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FULL LENGTH MANUSCRIPT

Experiences of Patients Taking Conditioned Open-Label Placebos for Reduction of Postoperative Pain and Opioid Exposure After Spine Surgery

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Abstract

Background Pain after spine surgery is difficult to manage, often requiring the use of opioid analgesics. While traditional "deceptive" or concealed placebo has been studied in trials and laboratory experiments, the acceptability and patient experience of taking honestly prescribed placebos, such as "open-label" placebo (non-deceptive placebo), or conditioned placebo (pairing placebo with another active pharmaceutical) is relatively unexamined.

Methods Qualitative thematic analysis was performed using semi-structured, post-treatment interviews with spine surgery patients ($n = 18$) who had received conditioned open-label placebo (COLP) during the first 2–3 weeks after surgery as part of a RCT. Interview transcripts were reviewed by 3 investigators using an immersion/crystallization approach, followed by iterative large-group discussions with additional investigators, to identify, refine, and codify emergent themes.

Results Patients' experiences and perceptions of COLP efficacy varied widely. Some emergent themes included the power of the mind over pain, how COLP might provide distraction from or agency over pain, bandwidth required and engagement with COLP, and its modulation of opioid tapering, as well as negative attitudes toward opioids and pill taking in general. Other themes included uncertainty about COLP efficacy, observations of how personality may relate to COLP efficacy, and a recognition of the greater impact of COLP on reduction of opioid use rather than on pain itself. Interestingly, participant uncertainty, disbelief, and skepticism were not necessarily associated with greater opioid consumption or worse pain.

Conclusion Participants provided insights into the experience of COLP which may help to guide its future utilization to manage acute pain and tapering from opioids.

Keywords Open-label placebo · Psychological conditioning · Postoperative pain · Opioid analgesics · Qualitative research · Spine surgery

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Introduction

Spine surgery is a common surgical procedure, often associated with prolonged, moderate to severe levels of postoperative pain [1, 2], particularly when surgery is more extensive, involving several levels and spinal fusion. Managing acute post-spine surgery pain is often challenging, making the use of opioid analgesics relatively inevitable [3], with patients often having to self-titrate opioid use at home in the weeks following their surgery, potentially increasing the risk for persistent use or misuse [4, 5]. Greater acute post-surgical pain is associated with increased inpatient length of stay, prolonged rehabilitation, a greater risk of chronic pain and opioid use, and decreased quality of life [6–8]. Both clinicians and researchers have identified a pressing need for novel treatments to help reduce consumption of opioid medication without increasing post-surgical pain [9]. In this search for non-pharmacologic adjunctive analgesic strategies, the placebo effect has garnered much attention [10].

Placebos have been commonly employed as a tool to blind patients and physicians/researchers in randomized controlled trials (RCTs), to detect differences between active medication/procedure and placebo controls [11]. When researchers first noted that patients improved when treated with placebo, the "power" of the placebo effect was initially recognized [12]. Psychologists later studied placebo effects in healthy volunteers and developed influential theories of expectancy and conditioning [13, 14]. Interviews of patients undergoing concealed placebo treatments in a large double-blind RCT demonstrated patients' concerns that placebo treatment–related improvements would imply that their illness was psychogenetic [15]. These patients never endorsed "expectation" of improvement as a reason for joining the RCT but spoke of "hope," a theme that has also been found by other investigators [16–18].

Evidence that placebo treatments modulate a variety of symptoms [10, 19], including pain [20, 21], is compelling. While the underlying mechanisms of placebo have not been fully delineated, neurophysiological studies provide compelling evidence that placebos may alter pain-relevant neurotransmitters (e.g., endorphins, cannabinoids, and dopamine) [22, 23]. Placebo also activates specific, pain-relevant areas of the brain (e.g., prefrontal cortex, anterior insula, rostral anterior cingulate cortex, and the amygdala) [24, 25]. Genetic variants associated with increased placebo response have also been identified [26]. Expectation theory views placebo effects as a kind of self-fulfilling prophecy due to a mind–body connection [13] and assumes that patients have previous positive experiences with health care that inform and fuel positive expectation of results. Conditioning theory similarly assumes that people have positive experience with pill taking, which conditions a positive response to the pill via classical Pavlovian "stimulus substitution" mechanisms [19]. Embodied cognition argues that human cognitions can be shaped by the body and its interaction with the environment, specifically the sensorimotor systems (e.g., taking pills) automatically producing psycho-physiological effects [10, 27, 28]. A recent more neurologically based theory called prediction coding/Bayesian brain advances the notion that the brain is not a passive organ; rather, bottom-up sensory signals and top-down predictions are inseparable. Symptoms like pain and non-conscious predictions of pain are a single unit. Through a method describable by Bayesian statistics, an embodied clinical encounter, including pill taking, can automatically reduce symptom amplification [29].

