipation of pain relief and/or in the evaluation of the actual pain.

2.8. Nocebo effects

Compared to placebo effects, much less is known about nocebo effects. Nocebo effects were originally introduced to describe the negative effect of a placebo treatment,[41] but today, they are primarily conceptualized as an independent phenomenon that mirror placebo effects. Generally, nocebo effects can be conceptualized as negative effects related to the patients' perception of the treatment[13,71,72,83] More specifically, a nocebo effect can be seen as the effect that follows the administration of an inert treatment along with behavioral procedures and/or verbal suggestions that worsen the symptom and it should be separated from changes in natural history.[16,71,72]

2.8.1. Psychological factors

Like placebo effects, nocebo effects may contribute greatly to the outcome of a treatment. Specifically, suggestions and expectations of worsening can induce negative effects on disease symptoms and treatment outcome.[24] Colloca et al. investigated the role of verbal suggestions and learning in nocebo hyperalgesia in healthy participants. By using a nocebo procedure, in which verbal suggestions of painful stimulation were given before the administration of either tactile or low-intensity painful electrical stimuli, their study indicated that verbal suggestions of a negative outcome can produce both hyperalgesic and allodynic effects and that conditioning did not produce an additional effect.[24]

In line with these findings, the open/hidden approach has been useful in the understanding of nocebo effects in patients with acute and chronic. In a study by Benedetti et al., morphine treatment in postoperative patients were interrupted either openly or hidden for the patient. Accordingly, the patients underwent one of 2 conditions; one where they were told that the morphine had been stopped (open condition) or one where the morphine was stopped without informing the patient (hidden condition). The result showed that pain was larger in the group that had undergone the open condition compared with the group in the hidden condition, suggesting that negative expectations of pain relapse may play an important role.[10] The above finding is important, especially from a clinical point of view. If nocebo verbal suggestions are producing a negative response, it is important to think about how information about a treatment is delivered to the patient.[24] Besides influencing expectations of improvement or worsening through information, it has been demonstrated that the interaction between the doctor and the patients does influence the treatment outcome.[44]

However, both open-hidden design and more traditional designs have not been able to demonstrate nocebo effects in patients with chronic pain tested in a laboratory setting.[53,71,90] This is surprising and may be related to the relatively safe environment in the laboratory setting. In uncontrolled randomized controlled trial studies, however, adverse events are frequently found in the placebo arm, thereby suggesting that negative nocebo-like effects do occur in chronic populations[3]

2.8.2. Neurobiological underpinning

Brian imaging techniques have been fundamental in the understanding of the neurobiology of nocebo effects and negative expectations. Overall, the brain imaging studies indicate that negative expectations may result in the amplification of pain, with anticipation of pain-activating brain regions such as the ACC, the PFC, and the insula.[48,54,61,74] However, besides neuroimaging, pharmacological studies provide an insight into the biochemistry of nocebo effects and negative expectations. Benedetti et al. have investigated neurotransmitters and found a release of the opioid antagonists CCK during nocebo hyperalgesia.[12] In general, when investigating the placebo–nocebo phenomenon, there seems to be opposite effects and mechanisms. The opioidergic and the CCK-ergic systems seem to be activated by opposite expectations of either analgesia or hyperalgesia, meaning that verbal suggestions of a positive outcome activate endogenous μ-opioid neurotransmission, whereas suggestions of a negative outcome activates CCK-A and CCk-B receptors.[12,13]

2.8.3. Nocebo effects in central nervous system conditions

Nocebo-like effects have primarily been investigated in AD, PD, and across CNS diseases such as depression and scleroses through meta-analyses of adverse events in the nocebo arm of RCTs.[65,69,73,85,90,97] For example, many patients with AD report adverse events, and they may be at greater risk of developing them, which could reflect nocebo responses. Yet, there is a need for further exploring nocebo effects in experimental studies. In PD, nocebo responses have been induced through negative verbal suggestions in experimental DBS trials. Studies have found some patients and certain symptoms to be susceptible to nocebo,[46,64] whereas others have not found nocebo effects.[47] Thus, further research is needed to identify exact nocebo effects and mechanisms in patients with AD and PD as well as across CNS diseases.

3. Future—where do we need to go?

Placebo analgesia effects are well documented in healthy participants. In this population, large placebo analgesia effects have been reported, and the knowledge of the psychological and neurobiological mechanisms is increasing substantially over time. Placebo analgesia is also reported in different pathological conditions, ranging from chronic pain to CNS diseases. Even if the study of placebo analgesia on pathological conditions is pivotal, our knowledge of the psychological and neurobiological underpinnings is still poor. For example, expectations for pain relief seem to be central for placebo effects across CNS diseases; it is, however, unclear whether a common neurobiological substrate can be delineated across diseases. Moreover, the role of learning mechanisms is still uncertain. On one hand, healthy participants experience robust placebo analgesic effects after a conditioning procedure, but, on the other hand, only few evidences of the role of learning come from patient populations. This aspect seems crucial because patients will often have negative treatment experiences during their lifetime and this may change the effectiveness of future pain treatments.

Brain imaging techniques have demonstrated neurobiological underpinning of placebo effects across all the reviewed CNS diseases. Yet, looking at the involvement of neurotransmitters, diverse findings emerge across diseases. In healthy participants, both the endogenous opioid, cannabinoid, and dopaminergic systems have been implicated in placebo analgesia effects, but none of these neurotransmitters seem to be involved in placebo effects in patients with chronic pain. Interestingly, the dopaminergic system seems to be central for placebo effects in patients with PD but the direct involvement of the dopaminergic system in placebo analgesia effects of patients with PD still needs to be investigated. Thus, this review indicates that the mechanisms of placebo analgesia effects are likely to differ across CNS diseases. Therefore, to understand the mechanisms and the contribution of placebo analgesia effects to pain treatments across CNS diseases, it is pivotal to investigate the placebo analgesia effect specifically within each disease, preferably using comparable designs.

In this article, it has been shown that the open/hidden design can be used to investigate placebo analgesia effects across CNS diseases, involving both pharmacological and nonpharmacological treatments, and specifying both psychological and neurobiological mechanisms. Importantly, this can be done within a clinically relevant context where active pain medication is given. We therefore suggest that this can be used as a comparable design across diseases to estimate the magnitude of placebo analgesia effects across CNS diseases. In this manner, we can begin to understand similarities and differences of placebo analgesia effects across CNS diseases. Currently, the primary knowledge of placebo effects is in pain, AD, and PD, and some in depression. Yet, it will be important to expand this knowledge to other CNS diseases including multiple sclerosis, autism, and attention-deficit/hyperactivity disorder. Both placebo and nocebo effects are important to consider in clinical practice because they may both have a great influence on treatment outcome through various factors and mechanisms.

The more we learn about placebo effects in specific CNS diseases, the better we can use this knowledge to optimize pain treatments. Specifically, it will be important to know which CNS diseases may benefit from optimized perception of the treatment and hence a placebo effect to adjust pain treatments accordingly. In this manner, the investigation of placebo analgesia effects across CNS diseases holds the potential to improve our

understanding of placebo analgesia mechanisms and to offer better treatments for large groups of patients who currently suffer from insufficient pain treatment.

Disclosures

The authors have no conflict of interest to declare.

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