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Original Article

# Hyperbaric Oxygen Therapy for Pain, Opioid Withdrawal, and Related Symptoms: A Pilot Randomized Controlled Trial

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ABSTRACT

*Background:* Pain, drug cravings, and opioid withdrawal symptoms can interfere with substance use disorder or opioid tapering treatment goals.
*Aim:* This pilot study investigated the feasibility of a protocol designed to test opioid withdrawal symptom relief relative to a sham condition after two consecutive days of hyperbaric oxygen therapy (HBOT) for adults prescribed daily methadone for opioid use disorder.
*Method:* Using a double-blind protocol, eight adults were randomized to receive either a full 90-minute HBOT dose in a pressurized chamber with 100% oxygen at 2.0 atmospheres absolute (ATA) or a sham condition receiving 21% oxygen (equivalent to room air within the chamber) at a minimal pressure of ≤1.3 ATA. Measures included study retention, treatment satisfaction, and pre- and post-intervention effects for opioid withdrawal symptoms, drug cravings, pain intensity and interference, sleep quality, and mood.
*Results:* Study retention and treatment satisfaction was high. All measurements improved more, on average, for participants receiving full-dose HBOT treatment than among participants receiving sham treatments except for clinically observed withdrawal symptoms. The largest positive effects were observed in measurements of pain intensity and drug craving.
*Conclusions:* These pilot results provide evidence to support a fully powered study of HBOT as a potential treatment adjunct for adults receiving methadone for opioid use disorder. Trends towards symptom improvements were detected from pre- to post-HBOT in the full treatment arm versus sham condition. More research into novel non-pharmacologic options to relieve distressing symptoms related to pain and opioid use disorder is essential to improve clinical outcomes.


Despite expanding treatment options for opioid use disorder (OUD), more than 80% of drug overdose deaths in the United States involve opioids (Centers for Disease Control and Prevention CDC, 2020). A portion of these deaths include people with co-morbid pain and opioid use disorder, and an estimated 20%-30% of opioid overdose deaths are attributed to suicide (Oquendo & Volkow, 2018). Pain has been identified as an important antecedent to suicide, as is access to prescription opioids (Ilgen, 2018). Well-intended efforts to reduce opioid prescribing have precipitated an increase of grave risks including severe opioid withdrawal, worsening pain, loss of function, overdose, and suicide (Darnall et al., 2019; Oliva et al., 2020).

Opioid withdrawal has been recognized as a significant clinical syndrome that can cause substantial discomfort, perpetuate drug use and misuse, and impede treatment goals in both people with OUD and those on long-term prescription opioids for persistent pain (Srivastava et al., 2020). The CDC has recognized an urgent need for overdose prevention intervention and lists treatment with medications for opioid use disorder (MOUD) as a crucial element (Centers for Disease Control and Prevention CDC, 2020). Yet, nearly 20% of those dying from opioid overdose had been previously treated for a substance use disorder (SUD) and as many as 70% of treatment-seeking adults discontinue MOUD within the first 30 days (Morgan et al., 2018). Factors that contribute to dis-

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continuing MOUD include the complex nature and stigma of a chronic SUD, type of treatment offered, drug cravings, and physical symptoms (e.g., pain, withdrawal) that may be difficult to manage (St. Marie & Broglio, 2020).

"Self-medicating" poorly controlled symptoms of pain, depression, and anxiety are often cited as reasons to continue or resume opioid use in OUD populations (Cicero & Ellis, 2017). Up to 60% of U.S. adults with OUD have comorbid persistent pain (Speed et al., 2018) and 8%-12% of those with persistent pain develop OUD (Volkow et al., 2018). Therefore, therapies are needed that can concurrently address pain and symptoms common to OUD. Historically, opioid treatment programs have not included pain management to be within their purview, although treating chronic pain and OUD as separate entities may miss the complexity of the whole individual. As coexisting problems, pain and OUD necessitate an integrated, multidimensional therapeutic approach (Manhapra & Becker, 2018). Potentially, therapeutics that can address pain and OUD concurrently could result in better outcomes for both pain and substance use recovery.

Oral methadone, a $\mu$-opioid full agonist, has a long history of safety when used for MOUD treatment to reduce withdrawal symptoms, drug cravings, recurrence of drug use, and risk of overdose (Bell & Strang, 2020). For people experiencing pain and OUD, it is also notable that methadone provides pain relief and can reduce hyperalgesia and opioid tolerance. Methadone is considered a challenging medicine to prescribe due to wide interindividual variability in pharmacokinetics making dose, plasma concentrations, and effects difficult to predict (Kreutzwiser & Tawfic, 2020). Methadone also has more drug-drug interactions due to metabolism via the cytochrome P450 enzyme systems (Ilgen, 2018). Overdose deaths attributed to methadone increased 5-fold when its use for pain increased between 1999 and 2009, resulting in a U.S. Food and Drug Administration (FDA) public health advisory about careful prescribing of methadone for pain (Kreutzwiser & Tawfic, 2020). It is important for people with comorbid OUD and pain to have non-opioid options that do not carry the risks of opioid overdose. Investigating safe, complementary therapies that address opioid withdrawal symptoms and pain simultaneously could help MOUD recipients succeed in their treatment goals.

