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Hyperbaric Oxygen to Assist Adults With Opioid Use Disorder in Reducing Methadone Dose

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Abstract

Opioid withdrawal symptoms can interfere with substance use disorder treatment goals. This study investigated the acceptability, feasibility, and treatment effects of hyperbaric oxygen therapy (HBOT) as an adjunct to reduce withdrawal symptoms for adults initiating a medically supervised methadone dose reduction. Adults prescribed methadone for opioid use disorder were randomized into either a hyperbaric oxygen group ($n = 17$) or an attention control group ($n = 14$). The study site was an outpatient opioid treatment program in the northwestern United States. Participants were asked to attend five consecutive daily 90-minute HBOT sessions offered at 2.0 atmospheres absolute with 100% oxygen in a pressurized chamber. Treatment attendance and reported satisfaction were measures of acceptability and feasibility. Medication doses were tracked posttreatment at 1 week, 1 month, and 3 months. Withdrawal symptoms were assessed at baseline and daily during the 5-day intervention period. After randomization, 13 (76.5%) followed through with medical screening and HBOT sessions, and of those, nine (69.2%) completed all five 90-minute HBOT sessions. At 3 months, the treatment group maintained, on average, a 4.3-mg methadone dose reduction compared with an average reduction of 0.25 mg for control group participants. Opioid withdrawal symptoms were reduced after Day 1 of HBOT by twice as much, on average, compared with the control condition. Satisfaction surveys found participants were generally satisfied with ease and comfort of the treatment. The evidence that HBOT is an acceptable, feasible adjunct warrants future trials to determine more conclusively effects on withdrawal symptoms associated with methadone dose taper.

Keywords: Hyperbaric Oxygen Therapy, Medication-Assisted Treatment, Methadone, Opioid Addiction, Opioid Use Disorder

Opioid overdose death rates have more than tripled in the past two decades and are now the second leading cause of accidental death in the United States (Centers for Disease Control and Prevention, 2017). Federal guidelines have established medications for addiction treatment (MAT)

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Marian Wilson, Karen Stanek, Matthew Layton, and Raymond Quock designed the study, wrote the protocol, and contributed feedback on the results. Joseph Muriungi, Alvina Jesse, and Trevor Roush assisted with data collection, literature review, and development and review of the introduction, methods, and discussion sections. Tamara Odom-Maryon and Marian Wilson planned and performed the data analysis and wrote the methods and results section. All authors contributed to and have approved the final manuscript.

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as the gold standard for preventing death from opioid overdose (Substance Abuse and Mental Health Services Administration, 2015). Although the number of adults receiving MAT for opioid use disorder (OUD) in the United States has climbed to more than 350,000 adults (Alderks, 2017), successful recovery remains suboptimal (Naji et al., 2016; Noe & Keller, 2020).

Retention rates within programs vary widely from 19% to 94% at the 3-month interval (Timko et al., 2016). The challenge of addressing noradrenergic hyperactivity symptoms related to opioid withdrawal could be one contributor to the rise in opioid overdose rates as people often use substances to "self-medicate" pain and other uncomfortable symptoms that occur during MAT (Alford et al., 2016). Mitigating increased pain, insomnia, and symptoms of depression and anxiety are oft-cited reasons to continue opioid use and/or relapse (Cicero & Ellis, 2017). In addition, adults in MAT are often reluctant to continue daily opioid therapy because of distance from facilities, cost, stigma, and the inconvenience of daily dosing (Ronquest et al., 2018). Opioid withdrawal symptoms can be exacerbated during an opioid taper (Substance Abuse and Mental Health Services Administration, 2015). Finding safe, complementary therapies for OUD that can ease withdrawal symptoms could help MAT recipients focus on other aspects of their treatment, such as cognitive and behavioral therapies (Substance Abuse and Mental Health Services Administration, 2015).

BACKGROUND

To date, few studies have examined adjuncts that specifically target symptom management to supplement usual care for MAT populations (Eyler, 2013). A single report and undocumented anecdotal reports find that hyperbaric oxygen therapy (HBOT) can relieve opioid withdrawal in human subjects (Epifanova, 1995). Preclinical studies in the laboratory of one of our senior authors reported that HBOT can reduce physical signs of naloxone-precipitated withdrawal in morphine-dependent mice (Nicoara et al., 2016). The mechanism of action is likely explained, at least in part, by neuroinflammation that contributes to the maintenance of substance use disorders (Kohno et al., 2019). The proinflammatory cytokine tumor necrosis factor alpha (TNFα) has been implicated in the genesis of opioid tolerance and dependence (Hao et al., 2011). These findings support the concept that proinflammatory cytokines are involved in the genesis of opioid withdrawal syndrome. Ibudilast, a drug with anti-inflammatory properties, upregulates the cytokine interleukin-10, an endogenous inhibitor of TNFα production, and reportedly inhibited morphine withdrawal-induced hyperactivity and weight loss in rats (Hutchinson et al., 2009). Although not an approved drug for opioid dependence in the United States, clinical trials found ibudilast reduced subjective ratings of withdrawal symptoms in opioid-dependent humans (Cooper et al., 2016), further implicating TNFα in opioid withdrawal. HBOT is reported to reduce elevated levels of cytokines, including TNFα, found in traumatic brain injury (Lim et al., 2013; Wee et al., 2015) and neuropathic pain models (Hu et al., 2015; Li et al., 2011). It is plausible, therefore, that HBOT can suppress signs of opioid withdrawal by inhibiting expression of proinflammatory cytokines.