Fundamental to the traditional biomedical placebo narrative is the belief that concealment and/or deception is essential to the placebo effect [11, 12, 30]. This poses an ethical and practical concern regarding the clinical application of placebo, given that it breaches informed consent and can undermine therapeutic trust [31]. More recently, it has been argued that concealment (as in double-blind RCT conditions) or deception (as in mechanistic placebo experiments or unethical clinical treatment) may not be necessary to evoke meaningful therapeutic benefits. Further, transparently prescribed placebos, or open-label placebos (OLP) [32], have been shown to modulate a variety of subjective clinical symptoms [33–36], including decreased severity of chronic back pain [37, 38]. The necessity of patients taking opioid medications after a relatively painful procedure like spine surgery provides an opportunity for combining OLP with a conditioning paradigm, with opioid analgesia potentially serving as a strong conditioning stimulus. Conditioned, open-label placebo (COLP) involves pairing open-label placebo pills with active treatment (opioid analgesics) in the perioperative period after surgery. By pairing the unconditioned stimulus (i.e., US: analgesics) with the conditioned stimulus (i.e., CS: placebo pill), the CS alone may begin to elicit a similar response, even in the absence of the US, presenting a reduced need for analgesics [39]. Although conditioned placebos have shown clinical benefits, including a reduction in medication without increasing morbidity/symptoms [40–44], there is limited research using conditioning on a partial reinforcement schedule or as a "dose extension" for pain management [45, 46].

The current qualitative study was embedded in a parent RCT and aimed to assess patients' insights and impressions of COLP after spine surgery, including its feasibility, acceptability, and perceptions of treatment efficacy. To our knowledge, there has been no qualitative study of adult patients' experience with honestly prescribed conditioned open-label placebo, specifically in patients undergoing the acute pain that typically occurs following spine surgery. The published parent quantitative report compared COLP

treatments to usual care, demonstrating an approximately 30% reduction in opioid utilization, earlier opioid tapering, and a 10% reduction in worst pain compared to a treatment-as-usual control [47].

Methods

Participant Recruitment

This qualitative study was embedded in a prospective RCT [47] which was approved by the Partners Institutional Review Board and was registered on ClinicalTrials.gov (NCT04574388). Patients scheduled for surgery for degenerative conditions of the spine with a single surgeon were recruited from Brigham and Women's Hospital (BWH) preoperative clinic in Boston, MA, between November 2018 and February 2020. Patients aged 18–75, who were English proficient and without cognitive impairment, were eligible for participation. Patients were approached at their preoperative visit where the details of the study were described, and interested patients provided informed consent. Key study points discussed with patients during recruitment included the following: (1) definition and explanation of placebo effects; (2) evidence highlighting placebos' ability to reduce pain in double-blind RCTs; (3) explanation of "open-label" concept (e.g., patient knowingly receiving a placebo); (4) introduction of several previous successful OLP studies, noting the absence of any evidence for post-surgical patients specifically; (5) explanation of conditioning paradigm (pairing the open-label placebo pills with their other analgesics); (6) suggestion that COLP treatment may or may not work to reduce their pain or opioid consumption; (7) emphasis that placebo effectiveness was not contingent on belief; and (8) repeated assurances that taking COLP would in no way restrict their access to other analgesics, including opioids, after surgery. Following consent, patients underwent baseline quantitative sensory testing (QST) in person and then completed preoperative baseline pain and psychosocial questionnaires via email link to REDCap, a secure electronic database. Upon completion of the questionnaires, the patients were randomly assigned to either treatment as usual (TAU) or TAU in conjunction with COLP.

Conditioned COLP Treatment and Parent Study Procedures

Following surgery, once patients were out of the recovery phase, study staff visited them to assess their pain, further explain study procedures, and answer any additional questions. Patients in the COLP group were instructed to self-administer one COLP pill with all analgesics (whether administered intravenously or orally) and record the pairing in a bedside diary. COLP initiation took place on either postoperative day (POD) 0 or early POD 1, depending on the acute postoperative state and time of transfer to the inpatient unit. Patients were further instructed at the beginning of POD 2 to take an additional three scheduled placebo pills every day, one pill at each of three times of their choosing, in addition to the placebos paired with all analgesics. Patients were asked to take both paired and scheduled COLP pills until their follow-up appointment.

While in hospital, physician and non-physician study staff visited patients in both groups twice daily (10–15-min visits) to collect a mini–Brief Pain Inventory (BPI) of daily pain scores (current pain, worst pain, self-averaged pain, and least pain in the preceding 24 h) and the number, type, and dose of opioid analgesics consumed each day. Patients in the COLP group also documented the number of paired and scheduled placebos taken each day. Discussion topics exclusive to the COLP group included instructions on taking placebos and re-explanation of the COLP rationale: (1) placebos may induce a physiological response in the brain to decrease pain even without deception (OLP concept); (2) pairing placebos with other pain-reducing medications may strengthen this effect (conditioning concept); and (3) it might not be necessary to believe in the effect for it to work (automatic response concept).

Study staff trained patients to document this information (i.e., mini-BPI, analgesic use, and COLP use [COLP group only]) in a daily diary that patients completed until their follow-up appointment, approximately 3 weeks after surgery. All patients self-treated their pain using opioids and other analgesics on an as-needed basis (typical prescription of 5–10 mg oxycodone taken as often as every 4–6 h as needed and acetaminophen 500–1000 mg every 6–8 h as needed). Following hospital discharge, study staff corresponded with patients daily, using the patients' preferred contact method (text, phone call on a secure study phone, or via secure email), to collect diary information from the previous day.

