

## Review

# A Review of the Theoretical and Biological Understanding of the Nocebo and Placebo Phenomena



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### ABSTRACT

**Purpose:** Placebos are commonly used in experimental and patient populations and are known to influence treatment outcomes. The mechanism of action of placebos has been investigated by several researchers. This review investigates the current knowledge regarding the theoretical and biological underpinning of the nocebo and placebo phenomena.

**Method:** Literature was searched using PubMed using the following keywords: *nocebo*, *placebo*, *μ-opioid*, *dopamine*, *conditioning*, and *expectancy*. Relevant papers were selected for review by the authors.

**Findings:** The roles of conditioning and expectancy, and characteristics associated with nocebo and placebo responses, are discussed. These factors affect nocebo and placebo responses, although their effect sizes vary greatly, depending on inter-individual differences and different experimental paradigms. The neurobiology of the nocebo and placebo phenomena is also reviewed, emphasizing the involvement of reward pathways, such as the *μ-opioid* and *dopamine* pathways. Neurobiological pathways have been investigated in a limited range of experimental paradigms, with the greatest efforts on experimental

models of placebo analgesia. The interconnectedness of psychological and physiological drivers of nocebo and placebo responses is a core feature of these phenomena.

**Implications:** Further research is needed to fully understand the underpinnings of the nocebo and placebo phenomena. Neurobiology pathways need to be investigated in experimental paradigms that model the placebo response to a broader range of pathologies. Similarly, although many psychological factors and inter-individual characteristics have been identified as significant mediators and moderators of nocebo and placebo responses, the factors identified to date are unlikely to be exhaustive. (*Clin Ther.* 2017;39:469–476) © 2017 Published by Elsevier HS Journals, Inc.

**Key words:** conditioning, dopamine, expectancy, *μ-opioid*, nocebo, pharmacology, placebo, treatment.

For the purpose of this review, a placebo response is an improvement in clinical symptoms when a person is administered an inert substance, whereas a nocebo response is a worsening of clinical symptoms or the experiencing of treatment-emergent adverse effects. Typically, a placebo tablet is administered in control arms of

Accepted for publication January 5, 2017.

<http://dx.doi.org/10.1016/j.clinthera.2017.01.010>  
0149-2918/\$ - see front matter

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clinical trials and is manufactured to look identical to the tablet in the active arm of a trial. Nocebo and placebo responses are also sometimes used to describe unexpected responses to active treatments that are not explained by the known mechanism of action of the treatment. It may not be possible to discern at an individual participant level between true placebo or nocebo responses and fluctuations in symptom severity due to the natural progression of the illness; however, insightful placebo and nocebo response data can often be obtained at a cohort level. While the importance of the placebo effect is widely understood, this is much less so for the nocebo effect. The biological bases of the nocebo and placebo effects are only now beginning to be unraveled. Attempts to understand the causes of the placebo effect have increased in the last 50 years, as placebo-controlled clinical trials have become the only accepted method for efficacy testing of new pharmaceuticals and the problems associated with placebos have become more apparent. Insights have been gained from exploring theoretical causes and influencing factors of the effect, which have probed the mechanisms underlying the phenomenon. This article reviews the theoretical and biological underpinning of the nocebo and placebo phenomena. A separate article also published in this issue reviews the clinical importance of the nocebo and placebo phenomena.

## PSYCHOLOGICAL UNDERPINNINGS

There are a multitude of psychological elements that have been identified as the leading factors underpinning the placebo and nocebo effects.

