Harnessing placebo effects to regulate emotions

Darwin A. Guevarra, Ethan Kross, and Jason S. Moser

Author Note

Correspondence regarding this chapter may be addressed to Darwin A. Guevarra, Ph.D., University of California, San Francisco, Department of Psychiatry and Behavioral Sciences, 675 18th Street, San Francisco, California, 94107 USA.

E-mail: Darwin.Guevarra@ucsf.edu

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Successful emotion regulation is essential for promoting psychological and physical health (DeSteno et al., 2013; Sheppes et al., 2015). However, people often experience difficulties regulating their emotions. Even with optimal self-regulation capacity, people have problems managing their feelings when fatigued or stressed (Grillon et al., 2015; Raio et al., 2013). Therefore, it is essential to find ways to make self-regulation less difficult. Placebo effects, which are brain-body responses to an inert treatment and the psychosocial context in which it is delivered (Ashar et al., 2017), offer an avenue to address these issues since they may regulate emotions automatically (Braunstein et al., 2017).

Some researchers use a broad conceptualization of placebo effects to include instances where an active treatment is enhanced by placebo-related mechanisms. Others maintain that the placebo effect requires administering an inert object (e.g., pill, nasal spray) or procedure (e.g., sham meditation). In addition to this complexity, placebo effects occur in many contexts, such as reducing pain, improving cognitive and physical performance, and managing anxiety and depression symptoms (Benedetti, 2021). In this review, we focus on placebo effects that use a placebo object or procedure to regulate emotions. This chapter has four goals. First, we discuss placebo effects and their mechanisms. Second, we review evidence of placebos regulating emotions. Third, we discuss the ethical dilemma in using placebos to regulate emotions and highlight work on placebos without deception. Lastly, we discuss basic science and translational application questions and suggest directions for future research.

The placebo effect

Placebo effects work through two interrelated mechanisms: expectations and learned associations (Ashar et al., 2017). In the placebo context, expectations refer to the probability of an intended beneficial effect. Expectations are typically induced through verbal suggestions. For

example, Koban et al. (2017) told participants experiencing a break-up that they would receive a nasal spray that would reduce their negative emotions when looking at pictures of their ex-partner. On the other hand, learned associations are automatic responses to stimuli or procedures. In the placebo context, learned associations refer to pairing a beneficial effect with a placebo object or procedure. For example, Petrovic et al. (2005) intravenously delivered an anxiolytic to participants before viewing distressing images. Participants paired the intravenous drip with feeling less negative when looking at these pictures. In the next session, they received a saline intravenous drip with the verbal suggestion it was the same anxiolytic.

Whether through expectations or learned associations, placebos appear to exert their effects automatically and with minimal cognitive effort (Braunstein et al., 2017). Buhle et al. (2012) examined whether engaging executive function would interfere with placebo effects on pain. The placebo reduced pain experience even when the person simultaneously completed a working memory task. Notably, the placebo did not interfere with cognitive performance, suggesting that it did not require extra mental resources to exert its effects. In an fMRI study comparing placebos with cognitive reappraisal (i.e., a strategy that requires more cognitive effort), placebos led to less dorsolateral prefrontal cortex (dlPFC) activation, a brain region associated with selective attention, working memory, and holding active appraisals (Schienle et al., 2017).

How can placebos regulate emotions?

There is substantial evidence that expectation-based placebos can effectively regulate emotions (Geers et al., 2021). In these paradigms, participants are deceptively told they will receive a treatment to reduce their negative emotions before undergoing a distressing task. In laboratory studies, placebos reduced the experience of distress from negative emotional images

(Schienle, Übel, & Scharmüller, 2014; Schienle, Übel, Schöngaßner, et al., 2014), sad movie clips (Glombiewski et al., 2019) and memories (Rebstock et al., 2020), the threat of shock (Meyer et al., 2015; Meyer et al., 2019), and a speech task (Abrams et al., 2001). Some evidence shows placebos can impact autonomic measures associated with emotional responses. For example, participants who received a placebo nasal spray showed reduced skin conductance levels when anticipating painful shocks (Meyer et al., 2015). These studies suggest that placebos influence subjective and objective emotional distress measures.