Qualitative Interviews

Of the 19 participants within the COLP arm of this pilot RCT, 18 completed post-study interviews and were included in this analysis to allow for the maximal diversity of viewpoints. One participant declined participating in the qualitative interview due to lack of time following his postoperative appointment. The remaining 18 participants underwent a semi-structured qualitative interview, responding to a series of questions, with opportunity to expand on answers and give additional input (Appendix A, supplementary material). Each patient provided verbal consent for the interviews to be recorded on a secure study phone using the Apple Voice Memos app. Interviews were performed and recorded by one of two investigators (MP or ES), who were trained by

an experienced qualitative researcher (TJK) and observed and received feedback from the PI (KLS). Interviews ranged from 10 to 20 min in length, and recordings were transcribed for analysis. Each interview queried about the patient's experience being in the study and with the placebo pills, including effects of the placebos, and beliefs about placebo effectiveness. Specific questions from the interview guide are listed in Appendix A.

Qualitative Analysis

Given the limited qualitative data on open-label placebos, a conventional content analysis approach was used, in which natural categories and subcategories emerge from the data [48], to understand patients' perspectives on taking COLP as part of their pain management following spine surgery. An iterative immersion/crystallization approach was used by coders when analyzing the interview transcripts, with the coders completely engaging with the collected data and then temporarily suspending analysis for reflection, until insights and patterns emerged that could be meaningfully articulated and substantiated [49]. Three study team members (VH, TM, ES) received training in coding by an experienced qualitative researcher (MLD). Next, those three members subsequently each read two-thirds of the transcripts (partially overlapping such that each transcript was read by at least 2 coders) and created an initial set of codes. The entire study team (VH, ES, TM, MLD, KLS, TJK, KMF) met to discuss the initial codes, relevant quotes, and overall impressions of the transcripts. Based on this discussion and notes from the three coders, study team members (KS and KMF) created a draft codebook based on this discussion. Coders subsequently went back to the transcripts, including the one-third of the transcripts that were not initially coded (had been coded on the first round by another coder) and applied the draft codebook, noting areas of discrepancy as well as any ideas that were not captured in the codebook. These results were brought back to the full research team, sample quotes were discussed, and the codebook was revised. This iterative process was repeated for several cycles, with codebook revisions based on team discussions and insights from the coders, until all team members were satisfied that the coding scheme accurately described the data. Through this process, a hierarchical coding structure emerged with four main categories, or topics, under which several themes emerged. Following several cycles of iterative analysis, several themes coalesced and repeated themselves among the participants' transcripts, suggesting saturation. Sample quotes were identified by coders from the transcripts based on representativeness and how well they captured the emergent themes, which were further reviewed and selected by the larger team. Additionally, coders re-read transcripts and quotes, and each separately assigned each participant to one of three categories, based on their overall sense of whether each participant felt that COLP had been effective for them: (1) yes, effective; (2) uncertain about efficacy; or (3) not effective. These assignments were assessed for agreement and further confirmed with the original interviewers.

Results

Participant Characteristics

Participants who completed interviews had a mean age of 58.7 ± 13.6 years and were 67% male, with 94% of the participants self-reporting as non-Hispanic White. All the participants had at least a high school degree, with some variation in amount of additional education (Table 1). Coders' categorization of participants based their sense of whether the participant felt COLP was efficacious revealed relatively few people clearly feeling certain that COLP was efficacious ($n = 3$), with the majority being uncertain about efficacy for them ($n = 9$), and some feeling quite certain that it was not effective ($n = 6$).

Table 1 Participant demographics

ID	Gender	Age	Race/ethnicity	Education	Sense of efficacy
5	Male	52	White	Some college	Uncertain
7	Female	51	Hispanic/ Latino	Associate's degree	Yes
10	Male	52	White	Master's degree	Uncertain
11	Male	74	White	Doctoral degree	Uncertain
14	Male	75	White	Master's degree	No
16	Male	72	White	Associate's degree	No
17	Female	66	White	Master's degree	No
27	Female	47	White	High school	Yes
30	Male	66	White	Master's degree	Uncertain
31	Male	60	White	Bachelor's degree	No
33	Male	45	White	Bachelor's degree	Uncertain
37	Male	58	White	Some college	Uncertain
41	Female	55	White	Bachelor's degree	Uncertain
45	Female	31	White	Technical school	Yes
48	Male	37	White	Some college	No
49	Male	68	White	Some college	Uncertain
54	Male	73	White	Master's degree	Uncertain
55	Female	74	White	Master's degree	No

Categorization of Themes

Themes emerged which could be placed into four main categories or topics: (1) conceptions about the mind, pain, and placebo; (2) pill taking; (3) variation in effectiveness of COLP; and (4) experience of taking COLP (Fig. 1).

Category 1: Conceptions About the Mind, Pain, and Placebo

Theme 1.1: The Mind Can Control Pain One striking feature of the interviews was participants' beliefs about the importance of their own mind in the pain experience. Subjects expressed that their own thoughts and feelings were impactful to the effectiveness of any treatment, including placebo. Several comments by participants linked placebo effects to mental processes and an idea of the mind being powerful when it comes to processing pain.

- *"Well, I think the mind is powerful so depending on the way they mentally incorporated this approach, would make a difference." (ID 11)*
- *"You're seeing if [the placebo pill] is connecting somehow to your mental concept of 'I take a pill that theoretically should make me feel less pain. So, by taking this I wonder if it will make me feel less pain because [the placebo] is tricking my brain.' That's how I would explain it." (ID 30)*

Other comments referred to the idea of pain "being in the mind." They often contained thoughts about the psychological state being important for pain and expressions of amazement about how powerful placebo could be and that such a thing as COLP might work.

Theme 1.2: Open-Mindedness About Pain Management Some participants remarked that being willing to take a pill while knowing that it does not have anything in it requires an open mind. In some cases, they cited open-mindedness as an integral factor that impacts whether COLP treatment would work and speculated that it would not be helpful to prescribe a COLP to someone that lacked open-mindedness.

