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Placebo effect in pain and pain treatment

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Placebo effect in pain and pain treatment

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EDITORIAL
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Editorial: Placebo Effect in Pain and Pain Treatment

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Editorial on the Research Topic

Placebo Effect in Pain and Pain Treatment

WHY WE NEED PAIN RESEARCH: CHRONIC PAIN, COVID-19, AND THE OPIOID CRISIS

Research into the biology, treatment, and prevention of pain has blossomed over the past decade. Recent data from the US suggest the nationwide prevalence of chronic pain is 20–21% (1, 2). Chronic pain appears more prevalent among women and older adults (3). A meta-analysis indicates that the prevalence of chronic pain in the UK is 35–51%. Cohen et al. (4) argue "It is difficult to over-estimate the burden of chronic pain," (p. 2082) given the considerable price we pay in terms of economic cost, disability, and mortality.

Unfortunately, the public health burden of chronic pain will likely increase with the COVID-19 pandemic. Research suggests that 10–30% of people who contract COVID-19 develop Long Covid (5, 6). Pain is a common Long COVID symptom; in one study of 616 adults who self-reported a prior COVID-19 diagnosis, 30.7% met criteria for Fibromyalgia (7). As of 22 February 2022, ∼428 million people world-wide have had COVID-19 (according to https://www.kff.org/coronavirus-covid-19/issue-brief/global-covid-19-tracker/). Using conservative projections based on the above statistics, if 10% of COVID-19 patients have long COVID, and 15% of long COVID patients develop chronic pain, then COVID has thus far coincided with an increase of 6.4 million chronic pain patients. This number will continue to grow with future infections.

The crisis of opioid misuse and death intersects heavily with pain management (8). In 2015–2016 ∼50,000 people died annually in the U.S. from a drug overdose (9). This figure has since almost doubled (10). A November 17 front-page story in *The New York Times* reads: "Overdose Deaths Reached Record High as the Pandemic Spread." It is imperative that we invest in research to understand the etiology of pain and develop effective pain treatments.

PAIN AND THE PLACEBO EFFECT

A wide and tantalizing body of research dating back to the mid-1950s has suggested that placebo may play an important role in pain treatment (11, 12). In randomized trials, patients improve on placebo for a variety of pain conditions (13). Although controversial (14, 15), this finding indirectly

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suggests placebo effects administered via placebos promote analgesia. Disentangling the placebo effect from other factors (e.g., assessment reactivity, passage of time) is critical to how we interpret Randomized Clinical Trials (RCTs) (16, 17). The placebo effect also features prominently in studies investigating analgesia from pain induced in the laboratory (18). Painkillers such as morphine are more effective when a patient is aware, vs. unaware, they are receiving the drug (19), which demonstrates the psychological nature of placebo analgesia. But the placebo effect is physiological as well. The endogenous opioid, endoconnabinoid, and dopaminergic systems are all implicated in placebo pain-relief (20).

SPECIAL ISSUE ARTICLES

The articles that follow show the diversity of topics related to the placebo effect and pain. Wampold and Smith et al. remind us that the placebo effect is often conceptualized broadly to include interpersonal factors (21) [see (22) for a lengthy discussion of placebo definitions]. Wampold situates the placebo effect within a healing context and argues for the importance of evolutionary considerations in how humans (and non-humans) improve through interpersonal contact. Smith et al. leverage the importance of empathy and optimism by describing a training program for primary care physicians, called *Empathico*, to enhance communication skills and ultimately reduce patient suffering.

Two experimental studies are published in this Special Topic. Wagner et al. observe that neither a dog nor a placebo increases pain tolerance among healthy volunteers in the lab. This paper serves as an important reminder about the need to publish non-significant results to mitigate the chance that we see a replication crisis within placebo studies, as has been observed across other scientific disciplines including the adjacent field of psychology (23). The paper by Lunde et al. further illustrates the importance of developing adequate placebo control conditions for non-pharmacological interventions like music analgesia. By introducing a placebo control to music analgesia, it is specified that the analgesic effect of music primarily steams from patients expectations rather than music *per se*.

With respect to placebo control arms in drug treatment trials, Koechlin et al. examined the placebo response to anti-depressant medication for Fibromyalgia in a meta-analysis of randomized trials. Pain, functional disability, and depression were all reported to have improved among patients taking a placebo. Again, disentangling the placebo effect from other confounding factors would be an invaluable follow-up should a no-treatment arm be deemed ethical.

Turning away from double-blind placebo, a growing number of studies suggest placebos can be effective even when given openly (24) (so-called Open-Label Placebo [OLP]), though some have raised methodological limitations with this line of research (15, 25). Four studies explore the topic of OLP. Estudillo-Guerra et al. report an interesting case study from a prior pilot OLP study (26) where a patient was successfully able to taper off oxycodone using a placebo conditioning paradigm without experiencing an increase in pain. Leveraging placebos to reduce opioid use is one of the most important translational aspects of placebo research (27) with some initial evidence of efficacy (26, 28). Sezer et al. report a pre-registration of another such trial where patients are randomized to Treatment as Usual (TAU) or TAU plus four OLP injections for post-operative pain. This will be the first randomized trial of OLP we are aware of to examine the efficacy of an honest placebo delivered intravenously. Heiss et al. argue that we re-examine the rationale provided in OLP studies by suggesting two new rationales that may be more effective than the standard rationale (29) for some patients. Finally, Wang et al., building off of the finding that there is a placebo genome [named the "placebome" (30)] show that there are genetic markers which can predict the placebo to honest placebo, namely being homozygous for rs4680, which is a single nucleotide polymorphism in catechol-O-methyltransferase.

CONCLUSION

With the ongoing opioid crisis and COVID-19 pandemic, chronic pain has become an especially serious public health concern. As the articles in this special issue demonstrate, understanding and leveraging the placebo effect may play an important role in addressing pain.

AUTHOR CONTRIBUTIONS

MB wrote the initial draft. All authors make corrections and edited the manuscript. All authors contributed to the article and approved the submitted version.

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REVIEW
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Healing in a Social Context: The Importance of Clinician and Patient Relationship

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When a patient presents to a health provider, the course of the disorder is composed of three effects: natural effects, specific effects, and contextual effects. Part of the contextual effect is due to the relationship between the healer and the patient. Social healing appears to be present in eusocial species and particularly well-developed in humans. Evidence for the importance of the relationship in healing is found in placebo studies, including placebo analgesics, medicine, and psychotherapy. Although the theory for how the relationship is therapeutic is not well-developed, four possible mechanisms are discussed. The implications for health care and the treatment of pain are discussed.

Keywords: healing, placebo, clinical relationship, social healing, psychotherapy, coregulation

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In 2017, the total expenditures for health care related spending in the United States, according to the Centers for Medicare and Medicaid Services, was 3.5 trillion dollars, which accounted for almost 18 percent of the United States gross domestic product. The incremental cost of health care due to pain is ∼300 billion dollars (1). Advances in medicine and public health have led to a dramatic rise in longevity, with life expectancy of nearly 80 years currently compared to around 40 years a century ago. When we think of advances in medicine, we think of various medications, surgeries, and vaccinations that are important for curing or preventing diseases and improving the quality of life. Many cancers are no longer death sentences. Gastric ulcers due to H. Pylori bacteria are successfully treated with antibiotics and medication to block acid production (histamine blockers or proton pump inhibitors), supplanting relatively ineffective treatments consisting of diets of bland foods and antacid tablets.

A misconception of medicine and other healing practices is the notion that the benefits of medical interventions primarily are due to technological advances and the specific ingredients or procedures found in those advances. The benefits experienced by patients who present to a clinician for relief are not due exclusively to the specific ingredients of the treatment, as the context in which the treatment is given produces a relatively large effect as well. In this article, the focus will be on the effects of the relationship between the patient and the clinician on health outcomes, examining its relative contribution to distress relief and disease cure or management.

COMPONENTS OF HEALING

An individual presenting to a clinician for a health-related problem seeks relief of the distress (symptom reduction), better health (cure of disease or disease management), and/or better quality of life. It is useful to identify the various factors that are responsible for the change in health status, particularly natural effects, specific effects, and contextual effects.

Natural Effects, Specific Effects, and Contextual Effects

There are three effects that compose humans' response to disease and injury, which here are labeled *natural effects, contextual effects,* and *specific effects*. Natural effects refer to the change in the patient's status due to the natural course of disease. Humans have biological mechanisms to protect the organism from disease and to aid in healing, including immune functions, blood coagulation, barriers such as skin, and so forth. When an individual is exposed to a pathogen or is injured, the organism often heals without intervention, a phenomenon referred to as *natural healing* (2). Of course, the natural course might involve deterioration (i.e., negative natural effect), say for Parkinson's disease.

There are effects due to the specific medications or procedures administered by the clinician. Removing the appendix, for example, will reduce symptoms and eliminate the sequelae of a bacterial infection of the appendix and will avoid a rupture. Antibiotics specifically destroy bacteria causing an illness or retard their growth. The *specific effects*, sometimes referred to as *technological healing* (2), typically characterize our views of the advances of modern medicine.

The final component of healing involves *contextual effects*. Contextual effects involve a host of factors, including patient expectations, symbolic meaning of a healing setting (e.g., a physician's white coat, syringes, diplomas on the wall), the relationship between the healer and the patient, conditioned responses to various medication or procedures, and so forth, as described by Di Blasi et al. [(3); see also (4)]. Miller et al. (2) have referred to the benefits of this component as *interpersonal healing*, but there are several aspects of this effect that involve aspects of the healing setting that do not necessarily involve an interpersonal relationship, such as the patient's response to a syringe as a healing symbol (4). Clearly, much of what is categorized as factors in the contextual effect are the factors that make placebos effective (2, 5–8), but the effect technically is not a placebo effect because in these examples, and for the most part in clinical practice, no placebo has been administered. Benedetti (9) has called such effects *placebo-like effects*.

Effects in Context—Considerations

In 1977, Engel recognized the limitation of an exclusively biological system of medicine and proposed a model that included psychological and social factors (i.e., factors included in the contextual effect), a model that is referred to as the *biopsychosocial model* of medicine. At the turn of the century, based on the efforts of Sackett, the Institute of Medicine defined *evidence-based medicine* as "the integration of best research evidence with clinical expertise and patient values" [(10), p. 142; see also (11)], recognizing that clinical practice based solely on biology was not sufficient in terms of quality of care. Despite these efforts, the psychological and social aspects of medicine are largely ignored in the literature. Compared to the hundreds of thousands of clinical trials examining various biological based treatments, recently Di Blasi et al. (3) found 25 trials that investigated "context effects" and Kelley et al. (12) found 13 trials that estimated the effect of relationship on health outcomes.

The focus on the specific effects has been central to medicine since the origin of modern Western medicine (13). In the mid-twentieth century, the randomized placebo control group was developed to estimate the effects due to the specific factors of treatment, over and above what was produced by psychological and social factors (i.e., the placebo) and controlling for natural effects (13, 14). Indeed, the Food and Drug Administration requires superiority of a medication to a placebo for drug approval (15). When it is reasonable to expect that contextual effects exist, they account for a sizable proportion of the treatment effect and can be in some cases larger than the specific effect (16, 17).

A final issue that needs clarifying is how the effects are produced conjointly. Optimal healing is a complex combination of natural effects, contextual effects, and specific effects. Consider acute pain resulting from a surgical intervention. The incision will be sutured (specific effect) and then the tissues will progress through stages as they heal naturally, analgesics will be administered to reduce the pain until the natural course of healing has progressed sufficiently. The effect of the analgesics has both a specific effect and a contextual effect. Amanzio et al. (18) demonstrated that post-operative patients experienced significantly less pain relief when they were unaware that they were receiving strong opioid analgesics automatically dispensed with a programmed infusion machine than when the same dose was dispensed by the machine but with a physician present who told the patient that "the medication was a powerful painkiller." (p. 206). Clearly, post-operative pain relief is a result of natural, specific, and contextual effects.

SOCIAL HEALING

From the beginning of human civilization, there have existed a variety of healing practices, involving an interpersonal relationship between a socially sanctioned healer and a person in distress (13, 19, 20). Until the advent of modern medicine in the twentieth century, the rituals involved in these healing practices often produced null or negative specific effects [i.e., the interventions were ineffective or harmful (13)], but presumably healing practices persisted over millennia due to the perceived benefits that may have been due to the contextual effects and/or misattribution of natural effects as a specific effect of the healing practice.

Social healing practices are not limited to humans but exist in other eusocial species. Remaining in close contact with infected conspecifics often creates epidemics as pathogens are communicated to healthy organisms, as is evident in the COVID-19 pandemic. There are interesting social phenomena in diseased eusocial species. For example, what might seem counter-intuitive, in ant colonies, healthy ants spend time grooming ants suffering from an infection. The grooming behavior results in a limited transmission of the pathogen from the infected ant to the healthy aunt, which elicits an immune response to the particular pathogen. The healthy ant, through social activity, acquires immunity to the pathogen, a process that has been labeled "social immunization" (21). Honeybees utilize a "social

fever" when an infection is present in the colony, induced by the bees fanning their wings, which raises the temperature of the hive (22). Relevant to the current pandemic, infections can change social behavior in socially isolating ways. In highly social vampire bats, immune challenged individuals experience lethargy and fatigue, which results in decreased social contact, particularly with non-kin conspecifics (23, 24). In social species, natural healing mechanisms at the organism level have social healing analogs, which evolved to promote group fitness: "At the interface between social and individual immunity, several findings indicate that a strong social defense may replace to a certain extent the need for a sophisticated individual immune system" [(22), p. 138]. Of course, as is the case of evolved characteristics of any species, what is adaptive in the typical situation may be catastrophic as biological and environmental conditions change.

Social healing raises the question with regard to how an organism signals that it needs others to care for it and how does the conspecific recognize the signal? The signaling/recognition issue can be understood by considering pain in humans. Pain is adaptive because it indicates situations that are harmful, initiates escape from a harmful situation, and teaches the organism to avoid similar harmful situations. However, importantly, pain can be used to elicit assistance from others (25–27). The facial features associated with pain evolved relatively early in humans and are consistent across various sources of pain, including emotion pain (27, 28). The fitness benefit of the facial expression of pain is that it signals to others to elicit social assistance (27). Steinkopf (25) has proposed a signaling theory of symptoms that proposes that symptoms such as inflammation, lethargy, and pain have a signaling component: "Symptoms signal the need for care and treatment to potential helpers. Once help and treatment are granted, the signaling function is fulfilled and the symptoms diminish" (p. 1). Social support, protection, and assistance elicited by the expression of pain are beneficial to healing.

EVIDENCE FOR SOCIAL HEALING: THE RELATIONSHIP

The healing relationship is defined as an interpersonal interaction between a clinician (or experimenter in some studies) where the clinician explains what is involved in the treatment. The relationship involves a cognitive component, where information is transmitted, as well as an emotional component that involves empathy, warmth, caring, and understanding (3, 12, 29).

The evidence for the relationship in healing is found primarily in three areas: placebos, somatic medicine, and psychotherapy. Placebo research is informative because by definition the specific effect is nil and therefore an interaction between specific factors and the relationship does not exist, making interpretation of studies less ambiguous. As well, it is relatively easy to manipulate the relationship in placebo designs. Medical/surgical investigations are informative because the importance of the relationship for health outcomes can be investigated in the setting where it is most important (i.e., when a specific treatment in administered). Finally, psychotherapy is a healing practice that involves the relationship as the vehicle by which the treatment is administered.

Placebos

Placebos are substances or procedures without ingredients that should not, from a biological perspective, affect the health status of an individual (30). The placebos can mimic any medical intervention—there are be sham pills, inoculations, creams, and surgery. There is convincing evidence that placebos have a demonstrable effect on subjective outcomes (e.g., symptoms) as well as on the physiology of the individual, despite the lack of biological ingredients (5–8). Placebo effects have been detected in many domains, including pain (acute, chronic, as well as experimentally induced), headaches, Parkinson's disease, irritable bowel syndrome osteoarthritis, respiratory illnesses, menopausal symptoms, mental disorders (primarily anxiety and depression) among others (5–7).

In general, there is agreement that the effects of placebos "depend on a person's psychological and brain responses to the *treatment context*, which influence appraisals of future well-being" [(5); emphasis added, p. 73]. Moreover, "recent research has revealed that… psychosocial-induced biochemical changes in a patient's brain and body in turn may affect the course of a disease and the response to a therapy" [(9), p. 33]. The central characteristic of the placebo response is the psychosocial context, which includes the relationship between the patient and the clinician, the information about the intervention that is communicated to the patient, the physical healing space, the healing rituals, cultural beliefs about healing and healers, and so forth. Clearly, the discussions of placebo effects are very close, if not identical, to how contextual effects were discussed earlier. The term contextual effect is preferred generally because the effects (i.e., contextual effects) can be obtained whether or not a placebo has been administered.

The conjecture relative to placebo effects is that the relationship between the clinician and the patient augments the placebo effect obtained without the relationship. Placebo effect can be obtained by written information [i.e., providing information without a relationship, e.g., (31–33)], can occur as a conditioned response (34), and can be induced by the symbolic meaning of medical paraphernalia (4). The issue is not whether a placebo effect can be detected without a relationship but rather whether the placebo response is augmented by the relationship. There are a number of well-conducted clinical trials that have examined relationship effects and placebos, as discussed elsewhere (35) and augmented and reviewed here.

The effect of the relationship was investigated in a study of placebos in the treatment of irritable bowel syndrome (IBS), conducted by Kaptchuk et al. (36). IBS, often treated in primary care, is a prevalent disorder with no known cause but a disorder that attenuates patient's quality of life. IBS has been found to be responsive to placebos and in this study the placebo used was an acupuncture placebo. The acupuncture placebo is given by a device that the patient believes pierces the skin but does not and therefore is not true acupuncture. In this study, IBS patients were randomly assigned to one of three arms: (a) a

treatment-as-usual group with no acupuncture (usual treatment from a physician), (b) the sham acupuncture twice a week for 3 weeks with *limited interaction* with the acupuncturist, and (c) sham acupuncture with the same frequency but with an *augmented interaction*. The acupuncturists participated in both conditions (i.e., in a crossed design). In the limited interaction, the acupuncturist matter-of-factly explained the procedure and indicated that they had reviewed the chart, but they did not exhibit warmth or caring. The augmented interaction included a preliminary interaction, which lasted about 45 min prior to the first acupuncture procedure, and included questions about the patient's IBS symptoms, curiosity about the effects of IBS on functioning, and inquiries about how the patient understood the cause and meaning of IBS, an interaction that the researchers called "an optimal patient-practitioner relationship" (p. 3). The acupuncturists in the augmented condition, however, were not allowed to use any specific interventions or give advice.

The outcomes measured at the end of the 3 week IBS trial were symptom severity, adequate relief from distress, global improvement, and quality of life. The results showed that the limited sham acupuncture was superior to treatment-as-usual on all outcomes, as expected. However, the augmented interaction provided additional benefit over the limited interaction, on all outcomes. With regard to global improvement, 3 percent of the treatment-as-usual patients reported moderate or substantial improvement, whereas 20 percent reported the same improvement in the limited condition, and 37 percent in the augmented condition. Interestingly, the largest effect was on the quality-of-life outcome, indicating that the relationship effect may target aspects of general distress rather than particular symptoms, as suggested by Wampold and Imel (37). According to Kaptchuk et al. (36), "The magnitude of non-specific effects in the augmented arm is not only statistically significant but also clearly clinically significant in the management of irritable bowel syndrome" (p. 6), supporting the notion that the relationship effect on healing is clinically important.

In the Kaptchuk et al. (36) study, although the acupuncturists were trained to be interpersonally warm, interested, and caring, some acupuncturist may have had a more well-developed set of interpersonal skills [see (38)]. Accordingly, there would be variability among the practitioners in the quality of their relationship with the patients regardless of the training, based on their interpersonal abilities. A follow-up analysis showed that there were significant differences among the acupuncturists: Some acupuncturists achieved better outcomes, regardless of acupuncture condition, than others (39).

The variability in outcomes due to acupuncturist in the IBS study suggests that some clinicians are more effective than others, a question studied in a double-blind randomized trial of antidepressant medication (ADM) vs. pill placebo (40). This study analyzed data from the drug arms (ADM and pill placebo) of the NIMH Treatment for Depression Collaborative Research Program (NIMH TDCRP). According to the NIMH TDCRP, psychiatrists in this study were coached to "provide a generally supportive atmosphere" (p. 311) during clinical management, which included a 45 to 60 min initial session and then weekly sessions of 20 to 30 min thereafter (41). Thus, the conditions were seen as medication (verum or placebo) "plus minimal supportive therapy" (p. 311). The antidepressant intervention was superior to placebo (42); ADM vs. placebo accounted for about three percent of the variability in outcomes, approximately equal to the usual ADM effect. However, psychiatrists accounted for about nine percent of the variability in outcomes. In this study the more effective psychiatrists delivering placebo had better outcomes than the less effective psychiatrists delivering the placebo. Because this was a double-blind randomized trial, the difference among the psychiatrists was due to differences in clinical management.

In a study designed to determine the additive effects of relationship to both placebo and verum, Fuentes et al. (43) examined the effect of the relationship on pain intensity and pain sensitivity of patients with chronic low back pain. Patients received either active interferential current therapy (IFC, the verum) or sham IFC in conjunction with either a limited relationship or an enhanced relationship, resulting in a 2 (verum IFC v placebo IFC) by 2 (enhanced relationship v limited relationship). In the limited relationship condition, the practitioners introduced themselves and explained the purpose of the treatment whereas in the other condition "the therapeutic interaction was enhanced through verbal behaviors, including active listening (i.e., repeating the patient's words, asking for clarifications), tone of voice, non-verbal behaviors (i.e., eye contact, physical touch), and empathy" (p. 480). The practitioners left the room during the procedure in the limited relationship condition but they remained in the enhanced condition. For both the verum and for the placebo, the augmented relationship condition produced superior outcomes relative to the limited relationship condition. The authors concluded, "The context in which physical therapy interventions are offered has the potential to dramatically improve therapeutic effects" (p. 477).

As mentioned previously, there is a conjecture that the therapeutic relationship is composed of two components, cognitive and emotional (44, 45). Howe et al. (45) attempted to tease out these two aspects of the clinical relationship. In this study, the participants were given a physical examination, which included assessment of vital signs as well as an "allergy test," as a screen for a subsequent purported medical study. The allergy test caused a reaction in all participants because the skin was pricked with histamine. The participants were informed that they were disqualified from the medical study and were given a sham placebo cream, which the participants were told would reduce their allergic reaction[1]. The histamine prick/placebo cream procedure was executed in four conditions—warmth (high vs. low) crossed with competence (high vs. low). High warmth involved having the physician use the participant's name, warm non-verbal behavior (eye contact, proximal seating, and smiling facial features), and inviting office furnishing (e.g., posters with calming images) and the low warmth condition had an absence of

[1]There was also a condition where the participants were told that the cream would aggravate their reaction, but that part of the study is not relevant to the current discussion of placebo as opposed to nocebo.

these features. In the high competence condition, the physician was verbally fluent (e.g., gave a cogent explanation delivered with confidence), the examination procedures were administered efficiently without mistakes, and the examination room was well-organized, whereas the low competence lacked these features. The rate of change in the reaction to histamine, which was assessed as wheal diameter, was the outcome measure. The wheal diameter decreased most quickly and the final wheal diameter was smallest in the high warmth/high competent condition, whereas the wheal diameter decreased most slowly and the final wheal diameter was largest in the low warmth/low competence condition The results of the mismatched conditions (low competence/high warmth and high competence/low warmth) were intermediate to the low/low and high/high conditions, suggesting that warmth and competence contributed to the effect of the placebo cream.

The final study reviewed examined pain tolerance threshold under two conditions (46). An actor portraying a physician administered placebo cream to healthy volunteers who participated in a cold-pressor test; tolerance and threshold were assessed before and after administration of the placebo. In one condition, the "physician" portrayed a traditional doctor/patient relationship and in the other the "physician" role emphasized "attentiveness and strong suggestion, elements… present in ritual healing" (p. 1). The latter condition, emphasizing attentiveness and suggestion, resulted in increased tolerance and threshold. The authors concluded that a "structured manipulation of physician's verbal and non-verbal performance, designed to build rapport and increase faith in treatment, is feasible and may have a significant beneficial effect on the size of the response to placebo analgesia" (p. 2).

Evidence for the importance of the clinician/patient relationship in producing a placebo effect appeared in a meta-analysis of randomized clinical trials that examined predictors of placebo analgesia response in chronic pain. In this meta-analysis placebo effects were associated with the number of face-to-face visits with the clinician; that is, studies with more face-to-face visits reported larger placebo effects (47).

The experiments that examined the relationship between the clinician and the patient when a placebo was administered found convincing evidence that a good (either warm and/or competent) relationship augments the effect of placebo. The evidence for relationship is particularly strong because placebos contain no specific ingredients that could interact with the relationship to produce better outcomes.

Somatic Medicine and Health Service

The evidence for the effects of relationship in the medical/surgical literature is less straightforward, primarily due to the paucity of such research. In 2001, Di Blasi et al. (3) conducted a review of context effects on health outcomes, some of which examined the relationship as a contextual factor. Their search strategy yielded only 25 trials that met inclusion criteria; the trials were rated as being predominantly poor quality (of the 25, only 5 were rated as "very good" and 6 as "good"). Of the 25 trials, 19 were classified as providing "cognitive care" but most studied the effects of provision of information rather than focusing on the quality of the relationship; generally, it was found that practitioners who attempted to influence patient's beliefs about the treatment had an effect on patients' health outcomes. No studies manipulated only emotional care, but four trials examined combining cognitive care with emotional care and the results of these studies suggested that providing information (cognitive care) in a warm and accepting way produced better health outcomes than a neutral situation. Di Balsi et al. concluded, "Practitioners who attempted to form a warm and friendly relationship with their patients, and reassured them that they would soon be better, were found to be more effective than practitioners who kept their consultations impersonal, formal, or uncertain" (p. 760). Unfortunately, insufficient statistics were reported in the primary studies to meta-analytically estimate the size of the relationship effect.

The most recent review of relationship in somatic medicine was a meta-analysis of studies that examined the effect of relationship on health (12). Inclusion criteria were that (a) studies had objective or validated subjective measures, such as pain ratings, and (b) studies that systematically manipulated the patient-clinician relationship. The aggregate standardized mean difference in favor of better relationship leading to better health outcomes was 0.11, which statistically significant, although small. The authors made the following conclusion:

> This systematic review and meta-analysis of RCTs suggests that the patient-clinician relationship has a small, but statistically significant effect on healthcare outcomes.… relatively few RCTs met our eligibility criteria, and… the majority of these trials were not specifically designed to test the effect of the patient-clinician relationship on healthcare outcomes. (p. 1).

The direct evidence for a relationship effect in medicine is sparse and the quality of evidence that is present is relatively poor. In the placebo literature, several well-conducted trials of the relationship have been conducted with the stated purpose of testing the relationship effect, whereas the relationship effect has not been the object of rigorous examination within the medical literature. This might be surprising given the effect of physician-patient relationship on medical patient malpractice intentions (48).

Psychotherapy

Although the evidence for relationship effects from psychotherapy is voluminous and persuasive (37, 49), there are logical and pragmatic limitations to the evidence for the importance of the relationship. The investigation of specific effects in medicine uses a placebo control to rule out psychosocial effects (i.e., the contextual effects) so as to isolate the biological effects (i.e., the specific effects). In the study of placebos, there are by definition no specific effects and the contextual effects can be investigated by manipulating various aspects of the context (e.g., a warm relationship vs. a cold relationship). In psychotherapy, the specific effects and the contextual effects are both produced by psychosocial factors. Classically, there has been a distinction made between the *common factors* and *specific ingredients* in the psychotherapy literature but they are logically both psychosocial

effects. Psychotherapy, as a healing practice, depends on the relationship between the therapist and the patient as any therapeutic actions (i.e., so called specific ingredients) cannot be delivered without a relationship. Furthermore, common factors include the acceptance and enactment of particular therapeutic actions and consequently the contextual factors of psychotherapy involve the patient's expectations that the therapeutic actions are effective, further confounding the two types of effects. The logical problems created by the artificial distinction between these two types of effects have been thoroughly discussed (37, 50, 51).

In addition to the conceptual problems related to contextual and specific effects in psychotherapy, there are pragmatic/ethical issues. In placebo studies, there is little difficulty in manipulating relationship factors, as was evident from the studies reviewed. In medicine, the emphasis is on isolating the biological specific effect and therefore the impediments to manipulating the relationship involved with the contextual effect is not objectionable, even if it is not of particular interest. In psychotherapy studies, it is not possible to deliver the treatment without a relationship (i.e., the intervention would no longer be psychotherapy) and furthermore it is not ethically allowed to have a condition with an intentionally weakened relationship, such as assigning patients to a condition where the therapist is proscribed from being empathic.

Despite the problems designing experimental studies that examine relationship effects in psychotherapy, there are hundreds of studies that have examined the association between the degree to which a relationship factor is present and psychotherapy outcome (49). Recently, Norcross and Lambert (52) summarized the results of meta-analyses of the correlation between a relationship factor and psychotherapy outcomes. These correlations, when converted to standardized mean differences (SMD), were moderately large for many relationship variables, including the therapeutic alliance (SMD = 0.57), patient-therapist collaboration (SMD = 0.40), therapist empathy (SMD = 0.58), therapist congruence/genuineness (SMD = 0.46), the real relationship (SMD = 0.80), and addressing ruptures in the alliance (SMD = 0.62).

The therapeutic alliance, which consists of agreement about the goals and tasks of therapy as well as the bond between therapist and patient, is the most extensively studied relationship variable in psychotherapy (37, 52, 53). There are over 300 studies that have examined the alliance-outcome association, involving over 30,000 patients (53); consistently, the alliance measured early in therapy is a predictor of the outcome of therapy. There is convincing evidence that this association is not confounded by early symptom change or other factors and is important for all types of therapies (37, 53–55). Moreover, it is the therapist contribution to the alliance that is important for producing therapeutic outcomes—that is, therapists who are better able to form an alliance across a variety of patients have better outcomes than therapists whose ability to form an alliance with patients is poorer (37, 56–59).

Increasingly, various psychological treatments are being effectively delivered electronically, with minimal contact with a therapist (60). The issue for the study of relationship is not whether such treatments are effective, but whether some form of relationship, perceived by the consumer of such intervention, contributes to outcomes. Somewhat surprising is evidence that consumer rated alliance with a therapist in internet delivered treatment is associated with outcome to the same extent as it is in face-to-face psychotherapy (53, 61).

Further evidence for the importance of relationship for psychotherapy outcomes comes from the therapist effects literature. Therapist effects refers to the situation that some therapists are more effective (i.e., produce better outcomes) than other therapists, regardless of characteristics of the patients or other factors. Therapist effects in psychotherapy have been detected in randomized clinical trials as well as naturalistic setting (59, 62). Indeed, therapist effects exist within various treatments and the size of the therapist effect is greater than the between treatment effect; that is to say, the particular therapist delivering the treatment is more important than the particular treatment being delivered (37, 59). As discussed earlier, providers effects have been detected in the delivery of placebos (39) and in psychopharmacology (40).

Of interest to the present topic is the question of what are the characteristics and actions of effective psychotherapists. Research has shown that the age, gender, experience, ethnicity, profession of therapist, size of therapist caseload, self-reported social skills, interviewer's rating of trainees' clinical skill, and therapist theoretical orientation do not differentiate more effective therapists from less effective therapists (59). There is some evidence that therapist attitudes, activities outside of therapy, and burnout explain some of the difference among therapists (59). However, the most important predictors of therapist effectiveness are the interpersonal skill of the therapists displayed in interpersonally challenging situations (38, 59, 63). Anderson et al. (38) had therapists respond to video-presented challenging patient vignettes and found that *facilitative interpersonal skills* (FIS) displayed by the therapist in response to the vignette predicted the outcomes obtained by the therapists—this was the first time therapists skills assessed outside of therapy predicted therapy outcomes. The FIS include verbal fluency; therapist communication of hope and positive expectations; persuasiveness; emotional expression; warmth, acceptance, and understanding; empathy; alliance bond capacity; and alliance rupture-repair responsiveness. Anderson and colleagues' studies, as well as others who have measured similar skills in challenging situations (63), have shown that psychotherapy trainees who are better able to exhibit these skills at the beginning of training have better outcomes 2 to 5 years in the future (63, 64).

The evidence from the psychotherapy literature clearly indicates that the relationship component of the treatments is critical to successful outcomes, regardless of the treatment being delivered. That psychotherapy is as effective as medications for many mental disorders (65–67), and that the relationship is key to successful psychotherapy, provides further evidence for social healing.

HOW IS THE RELATIONSHIP HEALING?—THEORETICAL CONSIDERATIONS

Although the evidence for social healing appears to be strong, the studies reviewed have not investigated the psychological

mechanisms involved in producing outcomes. What is it about the relationship with a warm and competent healer that leads to better outcomes? There have been a few theoretical discussions (29, 35, 68), which are summarized here.

Interactive Effects—Improving Adherence

One possible mechanism for the therapeutic value of relationship, which was alluded to earlier, is that the specific ingredients and aspects of the relationship interact. The most obvious way that this may happen in medicine is that a good relationship with the clinician augments patient adherence to the specific ingredients of the treatment. That is, if a patient has a good relationship with the practitioner, then the patient will follow the prescribed course of treatment, say, by taking the medication as prescribed. There is meta-analytic evidence that physician communication is positively correlated with patient adherence; there is almost a 20 percent greater risk of non-adherence if the physician communicates poorly (69, 70).

However, there is some evidence that makes interpretation of medical adherence studies ambiguous (71). Not surprisingly, patients have better outcomes if they adhere to effective drug therapies. A meta-analysis of adherence to effective drug therapy and mortality found that the odds of mortality were lower when patients used their medications as directed, not surprisingly, but interestingly odds of mortality were also lower when patients adhered to a placebo as well, suggesting the benefits of adherence might involve a contextual effect as well as a specific effect (72). Indeed, there several large clinical trials that show that adherence to placebos reduces morbidity and mortality (73, 74).

Interestingly, the interaction between the relationship and treatment has been a much-debated topic, in a slightly different guise. As discussed earlier, the alliance, measured early in psychotherapy, is a robust predictor of psychotherapy outcome. What is not clear is how the alliance is therapeutic. There is one camp who argue, with some supporting evidence, that the alliance is therapeutic by itself [i.e., independently of other therapeutic actions; see e.g., (75, 76)]. This view, which is espoused most persuasively by relational psychodynamic theorists and researchers, propose that a strong alliance, and particularly one that is "ruptured and repaired," provides the patient a learning experience in relationships generally that then leads to better mental health. On the other hand, there are those who conceptualize the alliance as a collaborative relationship that is necessary to do the difficult work of therapy (77), a perspective that was expressed by Bordin (78), when he described the alliance as a pan-theoretical construct. This perspective is articulated most clearly by those with a cognitive-behavioral therapy (CBT) orientation, who point to evidence that agreement about the goals and tasks of therapy is predictive of outcome in CBT (79, 80). The latter perspective is an interactive effect of relationship and specific ingredients.

Relationship Combats Loneliness

Humans, as a social species, rely on the assistance of others for survival [e.g., see (81)] Socially isolated individuals lack the social connections necessary to thrive and to survive, particularly when under threat. It is well-established that obesity, smoking, lack of exercise, excessive drinking, and failure to receive influenza vaccination, have deleterious effects on health and increase mortality. However, loneliness is a greater risk for mortality than any of these factors (82, 83). A warm, caring, and understanding clinician might well provide needed social support for patients who are socially isolated.

There are many related social isolation constructs, but the most predictive of mortality is perceived loneliness (83). Individuals may have adequate social support, but still may not feel supported by those in their network during difficult times; a caring and understanding clinician may be particularly valuable in such cases. Colbie Holderness, the first wife of former Trump White House staff secretary Rob Porter and victim of his physical abuse, poignantly made this point:

> Then there is the just-as-serious issue of being believed and supported by who you choose to tell. Sometimes people don't believe you. Sometimes they have difficulty truly understanding what you are trying to tell them. Both Willoughby [Porter's second wife] and I raised our cases with clergy. Both of us had a hard time getting them to fully address the abuse taking place. It wasn't until I spoke to a professional counselor that I was met with understanding. (https://www.washingtonpost.com/opinions/rob-porter-is-my-ex-husband-heres-what-you-should-know-about-abuse/2018/02/12/3c7edcb8-1033-11e8-9065-e55346f6de81_story.html).

The importance of provider warmth, caring, and understanding during times of distress is bolstered by the evidence that placebos are most effective when distress is high and individuals are seeking relief (8).

As discussed earlier several placebo studies that varied the emotional components (warmth, caring, and empathy) of practitioners found that these characteristics augmented response to placebos. Interestingly, the study of IBS found that the largest effect was for quality of life (36), which is not symptom specific. Wampold and Imel (37) hypothesized that emotional relationship variables would affect quality-of-life and well-being domains to a greater extent than symptom measures. As well, in psychotherapy, the bond between the therapist and the patient is most predictive of the outcome of the treatment when the patient has low social support (84), which supports the conjecture that the relationship reduces feelings of loneliness and leads to better outcomes.

Relationship Is Important for Creating Expectancies

Expectancies are thought to be central to the response to placebos. There are many ways to acquire expectancies. As discussed earlier, placebo effects, most likely due to expectancies, can be created without face-to-face interactions (32, 33), say by written information. As well, response to placebos can be conditioned or created by vicarious learning (34, 85). However, it may well be that the most efficient way that expectancies are created is through verbal persuasion.

Typically, people have an expectation that inserting a metal object, say a fork, into an electrical socket will create a

painful shock. It is doubtful this was learned by classical conditioning (insertion of the knife followed by a shock, a pairing that generalized to other metal objects) or by vicarious learning (say, by observing an older sibling being shocked), although in various workshops conducted by the author, typically there are one or two participants who report that they learned to avoid inserting metal object in electrical sockets by classical conditioning or vicarious learning. Most people have learned to avoid inserting a metal object into an electrical socket in the way we learn numerous important things—someone we trust informed us about the subject. That is, the expectation of an outcome (here a negative outcome) was created by a verbal transaction with a trusted person, which is a very powerful way to generate expectancies (86).

There is support for the importance of verbally transmitted information from trusted others in various fields. Many thoughts, behaviors, feelings, preferences, and mental states spread through social networks (87); that is, individuals are influenced by those with whom they are close. Lieberman (81), in his discussion of the neuroscience of social relations, makes this clear: "Our brains are designed to be influenced by others" (p. 8). Patients are neurologically predisposed to believe in the explanations provided by a clinician, particularly if the clinician is perceived to be competent and caring. Placebo research has begun to elucidate the components of persuasive explanations on response to placebos (31). A useful framework for understanding this process is persuasion theory (88), which has been used to explain response to placebos (86).

Relationship Result in Regulation of Emotion

Many mental health disorders are characterized by emotional dysregulation. In addition, medical patients often present with emotional distress due to worry about their medical condition as well the disruption of their lives that can result. Physiological equilibrium is needed for psychological, physical, and social well-being so attempts are made to help the patient regulate their emotions, which puts the locus of regulation on the patient. However, the physical presence of someone with whom we are close can reduce arousal and distress, a phenomenon called coregulation, social regulation, or interpersonal emotion regulation (89–91). Coregulation "refers to the process by which relationship partners form a dyadic emotional system involving an oscillating pattern of affective arousal and dampening that dynamically maintains an optimal emotional state" [(89), p. 202]. Thus, emotional regulation is conceptualized as a dyadic phenomenon rather than an individual one. There is evidence for co-regulation mechanisms. In a study of maritally satisfied women in a stressful situation, holding the hand of their husbands attenuated arousal in comparison to holding the hand of a stranger or not holding anyone's hand [(92); see also (93, 94)]. Coregulation has been detected in moment-to-moment emotional states of psychotherapists and patients (95, 96). Coregulation has been discussed as a mechanism involved in the beneficial aspects of empathy in medicine (29, 68).

DISCUSSION

The purpose of the present review was to present evidence that the relationship between a clinician and patient creates a sizable effect in response to treatment, which is important clinically and theoretically. Although the evidence for the effects due to the relationship is rather thin relative to evidence for the specific effects of various healing practices, further consideration of relationship effects in healing is warranted.

Although the majority of studies that have examined the relationship as a factor in healing have not involved pain as the health condition, there is good reason to believe that the relationship would be important for the treatment of pain. Comprehensive evidence exists that shows that pain is responsive to placebo interventions and that the expectations for pain relief are critical mechanisms of response to placebos [see (7), Chapter 10]. In this article, it is clear that the relationship with the healer is important for creating expectations for relief and augmenting the effect of placebos as well as specific interventions, including pain reduction or pain tolerance interventions. As well, as was mentioned earlier, awareness of receipt of analgesics through an interaction with a physician decreases the pain and increases pain tolerance (7, 18, 97).

Most obviously, more research is needed, particularly in the medical context. The focus on biological effects (i.e., separation of a pharmaceutical or procedure from a placebo) has diverted attention from what many medical providers recognize and act upon—relationship is important. In an age of cost containment and cost effectiveness, the importance of the relationship (and time to properly develop a therapeutic relationship) often is ignored. Additional research evidence would act to counter the focus on evidence-based treatments, in medicine and in mental health care, and an increased attention to harnessing the power of the relationship.

Clearly, the training of relationship skills in provider education should be emphasized. Recognition of the importance of the relationship is not sufficient and relational skills training is needed to develop expertise, in the same way that expertise is acquired in other domains (98). Moreover, medical and psychological education should consider interpersonal skill as an admission criterion. Anderson and colleagues, as well as others, have shown that the interpersonal skill of clinical psychologists when they begin their education is predictive of therapy outcomes up to 5 years in the future (63, 64).

In this review, the impression might be given that a "good" relationship is universal. Clearly, this is not the case and there are cultural and personal variations in what makes an effective relationship in a health care setting. Eye contact may be facilitative for many but for some cultural groups it is counterproductive. For some personalities and disorders, the intensity of a close relationship with a healer can be threathening and produce distress. Interpersonal relationship are complex and simple and univeral rules, such as making eye contact with a patient or calling the patient by their name, simplifies the endeavor in ways that may be ineffective and even discriminatory.