Hyperbaric oxygen therapy (HBOT) has an 80-year history of safe use. Third-party payments in the United States generally cover its costs for 14 approved clinical indications (United States Food and Drug Administration U.S., F.D.A, 2021). Promising results have been seen using HBOT for a variety of persistent pain conditions including chronic headache, fibromyalgia, and complex regional pain syndrome (Sutherland et al., 2016). A single scientific publication from Russia reported that HBOT can relieve opioid withdrawal in human subjects (Epifanova, 1995). Preclinical studies by one of our senior authors reported that HBOT reduced physical signs of naloxone-precipitated withdrawal in morphine-dependent mice (Nicoara et al., 2016). The mechanism of action may be partially explained by reduction of the neuroinflammation that contributes to the maintenance of SUDs (Kohno et al., 2019) along with actions involving monoaminergic neurotransmitters (Chen et al., 2018). Previous work by our team determined that a five-day course of HBOT sessions offered at 2.0 ATA with 100% oxygen in a pressurized chamber was well-tolerated and feasible for 17 adults with OUD (Roush et al., 2020). Opioid withdrawal symptoms showed, on average, twice as much improvement after one day of HBOT relative to a control condition, and participants were able to sustain a larger reduction in methadone dose at three months following HBOT (Roush et al., 2020; Wilson et al., 2022). Sleep improvements were also noted following HBOT sessions (Quock et al., 2019). The prior work could not control for placebo effects, however, so the present study adapted a sham condition to increase confidence in the findings. The previous study also failed to recruit persons with significant symptom burden, so new criteria were applied in this study to generate greater opportunity to detect post-HBOT symptom changes. We recruited participants who were in the first 90 days of methadone initiation based on evidence that this is a period of high dropout from treatment (Durand et al., 2021). The specific research questions were: (1) Is a two-day HBOT treatment protocol feasible for adults initiating methadone treatment for OUD?; (2) What changes in symptom burdens can be detected immediately and longer-term following a two-day HBOT treatment?; and (3) How do effects compare after full HBOT treatment relative to a sham condition?

## Methods

### *Design and Sample*

A randomized double-blind controlled pilot trial enrolling adults with OUD to either an HBOT full treatment group or a sham condition control group was approved by the primary investigator's university institutional review board. Participants receiving daily methadone at any dose were recruited between September 2019 to January 2020 from two urban outpatient Opioid Treatment Programs (OTP) in the Northwestern United States where usual treatment focuses on medical management of OUD (primarily methadone treatment) accompanied by group and individual counseling. Flyers were posted in waiting areas and given to clinic staff who were encouraged to distribute widely. Participants could self-refer via phone, email, or in person during research personnel's recruitment time that was scheduled in waiting areas at each clinic for several hours per week. Eligibility screening occurred during phone or in-person brief interviews to establish the ability to read, write, and speak in English; age $\geq$18 years; no diagnosis of a sleep disorder; and no serious ear or lung problems that would be contraindications to HBOT including conditions requiring surgery, pneumothorax, lung cysts, emphysema, currently taking Antabuse (Disulfiram) for alcohol use disorder, or current treatment for dental disease. To test the protocol on people with higher symptom burden, we limited participation to people within the first 90 days of methadone treatment initiation (verified by clinic records after consent). If qualified, a paper and pencil (if in person) or electronic symptom screening survey commenced to confirm the presence of at least "moderate" withdrawal symptoms on the Adjective Rating Scale for Withdrawal (ARSW), a score of at least 4 on a 0-10 Numeric Pain Intensity Scale (NPIS) and reported sleep burden >50 on the Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance (SD) and Sleep-Related Impairment (SRI) item banks. Ineligible were those who were pregnant or had a medical or psychiatric condition that investigators determined would compromise safe study participation.

If eligible and written informed consent was obtained, a tour of the HBOT facility was scheduled to coincide with a physical exam by the study HBOT physician to verify medical suitability to receive the intervention. The only absolute contraindications to HBOT considered for this study were pneumothorax and inability to equalize pressure in the middle ear. Relative contraindications included upper respiratory infection, emphysema, high fever, and claustrophobia (Foster, 1992; Camporesi, 2014). No participants were found to have excluding contraindications by the physician. Pre-sealed envelopes with a coded group assignment were used for randomization and given at the end of this appointment so that only the involved HBOT staff would be aware of participants' assigned condition and not the research team or participants.

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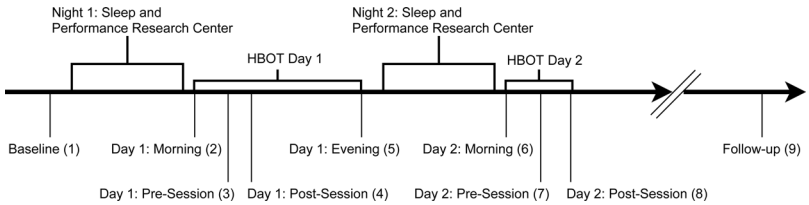


**Fig. 1.** Study timeline and activities.

*Procedures*

Participants were scheduled for a study appointment at the Sleep and Performance Research Center of Washington State University. Upon arrival, participants received an orientation to the overnight sleep laboratory, were shown sleep measurement equipment they would be required to wear, and were given instructions on when to arrive for their first sleep study night that would immediately proceed their scheduled early morning HBOT or sham session. Two consecutive in-laboratory overnight sleep phases were planned for the night before and night after the first HBOT session to capture cardiorespiratory polysomnography data (to be reported in full elsewhere). When participants reported back to the Sleep and Performance Research Center around 7:00 p.m. for their first overnight stay, a baseline survey (detailed below and in Table 2) was administered using a secure online format. Paper and pencil surveys were used for additional data collection scheduled throughout the study's 1-week period (timepoints outlined in Fig. 1). Transportation supervised by research staff was provided each morning from the sleep lab to the OTP clinic for methadone dosing and from there directly to and from the HBOT clinic.