- *"You've got to have somebody a little open-minded, definitely." (ID 41)*
- *"[Placebos] could be very beneficial to people with chronic pain. You've got to be a little open minded. I think you've got to have someone who understands the concept." (ID 45)*

  Another participant expressed that he was intentionally keeping an open mind even though the concept of a COLP did not exactly make sense and was not familiar to him before his participation in the study.
- *"I didn't think 'No-way [will the placebo have an effect]'. I was very open-minded." (ID 37)*

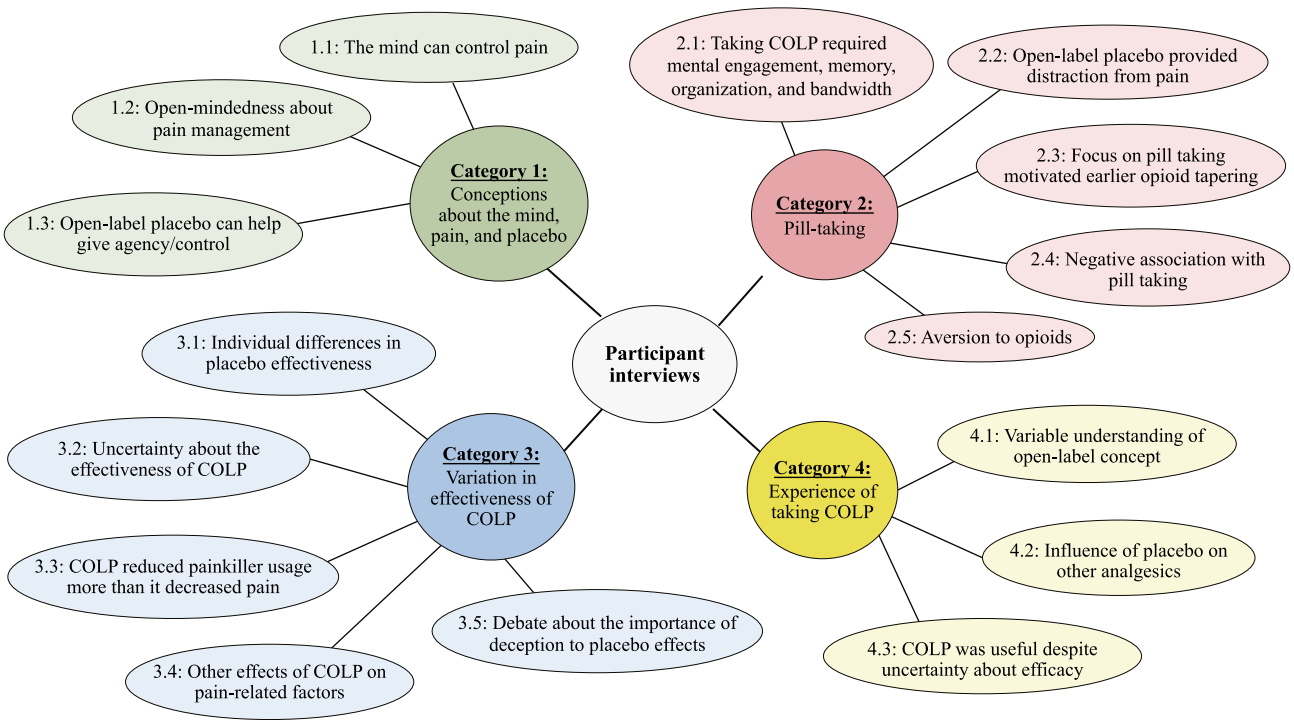

Fig. 1 Themes were placed into four main categories or topics

Theme 1.3: Open-Label Placebo Can Help Give Agency/Control Some participants who were favorable to the idea of COLP cited that part of its appeal was allowing them to be proactive or take an active role in their treatment. Others indicated that they were more comfortable psychologically being active rather than passive, as helplessness can often make pain worse.

- *"It was more of a feeling of like, 'At least I'm doing something. Whether it works or not, at least I'm doing something.'" (ID 11)*
- *"So, if you feel like you're doing nothing, I think that puts people into terrible places. Depression, anxiety." (ID 41)*

Category 2: Pill Taking

Theme 2.1: Taking COLP Required Mental Engagement, Memory, Organization, and Bandwidth Some participants expressed that the logistics of taking the pills post-surgery, particularly on a certain schedule or pairing with the normal analgesic pills, required effort and organization. In some cases, this was seen as an advantage and in others as a disadvantage.

- *"Well, I guess at first, I thought it was kind of a little diversion to occupy me and it seemed fine, and it was easy enough to comply with. I guess as we got further along and more things were going on in my treatment, I started to feel like it was sort of an annoyance. 'Oh darn, where is that bottle? I gotta remember to do that.'" (ID 59)*

  Another observation was that taking COLP in the recovery period when there were a lot of things going on required bandwidth that they did not always have.
- *"I mean it was, uh, an extra thing to have to worry about and to keep track of, and I have a lot of other stuff on my mind as well. I'm limited bandwidth. So, it wasn't welcome, but it was okay, it was doable." (ID 54)*

Theme 2.2: Open-Label Placebo Provided Distraction from Pain Sometimes, the increased attention to pill taking and the addition of COLP to the post-surgical treatment regime was identified as a welcome distraction from pain. One participant noted that a shift in focus to pill taking possibly helped distract from pain in the postoperative period.