HBOT has been safely used for at least 80 years, its adverse effects are relatively benign, and it is approved for 14 specific clinical indications (Weaver, 2014). To our knowledge, no recent studies have tested HBOT for its effect on withdrawal symptoms within MAT settings, and none has examined whether it might help with supervised opioid dose reduction. On the basis of our past research documenting a high burden of undertreated symptoms among adults in MAT (Wilson et al., 2018; Wilson & Shaw, 2017), we expect that HBOT could be a feasible, relatively safe means of offering symptom relief. Known adverse effects include middle ear barotrauma, claustrophobia, pulmonary dyspnea, progressive myopia that is usually transient and reversible, and, in rare instances, seizures at higher oxygen pressures (Camporesi, 2014).

We piloted a 5-day course of HBOT among adults enrolled in MAT who had a stated goal to reduce their methadone dose. As this was the first known randomized controlled trial of HBOT within a MAT population, our primary objective was to determine whether participants could engage and find any benefit. The specific study aims were to (a) investigate potential HBOT efficacy as it relates to opioid withdrawal symptoms experienced by MAT populations, (b) evaluate the ability of participants to achieve opioid dose reduction goals, and (c) determine acceptability and feasibility via participants' ability to adhere to the HBOT schedule and their satisfaction with treatment.

METHODS

Design

A randomized controlled study was conducted from November 2017 to January 2019. Participants were randomized to either immediate HBOT treatment group or wait-list attention control group.

Sample and Setting

Adult participants were recruited from one urban outpatient Opioid Treatment Program (OTP) in the northwestern United States. Usual treatment at the recruitment site focuses on medical management of OUD, primarily with daily methadone. Participants also generally attend group and individual counseling sessions. Participants were recruited via advertisements posted at the participating OTP site. Research assistants screened interested participants for eligibility either in person or by phone. Eligibility criteria included ability to read, speak, and write English; age ≥ 18 years; and enrollment in an OTP with a medically supervised plan to reduce opioid dose initiated by the clinical treatment team. Participants were ineligible if they were pregnant or had a medical or psychiatric condition that the investigators determined would compromise safe study participation. Individuals deemed eligible were scheduled for an in-person study interview where written informed consent was obtained. Sample size calculations were

based on detecting a statistically significant within–between interaction showing preliminary evidence of a difference in withdrawal symptoms between study groups across days of treatment. We conservatively used a small-to-medium effect (d = 0.46) for the within–between interaction, requiring 14 participants per group to achieve 80% power (alpha = .05).

One hundred eight potential participants were screened. Of those, 14 declined to participate, 12 were found to be ineligible, and 51 did not follow through with consent procedures, leaving 31 to successfully complete a baseline survey and be randomized into treatment (n = 17) or attention control (n = 14) arms. Once randomized into the treatment group, a medical evaluation was conducted by the study HBOT medical director to assess eligibility per the clinic's usual standards. 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). No participants were found to have excluding contraindications.

Ethical Considerations

Before conducting the research, approvals were obtained from the primary investigator's university institutional review board. Administrative approval was received from the OTP clinic where recruitment was planned and from the HBOT clinic where therapy was delivered. Participants had to provide written informed consent.

Measures

Demographics and Characteristics Sociodemographic and health history variables collected at baseline included age, gender, race/ethnicity, educational level, disease and mental health diagnoses, and medications.

Opioid Withdrawal Scales The primary outcomes of interest were reduced signs and symptoms of opioid withdrawal as assessed by self-report with the Adjective Rating Scale for Withdrawal (ARSW) and by clinical assessment using the Clinical Opiate Withdrawal Scale (COWS). The ARSW is a 16-item 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. Reliability as a one-factor model of withdrawal has been established for gender and single-time-point data collection (Barbosa-Leiker et al., 2014). 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 shown (Cronbach's alpha = .78) and concurrent validity has been established by correlations with the Clinical Institute Narcotic Assessment (r = .85; Tompkins et al., 2009).

