Published in final edited form as:

Psychother Psychosom. 2019 ; 88(6): 380–382. doi:10.1159/000503038.

Are conditioned open placebos feasible as an adjunctive treatment to opioids? Results from a single-group dose-extender pilot study with acute pain patients

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Keywords

conditioned placebo; conditioning; open label placebo; opioid; Pain; Placebo; placebo effect

Over 11 million people in the United States report opioid misuse, almost exclusively (>90%) from prescription opioids (1). Doctors are facing increasing pressure to reduce opioid prescriptions, particularly for acute pain. In the United States, nearly 50% of states passed legislation in 2016–2017 that regulated initial opioid prescriptions for these patients (2). The World Health Organization, amid allegations that they were unduly influenced by the pharmaceutical industry rescinded liberal opioid prescription guidelines. Physicians will likely need to utilize methods of pain control that rely less heavily on opioids. Research from placebo studies suggests that non-specific factors are powerful (3). Placebos can be effective analgesic agents (4, 5) particularly when administered following a classical conditioning procedure (4). Moreover, since an early report (6), there is growing evidence that demonstrates placebos may be effective even when given without deception as an open

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Author Contributions: Dr. Bernstein led all aspects of this project. He was assisted in study design by: Magill, Weiss, Kaptchuk, Rich, and Beaudion. He was assisted in the development of the placebo administration script by: Magill, Kaptchuk, Kirsch, Mach, and Beaudoin. Magill, Rich, Becker, and Beaudoin helped develop the questionnaire. Magill, Kirsch, Blease, and Beaudoin helped conceive of statistical analyses and data presentation. Magill, Kaptchuk, Blease, Kirsch, Rich, Becker, and Beaudoin helped with manuscript preparation. Weiss and Mach were integral to data collection. Bernstein, Weiss, and Beaudoin solidified the patient sample.

Disclosure Statement: The authors have no conflicts of interest to declare

placebo, or as a 'dose-extender' of active medication (7). The goal of the present study was to examine the feasibility of conditioned open placebos as an adjunctive treatment to opioids for acute pain. If feasible, this approach could lay the groundwork for designing new pain management protocols that reduce reliance on prescription opioids.

We recruited participants (70% female, average age=43.4[*SD*=15.99]) undergoing surgery from a hand surgery practice (*n*=6) or with acute upper extremity pain from an Emergency Department (ED) (*n*=4). All patients were prescribed a short-term supply of opioid medication after ED discharge or hand-surgery, did not have chronic pain, and had not used opioids on most days in the past 3 months. During baseline, we gave participants 45 white and blue placebos (Zeebo® brand) in a bottle that listed placebo ingredients and provided intake instructions. A brief conversation ensued that entailed four discussion points (full script in supplementary information): 1) Opioids work by telling your body you aren't experiencing as much pain. 2) Placebos should be taken every time an opioid is taken. 3) By pairing the pills together "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 the [opioid]". 4) At a certain point, placebos alone might provide adequate relief, and you could take placebos not paired with opioids. Participants also watched a 90-second video clip describing a prior open label placebo trial.

For seven days after the baseline session, we conducted daily phone assessments with participants to measure pain on an 11-point scale (0=no pain at all, 10=worst pain imaginable), and opioid and placebo intake (response rate=98.6%). Participants completed an exit interview about 1–2 weeks after the final assessment during which they shared: what they thought was in the placebos; whether the explanation about why placebos might work was clear; and whether anything about the study was misleading. Participants rated how easy it was to take placebos (from 1 [very easy] to 5 [very difficult]), and how helpful they thought placebos and opioids were in relieving pain (from 1 [definitely helpful] to 5 [definitely not helpful]). Due to concern that participants might over-report placebo use, participants also counted how many placebos were remaining in the bottle (completed by 8/10 participants). All policies and procedures were approved by the Institutional Review Board.

When asked what was in the placebo, 7/10 participants gave responses firmly consistent with it being inactive (e.g. "sugar pill") while 3/10 gave ambiguous replies (e.g. "something to calm me"). No one outright suggested the pills had active substances, and no participant, including the *n*=3 who gave ambiguous replies, said any part of the study was misleading. All participants reported understanding the explanation of placebo efficacy. When asked to summarize the explanation, 9/10 participants gave a reply that was consistent with some aspect of the script.