The theory underlying the relationship effects in healing is relatively underdeveloped, but clearly the healing

mechanisms are psychosocial. Further research in social psychology, clinical psychology, placebo studies, medical anthropology, and pain would elucidate the mechanisms of social healing.

AUTHOR CONTRIBUTIONS

BW is the sole author and is responsible for all aspects of the article.

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frontiers in Pain Research

CASE REPORT
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The Use of Conditioning Open-Label Placebo in Opioid Dose Reduction: A Case Report and Literature Review

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Introduction: Adequate pain management for inpatients in rehabilitation units is essential for achieving therapeutic goals. Opioid treatments are commonly prescribed, but these are associated with numerous adverse effects, including the risk of addiction and decreased quality of life. Conditioning an open-label placebo is a promising approach to extend the analgesic effect of the opioid while reducing its overall dosage.

Objectives: To describe a patient's experience in using conditioning open-label placebo (COLP) as a pharmaco-behavioral intervention to decrease opioid intake and its side effects after inpatient rehabilitation discharge, and to perform a literature review about the use of open-label placebo in pain.

Methods: This case study has been extracted from a clinical trial initiated in 2018. A 61-year-old male was recruited at a tertiary rehabilitation hospital after suffering a traumatic sport-related injury and orthopedic surgery. Pain management included prescription of non-steroidal anti-inflammatory drugs (NSAIDs) and short-acting oxycodone. After trial participation, the patient requested off-label COLP treatment to help him decrease outpatient opioid utilization.

Results: After COLP treatment, the patient could discontinue oxycodone intake (a reduction from 15 morphine equivalents/day) after rehabilitation discharge. Moreover, opioid side effects decreased from 46 to 9 points on the numerical opioid side-effects scale. A literature review identified five clinical trials using "honest" open-label placebo (OLP) or COLP as an experimental intervention for pain control. From these studies, two were in the area of chronic lower back pain, one in post spine surgery, one in irritable bowel syndrome, and another in spinal cord injury and polytrauma. Four studies reported positive outcomes related to pain control, while one study showed no significant differences in pain management between treatment-as-usual and the COLP group.

Conclusion: The case report illustrates how a pharmaco-behavioral intervention can facilitate downward opioid titration safely after inpatient rehabilitation. It initiates a discussion about new approaches for opioid management using conditioning and the patient's expectation of pain relief.

Keywords: opioids, conditioning, pain, pharmaco-behavioral, open-label placebo

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INTRODUCTION

Pain management is one of the biggest challenges in rehabilitation medicine. Standard pharmacological treatment has a wide range of undesirable side effects. Despite the recommendation of avoiding opioids to control acute pain, and to prefer multimodal analgesia alternatives, opioids are often used as adjunctive therapy at the forefront of treating mild to severe pain (1).

Overreliance on opioids increases the length of stay and hospital costs while decreasing patient satisfaction. The risk of opioids usage is the highest of all common analgesic categories, the list is long and serious, including respiratory depression (the most serious immediate and short-term risk), dizziness, nausea, vomiting, ileus, constipation, sedation, delirium, hallucinations, falls, hypertension, aspiration pneumonia, delayed gastric emptying, sexual dysfunction, sleep disturbance, opioid-induced hyperalgesia, risk of addiction, cognitive impairment, and mood alterations (2–5).

Greater opioid prescribing contributes to increasing availability for abuse and overdose (6). Patients previously naïve to narcotics who receive opioids during hospitalization and after discharge are at an increased risk of becoming chronic opioid users (7). In comprehensive pain rehabilitation programs there is lack of evidence of long-term improvements in pain and functioning attributable to opioid therapy, as opioid-induced hyperalgesia and opioid tolerance can exacerbate pain, as well as the impact on functioning, mood, and pain catastrophizing (8).

The risk of addiction and chronic pain has played a central role in the current national epidemic of drug abuse. Therefore, novel interventions aimed at preventing addiction among inpatients undergoing intensive rehabilitation and receiving opioids for pain, are needed.

Classical conditioning has been used to induce analgesia through learned responses without the need for drugs (9), while placebo administration can also lead to pain relief. Therefore, the conditioning of placebo analgesia can be considered a promising approach to prevent opioid addiction in patients receiving opioid treatment.

Placebo analgesia occurs when a substance known to be non-analgesic produces an analgesic response) (10). The placebo effect is a widespread phenomenon in medicine. It manifests through various mechanisms which include: (1) cognitive factors like the expectation of pain relief which triggers the release of endogenous opioids; (2) classical conditioning mechanisms where repeated associations between an active agent and inert substance promote conditioned responses; and (3) factors related to the therapeutic encounter, such as empathy, enhanced communication, and a comfortable healing environment (11). Also, Accumulating data, suggested that placebo analgesia, appears in response to the individual expectations and subsequent conditioning (10, 12–15). The effect of expectation and outcome associations on placebo is mediated by endogenous opioid release and m-opioid receptor system activation in the dorsal anterior cingulate cortex (dACC) (16).

As observed in neuroimaging studies the placebo effects on pain, suggests the activation of prefrontal areas including (dlPFC), rostral anterior cingulate cortex (rACC), orbitofrontal cortex (OFC), and ventromedial prefrontal cortex (vmPFC), influence the pain by activating endogenous opioids pain regulatory mechanism pathways in the brainstem, in the periaqueductal gray (PAG) (17–24).

Unfortunately, the use of placebos in clinical practice has typically presented an ethical challenge because of their association with deception and concealment. On the other hand, open-label placebo (OLP), also known as an honest placebo, which consists of providing patients with a non-active substance without deception or concealment (25) while explaining the purpose and possible benefits, has already been demonstrated to provide analgesic effects in patients suffering from pain (24, 26–29).

The neurobiology of pain processing includes the sensory-discriminative aspects of pain, which are regulated by direct projections from spinal nociceptive neurons and the primary somatosensory cortex, posterior insular cortex, and thalamus (30). These nociceptive inputs are modulated and then transmitted to cortical and subcortical structures, such as the primary somatosensory cortex and posterior insular cortex, which are responsible to encode the intensity of painful stimuli (31). The brain regions associated with the affective dimension of pain processing include the secondary somatosensory cortex and anterior insular cortex (32), while cognitive modulation of the pain experience is thought to be driven largely by regions within the prefrontal cortex, placebo response is associated with the activation of this network (33).

The neural substrates of placebos involve the activation of diverse neural centers such as the rostral anterior cingulate, orbitofrontal and dorsolateral prefrontal cortex, anterior and posterior insula, nucleus accumbens, amygdala, thalamus, hypothalamus, and periaqueductal gray area (16, 34). Some of these regions overlap with those involved in mood regulation and motivated behavior (34), including those associated with pain and endogenous opioids release that mediates placebo analgesia (35). The endogenous opioid system plays an essential role in placebo analgesia and studies have confirmed that placebo analgesia can be blocked by the opioid antagonist naloxone (18). Conditioning-open label placebo (COLP) is an innovative pharmaco-behavioral approach, that has been previously used as a "dose-extender" on children with ADHD (36). In an open-label prospective crossover trial, placebos were paired with stimulant medication to elicit a placebo response in children with ADHD that allow them to be effective treated at 50% of their optimal stimulant dose. In this clinical case, we intended to follow the same principle of extending the analgesic effects of an opioid drug while decreasing its total dosage. Based on the classical conditioning and learning principles, this paradigm associates the active drug (e.g., oxycodone) with a neutral stimulus (placebo), so the analgesic effect is bound to the intervention. The placebo then becomes a conditioned stimulus triggering a conditioned response (placebo-driven analgesia). The patient's awareness of the placebo's inert nature enables caregivers to bypass any ethical issues related to deception or concealment.

The proposed model is a reinforced conditioning placebo paradigm that also introduces a sensory stimulus in the form of

smell. Thus, the active intervention had the following assembly: opioid conditioning with a placebo pill plus an odorous stimulus as a booster of the learning experience.

CASE DESCRIPTION

We first contacted the patient when he participated in our COLP clinical trial ["Identifier: NCT03906721, Reduction of Opioid Dose Using Conditioning & Open-Label Placebo (COLP)"]. This trial explores the feasibility of a pharmaco-behavioral intervention for the reduction of opioids consumption in hospitalized patients. The patient was recruited in 2019, provided written informed consent, and was randomized to receive either COLP or treatment-as-usual (TAU) which was considered the control group. The randomization was performed using the order of entrance to the study and a previous randomization list generated by a computer using blocks of four, to minimize the risk of imbalanced groups.

After study participation, it was disclosed to the patient he was randomized to the TAU arm of the trial, the patient then asked if we would consider him for an off-label intervention after discharge. The patient was eager to try the open-label placebo intervention, as he was intrigued by the possible outcomes and aware of the side effects and risks associated with opioid intake.

The COLP intervention entailed two phases: acquisition, and evocation. The acquisition phase consisted of administering short-acting oxycodone as needed (PRN) paired with the open-label placebo (inert capsule), and an odorous stimulus (smelling cardamom oil) for three consecutive days. This was followed by the evocation phase where, for two alternate days, the patient received only the placebo and the odorous stimuli in the same PRN scheme. Between the alternated days, the patient took both the placebo and oxycodone to reinforce the conditioning (**Figure 1**).

The patient approved his data to be used for this report. Pain intensity was measured using the standard VAS 11-point-scale on average per day, opioid dose consumption was registered using morphine equivalents and opioids intake side effects were evaluated using the Numerical opioids side effects (NOSE), a simple, rapid, self-administered instrument, that rates gastrointestinal issues, fatigue, itching, sexual function, among other side effects (37). All data were collected by a phone call daily until the off-label treatment.

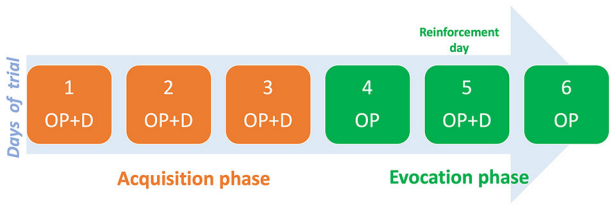

FIGURE 1 | Open label placebo intervention. OP, open-placebo; D, opioid drug.

DIAGNOSTIC ASSESSMENT, DETAILS OF THE THERAPEUTIC INTERVENTION, FOLLOW-UP, AND OUTCOMES, AS SPECIFIED IN THE CARE GUIDELINES

History of Present Illness

A 60-year-old white male (pseudonym "Dineen") with relevant history of left knee osteoarthritis since 2017 and right knee patellar tendinitis since 2018 and no other relevant medical history, was admitted to the emergency department in 2019 after falling while running a marathon. He suffered a right intertrochanteric hip fracture (closed, minimally displaced). Soon after, an open surgical reduction with internal fixation was performed. After surgery, the patient was transferred to a tertiary rehabilitation hospital for intensive rehabilitation. During hospitalization, Dineen reported mild pain in his right hip. However, his main complaint was localized pain in the right knee, with an average intensity of 7/10 on the visual analog scale for pain (VAS). The patient described achy right hip, leg, knee pain starting post-operatively that worsen with the activity of movement and weight baring, repositioning for comfort and ice packs were applied.

During the hospitalization a right knee MRI was performed, where they reported absent anterior cruciate ligament (ACL), and laxity of the posterior cruciate ligament (PCL), consistent with remote rupture, and muscular strain of the biceps femoris. No joint effusion or synovitis, nor fracture, edema, osteonecrosis, or focal marrow replacing lesion was reported.

Inpatient pain management consisted of 3,250 mg/day of acetaminophen, 400 mg/day of ibuprofen, 2 mg/day of tizanidine, and 5–10 mg/3 hr of oxycodone PRN, with an average consumption of 35 mg/day (**Table 1**). After discharge, Dineen received 400 mg/day of ibuprofen, 5–10 mg/3 h of oxycodone PRN and COLP as an off-label intervention for opioid management. The treating physician and our research team supervised treatment compliance on daily basis. We followed up with the participant by phone, calling him every day and at the same time for consistency. The pain was reported as a daily mean value—average pain experienced during each day considering the pain fluctuation.

During the first 3 days after discharge (**Figure 2**), Dineen received an open-label placebo together with oxycodone (acquisition phase) and reported moderate pain (VAS = 5). This was followed by the placebo-only period (evocation phase) (days 4 to 6) and a two-point increase in pain was reported (VAS = 7). On the reinforcement day, severe pain (VAS = 7) was reported. During the COLP treatment period, opioid side effects showed a steady decrease on the numerical opioid side effects scale (NOSE), from 46 to 9 points (80% decrease), as the patient had discontinued use of as-needed oxycodone.

DISCUSSION

This case illustrates how a pharmaco-behavioral intervention can be safely used to condition opioid analgesic effects while

TABLE 1 | Pain management over hospitalization, study participation and off label placebo intervention periods.

Time	Days	Acetaminophen (mg dose)	Ibuprofen (mg dose)	Tizanidine (mg dose)	Oxycodone (morphine equivalent Dose)	VAS
In patient	1	3,250			7.5	7
	2	3,250			15	6
	3	3,250			45	7
	4	3,250			75	6
	5	2,300			75	7
COLP study	6	3,000			45	5
	7	3,000			45	5
	8	3,000			15	6
	9	3,000			15	4
	10	3,000			15	5
	11	3,000		4	15	6
In patient	12	3,000	400	4	15	5
	13	3,000		4	15	5
	14	3,000	400	4	15	6
	15	1,000		4	7.5	6
Outpatient off label treatment	16		400		7.5	5
	17				7.5	5
	18		400		7.5	7
	19				0	7
	20				7.5	7
	21				0	5

VAS, visual analog scale; COLP, Conditioning open label.

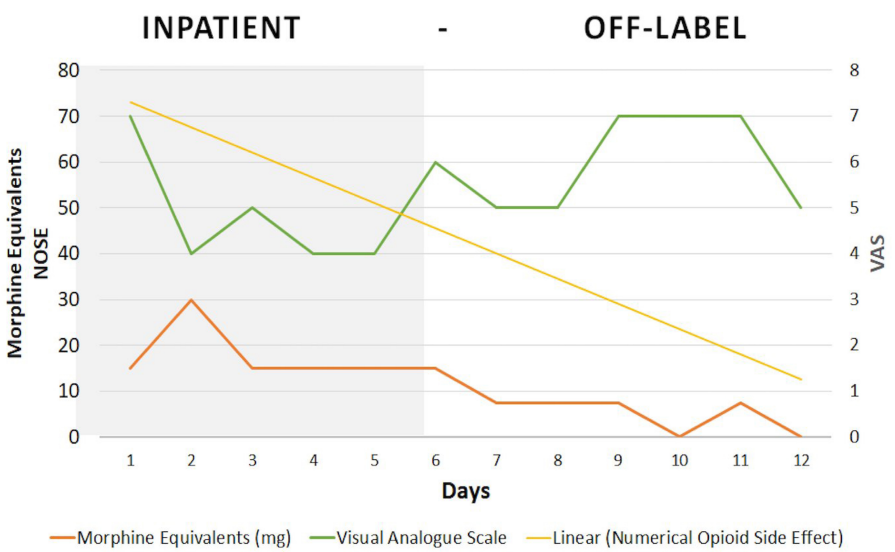

FIGURE 2 | Results. NOSE, numerical opioid side effect; VAS, visual analog scale.

decreasing total dose consumption and the associated side effects, within a relatively short period of 7 days. For the duration of the TAU period, Dineen kept his average opioid intake without changes at 15 mg/day. After starting the off-label placebo intervention, Dineen reduced his oxycodone consumption from 15 mg/day to 0 in 7 days.

Placebo effects are observed as improvements in the patient's symptoms in the absence of an active drug or medical

TABLE 2 | Published open label placebo randomized clinical trials for pain management with summary of the results.

Author	Intervention	Control	Condition	Study design	*N*	Outcome	Results
Flowers et al. **(author?)** (41)	Open label placebo pills paired with analgesics and opioids	Pain treatment as usual	Post spine surgery patients	RCT	$N = 51$ TAU = 25 COLP = 26	Daily morphine milligram equivalents Pain	- Opioid intake: Patients in the COLP group consumed ∼30% less daily morphine milligram equivalents compared with patients in the treatment as usual group - Pain No statistically significant difference between groups
Morales-Quezada et al. (42)	Open label placebo pills paired with opioids	Pain treatment as usual	In-patients with spinal cord injury and polytrauma	RCT	$N = 20$ COLP = 10 TAU = 10	- Daily morphine milligram equivalents - Pain	- Opioid intake: COLP significantly more reduction vs. TAU ($p = 0.001$) - Pain: reduction was significant in COLP group ($p = 0.005$) TAU showed a trend in pain reduction
Kleine-Borgmann et al. (29)	Open label placebo pills	No treatment	Chronic back pain	RCT	$N = 122$ OLP = 63 TAU = 59	- Change in pain intensity. Secondary outcomes: patient-reported functional disability - Spine mobility - Depression - Anxiety - Stress	- Pain intensity: OLP = larger reduction compared to TAU ($p =$ 0.001, d 5 20.44) reported - Functional disability: larger reduction in OLP vs. TAU ($p = 0.020$, $d = 0.44$) - Depression scores: larger reduction in OLP vs. TAU ($p = 0.010$, $d = -0.50$) - Mobility parameters: no difference - Anxiety and stress: no difference
Carvalho et al. (26)	Open-label placebo	Treatment as usual (TAU)	Chronic low back pain	RCT	$N = 83$ OLP = 41 TAU = 42	- Total pain score. Back-related dysfunction, assessed on the Roland–Morris Disability	- Pain: OLP greater pain reduction vs. TAU (P, 0.001), with moderate to large effect sizes - Disability: OLP more improvement compared to TAU ($p = 0.001$), with a large effect size
Kaptchuk et al. (43)	Open-label placebo	No-treatment controls (NTC)	IBS diagnosed by Rome III criteria	RCT	$N = 80$ NTC = 43 OLP = 37	- IBS Global Improvement Scale (IBS-GIS). Secondary - measures were - IBS Symptom Severity Scale (IBS-SSS) - IBS Adequate Relief (IBS-AR)–IBS Quality of Life (IBS-QoL)	- Global improvement scales (IBS-GIS) OLP = produced significantly higher improvement vs. TAU at midpoint and at endpoint ($p = 0.001$, $p = 0.002$). - Symptom severity (IBS-SSS) OLP greater decrease than TAU at midpoint and at the endpoint of study ($p = 0.008$, $p = 0.03$). - Adequate relief (IBS-AR): greater reduction in OLP vs. TAU - At midpoint and endpoint of the study ($p = 0.02$, $p = 0.03$) - Quality of life (IBS-QoL): Trend favoring OLP

OLP, Open label placebo; COLP, Conditioning open label placebo; TAU, treatment as usual; NTC, no treatment controls; IBS, irritable bowel syndrome.

intervention. This is not only related to the intake of an inert capsule but is bound to all the symbols and interactions associated with the medical interventions. The placebo effect is attributable to the patient's participation in the therapeutic encounter (for Dineen, knowingly taking a placebo capsule to decrease opioid consumption) including "healing rituals," while the neurobiology of placebos might be involved in promoting the release of endogenous opioids during the evocation phase. This diverse collection of emotions and behaviors include identifiable health care paraphernalia [e.g., pill, capsule, cardamom oil, daily phone calls) that can facilitate emotional and cognitive engagement with clinicians, and promote a positive treatment response (38)]. For Dineen, the "COLP ritual" immersed him into an experience where positive expectations reinforced his will to remove a "risky and dangerous medication." He engaged in receiving the COLP treatment because he was aware of the opioid's adverse side effects and risks of addiction and also believed that COLP would help him minimize issues associated with the opioids while keeping pain under control. Dineen reported increased pain during the placebo-only evocation period, but continued treatment until the end, highlighting Dineen's commitment to the treatment protocol while maintaining an emotional resilience to tolerate the pain increase. He did not use the rescue pain medication prescribed in case of unbearable pain. Dineen showed that personal motivation, treatment expectations, and communication with clinicians positively impacted his emotional and cognitive factors in pain perception during functional recovery. These elements are relevant in a variety of placebo studies across medical and psychological literature (39).

In this case, we believe the factors that made this intervention successful in reducing opioid consumption were: (1) The patient was highly motivated, (2) he had positive treatment expectations and, (3) he had a close relationship with the treating team (40). In our review of the literature, we identified five randomized clinical trials (RCT) using OLP as the main intervention for pain (**Table 2**). Two of them were in the area of chronic low-back pain (26, 29). In the first-mentioned study, they included patients with pain duration longer than 12 weeks and were randomized to receive treatment-as-usual (TAU) or OLP for 3 weeks, they found that the placebo treatment was tolerated and reduced pain, disability, and depressive symptoms but didn't affect objective mobility parameters, anxiety or stress.

In the second study, they randomized adults reporting persistent low back pain for more than 3 months to take placebo pills OLP or to TAU for 3 weeks, the main outcomes were pain intensity and back-related dysfunction. OLP elicited greater pain reduction and reduced disability compared to TAU. In another study evaluating the effects of OLP in irritable bowel syndrome (IBS), authors found that patients given OLP in the context of a supportive patient-practitioner relationship and a persuasive rationale had clinically meaningful symptom improvement in IBS, and that was significantly better than a no-treatment control group, concluding that placebos administered without deception may be an effective treatment for IBS (43). Two recent studies explored the use of COLP in patients with moderate to severe pain, in the first study, COLP was introduced as a pharmaco-behavioral intervention for opioid reduction in hospitalized patients. This exploratory study included participants suffering from spinal cord injury and polytrauma (42). Results showed that participants in the COLP group significantly reduced total opioid consumption by 66% of morphine equivalents at the end of the intervention period, and the pain was significantly reduced when compared to the TAU group. This was the first study using COLP in a hospital setting, where a short-acting opioid was paired with a placebo capsule as an "honest" intervention for opioid dose reduction. In the study from Flowers et al. (2021), in-patients who underwent spine surgery were included to receive, COLP in the immediate postoperative and after discharge periods to reduce daily opioid use, they found that participants in the COLP group, consumed 30% less daily morphine milligram equivalents compared with patients in the TAU group, with no significant pain differences between groups.

All five studies have shown OLP to be safe and effective in treating pain symptoms by applying principles of conditioning and positive treatment expectations. It is also of relevance that all studies showed the feasibility of using OLP in controlled clinical trials, and that patients (and clinicians) were positive about the use of this approach to manage pain. Moreover, the use of an honest placebo approach overcomes concealment and deception in clinical research, thus decreasing the clinician's liability while providing an opportunity to facilitate provider-patient interactions. This pharmaco-behavioral intervention opens the opportunity for clinical use of placebo as it promotes the patient's active participation in the healing process. The open-label placebo approach requires patient awareness and motivation—Dineen was highly motivated to reduce his opioid intake as well as to achieve full recovery—which may, in turn, lead to "self-regulation" processes associated with homeostatic regulation (e.g., endogenous enkephalins and endorphins release), as the patient is aware of the pharmacological "inert" nature of the placebo. Furthermore, the COLP approach implemented after hospitalization discharge could potentially decrease opioid intake across the community, reduce the risk of addiction, and in turn help with the national opioid crisis.

PATIENT PERSPECTIVE

Dineen reported the COLP paradigm was exciting and easy to follow.

CONCLUSION

We present the first case report where conditioning open-label placebo was used as a pharmaco-behavioral intervention to reduce dosage and ultimately terminate opioid treatment after hospital discharge. We showed the feasibility of this intervention within the clinical arena.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The patient approved his data to be used for this report.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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Harnessing Placebo Effects in Primary Care: Using the Person-Based Approach to Develop an Online Intervention to Enhance Practitioners' Communication of Clinical Empathy and Realistic Optimism During Consultations

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Background: Empathic communication and positive messages are important components of "placebo" effects and can improve patient outcomes, including pain. Communicating empathy and optimism to patients within consultations may also enhance the effects of verum, i.e., non-placebo, treatments. This is particularly relevant for osteoarthritis, which is common, costly and difficult to manage. Digital interventions can be effective tools for changing practitioner behavior. This paper describes the systematic planning, development and optimization of an online intervention—"Empathico"–to help primary healthcare practitioners enhance their communication of clinical empathy and realistic optimism during consultations.

Methods: The Person-Based Approach to intervention development was used. This entailed integrating insights from placebo and behavior change theory and evidence, and conducting primary and secondary qualitative research. Systematic literature reviews identified barriers, facilitators, and promising methods for enhancing clinical empathy and realistic optimism. Qualitative studies explored practitioners' and patients' perspectives, initially on the communication of clinical empathy and realistic optimism and subsequently on different iterations of the Empathico intervention. Insights from the literature reviews, qualitative studies and public contributor input were integrated into a logic model, behavioral analysis and principles that guided intervention development and optimization.

Results: The Empathico intervention comprises 7 sections: Introduction, Empathy, Optimism, Application of Empathico for Osteoarthritis, Reflection on my Consultations,

Setting Goals and Further Resources. Iterative refinement of Empathico, using feedback from patients and practitioners, resulted in highly positive feedback and helped to (1) contextualize evidence-based recommendations from placebo studies within the complexities of primary healthcare consultations and (2) ensure the intervention addressed practitioners' and patients' concerns and priorities.

Conclusions: We have developed an evidence-based, theoretically-grounded intervention that should enable practitioners to better harness placebo effects of communication in consultations. The extensive use of qualitative research throughout the development and optimization process ensured that Empathico is highly acceptable and meaningful to practitioners. This means that practitioners are more likely to engage with Empathico and make changes to enhance their communication of clinical empathy and realistic optimism in clinical practice. Empathico is now ready to be evaluated in a large-scale randomized trial to explore its impact on patient outcomes.

Keywords: placebo effects, primary medical care, doctor patient communication, clinical empathy, optimism, osteoarthritis, qualitative research, pain

INTRODUCTION

Placebo effects can be substantial and clinically meaningful; efforts to harness them in clinical practice to benefit patients are therefore warranted (1). There are at least two main ways in which this can be approached, depending on one's definition of placebo effects. Traditional, substance-based, definitions of placebo effects hold that placebo effects are elicited by the administration of a placebo substance (e.g., the archetypal "sugar pill") (2). From this perspective, harnessing placebo effects in clinical practice requires the prescription of placebos; concerns over the ethics of deceptive prescribing in clinical settings have led researchers to examine the effects of prescribing open label placebos. A different approach is suggested by process-oriented definitions of placebo effects, in which placebo effects are elicited by the psychosocial context within which treatment occurs and, especially, the doctor-patient interaction (2). From this perspective, harnessing placebo effects in clinical practice can be achieved by leveraging the psychosocial context that triggers the neuropsychological processes underpinning placebo effects. This approach also aligns with data suggesting that clinicians and patients may be more favorably inclined toward harnessing placebo effects through leveraging psychosocial context than through prescribing placebos (2, 3). It is this process-oriented perspective that guided our intention to develop an intervention to enable primary care practitioners to harness placebo effects by enhancing their communication of clinical empathy and realistic optimism in clinical consultations.

While there are multiple processes that occur within the psychosocial context that might trigger the neuropsychological processes underpinning placebo effects (4) we chose to focus specifically on clinicians' communication of clinical empathy and realistic optimism. This decision was guided by an analysis of key behavioral considerations according to the Behavior Change Wheel, which provides a systematic, theory-driven, "top-down," approach to specifying the behavior changes, components, and techniques likely to make interventions effective (5). The Behavior Change Wheel was developed based on a review of 19 existing frameworks and expert consultation, and was designed to be comprehensive, coherent, and to clearly link to an overarching model of behavior (5). Specifically, we considered the likely impact of the intended behavior change, the likelihood of being able to actually change each behavior, the likelihood of spill-over (to other individuals/settings) and the ease of measurement of each behavior.

We considered the likely impact of improving communication of clinical empathy and realistic optimism to be high. Clinical empathy involves the practitioner putting themselves in a patient's position, acknowledging their feelings, concerns and expectations and behaving in a way that communicates that understanding (6, 7). A compassionate, friendly consultation style using appropriate non-verbal cues can enhance the management of pain and related conditions and has been associated with greater patient satisfaction, adherence to treatment, and quality of life and health outcomes (8–10). Clinical empathy can also be beneficial to practitioners in reducing stress and burnout (11). Empathic communication has even been proposed as an essential prerequisite for enabling people to better cope with, understand, and self-manage their health (12).

Patients' positive expectancies about treatment outcomes are associated with better outcomes in laboratory and clinical studies of diverse symptoms, especially pain (13–15) and are an important part of the neuropsychological processes underpinning placebo effects (16, 17). For example, positive expectancies of analgesia alter pain perception via effects on central nervous system processing (18) and trigger a cascade of neurological changes that are very similar to those triggered by pharmaceutical analgesics (19). However, some of the methods used in placebo experiments to impart positive outcome expectancies, such as positive messages in the form of short verbal statements that an intervention is a potent painkiller,

may not be convincing for patients with pain in clinical practice (20, 21). Furthermore, for healthcare practitioners "expectancies" and "expectations" are terms associated with "expectation management" which typically involves encouraging patients to have more realistic beliefs about the outcomes of treatment; for example, a patient may expect a hip replacement within a few months of experiencing moderate osteoarthritis (OA) pain but this is unlikely to be the most appropriate initial management strategy, "expectation management" in this context involves tailored education on OA pain explaining the potential benefits of other options such as exercise, weight loss and analgesia prior to considering surgery and a realistic assessment of the risks vs. the potential benefits of surgery. Our digital intervention aims to promote effective ways of encouraging patients to have positive outcome expectancies, within the context of their clinical situation—hence our focus on *realistic* optimism, within an empathic practitioner-patient interaction (22).

The extensive literature on communication skills training suggested that we would be able to change practitioners' communication of clinical empathy and realistic optimism. As has been discussed by others (23), placebo studies can be seen to overlap with studies on doctor-patient communication and relationships, as well as topics such as patient-centered care more broadly. Our intervention is a good example of this overlap, as our fundamental aim is to enhance primary care practitioners' communication with their patients. Practitioners are generally willing to engage in communication skills training and evidence shows this training can be successful at changing the target behaviors (24–26). However, there is insufficient evidence that shows that training a practitioner impacts upon a patient's health (27). Moreover, there has been little consensus on what communication skills training should entail with most interventions being complex, expensive and time-consuming (24).

Considering the broad relevance of good communication in clinical practice, we considered there to be good potential for wider impact to other individuals and settings. We initially chose to focus on enhancing practitioners' communication of clinical empathy and realistic optimism in consultations with patients with OA. OA is a common, costly, and painful condition (28, 29). It is a top 20 cause of disability adjusted life years globally (30) and it can significantly impair quality of life (31) and function (32). Research indicates there is scope to improve practitioner communication with patients with OA (33) and improving communication can significantly improve OA pain (34). Improving communication and person-centered care is an important goal in healthcare worldwide (35). Excellent practitioner-patient communication has been shown to significantly improve patients' adherence to treatment, quality of life and satisfaction, comparable to pharmaceutical interventions (7, 25, 36). Moreover, poor consultations can have negative impacts on patients, such as non-adherence to treatment, decreased quality of life, increased costs and increased complaints and litigation (7). Practitioners typically draw on the same repertoire of communication behaviors for all consultations, thus learning new communication behaviors within the context of one condition is likely to also enhance communication in consultations for other conditions. Improving patient-practitioner communication can therefore have wide-ranging benefits for patients and health services.

The work presented in this paper aimed to plan and optimize a definitive, replicable, testable, and implementable brief digital intervention (DI) – called Empathico – to enhance primary healthcare practitioners' communication of clinical empathy and realistic optimism in consultations with patients presenting with OA. By describing our approach, we illustrate one way in which it is possible to identify, specify, and address the challenges of translating findings from placebo studies into clinical practice in a way that ensures findings can and will be implemented by healthcare practitioners for the benefit of patients. The challenges we have identified and our approaches to addressing them may be of interest to others also wanting to harness placebo effects and improve associated communication skills in clinical practice.

METHODS OVERVIEW

Ethical Approvals

Ethical approvals for all the studies in this paper were obtained from the National Research Ethics Service West Midlands-South Birmingham Research Ethics Committee (19/WM/0027 25th Jan 2019). All participants received a participant information sheet, were given the opportunity to ask questions and gave informed consent prior to taking part in the studies.

Public and Patient Involvement

Four public contributors with OA have been involved in different ways in different parts of the project including: as a full member of the project management group that met monthly to monitor progress and make key design decisions; contributing to patient-facing documents and interview topic guides; reviewing study protocols and commenting on ethics applications; providing feedback on intervention content; assisting with the analysis and interpretation of results; and contributing to article writing.

Design

We used the Person-Based Approach (PBA) (37) to develop the digital intervention. The PBA involves extensive qualitative research which can be integrated alongside theory and evidence mapping to assess the problem area, develop and iteratively refine an intervention. Using the PBA increases the likelihood that target users will engage with an intervention and minimizes resource waste from trialing a suboptimal intervention. Interventions must be used and engaged with in a meaningful way to successfully mediate behavior change. The concept and process of "effective" engagement is dynamic and multifaceted; users need to sufficiently engage with both the physical intervention and target behaviors, which can occur at a behavioral (e.g., logging in, practicing target behaviors etc.) and experiential (e.g., interest, perceived utility, relevance, practicality etc.) level and can be shaped by a range of contextual factors such as social support and organizational culture (38, 39). This meant that multiple mixed method studies were needed to adequately understand and optimize practitioners' engagement with Empathico. The PBA process has two main

phases, intervention planning and optimization. **Figure 1** depicts the studies that we conducted as part of intervention planning and optimization and shows the outputs of each phase. Some of these studies have been or are being published separately as stand-alone papers where readers will find full methodological details; the current paper explicates how the findings from these studies were used to develop our intervention. **Table 1** defines some of the technical terms associated with the PBA that we refer to throughout this paper.

Participants

In total, 39 primary healthcare practitioners and 33 patients with OA took part in our intervention development studies. Participants were recruited from primary care settings in Southern England and recruitment was supported by the Wessex NIHR Clinical Research Network. **Table 2** summarizes the characteristics of participants overall and in each of the studies reported in this paper.

PHASE 1: INTERVENTION PLANNING

Methods

Design

The aim of intervention planning is to gather the information necessary to plan the intervention content and design. To achieve this, we conducted two qualitative interview studies to better understand the contexts and situations within which practitioners would access Empathico and the potential issues that may be perceived or encountered when seeking to adopt the behaviors suggested. This contextual information was considered alongside three literature reviews to identify and guide the design of relevant theory and evidence-based intervention components. Using this mixed-method approach increases the likelihood of (a) practitioners engaging with and successfully changing target behaviors and (b) the target behaviors having an important impact on health outcomes.

Literature Reviews to Identify Relevant Existing Evidence and Theory on Our Target Behaviors and Approaches to Changing Them

A recent systematic review and meta-analysis identified 28 studies that trained healthcare practitioners in clinical empathy and/or positive messages (24). We conducted a secondary analysis of the seven empathy interventions from that review, aiming to identify effective components of existing training to enhance clinical empathy for healthcare practitioners (40). We also conducted a secondary analysis of the 22 positive messages interventions from that review, aiming to identify effective ways of imparting positive messages that could be used by healthcare practitioners to communicate realistic optimism in clinical practice (41). Finally, we conducted a systematic meta-ethnographic synthesis of 26 qualitative studies which aimed to elucidate and compare patients' and clinicians' perspectives on communication within consultations for OA (42). This was important to ensure Empathico was relevant to interactions for OA in primary care.

Qualitative Interviews to Explore Primary Healthcare Practitioners' Perspectives on Training in Clinical Empathy and Realistic Optimism

Semi-structured telephone interviews with 16 General Practitioners [GPs], two nurse practitioners and two primary care physiotherapists explored their perspectives on communication skills training, clinical empathy, and realistic optimism, within the wider socio-cultural and economic context of clinical practice, in particular OA management in primary care. Interviews were conducted by SH, JV, and KS, and were transcribed verbatim and analyzed using thematic analysis (43).

Think Aloud Interview Study to Explore Practitioners' Perspectives on KEPE-Warm

Early in the intervention planning phase, we selected the KEPE-Warm intervention as a starting point for Empathico (see Patients' Perspectives) and transferred it from the original paper-based format to a web-based format. We conducted a think-aloud study to explore practitioners' immediate reactions to potential intervention content and identify barriers, misunderstandings and opportunities for improvement. Three GPs and 4 GP trainees were opportunistically recruited to take part in audio-recorded one-to-one face-to-face interviews. After obtaining informed consent, the interviewer (RT) helped the participant to practice speaking their thoughts out loud before asking them to navigate through the online intervention while verbalizing their thoughts. Interviews were transcribed and analyzed using a "Table of Changes" approach (37). This is a rapid method of analysis that codes positive and negative comments against each section of the intervention. We categorized interviewee comments and assessed them against several criteria (important to behavior change, in line with the Guiding Principles—see Integrating Findings to Develop Guiding Principles and Guiding Principles, repeated by multiple participants, easy/uncontroversial) to determine whether and what changes should be made to the intervention.

Using Findings to Plan the Intervention

The findings from the literature reviews and qualitative work were used to draft the intervention, and to develop guiding principles, a logic model, and a behavioral analysis.

Building the Draft Intervention

We used PowerPoint initially to draft content. We first designated each behavior a page, described the behavior and provided examples of the behavior. Where appropriate, Behavior Change Techniques were added to enhance the information (e.g., adding evidence from studies, and endorsements from other practitioners or from patients). An intervention flow diagram was created to show the information architecture of the intervention (see **Figure 2** for the final version). The intervention draft was then implemented by KS in LifeGuide, an open source WYSIWYG ("what you see is what you get") web application development tool designed for creating interventions for trialing (44).

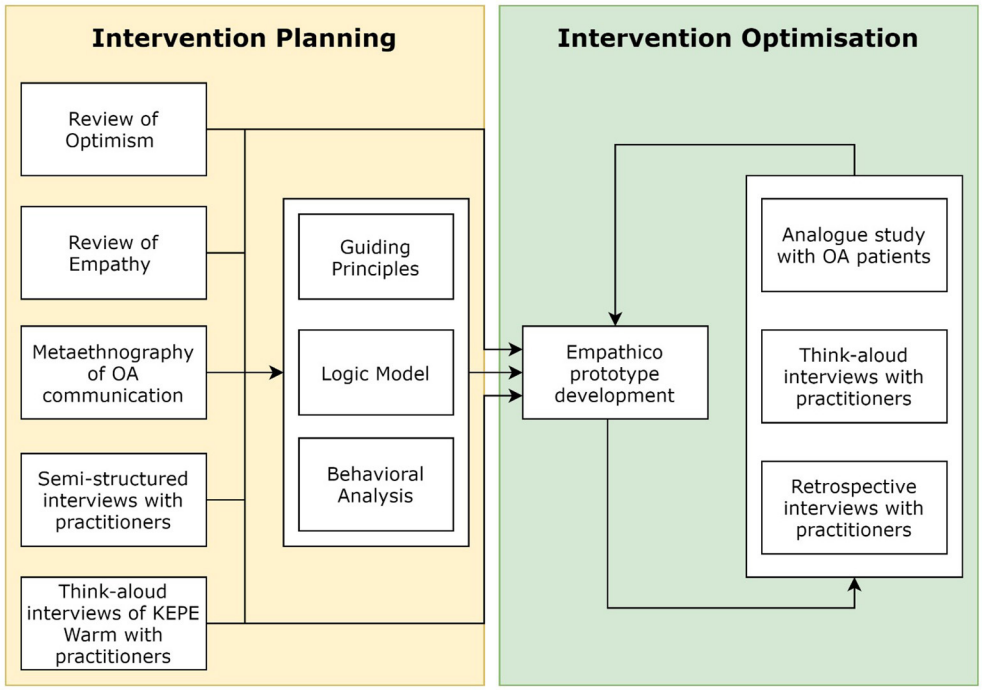

FIGURE 1 | Overview of studies and activities conducted within the intervention planning and optimization phases of Empathico's development.

TABLE 1 | Glossary of technical terms associated with the PBA.

Term	Definition
Person-Based Approach (PBA)	A systematic approach to developing digital interventions that involves extensive (primary and/or secondary) qualitative research to focus on and elucidate intervention users' engagement with the intervention. The PBA is typically integrated alongside theory and evidence mapping to assess the problem area, develop and iteratively refine an intervention (37).
Guiding Principles	Design objectives that the intervention must address to be optimally meaningful, relevant, acceptable, and practical for users. Guiding Principles also specify design features that will address those objectives.
Logic Model	A visual representation that maps how the intervention is hypothesized to effect change in the intended outcomes. Specifies variables that are thought to operate along the causal pathway between exposure to the intervention and its ultimate effects on health outcomes.
Behavioral Analysis	An analysis of the behaviors that must occur if a recipient is to engage effectively with the intervention, to initiate and maintain the intended behaviors. Includes identification of determinants (facilitators and barriers) of behavior change and techniques that are likely to support the intended behavior change.

Integrating Findings to Develop Guiding Principles

Guiding Principles are design objectives that the intervention must address to be optimally meaningful, relevant, acceptable, and practical for users specifying design features that will address those objectives. To devise our Guiding Principles, members of the multidisciplinary study team discussed study findings drawing on their experience of person-based digital interventions for health, professional experience in primary care consulting and PPI experience of OA. In this way, we identified key contextual or psychosocial issues likely to impact engagement with our intervention and specified how we would address these. We consulted and amended the Guiding Principles throughout planning and optimization as iterative feedback was received from end users.

Integrating Findings Into a Logic Model

The logic model is a visual representation that maps how the intervention is hypothesized to effect change in the intended outcomes. This helps researchers (1) to choose appropriate intervention components during planning and optimization and (2) to choose appropriate process measures during intervention evaluation. We developed the logic model based on the findings of our formal literature reviews and a broader reading of relevant literature and theory.

Using Findings in a Behavioral Analysis

The behavioral analysis (1) defines the target behaviors that the intervention seeks to change, including any necessary sub-behaviors and (2) identifies likely effective determinants of behavior change based on existing theory and evidence.

TABLE 2 | Demographic characteristics of study participants.