Nine adults were randomized to receive either a full HBOT dose or a sham condition. Treatment followed the HBOT clinic's usual protocol that takes place in a 12-seat, sealed, pressurized chamber where participants receive oxygen via individualized oxygen hoods. Four participants in the HBOT arm received 90-minute sessions on two consecutive days in a pressurized chamber with 100% oxygen at 2.0 ATA. Four participants in the sham condition arm received identical sessions except for substituting 21% oxygen at a minimal pressure of $\leq$1.3 ATA, a previously used placebo condition that reflects oxygenation equivalent to room air within the chamber (Lansdorp & van Hulst, 2018). Each session included 15 min pressurization, 60 minutes at target ATA, and 15 minutes depressurization. Participants received gift cards to compensate for time and travel. A $50 payment was provided each day of attendance during the two-day sessions and after completing the final questionnaire.

## Measures

*Demographics and Characteristics*

Socio-demographic and health history variables collected at baseline included age, gender, race/ethnicity, education level, disease and mental health diagnoses, and medications.

*Protocol Feasibility*

Pilot protocol feasibility was assessed with regard to participant recruitment and retention data, adherence to protocol (measured in days of attendance and treatment completion), and treatment satisfaction.

*Treatment satisfaction*

A post-test survey adapted from the IBM Computer Usability and Satisfaction Questionnaires (Lewis, 1995) was administered to participants in both treatment and sham groups at the end of the study week. These questionnaires are validated tools with internal reliability >.89. Four Likert-style questions under the broad topic of "satisfaction" were included asking about the ease of treatment, the amount of time it took to complete treatment, the in-person support available with treatment, and whether the participant felt comfortable participating in this treatment. Participants rate responses on a scale of 1 = "strongly disagree" to 7 = "strongly agree." Open comments were solicited to the questions: (1) Did you find anything about this treatment especially useful? What would it be?; (2) Is there anything you would change about this treatment if you could? What would that be?; and (3) What else can you share about your experience participating in this treatment?

*Treatment effects*

Effects were measured between treatment and sham conditions and across time to gather data in support of a future randomized controlled trial using outcome measurements detailed below.

*Opioid withdrawal scales*

Symptoms of opioid withdrawal were measured by clinical assessment using the Clinical Opiate Withdrawal Scale (COWS) and by self-report with the ARSW. The COWS is an 11-item scale designed to be administered by a clinician to rate common signs and symptoms of opioid withdrawal over time (Wesson & Ling, 2003). Acceptable internal reliability has been demonstrated (Cronbach's alpha = .78) and concurrent validity established by correlations with the Clinical Institute Narcotic Assessment (CINA) ($r$ = .85) (Tompkins et al., 2009). The ARSW is a 16-item reliable self-report scale of opiate withdrawal symptoms (e.g., muscle cramps, hot/cold flashes, runny nose, tenseness/jitteriness) in which individuals rate adjectives on a 9-point scale from none to severe, with a maximum summed score of 144 (Barbosa-Leiker et al., 2014). The COWS and ARSW were both administered by trained research assistants immediately before and after each HBOT treatment or sham session over the two-day treatment period and at additional scheduled timepoints as shown in Table 2 to assess withdrawal symptoms.

*Drug craving*

Drug craving was measured five times throughout the study using three items with a five-point scale ranging from "strongly disagree" to "strongly agree": (1) "Since waking, the idea of using drugs has intruded upon my thoughts"; (2) "Since waking, I have missed the feeling drugs can give me"; (3) "Since waking, I have thought about how satisfying drugs can be." The total score was summed at each assessment with higher scores indicating more craving. In the absence of a commonly accepted craving measurement for OUD (Kleykamp et al., 2019), we chose a scale with evidence of face and discriminant validity that was found to have internal reliability ($r$ = .89) and was sensitive to change over time in populations with OUD (Lydon-Staley et al., 2017).

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*Pain intensity and pain interference*

A 0-10 Numeric Rating Scale (NRS) was used at five scheduled timepoints to measure pain intensity "right now" with 0 = "no pain" and 10 = "worst pain ever." The NRS is strongly associated with other pain intensity measures and has been broadly validated across many patient populations; scores of 4-6 are generally considered to represent moderate pain and 7-10 severe pain (Karcioglu et al., 2018).

To measure pain interference, the 8-item PROMIS pain interference scale was used at baseline and 1 week post-intervention to ask how much pain interfered with work, socialization, chores, etc., in the past seven days. The scale has acceptable test-retest reliability (Cronbach's alpha = .84) and convergent validity ($r$ = .7) with the Brief Pain Inventory (BPI) interference measure (Cook et al., 2015).

*Sleep quality*

Sleep quality was assessed using the 8-item PROMIS Sleep Disturbance and Sleep-Related Impairment scales that have shown internal reliability >.9 for all items and scores with acceptable convergent validity (Yu et al., 2011). Items ask about trouble falling asleep, staying asleep, and next day effects of poor sleep.