Pain Intensity and Pain Interference The three-item pain intensity short form from the Patient-Reported Outcomes Measurement Information System (PROMIS) was used to measure baseline pain intensity on average, at its worst, and now. A 1–5 scale indicates 1 = *no pain* and 5 = *very severe pain*. A sum of the three items gives an overall intensity raw score that is converted to a T score (a score of 50 is the U.S. general population average with a standard deviation of 10). The short form has internal reliability > .80 and acceptable convergent validity (r = .83) with the Brief Pain Inventory severity measure (Cella et al., 2010). To measure baseline pain interference, the eight-item PROMIS pain interference scale was used and is similarly constructed. It ranges between 8 and 40, where a higher number indicates greater interference of pain on daily functioning. The scale has acceptable test–retest reliability (Cronbach's alpha = .84) and convergent validity (r = .7) with the Brief Pain Inventory interference measure (Cook et al., 2015).

Sleep Quality Sleep quality at baseline was assessed using the eight-item PROMIS Sleep Disturbance scale that has shown internal reliability > .9 for all items and scores (Buysse et al., 2010; Yu et al., 2011). Validity has been established through comparison with the Pittsburgh Sleep Quality Index and Epworth Sleepiness Scale (Yu et al., 2011).

Depressive Symptoms A shortened version of the Personal Health Questionnaire Depression Scale, the PHQ-8, was utilized in this study to quantify baseline depressive symptoms. The sum of participant responses indicates depressive symptom severity (Kroenke et al., 2010). Items ask how often one has been bothered by certain problems in the last 2 weeks and are rated as 0 = *not at all* to 3 = *nearly every day*. Published internal reliability scores are .86–.92 (Kroenke et al., 2010).

Anxiety Symptoms The seven-item General Anxiety Disorder scale (GAD-7) was used to quantify baseline 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, and 15–21 for severe. Overall, a score of ≥10 is the cutoff 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 (Kroenke et al., 2010).

Treatment Satisfaction A posttest survey adapted from the IBM Computer Usability and Satisfaction Questionnaires (Lewis, 1995) was administered to participants in the treatment group at the end of the HBOT week. These questionnaires are validated tools with internal reliability greater than .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 were asked to rate responses on a scale of 1 = *strongly disagree* to 7 = *strongly agree*.

Study Groups

Hyperbaric Oxygen Therapy Participants attended daily 90-minute medically supervised HBOT sessions (15-minute compression, 60-minute at final pressure, and 15-minute decompression) at 2.0 atmospheres absolute for five consecutive days. Treatment followed the HBOT clinic's usual protocol

that takes place in a 12-seat, sealed, pressurized chamber where participants receive 100% oxygen via individualized oxygen hoods. During the treatment sessions, participants could watch a movie or read a book. A trained research assistant was present in the chamber during the sessions to assist in managing issues related to study participation should they occur.

Wait-List Attention Control Attention control participants were asked to attend a 60-minute group session at the participating clinic for five consecutive days where they were offered an opportunity to watch a movie or read. The group was meant to simulate time with research assistants and peer interactions that occurred in the treatment group. After serving as a control for 3 months, wait-list members were given the opportunity to receive HBOT if they chose and three chose this option.

Procedures

Study Protocol After written informed consent was obtained, participants were asked to complete a survey (including PROMIS, PHQ-8, and GAD-7) using a secure online format. Participants were then randomized into study arms and given an appointment for the HBOT clinic orientation and medical screening examination if they were selected for the treatment group. The COWS and ARSW were both administered by trained research assistants immediately before and after each treatment or control group session over the 5-day treatment period to assess withdrawal symptoms. Participants were offered gift cards to compensate for time and travel. A $10 payment was provided each day of attendance during the 5-day sessions. HBOT participants completed the satisfaction survey via secure online survey at the end of the treatment week.

Methadone Dosing Methadone dose and dose reductions were determined according to clinic protocol by prescribing providers who were not part of the study team. Enrolled participants agreed to request a 10% reduction in dose on Day 2 of the study period. This process aligns with the clinic's protocol for gradual tapering that can occur whenever an individual chooses and the treatment team agrees. Specific dose adjustments could be altered by the prescribing provider based on clinical condition. The methadone doses at Days 1–5 of the treatment period and at 1 week, 1 month, and 3 months after the treatment period were collected through a review of clinic records.