Phase:	Planning Phase				Optimization Phase						Overall	
Study:	**Practitioner interviews ($n = 20$)**		**KEPE-Warm think-aloud ($n = 7$)**		**Patient interviews ($n = 33$)**		**Empathico think-aloud ($n = 15$)[a]**		**Practitioner retrospective ($n = 5$)[b]**		**Total ($n = 39$ practitioners, 33 patients)**	
	n	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Role												
Physiotherapist	2	10%	0	0%	0	0%	0	0%	2	40%	3	4%
Nurse	2	10%	0	0%	0	0%	0	0%	2	40%	4	6%
GP	16	80%	3	43%	0	0%	15	100%	1	20%	28	39%
GP Trainee	0	0%	4	57%	0	0%	0	0%	0	0%	4	6%
Patient	0	0%	0	0%	33	100%	0	0%	0	0%	33	46%
Ethnicity												
White	18	90%	0	0%	33	100%	14	93%	5	100%	62	86%
Asian	1	5%	0	0%	0	0%	1	7%	0	0%	2	3%
Other	1	5%	0	0%	0	0%	0	0%	0	0%	1	1%
Unknown	0	0%	7	100%	0	0%	0	0%	0	0%	7	10%
Gender												
Male	11	55%	4	57%	15	45%	4	27%	0	0%	32	44%
Female	9	45%	3	43%	18	55%	11	73%	5	100%	40	56%
Age												
31–40	7	35%	0	0%	0	0%	4	27%	0	0%	10	14%
41–50	8	40%	0	0%	0	0%	9	60%	1	20%	12	17%
51–60	5	25%	0	0%	4	12%	2	13%	0	0%	11	15%
61–70	0	0%	0	0%	9	27%	2	13%	0	0%	9	13%
71–80	0	0%	0	0%	15	45%	2	13%	0	0%	15	21%
81+	0	0%	0	0%	5	15%	2	13%	0	0%	5	7%
Unknown	0	0%	7	100%	0	0%	0	0%	4	80%	10	14%

[a] *Includes four who also took part in the planning phase and 2 who took part in two interviews.* [b] *Includes two who also took part in the planning phase.*

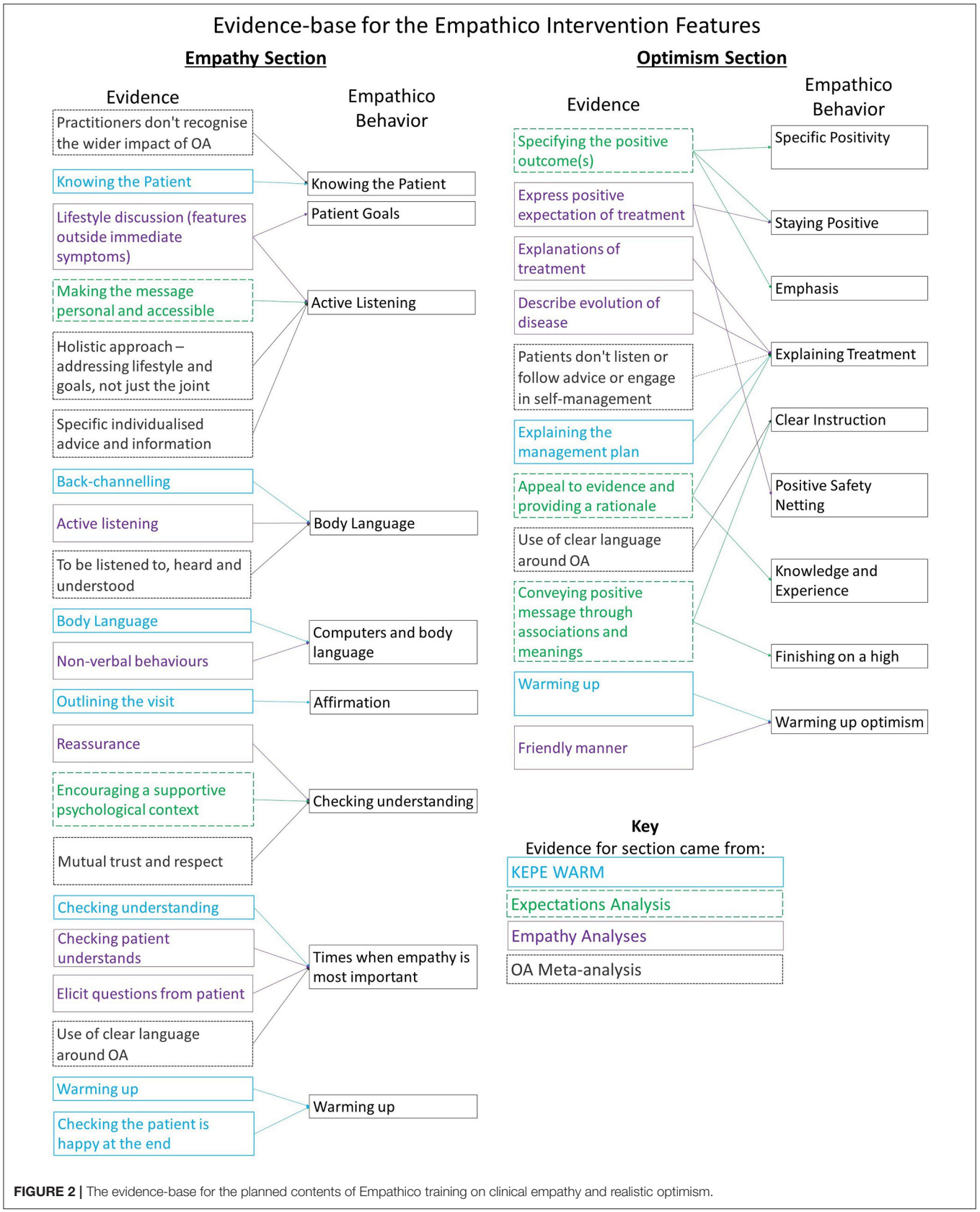

FIGURE 2 | The evidence-base for the planned contents of Empathico training on clinical empathy and realistic optimism.

Conducting a behavioral analysis supports transparent description of the intervention, encourages researchers to check the planned intervention is consistent with broader evidence and theory, and ensures there is sufficient and appropriate rationale for the inclusion of specific intervention components. We identified our target behaviors and necessary sub-behaviors with reference to our literature review work. We identified barriers and facilitators to performing these behaviors with reference to our literature reviews and qualitative interviews. We identified the likely effective determinants of these behaviors by characterizing them according to the COM-B model (5) as associated with the Capability of the practitioner to perform the Behavior, the practitioner's Opportunity to perform the Behavior, and the practitioner's Motivation to perform the Behavior. We used the Behavior Change Technique Taxonomy (a list of 93 behavior change strategies, e.g., goal setting, provision of information) (45) to specify behavioral techniques to incorporate into the intervention to support practitioners in changing their communication behaviors.

Findings

Effective Components of Existing Training to Enhance Clinical Empathy for Healthcare Practitioners

Analysis of seven empathy trials examined three questions (1) which empathy behaviors were trained, (2) how they trained practitioners, and (3) which behavior change techniques (BCTs) were used. Eighteen empathy behaviors were identified–the most common were providing explanations of treatment, providing non-specific empathic responses (e.g., expressing understanding), displaying a friendly manner and using non-verbal behaviors.

We used the training methods and BCTs identified in the seven trials in our behavioral analysis. We found that the most used training approaches were face-to-face training ($n = 5$), role-playing ($n = 3$) and videos (self or model; $n = 3$). Of these, only videos were compatible with our chosen online format for our training. The BCT used most frequently to encourage practitioners to adopt empathy behaviors was "Instruction on how to perform behavior" ($n = 5$; for example, providing a video demonstration), followed by "Credible Source" ($n = 4$; for example, delivered by a medical professional) and "Behavioral Practice" ($n = 3$; for example, role-playing). We incorporated the first two but could not implement "Behavioral practice" within the online format of our intervention.

Of all the empathy interventions that we reviewed we chose to use the evidence-based "KEPE Warm" (46) as the initial basis for our Empathico intervention, because (a) the published pilot data from a randomized controlled trial involving 16 GPs and 190 patients suggested KEPE Warm effectively modified practitioner behavior and patient satisfaction, and (b) its brevity (15 min instruction and up to 1 h reflection) appeared to make it feasible for implementation in busy primary care settings, particularly compared to other interventions which took half a day or more or were developed for hospital or other non-primary care settings. Some members of the current research team had been involved in developing KEPE-Warm (PL, HE) and were able to share additional insights into its strengths and limitations.

KEPE-Warm was originally delivered in-person by a medical student who instructed GPs in 4 key behaviors: demonstrating **K**nowledge of the patient; **E**ncouraging the patient (e.g., through active listening); being **P**hysically **E**ngaging (e.g., though the use of appropriate touch and body language); **Warm**ing-up: being cool and professional initially, becoming warmer and more empathic during the consultation and avoiding non-verbal cut-offs at the end of the consultation. After the instruction GPs were asked to review videos of their own consultations collected previously and select three things they wanted to change about their behavior. KEPE-Warm incorporated most of the empathy behaviors and training techniques from the other effective interventions we reviewed but did not include instruction on learning the patient's goals and affirming their worries and concerns. We therefore added this content to our plan for Empathico. We further built on the framework of KEPE-Warm during intervention planning by adding additional evidence-based behaviors, transforming it into a digital format, and further optimizing it through the studies described in this paper.

Effective Ways of Imparting Positive Messages to Patients

Analysis of 22 expectancy interventions found five clusters of techniques for imparting positive messages: specifying the positive outcomes; making the message personal; drawing on associations and meanings; providing a supportive psychological context; and providing a rationale. Two of these clusters ("Making the message personal and accessible" and "Encouraging a supportive psychological context") were a better fit conceptually with our planned Empathy section, and so techniques from these clusters were incorporated there instead.

We planned the contents of the Optimism section based on the three clusters not used in the Empathy section and focused on those techniques that could be achieved through practitioner communication behaviors within a consultation setting. This meant, for example, that we excluded techniques that required the immediate presence of a treatment (e.g., drawing attention to sensations, branding on packaging). This created 8 optimism elements, in addition to the "KEPE Warm" section on "Warming up" (increasing expressions of optimism toward the end of the consultation).

Patients' and Practitioners' Perspectives on Communication Within Consultations for OA

We synthesized 26 eligible qualitative studies to elucidate and compare patients' and practitioners' concerns and priorities regarding healthcare interactions for OA (47). The outcomes are summarized in **Table 3**. There were clear shortcomings in clinical communication about OA from patients' and clinicians' perspectives including a lack of perceived empathy, confirming the need for training on clinical empathy in relation to OA in particular. Patients and practitioners had discrepant understandings of OA and its management, supporting the need for better communication about the nature of the condition,

its management, and likely treatment outcomes. Our meta-ethnography provided an in-depth understanding of patients' and practitioners' perspectives, in relation to each other, which enabled us to construct an OA section of the intervention that (1) Addressed discrepancies between patient and practitioner understanding (2) Provided a practical example of how the techniques described in the intervention could be applied and (3) Provided information and resources, both for practitioners and patients.

Primary Healthcare Practitioners' Perspectives

Our analysis of primary healthcare practitioners' perspectives on training in clinical empathy and realistic optimism identified multiple barriers and facilitators to engaging them in our training (see **Table 4**). Based on these findings, our intervention needed to: (1) address practitioners' concerns that incorporating clinical empathy and realistic optimism would increase consultation duration; (2) convey the importance of optimism being realistic in a clinical context; (3) address practitioners' concerns that expressing empathy would increase their risk of burn-out; (4) explain that clinical empathy can be communicated authentically without over-investment of emotional capital. These findings fed into the guiding principles and behavioral analysis and thus informed how we presented the intervention content.

Practitioners' Perspectives on KEPE-Warm

Analysis revealed that although the practitioners agreed that the advice in KEPE-Warm was valuable, there were several barriers to engaging meaningfully with the intervention content and subsequently adopting the recommended behaviors. For a full description of issues arising please see **Supplementary Material 1**. Barriers included poor information coherence (i.e., the information architecture was poorly organized so that it was unclear or unmemorable); familiarity (i.e., practitioners already knew the information so did not feel a need to re-engage with it); misunderstandings and disagreements (i.e., participants misunderstood or disagreed with some suggestions); and low feasibility (i.e., practitioners did not think they would be able to enact the behaviors in a typical consultation). We addressed these issues in two main ways. Firstly, we highlighed them in our Guiding Principles. For example, Guiding Principle 4 (**Table 5**) emphasizes the need to ensure behaviors learned in Empathico can be implemented without increasing practitioner workload including consultation duration. Secondly, we reworked problematic aspects of KEPE Warm when drafting the Empathico prototype. For example, participants did not understand the KEPE Warm acronym or find it easy to remember, and so we removed this from Empathico.

Guiding Principles

The intervention Guiding Principles (**Table 5**) were developed primarily on the findings from the meta-ethnography and the primary qualitative research, as these studies provided the most direct evidence concerning intervention features that would facilitate engagement and should be included and those that might be a barrier to engagement and should therefore be avoided. Design objective (1) was introduced during the optimization phase of intervention development when the importance of buy-in became clearer.

Logic Model

The logic model was constructed in parallel with the other intervention planning work and is shown in **Figure 4**. On commencing our program of work, we had specified the problem we sought to address and our approach to accomplishing this—attempting to improve practitioners' communication of clinical empathy and realistic optimism (our intervention targets). Our literature reviews and behavioral analysis helped us to specify the other components of the logic model. The planned content of the intervention was summarized in the logic model ("intervention resources") and was designed to effect change in practitioner behavior through the processes of increasing practitioner knowledge about clinical empathy and realistic optimism, increasing practitioners' beliefs that communicating clinical empathy and realistic optimism would benefit their patients (outcome expectancies), increasing practitioners' beliefs that they could better communicate clinical empathy and realistic optimism (self-efficacy), and increasing practitioners' skills and intentions to enact the new behaviors. These processes together are proposed to effect change in the patient's clinical outcomes and satisfaction with the consultation through several mediators. The first mediators are increased expressions of empathy and optimism by the practitioner, through which all the other mediators act. These influence patient perceptions of empathy and optimism and decrease patient anxiety. Perceived practitioner optimism increases the patient's perception that the treatment is credible and their response expectancy from the treatment.

Behavioral Analysis

We identified the following behaviors necessary to impact patient outcomes: the practitioner would need to complete the online training, video their consultations, reflect on their consultations, plan their behavior changes and enact empathy and/or realistic optimism behaviors in consultation. We extracted the barriers and facilitators from the studies reported above, with expert discussion and PPI input. We then identified the target constructs needed to address these barriers and the intervention functions. We then used the Behavior Change Taxonomy to identify appropriate techniques and describe the required intervention components. For example, our planning studies suggested that practitioners might forget to perform the new behaviors (a barrier), which suggested a need to support automatic motivation [from the COM-B model (5)], which can be addressed through environment restructuring [from the BCW (5)] using prompts or cues in the environment [from the BCT taxonomy (45)]; this analysis led us to develop Empathico post-it notes for practitioners to put on their desk as a cue to perform the new behaviors learnt through Empathico. See **Supplementary Table 2** for a summary of the complete Behavioral Analysis.

TABLE 3 | Themes identified in the meta-ethnography.

	Patients	**Practitioners**
Priorities and Perspectives	To be listened to, heard and understood Mutual trust and respect Holistic approach—addressing lifestyle and goals, not just the painful joint Specific tailored advice and information Use of clear language when communicating about OA	Practitioners can normalize OA Uncertainty about what information OA patients need. Uncertainty about how to support self-management for OA
Concerns	OA not taken seriously by practitioners Practitioners don't recognize the wider impact of OA Practitioners are not experts in OA Unmet information needs about OA	Patients have variable and limited understanding of OA Patient expectations about OA are variable and unrealistic Patients need to be more informed about OA Patients don't listen or follow advice or engage in self-management Lack of time in the consultation

TABLE 4 | Barriers and facilitators to engaging with training, identified from practitioner interviews.

	Realistic optimism	**Clinical empathy**
Barriers to engaging with training	Practitioners talked about "patient expectations" in terms of managing expectations rather than optimizing expectations. Need to be realistic when communicating about likely clinical outcomes with patients; should not encourage overly positive expectations that would be unachievable clinically. There is limited time in primary care consultations such that it might be difficult to "fit in" any additional, optimistic, communications. Optimism may sound unempathetic or hollow. Optimism might clash with fatalistic or otherwise negative patient expectations, which can be very firmly entrenched especially for long term conditions.	Practitioners believe empathy comes naturally or with experience rather than through instruction or training. Empathy can be difficult in some circumstances, e.g., with "difficult" patients. Fear that clinical empathy (as understood by practitioners, to include a felt-emotional component) increases risk of practitioner burn-out. Practitioners have already been trained in clinical empathy and may not feel they need more training.
Facilitators to engaging with training	Practitioners find empathy easier if they know the patient's expectations for the consultation The idea of being upbeat and positive in consultations is attractive. The idea of communicating realistic optimism is novel.	Practitioners believe that empathy is fundamental to consultations. Clinical empathy comes more readily when patient shows emotion, when patient is likable, and when the practitioner has personal experience with the condition.

Intervention Plan

We called the intervention "EmpathicO—Improving care through Empathy and Optimism" (Empathico), as this title captured the core focus of our intervention using terminology that would be understood by practitioners without coming across as invalidating their existing knowledge and skills. Findings from our intervention planning work, including the guiding principles and behavioral analysis, were then integrated to formulate the overall structure and contents of Empathico. As depicted in **Figure 3**, the prototype intervention was divided into an introduction, three information sections, a reflection section, a goal-setting section and a resources section.

The introduction was designed to persuade users that the intervention is worth their time and effort by providing evidence for its efficacy and a brief persuasive introductory video from an authoritative and respected source (presented by co-author PL, a senior academic and GP). The introduction acknowledges the users' experience and provides an outline of the training and its evidence base.

The three informational sections focus on Clinical Empathy, Realistic Optimism and Applying Empathico in OA; these can be completed in any order, to give the user autonomy over their learning. Each of the information sections contain short paraphrased excerpts from patients and practitioners "Patients say…," "GPs say…" or evidence boxes "Research shows…" with links to summaries of academic papers. These serve to persuade the user of the validity of the information. Each information section also has a module certificate at the end, and the user can review any of the material again after viewing it for the first time.

The behaviors covered in the clinical empathy and realistic optimism sections are listed in **Figure 4** which also depicts the source of the evidence to support their inclusion.

The empathy section acknowledges the users' prior knowledge and provides a definition of clinical empathy. It then presents details of verbal and non-verbal behaviors to communicate empathy to patients, as well as strategies for implementing them and examples of how they can be used in the context of primary care consultations. To further illustrate the contents, videos showing three of the target behaviors are provided.

The optimism section defines optimism and explains how studies of placebo effects demonstrate the power of positive messages to improve patients' health outcomes through known neuropsychological mechanisms. It then presents strategies for

TABLE 5 | Empathico guiding principles.

Design objectives	Key (distinctive) intervention features
1. To persuade practitioners to access and engage with the intervention (buy-in)	• Acknowledge previous expertise • Highlight benefits of engaging with the intervention • Provide evidence that a brief intervention can improve the consultation, even with very experienced GPs • Provide evidence that adopting behaviors from the intervention can make the consultation easier
2. To raise awareness that being realistically optimistic about treatments can improve (OA) patient outcomes.	• Provide placebo evidence • Provide evidence on patient experience/satisfaction—modeled into evidence-based "patient stories" • Provide clear explanation of what outcomes realistic optimism can support
3. To persuade practitioners of the benefits of using the things learnt from Empathico in all contexts (including challenging ones).	• Acknowledge frustrations and times when it may be difficult to employ the target behaviors • Provide clear evidence-based rationale (e.g., patients feel valued and heard; avoid misalignment of expectations) • Demonstrate respect for clinical judgement and acknowledge that some aspects of the toolkit may not be relevant in some contexts
4. To enable practitioners to communicate empathically and with realistic optimism without negatively impacting workload.	• Intervention must be simple, short and accessible • Core target behaviors must be memorable • Provide concrete examples of words, phrases or non-verbal behaviors that can be used • Suggest time-saving strategies e.g., reminder of existing resources that can be provided to the patient (booklets, weblinks) to support self-management
5. To motivate practitioners to acknowledge the wider impact of illness on the individual patient's daily life and well-being.	• Provide concrete verbal strategies for opening the consultation and eliciting patient expectations

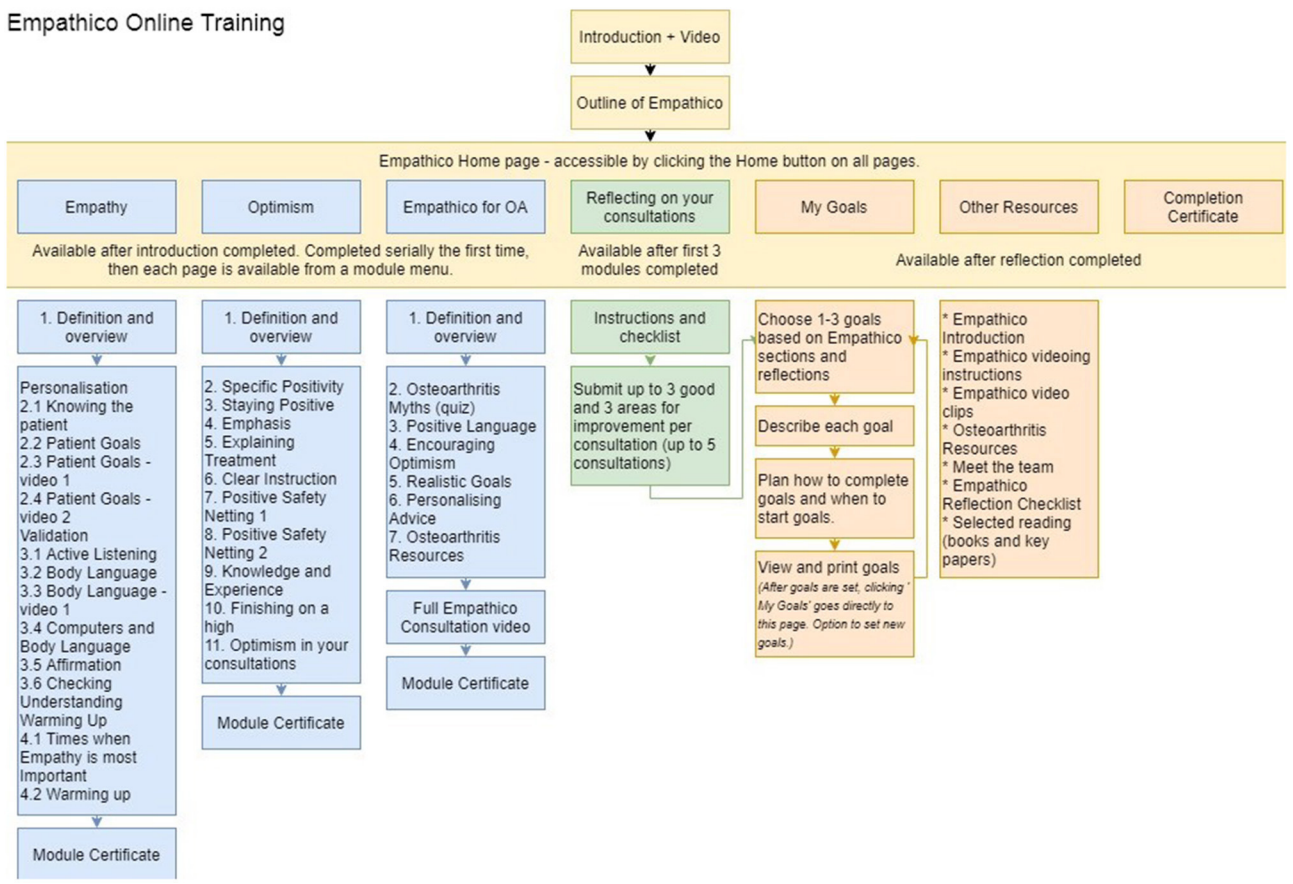

FIGURE 3 | Overview of the Empathico structure and contents.

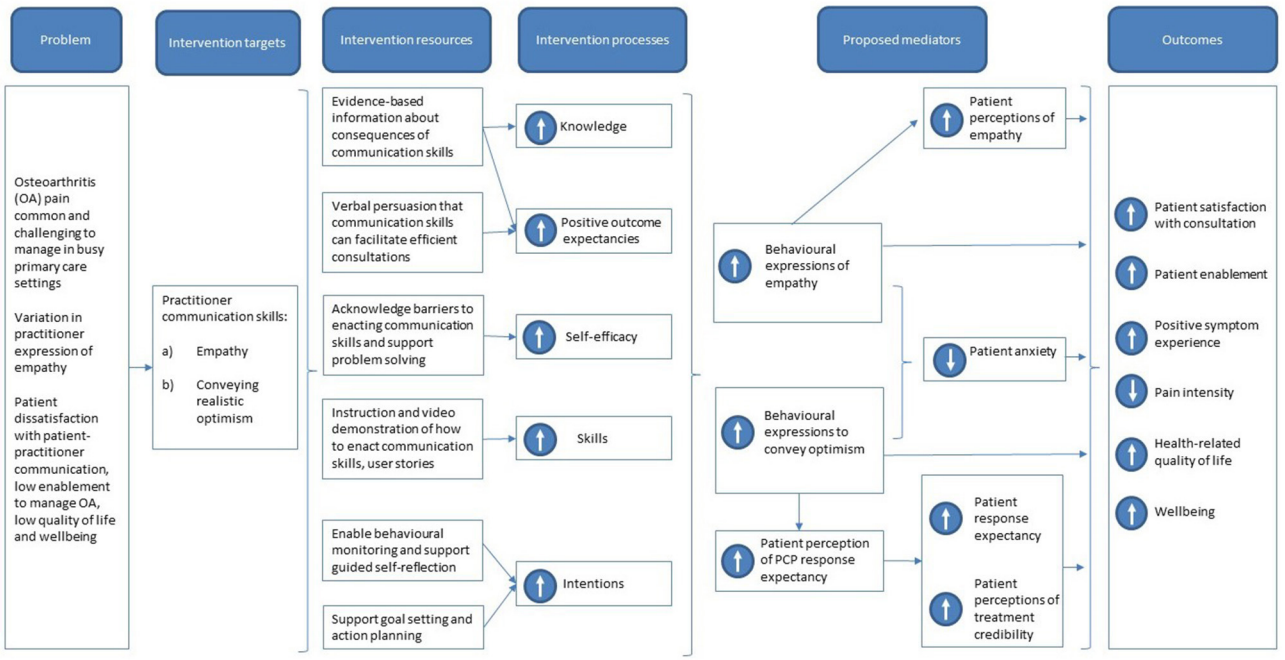

FIGURE 4 | Logic model for Empathico.

communicating realistic optimism to patients and gives examples of how this can be done within consultations. There are two short exercises for practitioners to identify ways they can make their consultations more optimistic.

The OA section contains a short quiz that addresses the misunderstandings between patient and practitioner beliefs. It presents strategies for addressing the specific challenges in communicating clinical empathy and realistic optimism in consultations about OA and provides examples of how these can be implemented. This section also includes an up-to-date treatment pathway for OA, links to OA resources for patients and practitioners and a film illustrating how Empathico behaviors can be integrated into a whole consultation about OA.

On completing the informational sections, the reflections section unlocks. This section directs users to review and reflect on video recordings of their own consultations that they made previously (instructions to record one's consultations were provided outside the main intervention). They are asked to do this with reference to a checklist of empathy and optimism behaviors covered in Empathico. The user is then prompted, for each consultation they have reviewed up to a maximum of five, to type into the intervention website between one and three things they did well and between one and three things they would like to improve on. On submitting these reflects the user is moved into the goal-setting section of the intervention.

In the goal-setting section, the user is directed to set up to three goals. Each goal should be to change one communication behavior, based upon their reflections and the Empathico material. For each goal, the user is instructed to plan when they will start the goal, i.e., when they will first attempt their planned behavior change, and to decide on a strategy to help remember the goal. "Empathico" branded sticky notes are supplied for this purpose.

On completing all sections, a completion certificate is made available for download. Further resources are made available for direct access from the main menu.

Summary of Intervention Planning

Our three literature reviews and qualitative interview study effectively identified potentially effective intervention components, barriers and facilitators to practitioners engaging with the intervention, and features of OA consultations that required consideration. The draft guiding principles focused our intervention on the most important features and the behavioral analysis identified appropriate features to support communication behavior change in the context of primary care consultations. The logic model outlined how the intervention was hypothesized to impact patient outcomes. On completing intervention planning, we had a complete draft of our intervention.

PHASE 2: INTERVENTION OPTIMIZATION

Methods

The aim of intervention optimization is to iteratively refine the intervention to ensure that it is optimally acceptable, motivating and feasible to use and adopt. To achieve this aim, we conducted

three qualitative studies with primary healthcare practitioners and patients to provide rich data on how Empathico was perceived, reacted to and used in practice. Findings were used to iteratively modify the intervention and the underlying guiding principles. Using this iterative qualitative approach ensures barriers to engagement are addressed and increases the likelihood that the intervention will support behavior change.

Interview Study to Explore Patients' Perspectives

The aim of this study was to identify barriers and areas for improvement in the behaviors that Empathico teaches, from patients' perspectives. To convey to participants the behaviors that Empathico encourages practitioners to use, we scripted and filmed a model Empathico consultation and a neutral consultation, and wrote vignettes describing optimistic and neutral consultations. We showed the films to one set of participants ($n = 15$) and gave the vignettes to another set of participants ($n = 18$), all of whom had OA and were recruited from general practices. All patients then took part in a semi-structured one-to-one interview with a researcher (JV, EL) and the interviews were audio-recorded and transcribed verbatim. Thematic analysis was used to identify patterns in the data that summarized patients' perspectives on empathy and optimism in OA consultations [published elsewhere (48)]; findings were also analyzed specifically to help us create an intervention that was acceptable to patients, using the table of changes method.

Think-Aloud Interview Study With Practitioners

This study aimed to identify barriers to adopting behaviors encouraged by the intervention, technical errors, and areas for improvement in the intervention. Participants were recruited from General Practices in the South of England. Participants were primary care practitioners (GPs, nurses or physiotherapists) who consulted with OA patients. Participants could choose to take part at the participant's workplace, or at the University of Southampton. After giving informed consent, participants were presented with the intervention and asked to speak aloud their thoughts as they looked at it. The interviewers (JV, KS) prompted participants with questions (e.g., what are you thinking now?) if they stopped speaking and asked additional questions at the end to further explore their experience. The think aloud interview topic guide is in **Supplementary Material 5**.

Retrospective Interview Study With Practitioners

The aim of this study was to identify barriers, errors and areas for improvement in the intervention when used independently. Five participants were recruited from General Practices in the South of England. Participants had to be primary care practitioners (GPs, nurses or physiotherapists) and see OA patients to be eligible for the study. Participants were given a link to the study with a username and password. After giving informed consent, participants could look at Empathico whenever they liked over 2 weeks. Participants were not required to video record consultations prior to taking part. After 2 weeks, a telephone interview was arranged. The interviewer (JV) asked participants about their thoughts and experiences of Empathico.

Data Analysis Methods

Interviews in all three optimization studies were audio-recorded, transcribed and analyzed using the "Table of Changes" approach described above (section **Think Aloud Interview Study to Explore Practitioners' Perspectives on KEPE-Warm**) (37). In this phase, we made changes every 2–5 interviews, so that upon analyzing the next set of interviews, we could assess whether there was evidence for the change being effective. The table of changes method can also reveal key barriers, which allowed us to modify the intervention Guiding Principles. Interviews were conducted iteratively until no important issues were identified and the feedback was predominantly positive. A team of researchers contributed to the analysis, bringing perspectives from different disciplinary backgrounds including general practice (MR, EL, HE), primary care research (JV, SH), human computer interaction and digital interventions (KS, MS), health psychology (LM, RT, FB), and philosophy of science and epidemiology (JH).

Findings

Patients' Perspectives

Patients were much more positive about the Empathico consultation than they were about the neutral consultation, regardless of whether they saw the filmed consultations or read the vignettes. Our table of changes analysis of patient interviews nevertheless highlighted some problems with the Empathico consultation, mainly in the form of omissions, and these are summarized in **Table 6**. Patients wanted the practitioner to have prior knowledge of themselves and their condition, they wanted their expectations to be acknowledged, and they wanted a clear and specific explanation of treatment and plan of action, and did not feel that the Empathico consultation fully met these needs. We therefore revised the Empathico intervention to ensure these points were incorporated.

Practitioners' Perspectives on Intervention Components

Participants were mostly very positive about Empathico but multiple problems were identified and addressed particularly with earlier versions. **Supplementary Table 3** presents examples of these problems, how they were raised by participants and how we addressed them. Proposed solutions took 1–2 iterations to optimize until the feedback on these sections was mostly positive and no further essential changes were identified through the table of changes analysis.

Problems were identified with the intervention in general (e.g., poor presentation on some cluttered pages, some omissions including strategies for dealing with difficult situations), and with the osteoarthritis section (e.g., instructions for the "Myths" quiz were unclear and an 8-min illustrative video was felt to be too long). Of particular interest were more conceptual problems identified with the empathy and optimism sections, illustrative examples of which are shown in **Table 7** (for more, see **Supplementary Table 3**). Many of these problems highlighted the need to adapt our evidence-based recommendations about

TABLE 6 | Problems with the Empathico consultation from patients' perspectives.

Problem	Sample quote	Solution
Practitioner did not explore the patient's expectations about treatment.	"I think the only person who knows your body is yourself - although I suppose, in my case, I could be completely wrong - but you think you do, and the assumption was that no surgical intervention was deemed necessary at this stage however correct that might be and it's those sort of possibilities that I would have like to know more about." (male, 61–70 yrs, knee OA)	Acknowledge patient's goal and expectations about treatment.
Lack of explanation for recommended treatment.	"She didn't go into […] the construction of the knee, and how if you can strengthen the muscles that are holding the knee in place. So she didn't fully explain. She just said these exercises will help the joints and muscles. I think she could have been far more explicit as to how important it is to strengthen the muscles holding the knee in place." (female, 71–80 yrs, hip and knee OA)	Where appropriate, explain underlying pathology and justification for treatment.
Balancing motivation with realistic outcomes.	"I suppose on reflection she perhaps could have pressed a bit more to try to motivate him a bit more, but then to try and motivate him you're probably going to give him a false expectation. If she makes too much of it, which motivates him, and it doesn't happen, that's worse. So it's six of one, and half a dozen of the other really." (male, 71–80 yrs, hip OA)	Ensure optimism is conveyed realistically and appropriately.
Practitioner didn't seem to know the patient's history	"The patient had to start at the beginning again and go through, which was not a good thing." (female, 71–80 yrs, hip and knee OA)	Recommendation to read patient notes prior to consultation.
No plan to review progress was made.	"[The doctor could have said] 'Let's do this 3 months, and let's come back and see me, and then we'll move forward;' rather than leaving it open-ended [...] That would give him much more confidence that he's been managed." (male, 51–60 yrs, hip OA)	Optimism about self-management, clear explanation (OA does not necessarily get worse), positive safety netting.

communication behaviors to make them more appropriate for implementation by primary healthcare practitioners.

Some recommendations conflicted with practitioners' beliefs or practice, such as the suggestion within the empathy section to act with "authority and professionalism" at the beginning of consultations; in this case, we removed the suggestion to act with "authority and professionalism" and instead emphasized the need to increase one's communication of empathy as the consultation progresses. The optimism section included material about "positive safety-netting" a phrase we used to refer to framing conversations about safety-netting positively (e.g., "If you feel that it isn't right for you…" promotes autonomy to decide if they like treatment) instead of negatively (e.g., "If that doesn't work…" suggests treatment might not be effective). This was a novel suggestion for practitioners and there was some concern about how this might risk patients not taking seriously any symptom exacerbations; we therefore added some additional guidance on positive safety-netting.

Some recommendations were felt to be overly simplistic to be of use in primary healthcare consultations. For example, eliciting and later referring back to patients' goals (within the empathy section) was felt to be challenging when patients have vague and/or unachievable goals; we addressed this by adding content on how to guide patients to formulate realistic goals. In the optimism section we had suggested using terms such as "strong" or "potent" to describe a prescribed drug (based on our review of positive message interventions). Practitioners were concerned that this might not always be an accurate description of prescribed medication and might be off-putting for some patients; we amended our guidance to remove the term "potent" and presented "strong" as an example of one way to communicate realistic optimism that could be used where appropriate.

Practitioners' Perspectives on the Whole Intervention

Feedback from the retrospective interviews was mostly positive, which was to be expected given the changes we had already made to address issues uncovered by the think aloud interviews. Very few problems with the empathy or optimism sections were identified at this stage. Most problems related to easily fixed technical problems or omissions, some of which came to light because—in contrast to the think aloud studies–practitioners in this study had been asked to work through the entire intervention in their own time. For example, participants wanted to see their progress through the intervention and so progress "breadcrumbs" were added to pages. The retrospective interviews also identified problems with the osteoarthritis and reflections and goal-setting sections. For example, the reflections that practitioners typed into the website could be lost if not saved, and so a "save" button was added to this page. Some problems were not acted on because they were impossible to address or were considered highly unlikely to act as a barrier to engagement with the intervention. **Table 8** presents illustrative examples of problems and solutions; **Supplementary Table 4** presents more examples.

Summary of Intervention Optimization

In this phase we began with a plan of intervention content and components for behavior change developed using the PBA. We prototyped the intervention and iteratively improved it using think-aloud interviews with end users. We developed

TABLE 7 | Illustrative examples of problems and solutions identified through "table of changes" analysis of think-aloud interviews on intervention components.

Intervention section	Problem	Sample quote	Solution
Empathy	Practitioners didn't like being told to act with "authority and professionalism."	"'I'm not sure whether, how people would feel about kind of changing to act with more authority and professionalism at the beginning of a consultation. I think most GPs would kind of, expect to be acting professionally all the way through the consultation, not just at the beginning, all the way through. And acting with authority… I'm not really sure what that means." (male GP, 31–40 yrs)	Remove this phrasing, change to emphasize increasing empathy throughout the consultation.
Empathy	Belief that "knowing the patient" takes time that is not always available.	"trying to make the time to add that in is actually really challenging and it's how we would all love to be working as GP's because it makes, it does help the consultation it everything more rewarding it does feel a much more natural way to communicate but I think time is the big barrier to that." (female GP, 41–50 yrs)	Reassure them that it doesn't have to add time, and provide examples.
Empathy	Patient goals are not always appropriate.	"Patient's goals can be wide and nebulous and difficult to come back to." (female GP, 41–50 yrs)	Provide a strategy to help practitioners help patients formulate realistic goals.
Empathy	Practitioners uncertain about avoiding use of non-verbal cut-offs to close a consultation.	"that might sometimes include standing up and, you know, walking the patient, in a nice way, toward the door. Sometimes. So yeah, I think it might be a bit over… over-simplifying the situation" (male GP, 31–40 yrs)	Remove directions to avoid "non-verbal cut-offs" and provide strategy for finishing the consultation empathically.
Optimism	Disagreement with advice to be "concrete" about treatment outcomes.	"'Research says – Being concrete and specific about treatment options……' I am not usually very concrete about this. You can't say it's going to get better if you leave it alone – it might not! You can say it probably will get better and lets see how it goes but you can always come back – that sort of thing." (female GP, 41–50 yrs)	Reword advice to talk about being specific when possible about expected outcomes.
Optimism	Practitioners uncertain about using the term "strong" or "potent" to describe a drug.	"Under the qualities of treatment I probably would refrain from using this as a strong drug just because in my experience, if you tell patients that something's very strong, then they worry about side effects, and they worry about it's too strong for them! Especially with the elderly patients, they want just something gentle that works" (male GP, 31–40 yrs)	Advise practitioners to use the terms when they are appropriate.
Optimism	Practitioners cautious about suggested phrases for "positive safety netting."	"sometimes you have to say if it gets worse (eg acute chest infection). Need to be careful that patients take getting worse seriously." (female GP, 31–40 yrs)	Make sure examples are appropriate for serious conditions, and that they are examples that don't fit all situations.
Optimism	Practitioners felt optimism is not always possible in challenging situations.	"the patient who is very negating of everything that you're suggesting, it might be something like, 'I know this is difficult but I'm hoping you're gonna-, I think we can come up with a plan, I hope that you're feeling positive about it too'. Because then they can say 'well not really,' and then you're back to square one." (female GP, 51–60 yrs)	Acknowledge that it is not possible in all situations.

model Empathico consultation videos and written vignettes and obtained feedback from patients. We tested the intervention by giving it to participants and letting them use it alone, making final improvements based on feedback. This iterative approach allowed us to make significant improvements to the Empathico intervention to maximize its potential efficacy and acceptability to practitioners.

DISCUSSION

This paper described the planning and development of the Empathico Intervention using a person-, evidence- and theory-based approach. By involving target users at all stages of development, and using a systematic approach to refining it, we have maximized the potential of the intervention to be effective. This focus on user engagement is particularly valuable when trying to implement evidence from the placebo literature into clinical practice, an endeavor that is often met with valid ethical concerns as well as objections founded on misunderstandings and myths about placebo effects (49, 50).

Other digital interventions for patients with OA typically aim to support rehabilitation and improve patient self-management [e.g., see interventions reviewed in (51)]. Empathico is different in that it targets those practitioners who treat patients with OA in primary care settings, and aims to enhance their communication skills for use in practitioner-patient conversations about

TABLE 8 | Illustrative examples of problems and solutions identified through "table of changes" analysis of interviews with practitioners who had tried Empathico.

Intervention section	Problem	Sample quote	Solution
General	Practitioners struggled to print/save the certificate.	"Big problems printing out the certificate. Had to copy and paste to a separate word document. Would normally just download and attach electronically to appraisal." (female GP, 41–50 yrs)	Provide instructions on how to save/print the certificate.
General	Practitioners wanted more detail on how to handle challenging situations.	"Yes. So sometimes the more your patients might be a bit challenged, you find it challenging with communication. So if you feel that there's a barrier to that, whether that's English isn't a first language, or culturally, or just you don't feel that they've necessarily got a level of comprehension, I find that difficult." (female physiotherapist, 13 years' experience)	Added challenging situations page.
Osteoarthritis	Not enough diversity in videos.	"Could have had another example. Just used the same bloke all the way through. Might add variety of someone with OA in a different joint (shoulder/hand etc). Have a couple of different scenarios might enable people to reflect further." (female GP, 41–50 yrs)	No other videos available—no change. Review in future if resource becomes available to create additional clips.
Reflections and Goal setting	Practitioners think the reflection and goal setting take too much time.	"I think that's helpful, but realistically we're time-poor, so we might not necessarily do that." (female nurse practitioner, 19 years' experience)	Nothing—this is already brief. Will investigate further in the feasibility trial.

many different forms of treatment (including, for example, pain medications, exercise, and even patient-facing digital interventions to support self-management).