*Mood*

Depressive symptoms and anxiety were measured at baseline and 1 week later. A shortened version of the Personal Health Questionnaire Depression Scale (PHQ-8) was utilized in this study to quantify depressive symptoms. The sum of participant responses indicates depressive symptom severity (Kroenke et al., 2010). Published internal reliability scores are .86*.92 (Kroenke et al., 2010).

The General Anxiety Disorder scale (GAD-7) was used to quantify anxiety and assesses four severity categories of GAD-7 on a scale of 0-21, with a score of 0-4 for no/minimal, 5-9 for mild, 10-14 for moderate, 15-21 for severe. Overall, a score of ≥10 is the cut-off for clinically significant anxiety symptoms (Kroenke et al., 2010). Published internal reliability scores are .86-.92 and convergent validity has been shown ($r$ = .72) with the Beck Anxiety Inventory (BAI) (Kroenke et al., 2010).

*Data Analyses*

All data were entered into a Qualtrics survey before export to a Microsoft Excel document for review and measurement calculations. Descriptive statistics (e.g., frequencies, means, standard deviations) were used for the reporting of study participant group allocation, recruitment, retention and attendance data, and comparison of measurement means at each study time-point. Treatment satisfaction was determined using a qualitative descriptive approach to evaluate participant satisfaction with the HBOT protocol. Numeric survey data was summarized using means and standard deviations while open-ended responses were coded using content analysis to identify main themes (Doyle et al., 2020). For COWS, ARSW, NRS, PHQ-8, and GAD-7 the total scores were analyzed. For PROMIS measures (Pain Interference, Sleep-Related Impairment, and Sleep Disturbance), the sum of the ratings for each scale is converted into a T-score, where a T-score of 50 is equivalent to the U.S. general population average and +/- 10 points is equivalent to the standard deviation (Rothrock et al., 2020). Repeated measures mixed analysis of variances (ANOVAs) were used to analyze measurement change over time and between group differences (HBOT arm versus sham arm); partial eta squared ($\eta\rho^2$) values were calculated and reported to illustrate treatment effect size with presumed norms determined to be small = .01, medium = .06, and large = .14. Missing data were handled using last observation carried forward. In reporting of repeated measures ANOVA, based on Mauchly's test of sphericity, if needed the Greenhouse-Geisser adjustment was used unless Huynh-Feldt's epsilon statistic was >0.75, then the Huynh-Feldt adjustment was utilized.

Although inferential testing was applied, the purpose was to determine effect sizes for future fully-powered intervention studies and determine the relative strength of the intervention on chosen measures. This is an acceptable approach to analyze data from small pilot samples when effects are unknown (Jacobson & Melnyk, 2012). The results from all statistical tests were interpreted as hypothesis-generating for a future study, and performed using IBM SPSS, version 27.0.

## Results

*Sample Characteristics*

Demographic and baseline characteristics of the participants are presented in Table 1.

*Protocol Feasibility*

Participant recruitment and retention data is detailed in Fig. 2. More than half (n = 25; 67.5%) of the 37 people assessed for eligibility did not meet inclusion criteria, most commonly because they had been in methadone treatment for longer than 90 days (n = 12; 32.4%). Regarding adherence to the protocol, of the four participants assigned to the HBOT arm, all (100.0%) completed both 90-minute HBOT sessions. Three individuals completed all sham arm protocols (75%). One female withdrew from the sham condition before completing the second session due to gastrointestinal symptoms.

*Treatment satisfaction*

Satisfaction surveys were received from three HBOT and three sham group members. Ratings for all four evaluation items were ≥6 for all participants, with 7 being the most favorable possible score. Relative to the sham condition, treatment group responses were slightly more positive with a total satisfaction sum score $M$ (standard deviation [SD]) = 6.9 (0.14) in full HBOT versus $M$ (standard deviation [SD]) = 6.3 (0.43) in sham. Two main themes emerged from the qualitative data: (1) positive research experience; and (2) study design improvements. Open-ended comments about their experience in the study were unanimously positive across groups. HBOT participants' open-ended comments shared positive treatment effects with statements such as, "It was amazing. The treatment helped so much," and "Lots more energy and seeming to be in a better mood." Sham participants' comments were also favorable, but more were regarding the research experience itself versus the treatment, such as, "Everyone was very kind and helpful," and, "I felt really comfortable and not judged, which is extremely important for me to even want to attempt something like this." No negative comments were offered regarding treatment experience or adverse events nor did any participants suggest they were aware of their treatment arm. Under the theme of study design improvements, participants suggested extending the treatment days, recruiting people earlier in their treatment initiation when they might have more withdrawal symptoms, and adding more food and entertainment options for their time in the sleep lab.