Data Analyses

Categorical and continuous data were summarized as frequencies (percentages) and means (standard deviations [*SD*s] or standard errors), respectively. For PROMIS measures (pain intensity, pain interference, and sleep disturbance), *T* scores were analyzed. For PHQ-8, GAD-7, COWS, and ARSW, the total scores were analyzed. Bivariate correlations were tabulated for all the instruments completed at the baseline visit. PROMIS measures (*T* scores for pain intensity, pain interference, and sleep disturbance) were dichotomized as high (above 50) and normal (at or below 50). The results from all statistical tests were interpreted as hypothesis-generating for a future later study. All statistical testing was two sided (alpha = .05) and performed using SAS 9.4 (Cary, NC).

Analyses Addressing HBOT Efficacy To descriptively explore group differences across days of treatment (Days 1–5), graphical displays of the means (±1 *SEM*) for the two primary outcome measures of withdrawal symptoms, COWS and ARSW, were used. These figures visually characterized the variability among individuals within a group and between-group differences across the 5 days of treatment.

To statistically test for differences in daily pretreatment measures of withdrawal, generalized linear mixed models (GLMMs) were fit that included main effects for group (1 = HBOT, 0 = control) and day (1–5), a covariate (pain intensity, pain interference, or sleep disturbance), and the Group × Day × Covariate interaction. An identity link function was specified. Correlations within participants over repeated measures of time were controlled for using a random intercept model and a variance component covariate structure. The significance of the interaction term was of central interest to characterize changes in each of the outcomes across time displayed graphically. A GLMM appropriately uses maximum likelihood methods to handle missing data. Sensitivity analyses were performed to examine the impact of missing not at random on intervention effects.

Analyses Evaluating Opioid Dose Reduction Goals At 1 and 3 months, dose reductions from the methadone dose administered on Day 1 of the treatment period were calculated. Two-sample *t* test was used to compare average 1-month and 3-month dose reductions between HBOT and control groups.

Analyses Addressing Feasibility and Acceptability Feasibility (recruitment, enrollment, retention rates) and acceptability (intervention engagement, usability, satisfaction) of HBOT were examined using descriptive statistics.

RESULTS

Baseline Characteristics

Thirteen (76.5%) of the 17 participants randomized into treatment and eight (57.1%) of the 14 randomized to attention control arms followed through to begin study activities on Day 1. Demographic and baseline characteristics of the two study groups are presented in Table 1. For the full sample, baseline depressive symptoms and anxiety fell into the "mild" range on average. On the PROMIS measures for the full sample, only pain interference scores were higher on average than known scores for healthy adults.

Correlations Among Symptoms

Withdrawal assessment taken in person and concurrently using the ARSW and COWS were significantly positively correlated (see Table 2). The ARSW was positively correlated with the PHQ-8, and the COWS was positively correlated with the GAD-7 (see Table 2). Affective symptoms (as measured by the GAD-7 and PHQ-8) were significantly related to each other and to pain measures, but not to sleep.

Treatment Effects

Daily Opioid Withdrawal Average daily withdrawal symptoms across the 5 days of treatment were less for the HBOT group

TABLE 1 Demographic and Baseline Symptom Measures Across Study Groups

Characteristics	Treatment ($n = 13$)	Attention Control ($n = 8$)	Early Dropouts ($n = 10$)
Demographics			
Age (years; mean [*SD*])	46.8 (16.7)	36.4 (10.6)	36.1 (11.3)
Gender, *n* (% female)	7 (54)	7 (88)	6 (67)
(missing, $n = 1$)			
Race, *n* (%)			
White/Caucasian	11 (92)	6 (86)	8 (89)
Multiracial	1 (8)	1 (14)	1 (11)
(missing, $n = 3$)			
Education, *n* (%)			
Less than high school	2 (15)	0 (0)	1 (10)
High school/GRE	4 (31)	3 (38)	0 (0)
Some college	6 (46)	4 (50)	8 (80)
College degree	1 (8)	1 (12)	1 (10)
Marital status, *n* (%)			
Single	5 (38)	2 (25)	5 (56)
Married/living with partner	5 (38)	2 (25)	2 (22)
Divorced/separated	3 (23)	4 (50)	2 (22)
(missing, $n = 1$)			
Employment, *n* (%)			
Employed	0 (0)	0 (0)	1 (10)
Unemployed	3 (23)	1 (12)	3 (30)
Disabled	6 (46)	3 (38)	3 (30)
Other[a]	4 (31)	4 (50)	3 (30)
Pain, sleep, and affect[b]			
Pain intensity *T* score (mean [*SD*])	48.9 (7.9)	53.6 (9.9)	49.4 (8.3)
Pain interference *T* score (mean [*SD*])	60.5 (10.9)	59.4 (10.9)	61.7 (8.7)
Sleep disturbance *T* score (mean [*SD*])	51.0 (5.4)	49.8 (4.6)	49.7 (8.2)
PHQ-8 (total score; mean [*SD*])	8.8 (4.9)	9.6 (5.8)	9.6 (3.3)
Anxiety (GAD-7; mean [*SD*])	7.8 (6.0)	7.1 (6.2)	6.7 (3.9)