- *"I don't know if it's the placebo effect. I don't know, I was just thinking that the scheduling helped me stay focused on something other than the pain." (ID 31)*

Theme 2.3: Focus on Pill Taking Motivated Earlier Opioid Tapering Another interesting phenomenon cited by participants was that the extra task of taking COLP raised their awareness of how many pills they were taking. For some individuals, this served as motivation to taper off opioids altogether.

- *"Possibly the action of just taking something extra just made me think I was taking more. Just a subconscious effect. Probably changed the amount of other pills I decided to take. Probably took less oxycodone because just seeing that stack of pills, I think I was just motivated not to take them." (ID 33)*

Theme 2.4: Negative Association with Pill Taking Many people who participated endorsed an identity of not being a "pill taker" and had a relatively negative connotation of any pills.

- *"I'm not really a pill taker, so initially having to take pills to begin with, I'm not crazy about, like taking narcotics. So, it was kind of like 'Ugh, another pill.' But when I know something is for a good cause, I'm okay with it." (ID 41)*

  Others reported an aversion to medications and/or unnatural chemicals, and some participants cited an advantage of COLP being a way to avoid taking medication, partly because they do not like the idea of the impact of unnatural chemicals on their physiology.
- *"Because I am telling you, I hate chemicals. I hate to be taking medicines. I hate to be taking pain killers, so if you can have something that can make pain go away without having to take chemicals, it is amazing." (ID 7)*

Theme 2.5: Aversion to Opioids Patients expressed many comments about taking opioid medication. Some were concerned about opioid addiction, going so far as to have their significant other hide them. Some reported filling their prescription but vowing not to use it, and others stated they were reluctant to use opioids even if they had not experienced any issues in the past.

- *"Yeah, I read somewhere someone got addicted in four days. So, I just sort of had that hanging over my head, thinking I'm going to be here [in the hospital] for four days, and I really don't wanna do this. We filled the prescription. My wife hid it. Not that I have an issue, but she just said, 'Let's just try to do without it.'" (ID 10)*

Others seemed to view COLP as an outright contrast or alternative to opioids.

- *"We can get [rid of] the pharma drug that is not good for our body, so that maybe we can find a different way to relieve the pain." (ID 45)*

Category 3: Variation in the Effectiveness of COLP

Theme 3.1: Individual Differences in Placebo Effectiveness There was notable variation in participants' experiences and overall perceived efficacy of COLP. Participants expressed that, based on each individual's life experience, they may have a unique way of processing pain, and so any kind of placebo may therefore have variable efficacy. Some participants identified that certain mindsets and beliefs (even if they themselves did not have them) might be paired with greater effectiveness:

- *"I would definitely advocate for COLP to friends or family. I don't know how their response would be, because everyone's mindset is different, but it wouldn't hurt to say try this over maybe taking a Tylenol to see how it would affect them." (ID 45)*
- *"I don't think it had any effect plus or minus. Because it was difficult for it to be credible to me; that the placebo would have any impact and so, ya know, I just wasn't a believer." (ID 54)*

Theme 3.2: Uncertainty About the Effectiveness of COLP A majority of those interviewed expressed some degree of uncertainty about whether COLP had been helpful. Patients often stated that unlike other OLP studies where participants were comparing pain before and after treatment, patients in our study did not have a reference point, i.e., "no way of knowing how their post-surgical pain experience would have been without COLP compared to how it was with COLP, since they only had the experience with COLP."

- *"I couldn't tell you because I generally don't take pain killers, so this is the first time for me with back surgery, it's not an ongoing thing for me, so I couldn't base it against anything." (ID 5).*

Theme 3.3: COLP Reduced Painkiller Usage More Than It Decreased Pain All of our patients experienced significant post-surgery pain. The impact of COLP on opioid sparing seemed to be much more present in participants' minds when reflecting on their experience, than actual pain reduction.

- *"I noticed as the days went by, I was taking less of the pain killer medication when I was taking the placebo with it. So maybe the mind reacted to it unconsciously." (ID 37)*
- *"There was a lot of stuff going on and I think a couple of times it probably seemed like, 'Oh good, at least I'm taking something,' but I never felt like 'Oh good, that makes the pain go away.'" (ID 11)*

Theme 3.4: Other Effects of COLP on Pain-Related Factors Although pain and opioid consumption were main topics of interest, other noteworthy effects of COLP were shared by participants, including improved sleep and smoking cessation.

- *"Yesterday I had one- it made me sleep for like 3–4 h." (ID 7)*
- *"I know this is going to sound strange, but I kind of became addicted to the placebo. Because of the rigidness of taking them with my medication." (ID 31)*

Theme 3.5: Debate About the Importance of Deception to Placebo Effects Participants were specifically asked whether they thought the intervention would have been more effective with deception (traditional placebo). Most endorsed that they thought deception was not necessary. Nonetheless, sharing dominant cultural beliefs about placebo, some felt that it would have made the placebo more effective, and that knowing for sure that there was nothing in the pill was counterproductive to efficacy.