There are some limitations to our work. Due to the time necessary to analyze rich qualitative data, the number of participants involved in the development was not high enough to ensure minority representation. Only 3 of our 72 participants were from non-White ethnic backgrounds (**Table 2**), meaning we may have missed opportunities to learn about the specific challenges and opportunities for communicating with people of different ethnicities. The practitioners involved in our study were self-selecting in that they signed up to take part in a study on empathy training, and in interview all agreed on its value. The beliefs and opinions of practitioners who do not value empathy (who arguably would benefit from the training most) were not represented. We also interviewed mostly senior GPs—junior GPs, nurses and physiotherapists were under-represented, and their training needs might be different.

Empathico would benefit from two final development activities: integrating advice for communicating clinical empathy and realistic optimism with patients from diverse, Black, Asian, and other non-White ethnic minority backgrounds; and integrating advice for communicating clinical empathy and realistic optimism when consulting with patients over the telephone or on video calls. The next step is to test Empathico in a feasibility trial to determine how best to assess its efficacy (including which outcomes to measure using which instruments), and then to move on to a fully powered RCT to assess whether using Empathico to train practitioners in Clinical Empathy and Realistic Optimism can have an impact on patient satisfaction, health and well-being.

DATA AVAILABILITY STATEMENT

The datasets generated for this article are not readily available due to ethical considerations; making the data available would breach confidentiality of participants in our qualitative studies. Requests to access the datasets should be directed to Felicity L. Bishop, F.L.Bishop@southampton.ac.uk.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by National Research Ethics Service West Midlands-South Birmingham Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LM, JB, JH, CM, PL, GL, HE, and FB: conceptualization. KS, JV, LM, SH, JB, JH, PL, MR, EL, GL, HD-M, HE, and FB: methodology. KS, SH, and MS: software. KS, JV, LM, SH, MS, RT, JH, MR, EL, PM, HE, and FB: formal analysis. KS, JV, SH, MS, RT, EL, HE, and FB: investigation. KS and FB: writing – original draft. JV, LM, SH, MS, RT, JB, JH, CM, PL, MR, EL, PM, GL, HD-M, and HE: writing – review and editing. KS: visualization. LM, JH, CM, PL, GL, HE, and FB: supervision. HE and FB: project administration. LM, JH, CM, PL, GL, HE, and FB: funding acquisition. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpain.2021.721222/full#supplementary-material

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OPINION
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Can the Open Label Placebo Rationale Be Optimized?

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INTRODUCTION—THE ROLE OF THE RATIONALE IN OPTIMIZING PLACEBO TREATMENT

The success of OLP treatment for chronic pain in clinical trials (1) holds promise for the eventual application of placebo in routine pain management. In preparation for the possibility of a clinical OLP roll-out, it is prudent to optimize OLPs for obtaining the maximum treatment effect. The first-author has previously identified three components (algorithm, rationale, placebo pill) of effective and safe placebo treatment design (2). As shown in **Table S1**, the algorithm refers to the identification of instances where an OLP may be beneficial and feasible. An algorithm could be implemented by posing a series of questions to the physician or healthcare provider, which would lead to a decision tree that determines if OLPs are suitable. The placebo pill refers to the physical features of the placebo. The focus of this article is the Rationale, which is the explanation given to the patient when administering an OLP.

STATE OF THE ART: PLACEBO RATIONALE PRACTICE IN RESEARCH

The OLP rationale refers to a verbal message wherein patients are told they are receiving a placebo and provided with an explanation regarding why the placebo may work. Almost every study that tested the effect of OLP included a rationale [though see (3)]. As such, patients do not just take a placebo, they are also told why taking a placebo might be efficacious. Both of these elements—the pill and the rationale—are important treatment components (4). In fact, in the only study to date where the presence of a rationale was manipulated, Locher et al. (5) found that OLPs with a rationale reduced experimentally-induced pain more than OLPs without a rationale. However, while this study suggests that including a rationale is important to maximizing the placebo effect, no prior research has examined OLP effects according to different types of rationales. In order to maximize the effect of OLPs, it is important to maximize the impact of the rationale.

In the initial Kaptchuk et al. (6) study, the OLP rationale entailed a 15-min discussion that centered on four points: "(1) the placebo effect is powerful, (2) the body can automatically respond to taking placebo pills like Pavlov's dogs who salivated when they heard a bell, (3) a positive attitude helps but is not necessary, and (4) taking the pills faithfully is critical." (p. 2). As shown in **Table 1**, this 4-point discussion has become standard across OLP trials in clinical populations. With few exceptions (7, 8), all studies that examined the efficacy of OLPs outside a dose-extension model have used a rationale almost identical to or a close variation of that used in the Kaptchuk et al. study (9–17). Regarding the exceptions, patients in Kleine-Borgmann et al. (7) simply watched a video describing OLPs and those in Nitzan et al. (8) were told about past efficacy of placebos in studies and that they would likely help alleviate some depressive symptoms.

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TABLE 1 | Overview of placebo rationales in OLP studies with clinical samples.

Reference	*N*	Condition	Standard rationale	Rationale components
Carvalho et al. (9)	83	Chronic low back pain	Yes+	Powerful, conditioning, positive attitude, compliance, video (discussing past efficacy, individual success story)
Hoenemeyer et al. (10)	74	Cancer-related fatigue	Yes	Powerful, conditioning, positive attitude, compliance
Ikemoto et al. (11)	48	Chronic low back pain	Yes+	Powerful, conditioning, positive attitude, compliance, past efficacy
Kaptchuk et al. (6)	80	Irritable bowel syndrome	Yes	Powerful, conditioning, positive attitude, compliance
Kelley et al. (12)	20	Major depressive disorder	Yes	Past efficacy, conditioning, positive attitude, compliance
Kleine-Borgmann et al. (7)	122	Chronic low back pain (independent replication)	No	Video (discussing past efficacy, individual success story)
Kube et al. (13)	54	Allergic rhinitis	Yes+	Powerful, conditioning, positive attitude, compliance, create expectation
Nitzan et al. (8)	38	Unipolar depression	No	Past efficacy, create expectation
Pan et al. (14)	100	Menopausal hot flushes	Yes	Powerful, conditioning, positive attitude, compliance
Schaefer et al. (15)	25	Allergic rhinitis	Yes	Powerful, conditioning, positive attitude, compliance
Schaefer et al. (18)	46	Allergic rhinitis	Yes	Powerful, conditioning, positive attitude, compliance
Zhou et al. (16)	40	Cancer-related fatigue	Yes+	Powerful, conditioning, positive attitude, compliance, past efficacy, create expectation

Powerful, conditioning, positive attitude, and compliance refer, respectively, to parts 1, 2, 3, and 4 of the standard rationale (see text). "Past efficacy" means there is reference to previous studies that have demonstrated OLP efficacy. "Create expectation" indicates participants were told something similar to "this is likely to help with symptoms of [insert their condition]." Yes+ refers to studies that use Standard rationale with additional component(s). This table excludes studies where the open label placebo is conditioned [e.g., (19–22)], and one study that included an OLP arm but was not designed to study OLP effects (3).

THE POSSIBLE MODERATING POTENTIAL OF THE RATIONALE

While the Algorithm component of OLP treatment design helps identify which cases or conditions might safely benefit from OLPs, the OLP Rationale and Placebo Pill enable, and possibly modify, the placebo response. The possibility that the OLP response may not just be enabled but moderated by the rationale is broadly consistent with research on deceptive placebos. According to Benedetti (23), "there is not one single placebo effect, but many" (p. 329). Indeed, the placebo effect depends on a variety of factors. For instance, consistent with **Table S1** Row 3, placebos that are ostensibly branded are more effective at treating migraine than ostensibly generic placebos (24). Price also influences the placebo effect. In one study, placebos that supposedly cost $2.50 per pill relieved pain in 85% of participants, while placebos allegedly costing $0.10 only relieved pain in 61% of the sample (25). Of particular relevance to the discussion of a rationale, verbal instructions modify the placebo effect. Thomas (17) gave placebos to patients with a minor illness; 2 weeks later, those who were told that they would feel better in a few days improved more than patients who were not given positive expectations. In another study, a negative skin reaction was induced with a histamine skin prick (26). Afterwards, a placebo cream was applied, and those who were told the cream would help had a lower physiological reaction to the allergen than those who were told it would exacerbate the itching. In summary, the effectiveness of deceptive placebos is dependent on situational factors such as verbal instructions. OLP effectiveness may also be moderated by these variables, although no one has yet explicitly examined the role of competing instructions (i.e., rationales).

AN APPROACH TO RATIONALE OPTIMIZATION AND INDIVIDUALIZATION

The design of OLP studies thus far is based on rational persuasion conveying a stance that could be described as clinical and authoritative. However, patients' individual dispositions and receptiveness regarding information framing may differ. Some patients may be more receptive to intuitive guidance (i.e., mindfulness) rather than rational persuasion. Patients with an oppositional stance to scientific authority may benefit from being encouraged to suspend disbelief and find out for themselves by observing what happens during their OLP treatment. Therefore, to optimize OLP treatment, we propose two alternative types of rationales: Mindfulness and Suspension of Disbelief. Components of these rationales are provided in **Table S2**. The potential efficacy of the mindfulness rationale is supported by a meta-analysis of 38 RCTs, where patients assigned to a mindfulness condition reported less pain (SMD = 0.32) compared to those in a control group (typically Treatment as Usual) (27). The potential efficacy of the suspension of disbelief rationale is supported by a pilot study (28) which indicated that while patients are skeptical about the effectiveness of OLPs, they would be willing to suspend disbelief (e.g., "If you say 'inert pills help you if you take 'em three times a day.. you'd be like 'wow, that's weird, but I'll try it… I guess he knows what he's talking about. Can't hurt me."). Thus, the two new rationales

we propose are grounded in the results of earlier research. One consideration of the new aforementioned rationale conditions is that they incorporate guided imagery, which is an effective treatment on its own (29) that may fall under the broad umbrella of mindfulness. The imagery we utilize is OLP-specific; another potential approach would be to dismantle the effect of guided imagery from the proposed rationales. It is likely that each of these components are additive.

CONCLUSIONS AND RECOMMENDATIONS

No study so far has examined the efficacy of competing rationales, even though the rationale is an important intervention component and differences in preferences for placebo information have been noted (30). While the rationale developed by Kaptchuk et al., and used widely by others, has been effectively applied, it is possible that patients may respond more positively to other types of rationales. The natural next step in this line of research is to examine the impact of OLP across multiple rationales. Given the large body of work showing that OLPs are effective for chronic low back pain (7, 9, 11) or other chronic pain conditions (3, 6), we suggest this is the appropriate clinical condition to examine rationale efficacy. We propose two additional rationales based on the concepts of mindfulness and suspension of disbelief to evaluate and optimize OLP treatment for chronic pain. Future studies with a clinical population could compare these rationales against each other, as well as to a condition where participants receive an OLP but without a rationale [as done by Locher et al. (5) with healthy volunteers]. This latter design would enable us to distill the effect of the Placebo Pill from the Rationale component [also see (4)]. We also suggest that patient's receptiveness to different rationales may vary with personality traits and patient preferences, marking the beginning of personalized OLP treatment.

AUTHOR CONTRIBUTIONS

UH and MB conceived the paper, wrote initial draft, and conceived of the mindfulness and suspension of disbelief rationales. MR created table and edited paper. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Lack of Effects of the Presence of a Dog on Pain Perception in Healthy Participants—A Randomized Controlled Trial

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Animal-assisted interventions (AAIs) have been shown to be effective in the treatment of pain. Studies suggest that relationships with animals can have comparable qualities to relationships with humans and that this enables animals to provide social support. Further, the presence of an animal can strengthen the therapeutic alliance between patients and treatment providers. This suggests that the analgesic effects of AAI might be mediated by social support from an animal or by strengthening the alliance between the patient and the treatment provider. To test these assumptions, we examined the effects of the presence of a dog on experimentally induced pain in a pain assessment and a pain therapy context. Hundred thirty-two healthy participants were randomly assigned to the conditions "pain," "pain + dog," "pain + placebo," or "pain + placebo + dog." We collected baseline and posttreatment measurements of heat-pain tolerance and the heat-pain threshold and of the corresponding subjective ratings of heat-pain intensity and unpleasantness as well as of participants' perceptions of the study investigator. The primary outcome was heat-pain tolerance. The presence of the dog did not influence the primary outcome ("pain" vs. "pain + dog": difference = 0.04, CI = −0.66 to 0.74, $p = 0.905$; "pain + placebo" vs. "pain + placebo + dog": difference = 0.43, CI = −0.02 to 0.88, $p = 0.059$). Participants did also not perceive the study investigator to be more trustworthy in the presence of the dog ("pain" vs. "pain + dog": difference = 0.10, CI = −0.67 to 0.87, $p = 0.796$; "pain + placebo" vs. "pain + placebo + dog": difference = 0.11, CI = −0.43 to 0.64, $p = 0.695$). The results indicate that the mere presence of a dog does not contribute to pain reduction and that the analgesic effects of AAI that previous studies have found is not replicated in our study as AAI did not increase perceived social support and had no effect on the alliance between the participant and the treatment provider. We assume that the animal most likely needs to be an integrated and plausible part of the treatment rationale so that participants are able to form a treatment-response expectation toward AAI.

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INTRODUCTION

Animal-assisted interventions (AAIs) are "goal-oriented and structured interventions that intentionally incorporate animals in health, education and human service for the purpose of therapeutic gains in humans" (1). AAIs have a wide range of clinically relevant effects, such as lowering symptoms in patients with depressive and anxiety disorders (2–7), improving neurohormone levels in adult patients diagnosed with advanced heart failure (8), and reducing cortisol levels in adult healthcare professionals as well as in children with insecure attachment (9, 10). Moreover, a recent meta-analysis has suggested that AAI can be an effective therapy for relieving pain in patients across all age groups (7). For example, children exhibited a significant reduction in pain perception and experience after an AAI compared to a control intervention without an animal present both in an acute pediatric setting (11) and after surgery (12). Similar effects have been reported in AAI studies on pain syndromes in adults. Patients who had 15-min visits with a therapy dog before receiving standard postoperative treatment had significantly lower perceptions of pain after total joint arthroplasty than patients who only received standard postoperative treatment (13). Adult patients with chronic pain perceived significantly less pain when they spent their waiting time with a therapy dog compared to patients in a waiting room without a dog present (14). Further, patients with fibromyalgia showed a greater decrease in pain when they were in a group that received a 20-min session with a therapy dog and its handler compared to a group that received the session with only the handler (15). However, not all studies found that AAI leads to pain reduction (16, 17). Further, previous studies differed with regard to the study design and also showed methodological weakness, such as lack of no randomization or insufficient control groups (7). Thus, the evidence base for the effects of AAI on pain is still weak, and high-quality studies are warranted to investigate the effects and the mechanisms by which AAI leads to pain reduction (7).

Although these results are promising, the mechanisms by which AAI leads to pain relief are yet to be fully understood, since it is still unclear how animals contribute to pain relief (7). Research on social support can suggest possible explanations. The mere presence of another person has been shown to lead to a reduction of perceived pain (18). This effect on pain can be found in both active (19, 20) and passive forms of social support (18), and it does not seem to depend on the degree of the relationship, that is, on whether the person is a partner, friend, or stranger (18, 21). Previous research has highlighted that relationships with animals can have comparable qualities to relationship with humans (22, 23) and that pets can provide social support for their owners (24). Furthermore, the presence of an animal can also positively influence how we perceive others and strengthen the therapeutic alliance between the patient and the treatment provider (25–27). This is of relevance since the therapeutic alliance is an important determinant of treatment outcomes in medical interventions (28), psychotherapy (29), and placebo interventions (30, 31).

The analgesic effects of AAI could thus be mediated by providing direct social support for the patient or by strengthening the alliance between the patient and the treatment provider. To test these assumptions, we examined the effects of AAI with a dog on experimentally induced pain in healthy participants, mimicking two different clinical settings: pain assessment and pain therapy. We hypothesized that participants would show increased heat-pain tolerance in both settings when a dog is present based on the assumption that the mere presence of a dog can act as direct social support. We also hypothesized that participants would show increased heat-pain threshold and decreased subjective ratings of pain intensity and unpleasantness of heat-pain tolerance and threshold in both settings where a dog is present. Moreover, we also hypothesized that the presence of a dog would strengthen the alliance between participant and the treatment provider. To examine possible effects of the presence of an animal on the therapeutic alliance, we assessed participants' perception of the study investigator in all pain assessments.

METHODS

Design

We conducted a randomized controlled trial with four experimental conditions and healthy participants. In the pain assessment context, experimental pain was induced and assessed with a standardized experimental heat-pain paradigm, simulating a setting in which persons experience pain without treatment. In the pain therapy context, experimental pain was induced, assessed with a standardized experimental heat-pain paradigm, and, in addition, we employed an established expectation-induced placebo paradigm. In this context, we introduced placebo as therapeutic intervention for the experimentally induced pain to simulate a setting in which persons experience pain and get a treatment. A positive verbal suggestion was administered to induce expectation in relation to the placebo intervention. No positive verbal suggestion was administered in relation to the dog's presence to suppress possible expectation effects. Participants were randomly assigned to pain assessment ("pain"), pain assessment in the presence of a dog ("pain + dog"), pain assessment and a placebo intervention only ("pain + placebo"), or pain assessment and a placebo intervention in the presence of a dog ("pain + placebo + dog").

The study protocol ensured the dog's welfare at any time. We conducted all dog sessions according to the guidelines of

the International Association for Human-Animal Interaction Organizations (1).

The study was conducted between April 2019 and July 2019. The study protocols and the informed consent of the study were approved by the Ethics Committee of the Faculty of Psychology at the University of Basel, Switzerland.

Participants

Through online advertisements, 284 participants were recruited for a study on pain perception at the University of Basel. The online advertisement did not contain any information about the possible presence of a dog to prevent attracting participants with an affinity for dogs. The online advertisement contained a link to a short questionnaire. Participants interested in participating had to complete this questionnaire first to check for eligibility and inclusion and exclusion criteria. Participants had to be (a) right-handed (32) and (b) 18 years or older to be included in the study. Exclusion criteria were (a) any acute or chronic disease as well as skin pathologies, (b) current medications or current psychological or psychiatric treatment, (c) pregnancy, (d) nursing, (e) current or regular drug consumption, (f) insufficient German language skills, (g) a fear of dogs, (h) dog-hair allergies, and (i) previous participation in studies using a heat-pain paradigm.

Of the total 284 screened participants, 201 met the inclusion criteria. All eligible participants received the study information, which contained the whole study procedure, aims, participants' rights, notification of the possible presence of a dog, and a selection of study appointments. After receiving all information about the study, a total of 159 participants were willing to participate in the study (a detailed overview of the enrollment can be found in the **Supplementary Material**, F1). Participants who were still willing to participate were asked to sign in for a study appointment. As soon as the scheduled $N = 132$ participants confirmed their study appointments, the remaining people were informed that there were no further appointments available. Participants attended one appointment that took about 70 min. The study compensation was CHF 80. Psychology students had the opportunity to obtain credit points for study.

Participants were blinded regarding the aims of our study and the placebo intervention. At the end of the study, all participants provided delayed informed consent, which debriefed them about the aims of the study. Participants were able to withdraw data from the study if they did not consent to participate anymore.

Randomization

We used an adaptive randomization to apportion male participants over all four conditions because we expected more women than men to participate in the study. This approach automatically considered the previous gender allocation in the four conditions and influenced the probability of the next gender allocation. This ensured that gender was equally represented in all four conditions ("pain," "pain + dog," "pain + placebo," "pain + placebo + dog," each $N = 33$). The randomization was conducted with Microsoft® Excel for Mac, version 16.16.17. The first author entered participant's code and gender into the Excelfile which then automatically allocated participants to one of the four study conditions. Participants did not know in which condition they were until the treatment phase. The study investigators, however, were not blinded as they knew in which condition the participant was.

Procedure

After guiding a participant into the room, the study investigator explained the study procedure to the participant and asked them to fill in the sociodemographic questionnaire, which took about 10 min. Then baseline measurements of heat-pain tolerance and threshold as well as subjective pain ratings were collected for each participant. This baseline procedure lasted 20 min.

After these baseline measurements, the treatment phase was conducted; it took a total of 15 min. Participants in the AAI conditions were introduced to the dog. They were deceived about the real reason for the dog's presence (to investigate the effect of the mere presence of a dog) so as to suppress possible expectation effects. Participants were informed that the dog had to be acquainted with the study procedure to be able to participate in a future study. They were told that the dog would rest quietly on a blanket and would not disturb the study procedure. To standardize the interaction between the participants and the dog, all participants were asked to greet and pet the dog as soon as it entered the room. We explained that it would be easier for the dog to relax on a blanket when allowed to greet the new person in the room. The duration of the interaction between the participant and the dog was kept to minimum, that is, under 1 min. During the greeting phase the study investigator also interacted with the dog, if the dog approached the investigator. After this greeting phase, the dog was asked to lie on its blanket, which was always next to the participant so that participants could still see the dog. Participants did not touch the dog during the further procedure. The study investigator also did not interact with the dog during the further procedure. The dog was a one-and-a-half-year-old female Golden Retriever used interacting with unfamiliar people. All conditions without a dog were carried out by three other female study investigators. All dog conditions were performed by the same female study investigator, who was the dog's owner. The reason for this was to ensure that the dog is not stressed. Leaving the dog in a setting with unfamiliar individuals without the dog's owner would have been inappropriate from an ethical standpoint. All study investigators were instructed to follow a study manual describing all the procedures and the instructions of the participants.

After this introduction, the study investigator applied an inert white cream on the participants in all four conditions. However, the rationale differed in the four conditions. Participants in the two placebo conditions ("pain + placebo" and "pain + placebo + dog") were told: "You will receive a generic analgesic cream with the active ingredient lidocaine. Lidocaine is the main ingredient of the analgesic cream Stilex (a local anesthetic commonly used in Switzerland). The cream prevents and treats itchy and painful skin problems, such as light burns, sunburns, or insect bites. The efficacy of lidocaine has been evidenced in several high-quality studies." Participants in the two pain-assessment conditions ("pain" and "pain + dog") were told: "You will receive

a cream (hand cream) to moisturize the skin. This allows accurate pain measurements."

After the treatment phase, posttreatment heat-pain measurements and subjective ratings of pain intensity and unpleasantness were performed in an identical manner to the baseline assessments and lasted 20 min. At the end of the study, all participants provided delayed informed consent (see **Figure 1** for the timeline of the study procedure).

MEASURES

Pain Ratings

We assessed heat-pain tolerance and heat-pain threshold following the design of previous trials (33–35). We defined posttreatment heat-pain tolerance as the primary outcome. Heat-pain tolerance is related to affective and motivational aspects (33, 36) and implies experiencing maximum discomfort, which results in greater subjective stress (33). In addition, it has been associated with pathological pain, as there is an inverse relationship between ischemic pain tolerance and the perceived severity of clinical pain (37). Posttreatment heat-pain threshold was defined as a secondary outcome. Both, the heat-pain threshold and heat-pain tolerance were determined using the Thermal Sensory Analyser (Medoc, Ramatishai, Israel; TSA 2). The heat-pain threshold was measured prior to heat-pain tolerance in order to minimize interference between the two outcomes (34, 35). The TSA 2 is a pain management system for qualitative assessment of pain and measures sensory thresholds such as heat-induced pain. The employed heat stimuli did not entail any significant danger and have already been used in previous studies in our lab (30, 34, 35, 38, 39). Participants were able stop the stimuli at any time during each experimental run.

The study investigator administered the heat stimuli to the right volar forearm of the participant using a 30 × 30 mm Peltier device (Medoc, Ramatishai, Israel; TSA 2). The thermode of the TSA 2 was fixed at two different locations (locations Y and X, determined using a positioning device). Location Y was placed one-third away from the elbow, while location X was placed two-thirds away from the elbow. Half of the participants were randomly assigned to start with location Y for the baseline heat-pain measurement and to switch then to location X for the posttreatment heat-pain measurement. The other half of the participants started with the opposite location, location X first for the baseline heat-pain measurement followed by location Y for the posttreatment measurement. The reason for moving the thermode was to avoid effects of sensitization or habituation (40).

Before starting with the actual heat-pain measurement, participants performed a practice round to experience how the heat stimuli work and how to handle the device including how to stop the heat stimuli. After this practice round, we started with the baseline measurements. We first assessed heat-pain threshold which was determined by the method of limits. Participants were instructed to press the button to determine the turning point from perceiving warmth to perceiving pain. The temperature was increased from the baseline (32°C) at a rate of 0.5°C/s. When participants indicated that the pain threshold had been reached, the device resumed from its baseline (32°C) with a rise of 0.5°C/s. This procedure was repeated three times in a row (35). The heat-pain threshold was defined as the average of the three measurements.

Afterward, heat-pain tolerance was determined using the method of limits. Participants were asked to stop the increasing heat stimulus at the moment they could not stand the heat any longer. The temperature increased from the baseline (32°C) at a rate of 0.5°C/s. As soon as participants indicated that their pain tolerance had been reached, the device resumed from its baseline (32°C) with a rise of 0.5°C/s. Again, this procedure was repeated three times in a row (35). To avoid physical injury, the pain tolerance measurement stopped at a temperature of 52°C (41). Heat-pain tolerance was defined as the average of the three measurements (42).

The secondary outcomes were the subjective pain-intensity rating of heat-pain tolerance, the subjective pain-intensity rating of the heat-pain threshold, the subjective unpleasantness rating of heat-pain tolerance, the subjective unpleasantness rating of the heat-pain threshold, and pain expectation.

Subjective pain-intensity and unpleasantness ratings of heat-pain tolerance and of the heat-pain threshold were measured with a visual analogue scale (VAS). The VAS ranged from 1 to 10 (1 = "not intense at all" or "not unpleasant at all"; 10 = "the most intense pain I have ever experienced" or "the most unpleasant pain I have ever experienced"). Participants were asked to evaluate subjective pain intensity and unpleasantness after each objective pain measurement. Subjective pain intensity and unpleasantness are assessed pain parameters in heat pain paradigm studies (43). Intensity refers to cognitive dimensions of pain, whereas unpleasantness refers to the affective dimension of pain (44).

After the treatment phase and before conducting the posttreatment heat-pain measurements, participants were asked to indicate on a VAS how intense they expect pain to be after the treatment phase. These expectation ratings were made on the same VAS (ranging from 1 to 10) as those for pain intensity and pain unpleasantness (35). Pain expectation was assessed to control if the expectation-induced placebo intervention was successful.

Participants' Perception of the Study Investigator

Participants' perception of the study investigator was assessed with the Counselor Rating Form–Short Version (CRF-S) (45). The CRF-S is a 12-item questionnaire for measuring an individual's perception of the therapist on the following three subscales: *trustworthiness*, *expertness*, and *attractiveness*. The questionnaire contains items on a 7-point Likert scale, ranging from 1 (not very) to 7 (very). For this study, only the subscale *trustworthiness* was analyzed because it is most central to the therapeutic alliance. Studies indicate that patient trust in the physician is of particular importance in clinical practice (46–48). The subscale *trustworthiness* included the following four items: *honest, reliable, sincere and trustworthy*. The CRF-S was used twice in the study: first after the baseline assessments and second after the posttreatment assessments. Due to an

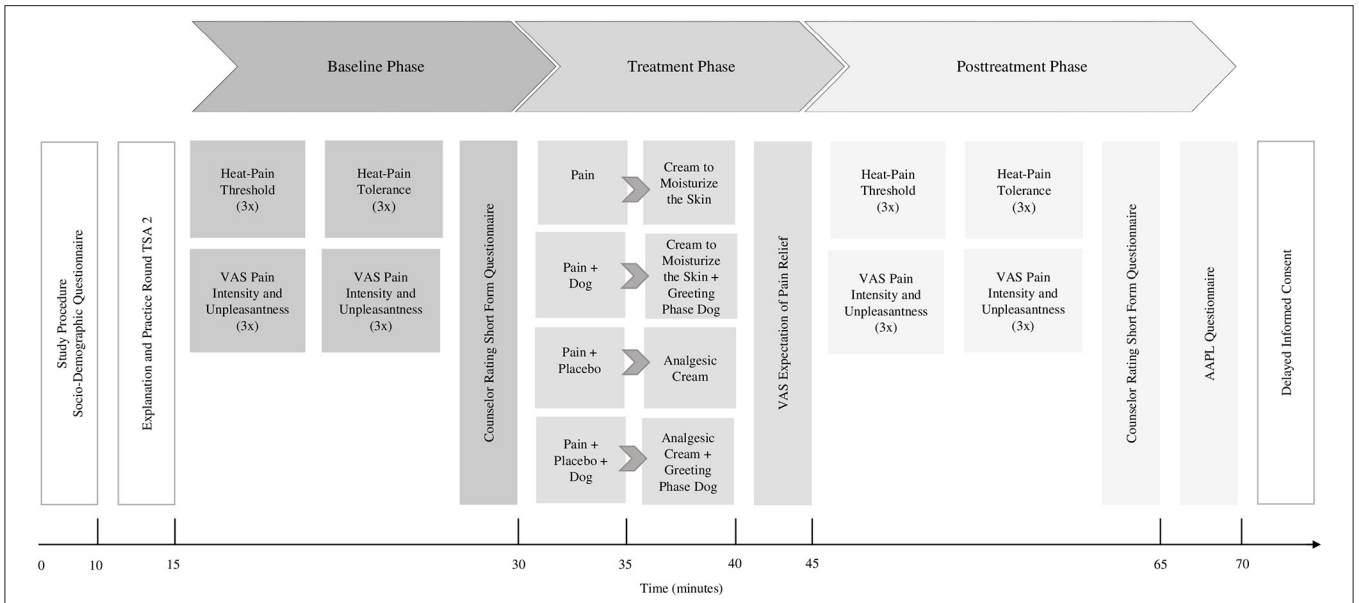

FIGURE 1 | Timeline of the study procedure.

online survey programming error the item *honest* of the subscale *trustworthiness* has not been collected within the first 31 participants. As the other tree items of the subscale *trustworthiness* were completed, this has been defined as item-level missingness (49). To treat these missing items, the mean across available items was taken, as recommended by Roth et al. (50).

Demographic Variables

Before the study start, we assessed demographic variables (i.e., age, sex, nationality, family status, educational level, employment situation, and income) with the sociodemographic questionnaire.

Dog Related Variables

The study investigator quantified the intensity of the contact between participant and dog during the greeting phase with a 5-stage Likert scale. The Likert scale ranged from 1 = "no contact at all" to 5 = "very high intensity of contact." Further, we assessed the participants affinity for dogs at the end of the study with a short self-developed questionnaire. We used a 5-stage Likert scale, with 1 indicating that participants like dogs "not at all" and 5 indicating "very much."

Data Analysis

We estimated that a sample size of $N = 128$ with a power of 0.8, an alpha error of 5% and a beta error of 20% would be necessary to detect a medium size effect of $f = 0.25$ between the four conditions, as well as interaction between them (7). We decided to add $N = 4$ (one person in each condition) in case of dropouts during the study or data loss due to technical problems. We therefore included 132 participants.

The primary outcome (posttreatment heat-pain tolerance) was analyzed using linear models (analysis of covariance, ANCOVA) with the corresponding baseline outcome of heat pain tolerance as a covariate. We wanted to investigate how the dog affects pain perception in the two different contexts—pain assessment and pain therapy—by comparing "pain" with "pain + dog" and "pain + placebo" with "pain + placebo + dog." We also run both models for the primary outcome twice, including gender and once including age (not pre-specified).

For the secondary outcomes (the posttreatment heat-pain threshold and the corresponding subjective pain-intensity and unpleasantness ratings of heat-pain tolerance and of the heat-pain threshold), we also conducted linear models (ANCOVAs) comparing "pain" with "pain + dog" and "pain + placebo" with "pain + placebo + dog." In each model, the respective corresponding baseline outcomes were used as covariates.

With regard to the subjective expectation ratings, we conducted a linear model (analysis of variance, ANOVA) using the four treatment conditions ("pain," "pain + dog," "pain + placebo," and "pain + placebo + dog") as an independent between-subject factor.

To analyze the subscale *trustworthiness* of the CRF-S questionnaire, we conducted a linear model (analysis of covariance, ANCOVA) to investigate whether the presence of the dog affected the perception of the participants. Dog was used as an independent factor and the corresponding baseline outcome of the subscale *trustworthiness* was used as a covariate. In a second step, the same model was run with the four study investigators as a covariate. To control whether there was a difference between the four study investigators, another model was calculated including the study investigator as a factor.

The requirements for the analyses were tested using Levene's test to determine the variance homogeneity of the four conditions, the homogeneity of the regression slopes, and the

TABLE 1 | Sociodemographic characteristics of participants.

Condition	*N*	Age mean (*SD*)	*N* (%) female	Family status *N*	Highest educational level *N* (%)	Employment level *N* (%)
Pain	33	26.58 (10.03)	23 (69.69%)	Single: 32 Married: 0 Registered partnership: 0 Divorced: 0 Other: 1	Primary school: 0 Secondary school: 1 (3.03%) High school: 19 (57.57%) University: 13 (39.39%)	Full time: 3 (9.09%) Part time: 8 (24.24%) None or student: 22 (66.66%)
Pain + Dog	33	26 (6.13)	22 (66.66%)	Single: 31 Married: 1 Registered Partnership: 0 Divorced:0 Other: 1	Primary school: 0 Secondary school: 0 High school: 17 (51.52%) University: 16 (48.48%)	Full time: 5 (15.15%) Part time: 14 (42.42%) None or student: 14 (42.42%)
Pain + Placebo	33	24.64 (7.06)	23 (69.69%)	Single: 31 Married: 2 Registered partnership: 0 Divorced:0 Other: 0	Primary school: 0 Secondary school: 3 (9.09%) High school: 18 (54.55%) University: 12 (36.36%)	Full time: 2 (6.06%) Part time: 8 (24.24%) None or student: 23 (69.70%)
Pain + Placebo + Dog	33	27.39 (9.38)	20 (60.60%	Single: 29 Married: 3 Registered partnership: 0 Divorced: 0 Other: 1	Primary school: 0 Secondary school: 1 (3.03%) High school: 20 (60.60%) University: 12 (36.36%)	Full time: 8 (24.24%) Part time: 6 (18.18%) None or student: 19 (57.58%)

SD, standard deviation.

normal distribution of the variables were tested using Shapiro-Wilk's test and quantile-quantile plot (Q-Q plot). All variables were normally distributed and all requirements were met. The prerequisites of ANCOVA were also met. There were no significant differences in baseline pain scores and in the CRF-S questionnaire between the four conditions. Further, there was a linear relationship between each covariate, in our case the corresponding baseline value, and the dependent variable, in our case the corresponding posttreatment value. We reported our outcomes according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines that suggest using the estimate with the confidence interval. The mean difference (estimate) was used as effect size, the confidence interval was defined at 95% and the significance level was set at 0.05. All statistical analyses were carried out using R for Mac, version 1.4.1103.

RESULTS

Sample Characteristics

All 132 participants were included in the analysis. Participants had a mean age of 26.2 ($SD = 8.3$). Eighty-eight participants were females, and 44 were males. Participants in the four conditions did not differ regarding age (pain: mean age = 26.58, SD = 10.03; pain + dog: mean age = 26, SD = 6.13; pain + placebo: mean age = 24.62, SD = 7.06; pain + placebo + dog: mean age = 27.39, SD = 9.38), gender, family status, educational level, or employment level (see **Table 1**). In addition, we also analyzed if there were differences between the conditions "pain" and "pain + dog" and the condition "pain + placebo" and "pain + placebo + dog" separately. No differences were found; detailed outcomes can be found in the (**Supplementary Materials 1**, **2**). Moreover, we also analyzed potential differences between the conditions "pain + dog" and "pain + placebo + dog" regarding the intensity of interaction between the participants and the dog or regarding the participants' dog affinity. No differences were found; detailed results can be found in the (**Supplementary Material 3**).

Primary Outcome: Heat-Pain Tolerance

We observed a mean posttreatment heat-pain tolerance of 47.64 in the "pain" condition which did not differ significantly from 48.02 in the "pain + dog" condition (difference = 0.04, CI = −0.66 to 0.74, $p = 0.905$). The posttreatment heat-pain tolerance mean value in the "pain + placebo" condition was 48.01 and did also not significantly differ from 48.38 in the "pain + placebo + dog" condition (difference = 0.43, CI = −0.02 to 0.88, $p = 0.059$) (see **Table 2**; **Figure 2**). Baseline heat-pain tolerance was associated with $p < 0.001$ in both models.

When including age in the model comparing the conditions "pain" and "pain + dog," age has no effect on posttreatment heat-pain tolerance (difference = 0.58, CI = −0.03 to 0.05, $p = 0.701$) and the conditions "pain" and "pain + dog" did not differ regarding posttreatment heat-pain tolerance (difference = 0.05, CI = −0.66 to 0.75, $p = 0.891$). In the comparison "pain + placebo" with "pain + placebo + dog" there was an age effect (difference = −0.04, CI = −0.07 to 0.01, $p = 0.002$) and the conditions "pain + placebo" and "pain + placebo + dog" significantly differed (difference= 0.54, CI = 0.12–0.97, $p = 0.013$).

TABLE 2 | Heat-pain tolerance and corresponding subjective intensity and unpleasantness ratings [mean, standard deviation (SD)].

		Condition			
		Pain (*N* = 33)	**Pain + Dog (*N* = 33)**	**Pain + Placebo (*N* = 33)**	**Pain + Placebo + Dog (*N* = 33)**
Baseline	Heat-pain tolerance (mean, SD)	48.06 (2.12)	48.41 (1.51)	48.29 (1.22)	48.22 (1.70)
	Subjective heat-pain intensity (mean, SD)	6.83 (1.52)	7.24 (1.45)	7.06 (1.43)	6.96 (1.45)
	Subjective heat-pain unpleasantness (mean, SD)	6.72 (1.73)	7.07 (1.30)	6.73 (1.85)	6.53 (1.79)
Posttreatment	Heat-pain tolerance (mean, SD)	47.64 (2.63)	48.02 (1.84)	48.01 (1.58)	48.38 (1.69)
	Subjective heat-pain intensity (mean, SD)	6.83 (1.49)	7.57 (1.36)	7.04 (1.75)	7.01 (1.66)
	Subjective heat-pain unpleasantness (mean, SD)	6.89 (1.87)	7.14 (1.41)	6.64 (2.12)	6.63 (1.91)

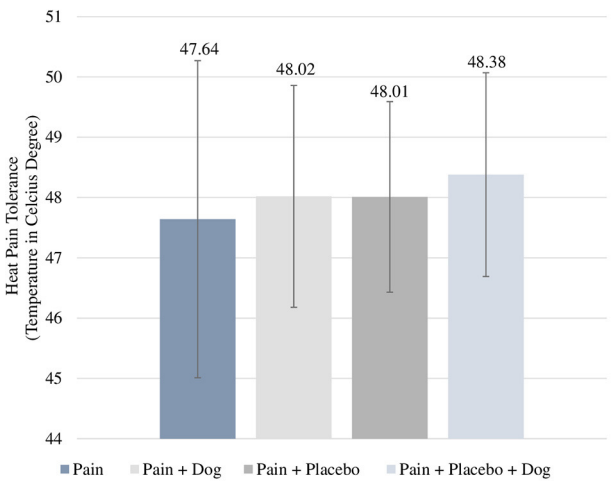

FIGURE 2 | Posttreatment mean scores of heat-pain tolerance. For each condition, the respective mean and standard deviation are displayed.

Baseline heat-pain tolerance was associated with $p < 0.001$ in both models.

When including gender into the model no changes to the original model were found. Gender had no effect on posttreatment heat-pain tolerance when comparing the conditions "pain" and "pain + dog" (difference = −0.10, CI = −0.87 to 0.66, $p = 0.785$). There was no difference between "pain" and "pain + dog" in posttreatment heat-pain tolerance (difference = 0.04, CI = −0.66 to 0.75, $p = 0.902$). When comparing the conditions "pain + placebo" and "pain + placebo + dog," we found no effect of gender (difference = 0.20, CI = −0.28 to 0.67, $p = 0.407$) and no group differences in posttreatment heat-pain tolerance (difference= 0.41, CI = −0.04 to 0.86, $p = 0.073$). Baseline heat-pain tolerance was associated with $p < 0.001$ in both models.

Secondary Outcomes

The Heat-Pain Threshold, Subjective Pain Intensity and Unpleasantness of Heat-Pain Tolerance, Subjective Pain Intensity and Unpleasantness of the Heat-Pain Threshold

There was no significant effect of the dog on the posttreatment heat-pain threshold; detailed outcomes can be found in the (**Supplementary Material 4**, T1).

With regard to the subjective intensity rating of heat-pain tolerance the "pain" had a mean value of 6.83 which was significantly lower than 7.57 in the "pain + dog" condition. This indicates that participants in the "pain + dog" condition experienced higher pain intensity of heat-pain tolerance compared to participants in the condition "pain" (difference = 0.40, CI = 0.02–0.79, $p = 0.041$) (see **Table 2**; **Figure 3**). Further, "pain + placebo" had a mean value of 7.04 which did not significantly differ from 7.01 in "pain + placebo + dog" condition (difference = 0.07, CI = −0.38 to 0.52, $p = 0.754$) (see **Table 2**). Baseline subjective ratings of pain intensity of heat-pain tolerance was associated with $p < 0.001$ in both models.

With regard to the subjective unpleasantness rating of heat-pain tolerance, the dog had no effect. There was no significant difference between mean value of 6.89 in the "pain" condition compared to the mean value of 7.14 in "pain + dog" condition (difference = −0.03, C = −0.59 to 0.53, $p = 0.913$) or between the mean value of 6.64 in the "pain + placebo" condition and the mean value of 6.63 in the "pain + placebo + dog" condition (difference = 0.19, CI = −0.29 to 0.67 $p = 0.44$). Baseline subjective ratings of pain unpleasantness of heat-pain tolerance was associated with $p < 0.001$ in both models.

With regard to the subjective intensity and unpleasantness rating of the heat-pain threshold there were no differences among the conditions; detailed outcomes can be found in the (**Supplementary Material 5**, T1).

