Collaborative Care for Opioid Dependence And Pain (CCODAP) Pilot Study

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A. SPECIFIC AIMS

Chronic opioid treatment for chronic pain has led to widespread opioid dependence.
Prescription of opioid medications for treatment of chronic non-cancer pain rose significantly in the 1990s and 2000s. At the prescribing peak of 2010, prescriptions outnumbered persons in many parts of the country, and this continues to be the case in many counties [1, 2]. The widespread availability of opioids has led to an increase in opioid dependence and subsequent overdose deaths, which has continued to rise despite a decrease in opioid prescriptions in recent years [3, 4]. One hypothesis for the increase in overdose death despite a reduction in opioid prescriptions is that opioid-dependent patients are turning to illicit opioids, leading to overdose. Trends in substances found in overdose deaths support this hypothesis [3]. Federal efforts to address the opioid overdose epidemic have focused primarily on educating prescribers to reduce prescribing and increasing access to opioid addiction treatment [5]. Less attention has been paid to ensuring that evidence-based treatment for chronic pain is provided alongside opioid tapering and/or addiction treatment. Many studies have demonstrated that opioids are non-superior to several alternatives for treating chronic pain [6-8]. While opioid tapering can be a challenge for both patients and providers [9, 10], structured opioid tapering programs have demonstrated both efficacy in opioid reduction and often either unchanged or decreased pain intensity [11]. However, these results have primarily been found in specialty centers providing intensive multi-modal treatment, often treating patients 8 hours per day for 5 days a week. Given the scarcity of such programs and the high prevalence of opioid-dependent patients, alternative care-models capable of greater scaling will be necessary to address the current epidemic.

Collaborative Care is a healthcare model capable of providing specialty care to far more patients than can be achieved through traditional one-on-one treatment models. Collaborative Care has proven effective in delivering treatments for managing depression and pain in primary care settings [12-15]. A few recent studies have also demonstrated efficacy in treating addiction and opioid dependence using a collaborative care approach [16, 17]. Several different pain interventions have been effective in these collaborative care trials, including medication optimization, cognitive behavioral therapy, and several different structured self-management programs. Recently, pain researchers have found positive psychology-based interventions to be effective, well-received, and easy to deliver [18-20], making this intervention well-suited to pair with collaborative care. In the proposed clinical trial, we will assess the feasibility of utilizing collaborative care to facilitate opioid tapering in patients with chronic pain using a positive psychology intervention.

Primary Aim: Determine the potential effectiveness of delivering Collaborative Care for reducing opioids in patients with chronic pain.

Hypothesis: Collaborative Care will be effective (30% reduction in mean morphine equivalent dose/day [MMED]) in reducing opioids while maintaining pain control (< 1 point increase in 0 to 10 pain rating scale).

Secondary Aim: Assess adherence to tapering and satisfaction of patients with this Collaborative Care approach.

Hypothesis: Patients will be satisfied with (mean score ≥ 3 on 0 to 5 satisfaction scale) and adhere to (≥ 70% retention) the 12-week opioid tapering program.

Impact of this research. Excessive prescribing of opioid medications for chronic pain has led to widespread opioid dependence, abuse, and rising overdose deaths. Preliminary research by others has demonstrated that multidisciplinary specialty care for patients with chronic pain on opioid therapy can produce successful opioid tapering without worsening of pain or mood symptoms. However, reducing opioid prescribing for chronic pain in the primary care setting has proven difficult given limited visit time, inadequate provider training, and constrained clinic resources for managing patients with opioid dependence [9, 10, 21]. This trial proposes a novel collaborative care approach for opioid weaning using proven, easy-to-deliver positive psychology tools for pain management that, if successful, could be implemented broadly in many clinics struggling to safely reduce opioid prescribing.

SIGNIFICANCE

Opioid Overdose Deaths are a Public Health Emergency. In 2016, there were over 42,245 overdose deaths involving opioids in the United States, representing a 292% increase from 2001[22] [3]. These deaths have struck the 24-35 year-old range especially hard, where 20% of deaths in 2016 in this age group were attributed to opioids, leading to 1,681,359 lost years of life [22]. This spike in overdose deaths follows a sharp increase in opioid prescribing for chronic pain, which preceded a rise in non-medical opioid use [23]. In theory, decreasing opioid prescribing to patients with chronic pain may reduce the risk of overdose to patients and the general population[24]. However, the current strategy of opioid prescription reduction actually has coincided with an increase in opioid-related overdose deaths [3].