PHQ-8 = eight-item Patient Health Questionnaire; GAD-7 = seven-item Generalized Anxiety Disorder; GRE = graduate record examination.
[a]Other includes student, homemaker, and retired.
[b]Participant responses were collected via a survey sent using Qualtrics Research Suite. PROMIS scales: pain intensity, pain interference and sleep disturbance.

compared with the attention control group (see Figures 1 and 2). The largest daily average decrease (pre to post) in COWS and ARSW for the HBOT group was 7 and 14 points, respectively, compared with 4 and 6 points for the control group. Daily average COWS before treatment was consistently lower for the HBOT group compared with controls (ranging from a difference between groups of 1–6 points). The HBOT group mean was consistently ≤12 indicating "mild" withdrawal symptoms each day before and after HBOT sessions, whereas the control group scored >12 in the "moderate" range for most days on the pre-session assessment after the methadone dose was reduced. From the GLMM analyses examining differences in the change in withdrawal (COWS and ARSW) across days between groups and across days, a statistically significant Group × Day interaction using ARSW was found ($p = .039$). The interaction term was nonsignificant using COWS ($p = .874$).

Opioid Dose Reduction No statistically significant differences were detected between treatment and control groups in their baseline, 1-month, or 3-month daily average methadone dose. On average, baseline daily methadone dose was 76.08 mg (*SD* = 35.92, range: 15–160 mg) for the treatment

TABLE 2 Correlation Between Measures of Pain, Sleep, Affect, and Withdrawal at Baseline (N = 21)

Measures[a]	Collected by Survey					Collected in Person	
	Pain Intensity *T* Score	Pain Interference *T* Score	Sleep Disturbance *T* Score	PHQ-8 Total Score	Anxiety (GAD-7) Total Score	COWS Total Score	ARSW Total Score
Collected by survey							
Pain intensity *T* score[b]	1.00						
Pain interference *T* score[b]	.85***	1.00					
Sleep disturbance *T* score[b]	.14	.18	1.00				
PHQ-8 total score	.70***	.71***	.40	1.00			
Anxiety (GAD-7) total score	.67**	.60**	.30	.67***	1.00		
Collected in person							
COWS total score	.23	.35	.12	.41	.50*	1.00	
ARSW total score	.22	.36	.24	.52*	.33	.48*	1.00

PHQ-8 = eight-item Patient Health Questionnaire; GAD-7 = seven-item Generalized Anxiety Disorder; COWS = Clinical Opioid Withdrawal Scale; ARSW = Adjective Rating Scale for Withdrawal.
[a]For each pairwise combination of instruments, reported is the Pearson correlation coefficient and significance under H0: rho = 0. $n = 17–21$.
[b]PROMIS scales: pain intensity, pain interference and sleep disturbance.
*$p < .05$. **$p < .01$. ***$p < .001$.

group and 73.63 mg (*SD* = 29.38 mg, range: 25–120 mg) for the control group. Daily methadone dose at the 3-month mark was 71.77 mg (*SD* = 35.02, range: 15–160 mg) for the treatment group and 73.38 mg (*SD* = 29.21 mg, range: 23–120 mg) for the control group. Figure 3 depicts methadone dose reduced over time. At 1 month, the average reduction in methadone dose from the Day 1 dose was 3.69 mg (*SD* = 4.09) for the HBOT group compared with 2.88 mg (*SD* = 2.70) for the control group ($t = 1.04$, $df = 19$, $p = .313$). Although not statistically significant, at 3 months, the average methadone dose for the control group returned to a level similar to the Day 1 dose (mean reduction = 0.25 mg [*SD* = 2.95] compared with an average dose reduction of 4.31 mg [*SD* = 9.03] for the HBOT group; $t = 1.22$, $df = 19$, $p = .237$).

Treatment Feasibility and Acceptability Thirty-one of the 96 eligible patients enrolled in the study (32.3%) and were randomized to one of the two study groups. Reasons cited by eligible participants for refusing to participate included most often scheduling conflicts or change of mind. Because of difficulty finding eligible participants willing to follow through with the control condition assignment and agree to a dose reduction, recruitment was stopped after the fourth HBOT cohort before reaching the targeted sample size of 36. After