Expectation of Pain Reduction

We found no differences between the four conditions regarding their expectation of pain reduction after treatment (difference

TABLE 3 | Counselor Rating Short Form Questionnaire (CRF-S): Subscale Trustworthiness [mean, standard deviation (SD)].

		Condition			
		Pain (*N* = 33)	**Pain + Dog (*N* = 33)**	**Pain + Placebo (*N* = 33)**	**Pain + Placebo + Dog (*N* = 33)**
Trustworthiness	Baseline (mean, SD)	25.42 (3.25)	26.58 (2.18)	25.70 (3.10)	26.58 (2.19)
	Posttreatment (mean, SD)	25.94 (2.90)	26.76 (2.28)	25.52 (3.26)	26.48 (2.36)

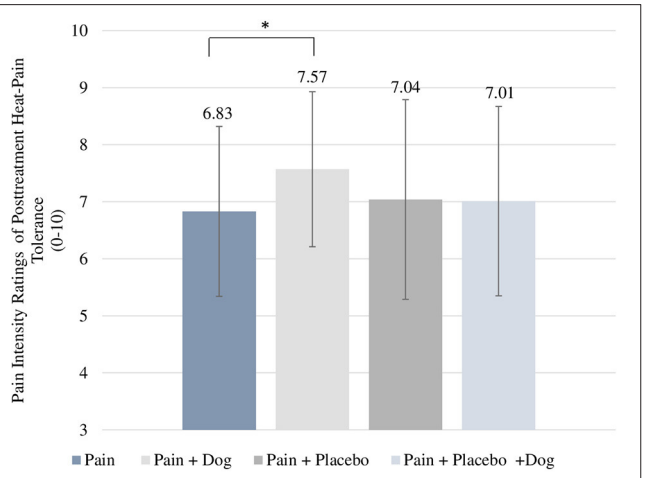

FIGURE 3 | Posttreatment scores of subjective intensity ratings for heat-pain tolerance. For each condition, the respective mean and standard deviation are displayed. *p-value < 0.05.

= −0.17, CI = −0.45 to 0.11, p = 0.241). Separate analysis of the conditions also showed no difference regarding pain expectation between the conditions "pain" with a mean value of 5.41 and the mean value of 5.36 in the "pain + dog" condition (difference = 0.04, CI = −0.88 to 0.97, p = 0.927) or the conditions "pain + placebo" with a mean value of 4.81 and the mean value of 5.03 in the "pain + placebo + dog" condition (difference = −0.22, CI = −1.09 to 0.66, p = 0.620).

Perception of the Study Investigator

There was no significant effect of the dog on the trustworthiness of the study investigators (see **Table 3**). The ratings of trustworthiness of the study investigators in the condition "pain" with a mean value of 25.94 did not differ from the mean value of 26.76 in the condition "pain + dog" (difference = 0.10, CI = −0.67 to 0.87, p = 0.796). The ratings of trustworthiness of the study investigators in the condition "pain + placebo" with 25.52 did not differ from 26.48 in the condition "pain + placebo + dog" (difference = 0.11, CI = −0.43 to 0.64, p = 0.695). Baseline trustworthiness ratings of the study investigators was associated with $p < 0.001$ in both models. When we controlled for study investigator, there was still no significant difference in the subscale *trustworthiness* of the study investigators between the four different investigators comparing the conditions "pain" with "pain + dog" (difference = −0.06, CI = −1.46 to 1.35, p = 0.936) or between the conditions "pain + placebo" and "pain + placebo + dog" (difference = 0.26, CI = −0.74 to 1.27, p = 0.601). Baseline trustworthiness ratings of the study investigators was associated with $p < 0.001$ in both models.

The results of the subscales attractiveness and expertness can be found in the (**Supplementary Materials 6**).

DISCUSSION

AAIs have been shown to be effective in the treatment of pain, but the mechanisms of this analgesia have not yet been elucidated. This study investigated whether the analgesic effects of AAI could be mediated by providing direct social support through the presence of a dog or by strengthening the alliance between the patient and the treatment provider. We tested these hypotheses with established paradigms for pain assessment and pain therapy, i.e., expectancy-induced placebo analgesia.

The results of our randomized controlled trial show that participants heat-pain tolerance did not increase in both pain assessment and pain therapy when a dog was present. Instead, subjective measures show that participants experienced heat-pain tolerance to be more intense when the dog was present compared to when no dog was present in the pain assessment condition where no treatment was offered. Further, participants did not perceive the study investigator to be more trustworthy when a dog was present compared to when no dog was not present. These results contradict our assumption that the analgesic effects of AAI could be mediated by providing direct social support or by strengthening the alliance between the participant and the treatment provider.

These findings also contradict previous observations of analgesia in the presence of a dog in a clinical setting (11–14, 51) but are in line with studies that found no effect of AAI in pain (16, 17). Moreover, we did not only find no analgesic effect of the dog but instead a negative effect in the subjective pain intensity of heat-pain tolerance. To our knowledge, this is the first study that found a negative effect of AAI on pain. There are several possible explanations for this discrepancy between our findings and previous studies.

These contradict results could be a consequence of differences in the study setting as we employed an experimentally induced acute pain paradigm in healthy participants, whereas previous studies reported pain reduction in patients in the presence of a dog compared to patients without a dog present in a clinical setting (11–14, 51).

Further, it is possible that for AAI to be effective, the animal (in our case, a dog) needs to be actively involved in giving social support to modulate pain, for example, through direct physical contact or a clear attentional focus of the animal toward the human. This would be in line with a previous meta-analysis on the analgesic effects of human social support suggesting that the mere presence of another person is not sufficient to affect pain perception and experience and that social support needs to be expressed clearly in order to reduce pain, for example, through verbal communication or holding hands (19). It is therefore possible that a dog also needs to be actively involved in the therapeutic process in order to modulate pain. Accordingly, in previous studies that have suggested that dogs affect patients' pain perception, patients typically interacted with the dogs for 10–20 min (11–13, 51). This would also be in line with previous studies showing that physical contact between a human and an animal is important to stimulate biological reactions in humans (52–54). Notably, these effects might not only rely on physical contact since both physically interacting with and just seeing a dog increases oxytocin level in humans (23). Based on these findings as well as on our results, we assume that the mere presence of a dog is not sufficient to affect pain perception and that at least a longer interaction phase and some form of contact between the human and the animal might be needed. Further, it can be important whether the person knows or owns the animal. Support for this assumption comes from a study that examined the effect of the presence of friends, spouses and pet on cardiovascular responses to psychological and physical stress. The authors showed that pet owners perceive their pets as an important, supportive part of their lives, and significant cardiovascular and behavioral benefits are associated with this perception (55, 56). In our study, participants did not know the dog. So, it is possible that a relationship needs to exists between human and animal for the presence of an animal to have a positive effect. Future studies should investigate if the relationship to the animal mediates a possible analgesic effect.

Another explanation is based on findings from placebo and psychotherapy research. Studies have shown that a treatment rationale is an important prerequisite for a treatment response (30, 35, 39). In our experiment, we used a deceptive rationale for the dog's presence, and we intentionally avoided a therapeutic narrative for the dog. However, research has indicated that interventions evoking expectations of pain reduction—either by verbal suggestion, conditioning, or imagery techniques—are likely to contribute to improving the effectiveness of standard analgesic treatments in clinical practice (57). Further, depending on the information given in verbal suggestions, the verbal suggestion of an analgesic treatment can lead to different magnitudes of analgesia (58–61). For example, a positive expectation leads to significant pain reduction, whereas a verbal suggestion inducing negative expectations can even block a painkiller's analgesic effect. This leads to the assumption that positive and negative expectations can have an impact on the outcome of an intervention (62). Hence, it is possible that we did not find an analgesic effect of the dog because participants lacked the grounds to incorporate the dog in their treatment expectations. Moreover, it is even possible that the dog was then perceived as a negative distraction. This would also explain why participants in the "pain + dog" condition experienced greater pain intensity compared to participants in the "pain" condition. This would also mean that the effect of AAI on pain reduction cannot be explained solely by the animal but is rather influenced by contextual factors, such as expectation.

Further, it could be that by not providing any information regarding the presence of a dog during the recruitment process, we might have attracted participants with no specific attitudes toward dogs. In our study dog affinity was only collected to check that groups did not differ regarding their dog affinity. However, it has been suggested that individuals with an affinity for animals may be more likely to benefit from their presence (14). It is possible that people with an affinity for dogs would more strongly benefit from a dog's presence. Thus, not limiting the study to people with an affinity for dogs could have led to a smaller effect of the dog's presence on pain perception and experience.

Last, the presence of a dog did not positively affect how participants perceived the study investigator. These results do not support findings of previous studies suggesting that the presence of an animal positively influences how we perceive others (25, 63). In both studies, participants perceived psychotherapists in images or videos with an animal present to be more attractive, and in a study by Schneider et al. (63), participants perceived the same psychotherapists as more trustworthy when an animal was present. However, our results are in line with the study by (26), who also found that the presence of a dog had no effect on participants' perception. A plausible explanation for the difference in results between, on the one hand, previous studies supporting a positive effect of animals on our perception (25, 63) and, on the other, our study and Goldmann et al.'s study is the study setting. In our study and in Goldmann's study, the effect of the presence of a dog on participants' perception was investigated *in vivo*. In both studies, there was direct interaction between the participant and the study leader, whereas in the previous studies the participants had to judge an image or video of a person with or without an animal and the participants did not interact with an animal or study leader. It is therefore possible that through this direct interaction between participant and study investigator, the dog was not the focus of participants and had no effect on their perception of the study investigator (26). However, since the dog conditions were only performed by one study investigator, these results must be interpreted with caution. With our design, it is difficult to compare the study investigator that worked with the dog with the other three study investigators.

Overall, the results of this study are not only interesting for research on AAIs but also for placebo research, especially from a methodological perspective. In this study, we used a placebo as an intervention paradigm to examine whether the presence of a dog could amplify the placebo effect. The placebo was thus not used as a control intervention to eliminate specific factors as is usually the case. Using a placebo as an intervention paradigm has been implemented in a few previous studies, for example, in those by (30, 31) investigated the effect of the patient–practitioner relationship on patients with irritable-bowel syndrome using a placebo acupuncture intervention; they suggested that an enhanced relationship with a practitioner is the most robust

component in therapy. Further, Gaab et al. (30) examined the impact of expectation and relationships in healthy participants using a placebo intervention consisting of animated videos. The authors showed that placebos with a psychological treatment rationale are effective when provided in a trustworthy, friendly, and empathic relationship. In our study, we used the presence of a dog to examine whether the presence of a dog could amplify the placebo effect and found that the mere presence of a dog has no impact on the placebo effect.

However, it should also be emphasized that in this study, we did not succeed in inducing placebo effects. This finding contradicts results from previous studies (34, 35). A possible explanation for the lack of placebo effect might be that in this study, the expectation induction was not successful. As known from previous research treatment response expectation is generally seen as the main contributor to placebo-induced analgesia (64–66). Hence, we may not have been able to produce placebo effects since participants had no expectation of pain relief. Another possible explanation might be that the dog and not the placebo was the focus in our study. We used a placebo as an intervention paradigm and not to study placebo effects like in previous studies. As a result, it is possible that the study investigators did not have a placebo allegiance in this study. As known from psychotherapy research there exists a robust relationship between researcher allegiance and outcome (67). Hence, a potential missing placebo allegiance could lead to a lower expectation of pain reduction among participants and explain the lack of placebo effect in this study.

The findings of this study have to be seen in light of some limitations. Our sample consisted of young and healthy people who were not suffering from acute or chronic pain. While valuable evidence can be provided from studies in healthy participants, it is important to stress that short-term experimentally induced or acute pain in healthy participants differs from chronic pain in patients (68). Hence, our results only provide information about how the presence of a dog affects experimentally induced acute pain of healthy participants. Therefore, our results need to be treated with caution in the context of acute or chronic pain. Future studies should apply this design also with patients with pain disorders or patients experiencing acute pain in clinical settings. Further, the dog conditions were performed by the same person, while the other interventions were performed by different people. The results of the CRF-S questionnaire showed, however, that even when controlling for the investigator, there was no significant difference in how participants rated the study investigators. Finding no difference can lead to the assumption that all four investigators performed the intervention in the same standardized manner according to the manual. However, even though this analysis made us assume that all our study investigators performed the conditions in the same manner we need to highlight that with our design, it is not possible to distinguish between the effects of the dog and the study investigator. Future studies should make sure that the study investigators carry out both conditions with and without an animal present to entangle the effects of the animal and the effects of the study investigator. Further, participants had only limited contact with the dog since the aim of this study was to investigate whether the mere presence of a dog had an analgesic effect.

Last but not least, the intensity as well as dog affinity were collected in this study, but only to roughly investigate if the dog groups differ regarding the intensity of contact and their dog affinity. It would have been interesting to investigate whether dog affinity and intensity of the contact between the participants and the dog mediates the effect. We therefore suggest that future studies should specifically address the affinity of participants for animals in general as well as for the animal that is presented.

Considering the findings and limitations of this current study, future studies are warranted that would investigate whether animals need to be integrated in the treatment rationale in order to have effects on pain. Further, it is important to examine whether physical contact with a dog is needed for an analgesic effect or not and whether affinity toward dogs mediates this effect.

In conclusion, our results indicate that the mere presence of a dog does not contribute to pain reduction and that the previously reported analgesic effects of AAI is not replicated in our study. The presence of a dog did not seem to provide social support or had an effect on the alliance between the participants and the treatment provider. We assume that the animal might need to be an integrated and plausible part of the treatment rationale so that participants are able to form a treatment-response expectation toward AAI.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Faculty of Psychology at the University of Basel, Switzerland. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JG had the idea for the study. CW, KH, JG, and CL designed the study. CW contributed to acquiring the data. CW and CL carried out the analysis. CW, KH, JG, and CL wrote the manuscript, which was revised by all authors. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpain.2021.714469/full#supplementary-material

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STUDY PROTOCOL
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Open-Label Placebo Treatment for Acute Postoperative Pain (OLP-POP Study): Study Protocol of a Randomized Controlled Trial

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Introduction: Open-label placebos have been proposed as way of using long recognized analgesic placebo effects in an ethical manner. Recent evidence shows efficacy of open-label placebos for clinical conditions, but there is need for more research on open-label placebos in acute pain. In the treatment of acute postoperative pain, minimization of opioid related side effects remains one of the key challenges. Therefore, this study aims at investigating the potential of adding unconditioned open-label placebos to treatment as usual as a means of reducing opioid consumption and its related side effects in patients with acute postoperative pain.

Methods and Analysis: This is the protocol of an ongoing single site randomized controlled trial. The first patient was enrolled in May 2020. In total, 70 patients suffering from acute postoperative pain following dorsal lumbar interbody fusion are randomized to either a treatment as usual group or an experimental intervention group. The treatment as usual group consists of participants receiving a patient-controlled morphine pump. On day 1 and 2 post-surgery, patients in the intervention group receive, in addition to treatment as usual, two open-label placebo injections per day along with an evidence-based treatment rationale explaining the mechanisms of placebos. The primary outcome is measured by means of self-administered morphine during day 1 and 2 post-surgery. Several other outcome measures including pain intensity and adverse events as well as potential predictors of placebo response are assessed. Analysis of covariance will be used to answer the primary research question and additional statistical techniques such as generalized linear mixed models will be applied to model the temporal course of morphine consumption.

Discussion: This study will provide valuable insights into the efficacy of open-label placebos in acute pain and will potentially constitute an important step toward the implementation of open-label placebos in the clinical management of acute postoperative pain. In addition, it will shed light on a cost-efficient and patient-centered strategy

to reduce opioid consumption and its related side effects, without any loss in pain management efficacy.

Ethics and Dissemination: The "Ethikkommission Nordwest- und Zentralschweiz" (BASEC2020-00099) approved the study protocol. Results of the analysis will be submitted for publication in a peer-reviewed journal.

Clinical Trial Registration: The study is registered at ClinicalTrials.gov (NCT04339023) and is listed in the Swiss national registry at kofam.ch (SNCTP000003720).

Keywords: open-label placebo, acute postoperative pain, opioids, postoperative analgesia, placebo analgesia, lumbar interbody fusion

INTRODUCTION

Placebo effects have been shown to have a clinically significant impact on subjective and objective health outcomes for a variety of somatic and mental disorders (1, 2). However, since the administration of deceptive placebo violates patients' right to autonomy [e.g., (3, 4)], alternative means of harnessing the placebo effect in an ethical manner—so-called Open-Label Placebos (OLP)—have been proposed and found to be effective in both healthy (5–10) as well as clinical populations [see (11, 12) for an overview].

Clinical investigation of OLP effects has mainly focused on chronic pain (13–17), allergic (18, 19), opioid use disorder (20), mental illness and psychosomatic symptoms (21–29). Evidence on OLP effects in acute pain on the other hand is limited, yet promising: Findings of two studies investigating the potential of Conditioned OLP (COLP) to reduce pain intensity and opioid dose in patients with spinal cord injury/polytrauma (30) and following spine surgery (31) suggest that COLP might also be effective in acute pain by showing reductions of opioid doses compared to Treatment As Usual (TAU). These results are supported by the findings of several experimental OLP analgesia studies in healthy populations (7, 8, 32–34). However, there is lack of investigations of unconditioned OLP in acute pain.

Patients undergoing dorsal Lumbar Interbody Fusion [LIF (35–37)] suffer from a great amount of acute postoperative pain (38) requiring intensive analgesia. Since Non-Steroid Anti-Inflammatory Drugs display a higher postoperative bleeding risk (39–42), opioids remain the primary systemic pharmacotherapy for intraoperative and postoperative analgesia. Therefore, minimization or prevention of opioid-related side effects is one of the key challenges of postoperative analgesia in dorsal LIF patients.

In the light of these current challenges in postoperative pain management in dorsal LIF patients and the promising results of above mentioned OLP studies, adding OLPs to an opioid-based TAU could provide a means of harnessing analgesic placebo effects (43–45) in acute postoperative pain. This approach could lead to a reduction in postoperative opioid consumption and less opioid-related side effects, without any loss in pain management efficacy.

In this randomized controlled trial, TAU mainly consists of a patient controlled, morphine-based analgesia. Patients in the OLP group will receive additionally two saline injections a day, which will be disclosed openly to the patients as placebo injections. By choosing injections instead of pills, we hope to maximize the OLP response, as it has been shown that placebo effects are bigger the more invasive a treatment is (46, 47). In addition, the setting of this study is suitable to test for the first time OLP injections as venous access is already established due to the postoperative setting.

By adding OLP injections to the TAU this study is the first to investigate OLPs potential to reduce morphine consumption in acute pain without conditioning and thus by solely relying on expectancies induced by verbal suggestions and previous experiences (48–51). We hypothesize that patients receiving the OLP injections in addition to TAU will administer themselves less morphine. Furthermore, the study design also allows to assess the effect of OLP injections on morphine desire (i.e., clicks on the patient-controlled analgesia pump exceeding the maximum of allowed morphine consumption), self-reported pain intensity, interference of pain with different areas of functioning, amount of requested rescue analgesics, number of reported side effects, and length of hospitalization. Finally, this study provides the opportunity to investigate the influence of several psychological factors associated with the OLP response.

METHODS AND ANALYSIS

Study Design

This ongoing assessor blinded study is designed as a single center, randomized controlled trial with a parallel group design using block randomization with a 1:1 allocation, comparing an OLP intervention group and a TAU control group (see **Figure 1**). The first participant was enrolled and randomized in May 2020, and the study is expected to be concluded by December 2023 with the planned inclusion of 70 study participants, this corresponds to a recruitment rate of two patients per month. The study is being conducted at the University Hospital of Basel by the Pain Unit and the Faculty of Psychology at the University of Basel in collaboration with the Department of Spinal Surgery of the University Hospital of Basel.

Study Population

The study population consists of patients receiving elective dorsal LIF surgery at the University Hospital of Basel.

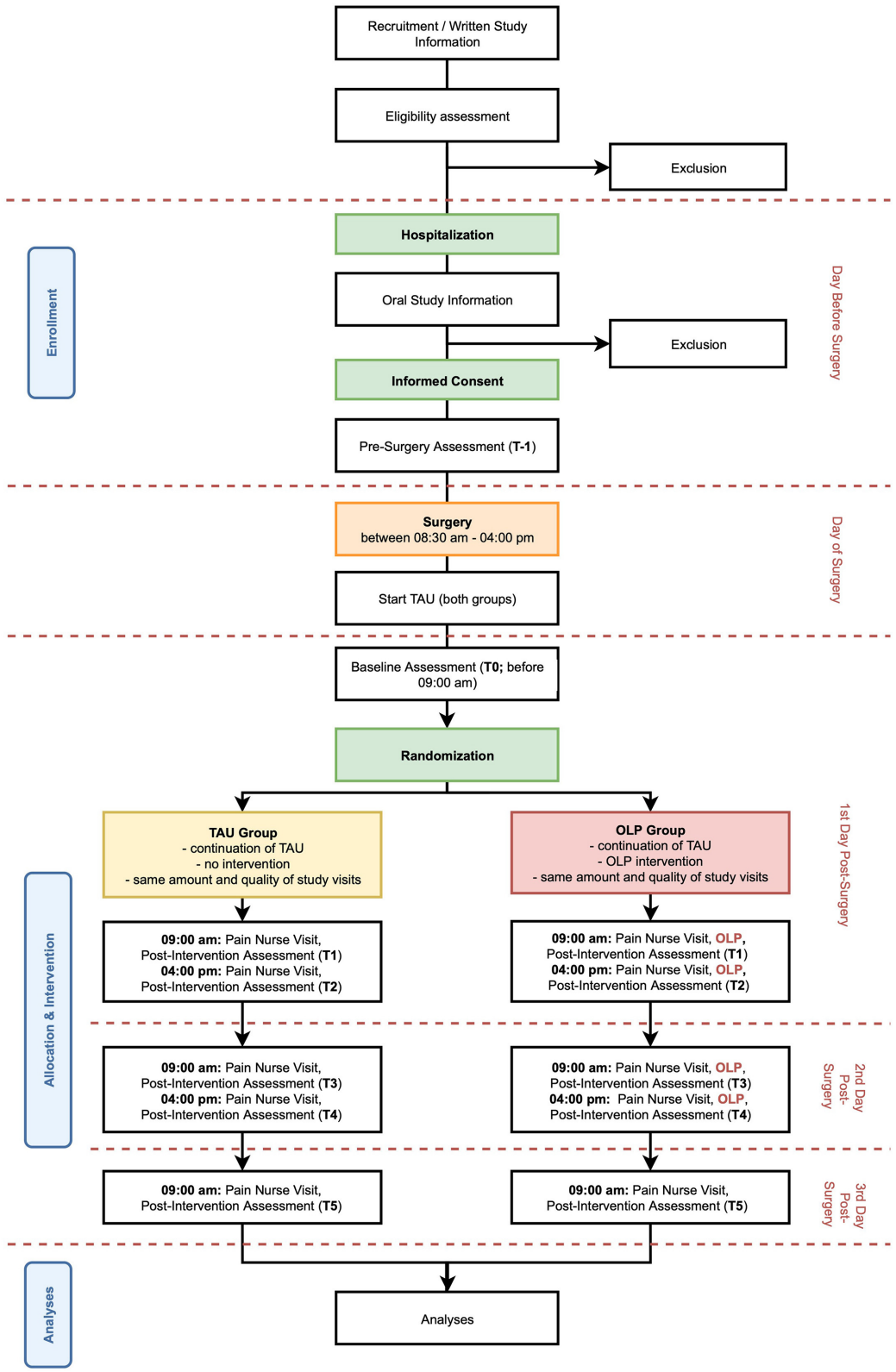

FIGURE 1 | Study design and flow. TAU, Treatment as usual; OLP, Open-label placebo.

Inclusion Criteria

All patients scheduled for elective surgery with decompression and posterior fusion of the lumbar spine are potential study candidates. To facilitate an acceptable comparability between the study patients regarding wound surface and surgical trauma, operation procedures acceptable for inclusion are closer specified. Patients can be included if:

- The primary operation includes only the segments of the lumbar spine (L1-L5), plus the first sacral segment (S1).
- In this defined area, fusions of up to two levels (for example: L1-L3) are allowed.
- Additional decompressions are allowed, if performed at the segments of the stabilization or the direct proximate segments above or below, if the procedure does not exceed the segments L1-S1.

In addition, participants also have to fulfill all of the following inclusion criteria for study eligibility:

- 18 years or older.
- German speaking.
- Able to understand the study and its outcome measures.
- Able to provide Informed Consent (IC).

Exclusion Criteria

The presence of any one of the following exclusion criteria leads to exclusion of the participant:

- Known chronic pain, which is unrelated to the problem targeted by the surgery.
- Known neuromuscular disease.
- Known mental disorders.
- Known drug or massive alcohol intake or intake of other psychoactive substances.
- Known kidney or liver disease (glomerular filtration rate < 30).
- Contraindications to the class of drugs under investigation, e.g., known hypersensitivity or allergy to the investigational product.
- Parallel participation in another study with investigational drugs.
- More than 30 mg/day (equivalent dose of oral morphine) preoperative opioid consumption.

Participants may continue to use their regular medication (e.g., hypertension, diabetes, etc.; cf. Concomitant Treatments). However, participants should not change the routine or dosage during the trial, if possible. Any medication intake and changes are assessed thoroughly.

Recruitment and Screening

Inclusion and exclusion criteria of patients scheduled to receive dorsal LIF are being verified by using the electronic hospital records and double-checked by physicians. If patients are eligible for participation, they receive written and oral information about the study provided by study team members. After hospital admission on the day before surgery, eligibility is assessed again, open questions are answered, and IC is obtained. After IC patients fill in several questionnaires (see **Table 1** for an overview of study assessments).

Randomization and Treatment Allocation

A random treatment allocation was generated by an independent investigator. Treatment assignments were drawn from a computer-generated random number sequence. Sequentially numbered opaque envelopes containing treatment allocation are used to assign participants to either the OLP group or the TAU group. In order to guarantee equal distribution of conditions, randomization was performed in blocks of ten, leading to five TAU and five OLP participants for each block of 10 participants.

Treatment allocation occurs prior to the first study visit on day 1 post-surgery (i.e., T1). The pain nurse performing the subsequent study visit opens the corresponding envelope and reveals the treatment assignment by letting the patient know the group to which they have been assigned to.

Blinding Procedures and Other Methods of Minimizing Bias

Blinding participants is not possible, as it is an open-label trial. However, the primary outcome of interest (morphine dose) is never explicitly mentioned to the participants of both groups. They are only informed about the non-specific therapeutic benefits that are associated with placebo analgesia.

As treatment allocation occurs after baseline assessments are completed, study pain nurses are blinded up to day 1 post-surgery (T1). Team members responsible for assessments of outcomes subsequent to the pain nurse visits are blind to the group assignment during the whole study. Furthermore, hospital staff not involved in the study (e.g., ward nurses and doctors, who assess some side effects) is not aware of the group allocation and thus blinded.

As disappointment may result from allocation to the control group (52) which can lead to nocebo effects (53, 54), participants of the control group are reminded of the importance of the control group after randomization (cf. **Supplementary Material** for exact wording). Disappointment in the control group is also assessed at the end of the trial (T5).

Moreover, manualized instructions are used during all study specific contacts and study team members are instructed to treat participants in both groups equally supportive with empathy and warmth. In addition, mostly validated questionnaires are used in this study. If no validated German version of a particular questionnaire was available, we translated the questionnaire using back translation following the procedure proposed by Beaton, Bombardier et al. (55).

Study Visits and Study Procedures

After inclusion of patients into the study, there are several study visits (cf. **Figure 1** for an overview of study timeline). Procedures and timeline of visits are described in the following. An overview of all assessments made at each visit can be found in **Table 1**.

- **T-1:** After the IC is signed (cf. 3.3 Recruitment and Screening) patients answer a series of questionnaires including patient's

TABLE 1 | Assessment timeline.

		Screening	Pre-Surgery	Baseline	Intervention					Completion of Each Participants Data
		Screening	T-1	T0	T1	T2	T3	T4	T5	
Activity/Variable	**Duration in minutes**			**before 09:00a.m.**	**09:00a.m.**	**04:00p.m.**	**09:00a.m.**	**04:00p.m.**	**09:00a.m.**	
Patient information and informed consent	15	x								
In-/Exclusion criteria	1	x								
Socio demographics	1		x							
Medical History (i.e., Medication at hospital admission analgesic consumption)	0		x							
Preoperative anxiety	2		x							
Pain catastrophizing	3		x							
Depression	2		x							
Placebo beliefs and understanding	1		x							
Opioid beliefs	2		x							
Comprehensive pain assessment	5		x	x			x		x	
Back and leg pain intensity at rest	1		x	x	<– –>*					
Back and leg pain intensity while walking	1		x	x		x		x		
Expectancy of pain relief	2		x	x	x	x	x	x	x	
Randomization	0				x					
Check and if needed adjust PCA	2				x	x	x	x	x	
Morphine consumption and desire	0				x	x	x	x	x	
Intervention (OLP group only)	2				x	x	x	x		
Intervention credibility	3/1				x				x	
Disappointment (TAU group Only)	1								x	
Open qualitative questions	3								x	
Side-effects-related medication request	0									x
Concomitant medication/interventions	0									x
Length of hospitalization and details on the surgery	0									x
Rescue medication request	0									x
estimated duration for patients (Min)		16	20	9	10	8	12	8	15	0

*PCA, Patient controlled analgesia; TAU, Treatment as usual; OLP, Open-label placebo; *continuous assessment every 2 h.*

preoperative anxiety, depression, beliefs regarding placebos and opioids, pain and postoperative pain expectancies.

- **T0:** Before 09:00 a.m. on day 1 post-surgery, a study team member visits the patient. Baseline assessments of current pain are made.
- **T1:** At circa 09:00 a.m. on day 1 post-surgery, a specialized pain nurse checks and if needed adjusts the PCA pump and assesses morphine consumption since installation of the pump on the day of surgery. The pain nurse reveals the treatment allocation to the patient. In addition, if the patient is in the OLP group, the experimental intervention is performed (cf. Intervention for more information on the intervention). After the pain nurse visit, patients of both groups answer again questions regarding treatment expectancy under supervision of a study team member.
- **T2:** At circa 04:00 p.m. on day 1 post-surgery, the pain nurse checks and if needed adjusts the PCA pump again. Morphine consumption since the last study visit is assessed. In addition, if the patient is in the OLP group, the experimental intervention is performed again. After the pain nurse visit, the patient answers again several questions regarding pain and pain expectancy under supervision of a study team member.
- **T3:** Same procedure as T2 at circa 09:00 a.m. on day 2 post-surgery.
- **T4:** Same procedure as T2 at circa 04:00 p.m. on day 2 post-surgery.
- **T5:** Same procedure as T2 but without intervention in the OLP group, at circa 09:00 a.m. on day 3 post-surgery.

Intervention

Control Intervention (Treatment as Usual)

In this study, the TAU group serves as a control group. After randomization, all participants in this group continue TAU and concomitant medication and have the same amount and quality of contacts with the study team. However, participants of this group do not receive any intervention.

TAU consists in both groups of:

- **Basic analgesia:** 3 grams of Paracetamol per os a day
- **Patient controlled analgesia (PCA):** Patient-controlled morphine pump configured to release a maximum of 2 mg of morphine every 12 min; dosage can be adjusted in the course of treatment if rescue medication is not effective enough or if side effects occur
- **Rescue medication:** 1,000 mg of Metamizol, maximum every 6 h or in case of allergy to Metamizol 400 mg of Ibuprofen, maximum every 6 h.

Experimental Intervention

All participants in the OLP group also receive TAU as described above. In addition, they receive an experimental OLP intervention. This intervention consists of two components: An evidence-based treatment rationale and OLP injections.

Treatment Rationale

The idea of delivering an evidence-based treatment rationale alongside with the OLP injections has been driven by the known underlying mechanisms of deceptive placebo analgesia (e.g., treatment expectation, classical conditioning). Thus, eliciting a positive treatment expectation (10) by informing the patient about the evidence supporting OLPs as well as assumed mechanisms of action (e.g., classical conditioning) has been thought to be an incremental component of OLP interventions (56, 57). However, evidence on the necessity to deliver an evidence-based treatment rationale alongside the OLP intervention as introduced by Kaptchuk, Friedlander et al. (22) is mixed: On the one hand, findings of different OLP studies including our own study in experimental pain (7) suggest that an evidence-based rationale is indispensable in OLP efficacy (10). On the other hand, there have also been investigations showing no additional improvement when a treatment rationale was delivered alongside placebo administration: For example, allergic symptoms were similarly reduced even when pills were given without further explanation (19). In line, our recent study on OLP analgesia in healthy male adults (32) showed a comparable effect on pain reduction in both a short education group as well as in a detailed education group. This result is of great importance, because the possibility of providing OLPs with a short education makes them feasible in clinical practice.

Despite the conflicting evidence base, patients in this study receive an evidence-based treatment rationale (cf. **Supplementary Material**) prior to the administration of the first OLP injection (T1). This treatment rationale is thought to increase patients' perceptions of practitioner competence and empathy (58, 59) as well as the plausibility of the placebo intervention treatment (60), which in turn may enhance placebo effects. Thus, the treatment rationale is perceived as an incremental component of the OLP intervention and is therefore not given to the control group.

The rationale states clearly the fact that the placebo injections are inactive (inert) and contain only saline (i.e., salt and water). Further, based on previous OLP studies (22), it contains the following discussion points, which have been adapted to refer to the specific placebo analgesia and study context (i.e., adding treatment expectation, a second placebo analgesia mechanism and dismissing the "original" discussion point on the importance of adherence):

- Placebo effects of OLP can be **powerful** in some patients, especially in analgesia.
- **Treatment expectations** are found to be an important mechanism in placebo analgesia.
- In response to placebos the body can **automatically** release **endogenous opioids** which are targeting the pain, experienced due to the surgery.
- A **positive attitude** is helpful but is not absolutely necessary.

At every subsequent placebo application (T2, T3, T4), the patient is reminded of the inertness of the injection and that OLPs might help with regulating pain (cf. **Supplementary Material**).

OLP Injections

Five milliliter syringes containing 5 ml of saline 0.9% are used as placebo. The syringes are labeled with a blue "Placebo" sticker which is visible to the patients. These placebo injections are given

twice a day (at 09:00 and at 04:00 p.m.) on day 1 and 2 post-surgery (i.e., patients receive a total of four placebo injections). The injections are administered intravenously; the access is the same as for TAU. It is ensured that patients watch the injection. Since the intervention is delivered by pain nurses, treatment adherence is warranted.

It is important to note that saline and its effects are not the product under investigation, but the presumed psychological mechanisms of the therapeutic procedure—the act of receiving a treatment and a plausible explanation alongside—is expected to have the most important impact on pain perception of patients. Therefore, saline could be replaced by any other carrier solution without analgesic properties (e.g., Ringer lactate).

Dose Modifications

TAU can be modified, if necessary, according to this scheme:

- **Analgesia, including rescue medication, is not sufficient and opioid-related side effects are tolerable:** The PCA pump can be adjusted, so that 2 mg of morphine can be administered every 8 min. A limit of 14 mg morphine per hour is set.
- **Opioid-related side effects are not tolerable, and analgesia is sufficient:** The PCA pump can be adjusted, so only 1 mg of morphine can be administered every 12 min. Increasing the lock-out time to 15 min, with or without a bolus reduction, is also possible.
- Treatment of opioid related side effects according to in house standards (i.e., antiemetic's, laxatives) is possible at any time.

Dose modifications beyond these defined adjustments lead to study discontinuation. Discontinuation or modification of the experimental intervention (cf. Experimental Intervention) and its dose is not intended. Premature ending of the intervention is being encouraged if a given participant reports serious deterioration, which is not to be expected.

Concomitant Treatments

There are no restrictions regarding concomitant interventions or treatments (e.g., opioid-related side effects medication, or physiotherapy), except for simultaneous participation in other studies with investigational drugs. Concomitant interventions or treatments are regularly documented within hospital standard documentation routines. After study completion of each patient, data is extracted from the electronic patient record of the patient and entered into the electronic case report form (eCRF; cf. Data Collection, Management and Storage).

Outcome Measures

A detailed timeline of all outcome assessments is provided in **Table 1**.

Due to the characteristics of the study population (i.e., not being digital natives), self-reported bi-hourly assessments of pain intensity is being delivered in paper-pencil format. All other assessments are administered digitally on a tablet-PC and are supervised by a study team member. Thus, adherence to all assessments with exception of the bi-hourly assessments of pain intensity is warranted.

Primary and secondary outcome measures will be presented as means with SD if appropriate.

Primary Outcome

Primary study outcomes are assessed by means of the cumulative dose (i.e., total amount) of self-administered morphine within 48 h starting on day 1 post-surgery and ending on day 3 post-surgery.

Secondary Outcomes

Secondary outcomes comprise the following:

Morphine Desire Rates

Morphine demand behavior is measured by the total number of unsuccessful clicks on the PCA pump, allowing to quantify participants desire of morphine, exceeding the maximum amount they can administer themselves.

Pain Intensity at Rest and While Walking

Following the recommendations made by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials [IMMPACT (61)] back and leg pain intensity at rest and while walking are measured separately several times a day (cf. **Table 1**) by four eleven-point Numeric Rating Scales (62, 63).

Comprehensive Pain Assessment and Patients' Perception of Postoperative Pain Management

Comprehensive pain intensity, frequency, duration, and interference as well as side effects of pain medication are assessed by the German version of the International Pain Outcomes Questionnaire (64). To be able to administer the questionnaire several times, the time period statements (i.e., "since your surgery") was changed to "the last 24 h" (cf. **Supplementary Material** for information on additional minor adaptions).

Requested Rescue Analgesics

Amount of administration, dosage and time of administration are assessed for the time period of T0–T1 (i.e., baseline consumption of rescue analgesics) and T1–T5 (i.e., post-intervention consumption of rescue analgesics).

Opioid-Related Side Effects

Nausea, vomiting and constipation (i.e., stool frequency, vomiting and amount of delivered laxatives and antiemetics) as well as serious adverse events (e.g., oxygen desaturation) are assessed within the routine hospital documentation for the time period of T0–T1 (i.e., baseline rate of opioid-related side effects) and T1–T5 (i.e., post-intervention amount of opioid-related side effects). Other opioid-related side effects (e.g., nausea, drowsiness, itching, and dizziness) are assessed within the International Pain Outcomes Questionnaire (i.e., each morning post-surgery).

Length of Post-surgery Hospitalization

Data is collected upon participants trial completion.

Other Variables of Interest

Other variables of interest are:

Expectancy of Pain Relief
Expectancy of pain relief are assessed separately for leg and back pain with an eleven-point Likert-scale each (cf. **Supplementary Material**). Thereby, the influence of the OLP-intervention on patient's expectancy of pain relief as well as its effects on morphine consumption are investigated.

Intervention Credibility
After the first OLP injection and at the end of the trial the OLP group is asked about the credibility of the OLP intervention (for details cf. **Supplementary Material**).

Depression
In order to assess the influence of depressive mood on the placebo response (65, 66), the depression scale of the German version of the Patient Health Questionnaire (67) is administered on the day before surgery (i.e., T-1). This questionnaire assesses depressive symptoms according to the criteria of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (68).

Pain Catastrophizing
High levels of pain catastrophizing are associated with a heightened pain experience and appear to contribute to the development of chronic pain in patients suffering from postoperative pain (69). To assess the influence of pain catastrophizing on the outcomes of this study, the German version of the Pain Catastrophizing Scale (70) is administered prior to study start (i.e., T-1).

Preoperative Anxiety
Preoperative anxiety is known to influence postoperative pain levels (71) and is thus assessed, using the German version of the Amsterdam Preoperative Anxiety and Information Scale.

Placebo Beliefs and Understanding of Patients
Placebo beliefs and understanding of patients are assessed by two different means:

- In order to assess the influence of patients pre-existing placebo beliefs on the OLP effect, a translation of a four-item questionnaire introduced by Leibowitz, Hardebeck et al. (6) is administered.
- Placebo understanding is assessed by the first two items of a questionnaire introduced by Fassler, Gnadinger et al. (72) which assesses responders' attitudes regarding non-specific therapies. The first two items specifically assess the placebo understanding of responders.

Opioid Beliefs of Patients
In order to assess the influence of patients pre-existing opioid beliefs on the amount of morphine consumption (73), we apply a translation of a ten-item questionnaire assessing beliefs regarding opioids which has been introduced by Lai, Dalton et al. (74).

Safety Outcomes
No specific adverse events, serious adverse events or side effects due to the placebo intervention are expected. Moreover, if the OLP intervention provided in this study can reduce morphine intake in some patients, side effects due to TAU can potentially be decreased. Thus, patients in the intervention group might even be exposed to less harm, than patients in the TAU group. Side effects due to TAU are therefore assessed as a secondary outcome. Furthermore, only serious adverse events are assessed.

Data Collection, Management, and Storage
For data collection and management of participants responses at study visits, the secure web application REDCap (75) is used as eCRF. The system is hosted by the Center for Scientific Computing of the University Basel (sciCore). Due to password protection, only authorized personal is able to enter the system and to view and edit data. Entries and actions within the application are marked with a date and time stamp and the name of the respective study team member who locked into the system. Double data entry is performed in REDCap to digitalize all source documents. In addition, data preparation of PCA protocols is done by two independent study team members. All data entries in REDCap are deidentified. Regular back-ups of study data take place and back-ups are stored on secure webservers of the University Hospital of Basel.

Sample Size
Reported effects sizes for OLP effects in clinical and sub-clinical trials are generally medium to large (11, 12) with overall Standardized Mean Differences (SMD) of 0.72–0.88. The confidence intervals reported in the larger meta-analysis by von Wernsdorff, Loef et al. (12) suggests that there is substantial variability in the observed effect sizes among the different studies, ranging from SMD 0.39 to 1.05. Therefore, using the statistical software G*Power we conducted a conservative power calculation on the basis of an F-test for an ANCOVA for two groups. This analysis showed that we would need a sample size of $n = 84$ for a power of 0.8 to detect a medium effect size of $d = 0.55$ with a one-sided alpha-level of 0.05 when disregarding any covariates. We then estimated by which factor the residual variance in our primary outcome variable would decline as a consequence of the additional explained variance by our two covariates (see description below). We thereby assumed that they would explain an additional 25 percent of the variance of the outcome as an upper limit ($r^2 = 0.25$). This assumption is based on a suggested correlation of $r = 0.5$ between the baseline morphine consumption and the post-randomization consumption. In terms of the reduced residual variance this would lead to a decline by a factor of $1- r^2 = 0.75$ and as a consequence to an increase of the effect size d by 1/sqrt(0.75) = 1.15 yielding an expected effect size of $d = 0.635$. This in turn would reduce the sample size necessary as computed above to $n = 64$.