- *"I do think it can work maybe if you are deceived into thinking it's a pain reliever, it might possibly do that. But, knowing flat out from the beginning that it's not, I think that also has an effect on your brain. It tells you it's not doing anything. I think it has the same negative effect as it could have positive effect, in other words." (ID 59)*

  Conversely, a couple of participants reacted negatively to the idea of deception, saying that they would not have participated in a study that had deception, especially if opioids were involved.
- *"I probably wouldn't have done the study if I didn't know what I was taking in terms of an opioid. Probably, I would think if it was an opioid, I probably would've thought it was an opioid and I would've reacted [negatively] to that." (ID 30)*

Category 4: Experience of Taking COLP

Theme 4.1: Variable Understanding of the Open-Label Concept Patients understood the concept of COLP to varying degrees and provided variable responses when asked how they would explain the purpose of COLP in this study. Despite the multiple explanations of COLP provided by study staff throughout the duration of the study, one patient

reported still not understanding the point of taking an open-label placebo at the end of the study, perhaps suggesting that this is a difficult concept for some patients to comprehend:

- *"No, I guess I don't understand how it could help, I really don't understand it." (ID 16)*

Theme 4.2: Influence of Placebo on Other Analgesics Understanding the purpose of pairing placebo pills with the self-administration of other analgesics to condition a stronger placebo response seemed logical to some participants, but confusing to others. The pairing of COLPs with other analgesics seemed to take on meanings other than simple conditioning, serving to drive a decrease in oxycodone use in some participants.

- *"I think that I subconsciously felt that if stopped right now in taking the oxy, I won't be necessarily having to take the placebo. I don't know if that's a little twist to what the whole program was, but I believe that it probably began to reinforce the fact that I was taking pills, and maybe if I wind down, I won't need them." (ID 49)*

Theme 4.3: COLP Was Useful Despite Uncertainty About Efficacy One interesting observation among participants was that, despite their lack of belief that COLP was effective, some participants indicated that they may take it again, keeping their leftover placebo pills.

- *"I didn't think it would be helpful to me personally, but maybe I didn't know, perhaps after the study was over, if I still had pain, maybe it would work." (ID 17)*

This idea also emerged when comparing patients' expressed degree of certainty with the objective pain and opioid utilization scores, such that an individual's impression of certainty did not align with the quantitative assessment of efficacy. As part of the interview, participants were asked to indicate their perception of the efficacy of COLP for them. Coders assessed participants' answers to the question: "Did you think this was efficacious?" Unanimous categorization was achieved based on the reading of these responses by all coders. The patient's overall subjective sense of efficacy was used to place them into three categories (yes, uncertain, no) (Table 1). The actual daily opioid utilization as well as pain scores were compared between participants who fell into these 3 categories (Fig. 2). No obvious differences in opioid consumption or pain scores were apparent between those who were certain that COLP worked, compared to those who were uncertain or thought it did not work. Of note, the small sample size and high degree of interindividual variability limit any statistical assessment.

Discussion

Clinical Implications

This qualitative study revealed insights into the patient experience of participating in a study using COLP as an analgesic adjunct to reduce postoperative pain and opioid consumption in the first 2–3 weeks following spine surgery. Patient comments fell into four distinct categories (conceptions about the mind, pain, and placebo; pill-taking; variation in the effectiveness of COLP; and the experience of taking COLP), with several subthemes within each category. Some emergent themes included that COLP can bring focus

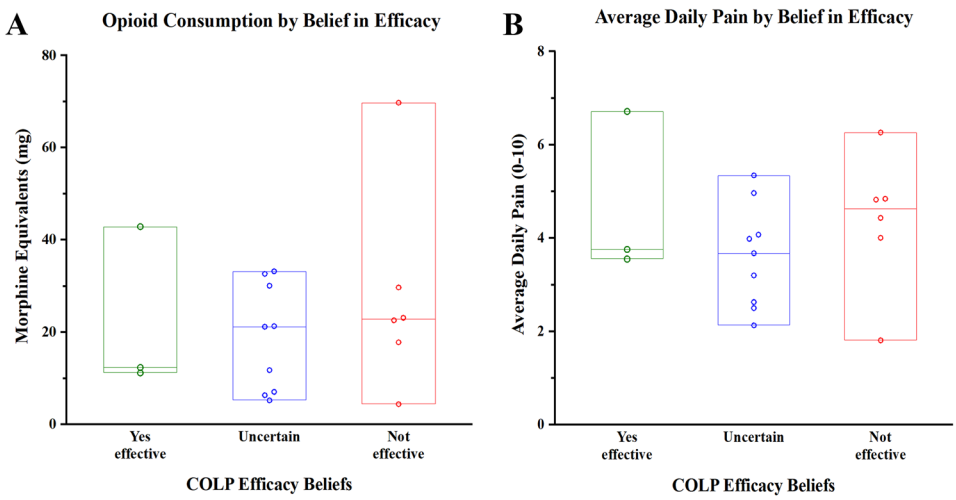

Fig. 2 Daily Opioid Utilization and Pain Scores among participants expressing different degrees of certainty about COLP efficacy

and attention to pill taking, which can engage the power of the mind in favorable ways. The idea of leveraging this self-healing power of the mind to gain agency over one's own recovery may be particularly salient in the postoperative period when patients are asked to manage their own analgesic consumption after they leave the hospital. Another theme was that COLP likely has more impact on the reduction of opioid use as opposed to reducing pain severity and that this may occur regardless of the degree of certainty about its effects. Given the limited previous reporting specifically on patients' experiences and perceptions regarding COLP, this study offers valuable insight into the overall feasibility of employing COLP, particularly in post-surgical pain management, and some of the inherent processes involved in its use and the overall positive outcomes.