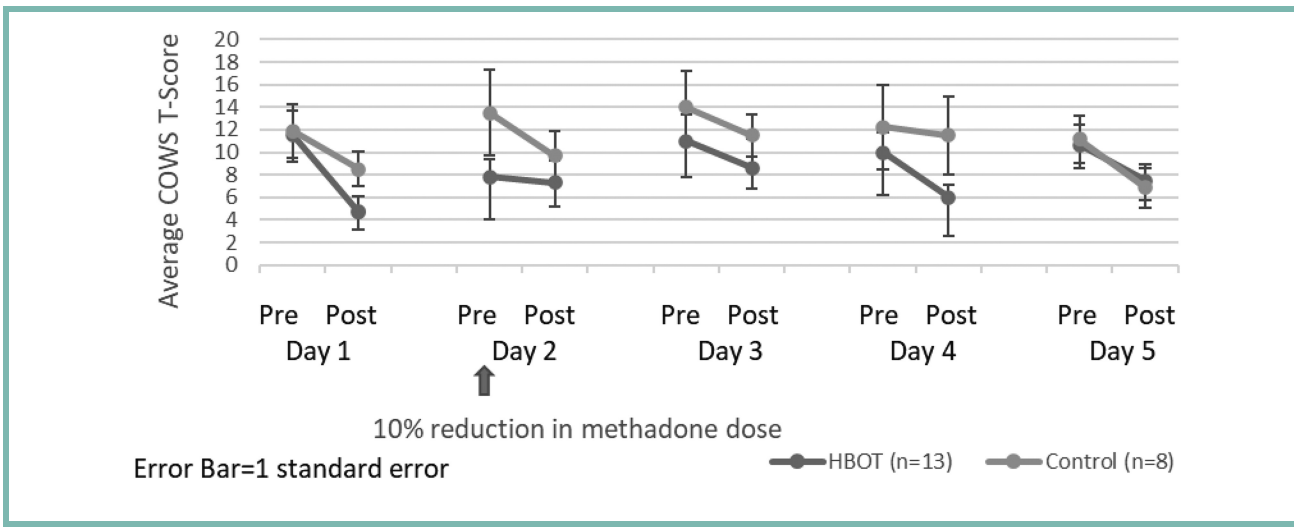

Figure 1. Clinical Opiate Withdrawal Scale (COWS) total score across days of hyperbaric oxygen therapy (HBOT). Error bars show 1 *SE*.

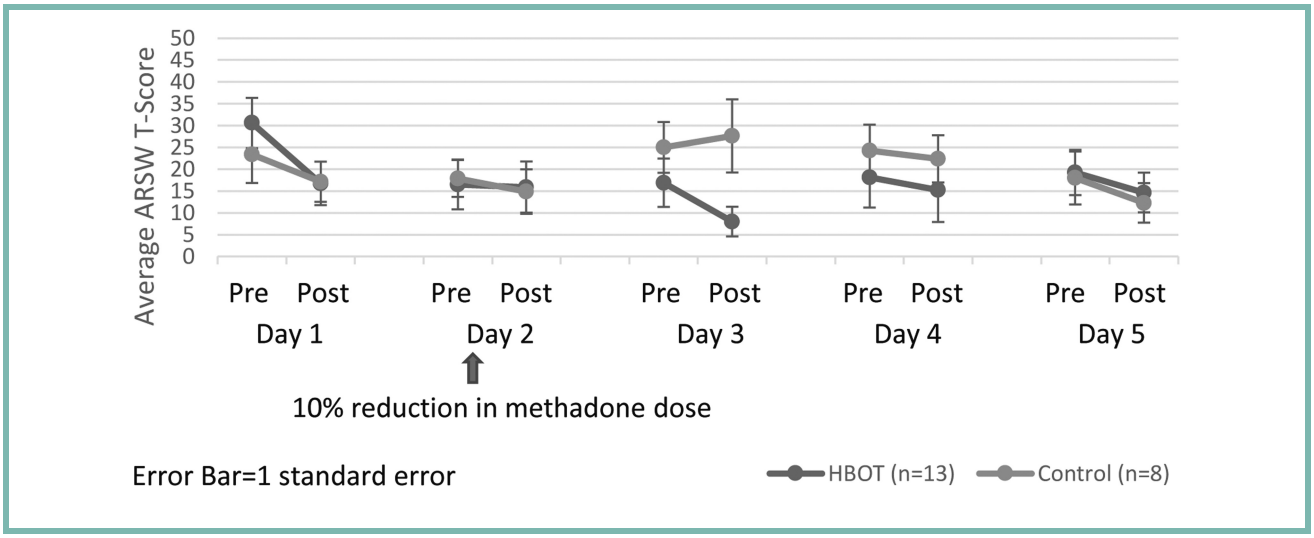

Figure 2. Adjective Rating Withdrawal Scale (ARSW) total score across days of hyperbaric oxygen therapy (HBOT). Error bars show 1 *SE*.

randomization to the HBOT group, one of the participants became ineligible because of medical concerns, and two did not show up to any offered treatment sessions. Of the 13 participants who engaged in HBOT, nine (69.2%) completed all five 90-minute HBOT sessions, two (15.4%) completed four sessions, one (7.7%) completed three sessions, and one (7.7%) completed two sessions. No serious adverse events were reported. One participant was removed from the HBOT chamber because of inability to equalize ear pressure but resumed the remainder of available sessions.