Opioids are non-superior to other pain-management strategies. Although opioid medications perform better than placebo for the treatment of chronic non-cancer pain, the current evidence available does not suggest that opioids are superior to other treatments for chronic pain [6-8]. In a multidisciplinary intensive outpatient setting, patients were successful in opioid tapering without worsening pain, mood, or functioning [11].

Managing patients with opioid dependence is a challenge in primary care settings. Primary care providers struggle to reduce opioids for chronic pain given limited resources available to help with this [9, 10]. Despite clinical guidelines being available, insufficient time and difficulty having discussions about opioid misuse have hampered their utilization [21].

C. INNOVATION

CCODAP is the first trial to combine collaborative care with positive psychology pain management tools to support opioid weaning in patients with chronic pain. This dual focus on reducing opioids while simultaneously addressing the patient's pain has been absent from many regulatory and practice initiatives which have focused solely or predominantly on opioid reduction or discontinuation as the principal benchmark.

D. APPROACH

Previous Work

Symptom management trials by study team members. As shown in **Table 1**, the study team has a strong track record in conducting symptom management RCT's. Seven of the eight trials have focused on patients with pain. All of the trials have relied on collaborative telecare-delivered interventions, either fully/mostly (n=3) or in part (n=5). The studies have ranged from 6 to 12 months in duration and have had high retention and follow-up rates. Interventions have included medications, self-management, physical therapy, and behavioral treatments. Finally, this application's trialists have complementary expertise including internal medicine/symptom management (Kroenke) and psychiatry/behavioral therapy (Bushey).

Table 1. Previous Work by Team Relevant to CCODAP Trial

Trial	Kroenke Role	N	Mo.	Symptoms Targeted	Patient Sample	Tele-care	Intervention	Benefits
AIM[25]	Co-PI	176	9	Depression	Neurology (stroke)	Partly	Medications	Intervention > Usual care
SCAMP[26, 27]	PI	250	12	Pain Depression	Primary care	Partly	Medications & Self-management	Intervention > Usual care
INCPAD[13, 28]	PI	405	12	Pain Depression	Cancer (all types)	Fully	Medications	Intervention > Usual care
SCOPE[14, 29]	PI	250	12	Pain	Primary care	Fully	Medications	Intervention > Usual care
CAMMPS[15, 30]	PI	300	12	Pain, Anxiety, Depression	Primary care	Fully	Medications & Self-management	NCM + ASM > ASM alone†
COPE[31, 32]	Co-Invest	495	6	Function Pain	Cancer (advanced)	Partly	Physical therapy & Pain management	Intervention > Monitoring only
SPACE[8, 33]	Co-Invest	240	12	Pain	Primary care	Partly	Medications	Non-opioids = Opioids
ESCAPE[34]	Co-Invest	241	9	Pain	Primary care	Partly	Medications + CBT	Intervention > Usual care

† NCM = nurse care management, ASM = automated symptom management

Study Design. Forty patients with non-cancer chronic pain on long-term oral opioid therapy will be recruited into this pilot trial. Patients will be randomized to receive either the treatment intervention (n = 20) or usual care (n = 20). Assignment to treatment arm will be determined by a computer-generated randomization list in permuted blocks of 4 to maintain balanced assignment throughout the trial. Participants must: (1) be age 18 or older, (2) have an established chronic pain disorder of at least 6 months, and (3) be receiving chronic daily oral opioid treatment. Exclusion criteria are: (1) not speaking English, (2) significant cognitive impairment that would hinder participation.

Theory of the Intervention and Conceptual Model

The intervention is based on the observation that patients often have unchanged or improved pain when tapered from chronic opioids with a structured weaning protocol and adequate support. However, successful weaning in current practice is hindered by a lack of provider training and comfort in tapering and insufficient patient support. By providing symptom monitoring and management along with simple interventions to help patients increase their self-efficacy, we believe that patients can successfully wean from opioids. We postulate that factors such as depression, personality, catastrophizing, and severity of opioid difficulties may moderate this outcome, and will be measuring these at baseline and at 12 weeks.