Much of what we know about neural systems associated with placebo effects come from pain analgesia studies. However, there is evidence that placebos also influence neural measures such as BOLD fMRI signals (Koban et al., 2017; Petrovic et al., 2005; Schienle, Übel, Schöngaßner, et al., 2014) and electrocortical activity (Meyer et al., 2015; Schienle et al., 2020) in emotion regulation contexts. Collectively, these studies show placebos down-regulate brain regions involved in emotional experience (e.g., insula, amygdala). Nevertheless, more research is needed to understand the unique neural systems consistently associated with placebos regulating emotions.

Placebos are also effective in regulating acute emotional distress in clinical samples, including those with social anxiety disorder (Abrams et al., 2001), spider phobia (Gremsl et al., 2018), and depression (Haas et al., 2020). The regulatory effects of placebos also extend to reducing affective symptoms. Meta-analytic findings show that placebos decrease anxiety (Bandelow et al., 2015) and depression symptoms (Khan et al., 2012). It should be noted, however, that active treatments such as SSRIs still outperform placebos (Cipriani et al., 2018), albeit with important moderators. For example, Fournier et al. (2010) showed that placebos

performed just as well as antidepressants for patients with mild to moderate depression; antidepressants only outperformed placebos for patients with very severe depression.

In summary, placebos effectively regulate acute bouts of emotional distress for both non-clinical and clinical samples. The positive effects in clinical samples are noteworthy since people with affective disorders often have difficulties regulating their emotions (Sheppes et al., 2015). Moreover, placebos can reduce mild and moderate affective symptoms, which open-up their clinical application across the full spectrum of people struggling with emotional problems.

Addressing the ethical dilemma of placebos: Introducing placebos without deception

Placebos are remarkably effective in regulating emotions, with 25+ studies showing positive effects with medium to large effect sizes (Ashar et al., 2017; Geers et al., 2021). However, to get placebos to work, participants are deceived into believing they are taking an active treatment. On the one hand, placebos can effectively regulate emotions. But on the other hand, people must be deceived to activate their regulatory effects, creating an ethical dilemma. Fortunately, there is growing evidence that placebos can work without deception (i.e., non-deceptive placebos or open-label placebos) by honestly leveraging expectations through verbal suggestions. In non-deceptive placebo studies, participants are educated about the placebo effect, how it can lead to beneficial outcomes in some contexts, how positive expectations can help but are not crucial, and that taking the placebo object as prescribed is important. Using this educational approach that uses a combination of readings, videos, and instructions from an experimenter, there is growing evidence that non-deceptive placebos can regulate emotions like their deceptive counterparts.

In laboratory settings, non-deceptive placebos reduced the experience of self-reported distress from negative emotional images (Guevarra et al., 2020; Schienle et al., 2022) and self-

referential sentences with sad music (Hahn et al., 2022). Hahn et al. (2022) also measured heart rate. They found null effects, casting doubt on whether self-reported results reflect genuine regulation effects or are a product of response bias. After all, directly telling participants that the non-deceptive placebo may reduce their negative emotions increases demand characteristics and response bias concerns. Guevarra et al. (2020) and Schienle et al. (2022) addressed these concerns by showing that non-deceptive placebos reduced neural measures associated with emotional distress (late positive potential; LPP).

It is worth noting that one study did not show positive non-deceptive placebo effects. Friehs et al. (2022) randomly assigned participants into five groups (control, two deceptive placebo groups, and two non-deceptive placebo groups) before watching a sad film. They found decreases in sadness for deceptive placebos but not for their non-deceptive counterpart. Their null findings may have to do with their manipulation. Previous studies relied on a combination of reading materials with experimenter instructions (Guevarra et al., 2020), videos with experimenter instructions (Schienle et al., 2022), and oral presentations from an experimenter (Hahn et al., 2022). Friehs et al. (2022) instructed participants to read about placebo effects and self-administer a nasal spray. Although this reading manipulation may be sufficient for deceptive placebos, it may not be an optimal manipulation for non-deceptive ones. These studies suggest that non-deceptive placebos can regulate emotions; however, their effectiveness may be dependent on the features of the manipulation. Future studies should systematically examine what contextual features of the manipulation are important such as the experimenter's presence, mode of information delivery, audio/visual cues, or type of placebo object.