Satisfaction surveys were received from 12 treatment group members. Ratings for all four evaluation items were ≥6, with 7 being the most favorable possible score: (a) ease of treatment (M = 6.2, SD = 0.59), (b) time to complete the treatment (M = 6.0, SD = 0.85), (c) in-person support available during treatment (M = 6.4, SD = 0.52), and (d) how comfortable participating in treatment (M = 6.5, SD = 0.52).

DISCUSSION

In this sample of adults in MAT with OUD, HBOT was well tolerated and feasible. Most participants who started treatment attended 100% of the 90-minute HBOT sessions. Reported satisfaction was high with no significant adverse

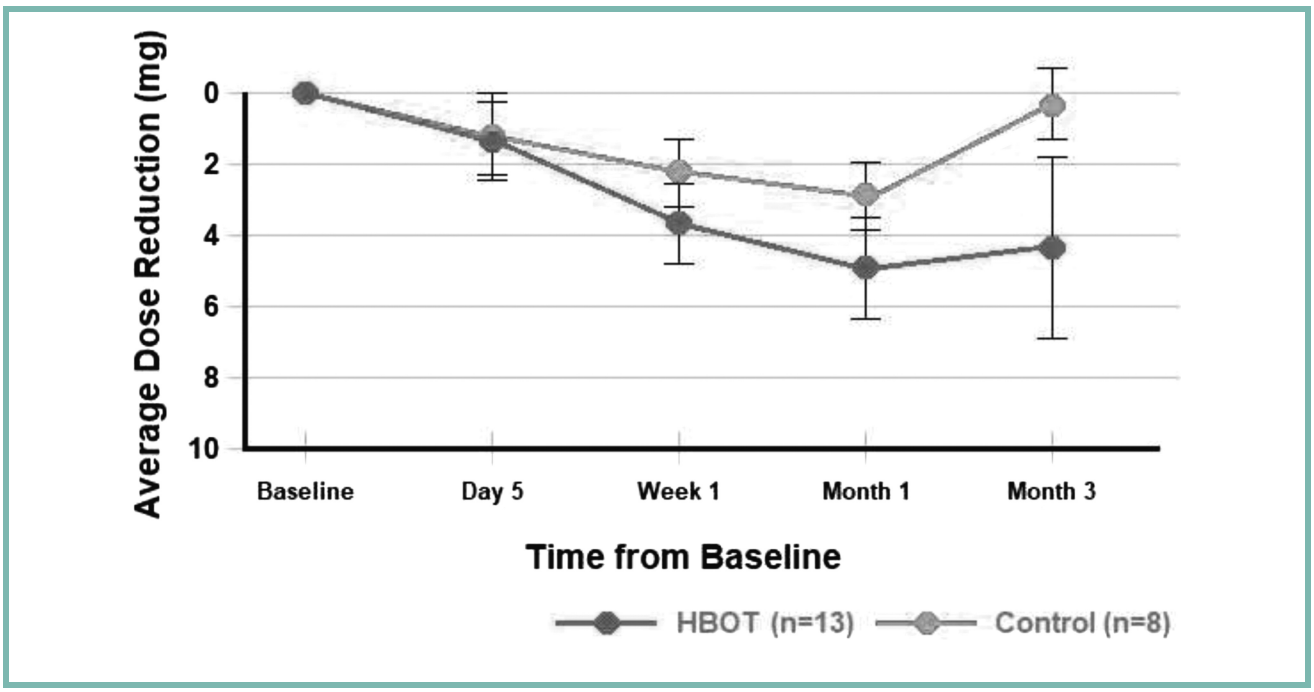

Figure 3. Mean methadone dose reduction in milligrams for the treatment and control groups from baseline to 3 months.

effects. On average, participants in the HBOT group were able to sustain a larger reduction in methadone dose at 3 months after treatment compared with the control group. Withdrawal symptoms trended toward improvements after HBOT sessions. Although the measurable improvements were slight and are based on a small number of participants, when paired with compelling animal study data (Nicoara et al., 2016), our findings justify further investigation into HBOT as a nonpharmacological, safe, opioid withdrawal treatment option.