Procedures

Recruitment and Consent. Prior work in this field has demonstrated that enrollment in trials of opioid tapering can be challenging due to low rates of referral by providers and high patient refusal rates [17, 35]. We will take 2 approaches to patient recruitment. The first approach will be to invite providers who treat patients with chronic opioid therapy to refer patients to the study. This is our preferred method as it will engage the patients' current providers with whom collaboration will be crucial. We will also directly outreach to patients. The Cerner electronic medical record (EMR) can be queried by Indiana University Health (IUH) information technologist to generate a list of patients on chronic opioid therapy within the IUH System. Eligible patients will be sent a study invitation letter or text providing information unless their primary care provider disapproves. Patients interested in participating will be scheduled for a baseline study consent session. In light of ongoing fluctuations in coronavirus activity, all study activities are designed to take place virtually either over telephone or video conferencing software. Patients will be provided a copy of the study information sheet (either through U.S. post, e-mail, or access to a digital download) so they can read along during their consent session. All subjects will provide verbal informed consent and HIPAA authorization. Documentation of the informed consent process and HIPAA authorization process will bedocumented via the consent log in the study binder We believe the activities in this trial satisfy the requirements outlined in 45 CFR 46.116 Part F.3 for a general waiver of written consent:

(1) **The research involves no more than minimal risk to subjects.** All subjects eligible for the trial are on chronic opioid therapy, which puts them at risk for developing dependence, accidental overdose, and forced tapering or opioid therapy discontinuation by providers increasingly under pressure to reduce or discontinue opioid prescribing. Our intervention provides evidence-based, non-pharmacologic pain treatment that may improve pain outcomes and allow patients to decrease the doses of opioid medications they take, which would decrease their risk of the above opioid therapy-related adverse outcomes. If patients are interested in lowering their opioid dose, our program of weekly check-ins will provide a greater level of care than usual care. Patients in the usual care group are at no greater risk for adverse clinical outcomes than if they were not enrolled in the trial. The maintenance of research records and audio recordings from intervention sessions is associated with the minimal risk of potential loss of confidentiality, which is mitigated by records being maintained in a secure research environment on enterprise Microsoft Storage or REDCap databases.

(2) **The research could not practicably be carried out without the waiver.** Written informed consent will be obtained whenever a participant is able to access and utilize the electronic consent system. However, for patients without this capability, verbal consent will be obtained instead. This is preferrable to the alternative approaches of either having participants return consent forms by mail or requiring participants to present to the clinic to sign consent forms. Our experience with attempting to recruit this population has demonstrated that mailing forms results in excessive delays, confusion, and frustration on the part of participants. In-person visits would result in unnecessary burdens (related to travel and parking) and potential coronavirus exposure.

(3) **The research could not practicably be carried out without identifiable data.** This is a randomized clinical trial that requires following participants over time, as well as accessing medical records to verify medication prescription information and communicate with their providers. Identifying, outreaching, and following patients longitudinally cannot be accomplished without utilizing identifiable data.
(4) **The waiver will not adversely affect the rights and welfare of subjects.** Participants will continue to receive clinical services as usual whether or not they participate in this study, and the waiver of written consent will in no way affect this.
(5) **When appropriate, subjects will be provided with additional pertinent information after participation.** All participants will continue to receive additional pertinent information whether or not they complete a written informed consent electronic document.

Baseline Data Collection and Orientation. Enrollment and baseline data collection will occur in 75-minute sessions over telephone or teleconferencing software. This remote approach is especially important so long as social distancing precautions are in effect to mitigate the spread of the novel coronavirus. During the first 30 minutes of the enrollment session, participants will be provided a brief overview of the study by a member of the study team, followed by distribution and explanation of the informed consent document and an opportunity for participants to ask questions. In particular, they will be given information about opioid dependence, opioid use disorder, and the potential benefit of opioid dose reduction to improve pain and reduce adverse events. They will also be informed that opioid substitution therapy is a possibility if there is concern for opioid use disorder. Once informed consent is obtained, the next 45 minutes will provide time for participants to complete baseline measures, , and receive a $40 gift card.

Intervention
The intervention will be a 12-week supportive opioid taper utilizing a collaborative care program consisting of 2 components: a telecare intervention and a telecare-reinforced positive psychology self-management program.

Opioid Reduction`

Table 2. Positive Psychology Self-Management Intervention

Week	Program
1	Noticing and capitalizing on positive events and gratitude
2	Mindfulness
3	Positive reappraisal
4	Strengths and Attainable Goals
5	Altruism
6 - 12	Practice Your Favorite(s): Pick at least one of the prior activities you liked and practice it again.