*Treatment Effects*

Means and standard deviations to evaluate changes in variables across study time points are detailed in Table 2. Statistical results of repeated measured mixed ANOVA used to generate effect size

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**Table 1**
Sample Characteristics.

| Variable | Active HBOT (n = 4) | Sham (n = 4) | Total (N = 8) |
|---|---|---|---|
| Mean age (years; SD) | 47.8 (15.8) | 41.0 (13.4) | 44.4 (14.1) |
| Gender (n; % female) | 4 (100%) | 2 (50%) | 6 (75%) |
| Chronic pain diagnosis (n; %) | 3 (75%) | 2 (50%) | 5 (62.5%) |
| Mental health diagnosis (n; %) | 2 (50%) | 4 (100%) | 6 (75%) |
| Mean daily methadone dose (mg; SD) | 87.5 (25) | 58.8 (19.3) | 73.1 (25.8) |
| Race (n; %) | | | |
| White | 4 (100%) | 4 (100%) | 8 (100%) |
| Education (n; %) | | | |
| High school/GED | 2 (50%) | 3 (75%) | 5 (62.5%) |
| Some college | 1 (25%) | 1 (25%) | 2 (25%) |
| Associates or technical certification | 1 (25%) | N/A | 1 (12.5%) |
| Marital status (n; %) | | | |
| Single | N/A | 3 (75%) | 3 (37.5%) |
| Married/Living with | 4 (100%) | N/A | 4 (50%) |
| Divorced/Separated | N/A | N/A | N/A |
| Widowed | N/A | 1 (25%) | 1 (12.5%) |
| Employment (n; %) | | | |
| Employed | N/A | 1 (25%) | 1 (12.5%) |
| Retired | 1 (25%) | 1 (25%) | 2 (25%) |
| Unemployed | N/A | 1 (25%) | 1 (12.5%) |
| Disabled | 1 (25%) | N/A | 1 (12.5%) |
| Homemaker/Stay home | 2 (50%) | N/A | 2 (25%) |
| Other | N/A | 1 (25%) | 1 (12.5%) |

HBOT = hyperbaric oxygen therapy; SD = standard deviation; GED = General Educational Development; N/A = not applicable.

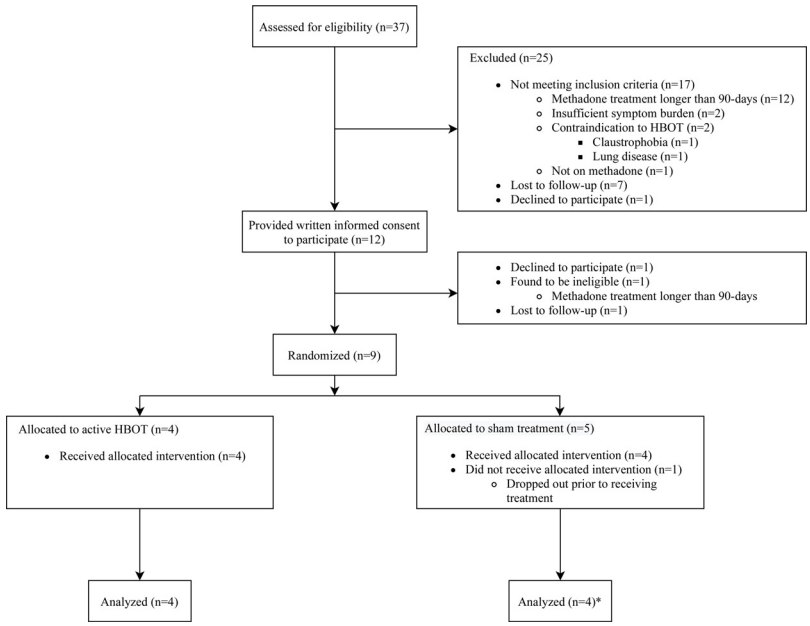


**Fig. 2.** CONSORT diagram of hyperbaric oxygen therapy for pilot RCT. *One participant received only day 1 of sham HBOT owing to illness but was included in the analysis with last observations carried forward. CONSORT = Consolidated Standards of Reporting Trials; RCT = randomized controlled trial; HBOT = hyperbaric oxygen therapy.

values ($\eta\rho^2$) between groups are reported in Table 3. Supplemental Table 1S reports within group ANOVA data analysis across time. The largest between group effect sizes were detected in measurements of pain intensity (large effect) the morning after the first full HBOT treatment dose (timepoint 6) and in drug cravings at the 1 week follow up (timepoint 9) (large effect).

*Opioid withdrawal scales*

Clinically observed withdrawal scores measured by the COWS were in the "mild" range at nearly all timepoints with scores <12 for both HBOT and sham conditions. The COWS reduced from baseline (timepoint 1 [T1]) through immediate post-intervention (timepoint 8 [T8]) for both arms with a very small treatment effect observed between groups. When testing for any sustained response, there was again a reduction from baseline to 1-week follow up (timepoint 9 [T9]) in both arms and a very small effect by treatment group.

Self-reported withdrawal scores measured by the ARSW were on average lower in the HBOT versus sham at nearly all timepoints. The ARSW reduced from baseline through immediate post-intervention (T8) for both arms with a small treatment effect. When testing for any sustained response, there was again a reduction from baseline to 1-week follow up (T9) in both arms and a small effect by treatment group.