Most qualitative studies of patients' experiences with placebo treatment find a persuasive popular belief in the power of the mind and "mind–body" effects [15–18, 50–55], which also emerged as a separate theme in this study. The belief that the mind can be used to control pain converges with an expressed sense of agency that managing the COLP therapy seemed to provide to some participants. Tandjung et al. conducted a qualitative study examining patients' perspectives of placebo use in daily practice in which they found that 75% of participants endorsed a belief in mind–body association [55]. Another qualitative study which conducted telephone interviews on patient attitudes about the clinical use of placebo also found that 85–96% of respondents believed that a person's mind can influence clinical care [52].

Our study is the first qualitative study of COLP in post-surgical pain management embedded in a RCT. Other earlier qualitative COLP studies should be mentioned. The earliest one was a COLP study conducted in children ($n=70$), where a "conditioned dose extender" helped pediatric patients with attention deficit hyperactivity disorder to continue to do well on 50% dose of stimulant medication [56]. Nonetheless, the findings of that embedded qualitative study are similar to ours, in that most parents expressed skepticism that COLP would work, and most did not have high expectations. Many of the participants in our study were also quite uncertain or even skeptical about COLP's effects. Interestingly, the average pain scores and opioid utilization of patients who fell into the category of "uncertain" were not noticeably higher than those who felt certain that COLP was effective. In contrast, theoretical models of expectation have dismissed the concept of uncertainty, highlighting the exact opposite, certainty or positive expectations [13]. Subsequently, laboratory studies with healthy volunteers showed expectations based on previous experiences and verbal suggestions strongly impact placebo responses [57–59].

A recent pilot observational study treated ten acute-pain patients with COLP [60]. The patients were mostly comfortable with the intervention, and the results supported the feasibility of undertaking a full study. There are also at least two qualitative studies of OLP without conditioning. One of these studied patients with irritable bowel syndrome (IBS) [61]. The qualitative study contained 33 participants and was embedded in a larger RCT of IBS patients that compared OLP and double-blind placebo treatment ($n=262$). The qualitative results found that people on double-blind placebo had passive attitudes to double-blind treatment and were waiting for a "fix," while those on the paradoxical cognitive dissonant OLP with its implicit self-healing message engaged in significant self-examination and self-reflection on their symptoms, behaviors, and lifestyle. Because participants had baseline symptoms, they could actually detect improvement. These patients also spoke of "hope" and were interested in mind–body connections [62]. We did not notice this self-examination in our COLP patients. Also overlapping our findings, this IBS mixed-methods paper found that patients' narratives of symptom improvement (certainty, unsure or absence of improvement) did not correlate with actual improvement. A fourth well-performed qualitative OLP study was based on a laboratory experiment with brief artificial heat pain stimuli on healthy volunteers ($n=160$). The study compared different types of OLP (with rationale and without rationale) and deceptive placebo [63]. The nested qualitative interviews of subjects ($n=30$) in this study are difficult to compare to our study of patients, especially as treating without a rationale is problematic in clinical practice and the duration of the pain is very short [64].

Well over half of the participants in our study expressed skepticism or uncertainty toward COLPs' efficacy, which seemed to make it more likely that any positive expectations were non-conscious, in accordance with prediction coding theory. Recent research experiments have shown that non-conscious placebo cues (12 ms) activate placebo effects in healthy volunteers through engaging relevant brain regions [65, 66]. Reports from other open-label placebo RCTs support our finding that higher expectations are not predictive of placebo response [38, 67] or even inversely predictive (lower expectations produce greater placebo responses) [61]. Some previous mechanistic laboratory evidence suggests that uncertainty can also enhance placebo responses in certain clinical populations. For instance, Lidstone and colleagues demonstrated that Parkinson's patients responded better to placebo when they were uncertain whether the placebo was levodopa or a placebo, as compared to when they knew that the placebo was levodopa [68]. Furthermore, evidence in chronic pain suggests that both uncertainty and baseline variability of pain are associated with greater placebo responses [10, 69].

One theory that offers a proposed mechanism of how uncertainty may relate to pain perception is Bayesian brain/prediction coding [10, 29, 32]. A critical component of this theory is that what one perceives is not actually the world

as it is, but what one's brain *predicts*. Sensory perceptions like pain are based on non-conscious top-down predictions continuously refined by bottom-up incoming sensory evidence. This theory may be relevant in a large majority of clinical situations, where there is simultaneously a hope for and uncertainty of a clinical benefit, even in the intervention of "nothing" (placebo). This uncertainty and hope are considered to have the potential to automatically and non-consciously shift prior neutrally encoded sensory biases of heightened pain to sensory biases of reduced pain [10, 27]. The Bayesian models provide an alternative view for how the brain perceives symptoms and relief through placebo intervention.

Other studies indicate a more actively pessimistic or negative attitude in general toward placebos. Some patients reported a fear of stigma around placebo, as well as concern that their symptoms may not be seen as "real" and were "all in the mind" [16]. Similar to other reports, some saw placebo pills as not real therapy for real symptoms [70, 71]. Other studies suggest that individuals' negative reaction about placebos stems from beliefs that placebos do not work and that they necessitate deception [53, 71]. One large survey of patients ($n=853$) found that 80% of patients would consider OLP if a physician thought it could help [51]. In our study, some participants also reacted negatively to the idea of deception, and expressed that they preferred the open-label concept.