During the initial orientation, participants will be given information about opioids and the potential benefits of opioid dose reduction. If participants are interested in reducing their opioid dose, tapering approaches will be discussed. Participants will receive education on what to expect during tapering, including possible opioid withdrawal symptoms and common treatments for each symptom. A handout describing appropriate use of non-prescription remedies for common withdrawal symptoms will be provided. The standard tapering guideline is adapted from the Mayo Clinic guidelines on opioid tapering [36]. Patients will decide whether they would like to attempt opioid dose reduction based on the standard guideline or a negotiated alternative approach as empowerment and shared decision-making can improve both patient satisfaction and adherence [37]. Any potential change in the participant's opioid dose will be discussed with the patient's treating physicians (including relevant specialists such as pain medicine providers or maternal-fetal medicine providers in pregnant participants), who will prescribe the medication. During the trial, the taper schedule can be adjusted to maximize patient tolerability, so long as the patient's treating physicians agree with the adjustment. Forced tapering can lead to negative patient outcomes including worsening pain, withdrawal symptoms, functional decline, and seeking illicit opioids [38, 39].

Positive psychology self-management intervention:
Recent studies have demonstrated the efficacy of positive psychology self-interventions in the management of chronic pain [18-20]. Our intervention (Table 2) will be modeled on the program used by Moskowitz and colleagues, who have demonstrated efficacy of their intervention in numerous randomized clinical trials for a myriad of conditions including substance use and pain [40-43]. Patients will receive instruction on how to complete the intervention during their initial visit. During the skill acquisition phase (scheduled for the first 5 weeks of the intervention), participants work through the interventions according to the schedule and will be asked to record their progress into a trial logbook. If participants are unable to meet, need to cancel a session, or require some additional time to acquire a skill, the skill will be covered in the next session. Once participants finish the skills acquisition phase, they will enter the habit solidifying phase for the remainder of their 12 week intervention period.

During the habit solidifying phase, patients will be encouraged to incorporate a positive psychology technique into their daily routine, with the goal of forming a habit [44]. Progress in habit formation will be assessed during the scheduled weekly peer check-in sessions.

Telecare Intervention
We will utilize an evidence-based telecare approach to facilitate symptomatic management. We have successfully utilized this technique to manage pain, depression, and anxiety in several previous trials (Table 1). The telecare intervention consists of two main parts (1) symptom monitoring and (2) peer coach-facilitated treatment support.

During the trial, a peer coach will contact patients weekly by telephone (with or without video) to discuss how they are doing. Patients will be encouraged to share their logbook information with peers to facilitate discussion. Peer coaches will provide reinforcement and accountability for patients to keep up their symptom and positive psychology intervention logging. If patients report new or worsening symptoms, peer coaches will discuss with patients whether they have been able to use the treatments suggested at the trial start and will provide reminders to use these treatments if warranted. If the patient reports elevated distress, intolerance of symptomatic treatments, opioid cravings or opioid use disorder behaviors, the peer and participant will relay this information to the physician-investigator. If an adjustment to the treatment plan is indicated, the physician-investigator will make adjustments in collaboration with the patient's primary treating physician.

The peer coach will meet with the study PI (Dr. Bushey) weekly to discuss new cases and treatment plans as well as participants for whom treatment adjustments based upon symptom monitoring may be warranted.

Usual care arm:

Patients randomized to usual care will continue to receive care from their primary physician, with no active involvement by study personnel. Patients in this group will fill out the same baseline and 12 week questionnaires as patients in the intervention arm.

Outcome measures. In addition to demographic and clinical characteristics that will be assessed at baseline, numerous symptom measures will be assessed at baseline and at the conclusion of 3 months of treatment (Table 3). Participants will receive a $40 gift card for each of the two outcome interviews (baseline and conclusion) that they complete. Opioid daily dose reduction is the primary outcome and will be measured in morphine-equivalent daily dose (MEDD). Secondary outcomes will include pain intensity, pain interference, positive affect, depression, anxiety, and disability. We will attempt to collect follow-up questionnaire data for up to 3 additional months after the conclusion of the trial to maximize the likelihood of data capture.