*Drug cravings*

Self-reported drug craving scores were, on average, lower in the HBOT versus sham at all timepoints. Craving was reduced from

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**Table 2**
Study Variables at All Time Points for Both Active HBOT and Sham Arms (Means/Standard Deviations)

| Variable study arm | Study time point | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | **3** | 4 | **5** | 6 | **7** | 8 | 9 |
| COWS | | | | | | | | | |
| HBOT | 7.8 (6.8) | 10.3 (6.7) | 8.8 (4.6) | 7.3 (4.3) | 11 (7.8) | 7.8 (7.3) | 6 (2.7) | 4.5 (3.4) | 11 (7.1) |
| sham | 11.8 (5.4) | 14.3 (9.8) | 13.3 (7.3) | 3.8 (1) | 10.7 (4) | 7.7 (3.8) | 6.3 (3.1) | 3.7 (0.6) | 15 (7) |
| ARSW | | | | | | | | | |
| HBOT | 93.5 (18.2) | 65.5 (34.8) | 55 (39.3) | 41.5 (46.4) | 49 (44) | 45.3 (45.5) | 49.5 (38.9) | 33.8 (33.7) | 53.3 (46.9) |
| sham | 83 (22) | 87 (38.8) | 76 (27.5) | 33.3 (10.3) | 64 (20.3) | 66.7 (25) | 65 (32.2) | 62.3 (24.6) | 81 (22.8) |
| Drug craving | | | | | | | | | |
| HBOT | 9 (2.2) | 10.5 (3) | – | – | 7.5 (3.4) | 7 (2.8) | – | – | 7.3 (4.7) |
| sham | 11 (5.7) | 12.5 (3.3) | – | – | 12.7 (3.2) | 10.7 (4.5) | – | – | 10.5 (1.7) |
| Pain intensity | | | | | | | | | |
| HBOT | 5.3 (0.5) | 5.8 (1.3) | – | – | 3.8 (2.6) | 3.5 (2.9) | – | – | 4.8 (3.2) |
| sham | 5 (2.2) | 7.3 (0.5) | – | – | 6 (2.6) | 6.7 (1.5) | – | – | 5.8 (1.5) |
| Pain interference[a] | 64.2 (2) | | | | | | | | 59.3 (12.4) |
| HBOT | 66.9 (6.5) | – | – | – | – | – | – | – | 63.7 (4.3) |
| sham | | – | – | – | – | – | – | – | |
| Sleep disturbance[a] | | | | | | | | | |
| HBOT | 62.6 (2) | 57.9 (2.7) | – | – | – | 51.3 (4.1) | – | – | 51 (14.9) |
| sham | 61.6 (6.6) | 53.5 (5) | – | – | – | 51.4 (5.2) | – | – | 59.2 (9.8) |
| Sleep-related impairment[a] | 65.8 (1.3) | 63.8 (1.7) | – | – | – | 58.1 (5.4) | – | – | 56 (17.7) |
| HBOT | 66 (6.3) | 66 (9.5) | – | – | – | 62.2 (6.4) | – | – | 64.7 (10.6) |
| sham | | | | | | | | | |
| PHQ-8 | | | | | | | | | |
| HBOT | 13.8 (2.1) | – | – | – | – | – | – | – | 8.5 (0.6) |
| sham | 13.5 (5.1) | – | – | – | – | – | – | – | 12.3 (4.2) |
| GAD-7 | | | | | | | | | |
| HBOT | 16.3 (3.9) | – | – | – | – | – | – | – | 9.5 (5.1) |
| sham | 14.5 (5.2) | – | – | – | – | – | – | – | 13.5 (4.2) |

[a] PROMIS scales are represented as T-scores (Pain Interference, Sleep Disturbance, Sleep-Related Impairment) which are standardized scores with a mean of 50, utilizing the general U.S. population as a reference.HBOT = hyperbaric oxygen therapy; COWS = Clinical Opiate Withdrawal Scale; ARSW = Adjective Rating Scale of Withdrawal; PHQ-8 = Patient Health Questionnaire (Depressive Symptoms); GAD-7 = Generalized Anxiety Disorder.

**Table 3**
Mixed ANOVA Between Group Variable Results for Full HBOT versus Sham Control

| Variable time interval | *df* | *F* | *p* | $\eta\rho^2$ |
|---|---|---|---|---|
| COWS | | | | |
| Pre- to post-intervention | 5, 30 | 5.47 | .001 | .004 |
| Pre-intervention to follow up | 6, 36 | 6.77 | <.001 | .001 |
| ARSW | | | | |
| Pre- to post-intervention | 1.7, 10.4 | 6.14 | .02 | .01 |
| Pre-intervention to follow up | 1.9, 11.5 | 6.93 | .01 | .03 |
| Drug craving | | | | |
| Pre- to post-intervention | 2, 12 | 4.44 | .04 | .33 |
| Pre-intervention to follow up | 3, 18 | 1.49 | .25 | .36 |
| Pain intensity | | | | |
| Pre- to post-intervention | 2, 12 | 1.01 | .39 | .34 |
| Pre-intervention to follow up | 3, 18 | 0.72 | .55 | .25 |
| Pain interference | | | | |
| Pre- to post-intervention | – | – | – | – |
| Pre-intervention to follow up | 1, 6 | 1.48 | .27 | .12 |
| Sleep disturbance | | | | |
| Pre- to post-intervention | 2, 12 | 23.26 | <.001 | .03 |
| Pre-intervention to follow up | 1.3, 7.8 | 3.74 | .08 | .02 |
| Sleep-related impairment | | | | |
| Pre- to post-intervention | 2, 12 | 1.75 | .22 | .11 |
| Pre-intervention to follow up | 3, 18 | 1.13 | .37 | .13 |
| PHQ-8 | | | | |
| Pre- to post-intervention | – | – | – | – |
| Pre-intervention to follow up | 1, 6 | 14.28 | .009 | .09 |
| GAD-7 | | | | |
| Pre- to post-intervention | – | – | – | – |
| Pre-intervention to follow up | 1, 6 | 4.91 | .07 | .03 |

Means and standard deviation values for all corresponding time points are presented in Table 2. Time intervals represented are pre-intervention to immediate post-intervention (hyperbaric oxygen therapy [HBOT] or sham) and pre-intervention to 1-week follow up.
ANOVA = analysis of variance; HBOT = hyperbaric oxygen therapy; d$f$ = degrees of freedom; $\eta\rho^2$ = partial eta squared; COWS = Clinical Opiate Withdrawal Scale; ARSW = Adjective Rating Scale of Withdrawal; PHQ-8 = Patient Health Questionnaire (Depressive Symptoms); GAD-7 = Generalized Anxiety Disorder.