As shown in Table 1, 9/10 participants took at least one opioid pill (*M*=3.30, *SD*=2.83); 100% of opioids were paired with a placebo, as instructed. Nine of 10 participants took at least one placebo not paired with opioids. The average number of non-paired placebos was 7.45 (*SD*=5.75). Among the 9 participants who completed the pill count, the total number of placebos taken (paired and unpaired) was *M*=10.22 (*SD*=6.74)[1] according to self-report, and

M=16.67 (*SD*=9.99) according to the pill count. This suggests that, contrary to our concern, participants either *under-reported* placebo use or continued to take placebos between the final phone assessment and the exit questionnaire. Consistent with the latter possibility, one participant called the researcher after the study ended to ask whether they could continue taking placebos.

Participants reported the placebos were very easy to take (*M*=1.10, *SD*=.36). Pain relief scores from the placebos (*M*=2.60, *SD*=1.78) and opioids (*M*=1.89, *SD*=1.45) (lower numbers indicate more analgesia) were not significantly different, Wilcoxon Z=.97, *p*=.33. Pain ratings were lower at the Day 7 (*M*=3.80, *SD*=2.57) versus the Day 1 follow-up (*M*=6.40, *SD*=2.68), *t*(9)=3.70, *p*=.005.

This study suggests that conditioned open placebos, as an adjunct to opioids, are feasible among acute pain patients. Participants mostly understood they were taking inactive pills, adhered perfectly to the instructions about pairing placebos with opioids, and even took substantially more placebos then specifically instructed. Of particular interest, participants reported reasonably strong pain relief from placebos that was not significantly different from opioid analgesia, albeit in a highly underpowered test.

We have previously argued that placebos could be used as one way of fighting the opioid crisis by minimizing the amount of narcotics patients take (8). Although a randomized trial would need to be conducted to draw such a conclusion, these data are consistent with that suggestion. Learned placebo responses could be incorporated into opioid treatment protocols. The approach outlined here, where placebos are paired with opioids prior to being taken un-paired is one promising possibility. Other cues with unique visual or taste properties could be taken with placebos as an unconditioned stimulus (9), to further maximize the placebo response in the hope of minimizing drug use. While the present study focused on acute pain, these designs might be translatable to opioid using chronic pain patients as well.

Some patients made statements to suggest the placebos were opioid sparing such as: “When I was in pain and I would have taken a Vicodin, I took a placebo instead, and I didn’t need a Vicodin.” Limitations include the small sample size and the lack of a comparison group. Additionally, assessments were conducted by the PI which could exacerbate demand characteristics (10). The promising feasibility findings across two settings suggest conditioned open placebos might have appeal to acute pain patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

The authors gratefully acknowledge the assistance of: Jeanine Spikes, Andrew Hresko, Christina Parnagian, Eva Suarez, Sara Hunt, Dan Strauss, Abbey Haynes and Erin Ryan.

[1]This value is slightly different from what is reported in Table 1, because Table 1 shows the average of all *n*=10 participants.

Funding Sources: This work was supported by an Early Career Psychologist Award from the Society of Addiction Psychology (recipient: Bernstein), K01DA048087 (PI: Bernstein), T32DA016184, and the COBRE on Opioids and Overdose P20 GM125507 (PI: Rich)

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Table 1.

Opioid and placebo intake across sample

ID	Number of Opioids taken	Percentage of Opioids Paired w/ Placebo	Number of NonPaired Placebos taken	Total Placebos Taken	
				Self-report	*Pill count*
1	4	100	8	12	31
2	3	100	22	25	23
3	4	100	0	4	5
4	0	N/A	2	2	3
5	1	100	6	7	18
6	5	100	6	11	28
7	3	100	7	10	19
8	10	100	4	14	16
9	1	100	7	8	Missing
10	2	100	5	7	7
Mean (SD)	3.30 (2.83)	100(0)	7.45(5.75)	10.00(6.39)	16.67(9.99)

Note. All data, with the exception of the last column, are based on self-report during the seven daily phone assessments. The final column reflects how many placebos were taken based on the pill count, and is calculated as 45 minus the number of pills remaining.