Despite the fact that our study included a relatively intensive and frequently repeated set of instructions, explanations, and interactions with study staff throughout the course of the study, there still appeared to be some confusion among study participants about the overall purpose of taking COLP. This may be important when considering how feasible it might be to teach people the self-administration of placebos in a post-surgical setting. Previous OLP studies have never reported this problem. For surgery patients, OLP might require significant effort and probably will only work for some patients. As such, the logistics of taking the placebo pills on a regular basis was variably embraced by patients. For instance, there were a couple of participants that found the process of taking the placebos, in conjunction with recording their pain levels and the number of pills consumed, to be a taxing and even bothersome process, that added to their already burdensome recovery. Alternatively, for other patients, taking their placebo pills was identified as a useful distraction from pain and a motivator to discontinue their opioid use. Some participants even expressed that taking placebos and recording the number of pills consumed brought a consciousness and increased awareness to their analgesic management that may have encouraged them to reduce their overall pain medication, and at a much quicker rate. Furthermore, the aversion to being identified as a "pill taker" was also expressed by some, which has also been reported in previous research [72, 73] and is contrary to the idea that pills always have a positive, beneficial connotation for patients, even if they are needed to reduce pain. Regardless of whether it was viewed as annoying or beneficial, it was evident that the majority of participants expressed that this process of taking COLP post-surgery required bandwidth, motivation, and organization in the context of recovery from surgery.

Interestingly, some patients reported that there was a stronger impact on reduction of opioids and an increased level of awareness around their pill taking behavior, rather than an actual impact on pain. This parallels our quantitative findings, which showed the COLP group consumed 30% less daily opioids, but pain scores were only marginally lower compared to patients in the TAU group [47]. Nonetheless, the main goal of our intervention was to reduce opioid consumption without reducing analgesia. Reduction in daily opioid dose or hastened tapering off opioids might lead to fewer side effects and improve activity and functioning, and this decreased opioid exposure, theoretically, may prevent patterns of misuse. Beyond impact on opioid consumption and pain, a few patients reported other positive and unanticipated effects such as improvements in sleep and reduced tobacco use. For these participants, the conditioning of their paired placebos may have impacted these behaviors as well. Similar findings were noted in a previous qualitative study in which patients who had taken double-blind placebo claimed that it provided insight to unhealthy relationships which ultimately encouraged them to pursue divorce, enhanced sleep hygiene, and increased feelings of calm and optimism [15].

Analysis of interview transcripts also revealed insights into the motivations of the patients to participate in the research study. For instance, some participants expressed that they were open-minded to the concept of COLP and had a desire to contribute to medical research, which likely also influenced their overall perception and outcome of COLP. Several participants also expressed a "why not" mentality, suggesting open-mindedness, especially if COLP would benefit their overall pain and analgesic outcomes. These comments are consistent with reports in other OLP trials of an attitude of "let's see what happens" [61, 62, 74].

Limitations

While this study provides many important insights into the experience of patients who are taking COLP during post-spinal surgery recovery, several limitations should be considered. Given the limited sample size and number of questions asked in the interviews, it is likely that some key insights into the experience of COLP may have been overlooked. Similarly, the rigorous attention and interaction of study staff with participants may have affected their perceptions to be more favorable than they might be in a more pragmatic use of

COLP in a non-research setting, where extensive explanation and monitoring are less feasible. However, we did control for the attention and interaction with a TAU control group.

Additionally, several participants stated that they were hoping that COLP would help to manage their pain or affect their pill-taking in some way and, thus, they may have been more biased toward experiencing positive outcomes. However, many participants openly expressed skepticism, suggesting that most participants were reflecting on the experience, and that the interview process allowed people to speak openly about their participation in the clinical trial. Participants had to make judgments regarding COLP's efficacy that were necessarily uncertain and indefinite, given that most of them did not have a comparable experience in the absence of taking COLP. However, our qualitative study provides valuable contributions regarding this uncertainty and difficulty with self-assessment in acute-pain situations, which may be valuable in serving as a foundation for future research.

As noted, the participants were recruited by convenience from an academic tertiary referral medical center in Massachusetts. This limits generalizability as this sample consisted of a well-educated, White and socioeconomically advantaged group compared to the general population, who were also willing to engage in a relatively non-traditional study. Of note, in our quantitative analysis of pain and opioid use, we conducted a moderation analysis by gender, which interestingly suggested that COLP showed greater efficacy among the female participants compared to females in the treatment-as-usual group. The small sample size, and the fact that we only interviewed patients receiving COLP, make any definitive conclusions about sex differences in the experience of taking COLP tenuous at best. Future studies should expand the investigation of the acceptability of COLP to more diverse groups of patients to increase generalizability.

Conclusion

The themes that emerged give important clues about what may underlie the beneficial aspects of COLP, including decreasing reliance on opioids, distraction from pain, and providing a sense of agency, but also the barriers which may be faced during implementation in a postoperative setting to manage acute pain, such as variable degrees of skepticism about efficacy, difficulty understanding the concept, and the sense that it was burdensome for some patients. Given these insights, it seems likely that the utility of COLP for managing analgesia in spine patients may be limited to a subset of patients, although notably, belief in its efficacy did not seem to be required to derive a benefit. Understanding the differential utility of this intervention among patients based on their phenotypic characteristics may allow COLP and other behavioral therapies to be employed in a personalized way [75], although additional research is needed to better identify biopsychosocial characteristics of patients who would respond well to COLP.

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Declarations

Ethics Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

Conflict of Interest The authors declare no competing interests.

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