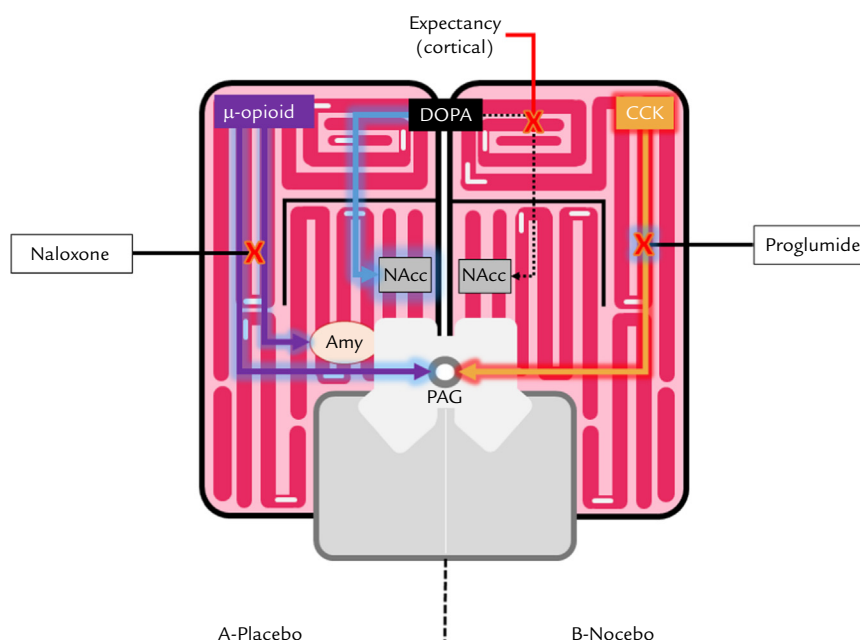
The most well-known theories pertaining to the placebo and nocebo phenomena are the conditioning and expectancy hypotheses. Conditioning can occur when a person was pre-exposed to an active substance and had a reaction that imprints in memory. When they are then given an inert substance, they might respond to the inert substance in the same or similar way as they would to the active substance. A conditioned response is a triggering of a memory loop and, therefore, is driven by learning and adaptation.<sup>1</sup> The effect is mediated by many variables. The conditioning hypothesis alone is insufficient to explain the placebo and nocebo phenomena, for example, the extinction phenomenon in classic conditioning does not necessarily occur with placebos.<sup>1</sup>

Expectancy occurs where a pre-existing belief, or information received before being given an inert substance (or before reporting a response<sup>2</sup>), elicits a response

to the inert substance predicated on what the person thinks will happen. It is not necessary to have ever been exposed to an active substance to have an expectation of response. This may be responding to a treatment that is not pharmacologically active because of a pre-existing belief that the treatment either works or might cause a specific reaction, and can be an important factor in alternative therapies in which pharmacologically active compounds are not included in the treatment.<sup>3</sup> Similarly, expectation can be a driver of inappropriate or over-prescription of some medications, including antibiotics, in a phenomenon that shares much in common with the placebo effect.<sup>4</sup> As with conditioning, expectancy also requires learning, which may come through direct receipt of information, suggestion, social cues, or the interaction of all these learning modalities.<sup>5</sup> Suggestion has also been used experimentally to extinguish a conditioned placebo response.<sup>6</sup> Extinction of a conditioned response requires learning, which in the case of a placebo response can be facilitated by suggestion, but may not necessarily occur solely through repeated administration of a placebo.

Hope for improvement has also been suggested as a driver of the placebo effect<sup>1</sup> and this has face validity; however, data have not been presented to support this theory. A corollary, where despair is suggested to drive the nocebo effect, has not been proposed in peer-reviewed literature. However, personality traits have been associated with placebo response,<sup>7</sup> leaving the possibility open to an association between personality traits, such as optimism and pessimism, being factors in the placebo and nocebo phenomena. However, considerable work needs to be done to unravel the relationship between personality and placebo response, including expanding the theoretic underpinnings of the association through hypothesis-driven research in addition to the current works that have focused on association between personality measures and placebo response.<sup>8</sup> State and trait variance are a limitation with personality measures<sup>9</sup> and may be relevant for the placebo response, for example, where there is variance in dependence.

The nature of the therapeutic alliance may also be a driver of the nocebo effect, with a hostile-dependent relationship being an exemplar. This relationship pattern occurs when one party is dependent on another, and the former is hostile or mistrusting of other people. This is a not uncommon but poorly recognized pattern in clinical practice, where people with insecure attachment styles are forced into trusting a clinician, and their interactional style makes this difficult [Figure](#).