Based on these calculations and considerations, we decided to enroll a total sample size of 70 (i.e., 35 per group) which takes a drop-out rate of c.10% into account. This sample size is comparable with previous two-armed clinical OLP studies which have found medium to large effect sizes [e.g., (13): $n = 83$, $d = 0.76$, (22): $n = 80$, $d = 0.79$].

Statistical Analysis
The primary research question of this study is whether there is a difference in the total amount of morphine consumed over the course of the intervention period (i.e., across 48 h) between the

two groups. In order to answer this question, we will compare the total amount of consumed morphine across the two groups using a one-way ANCOVA. Baseline morphine consumption (i.e., consumption prior to randomization) and patients' history of morphine consumption [calculated as morphine equivalent dose by the in-house opioid calculator (76)] prior to study start are the two covariates, and treatment group the between subject factor. We expect that the OLP intervention group will show significantly lower morphine consumption over the course of 48 h (T1–T5) in comparison to the TAU control group.

Regarding our primary outcome, we are in addition interested in answering the following questions:

1. **Do the temporal fluctuations of morphine consumption differ over the course of 48 h between the two groups?** To answer this question, we will calculate the amount of morphine consumption for intervals of 12 min (corresponds to the lock-out period of the PCA) starting at the time of the first study visit (i.e., start of the intervention period) for a total of 48 h. This yields a total of 240 intervals each indicating if morphine was consumed within this time period or not. We will then calculate the Root Mean Square of Statistical Differences (RMSSD) indices for each patient as a measure of variability over time and compare them between the two groups using an ANCOVA with baseline RMSSD of morphine consumption as covariate.
2. **How does the course of consumption of the two groups evolve over time?** This question will be answered by using again the data with the 12 min intervals and by performing Generalized Linear Mixed Model (GLMM) analyses with morphine consumption (yes/no) as dichotomous dependent variable, group as between subjects factor, time as within subjects predictor, including the interaction time x group. The predictor time may be included as a linear term or, depending on the observed temporal course, as a curve-linear term. In case of a more complex temporal pattern, the use of Generalized Additive Mixed Models (GAMMS) might be useful as these models allow for a smoothing function to more flexibly model the temporal course.

Analyses of secondary outcomes (e.g., morphine desire rates, pain intensity, etc.; cf. Secondary Outcomes) will also focus on group differences, whereby covariates (such as baseline variables) will be included in the statistical model if they are known to be predictive of the respective outcome. In case no covariates are included, we will use a *t*-tests instead of an ANCOVA to analyze group differences. Furthermore, explorative regression analysis of potential predictors (e.g., preoperative anxiety, placebo beliefs, etc.) of morphine consumption will be performed.

In case of missing data, multiple imputation will be adopted prior to the analysis. All analysis will be performed using RStudio for Mac. Any deviation from the here reported statistical plan will be described and justified in the final report, as appropriate.

Monitoring

The study is monitored for quality and regulatory adherence by an independent monitor of the University Hospital of Basel. The monitor verifies the qualification of the investigators and study team members and monitors sound and appropriate documentation. In addition, monitoring visits serve to approve that:

- The study is conducted according to the study protocol and within the specified time frame.
- Data is collected accurately and completely documented in REDCap and the source documents.
- The intervention medication (placebo injections) is correctly prepared, dispensed and accounted for.
- Side effects are correctly defined, assessed and documented.

DISCUSSION

Despite intense research during the last 50 years, adequate pain management—especially in the postoperative phase—is still a challenge. The available selection of pharmacologic agents is limited, and their clinical use is often restricted by their (dose dependent) side effects. Even more, high dosages of analgesics can harm the patient. Respiratory failure, due to opioid overdose, or gastric toxicity of non-steroidal anti- inflammatory drugs (40), especially in the most vulnerable (old and multi-morbid patients) are only two examples. Furthermore, since the opioid crisis in the US (77) and raising opioid prescriptions even in Switzerland and worldwide (78, 79), there is a great interest in developing new medications and treatment strategies to reduce acute pain, analgesic demands and thereby improve patient's safety.

OLPs hold the potential of using placebo effects in an ethical manner. This is of special interest in the area of pain where placebo effects and placebo responses have been long recognized and are well investigated. OLPs have been shown to be effective in some clinical populations [see (11, 12) for an overview], e.g., in chronic low back pain (13, 15–17). In addition, there are promising results by several experimental OLP analgesia studies (7, 8, 32–34). However, concerning OLP effects in acute pain, there is only limited evidence. So far, only two Randomized Controlled Trials (RCTs) have investigated OLP in acute pain (30, 31). Both of these studies have used an OLP conditioning paradigm in order to reduce opioid doses compared to TAU. To our knowledge, the present study is the first RCT investigating an OLP intervention without conditioning in the clinical management of acute postoperative pain. Results of this trial will thus inform about the efficacy of adding OLP to TAU as a potential means to reduce opioid doses, but also about the feasibility to integrate OLPs in the management of acute postoperative pain.

A main strength of our study design is the use of the PCA pumps. The pump enables the patient to self-administer 2 mg of morphine every 12 min which allows us to measure the exact consumption of morphine. During the 12 min lock out time it is not possible to administer a second bolus, but each click on the PCA will be saved by the pump. Therefore, we are also able to assess the amount of morphine desire (i.e., number of clicks on the pump without bolus application). Thus, using the PCA as primary outcome measure allows to measure continuously and indirectly patient's pain perception in addition to the self-reported pain intensity ratings. This indirect

measure addresses one of the primary shortcomings of previous OLP studies which mostly rely on subjective self-reported questionnaires. In addition, measuring morphine consumption as indirect indicator of participant pain can minimize reporting bias (e.g., wishing to please the experimenter), when comparing to subjective pain ratings. Furthermore, the continuous nature of our primary outcome can provide information on how long OLP effects can last. Beyond that, finding adequate control groups has been identified as an issue in previous OLP trials (11). We address this problem by offering the same amount and quality of contacts with the study team in the control as well as the intervention group. In addition, the TAU group allows to control for the natural course of postoperative pain, regression to the mean, and other biases inherent to clinical trials (80). Finally, the assessment of many different questionnaires including attitudes and experiences of participation enables us to investigate underlying mechanisms and factors influencing the placebo response.

The chosen design and setting of this study entail some limitations. Firstly, due to the specific study population of dorsal LIF patients the results might not be generalizable to all patients suffering from acute postoperative pain. Secondly, although we tried to implement blinding procedures as much as possible, due to the nature of OLPs, reporting bias cannot be ruled out. Thirdly, we are aware that giving a rationale only to the intervention group differs from procedures of prior studies investigating OLPs (19, 21–23), which raises questions regarding balanced patient-provider interaction time across conditions. However, TAU in the postoperative pain care normally does not include an OLP rationale. In addition, providing the rationale might lead to disappointment in the control group and even increase the possible difference between OLP and TAU. Finally, as the sample size is relatively small and the intervention phase is short, more investigation will be needed to allow clinical recommendations.

To sum up, this study strives to contribute to the young research field of OLP, which aims at elaborating ways of harnessing placebo effects ethically in clinical practice and thereby enabling a new cost-efficient way of evidence-based patient-centered medicine. It is the first study to investigate OLP effects without conditioning in a clinical sample suffering of acute pain and might therefore be of great importance in answering the question whether the knowledge we have about deceptive placebos in acute pain can also be applied to OLP. Furthermore, due to its interdisciplinary set up at the University Hospital of Basel, this study contributes to the process of raising awareness about placebos in the clinical day to day live and contributes to answering questions about the real-life applicability of placebo treatments in clinical practice.

ETHICS AND DISSEMINATION

This study is carried out in accordance with the protocol and principles enunciated in the current version of the Declaration of Helsinki (81), the guidelines of Good Clinical Practice (GCP) issued by the International Council for Harmonization of Technical Requirements for Pharmaceutics for Human Use [ICH (82)], the ISO norm 14155 [International Organization of Standardization (83)], the ISO norm 14971 (84), and the Swiss law and Swiss regulatory authority's requirements. In compliance with our in-house ethical guidelines, patients received no compensation for taking part in the study.

Confidentiality

Data will be handled confidentially, be protected and encoded. Participants' confidentiality will be maintained at all times. Direct access to source documents will be permitted for purposes of monitoring, audits, and inspections, however while respecting medical secrecy and refraining from divulging participants' identity. Co-investigators and study team members (i.e., pain nurses and master students) will have access to the protocol, datasets, and statistical codes during and after study conduct.

Access to Data

Only investigators and study team members will have access to relevant data on the computer system of the University Hospital of Basel.

Dissemination Policy

The results of the planned analyses will be published in a peer-reviewed journal. Talks at conferences and other occasions (e.g., teaching) are also planned.

ETHICS STATEMENT

The study protocol for this study was approved by "Ethikkomission Nordwest- und Zentralschweiz" (BASEC2020-00099) on April 4, 2020. Trial and protocol design were developed according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (85). Substantial protocol amendments are only implemented after approval of the competent ethics committee. Patients interested in study participation are provided with sufficient oral and written information for an informed decision concerning participation. IC is only obtained if participants meet the inclusion criteria and thus are over the age of 18, can understand the study and are able to provide IC. Withdrawal from the study is possible at any stage of the study without the need to state a reason and does not entail any negative consequences.

AUTHOR CONTRIBUTIONS

DS, CN, MD, SB, CL, WR, JG, and TS conception and design of the study. DS, ML, AM, and TS drafting of the manuscript. All authors critical revision, proofreading and approving of the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.687398/full#supplementary-material

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Placebo Responses and Their Clinical Implications in Fibromyalgia: A Meta-Analysis Using SSRI and SNRI Trials

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Background: Fibromyalgia (FM) is a chronic primary pain condition, associated with widespread musculoskeletal pain, disturbed sleep, fatigue, cognitive dysfunction, and a range of comorbid conditions such as irritable bowel syndrome, and depression. Despite its high prevalence of 2% in the general population, FM continues to pose scientific and clinical challenges in definition, etiology, and day-to-day management. In terms of treatment, FM can be treated with selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs).

Objective: Patients with FM and other chronic primary pain syndromes are known to experience substantial and clinically relevant placebo effects. An update of the placebo responses for various outcomes in the FM population and especially a discussion about clinical implications is therefore needed.

Methods: We used data from a large data pool that includes randomized controlled trials (RCTs) examining within-placebo mean change scores of baseline vs. follow-up assessments in FM trials of SSRIs and SNRIs. The primary outcomes were pain, functional disability, and depression and using different scales. We assessed heterogeneity of included trials.

Results: A total of 29 RCTs with $N = 8{,}453$ patients suffering from FM were included in our analysis. Within-placebo mean change scores of baseline vs. follow-up assessments were large for pain (mean change = 2.31, 95% CI: 0.42–4.21, $p = 0.017$), functional disability (mean change = 3.31, 95% CI: 2.37–4.26, $p < 0.000$), and depression (mean change = 1.55, 95% CI: 0.92–2.18, $p < 0.000$). Heterogeneity was found to be large for all outcomes.

Impact: Our results provide preliminary evidence that placebo responses, which also consist of non-specific effects, might play a role in the treatment of FM. Furthermore, we highlight limitations of our analyses and make suggestions for future studies.

Keywords: placebo, fibromyalgia, antidepressants, SSRIs, SNRIs, meta-analysis

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INTRODUCTION

Fibromyalgia (FM) is a Chronic Primary Pain condition classified under MG30.01 Chronic Widespread Pain in the ICD-11. The cardinal markers of FM include non-specific musculoskeletal pain, fatigue, chronically disturbed sleep, and mild cognitive dysfunction (1). FM is common, with estimated prevalence in the general population to be between 2 and 10% (2), and a majority of patients being female (3). Significant challenges, however, in the diagnosis and long-term management of the syndrome persist. On paper, since 1990 reaching a diagnosis has relied on the American College of Rheumatology (ACR) criteria, which are regularly updated to better the quantification of the central FM symptoms and comorbidities (4–6). In clinical practice, both poor knowledge of (7) and poor adherence (8) to the ACR criteria has been observed. Instead, in line with newer recommendations, differentiation (9) from symptomatically similar conditions such as such as somatic or rheumatic diseases and a comprehensive review of patient history drive diagnosis (10).

It remains undetermined what causes FM but separate mechanisms have been suggested for the individual symptoms. Chronic pain, for example, has been linked to central sensitization, a physiological process, in which nociceptive input is abnormally amplified in dorsal horn neurons (11). This leads to both allodynia, perception of otherwise innocuous stimuli as painful, and hyperalgesia, the heightened sensitivity to painful stimuli. A more comprehensive explanation of FM is offered by the biopsychosocial framework, which acknowledges the interactive contribution of biological, psychological and social factors to the syndrome (12). Importantly, it proposes that concurrent management of affective distress such as depression is an integral part of managing FM (13). Still, long-term treatment strategies are effectively reduced to management of individual symptoms, guided by patient treatment preferences (14) and thus lack global standardization (15). Central healthcare goal is pain management (16) and it is commonly addressed through pharmacological interventions.

There are several options for pain management through pharmacotherapy in FM. The most common include non-steroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs) and gabapentinoids (17). None of these, however, have shown universally beneficial effects in FM patients. NSAIDs, for example, have not been found to be significantly better than the placebos (18). Research on SSRIs and SNRIs, which were deemed promising as they target the typical for FM low serotonin levels, has shown mixed results, with some finding strong evidence for their analgesic efficacy compared to placebo (19), but others failing to find the same (20). Other antidepressants such as tricyclic antidepressants follow a similar pattern with most promising benefits being in terms of sleep quality (21). Opioids, which are not indicated by clinical guidelines but remain common in clinical practice, have been repeatedly rejected in research as a long-term pain management solution due to their lesser effectiveness compared to other medication, but their high incidence of misuse (22). The mixed success rate raises the question if non-specific factors, reflected by the placebo response, have an impact on symptom improvement.

The placebo response is well-established effect across various pharmacological interventions (23). The placebo response is defined as the improvement of patients randomly assigned to the placebo group (24), thus is determined not only by the placebo effect, but also by the natural course of the disease (e.g., spontaneous remission) and statistical artifacts (e.g., regression to the mean) (25). Patients with Chronic Primary Pain (CPP) diagnoses (23), which includes FM, and affective disorders (particularly depression) (26, 27) have been found to be particularly susceptible to placebo (23). Patients with FM have also shown clinically relevant and statistically significant placebo effects (28). However, clinical implications of these findings in the field of FM have only rarely been discussed. A comprehensive assessment of the impact on both pain and concurrent affective distress is needed to reflect the interaction of biopsychological manifestations of FM and the new diagnostic criteria for CPP as stated in the International Classification of Diseases, 11th Edition (ICD-11) (29, 30). Therefore, an updated meta-analysis that takes clinical considerations into account is needed. The main aim of this meta-analysis was to analyze the placebo response in pain, functional disability, and depression in trials examining SSRIs and SNRIs in patients living with FM.

METHODS

Search Strategy and Study Selection

A systematic literature search of RCTs was undertaken in the following electronic databases: MEDLINE, Embase, PsycINFO, Cochrane Central, and Web of Science, without applying restrictions to language or date of publication. A first search was conducted until April 5, 2018 and was updated in October 2019. The search revealed a total of 72215 records. After removing 9,800 duplicates, 62,415 records remained. Note that the search strategy also included all other categories of CPP (i.e., chronic primary musculoskeletal pain, chronic widespread pain, complex regional pain syndrome, chronic primary headache and orofacial pain, and chronic primary visceral pain), as this analysis is part of a larger project (31). See **Appendix 1** for the search strategy for the larger project. Within this larger pool of included RCTs, we went through all full-texts and specifically tagged FM papers, which were then included in the presented analysis. We included RCTs that compare an SSRI and/or an SNRI to a placebo control group or another SSRI and/or SNRI in the treatment of FM. Parallel and crossover trials were included. Protocols and conference papers, randomized single control studies, prophylactic interventions, as well as case-control studies, *post-hoc* analyses or secondary analyses, and results reported solely on clinical trials were excluded. RCTs had to be either in English or German. Patients of both sexes from the age of 18 up, with a primary diagnosis of FM diagnosed by the

American College of Rheumatology (ACR) 1990, 2010, or 2016 were included.

Data Assessment

The following information was extracted from all included studies: study characteristics (lead author, publication year, sponsor, country of study conductance, setting, number of clinical sites), participant characteristics (such as diagnostic criteria, duration of diagnosis, age, sex, duration of symptoms, age of onset, comorbidities), study design (type of study such as parallel or crossover design, special population (if 80% or more of the sample share a particular characteristic), special inclusion criteria, special exclusion criteria, emergency medicine, co-intervention), intervention details (such as a description of the intervention by the authors, provider, treatment duration, dose intended, dose delivered, number of randomized people in the treatment arm, timeframe for post [measured at the time point closest to the end of treatment], timeframe for follow-up 1 [at least 3 months/12 weeks but less or equal to 6 months/24 weeks after randomization], timeframe for follow-up 2 [more than 6 months/25 weeks but less or equal to 12 months/52 weeks after randomization]). If several assessments were reported, we chose the one with the longest timeframe since randomization (i.e., FU2 > FU1 > post). For the continuous outcomes, sample sizes (*N*), means (*M*), standard deviations (SD), CIs, and changes from baseline were noted for each extracted treatment arm of the

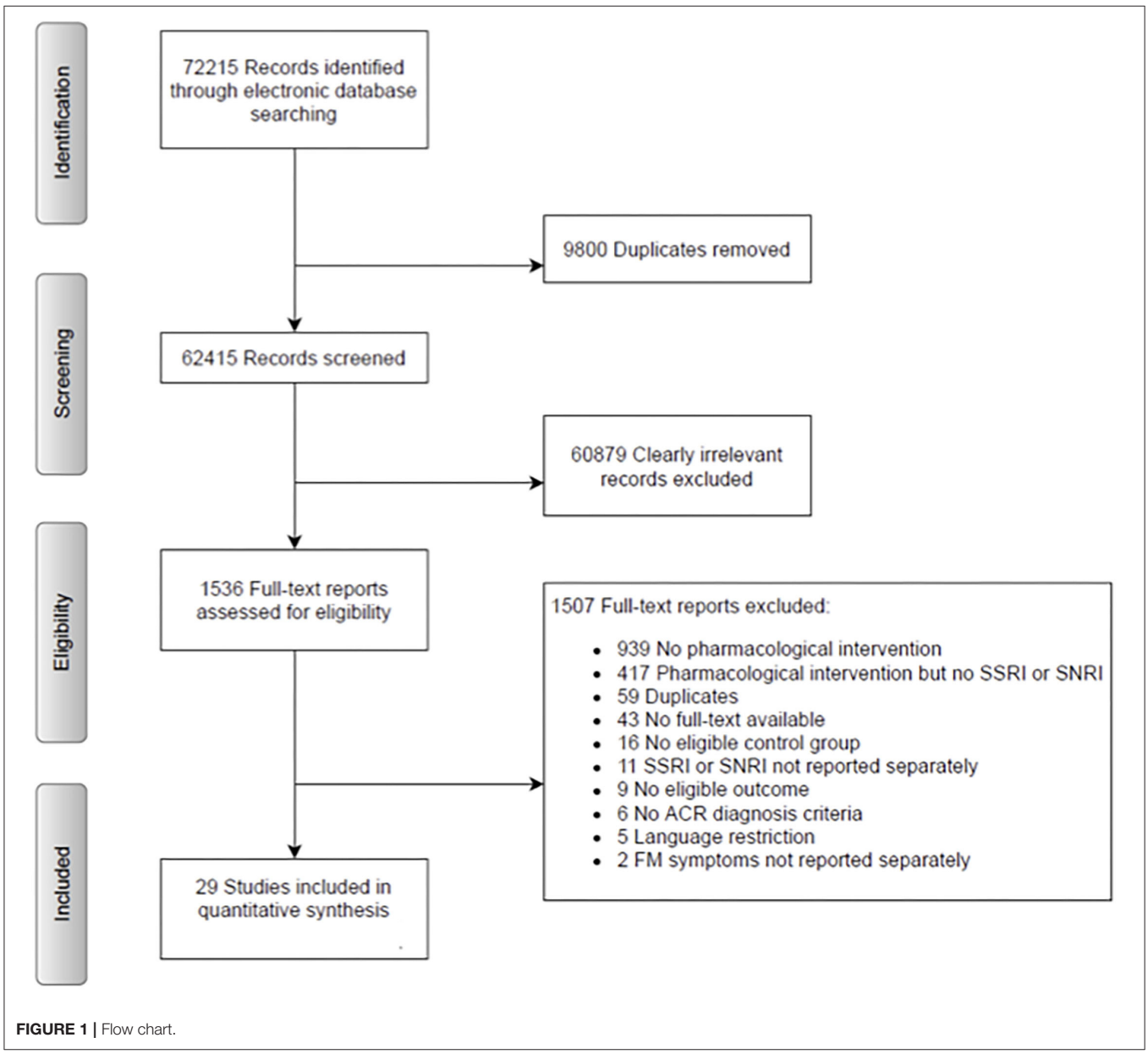

FIGURE 1 | Flow chart.

TABLE 1 | Characteristics of included studies.

Study ID	Intervention	*N* randomized	% Female	Age	Co-intervention	Treatment duration (weeks)	Timeframe post assessment (weeks)
Ahmed 2016	Milnacipran Placebo	9 9	89.5% (overall)	49.2 (overall)	Yes	4	4
Allen 2017	Desvenlafaxine Placebo	566 130	93.78% 97.7%	48.6 50.46	NR	15	15
Anderberg 2000	Citalopram Placebo	21 19	100% 100%	48.6 (overall)	Yes	16	16
Arnold 2002	Fluoxetine Placebo	30 30	100% 100%	46 46	Yes	12	12
Arnold 2004	Duloxetine Placebo	104 103	88.5% 89.3%	49.9 48.3	Yes	12	12
Arnold 2005	Duloxetine Placebo	234 120	100% 100%	49.6 (overall)	Yes	12	12
Arnold 2010	Duloxetine Placebo	263 267	92.8% 93.6%	50.7 49.6	Yes	12	12
Arnold 2010	Milnacipran Placebo	516 509	96.9% 93.7%	49.1 48.7	Yes	12	12
Arnold 2012	Duloxetine Placebo	155 153	94.2 96.1	50.9 50.7	Yes	12	12
Branco 2010	Milnacipran Placebo	435 449	95.1% 93.5%	48.3 49.2	Yes	16	16
Chappell 2008	Duloxetine Placebo	162 168	91.98% 94.64%	50.75 50.23	NR	27	27
Clauw 2008	Milnacipran Placebo	802 405	97% 94.8%	49.95 50.7	NR	15	15
Clauw 2013	Milnacipran Placebo	100 51	96% 96%	54.5 54	No	12	12
Gendreau 2005	Milnacipran Placebo	97 28	98% 96%	46.83 48	Yes	12	12
Giordano 1999	Paroxetine Placebo	20 20	100% 100%	31 (overall)	NR	12	12
Goldenberg 1996	Fluoxetine Placebo	15.5 (overall)	90.3% (overall)	43.2 (overall)	No	6	6
Matthey 2013	Milnacipran Placebo	40 40	100% 100%	48.5 50.9	NR	8	7
Mease 2009	Milnacipran Placebo	665 223	95.63% 95.5%	49.44 49.4	Yes	27	27
Murakami 2015	Duloxetine Placebo	196 197	82.2% 84.1%	47.8 49.5	Yes	14	14
Natelson 2015	Milnacipran Placebo	17 17	97.06% (overall)	48 45.6	Yes	8	8

(Continued)

TABLE 1 | Continued

Study ID	Intervention	*N* randomized	% Female	Age	Co-intervention	Treatment duration (weeks)	Timeframe post assessment (weeks)
Norregaard 1995	Citalopram Placebo	21 21	NR	48 50	Yes	8	8
Patkar 2007	Paroxetine Placebo	58 58	95% 93%	47.9 49.1	Yes	12	12
Pickering 2018	Milnacipran Placebo	29 25	100% 100%	48 44.3	NR	4	4
Russell 2008	Duloxetine Placebo	376 144	94.71% 95.1%	51.34 50.3	Yes	28	28
Sencan 2004	Paroxetine Placebo	20 20	100% 100%	32.65 35.55	No	6	26
Schmidt-Wilcke 2014	Milnacipran Placebo	11.5 11.5	100% 100%	40.7 (overall)	Yes	6	6
Vitton 2004	Milnacipran Placebo	97 28	NR	NR	Yes	12	12
Wolfe 1994	Fluoxetine Placebo	21 21	100% 100%	48 52.9	No	6	6
Zijlstra 2007	Venlafaxine Placebo	45 45	97.78% 93.33%	47.8 44.8	Yes	6	6

respective study. If the study reported different doses of either an SSRI or an SNRI, Ms, SDs, and changes were averaged, and *N* was merged. If *N* was reported as a total of all treatment arms, it was divided through the number of treatment arms. Additionally, intention to treat was prioritized over the completer analysis.

As recommended by the Cochrane Handbook for systematic reviews, we always tried to calculate Ms and SDs before imputing them, as imputation methods are based on making assumptions about the trial (32). If a study did not report the mean values numerically, data was extracted from figures using the software DigitizeIt version 2.5 (33). If SDs were not provided, they were calculated from standard errors (SE), *N*, Ms, and/or *p*-values. If SDs could not be calculated, the mean of SDs from studies using the same outcome measure was imputed (34).

Primary Outcomes

Global pain intensity and the global measurement of pain were our primary outcomes. We extracted both outcomes where both were reported. Additional primary outcomes were a generic measure of functional disability and depression. For all outcomes, we used a pre-defined hierarchy of validated and standardized measurements. For global pain intensity, the hierarchy was as follows: Visual Analog Scale (VAS) > Fibromyalgia Impact Questionnaire (FIQ) (35) > Numeric Rating Scale (NRS) (36); for the global measurement of pain: Brief Pain Inventory (BPI) (37) > Short-Form McGill Pain Questionnaire (SF-MPQ) (38). For emotional distress, we applied the following hierarchy: Beck Depression Inventory (BDI) (39) > FIQ depression subscale (35) > Patient Health Questionnaire 8 (PHQ-8) (40) > Hamilton Depression Rating Scale (HMD) (41) > Montgomery Åsberg Depression Rating Scale (MADRS) (42). For the generic measures of functional disability, studies applied the BPI (37), the Health Assessment Questionnaire (HAQ) (43), or the FIQ (total score or subscale). If different primary outcomes were given in an individual study, the measurement highest in our hierarchy was extracted. The choice of our primary outcomes is in line with recommendations for clinical trials studying chronic pain (IMMPACT initiative) (44). Furthermore, we decided to focus on self-reported measures. Finally, we intend to prioritize global scores over syndrome-specific scores since the definition of CPMP includes various syndromes (45).

Statistical Analyses

The placebo responses was assessed as the mean change scores of baseline vs. follow-up assessments. A bar chart was created in order to visualize the mean change scores for the placebo group. Analyses were applied within a frequentist framework. We chose to use random-effects models rather than fixed-effects models because the studies that we included were assumed to be heterogenous and the number of included studies was relatively small. Heterogeneity was assessed by calculating the *Q* statistic (46), the τ^2 (47), and the I^2 (48). An I^2 value of 0% indicates no heterogeneity, a value of 25% is classified as low, 50% as moderate and 75% as high (48).

TABLE 2 | Measurements for all outcomes across included studies.

Study ID	Intervention	Pain (range)	Mean (SD) Baseline	Mean change (SD)	Disability (range)	Mean (SD) baseline	Mean change (SD)	Depression (range)	Mean (SD) baseline	Mean change (SD)
Ahmed 2016	Milnacipran Placebo	BPI mean severity score (0–10)	5.4 (1.2) 5.4 (1.2)	−1.3 (2.32)* −0.7 (1.55)*	BPI mean interference score (0–10)	6.4 (1.5) 6.4 (1.5)	2.6 (2.04)* 2.1 (1.76)*	NR	NR NR	NR NR
Allen 2017	Desvenlafaxine Placebo	NRS (0–10)	6.7 (1.29) 6.7 (1.29)	−2.14 (0.23) −2.21 (0.23)	FIQ total score (NR)	NR NR	15.97 (2.95) −15.1 (2.95)	NR	NR NR	NR NR
Anderberg 2000	Citalopram Placebo	VAS pain score (0–10)	5.8 (2) 6.9 (1.4)	−0.71 (0.58) −0.312 (0.58)	NR	NR NR	NR NR	MADRS (1–6)	7.5 (5.9) 7.3 (4.3)	−4.22 (3.46) 0 (3.46)
Arnold 2002	Fluoxetine Placebo	FIQ pain subscore (0–10)	6.1 (1.9) 6 (1.9)	−1.8 (2.4) 0.4 (2.4)	FIQ total score (0–80)	42 (14) 44 (14)	−8.6 (14.5) 2.9 (13.6)	FIQ subscale Depression (0–10)	2.7 (2.7) 2.5 (2)	−0.9 (2.8) 1.1 (2.5)
Arnold 2004	Duloxetine Placebo	FIQ pain subscore (0–10)	6.9 (2.1) 7 (2)	−1.98 (2.96) −1.35 (2.96)	BPI average pain interference (0–10)	5.5 (2.4) 5.5 (2.3)	−2.01 (2.59) −0.95 (2.59)	BDI–II Total score (0–63)	12.7 (9.6) 13.2 (8.9)	−3.32 (7.82) −1.02 (7.82)
Arnold 2005	Duloxetine Placebo	BPI average pain severity (0–10)	6.4 (1.5) 6.5 (1.5)	−2.39 (3.34) −1.16 (2.28)	BPI average pain interference (0–10)	5.9 (2.25) 6 (2.1)	−2.57 (3.34) −1.43 (2.28)	HAMD (0–52)	11.3 (6.3) 11.5 (6.5)	−3.38 (6.69) −2.24 (4.7)
Arnold 2010	Duloxetine Placebo	BPI average pain severity (0–10)	6.5 (1.5) 6.5 (1.6)	−2.3 (2.74) −1.5 (2.82)	BPI average interference (0–10)	6 (2) 6 (2.1)	−2.6 (2.74) −1.7 (2.81)	BDI total score (0–36)	16.2 (10.4) 16.2 (10.4)	−5.5 (8.11) −3.6 (8.17)
Arnold 2010	Milnacipran Placebo	VAS pain score (0–100)	66.8 (16.4) 68.8 (17)	−19.96 (1.57) −12.83 (1.55)	BPI average pain interference (0–10)	NR NR	−1.49 (0.14) −0.91 (0.13)	BDI total score (0–36)	9.1 (6.3) 8.7 (6.5)	−2.12 (0.31) −1.24 (0.31)
Arnold 2012	Duloxetine Placebo	BPI average pain severity (0–10)	6.5 (1.47) 6.37 (1.67)	−2.14 (2.47) −1.86 (2.47)	BPI interference score (0–10)	5.97 (2.17) 5.78 (2.28)	−2.28 (2.47) −1.78 (2.47)	BDI–II total score (0–63)	15 (9.64) 16.84 (11.47)	−5.47 (7.1) −3.91 (7.06)
Branco 2010	Milnacipran Placebo	VAS 24–h recall pain (0–100)	NR NR	−21.9 (25.27) −16.09 (25.27)	BPI SF pain interference (NR)	NR NR	−1.26 (1.98) −0.93 (1.98)	BDI total score (0–36)	10.3 (6.6) 10.9 (6.7)	−0.74 (6.45) −0.29 (6.45)
Chappell 2008	Duloxetine Placebo	FIQ pain score (NR)	NR NR	−1.69 (2.73) −1.06 (2.81)	BPI average interference (0–10)	NR NR	−1.69 (2.51) −1.03 (2.46)	BDI–II Total score (0–63)	NR NR	−3.42 (7.82) −1.45 (7.81)

(Continued)

TABLE 2 | Continued

Study ID	Intervention	Pain (range)	Mean (SD) Baseline	Mean change (SD)	Disability (range)	Mean (SD) baseline	Mean change (SD)	Depression (range)	Mean (SD) baseline	Mean change (SD)
Clauw 2008	Milnacipran Placebo	Patient experienced pain (0–100)	64.55 (13.65) 65.7 (13.3)	−16.55 (29.54) −13 (29.54)	FIQ total score (NR)	62.1 (13.9) 62.5 (14.1)	−16 (22.71) −12 (22.71)	BDI total score (NR)	13.95 (8.7) 13.8 (9)	−3.3 (8.32) −2.3 (8.32)
Clauw 2013	Milnacipran Placebo	VAS pain score (0–100)	16.6 (9.6) 19.3 (11.6)	8.94 (27.35) 21.3 (27.35)	FIQR total score (0–100)	19.4 (11.9) 21.4 (15.8)	3.78 (16.89) 13.6 (16.89)	SF−36 MCS score (NR)	53.6 (9) 53.6 (11.3)	−2.79 (5.41) −4.64 (5.41)
Gendreau 2005	Milnacipran Placebo	VAS pain score (0–10)	NR NR	−2.26 (3) −0.9 (2.9)	NR	NR NR	NR NR	NR	NR NR	NR NR
Giordano 1999	Paroxetine Placebo	Average score of tender points (1–5)	4.19 (0.35) 3.8 (0.35)	−2.24 (1.91)* 0.3 (1.91)*	NR	NR NR	NR NR	NR	NR NR	NR NR
Goldenberg 1996	Fluoxetine Placebo	VAS pain score (0–100)	68.4 (20.4) 68.4 (20.4)	−10.9 (23.5)* 13.1 (18.76)*	FIQ total score (NR)	57.3 (17.6) 57.3 (17.6)	−9.7 (18.8)* 1.2 (17.36)*	BDI (NR)	12.4 (8.5) 12.4 (8.5)	−4.6 (7.37)* −3.1 (7.7)*
Matthey 2013	Milnacipran Placebo	Current Pain VAS (0–100)	46.8 (18.7) 50.8 (21.8)	−7.2 (21.24)* −2.5 (23.62)*	FIQ total score (0–100)	53.6 (17) 54.7 (14.4)	−9.5 (19.18)* −0.6 (16.9)*	BDI–II Total score (0–63)	10.6 (7.1) 12.6 (7.6)	0.2 (8.84)* 2.4 (8.84)*
Mease 2009	Milnacipran Placebo	VAS 24–h recall pain score (0–100)	73.57 (16.2) 74.3 (15.1)	−30.29 (32.71)* −21.94 (32.81)*	FIQ total score (0–100)	64.57 (14.17) 64.7 (13.4)	−17.41 (18.28) −15.91 (18.28)	NR	NR NR	NR NR
Murakami 2015	Duloxetine Placebo	FIQ pain subscore (NR)	6.83 (1.52) 7.01 (1.67)	−2.37 (4.7) −1.76 (4.89)	BPI interference scores (NR)	5.1 (2.07) 4.95 (2.09)	−1.95 (3.73) −1.44 (3.77)	BDI–II total score (0–63)	15.34 (9.73) 14.89 (9.62)	−4.09 (11.61) −1.19 (11.87)
Natelson 2015	Milnacipran Placebo	VAS pain (NR)	6.43 (1.54) NR	−1.24 (1.57) 0.66 (1.75)	NR	NR NR	NR NR	NR	NR NR	NR NR
Norregaard 1995	Citalopram Placebo	VAS pain (0–10)	6.3 (2) 6.7 (1.9)	−1 (2.1) −0.7 (1.7)	FIQ Physical function (0–3)	1.7 (0.6) 1.7 (0.5)	0 (0.4) 0 (0.4)	BDI (0–36)	16.4 (8.3) 16.3 (8.3)	1 (6.1) 0.9 (7.9)
Patkar 2007	Paroxetine Placebo	VAS pain score (0–100)	74.2 (22.7) 75.3 (19.8)	−12.2 (18.5) −8.8 (16.6)	FIQ total score (0–100)	53 (8.9) 49 (12.2)	−19.7 (13.74) −13.4 (13.74)	NR	NR NR	NR NR
Pickering 2018	Milnacipran Placebo	NRS (0–10)	NR NR	−1 (2.1) −1 (1.7)	NR	NR NR	NR NR	NR	NR NR	NR NR
Russell 2008	Duloxetine Placebo	BPI pain severity score (0–10)	6.52 (1.52) 6.6 (1.7)	−2.14 (4.46) −1.43 (2.52)	FIQ total score (NR)	52.18 (12.67) 53.0 (11.2)	−13.42 (29.67) −10.42 (17.52)	SF-36 mental component (NR)	NR NR	3.73 (20.17) 1.75 (12)

(Continued)

TABLE 2 | Continued

Study ID	Intervention	Pain (range)	Mean (SD) Baseline	Mean change (SD)	Disability (range)	Mean (SD) baseline	Mean change (SD)	Depression (range)	Mean (SD) baseline	Mean change (SD)
Sencan 2004	Paroxetine Placebo	VAS pain score (0–10)	6.62 (1.42) 7.7 (1.72)	−1.61 (1.72)* −1.86 (1.94)*	NR	NR NR	NR NR	BDI (NR)	20.8 (5.25) 18.5 (5.31)	−10.68 (4.55)* −3.35 (4.63)*
Schmidt–Wilcke 2014	Milnacipran Placebo	BPI sev change score (NR)	NR NR	−0.88 (1.8) −0.17 (2.3)	BPI change score (NR)	NR NR	−1.1 (1.7) −0.56 (2.1)	NR	NR NR	NR NR
Vitton 2004	Milnacipran Placebo	VAS pain score (0–10)	NR NR	−2.3 (3) −0.9 (2.9)	NR	NR NR	NR NR	NR	NR NR	NR NR
Wolfe 1994	Fluoxetine Placebo	VAS pain score (0–3)	1.7 (0.48) 1.8 (0.81)	−0.1 (0.69)* −0.2 (0.8)*	HAQ score (0–3)	0.9 (0.48) 1.1 (0.66)	−0.2 (0.46)* −0.3 (0.72)*	BDI (0–36)	11.8 (7.65) 13.9 (8.86)	−3.5 (6.93)* 0 (9.99)*
Zijlstra 2007	Venlafaxine Placebo	FIQ pain subscore (0–10)	6.4 (1.8) 6.6 (1.6)	−1.3 (2.3) −0.1 (2.1)	FIQ total score (0–80)	44.6 (10) 46.4 (11)	−9 (13) −2.7 (12)	BDI (0–36)	13.6 (6.8) 15.4 (8.2)	−3.4 (4.9) −3.2 (5.8)

*Mean change scores have not been reported in the original study and were thus calculated by the authors.

RESULTS

Study Selection

There were a total of 72,215 identified records for the large project. After removing 9,800 duplicates, 62,415 records were taken into consideration for potential inclusion. For this analysis, 1,536 full texts were screened (see **Figure 1**). Abstracts and full texts were screened by two independent researchers, consensus was reached in consultation with the first and last author (HK and CL). Finally, 29 RCTs were included in this analysis.

Study Characteristics

A total of $N = 8{,}453$ patients were included in the analysis. RCTs were conducted between 1994 and 2018 and compared seven SSRIs and SNRIs with placebo. No study compared two or more pharmacological interventions. Mean sample size was $N = 146$ ($SD = 184.90$). In total, 5,126 (M sample size $= 176.76$, $SD = 220.42$) participants were randomly assigned to pharmacological treatments and 3,327 (M sample size $= 114.73$, $SD = 137.92$) were randomly assigned to placebo. Weighted mean age was 49.15 years. In those studies that reported sex, 94.40% of patients were female. Seventeen of 29 trials (58.62%) recruited patients from the USA, eight from Europe (27.59%), three recruited patients cross continental (10.34%), and one from Asia (3.45%). On average 21.91% of patients suffered from Major Depressive Disorder (MDD). Mean treatment duration was 12.5 weeks (range 4–28 weeks). More detailed information and individual characteristics of the included studies can be found in **Table 1**. **Table 2** shows individual measurements including mean, mean change, and standard deviation for all outcomes across studies.

Within-Placebo Mean Change Scores of Baseline vs. Follow-Up Assessments

The mean change score for pain reduction in the placebo group was large and statistically significant (mean change score of baseline vs. follow-up$p = 2.31$, 95% CI: 0.42 to 4.21, $p = 0.017$; see **Figure 2**). Heterogeneity was large with $\tau^2 = 25.49$, $I^2 = 99.9\%$, and $Q = 23{,}728.42$ ($p < 0.000$).

For functional disability, the mean reduction was large and statistically significant with a mean change score of baseline vs. follow-up $= 3.31$, 95% CI: 2.37–4.26, $p < 0.0001$ (see **Figure 2**). Heterogeneity was found to be large with $\tau^2 = 4.02$, $I^2 = 99.4\%$, and $Q = 2{,}561.9$ ($p < 0.000$).

Finally, for depression, the mean change score of baseline vs. follow-up assessment was large and statistically significant again, with a mean change $= 1.55$, 95% CI: 0.92–2.18, $p < 0.0001$ (see **Figure 2**). Heterogeneity was large with $\tau^2 = 1.32$, $I^2 = 87.7\%$, and $Q = 146.38$ ($p < 0.0001$).