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baseline through immediate post-intervention (timepoint 6 [T6]) for both arms with a large treatment effect and reduced from baseline to 1-week follow up in both arms and a large treatment effect.

*Pain intensity and pain interference*

Baseline pain intensity scores were "moderate" on average for the full sample as measured by the NRS. NRS values were reduced after Day 2 of HBOT by twice as much, on average, in the full treatment arm compared to the sham arm (Table 2). NRS reduced from baseline through immediate post-intervention in the HBOT arm (T6) while the sham arm increased pain intensity over time. A large immediate effect was seen by treatment group in pain intensity (Table 3). There was only a reduction from baseline to 1-week follow up in the HBOT arm and a large effect in pain intensity by treatment group.

Baseline PROMIS Pain Interference T-scores indicated higher-than-healthy-normal scores on average (>50) for all participants at both measurement timepoints, indicating a higher burden of pain interference. The PROMIS Pain Interference T-score reduced from baseline through follow up post-intervention (T9) in both arms with a mid-sized effect by treatment group.

*Sleep quality*

PROMIS Sleep Disturbance (SD) and Sleep-Related Impairment (SRI) T-Scores during the study period indicated higher-than-healthy-normal scores on average (>50) for all participants throughout the study period. The HBOT arm showed a trend in improved scores from baseline to follow up on both PROMIS sleep measurements that was, on average, more than three times the improvement seen in the sham condition. Reduction in the PROMIS SD from baseline through immediate post-intervention was noted in both arms with a small treatment effect. Again, a reduction from baseline to 1-week follow up was noted in both arms with a small effect by treatment group in sleep disturbance.

The PROMIS SRI from baseline through immediate post-intervention was reduced in both arms with a medium treatment effect. Again, a reduction was noted from baseline to 1-week follow up in both arms with a medium effect by treatment group in sleep-related impairment.

*Mood*

On average, the HBOT group depressive symptom scores improved from baseline scores that indicated major depression on the PHQ-8 (>10) to scores below that cut-off at 1-week follow up, while the sham arm had minimal change over time and scores remained on average >10. The reduction in the PHQ-8 from baseline through post-intervention follow up (T9) was noted in both arms with a medium treatment effect.

Similarly, the HBOT arm's baseline anxiety score as measured by the GAD-7 improved from a range indicating severe anxiety (15-21) at baseline to mild anxiety (5-9) at 1-week follow-up. The sham arm had minimal change over time and scores remained on average in the moderate range (10-14). The reduction in anxiety symptoms from baseline through post-intervention follow up (T9) was noted in both arms with a small treatment effect.

## Discussion

In this sample of adults receiving methadone-based MOUD, a 2-day HBOT session was well-tolerated with treatment effect size ranging from small to large on several variables important to recovery outcomes. Participant retention, treatment attendance, and satisfaction with the protocol were favorable. Study recruitment was limited by the high percentage of interested participants not meeting the eligibility criteria or not following through with enrollment. The sham condition was sufficiently believable and resulted in fewer improvements of health variables, on average, relative to the full HBOT sessions. The largest between group effect sizes observed from baseline to post-HBOT were with measurements of drug craving at the 1-week follow-up timepoint and pain intensity immediately after the first day of HBOT. Large pain intensity treatment effects were sustained after 1 week. Of note, the pain intensity reduction in the HBOT arm was a clinically important reduction (>30%; Dworkin et al., 2008).

The improvements reported by our participants in pain intensity were greater, on average, after HBOT than in the sham condition; this was expected due to the many documented clinical benefits of HBOT for painful conditions (Sutherland et al., 2016). It is also well-established that people in OUD often have comorbid pain that can interfere with recovery goals. The risk of additional opioids for those in OUD treatment may outweigh the benefits and requires careful consideration. It is crucial to offer non-pharmacologic approaches that address pain as part of a multimodal treatment plan (St. Marie & Broglio, 2020). Pain intensity was in the moderate range for nearly all of our participants at baseline. It reduced to a "mild" level for those in the full HBOT group after the first session and remained that way for 24 hours. On average, our participants also reported higher pain interference scores than healthy normal adults. Our previous HBOT trial found that withdrawal symptoms responded more to HBOT treatment when pain interference burden was higher (Wilson, 2021) pointing towards potential populations that might be most helped by HBOT session—those prescribed opioids who have greater pain burdens.

Although this was a pilot study and not powered to detect statistical significance, the mean ARSW scores for self-reported opioid withdrawal showed reductions that were more than twice the reduction of the sham condition after the second day of HBOT. When paired with our initial HBOT study showing similar withdrawal improvements using an attention control group (Wilson et al., 2022), our findings justify a fully powered investigation testing HBOT as a non-pharmacologic opioid withdrawal treatment adjunct. Future studies with larger samples could also examine important mechanistic questions, such as whether it is by reducing pain that the withdrawal symptoms were also improved as several items on the ARSW ask about pain (e.g., painful joints, muscle, or abdominal cramps).