**Figure.** Summary of regions, circuits, and neurotransmitters implicated in placebo and nocebo. **A-Placebo:** Expectation activates cortical area signaling of dopamine to the nucleus accumbens and  $\mu$ -opioid to the periaqueductal gray and elsewhere in the brain (the amygdala and other regions: not shown). The placebo effect is blocked by naloxone. **B-Nocebo:** Negative expectation has the opposite effect in the dopamine signaling and also activates cholecystokinin from the prefrontal cortex to the periaqueductal gray. The nocebo effect is blocked by proglumide. Amy = amygdala; CCK = cholecystokinin; DOPA = dopamine; NAcc = nucleus accumbens; PAG = periaqueductal gray.

In an open-labeled study, 80 women with irritable bowel syndrome were randomly assigned to placebo with a persuasive rationale but without deception, or to a control group with no treatment. Both groups received the same patient–provider relationship and contact time. Participants in the placebo-treated group had significantly higher global improvement scores.<sup>10</sup> In this study, the placebo effect occurred even though the participants were told they would be receiving an inert substance “like sugar pills.” This may suggest that the placebo effect has multiple drivers, including expectancy, as participants were told that placebo “has been shown to produce significant improvement to [irritable bowel syndrome] symptoms,” as well as the importance of the treatment rituals and therapeutic environment.

There is evidence that anxiety about the tolerability or efficacy of a treatment can be a driver of the nocebo effect. In a meta-analysis of placebo-treated participants in clinical trials of duloxetine versus placebo, treatment-emergent adverse events were reported more commonly

in Phase II trials, then Phase III, and least in Phase IV.<sup>11</sup> This suggests that a nocebo response is more likely for a treatment that is more experimental and uncertain compared with one that is more established.

Choice of treatment and sense of control was found to influence both placebo and nocebo responses in an experiment where healthy participants ( $n = 61$ ) were randomly assigned to choose between 2 equivalent  $\beta$ -blocker medications or be assigned to the medications. All study medications were actually placebos. There was an increased placebo response in the choice group and an increased nocebo response in the no-choice group.<sup>12</sup>

### Neurobiological Findings

Numerous experiments have revealed insights into which regions of the brain are involved in the placebo response and which biochemical processes are occurring in association with placebo and nocebo events. Imaging studies have often used a placebo analgesia paradigm, as it is a reliable and convenient model.

Many variations of the analgesia paradigm exist. Placebos to replace psychotropic drugs are also a reliable and convenient paradigm, and a placebo antidepressant has been used for at least one imaging study. The placebo and nocebo phenomenon has been found in numerous medical conditions, across drug classes, and in non-pharmacologic contexts. It may be difficult to disentangle if a neurobiological response is applicable to the placebo and nocebo phenomena in general or only to a specific context or as treatment for a specific stimulus. The Figure summarizes brain regions, circuits, and neurotransmitters implicated in placebo and nocebo phenomena.

### Neuroanatomic Regions

Studies using functional nuclear magnetic imaging (fMRI) and positron emission tomography (PET) have identified multiple brain regions involved in the placebo response. Several studies and a meta-analysis have identified the thalamus, primary and secondary somatosensory cortex, anterior cingulate cortex (ACC), amygdala, basal ganglia, and right lateral prefrontal cortex as brain regions; these were less activated when measured by fMRI, when placebo analgesia was used to modulate a response to a pain stimulus.<sup>5</sup> PET studies of placebo analgesia have identified the rostral ACC, prefrontal cortex, insula, thalamus, amygdala, nucleus accumbens and periaqueductal gray using a  $\mu$ -opioid receptor radiotracers, and the basal ganglia using D2 and D3 receptor radiotracers as brain regions with neurotransmitter response to placebo analgesia.<sup>13</sup>