DISCUSSION

The present meta-analysis intended to examine the placebo response in the baseline vs. follow-up comparison in pain, functional disability, and depression in trials examining SSRIs and SNRIs in patients with FM. In total, 29 RCTs were included with a mean treatment duration of 12.5 weeks, which is longer

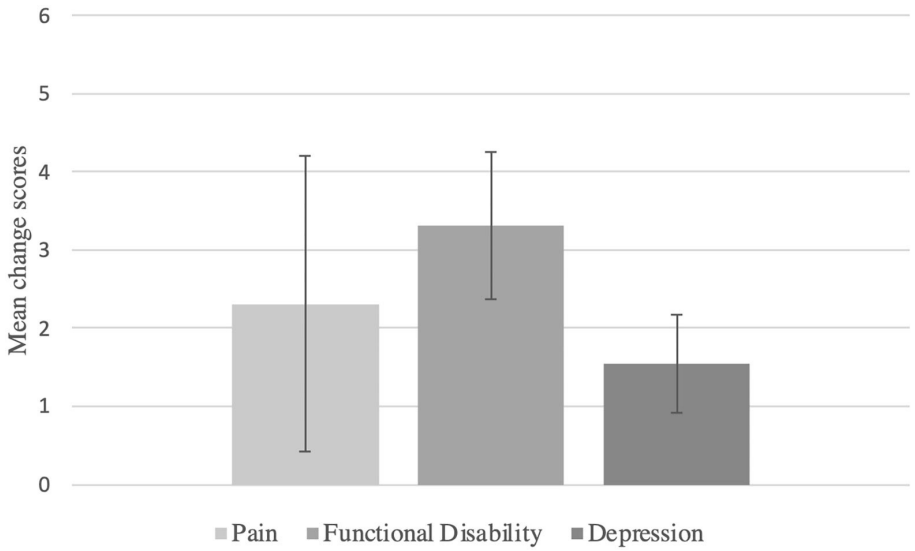

FIGURE 2 | Within-placebo mean change scores of baseline vs. follow-up assessments.

than in previous meta-analyses on antidepressants for FMS (19). We found large and statistically significant within-placebo mean change scores of baseline vs. follow-up assessments.

Notably, the placebo response was highest for the outcome functional disability with a mean change score of baseline vs. follow-up = 3.31 (95% CI: 2.37–4.26, $p < 0.0001$). In the included studies, functional disability measures assessed the impact of FM on a broad range of activities: from mundane everyday tasks, such as self-care and mobility, to general well-being, and engagement in vocational tasks. It has been long-recognized that FM can disrupt these common actions and thus considerably disable patients (49). For many patients maintaining work ability is a primary health concern (50). This is understandable as up to 46% of patients point to their FM as the reason for losing their jobs (51). However, no single treatment option has been established as best to address all the challenges encompassed by functional disability.

Our results indicate that not only a change in pain intensity is possible, but also in other important domains, namely functional disability and depression. These results support the claim that, in many cases, chronic primary pain disorders require a multidisciplinary treatment approach, also referring to the biopsychosocial framework (52–54). Given that placebo responses consists of non-specific effects (besides statistical artifacts and the natural course of the disease), and FM presents as a complex condition, a single-component treatment such as SSRIs and SNRIs falls short (55). From a patients' perspective, however, a reduction in pain intensity is frequently declared to be the most desired treatment outcome (56). Importantly, improvements in different outcome domains do not necessarily correlate with each other, as has been shown in a study that analyzed within-treatment trajectories of patients with chronic pain (57).

Our findings reveal preliminary suggestions for clinical implications. Considering the large placebo response on the different outcome domains, the question arises how these effects can be harnessed in clinical practice. First of all, it is important to clearly define what a placebo is. In research, placebos in randomized controlled trials are used to control for confounders associated with clinical trials, such as spontaneous remission and regression toward the mean (58). In clinical practice, however, placebos can be utilized to enhance positive outcomes by means of well-known placebo mechanisms. These include positive treatment expectations, a patient-physician relationship that is built on trust, and a plausible treatment narrative (59). With the aim to actively harness these mechanisms, the following suggestions might be taken into account when treating patients living with FM: (1) to address key ethical principles such as autonomy and transparency during the administration of SSRIs and SNRIs, i.e., by talking about the empirical evidence for the intervention, including placebo responses and their underlying processes (60); (2) to foster a patient-physician relationship that is based on trust, i.e., by ensuring that patients feel understood and cared for (61); and (3) to address and discuss patients' expectations, i.e., by asking what they expect about the treatment, what wishes and fears are associated with the prospect of receiving SSRIs and SNRIs (62).

Two additional approaches that have been studied in the past and enable to harness placebo effects in the clinical practice are the following: First, placebos could be used as dose extenders. By pairing placebo pills with a physiologically active drug, studies have revealed that medication dosages can be substantially lowered without decreasing the efficacy of the drug (63, 64). A second strategy is known as open-label placebo administration, i.e., the placebo treatment with full disclosure. Open-label placebos are administered with a scientific rationale, i.e., patients

are told that 'we know that placebos have powerful effects' (65). Two meta-analyses reveal that the open-label placebo therapy shows statistically significant and clinically meaningful effects in pain and non-pain conditions (66, 67).

Our analysis has several limitations. First and foremost, within-group analyses have limited validity (68): Mean change scores of baseline vs. follow-up assessments are not independent of each other, since baseline and follow-up scores are correlated. Furthermore, they are affected the natural course and characteristics of the patients and settings, and these cannot be disentangled from the effects of the intervention. However, we were especially interested to research preliminary indication for the potential of placebo in this population and to focus on first recommendations for the clinical routine. Second, since included studies span more than two decades, it cannot be ruled out that a change in the diagnostic criteria over time may have influenced the findings. Third, due to small sample sizes in some SSRI/SNRI treatments, these results might be statistically underpowered. Therefore, some effects might be due to the so-called small-study effect. This means that smaller trials show different, sometimes larger, treatment effects than bigger studies (69). Fourth, treatment duration of included interventions varied largely between 4 and 28 weeks. The optimal duration of treatment therefore remains unclear, and the short duration of several studies leads to open questions with regard to long-term beneficial effects of SSRI/SNRI treatments on FMS symptoms. In a similar fashion, the time points for follow-up assessments varied, which might have contributed to heterogeneity in our results. Finally, the systematic literature search was conducted 2 years ago, hence we cannot rule out that the inclusion of newer studies would have changed the results of our analyses.

Future studies should have an in-depth examination of the placebo response by using individual patient data instead of aggregate data. This would allow to determine patient-related and trial-related placebo moderators and would therefore be in line with the personalized medicine approach (70). This is also strengthened by our data that showed substantial heterogeneity across outcomes. Furthermore, and in order to disentangle placebo effects from the natural course and statistical artifacts, it would be advantageable to compare a placebo arm with a no-treatment arm in SSRI and SNRI trials (25).

In conclusion, our results provide preliminary evidence that placebo responses, which also consist of non-specific effects, might play a role in the treatment of FM.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

HK and CL initiated the study concept, conducted the analyses, and drafted the paper. HK, CL, and AK designed the extraction template. TP and JP extracted the data. HK, CL, TP, JP, AK, and SB wrote the final paper, critically revised the manuscript, and gave important intellectual contribution to it. All authors have read and approved the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpain.2021.750523/full#supplementary-material

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Genomic Effects Associated With Response to Placebo Treatment in a Randomized Trial of Irritable Bowel Syndrome

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Background and Aims: Irritable bowel syndrome (IBS), a functional pain disorder of gut-brain interactions, is characterized by a high placebo response in randomized clinical trials (RCTs). Catechol-O-methyltransferase (*COMT*) rs4680, which encodes high-activity (val) or low-activity (met) enzyme variants, was previously associated with placebo response to sham-acupuncture in an IBS RCT. Examining *COMT* effects and identifying novel genomic factors that influence response to placebo pills is critical to identifying underlying mechanisms and predicting and managing placebos in RCTs.

Methods: Participants with IBS ($N = 188$) were randomized to three placebo-related interventions, namely, double-blind placebo (DBP), open-label placebo (OLP), or simply trial enrollment without placebo treatment [no placebo (i.e., no pill) treatment control (NPC)], for 6 weeks. *COMT* rs4680, gene-set, and genome-wide suggestive ($p < 10^{-5}$) loci effects on irritable bowel symptom severity score (IBS-SSS) across all participants were examined.

Results: Participants with IBS homozygous for rs4680 met (met/met) had the greatest improvement across all arms, with significantly greater improvement compared to val/val in DBP (beta (SE), −89.4 (42.3); $p = 0.04$). Twelve genome-wide suggestive loci formed a gene regulatory network highly connected to *EGR1,* a transcription factor involved in placebo-related processes of learning, memory, and response to stress and reward. *EGR1* gene expression in peripheral blood mononuclear cells (PBMC) was significantly reduced at the endpoint across all treatment arms (log fold-change, −0.15; $p = 0.02$). Gene-set enrichment analysis returned three genome-wide significant ontology terms (GO:0032968, GO:0070934, and

GO:0070937) linked to transcription regulation and GO:0003918 associated with DNA topoisomerase regulation.

Conclusion: These results suggest common molecular mechanisms in response to varying forms of placebo that may inform personalized IBS treatment and placebo response prediction.

Clinical Trial Registration: ClinicalTrials.gov, Identifier: NCT0280224.

Keywords: irritable bowel syndrome (IBS), placebos, catechol-O-methyltransferase (*COMT*), randomized control trial (RCT), gene expression

INTRODUCTION

Irritable bowel syndrome (IBS) is a highly prevalent disorder of the gut-brain interaction, characterized by abdominal pain and altered bowel function. Early life events, including psychological trauma and environmental exposures, such as gastrointestinal infections, increase susceptibility to IBS, and psychological stress frequently exacerbates symptoms. The use of double-blind placebo (DBP) controls in randomized clinical trials (RCT) is associated with high placebo response rates (average 40%) among participants with IBS. Recently, our group completed a 6-week RCT in IBS comparing DBP, open-label placebo (OLP), and simply enrolling in a trial with the patient-researcher engagement but no placebo (i.e., no pill) treatment control (NPC) (1). More than half of the participants in each placebo treatment arm had a >50-point improvement in the primary outcome IBS-symptom severity score (IBS-SSS). Participants randomized to DBP and OLP had similar improvement in IBS symptoms, and both had significantly greater improvement compared with NPC. Understanding the mechanisms underlying response to placebo treatment is critically important to managing placebo effects in IBS clinical care, RCT design, and drug development.

Neurological changes in response to placebo treatment have been mapped to specific brain regions implicated in reward salience, pain, and emotional processing. In the prefrontal cortex (PFC), activation of dopaminergic signaling pathways has been observed in models of placebo response in depression and Parkinson's disease (2). A key regulator of dopamine turnover in the PFC is catechol-O-methyltransferase (*COMT*), an enzyme that metabolizes endogenous catechol-containing neurotransmitters and hormones, including dopamine, norepinephrine, epinephrine, and catechol estrogen. The most studied single nucleotide polymorphism (SNP) in *COMT*, rs4680, encodes a G-to-A transversion, resulting in a valine (val)-to-methionine (met) substitution, and a three-to four-fold reduction in enzymatic activity (3, 4). In a previous randomized trial of placebo treatments in IBS, we reported the association of genetic variation at *COMT* rs4680 with placebo response to single-blinded sham acupuncture augmented with a warm-caring clinical interaction (5).

Response to placebo treatments is a complex phenotype likely influenced by multiple genomic factors in addition to genetic variation in *COMT*. However, large sample size is required to have adequate power to discern the small genomic effects typically observed in a genome-wide association study (GWAS). Hence, we combined the DBP, OLP, and NPC treatment arms, assuming that placebo-related effects would be present and contribute to response in each of the three treatment arms. Because this study was not well-powered to conduct a GWAS, we used gene-set analysis, which aggregates genome-wide association data into pathways and functions, to achieve the power required to identify significant biologically relevant effects.

To broaden our understanding of how genomic variation influences placebo response in IBS, here we examine candidate *COMT* rs4680 and genome-wide effects using gene-set and transcription network analysis across participants in our recently completed IBS RCT of three placebo treatments (i.e., DBP, OLP, and NPC) (1).

Abbreviations: COMT, Catechol-O-methyltransferase; DBP, Double blind placebo; DBM, Double blind mint; IBS-SSS, IBS symptom severity scale; OLP, Open label placebo; NPC, No-pill control.

MATERIALS AND METHODS

Study Design

Effects of open-label vs. double-blind treatment in IBS was a clinical trial that randomized IBS participants to one of three placebo treatments: DBP, OLP, or NPC (1). A small number of participants were randomized to a fourth arm [double-blind peppermint oil (DBM)] to allow for the DBP treatment arm. Because peppermint oil (6) is considered an active treatment, participants in this treatment arm were not included in the present analysis. Full details of the trial participants, design, and results have been previously published (7). Briefly, 340 IBS participants were randomized to one of the treatment arms for 6 weeks; 242 participants completed the study and had baseline and 6-week IBS-SSS, 188 of whom were randomized to one of the three placebo treatment arms (DBP, OLP, and NPC), consented to genetic analysis, and were successfully genotyped. The dual aims of the parent study were to compare OLP to NPC, and OLP to DBP. All participants attended in-person study visits at baseline, and at weeks 3 and 6, in which they met with a study clinician and completed the questionnaires. Blood for genotyping was drawn at the first visit. Blood for transcription analysis using RNA sequencing was drawn at baseline and 6 weeks.

Ethics Approval Statement

This study and the parent trial were conducted according to the criteria set by the Declaration of Helsinki. All participants provided informed consent, and the study was approved by the

ethics review board at Beth Israel Deaconess Medical Center under protocol 2015P000282.

Outcome Measures

Outcome assessments were performed by blinded research assistants. OLP and NPC participants were not blinded; participants assigned to DBP or DBM were told they enrolled for a double-blind RCT but were not informed of their randomized treatment assignment. The primary outcome was changed in the irritable bowel symptom severity scale (IBS-SSS). IBS-SSS is a validated five-item questionnaire used to assess IBS symptoms and severity of the disease consisting of pain severity, pain frequency, bowel distension, satisfaction with bowel habits, and quality of life (6). Each item is scored on a scale of 1–100, and, thus, the maximum possible composite IBS-SSS score is 500. Higher scores are associated with more severe symptoms; the primary outcome, change in IBS-SSS, was determined as:

$$(\textit{IBS-SSS at baseline}) - (\textit{IBS-SSS at 6 weeks})$$

Generally, in pharmaceutical RCTs, the time course of placebo responses for functional pain illnesses follows the time trajectory of the drugs (7). In IBS, even at a 1-week placebo, the drug effects are evident (8). In long term IBS drug RCTs (i.e., 26 weeks), placebo responses continue as long as the drug effect, and if there is any reduction in placebo effects, it matches with what happens with the drug (9). We chose 6 weeks as a primary endpoint measure because previous studies suggested that 6 weeks is a reasonable time frame to detect placebo and peppermint effects, and subsequent studies have confirmed this assumption.

Power Calculations

In a previous IBS trial (5), the mean (SD) in IBS-SSS score change by *COMT* rs4680 genotype with sham acupuncture was 87.4 (85.3) for met/met; 69.2 (70.5) for val/met; and 36.3 (74.4) for val/val. Thus, we estimated that we had >80% power to detect a difference between the two homozygous groups with an n of 188.

Genotyping and Gene Expression

Additional information regarding genotyping on the Infinium Global Screening Array v2.0 (Illumina, San Diego, and Calif) and RNA-seq (Differential Gene Expression Analysis) performed at Admera Health (Plainfield NJ) on RNA extracted from human blood using PAXgene Blood RNA kit (Qiagen, Hilden, and Germany) at baseline and 6 weeks is available in the **Supplementary Material**.

Candidate Gene, Gene-Set, and GWAS Analysis

For the GWAS, the following model was utilized:

$$\textit{IBS-SSS change} \sim \textit{SNP} + \textit{age} + \textit{sex} + \textit{treatment arm} + 5\ \textit{principal components}\ (\textit{PCs})$$

The top five principle components were used to correct for genetic heterogeneity across different races/ethnic groups. Principle components analysis (PCA) was performed on the whole genome SNP data using PLINK (10). In GWAS of quantitative change, the baseline measure has been shown to bias the effect of variants on treatment response; therefore, we did not include baseline IBS-SSS as a covariate in the model (11).

For this analysis, plink (10) was used to determine the effects of gene dosage for SNPs with a frequency >0.05. SNPs were considered to be genome-wide suggestive or significant if they were associated at thresholds of $p < 10^{-5}$and $p < 5.0 \times 10^{-8}$, respectively. The GWAS output was cleaned using EasyQC with standard settings. Manhattan and QQ plots were generated with R package qqman.

We used FUMA (http://fuma.ctglab.nl/) to generate gene-based tests and extract functional annotations for genome-suggestive loci ($p < 10^{-5}$). Summary statistics from the FUMA GWAS analysis were used to run multimarker analysis of GenoMic annotation (MAGMA) (12). In the gene-set analysis, MAGMA tests if the results from the gene-based analysis point to the involvement of specific pathways; $p < 4.6 \times 10^{-6}$ is considered to be significant. Analysis of transcription factor networks was performed using NetworkAnalyst 3.0 (13).

TABLE 1 | Demographics, baseline characteristics, and COMT rs4680 distribution by treatment arm.

	Double-blind placebo (DBP)	Open-label placebo (OLP)	No-pill control (NPC)
N	63	63	62
Age, mean (SD)	43.2 (19.8)	43.2(17.3)	40.1 (17.6)
Female, *n* (%)	45 (70)	48 (76)	44 (71)
White, *n* (%)	54 (86)	53 (84)	52 (84)
IBS-SSS, mean (SD)	283.1 (69.8)	282.7 (57.4)	261.8 (66.2)
***COMT* rs4680**			
met/met (%)	14 (22)	12 (19)	12 (19)
val/met (%)	38 (60)	26 (41)	32 (52)
val/val (%)	11 (18)	25 (40)	18 (29)

RESULTS

Demographics and Baseline Measures of Participants

This study examined 188 participants with IBS enrolled in a RCT (1, 14) who were randomized to DBP ($N = 63$), OLP ($N = 63$), or NPC ($N = 62$). The distribution of demographic and baseline clinical characteristics did not vary by randomized treatment allocation (**Table 1**). The average age of participants was 42.1 ± 18.2 years, 73% were women, and a majority (85%) self-reported their race as white. The distribution of *COMT* rs4680 was in Hardy-Weinberg equilibrium ($p = 0.93$). At baseline, IBS-SSS did not vary by treatment arm (**Table 1**) or by *COMT* rs4680 genotype across all arms combined (**Figure 1A**).

COMT Association With Change in IBS-SSS

In *COMT* rs4680 gene dosage models of change in IBS-SSS from baseline to 6 weeks, increasing the number of met alleles was

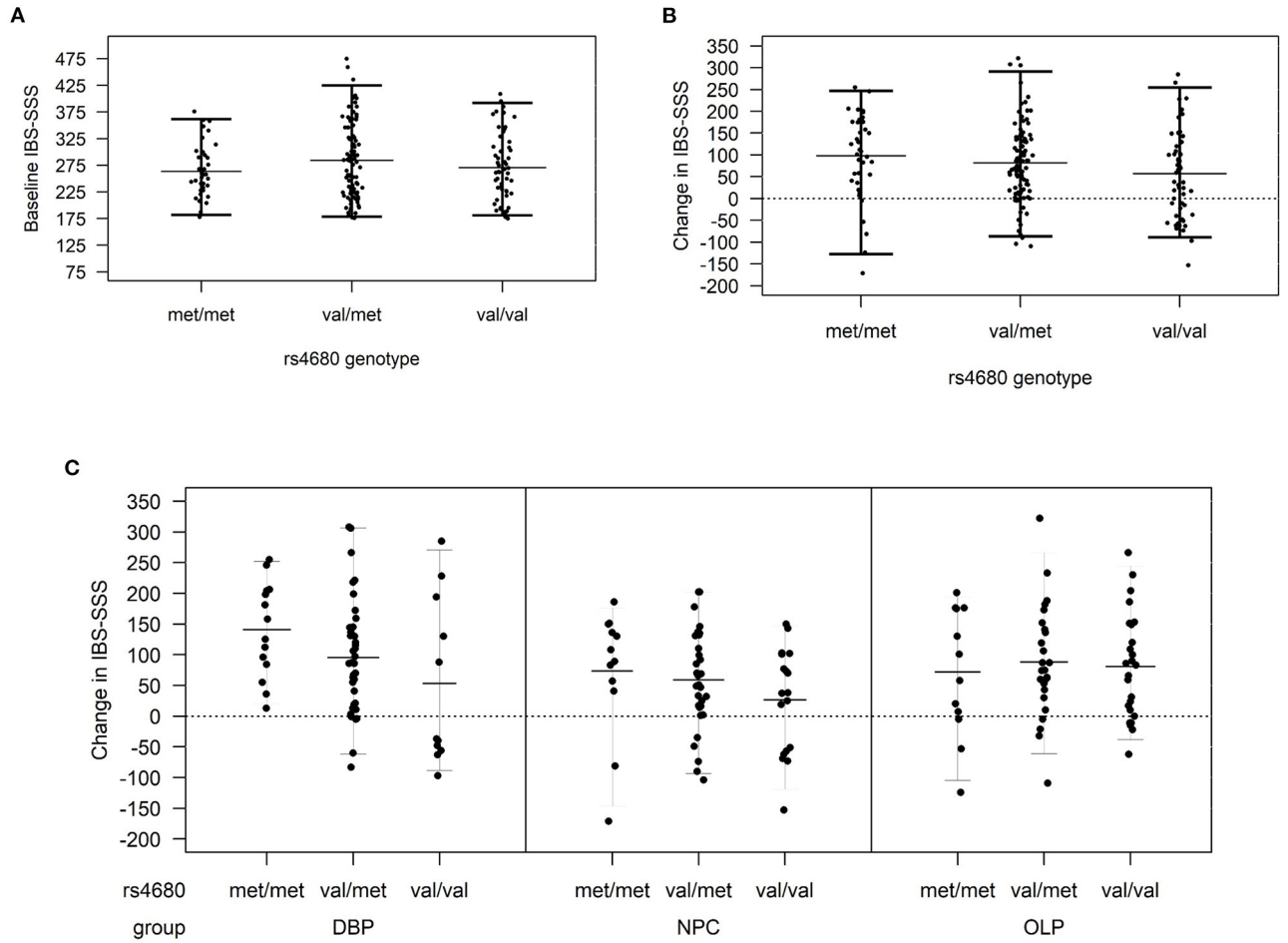

FIGURE 1 | (A) Baseline irritable bowel symptom severity score (IBS-SSS) by *COMT* genotype across all treatment arms, **(B)** change in IBS-SSS by *COMT* rs4680 genotype overall, and **(C)** by treatment arm (DBP, double-blind; OLP, open-label and NPC, no-pill control).

associated with a greater reduction in IBS symptom severity (beta (SE), −22.3 (10.0), $p = 0.027$) such that participants homozygous for the low activity met allele (met/met) had the greatest placebo response across all participants in the three treatment arms combined (**Figure 1B**).

In gene dosage models stratified by treatment arm, the largest difference by *COMT* genotype was observed in the DBP. Specifically, met/met participants had the largest improvement with DBP (140.6 ± 77.2), val/met participants were intermediate (95.10 ± 92.6), and val/val (53.1 ± 136.5) participants had the smallest change (beta (SE), −90.1 (40.6); $p = 0.04$) (**Figure 1C**). In the NPC arm, the pattern was similar to DBP, but the change in IBS-SSS was lower in magnitude and the differences by *COMT* genotype were non-significant (beta (SE), −27.1 (16.7); $p = 0.11$). There was no difference by *COMT* genotype in OLP ($p = 0.79$).

Stratification by sex revealed a similar pattern of *COMT* rs4680 effects across all three treatment arms in women, such that met/met women had the greatest improvement (109.9 ± 96.5) and val/val women the least improvement (67.4 ± 97.4; **Supplementary Figure 1**). This pattern was observed in men in the DBP and NPC, but not in men randomized to OLP.

Genome-Wide Association Analysis

No inflation of data was observed in the GWAS of change in IBS-SSS from baseline to 6 weeks across all treatment arms (**Figure 2** and **Supplementary Figure 2**). The 12 loci associated with a change in IBS-SSS at the genome-wide suggestive level (set at $p < 10^{-5}$) are described in **Table 2**. Seven loci mapped to introns, one to an exonic region in a non-coding RNA, and the rest were located in intergenic regions. Several loci had links to neuronal and gastrointestinal function and one, *NAV2* (neuron navigator 2), had links to placebo response (15). *NAV2* is critical to vagus nerve development (16), is associated with gut microbiome composition (17), and was previously associated with placebo response in asthma (15). *CTNND2* is associated with severe pain (18) and anxiety (19). *LINC02006*, a non-coding RNA, is associated with gut microbiota (20), serotonin levels (21), and infantile hypertrophic pyloric stenosis (22). Other genome-wide suggestive loci were linked to genes involved in neuronal

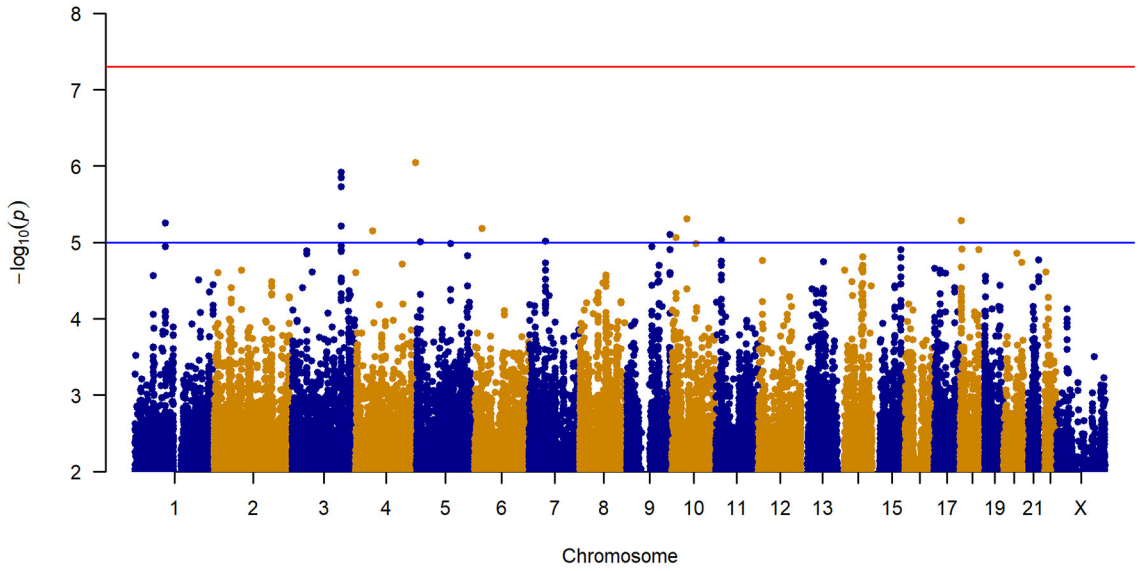

FIGURE 2 | Manhattan plot of GWAS of change in IBS-SSS among 188 IBS patients controlling for age, sex, treatment arm, and the first five principal components for genetic ancestry.

growth, connection, and signaling [*COBL* (23), *DCDC2* (24), *PTBP2* (25), *CTNND2* (19), and *ZBTB14* (26)].

Gene-Set Analysis

We used gene-set enrichment analysis (12) to identify pathways or genes with common functions associated with IBS symptom improvement. Four gene ontology (GO) terms were identified that were genome-wide significant after Bonferroni correction (**Figure 3** and **Supplementary Table 1**). Three pathways were involved in transcriptional regulation: GO:0032968, $p = 1.23 \times 10^{-6}$, which is involved in the regulation of transcription elongation from RNA polymerase II promoter; GO:0070937, $p = 1.66 \times 10^{-7}$, and the related GO:0070934, $p = 7.14 \times 10^{-8}$, which mediate stabilization of mRNA by RNA-binding proteins associated with the open reading frame (27); and GO:0003918, $p = 3.06 \times 10^{-6}$, which is associated with DNA topoisomerase activity (28).

Gene Expression Network Analysis

Gene regulatory network analysis of the genome-suggestive loci identified a transcription factor network that included 10/12 loci plus *COMT* (**Figure 4**). *EGR1* was the transcription factor with the highest degree (7) and betweenness centrality (407); *TP53* also had a degree of 7 (**Supplementary Table 2**). *EGR1* is rapidly induced by physiologic or emotional stress to upregulate transcription of a wide set of genes, including those involved in dopamine synthesis.

Comparison of transcript levels in peripheral blood samples from the IBS participants across all three treatment arms at baseline and 6-weeks indicated that *EGR1* gene expression was significantly reduced across all treatment arms (log fold-change -0.15; $p = 0.02$; $N = 188$). Changes in *TP53* gene expression were not significant ($p > 0.05$).

DISCUSSION

In this study, in a clinical trial of patients with IBS, randomized to three placebo-related interventions (DBP, OLP, and NPC), we found the effects of *COMT* rs4680 in response to placebo treatments. Particularly in DBP, met/met participants had a significantly greater improvement in IBS symptoms compared with participants who were met/val and val/val. Furthermore, assuming that placebo-related response would be present to varying degrees in each arm, we identified transcription regulation and *EGR1* gene expression as novel epigenetic processes that potentially influence response to placebo treatment in IBS.

The COMT enzyme metabolizes several hormones and neurotransmitters, including norepinephrine, dopamine, and catechol estrogen, which have been implicated in IBS pathophysiology, stress, and response to placebo treatments. The low-activity form of the COMT enzyme, encoded by a methionine (met) allele in the rs4680 genetic polymorphism, ostensibly results in higher levels of these COMT substrates. Notably, there was no difference in IBS-SSS by *COMT* rs4680 at baseline, so it is unlikely that the changes in response to placebo treatment observed in this study were attributed to regression to the mean. Across the three placebo treatment arms in this study, participants homozygous for the met allele (met/met) had significantly greater improvement in the primary outcome measure, change in IBS-SSS, compared to homozygotes for the high-activity form of the enzyme (val/val). In women, the direction of the *COMT* rs4680 effect was consistent across all three arms. Apart from the OLP arm, the direction of *COMT* effects in men was similar to this overall trend of met/met > val/val. However, with so few men with the met/met genotype enrolled in this trial, follow-up studies are needed to understand

TABLE 2 | Genome-wide suggestive loci associated with the change in IBS-SSS from baseline to 6 weeks in three placebo treatment arms combined.

rsID	Location	MAF	Gene (nearest)	*P*-value	Type	Description	TP53	EGR1
rs6701417	1:97071826	0.24	(PTBP2)	5.60E-06	intergenic	This SNP maps upstream of and is an eQTL for PTPBP2.		
rs57519743	3:153297025	0.18	LINC02006/ LINC02877	1.87E-06	intronic	In GWAS LINC02006 was associated with gut microbiota, serotonin levels, infantile hypertrophic pyloric stenosis.		
rs28652757	4:53881711	0.23	SCFD2	7.17E-06	intronic	In GWAS sec1 family domain containing 2 was associated with testosterone levels and uterine fibroids.		
rs6815638	4:188225599	0.21	AC097652.1 (FAT1)	9.08E-07	non-coding RNA exonic	NA		
rs31947	5:11461390	0.07	CTNND2	9.85E-06	intronic	Catenin delta 2 plays a critical role in neuronal development and formation and maintenance of dendrites and synapses.		
rs62400400	6:24266331	0.12	DCDC2	6.59E-06	intronic	Doublecortin domain containing 2 - plays a role in neuronal migration and ciliogenesis.		
rs9649794	7:51649139	0.41	AC005999.2	9.75E-06	intergenic	Cordon-bleu WH2 repeat protein regulates neuronal morphogenesis and increases axon and dendrite branching. It is required for growth and assembly of brush border microvilli that maintain intestinal homeostasis.		
rs11244033	9:136079182	0.34	(OBP2B)	7.87E-06	intergenic	This SNP maps proximal to and is an eQTL for odorant binding protein 2B		
rs12266806	10:12978973	0.08	CCDC3	8.76E-06	intronic	Coiled-coil domain containing 3 is highly conserved secretory protein that represses TNF-alpha/NF-KB and regulates liver lipid metabolism.		
rs11259792	10:47691930	0.15	ANTXRL	4.93E-06	intronic	Anthrax toxin receptor-like—is associated with bipolar disorder		
rs11025279	11:19853393	0.34	NAV2	4.93E-06	intronic	Neuron navigator 2—may play a role in neuronal growth and migration, is associated with gut microbiome composition and was associated with placebo response in asthma		
rs142674057	18:5307474	0.08	(ZBTB14)	5.18E-06	intergenic	Zinc Finger And BTB Domain Containing 14—transcriptional activator of dopamine transporter (DAT) and IL-6.		

Columns correspond to SNP name, chromosomal location, (MAF), gene symbol for gene or nearest gene in brackets, p-value, SNP type, description of the function of the protein. Gray shaded boxes indicate genes that contain transcription binding sites for TP53 or EGR1.

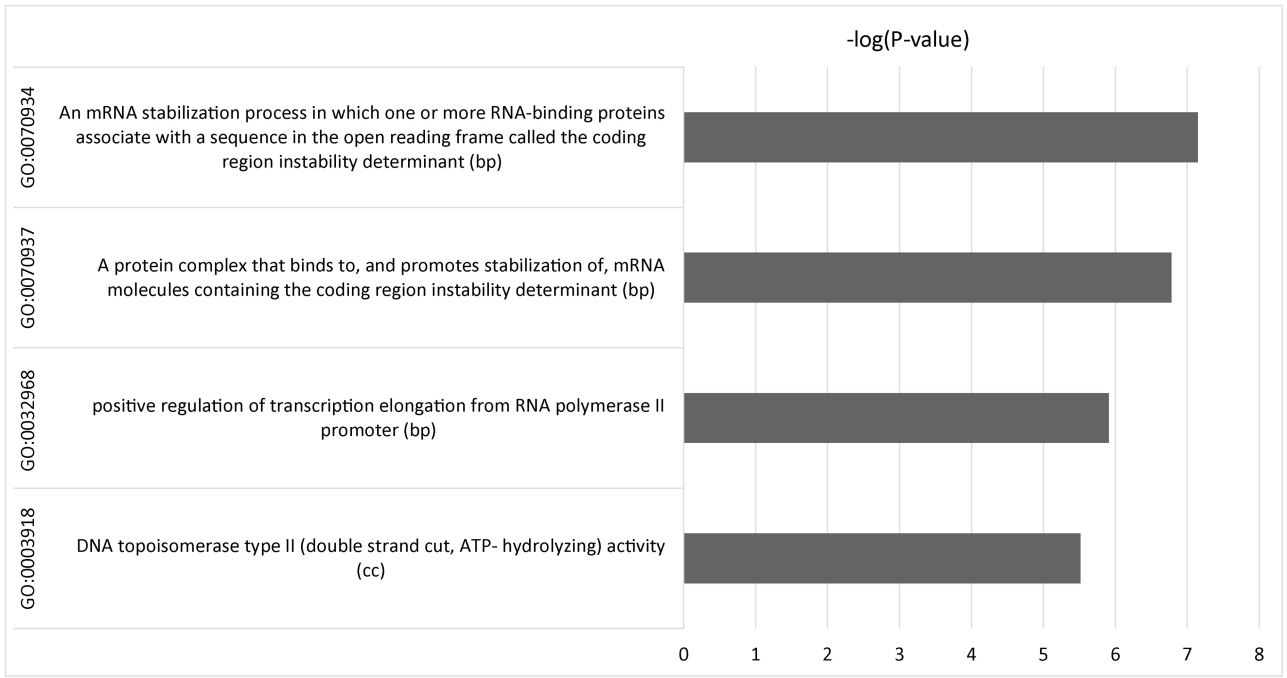

FIGURE 3 | Multimarker analysis of GenoMic annotation (MAGMA) output of significant gene sets after gene set analysis of 15,488 tests was performed and Bonferroni corrected. Relative GO terms are biological processes (bp) and cellular components (cc).

if there are sex-specific responses to OLP. Taken together, this study extends our previous finding that genetic variation in *COMT* differentially influences IBS symptom improvement in response to placebo treatment (5), in particular DBP, and suggests that the *COMT* rs4680 genetic variant may be useful in predicting, managing, and targeting placebo response in IBS trials and drug development.

As a complex phenotype, placebo treatment response in IBS is likely to be polygenic, with influence from many genetic loci each with small individual effects. However, identifying small genetic effects requires a large sample size to provide power to discern statistically significant effects. As expected in a study with a sample size having limited power, none of the loci in the GWAS reached genome-wide significance. Gene-set analysis aggregates data for complex traits based on biological data to reduce the sample size required to detect important signals. In this study, we used gene-set analysis of the GWAS for SNP-level associations with change in IBS-SSS to explore genome-mediated responses to treatment. To maximize power, we also combined participants from the three placebo treatment arms assuming placebo-related responses, which would contribute to the outcome in each of the three treatment arms. Four statistically significant GO terms were identified: three linked to transcription regulation (GO:0032968, GO:0070934, and GO:0070937) and one associated with DNA topoisomerase regulation (GO:0003918).

The genome-wide suggestive genetic loci plus *COMT* were densely connected in a transcription factor network in which *EGR1* was the transcription factor node with the greatest betweenness centrality. Gene expression analysis in this study demonstrated that *EGR1* was significantly downregulated from baseline after 6 weeks of the various forms of placebo treatment. *EGR1* is a critical mediator of gene-environment interactions and is tightly associated with neuronal activity and learning, memory, and sensitivity to reward. In rodents, water immersion restraint stress rapidly induces *EGR1* expression in blood vessels and gastroduodenal smooth muscle (29, 30). Similarly, *EGR1* expression is rapidly induced in jejunal smooth muscle and enteric neurons following surgical manipulation of the intestine, and *EGR1* expression in infiltrating mononuclear inflammatory cells correlates with postoperative ileus (31). Child abuse is associated with methylation of *EGR1* binding sites in the glucocorticoid receptor promoter region in PBMCs, thereby providing a mechanism by which social experience modulates hypothalamic–pituitary–adrenal axis activity (32). Similar epigenetic regulation by *EGR1* may be one of the mechanisms involved in IBS symptoms. As used in this study, the gene-set analysis provided potentially important insights into functional and biological mechanisms underlying the genetic component of placebo response.

Although the combined GWAS of all participants increased our power to detect loci associated with response to treatment in IBS, we were underpowered for a GWAS of the effects in the individual treatment arms, or stratified analyses by sex and IBS type (constipation or diarrhea). Despite the many known links of *COMT* to placebo and IBS, it did not emerge as a top hit in this GWAS. One possibility is that *COMT* effects are strongest with blinded-placebo, and the DBP arm

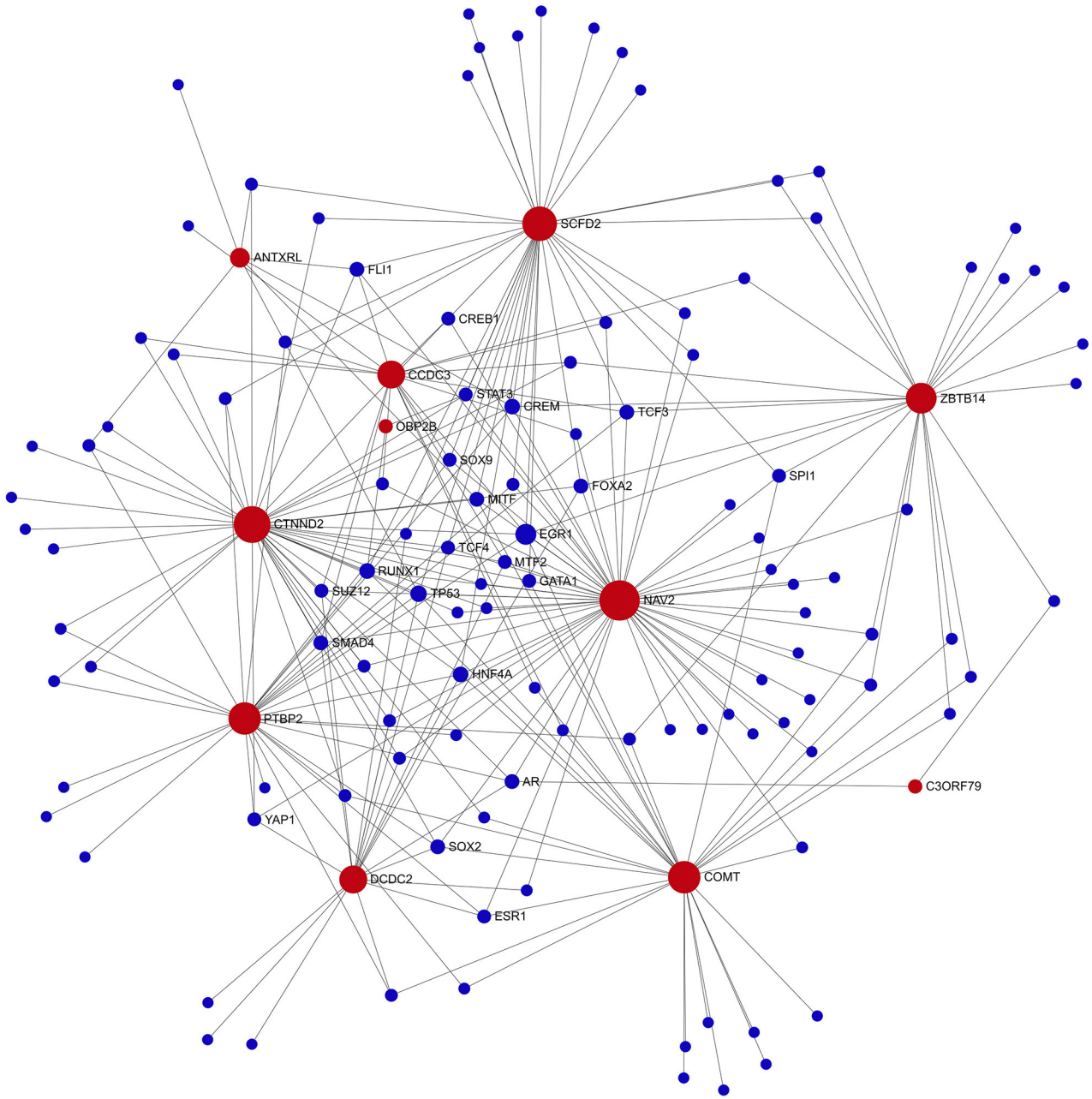

FIGURE 4 | Transcription factor network diagram consisting of seed genes (11-top genome-wide suggestive (red) genes and *COMT*). Seed genes (red) with interaction partners (blue).

in this study was underpowered for genome-wide significance. Another possibility is that the pharmacogenetic effects of *COMT*, which is known to interact with a wide variety of drugs and supplements, masked these effects (33–35). Although we were limited to PBMCs in this study to assess changes in gene expression, there is evidence that changes in PBMCs correlate with neurological changes in gene expression. Finally, in designing this trial, we expected that the NPC arm would serve as a control for "placebo effects." However, with improvements among some IBS participants in the NPC, simply from enrolling in the trial, interacting with study staff, and responding to questionnaires at the study visits, we still cannot distinguish whether these effects are attributable to natural history or a modest placebo.