Pharmacological options to treat noradrenergic hyperactivity associated with opioid withdrawal symptoms are limited by increased risks when used in conjunction with methadone or other opioids. Opioid alternatives and adjuncts are critically important for people in MAT who increase overdose risk when combining treatment medications with other opioids or benzodiazepines for symptom control (Hermann et al., 2005). Finding new, safe nonpharmacologic treatments to manage withdrawal symptoms is an important area for investigation. As anticipated, symptoms of pain and negative mood were correlated in this sample, and withdrawal was likewise associated with mood (Wilson et al., 2018; Woo, 2010). Therefore, if withdrawal symptoms can be reduced, related symptoms of pain and mood may also be improved. Only about 35% of people with OUD currently receive MAT (Hagedorn et al., 2018). Potentially, receptivity to MAT would increase if distressing symptoms could be better managed. Symptom relief, including how it affects functional outcomes of MAT, is an important area that has been rarely studied (Maglione et al., 2018).

The self-reported nature of the collected data presents a limitation; however, our ability to collect data using the COWS as an observed assessment of withdrawal and compare it with the ARSW is a strength. The two instruments were significantly and positively correlated. We used well-validated instruments that performed as expected, with the exception of the sleep disturbance score that was anticipated to be significantly, positively related to symptoms of pain, mood, and withdrawal. Further investigation might be necessary to validate that the PROMIS scale accurately captures sleep disturbance in populations with OUD.

We recruited from a single clinic in one region of the United States, so replication studies are needed with more diverse groups and larger samples. Populations with OUD are often difficult to retain for treatment and research purposes (Gorodetzky et al., 2017; Maglione et al., 2018). Our retention rate after randomization to HBOT was acceptable at 76.5%, whereas retention to the control group was less favorable at 57.1%. We show that MAT populations are willing and able to participate in HBOT treatment and at least some are motivated to reduce their methadone dose. We did not know the optimal HBOT dose needed to achieve clinically meaningful results; therefore, studies examining dose response are needed. It is possible that, because our participants had relatively low withdrawal symptom burdens at baseline, we were limited in the ability to detect meaningful improvements. The baseline ARSW scores in our sample were lower on average than those in other published studies (Barbosa-Leiker et al., 2014; Brown et al., 2010) and much lower than in our previous study of adults in MAT with comorbid pain (Wilson et al., 2018). Anxiety and depressive symptoms were milder too (Wilson et al., 2018). Future studies can examine whether targeting MAT recipients with higher symptom burdens might yield greater effects. Perhaps HBOT could be administered during MAT induction instead of in conjunction with a gradual dose reduction.

Clinical Implications

In developing HBOT as a plausible treatment for withdrawal, cost and access to treatments require consideration and can vary considerably among nations. Approximately 1,000 chambers are in use in the United States with about one quarter of those sites receiving accreditation from the Undersea & Hyperbaric Medical Society (Undersea & Hyperbaric Medical Society, 2020). Third-party payments in the United States generally only cover HBOT for the 14 approved conditions, and fees can vary widely per treatment session from $100 USD at an HBOT clinic to $1,000 at medical centers (Hyperbaric Link, 2020). The number of sessions necessary for benefit can vary as do individual responses and side effects. For example, recommended wound healing treatment can consist of 20–60 treatments over several weeks. Placebo effects should be investigated, yet double-blind controlled studies with HBOT are challenging. Creating sham HBOT conditions requires using at least a small amount of pressure to be believable, which may yield some therapeutic benefits (Lansdorp & van Hulst, 2018). Besides subduing inflammation, HBOT effects are diverse and include changes in DNA transcription, improved structure of tissue, and angiogenesis, the formation of new red blood cells (Choudhury, 2018). Therefore, whether or not HBOT proves to be a feasible option within MAT, exploring its other mechanisms of action as they relate to opioid withdrawal may be useful in developing novel treatments. Biobehavioral approaches to opioid tapering may be equally beneficial (Chandwani et al., 2008), yet current research is scant (Mumba et al., 2018). Comparisons of HBOT efficacy with other options should be explored. Nurses are well positioned to advocate for holistic care that can address physical dependence, psychological cravings, and lack of self-control related to opioid use (Kidd et al., 2020).

CONCLUSION

Our sample of MAT outpatients was willing and able to attend a 5-day course of HBOT scheduled to align with a planned methadone dose reduction. Dose reductions were larger in the HBOT treatment group versus the attention control group when examined over 3 months' time, although the difference between groups was not statistically significant within this small pilot sample. Participants assigned to the HBOT arm were sufficiently adherent to the daily sessions and generally satisfied with the process. Further investigation on how HBOT can be used as a nonpharmacological adjunct to reduce withdrawal symptoms is indicated along with longer-term

studies that determine whether HBOT can improve overall symptom burdens and recovery goals for OUDs.

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