In a deceptive placebo analgesia paradigm fMRI study for visceral pain where participants are randomized to receive placebo and being told the substance is inert or placebo and being told that the substance is an analgesic, greater modulation by placebo analgesia of the posterior insula and dorsolateral prefrontal cortex was observed in women compared with men, although the efficacy of placebo analgesia in controlling expected or perceived pain did not differ between sexes.<sup>14</sup> A deceptive placebo analgesia paradigm fMRI study for noxious heat pain, where placebos were labeled as a popular branded original or a generic analgesic, original branded and generic labeled placebos were both associated with activation of the anterior insulae at baseline and activation of the dorsomedial prefrontal cortex after the interventions. Greater activation of the bilateral dorsolateral (as well as dorsomedial)

prefrontal cortex (PFC) was observed for the placebo labeled as the original brand. The placebo labeled as the original brand was also associated with decreased pain intensity compared with the generic-labeled placebo.<sup>15</sup> A recent PET study using a  $\mu$ -opioid receptor radiotracer, patients with major depressive disorder were treated with placebo in a crossover study in which one placebo was labeled “active” and the other “inactive,” and told that the active treatment was a fast-acting antidepressant and the inactive treatment was a control. Active treatment was superior to inactive treatment for placebo-induced opioid release in brain regions subgenual ACC, nucleus accumbens, amygdala, thalamus, and hypothalamus.<sup>16</sup> Placebo activation of endogenous opioid neurotransmitters that bind to receptors in the pregenual and subgenual rostral ACC, the dorsolateral PFC, the insular cortex, and the nucleus accumbens, has also been observed in an analgesia paradigm using PET.<sup>17</sup> Substantial inter-individual variation has been reported for brain regions involved in placebo response to expectations of analgesia.<sup>18</sup>

An fMRI study of 24 healthy adults investigated neural activation in response to stimuli associated with different expectations. In 3 separate sessions (ie, training, conditioning, and scanning sessions) on different days, participants were subject to 12-second heat pain stimulus to their right forearm. At the conditioning and training sessions, participants' skin was treated with an inert cream before the heat pain stimulus. One cream was labeled “lidocaine” (positive expectancy), one was labeled “neutral,” and the third cream was labeled “capsaicin” (negative expectancy). Difference between positive and negative expectancy conditions were observed, either pre or post stimulus, in the dorsal ACC, right orbito-PFC, anterior insula, right dorsolateral PFC, left ventral striatum, orbitofrontal cortex, periaqueductal gray, and left operculum and putamen.<sup>19</sup> This experiment found that placebo and nocebo expectancies have effects on different brain networks in response to a pain stimulus.

There are limitations to using fMRI and PET to study models of the nocebo and placebo effects. Firstly, most experiments are conducted on health volunteers, so important drivers of the placebo response, such as hope and therapeutic alliance, are not included in the experimental construct. Secondly, study participants are inside a large piece of medical equipment, which is a specific experimental environment. Thirdly, the experimental environment limits the study design and duration.

## Neurochemical Processes

The placebo response has been associated with the release of endorphins and dopamine, providing a neurochemical explanation of the efficacy of placebo analgesia.<sup>13</sup> Early evidence of the elevation of endogenous opioids in placebo analgesia was reported in 1978, when Levine et al<sup>20</sup> used placebo as an analgesic for dental postoperative pain and reversed the analgesic effects by administering the opiate antagonist naloxone. Endorphin and dopamine release and opioid and dopamine receptors are widely distributed, but are also clustered in specific brain regions that correspond with many of the regions identified by fMRI studies. There are 3 major types of opioid receptor,  $\mu$ -opioid receptor,  $\delta$ -opioid receptor, and  $\kappa$ -opioid receptor, which can be further divided into subtypes, and a fourth nociception or orphanin receptor.<sup>21</sup> These receptors are widely distributed through the brain and other organs, but with differences in expression and distribution.<sup>21</sup> Opioid receptors have a range of functions, including pain modulation and their association with analgesia, however, they are also associated with various functions, including mood regulation, homeostasis, cell proliferation, and neuroprotection.<sup>21</sup>