In the context of a randomized clinical trial largely consisting of placebo treatments, we have generalized the finding that

COMT rs4680 genotype influences response to blinded placebo and used multi-omics analyses to acquire a more comprehensive view of the loci and pathways associated with treatment response in IBS. A deeper understanding of these pathways may guide the development of novel therapies for IBS (e.g., targeting *EGR1*) and improve the clinical trial design (e.g., excluding participants whose *COMT* genotype may predispose them to a significant placebo response).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Beth Israel Deaconess Medical Center under protocol 2015P000282. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KH, AL, TK, JL, JS, and VC: project design, analysis, and writing manuscript. R-SW: analysis and writing manuscript. MR, JI, and JN: irritable bowel syndrome (IBS), trial design, execution, and writing manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpain.2021.775386/full#supplementary-material

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Music-Induced Analgesia in Healthy Participants Is Associated With Expected Pain Levels but Not Opioid or Dopamine-Dependent Mechanisms

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Music interventions accommodate the profound need for non-pharmacological pain treatment. The analgesic effect of listening to music has been widely demonstrated across studies. Yet, the specific mechanisms of action have still to be elucidated. Although the endogenous opioid and dopamine systems have been suggested to play an important role, a direct link has not been established. In addition, the involvement of placebo mechanisms is likely while largely unexplored. We examined the analgesic effect of music in healthy participants ($n = 48$) using a 3×3 within-subjects design with pharmacological manipulations and a matched, auditory control for music. Participants were exposed to thermal pain stimuli while listening to three auditory excerpts: music (active condition), nature sound (matched, auditory contextual condition), and noise (neutral control condition). The participants rated their expected and perceived pain levels in relation to each of the auditory excerpts. To investigate the involvement of the endogenous opioid and dopamine systems, the test session was performed three times on separate days featuring a double-blind randomized oral administration of naltrexone (opioid antagonist), haloperidol (dopamine antagonist), and an inactive agent (control). Our results support an analgesic effect of music. Contrary to current hypotheses, neither of the antagonists attenuated the effect of music. Yet, the participants' expectations for pain relief predicted their perceived pain levels during the auditory excerpts—even when controlling for a gradual learning effect. In conclusion, we demonstrate that the analgesic effect of music is at least partially mediated by expectations of an analgesic effect—a core mechanism in placebo effects—but not by opioid and dopamine-dependent mechanisms.

Clinical Trial Registration: www.clinicaltrials.gov, identifier: NCT03410563.

Keywords: music-induced analgesia, endogenous opioids, dopamine, expectancy, context, placebo

INTRODUCTION

Facing a high prevalence of chronic pain worldwide and a rise in the use of pharmacological analgesics associated with profound human and societal costs (1–3), there is a great need for complementary, non-pharmacological pain treatments (4). Music can provide a safe and non-invasive intervention to reduce pain (5). The pain-relieving effect of music, termed music-induced analgesia (6), has been demonstrated in both acute (7–11) and chronic pain (12–15). Prevailing hypotheses regarding the mechanisms of action suggest that music may act to reduce pain through the release of endogenous opioids and dopamine (16–18). Yet, this has not been addressed directly by empirical investigations. In addition, due to methodological challenges, the general conclusion of music's eligibility in clinical practice may be at risk of overestimating the analgesic effect of music (19). Particularly, the lack of adequate control conditions may conceal a contribution from contextual treatment factors such as expectations about treatment efficacy (20, 21).

The assumption of neurotransmitter involvement in music-induced analgesia primarily derives from studies associating musical *pleasure* with endogenous opioid and dopamine transmission using ligand-based positron emission tomography and pharmacological agonist/antagonist paradigms (22–25). The opioid and dopamine systems contribute to a shared neurobiological foundation for pleasure and pain modulation (26), making them eligible candidates for mediating the analgesic effect of music. Among studies on music-induced analgesia, functional magnetic resonance imaging (fMRI) studies suggest that music taps into the descending modulation of pain (16, 18). Yet, although probable, these findings do not constitute direct evidence that this pain modulation is mediated by opioid and dopamine-dependent mechanisms. Moreover, the comparison between a music condition and a no-music condition (16, 18)—a standard design for examining the analgesic effect of music (27–29)—entails a risk of overestimating the specific effect of *music* itself (19).

In randomized controlled trials evaluating the effect of a pharmacological treatment, the active agent in question must show an effect beyond an inactive placebo (30). Put simply, this comparison against a placebo control allows for a distinction between improvement due to the specific treatment itself and improvement due to contextual factors—such as expectancy—embedded in the patient's perception of receiving the treatment (21, 30, 31). The importance of a contextual control is evidenced by findings demonstrating that expectations of treatment efficacy can double the analgesic effect of active pain medication (32). Among trials investigating non-pharmacological pain interventions such as surgery and acupuncture, the inclusion of matched contextual conditions omitting the treatment specific characteristics is currently being debated and implemented (33–39), and the general need for well-controlled trials in relation to alternative or complementary pain interventions is being recognized (40). As expressed in a recent article on grand challenges in non-pharmacological treatment of pain, it is essential to both demonstrate an effect of these interventions beyond a placebo effect, and to specify their biological underpinnings (40). At this point, however, only few studies have used a contextual control or taken expectations for pain relief into account when evaluating the analgesic effect of music (8, 41–43). Thus, it is largely unknown to which extent placebo mechanisms contribute to this effect.

The present study was undertaken to investigate the role of neurotransmitter activity and expectancy in music-induced analgesia in healthy participants exposed to thermal stimuli. Using a 3 × 3 within-subjects design (**Figure 1**), each participant rated their expected and perceived pain levels in relation to 3 auditory excerpts: music (active condition), nature sound (matched, auditory contextual condition), and noise (neutral control condition). This was repeated on 3 separate days to test the involvement of the endogenous opioid and dopamine systems pharmacologically by double-blind administration of naltrexone (opioid antagonist), haloperidol (dopamine antagonist), and an inactive agent (control). Order of both auditory and pharmacological conditions was randomized and counterbalanced. It was hypothesized that the analgesic effect of music would be attenuated by naltrexone and haloperidol, respectively—i.e., suggesting that opioids and dopamine mediated the effect—and that expectations for pain relief would contribute to the magnitude of the analgesic effects observed across auditory excerpts.

MATERIALS AND METHODS

Participants

Forty-eight healthy participants (21 males, 27 females) aged 19–56 years (mean = 24.65, SD = 7) completed the study (see **Supplementary Materials and Methods** for dropouts). A power calculation based on a previous study by Villarreal et al. (42) showed that 50 participants would be sufficient, α (two-tailed) = 0.05, $\beta = 0.80$. Due to the randomization and counterbalanced distribution of conditions (**Supplementary Figure 1**), however, 48 participants were included in the study.

Eligibility was assessed using the following inclusion criteria: Normal health, normal hearing, age 18–60 years, and fluent in Danish. Exclusion criteria were chronic pain, other medical, neurological, or psychiatric conditions, use of antidepressants, daily use of analgesic medication or 24 h prior to testing, substance abuse, pregnancy, and enrollment in/completion of an education in musicology/at a music academy. In average, participants reported 4.56 years of musical experience (SD = 5.39) and scored 74.29 (SD = 9.55) on the Musical Ear Test (44) measuring their musical competence (score range: 0–100). Smoking was not included as an exclusion criterion. However, participants were not allowed to smoke during their participation in the study.

Prior to inclusion in the study, participants were informed (verbally and in writing) that the aim of the study was to investigate the analgesic effect of music and nature sound. Specifically, the participants were told that both of these auditory excerpts had been associated with pain relief in a previous study (42). Noise was introduced as a neutral control condition (see **Supplementary Materials and Methods** for scripted information). Participants were also informed that

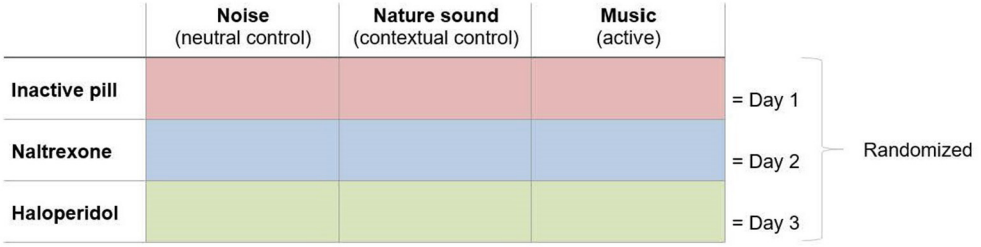

FIGURE 1 | Study design. On each test day, participants were exposed to individually calibrated pain stimuli while listening to noise, nature sound, and music in randomized order accompanied by administration of either an inactive agent, naltrexone, or haloperidol in a double-blind, randomized order.

we wanted to examine whether the medications (naltrexone and haloperidol) would modify their pain experience. However, they were blinded to the hypotheses regarding antagonism and a matched auditory condition to control for contextual factors.

Participants gave informed consent before entering any study procedures and received monetary compensation (200 DKK/test day; 600 DKK in total). The study was approved by The Central Denmark Region Committees on Health Research Ethics (1–10–72–317–16) and registered at ClinicalTrials.gov (Identifier: NCT03410563).

Randomization

Using random draw, participants were assigned to different groupings specifying a counterbalanced distribution of conditions across test days (Latin and Graeco-Latin squares; see detailed information in the **Supplementary Materials and Methods** and in **Supplementary Figure 1**). The distribution of pharmacological manipulations was blind for everyone involved in the study until completion of the data analysis—except for 2 consulting physicians who broke the blinding code only in case a participant felt unwell during testing. Aside from these consultations, the physicians did not have contact with the participants and were not involved in the data analysis.

Procedures

Thermal Stimuli

Participants were exposed to painful thermal stimuli produced by a 3 × 3 contact thermode (Pathway Model ATS; Medoc Ltd. Advanced Medical System, Israel) placed on the anterior surface of the forearm. Calibration trails were performed to obtain individual pain stimuli reflecting a perceived pain intensity of 60–70 mm (moderate to high pain) on a 0–100 mm mechanical visual analogue scale (42, 45) (see **Supplementary Materials and Methods** for detailed information). The individually calibrated temperature was kept constant for each participant in all test sessions. Each auditory excerpt was accompanied by 3 thermal stimuli consisting of a 16-s plateau with a rise and fall time of 2°C/s and a baseline temperature of 35°C during rest intervals (42) (**Supplementary Figure 2**).

Auditory Excerpts

Three auditory excerpts were employed in different order on all 3 test days. The active music condition consisted of a Mozart string composition, the matched, auditory contextual condition consisted of the sound of water, and the control condition consisted of pink noise. Pink noise was included as a neutral auditory input, whereas the music piece and the nature sound were chosen for their compatibility on 3 emotional measures (valence, liking, and arousal) obtained in a previous study (42). Aside from this compatibility, one important element set the two conditions apart. When we listen to music—contrary to random sound—the intentional compositions of, e.g., harmonies, melodies, and rhythms cause us to build expectations for what will come next (46, 47). Musical pleasure can come from the confirmation or skillful violation of these expectancies (48). This element of musical expectancy is considered to be a key factor in the musical experience (49), and the anticipation of peak pleasure moments during music listening has been associated with dopamine release (24). By administering a nature sound without musical structure that enable anticipation, nature sound was conceptualized as a matched, auditory contextual control for music. Thus, the nature sound and the music piece shared the fundamental transmission of content (constituting a pleasant auditory stimulus) without sharing the actual content and element of musical expectancy (see **Supplementary Materials and Methods** for detailed information).

Each auditory excerpt was peak normalized and lasted 300 s (42). The 3 thermal stimuli were delivered during the last 150 s (**Supplementary Figure 2**).

Pharmacological Manipulations

Three identical white capsules containing an inactive agent, naltrexone (25 mg), or haloperidol (3 mg) were administered orally with a glass of water (200 ml) 2 h prior to testing to allow the medications to take effect (50, 51). All test sessions were arranged to take place at approximately the same time for each participant across the 3 test days (mean divergence in min = 56.88; SD = 41.62), and the test days were placed minimum 3 days apart in order for the medication to wear off (see **Supplementary Materials and Methods** for detailed information and **Supplementary Table 1** for reports of adverse events).

Measures

Ratings of Expected and Perceived Pain Intensity and Pain Unpleasantness

In order to examine the participants' expectations as a predictor of the analgesic effects, participants were asked to rate their expected pain intensity and pain unpleasantness immediately before the administration of each auditory excerpt knowing what they were about to listen to. Expectancy ratings were obtained on mechanical visual analogue scales (M-VAS; 0–100 mm) anchored by the descriptors "no pain"/"no unpleasantness" (=0) and "worst imaginable pain"/"worst imaginable unpleasantness" (=100) (52, 53). After each thermal stimulus, participants were asked to rate their perceived pain intensity and pain unpleasantness on the M-VAS (52) (**Supplementary Figure 2**).

Emotional Measures

To test the compatibility in emotional ratings between music and nature sound, participants were asked to rate all auditory excerpts on an 11-point Likert scale for valence (0 = unpleasant, 10 = pleasant), liking (0 = do not like, 10 = like), and arousal (0 = relaxing, 10 = stimulating) on all 3 test days immediately after listening to each of the excerpts (6, 42).

Statistical Analysis

We assumed a normal distribution of data based on the Kolmogorov–Smirnov test. Two-way repeated measures ANOVAs and pairwise comparisons were conducted to determine the differences in pain ratings (for pain intensity and pain unpleasantness, respectively) across auditory excerpts and pharmacological manipulations. Furthermore, two-way repeated measures ANOVAs and pairwise comparisons were conducted to determine the differences in expectancy (for expected pain intensity and expected pain unpleasantness, respectively) across auditory excerpts and pharmacological manipulations. Pearson correlation analyses were conducted to determine the association between pain ratings and pain expectancy in relation to the first auditory excerpt on test day 1 (regardless of type of auditory input and regardless of pharmacological manipulations) in order to examine this association without preceding familiarity with the test situation. To examine this association on test days 2 and 3, respectively, zero-order correlation analyses were conducted to examine how pain levels were associated with prior pain experience and pain expectancy. Furthermore, controlled partial correlation analyses were conducted to examine the association between pain levels and pain expectancy on test days 2 and 3, respectively, when controlling for prior pain experience. In order to examine how expectancy and prior pain experience predicted later expectancy and pain ratings across the 3 test days, path regression analyses were conducted for each of the 3 auditory excerpts (for pain intensity and pain unpleasantness, respectively).

Secondary, two-way repeated measures ANOVAs and pairwise comparisons were conducted to determine the differences in emotional ratings (valence, liking, and arousal, respectively) across auditory excerpts and pharmacological manipulations, and Pearson correlation analyses examined the association between the emotional ratings and pain levels (pain intensity and pain unpleasantness, respectively) during each of the auditory excerpts.

RESULTS

Perceived Pain Intensity and Unpleasantness

Results of the two-way repeated measures ANOVA for perceived pain showed significant main effects for the type of auditory

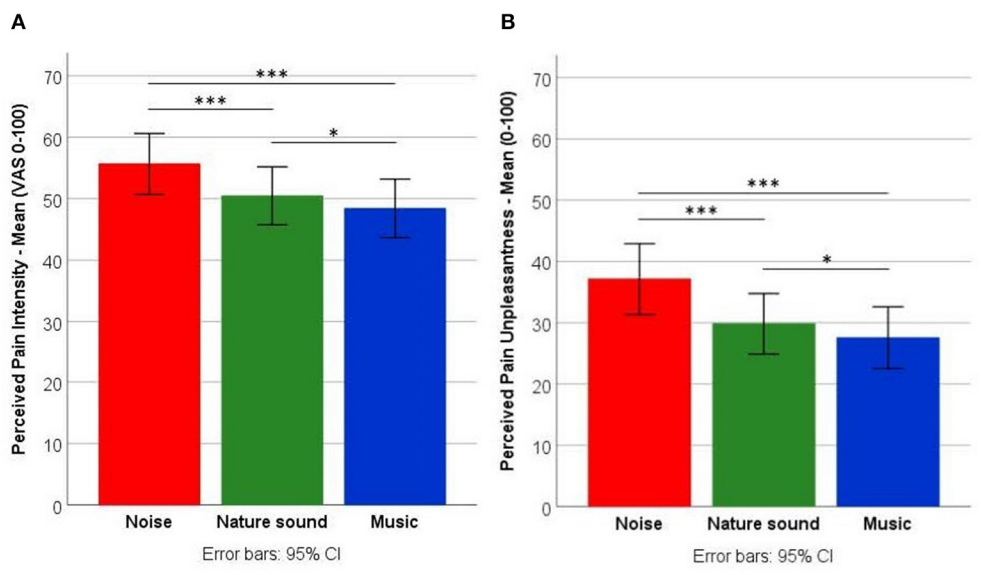

FIGURE 2 | Pain levels. Comparisons of noise, nature sound, and music on **(A)** pain intensity and **(B)** pain unpleasantness (regardless of pharmacological manipulations). *$p < 0.05$; ***$p < 0.001$.

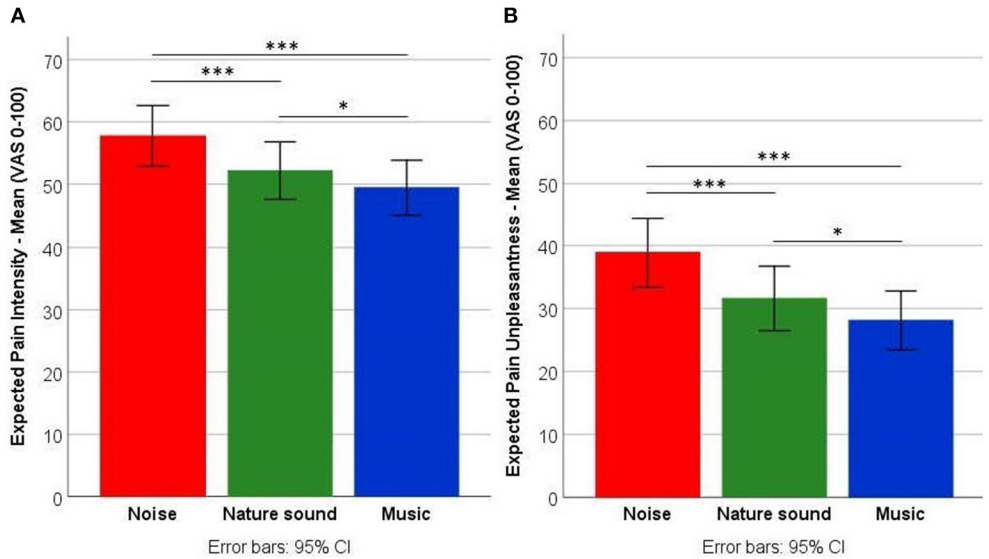

FIGURE 3 | Expected pain levels. Comparisons of noise, nature sound, and music on **(A)** expected pain intensity and **(B)** expected pain unpleasantness (regardless of pharmacological manipulations). *$p < 0.05$; ***$p < 0.001$.

excerpt in relation to pain intensity [$F_{(2, 94)} = 28.96$, $p < 0.001$, eta$^2 = 0.381$], and pain unpleasantness [$F_{(1.55, 72.65)} = 32.52$, $p < 0.001$, eta$^2 = 0.409$, using the Greenhouse-Geisser correction]. Bonferroni-corrected contrasts revealed that music and nature sound reduced pain intensity ($p < 0.001$) and pain unpleasantness ($p < 0.001$) significantly compared with noise. Ratings of pain intensity ($p = 0.046$) and pain unpleasantness ($p = 0.04$) were significantly lower when participants listened to music than when they listened to nature sound (**Figure 2**). There were no significant main effects of pharmacological manipulations [pain intensity: $F_{(2, 94)} = 0.14$, $p = 0.869$, eta$^2 = 0.003$; pain unpleasantness: $F_{(1.68, 79.12)} = 0.053$, $p = 0.92$, eta$^2 = 0.001$, using the Greenhouse-Geisser correction], and there were no significant interactions between the type of auditory excerpt and the pharmacological manipulations [pain intensity: $F_{(4, 188)} = 0.14$, $p = 0.968$, eta$^2 = 0.003$; pain unpleasantness: $F_{(4, 188)} = 0.73$, $p = 0.570$, eta$^2 = 0.015$]. See **Supplementary Figure 3** and **Supplementary Table 2** (mean scores).

Expected Pain Intensity and Unpleasantness

Results of the two-way repeated measures ANOVA for expected pain showed significant main effects for the type of auditory excerpt in relation to pain intensity [$F_{(2, 94)} = 36.78$, $p < 0.001$, eta$^2 = 0.439$] and pain unpleasantness [$F_{(2, 94)} = 36.33$, $p < 0.001$, eta$^2 = 0.436$]. Bonferroni-corrected contrasts revealed that participants expected significantly lower pain intensity ($p < 0.001$) and pain unpleasantness ($p < 0.001$) from music and nature sound compared to noise. Also, the participants expected significantly lower pain intensity ($p = 0.026$) and pain unpleasantness ($p = 0.011$) from music compared to nature sound (**Figure 3**). There were no significant main effects of pharmacological manipulations [pain intensity: $F_{(2, 94)} = 0.24$, $p = 0.787$, eta$^2 = 0.005$; pain unpleasantness: $F_{(2,94)} = 0.07$, $p = 0.929$, eta$^2 = 0.002$], and there was no significant interaction between the type of auditory excerpt and the pharmacological manipulations [pain intensity: $F_{(3.25, 152.63)} = 1.60$, $p = 0.189$, eta$^2 = 0.033$, using the Greenhouse-Geisser correction; Pain unpleasantness: $F_{(3.21, 150.94)} = 1.28$, $p = 0.283$, eta$^2 = 0.027$, using the Greenhouse-Geisser correction]. See **Supplementary Figure 4** and **Supplementary Table 3** (mean scores).

Expected and Perceived Pain Intensity and Unpleasantness on Test Day 1

Given the non-significant effect of the pharmacological manipulations, we tested the relationship between expected and perceived pain intensity and unpleasantness by day, examining the first auditory excerpt presented to the participants, to explore the relationship between expectations and perception of pain without interference of previous experience from taking part in the study. Results of Pearson correlation analyses for the first auditory excerpt on test day 1 (regardless of the type of auditory excerpt and pharmacological manipulations) showed that expected pain intensity and perceived pain intensity were strongly correlated, $r_{(46)} = 0.66$, $p < 0.001$, and that expected pain unpleasantness and perceived pain unpleasantness were strongly correlated, $r_{(46)} = 0.83$, $p < 0.001$. See **Supplementary Figure 5**.

Distinguishing Expectancy From Prior Pain Experience on Test Day Two and Three

Given the 3 × 3 within-subjects study design in which the participants were tested on 3 separate test days, we tested how perceived pain intensity and unpleasantness (on test day 2 and 3, respectively) were associated with prior pain experience (perceived pain intensity or unpleasantness on the previous

TABLE 1 | Correlations between expected and perceived pain intensity and between prior and perceived pain intensity across auditory excerpts.

			PI_2		PI_3	
			Zero	**Partial**	**Zero**	**Partial**
Noise	PI_{prior}	*r*	0.73***	0.30*	0.76***	0.15
	EXP	*r*	0.88***	0.75***	0.89***	0.72***
Nature sound	PI_{prior}	*r*	0.81***	0.42**	0.90***	0.43**
	EXP	*r*	0.87***	0.67***	0.94***	0.69***
Music	PI_{prior}	*r*	0.74***	0.19	0.83***	0.47**
	EXP	*r*	0.89***	0.74***	0.86***	0.57***

*Zero-order correlations (Zero) and controlled correlations (Partial) between expected pain intensity (EXP) and perceived pain intensity on test days 2 and 3 (PI_2 and PI_3) and between prior pain intensity (PI_{prior}) and perceived pain intensity on test days 2 and 3 (PI_2 and PI_3) for noise, nature sound, and music. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.*

test day) and pain expectancy (expectations for pain intensity or unpleasantness on the present test day). Results of zero-order correlations showed that both prior pain experience and expectations were strongly correlated with perceived pain intensity and unpleasantness (**Tables 1**, **2**). Results of controlled partial correlations, controlling for prior pain experience and pain expectancy, respectively, showed that expectations for pain intensity and unpleasantness were still strongly correlated with perceived pain intensity (**Table 1**) and unpleasantness (**Table 2**) when controlling for prior pain experience. Results of path regression analyses, examining how expectancy and prior pain experience predicted later expectancy and pain ratings, showed that expectations for pain intensity (**Figure 4**) and unpleasantness (**Figure 5**) on the present test day significantly predicted perceived pain intensity and unpleasantness when including all previous expectancy and pain ratings in the regression model.

Emotional Measures

Music and nature sound were compatible (non-significant differences in ratings) on valence and liking, whereas nature sound was rated to be significantly more relaxing (low arousal) than music. Both music and nature sound were rated significantly higher on valence and liking and significantly lower on arousal compared with noise. See **Supplementary Results** for results of the analyses, **Supplementary Table 4** for mean scores, and **Supplementary Table 5** for correlations between emotional ratings and pain ratings.

DISCUSSION

Our results suggest that music relieves pain regardless of opioid and dopamine-dependent mechanisms. Importantly, the analgesic effect of music was strongly predicted by the participants' expectations for pain relief, pointing to a substantial contribution from contextual factors (21) not associated with music *per se*. These results encourage a new understanding of the mechanisms that drive music-induced analgesia and emphasize the importance of adequate control conditions when evaluating the analgesic effect of music.

Overall, the findings of the present study substantiate an analgesic effect of music as shown in previous studies (6, 8, 11, 16, 41, 42). Participants reported significantly lower pain levels when listening to music than when listening to nature sound and noise. However, pertaining to the underlying neurobiological mechanisms—and contrary to our first hypothesis—neither of the antagonists attenuated this analgesic effect of music. In one fMRI study on music-induced analgesia (16), playing pleasant and preferred music to healthy participants exposed to experimental pain was associated with a decrease in subjective pain ratings as well as an increase in blood oxygen level dependent (BOLD) responses in anatomic proximity to the periaqueductal gray (PAG). Considering the central role of the PAG in the descending pain modulatory system (54) together with its high expression of endogenous opioids and opioid receptors (55), these findings are compatible with the hypothesis that music activates descending pain modulation through the release of endogenous opioids (16, 18). Furthermore, in another fMRI study, pleasant and preferred music was found to activate the nucleus accumbens (NAc) and alter connectivity between NAc and key regions in the corticostriatal circuits during pain onset (56). When comparing these findings to studies that associate dopamine release in NAc with music-induced pleasure (24) and substantiate the role of dopamine signaling in pain (57), it seems likely that dopamine is involved in music-induced analgesia. Importantly, however, the fMRI BOLD response may be interpreted as a proxy for neural activity but with no specification of *neurotransmitter* activity (25, 58), leaving no direct evidence to suggest that music in fact activates the descending pain modulatory system through the release of endogenous opioids and dopamine. Thus, although interpretations in favor of an opioid and dopamine mediated analgesic effect of music seem highly probable based on indirect measures, our pharmacological paradigm—targeting neurotransmitter activity *directly*—challenges this interpretation and encourages more investigations to specify the role of neurotransmitters.

Adding to the methodological considerations, future studies may also benefit from specifying the contribution from contextual factors when evaluating the analgesic effect of music. Our findings suggest that a considerable part of this effect may not be ascribable to the music excerpt, but rather to the participants' expectations. In agreement with our second hypothesis, our results show consistently strong

TABLE 2 | Correlations between expected and perceived pain unpleasantness and between prior and perceived pain unpleasantness across auditory excerpts.

			PU_2		PU_3	
			Zero	**Partial**	**Zero**	**Partial**
Noise	PU_{prior}	*r*	0.81***	0.38**	0.87***	0.40**
	EXP	*r*	0.83***	0.47**	0.88***	0.50***
Nature sound	PU_{prior}	*r*	0.80***	0.39**	0.85***	0.41**
	EXP	*r*	0.87***	0.64***	0.90***	0.66***
Music	PU_{prior}	*r*	0.68***	0.28	0.83***	0.43**
	EXP	*r*	0.84***	0.70***	0.90***	0.71***

*Zero-order correlations (Zero) and controlled correlations (Partial) between expected pain unpleasantness (EXP) and perceived pain unpleasantness on test days 2 and 3 (PU_2 and PU_3) and between prior pain unpleasantness (PU_{prior}) and perceived pain unpleasantness on test days 2 and 3 (PU_2 and PU_3) for noise, nature sound, and music. **$p < 0.01$; ***$p < 0.001$.*

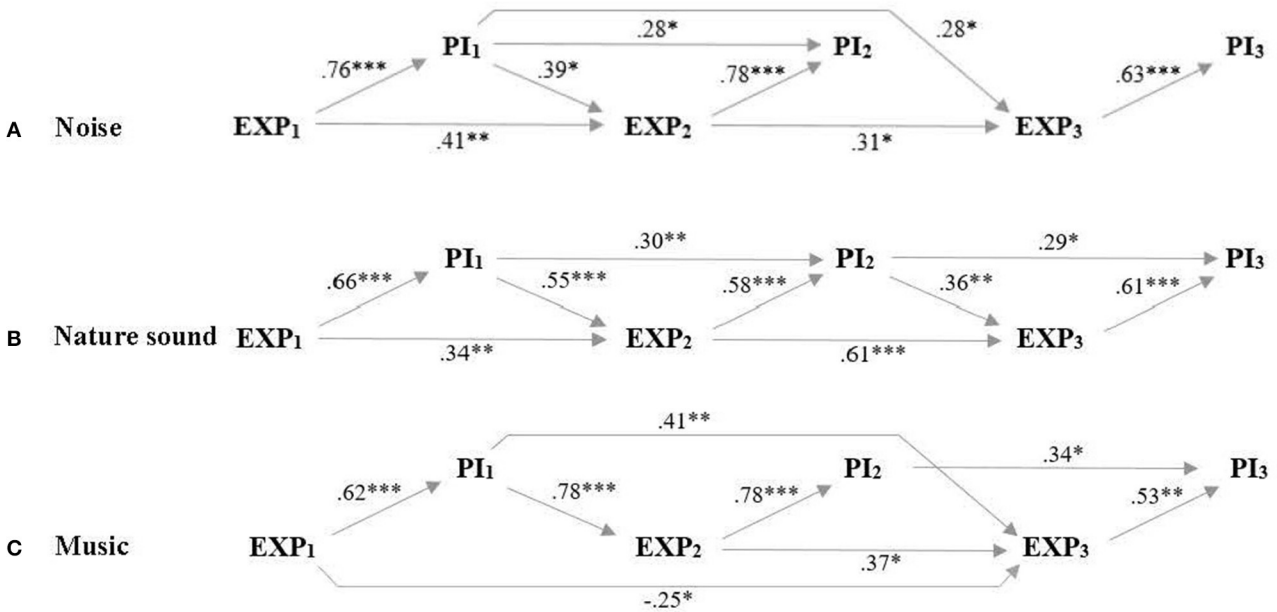

FIGURE 4 | Perceived and expected pain intensity. Path regression analysis of expectancy ratings on the 3 test days (EXP1, EXP2, EXP3) and perceived pain intensity on the 3 test days (PI1, PI2, PI3) as predictors for later expectancy and pain ratings when participants listened to **(A)** noise, **(B)** nature sound, and **(C)** music. Arrows and beta-values mark significant predictions and demonstrate that expected pain intensity predicted perceived pain intensity on all respective test days when including all previous expectancy and pain intensity ratings in the regression model. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

associations between expected and perceived pain intensity and unpleasantness (**Tables 1**, **2**) for all 3 auditory excerpts throughout the study. These associations were also significant when controlling for prior pain experiences from previous test days arguing that the pain-relieving effects observed throughout the study were not attributable to a gradual learning effect (i.e., an effect of prior pain levels). Furthermore, the path regression analyses (**Figures 4**, **5**) establish expectancy as a significant predictor of perceived pain intensity and unpleasantness for all 3 auditory excerpts on each of the 3 test days while, at the same time, demonstrating a continued interplay between expectancy and experience carrying over to subsequent pain expectations. For further discussion of the contribution from contextual factors in music-induced analgesia, see (19).

Together, these findings accentuate the importance of not only demonstrating an effect of music, but also specifying the factors contributing to the effect. Although participants *experienced* significantly lower pain levels during music compared with nature sound and noise, they also *expected* significantly lower pain levels in relation to music compared with nature sound and noise (as demonstrated by similar patterns in **Figures 2**, **3**). Thus, adding to mixed findings from previous studies (8, 41, 43), results from this study suggest that expectations of pain relief—a core element in placebo effects (59)—contribute significantly to the analgesic effect of music.

Limitations and Implication for Future Research

When discussing the current results, some methodological limitations and implications may be addressed. Firstly, a possible dose-dependent effect should be considered in relation to results

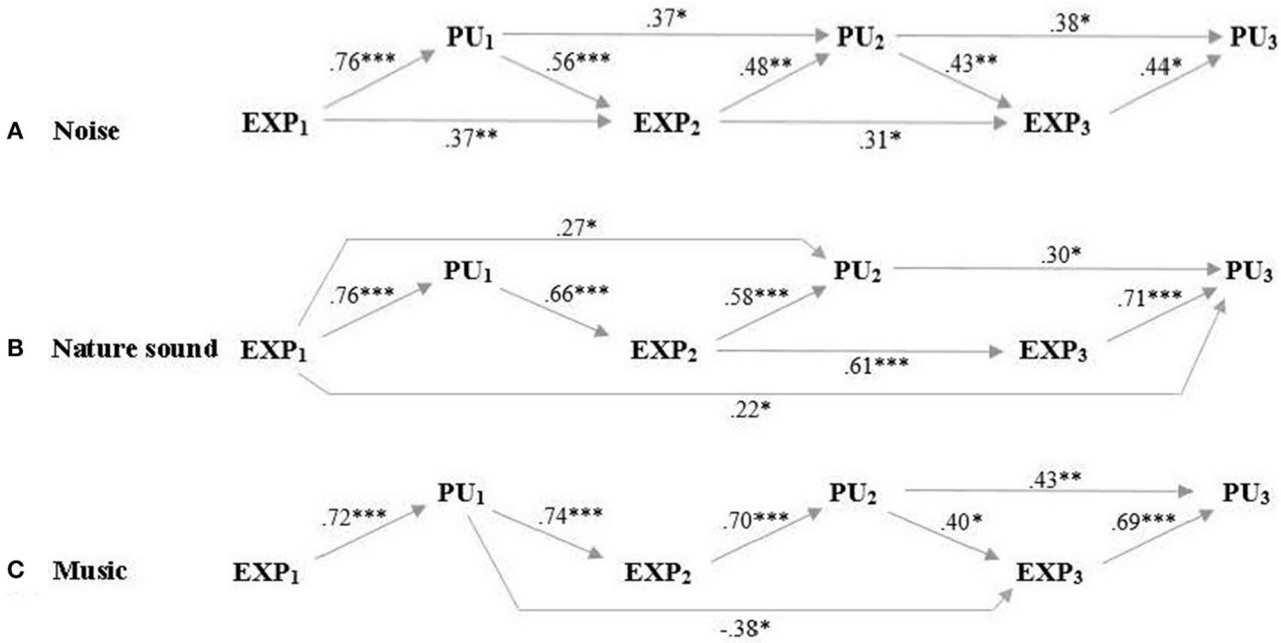

FIGURE 5 | Perceived and expected pain unpleasantness across test days. Path regression analysis of expectancy ratings on the 3 test days (EXP_1, EXP_2, EXP_3) and perceived pain unpleasantness on the 3 test days (PU_1, PU_2, PU_3) as predictors for later expectancy and pain ratings when participants listened to **(A)** noise, **(B)** nature sound and **(C)** music. Arrows and beta-values mark significant predictions and demonstrate that expected pain unpleasantness predicted perceived pain unpleasantness on all respective test days when including all previous expectancy and pain unpleasantness ratings in the regression model. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.

on opioid and dopamine-dependent mechanisms. Whereas the 3 mg haloperidol used in the study corresponds to the recommendations for single doses in healthy participants (50, 60), the 25 mg naltrexone balances dose efficacy and risk of adverse events. In a study examining the role of endogenous opioids in music and emotion, Mallik and colleagues argued for 50 mg naltrexone as lowest effective dose (22). Importantly, however, in our pilot study, 50 mg caused substantial discomfort and adverse events among participants, and even the 25 mg naltrexone administered in this main study was associated with adverse events (**Supplementary Table 1**) substantiating that the antagonist did take effect. Adding to these considerations, Lee and colleagues (51) suggested that a dose of 50 mg oral naltrexone may be far greater than what is needed to occupy opiate receptors and that lower doses may be sufficient and result in fewer side effects. Accordingly, on the one hand, the dose of naltrexone necessitates some caution when interpreting the results of the present study in regard to opioid-dependent mechanisms. On the other hand, it cannot be ruled out that the experience of adverse events following haloperidol and naltrexone may have had an effect on the participants' overall experiences (e.g., expected and perceived effects) on the present and following test days. Furthermore, despite results showing no effects of the pharmacological manipulations (i.e., no attenuation of analgesic effects), it should be noted that no physiological criteria were used to assess that the action of the medication had actually ceased during the washout periods (between test days).

Secondly, the implementation of carefully matched, auditory contextual controls for music composes a new area of research within studies on music-induced analgesia, and various modifications may be pursued in future study designs. Exemplifying this, it would be beneficial to include measures of baseline pain levels without auditory stimuli (silence). This would also allow us to verify if pink noise indeed acts as a neutral control with no positive or negative effect on pain levels—compatible to previous findings showing no differences in pain levels when comparing white noise to silence (61). Other approaches to specifying the role of specific and contextual factors may be to vary and directly compare the outcomes of different music parameters and characteristics (62), to vary the information given about the different auditory excerpts (e.g., a mixed design in which only some participants receive information on the hypothesized analgesic effects of music and nature sound) (63–65) and explicitly targeting other contextual and emotional factors such as familiarity and preference (8, 19).

The auditory paradigm used in this study (i.e., the specific auditory excerpts with an exposure phase of 5 min) is based on a previous study showing an analgesic effect of music and nature sound compared to pink noise (42). It should be recognized, however, that there is generally no consensus across the literature as to how long these exposures should be—ranging from, e.g., 4 min in experimental studies with healthy participants (8) to 15–60 min in clinical studies on patients with chronic pain (66–68). Furthermore, whereas previous studies investigating neural

underpinnings of music-induced analgesia and musical pleasure have used participants' favorite music (16, 56), participants in this study all listened to the same auditory excerpts. This inclusion of researcher-chosen music may be regarded as both a disadvantage and advantage. On the one hand, self-chosen music has been suggested to be superior to researcher-chosen music in relieving pain (12). On the other hand, researcher-chosen music may be more compatible with clinical applications of music requiring no further preparation. Moreover, although our data on pharmacological antagonism and neurotransmitter-dependent mechanisms in music-induced analgesia should be interpreted in relation to researcher-chosen music, the pharmacological paradigm used in the study can be applied also in relation to highly preferred and familiar music.

Finally, acknowledging that findings obtained in healthy participants exposed to acute pain may not necessarily be transferred to patients experiencing chronic pain (69, 70), more studies are needed to specify similarities and dissimilarities in the mechanisms underlying music-induced analgesia in acute and chronic pain.

Independently of the type of music or study population, however, future study designs should take into account that a substantial part of the analgesic effect may be explained by contextual factors that exceed the characteristics and qualities of music. Thus, in order to fully evaluate the beneficial effects of music *per se*, the inclusion of carefully matched, auditory contextual controls may be utilized further to elaborate on how music acts to relieve pain.

CONCLUSION

In conclusion, the present findings show that expectations for pain relief is an important predictor for the analgesic effect of music—as well as for other auditory material. They also suggest that the assumed key role of the endogenous opioid and dopamine systems in music-induced analgesia has to be tested directly in more studies before we can infer if and how they contribute to this analgesic effect. The methodological approach used in this study provides a model for further investigations of music-induced analgesia, the mechanisms by which music acts to relieve pain as well as the specific—and contextual—factors contributing to this effect.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors upon request, without undue reservation.

ETHICS STATEMENT

The study was reviewed and approved by the Central Denmark Region Committees on Health Research Ethics. The participants provided their written informed consent to participate in the study.

AUTHOR CONTRIBUTIONS

SJL: data acquisition, analysis, and drafting the article. SJL, PV, EAG-V, and LV: conception and design of the study. PV and EAG-V: revising the article critically for important intellectual content. IK and LV: data analysis. IK, LV, and SJL: interpretation. IK and AM: revising the article critically for important intellectual content. AM: medical supervision and responsibility during data acquisition. LV: drafting the article. All authors contributed to the article and approved the submitted and final version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpain.2022.734999/full#supplementary-material

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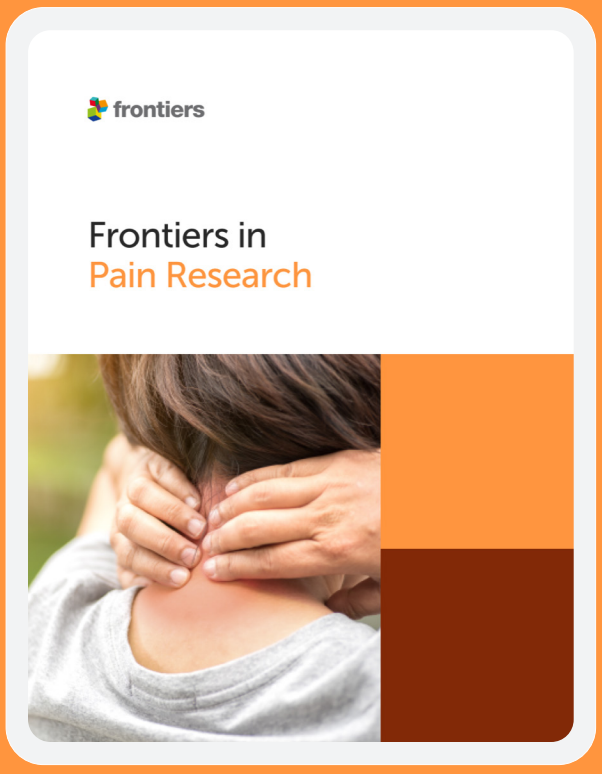

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