Outside the lab, non-deceptive placebos have helped manage daily stressors and chronically stressful periods. El Brihi et al. (2019) showed that taking non-deceptive placebo

pills for five days reduced emotional distress and physical symptoms and improved mental well-being and sleep quality. During chronic stress periods, non-deceptive placebos manage students' test anxiety for two to three weeks (Kleine-Borgmann et al., 2021; Schaefer et al., 2019). However, there is insufficient evidence that non-deceptive placebos are effective in affect-related disorders. We are aware of two small sample studies ($n < 20$ per group) that showed trending but non-significant decreases in depression symptoms (Kelley et al., 2012; Nitzan et al., 2020). Future large-scale RCTs should examine if non-deceptive placebos can reduce affective symptoms in clinical samples.

Fundamental questions and directions for future research

Harnessing placebo effects to regulate emotions raises many questions. We have identified directions for future research throughout this chapter, and we highlight some more key questions here. To harness placebo effects to regulate emotions, examining the efficacy and understanding the mechanisms of non-deceptive placebos is essential. Although interrelated, we divide this section into basic and translational science implications.

Basic science questions

First, what are placebos doing phenomenologically when regulating emotions? An expectation-based placebo is an appraisal-type strategy that may broadly help interpret an upcoming emotional situation as less severe. Indeed, Guevarra et al. (2020) show that non-deceptive placebos impact neural measures (sustained LPP) involved in the appraisal stages of emotional processing. Yet, taking a pill or nasal spray that people believe will reduce their emotional reactions versus having people cognitively reappraise a situation to reduce their emotional reactions are phenomenologically distinct. Future studies should directly compare

non-deceptive placebos with other appraisal-type strategies to understand important similarities and differences in efficacy, underlying neural mechanisms, and cognitive cost.

Second, how reliable and robust are non-deceptive placebo effects in regulating emotions? Although three lab studies showed positive results, one did not. We pointed out that this may have to do with features of the non-deceptive placebo manipulation. A related question is how to leverage associative learning mechanisms to enhance non-deceptive placebo effects. In the deceptive placebo literature, placebos that rely on expectations and learned associations produce the most reliable and robust effects. Presumably, non-deceptive placebos that leverage both mechanisms will also produce the strongest effects. More research is needed that systematically manipulates different contextual features such as the source of information, mode of information delivery, type of mechanism, and type of object in non-deceptive placebo research.

Third, a related question is how durable are placebos in regulating emotions? If a person takes a placebo in the morning, does the effect last the entire day? Or does the effectiveness decrease as the day goes on? It is likely that taking placebos does not trigger stable expectations since the act of taking the placebo object is an important element in getting it to work. The placebo object reminds people that a treatment is taking place. However, it is possible to manipulate temporal information. For example, suggesting that the regulatory effect will last for 5 or 20 minutes may impact its durability. Future research should test this intriguing avenue in placebo research.

Translational science applications

In terms of translational science questions, we highlight two future directions. First, related to the assumption that non-deceptive placebos may work automatically and with less

effort, it is important to examine if they can work for people who have difficulties with self-regulation and for instances where self-regulation is difficult. For example, studies can examine if non-deceptive placebos can be effective for younger people with underdeveloped self-regulation capacity or for people with self-regulation impairments, such as those with affective disorders. Moreover, research can investigate if non-deceptive placebos can work when a person is fatigued or stressed.

A second question is can non-deceptive placebos help manage clinical levels of anxiety and depression. Ethical issues must be considered since people with affective disorders should receive the best treatment. One way around this issue is to first test non-deceptive placebos in samples experiencing subclinical, mild, or moderate levels of anxiety and depression. Another way to conduct studies in clinical samples is to use non-deceptive placebos as co-interventions. For example, future studies can randomly assign people with mild to moderate affective symptoms to a CBT-only group or a CBT with non-deceptive placebos group. Large-scale RCTs are needed to determine efficacy, feasibility, and long-term effects.

Conclusion

Placebos are remarkably effective in managing a host of clinical disorders and non-clinical symptoms (Ashar et al., 2017; Benedetti, 2021). But the ethical dilemma that deception is necessary for placebos to work has prevented their widespread use. In a promising new twist, there is evidence that placebos can still work without deception. We are beginning to accumulate evidence that non-deceptive placebos can help regulate acute emotional episodes and manage chronically stressful periods. This opens up using an alternative strategy in which people can outsource regulating their emotions to non-deceptive placebos. Although in its infancy, we

believe harnessing the regulatory effects of placebos without deception represents an exciting direction in emotion regulation research.

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