Similarly, mechanistic questions exploring drug cravings and sleep could be expanded upon in future work. Our participants showed improved craving scores over the study period that were not mirrored by the sham treatment. They also showed sleep quality and mood improvements, which could be important for both substance-use cravings and pain. Improved sleep quality has been found to reduce drug craving, in part through its influence upon affect (Lydon-Staley et al., 2017). Non-pharmacologic sleep treatments have been shown to improve pain and sleep for people with chronic pain (Tang et al., 2015). If sleep quality can be improved during MOUD treatment, potentially both pain and cravings could be reduced as a result. Whether HBOT could serve multiple purposes by addressing pain, sleep, and cravings is worth further exploration.

For the full sample, COWS scores at baseline fell into the mild range on average, and lower scores were seen in the HBOT arm. It is possible treating a population with higher symptoms, such as those in earlier treatment induction, would result in greater ability to reduce those symptoms. It is also possible that initiating HBOT at the start of an opioid taper for people attempting to reduce use for either pain or OUD conditions could provide some benefit. The ARSW scores for our participants were higher than average scores published in other studies of general MOUD populations, so our

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participants did report a significant burden of withdrawal symptoms despite their daily methadone dose (Barbosa-Leiker et al., 2014).

### *Limitations*

Limitations of our study include the self-reported nature of some collected data. At the time of our study planning, there was no established consensus on the optimal drug craving measurement to use for OUD (Kleykamp et al., 2019). The craving scale we selected had minimal published validity data, so caution is needed when interpreting those results. A larger randomized trial would help control for confounding variables such as that participants received a daily dose of methadone each morning. While the full sample fell within the normal range for daily methadone dose (60-120 mg) on average (Ilgen, 2018), the HBOT arm had a slightly higher dose which could impact measurements and explain improvements. Placebo and small treatment effects may be occurring as part of the sham condition, which requires at least a small amount of pressure to be believable and could yield some therapeutic benefits (Lansdorp & van Hulst, 2018).

### *Clinical and Research Implications*

Expanding the arsenal of primary treatment options for opioid withdrawal symptoms should be a high priority for nurses and other health professionals. Once patients make it past the early phase of MOUD treatment, they are much more likely to stay in treatment (Zheng et al., 2017). Receptivity to MOUD might increase if distressing symptoms could be better managed. Also needed are novel avenues to assist people in reducing use of long-term opioids prescribed for pain; they also experience withdrawal symptoms that impede tapering success.

Despite the efficacy of MOUD in reducing morbidity and mortality, access to medications like methadone and buprenorphine are not available in some countries (World Health Organization [WHO], 2020). There is a need to develop non-opioid therapies to ameliorate acute and protracted opioid withdrawal syndromes. Alpha-2 agonists such as clonidine and guanfacine, have been used “off-label” for OUD withdrawal symptom control for years (Jahagirdar & Campbell, 2018). Lofexidine hydrochloride is the first medication with an FDA approval granted in 2018 for management of opioid withdrawal symptoms in adults. Several trials confirm its efficacy in alleviating withdrawal symptoms (Rehan et al., 2019; Renfro et al., 2020). Future investigations could compare such pharmacologic to non-pharmacologic approaches while considering cost, access, and potential side effects.

Hyperbaric chambers are available in many cities globally with approximately 200 accredited facilities in the United States and thousands more worldwide (Undersea & Hyperbaric Medical, 2021). Fees can vary widely per treatment session from 100 USD at an independent HBOT clinic to 1,500 USD at medical centers. The number of sessions for optimal treatment varies depending on condition and requires more study in OUD populations. Although fewer clinics have multiplace than mono-chambers (Chin et al., 2016), our participants seemed to enjoy the camaraderie of attending sessions together, and it also allowed for a more economical approach. Of note, those receiving full HBOT dose unanimously endorsed the experience as positive and believed it was helpful. While it is possible their enjoyment with the research experience and monetary rewards may have influenced their opinion, the fact that all full HBOT participants showed up for a second day of treatment adds confidence that their benefits were tangible and the protocol feasible. Although our collected data suggests that measurable treatment effects can be captured, clinicians’ judgements could be considered in future evaluations to identify minimally important changes. Paired with patient perspectives, clinician goals can be used to calculate desired effect sizes for future trials.

## Conclusions

Finding safe, effective opioid alternatives and adjuncts to help manage symptoms is a critical priority for the many people with OUD, along with those on long-term opioid therapy for chronic pain who are urged to reduce opioid use. Non-opioid multimodal analgesia has been called “the cornerstone of care” for people with chronic pain and OUD (St. Marie & Broglio, pg. 11). HBOT is but one of many non-opioid pain management options that could be considered. There was no apparent ability to distinguish full HBOT treatment from the sham, thus controlling for placebo effects in this pilot study. Participants were generally adherent to and satisfied with the protocol and no serious adverse events occurred. Non-pharmacologic options such as HBOT with a high safety profile deserve further exploration as a viable treatment adjunct. The encouraging trends we found on reducing pain, drug cravings, mood, and reported withdrawal symptoms show promise for and support of testing HBOT further in a fully powered sample as a novel therapeutic for a population in dire need of solutions.

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## Supplementary materials

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