Much placebo neurobiological research has focused on analgesia, often investigating the  $\mu$ -opioid receptor. Where major depressive disorder has been investigated<sup>16</sup> increased  $\mu$ -opioid neurotransmission has been observed, similar to observations in analgesia research, which may suggest similarities to, or be a consequence of, using a similar research method. Inter-individual variation in  $\mu$ -opioid neurotransmission has also been observed in a study of 50 healthy controls with and without placebo administration, where psychological trait scores measured with scales for altruism, straightforwardness, and angry hostility accounted for 25% of the variance in placebo analgesic response and also found that participants scoring above the median in a composite score of all 3 traits had increased  $\mu$ -opioid neurotransmission in response to placebo administration.<sup>22</sup>

An experiment where hypertonic saline was injected into the masseter muscle of 20 healthy individuals to induce pain, with or without placebo analgesia, was investigated using PET to examine changes in dopamine and opioid neurotransmission. The study used [ $C^{11}$ ]-labeled raclopride (selective for  $D_2$  receptors) and carfentanil (selective for  $\mu$ -opioid receptors). Participants were asked to rate the efficacy of the

analgesic and describe adverse events. Effective placebo analgesia was associated with increased dopamine and opioid neurotransmission in multiple brain regions. A nocebo effect was identified in 5 participants who reported increased pain intensity during placebo administration. Nocebo responders showed decreased dopamine and opioid neurotransmission in the same brain regions where increased neurotransmission was observed in placebo responders.<sup>23</sup>

In a study where patients reporting mild perioperative pain were given saline solution and were told that the solution produced an increased pain (nocebo hyperanalgesia), pain was abolished when proglumide was added to the solution. Proglumide is a cholecystokinin antagonist, which blocks both the  $CCK_A$  and  $CCK_B$  receptor subtypes, suggesting that nocebo hyperanalgesia is mediated at least in part by cholecystokinin.<sup>24</sup>

PET studies have found that administration of a placebo to people with Parkinson's disease can induce dopamine release in the striatum.<sup>25</sup> Furthermore, in a study of 24 participants with Parkinson's disease undergoing deep brain stimulation, the firing rate of selected neurons was changed in participants who showed a clinical response to placebo, but not in nonresponders or partial responders to placebo. Mean firing frequency decreased in subthalamic and substantia nigra pars reticulata neurons and increased in ventral anterior and anterior ventral lateral thalamus neurons. The placebo effect had a duration of no more than 45 minutes. Other parts of the brain circuitry were not measured.<sup>26</sup> Another study found that placebo was enhanced with preconditioning by apomorphine exposure, with the greater number of exposures to apomorphine associated with a greater change in neuronal firing rates.<sup>27</sup>

Endocannabinoids have a role in placebo-induced analgesia, as reported in a study analogous to the 1978 naloxone experiment that reported on the role of endorphins.<sup>20</sup> Placebo was effective as an analgesic against tourniquet pain after preconditioning participants to analgesia with either the opioid morphine or the nonsteroidal anti-inflammatory drug ketorolac. In these preconditioned participants, the CB1 cannabinoid receptor antagonist rimonabant reversed placebo analgesia after preconditioning with ketorolac, but did not reverse placebo analgesia in participants preconditioned with morphine.<sup>28</sup>

Prostaglandin levels have also been found to change in response to placebo. In an experiment,



placebo was used to treat headache caused by high-altitude (3,500 m) hypobaric hypoxia, after preconditioning by treating headache with inhaled oxygen and later giving placebo (sham) oxygen, or by preconditioning with aspirin and later giving a placebo tablet. In both scenarios, the placebos were effective for reducing headache pain, but the analgesic effect of placebo oxygen was superior to placebo aspirin. Placebo oxygen was found to specifically reduce salivary prostaglandin E<sub>2</sub>, mimicking the therapeutic pathway of oxygen therapy, whereas placebo aspirin had a more general effect on prostaglandin synthesis, mimicking the effect of cyclooxygenase inhibition.<sup>29</sup>

