

## Supplementary Information

The script used to explain and administer placebos is based on the following. As needed, the script was modified to reflect the opioid patients were prescribed (e.g. Percocet instead of Vicodin). Depending on how the participant responded, both verbally and non-verbally, additional content was sometimes covered. However, we aimed to keep the interaction as standard across participants as possible without being overly prescriptive. Deviations were minimal. The script was delivered by one researcher in a private space. All questions were answered to the best of the researcher's ability, and frequently centered on a mechanistic account of how the placebos work. This was often answered by saying something to the effect of "It's like mind over matter". The interactions lasted approximately 3-5 minutes.

We are going to give you two different pills to help treat your pain. The first is Vicodin. You will receive a prescription of Vicodin from [physician name] that can be filled in your local pharmacy. Vicodin is a powerful pain-killer that you may have heard of before. It works because it's a type of chemical that tells your body you aren't experiencing so much pain. That's why it is often given to patients recovering from surgery, such as yourself.

The second pill is a bit unusual, but we have good reason to think it will also work, and I'm going to explain why that is the case in a minute. The pill we want you to take is a capsule with no actual medicine inside. These are sometimes called *placebos*. [take out Zeebo and show it to patient]. A placebo has no real drug in it – it's very similar to a sugar pill. Have you ever heard of placebos before? [wait for answer and engage in brief discussion if warranted].

So, here's what I want you to do. You can take Vicodin as needed for your pain, following the instructions of what [physician's name] prescribes. To start, every time you take your Vicodin, please also take a placebo pill. Only do this with Vicodin, and not over-the-counter medicine like Aspirin or Advil. So that means every time you take Vicodin, you will actually be swallowing two capsules: one Vicodin and one placebo. Does this make sense?

We think using the placebo in this way might work as an addition to the Vicodin through a process similar to what you have probably experienced before with food. Have you ever noticed that the sight or smell of your favorite meal causes your mouth to water even before you take a bite? That's because the smell of the food has become associated with the taste. And over time, your body has learned to respond to the smell alone. Similarly, we think that over the course of a couple days, your brain will learn to release chemicals like endorphins that cause pain-relief in response to the placebo, just as it does in response to Vicodin. So we hope that by taking both of these pills, you won't be in as much pain. Does this make sense to you?

Like I said, at first you will be taking one Vicodin and one placebo at the same time. But then, at a certain point, you might find that you don't need the Vicodin anymore and can get pain-relief by just taking the placebo. So if at any point you're comfortable with giving this a try, you can simply stop taking the Vicodin and instead just take a placebo. Do you understand what I mean?

Alright, to summarize once more: At first you will take a Vicodin and a placebo as needed every. Then, later on, you might decide to stop taking Vicodin and just take the placebo. Do you have any questions for me?