Qualitative Interview. At the conclusion of the study, participants will be invited to participate in semi-structured individual interviews to discuss their experience with chronic pain and the trial, what worked well, what could be improved, and potential strategies to bolster recruitment of additional patients in future studies. We will aim to conduct interviews of 10 patients in the intervention arm. Each interview will be audiotaped, transcribed, and independently analyzed by 2 reviewers to determine key themes related to barriers and facilitators using qualitative methods used in previous trials by Dr. Kroenke [49, 50]. Participants will receive a $50 gift card for completion of a qualitative interview.

Data Analysis Plan. Descriptive statistics (means, medians, standard deviations, inter-quartile ranges, and frequencies) will be computed to assess variables' distributional properties and to describe the sample when disseminating results. Since this is a small pilot study to test feasibility and patient acceptance, it is not formally powered to test a specific treatment effect size. Instead, whatever treatment effect is found will be useful in planning the sample size for a more definitive trial. However, a sample of 20 participants per arm has 80% power with an alpha of .05 to detect a 30 mg MEDD greater dose reduction in the intervention group (e.g., from 70 MMED to 40 MMED) assuming a SD for the MEDD of 30[8] and 20% attrition (i.e., 32 of the 40 participants completing the trial). We will also explore treatment effect moderators, including medical comorbidity (using a 9-item checklist), personality (TIPI scores), baseline pain interference, pain catastrophizing, pain self-efficacy, baseline somatic symptoms (SSS-8), mental health (PROMIS depression and anxiety), and baseline opioid difficulties (PODS).

Feasibility. Several factors support the feasibility of our trial. First, as noted in the Preliminary Work section (**Table 1**), our team has successfully conducted multiple telecare-centered intervention trials [8, 13, 15, 25-33, 51]. Second, several of these trials have demonstrated efficacy in managing pain [8, 13, 15, 25-33, 51]. Third, we will be utilizing a positive psychology intervention that has been shown to improve pain outcomes in patients with chronic pain [42]. Finally, others have demonstrated success in recruiting patients for and completing an opioid tapering program [17, 35]

Potential Problems and Alternative Approaches. As described above, should patient recruitment prove challenging, we have several recruitment strategies. Further, adding additional clinical sites for recruitment would be another potential approach. High drop-out rates are an additional concern. If this occurs, identifying factors contributing to drop-out can inform further refinement of the treatment protocol in a subsequent study.

Table 3. Outcome Assessment: Measures and Schedule of Administration

Domain	Measure	# Items	Schedule (month)	
			0	3
Primary outcome				
Opioid Daily Dose	Morphine-Equivalent Daily Dose (MEDD).	1	X	X
Secondary outcomes				
Pain	PROMIS Pain	9	X	X
Pain Catastrophizing	CSQ Catastrophizing	4	X	X
Pain Efficacy	Pain Self Efficacy Questionnaire (PSEQ)	4	X	X
Depression, Suicidality	PROMIS Depression / *P4 Screener	5	X	X
	Remission Evaluation and Mood Inventory Tool (REMIT)	5	X	X
Anxiety	PROMIS Anxiety	4	X	X
Positive Affect	Positive and Negative Affect Scale – Short Form (PANAS – SF)	10	X	X
Somatic Symptoms	Somatic Symptom Scale – 8 (SSS8)	8	X	X
Disability	Sheehan Disability Scale (SDS)	3	X	X
Opioid Problems	Prescription Opioids Difficulties Scale (PODS)	16	X	X
	PROMIS Prescription Opioid	7	X	X
	Craving State, OUD Intensity/Interference Scale (ORG)	4	X	X
Substance Use	Substance Use Questionnaire	13	X	
Medical Co-Morbidity	Chronic disease checklist	9	X	
Demographics		8	X	
Personality	Ten Item Personality Inventory (TIPI)	10	X	X
Global Rating of Change		2		X
Satisfaction with treatment		2		X

Interview time in minutes (est.)			45	45

*P4 screener only used at baseline

Benchmarks of Success. The following will provide benchmarks to evaluate the success of the proposed study: (1) Secure IRB approval for the study; (2) Recruit and consent the first 20 participants, conduct the interventions with these participants, and collect data; (3) Repeat with the second set of 20 participants; (4) Enter and clean the data; (5) Analyze data; (6) Write manuscript(s) and submit for publication; and (7) Develop an NIH K-23 grant application based on results of this trial.

E. POTENTIAL FOR FUTURE FUNDING AND TRANSLATION

We will use the results of CCODAP as preliminary data to prepare a K-23 application to either NIDA or the NIMH.

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