### Interaction of Psychological and Physiological Factors

Placebo and nocebo responses occur within a psychological and physiological context. This context is critical for all aspects of the response, including the neurobiological elements. The context includes characteristics of the study or treatment in which the placebo or nocebo effect is observed and characteristics of the study participant or patient, as well as other characteristics, including the environment in which the study or treatment is being conducted. The doctor–patient relationship, for example, can include trust, where untrustworthiness has been associated with increased amygdala activity, and trustworthiness can be modulated by oxytocin.<sup>30</sup> Trust may be a characteristic not only of the active relationship, but is powerfully influenced by personality and developmental factors that set individuals levels of trust. Similarly, hope and hopelessness have been associated with serotonergic and noradrenergic systems,<sup>30</sup> showing the potential for variables relevant to placebo having a direct effect on neurotransmitter systems directly implicated in mood. Also relevant to the placebo response, admiration and compassion by a participant have been found through fMRI to result in a pattern of activation within the posteromedial cortex.<sup>31</sup> Learned helplessness has been found to effect serotonin regulation.<sup>32</sup> The relationship between pain and stress and anxiety with the hypothalamic–pituitary–adrenal axis and cortisol is well established.<sup>33</sup>

Negative and positive expectations, which are suggested to be major drivers of the placebo and nocebo responses, have been found to induce changes in reward circuitry in the nucleus accumbens, and similarly, conditioning may induce changes in learning mechanisms.<sup>30</sup>

### DISCUSSION

The drivers of the placebo and nocebo phenomena may be a synergy of multiple biological and psychological variables, mediated by a further multitude of contextual and individual variables. There is clear evidence of physiological factors that underpin the phenomena, as well as a contribution by psychological factors. This is further complicated by considerable inter-individual differences. Although there is consistency in the literature in terms of which pathways are implicated in placebo and nocebo responses, neurotransmitter activation does not occur with all individuals experiencing the same stimulus. Factors such as conditioning, expectancy, hope and despair, wanting to please the experimenters, treatment setting, caring nature of the clinician, and personal beliefs about medications, all play a role.

Furthermore, while the placebo and nocebo effect has been observed for treatment for a broad range of medical conditions, it has only been carefully studied in experimental models of a narrow range of conditions, especially pain and analgesia. It is possible, or even likely, that the neural pathways involved in a placebo analgesia response are different, or only partly overlapping, from the neural pathways involved in a placebo response for a different treatment. The investigation of the biological and theoretical underpinning of the placebo and nocebo phenomena is at an early stage and much additional research is required.

### ACKNOWLEDGMENTS

Michael Berk is supported by a National Health and Medical Research Council Senior Principal Research Fellowship 1059660. All authors contributed to preparing the paper and gave final consent for publication. SD wrote the first draft. OMD and MB extended the draft and edited the full manuscript. JV prepared the figure and edited the full manuscript.

### CONFLICTS OF INTEREST

SD has received grant support from the Stanley Medical Research Institute, NHMRC, Beyond Blue, ARHRF, Simons Foundation, Geelong Medical Research Foundation, Fondation FondaMental, Eli Lilly, Glaxo SmithKline, Organon, Mayne Pharma and Servier, speaker's fees from Eli Lilly, advisory board fees from Eli Lilly and Novartis and conference travel support from Servier. OMD has received grant support from the Brain and Behavior Foundation, Simons Autism Foundation, Stanley Medical

Research Institute, Deakin University, Lilly, NHMRC and Australasian Society for Bipolar and Depressive Disorders (ASBDD)/Servier. JV has no conflicts of interest. MB has received Grant/Research Support from the NIH, Cooperative Research Centre, Simons Autism Foundation, Cancer Council of Victoria, Stanley Medical Research Foundation, MBF, NHMRC, Beyond Blue, Rotary Health, Geelong Medical Research Foundation, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Meat and Livestock Board, Organon, Novartis, Mayne Pharma, Servier, Woolworths, Avant and the Harry Windsor Foundation, has been a speaker for Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck, Merck, Pfizer, Sanofi Synthelabo, Servier, Solvay and Wyeth, and served as a consultant to Allergan, Astra Zeneca, Bioadvantex, Bionomics, Collaborative Medicinal Development, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck Merck, Pfizer and Servier. He is a co-inventors of two provisional patents regarding the use of NAC and related compounds for psychiatric indications, which, while assigned to the Mental Health Research Institute, could lead to personal remuneration upon a commercialization event.

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