ORIGINAL ARTICLE

Comparing opium tincture and methadone for medication-assisted treatment of patients with opioid use disorder: Protocol for a multicenter parallel group noninferiority double-blind randomized controlled trial

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Abstract

Objectives: This is the first study to compare the safety and efficacy of opium tincture (OT) with methadone for treatment of opioid use disorder.

Methods: In this multicenter, double-blind, noninferiority controlled trial, a stratified sample of 204 participants with opioid use disorder were recruited from community outreach, drop-in centers, and triangular clinics. Participants were excluded in case of active participation in another treatment program for opioid use disorder, hypersensitivity to trial medications, pregnancy, and certain serious medical conditions. They were randomized to receive either OT or methadone with an allocation ratio of 1:1 using a patient-centered flexible dosing strategy. Eligible participants were followed for a period of 12 weeks. Primary outcome is the difference in percentage of patients retained in the treatment. Secondary outcomes are craving, withdrawal symptoms, physical health, mental health, quality of life, and severity of substance use problems, cognitive function, safety profile, cost-effectiveness, and participants' satisfaction. Both intention-to-treat and per-protocol analyses will be conducted.

The Ethics Board of the University of British Columbia and Tehran University of Medical Sciences approved the study. (clinicaltrials.gov; NCT02502175).

Results: To be reported after final analysis.

Conclusions: If shown to be effective, OT will diversify the options for medication-assisted treatment of opioid use disorder.

KEYWORDS

clinical trial, methadone, opioid, opium, substance use

1 | INTRODUCTION

1.1 | Background

Because methadone is the most widely administered substitution treatment for opioid use disorder across the globe, opium tincture (OT) has gained increasing popularity in certain countries (Maguet & Majeed, 2010; Mehrjerdi & Zarghami, 2013). In Iran, approximately 64,000 patients are receiving OT, and OT after methadone (with half a million patients being treated with methadone) is the second most used medication for medication-assisted treatment of opioid use disorder (Ministry of Health and Medical Education, 2014; Momtazi, Noroozi, & Rawson, 2015; United Nations Office on Drugs and Crime, 2010).

OT is an interesting candidate in Iran and Middle East and the golden triangle region of Southeast Asia for several reasons. First, the retail prices of opium in these areas (0.1–2.1 US dollars per gram) are prominently lower than other parts of the world (22–184 US dollars per gram; United Nations Office on Drugs and Crime, 2011). Second, the major production sites of opium are in these regions, which increases its availability (United Nations Office on Drugs and Crime, 2014). Third, opium is culturally more acceptable and less stigmatized in these countries, which can result in an increased compliance with the treatment (Zarghami, 2015). Even more, many patients are inclined towards using OT rather than methadone due to false beliefs and misconceptions about methadone (Daneshmand, Mehrjerdi, & Samiee, 2014). Finally, limited variety and the side-effect profile of the current treatment options for opioid dependence has provoked continuous investigations for expanding the repository of available treatments. Considering the scarcity of evidence on safety and efficacy of OT compared with other treatment options (e.g., methadone; Nikoo et al., 2016), further investigations are required and may conclude advantages of OT not confined to the above-mentioned regions, but also in other parts of the world.

According to a recent systematic review (Nikoo et al., 2016), only a few number of reports are available on treatment with OT in patients with opioid use disorder. The three existing randomized clinical trials investigated only detoxification with OT but not its use in the medication-assisted treatment. Beyond that, although OT demonstrated an acceptable retention rate of 71–78% in previous reports, there is no comparison between OT and other standard treatments, in particular methadone, using a controlled design.

1.2 | Aims

In this study, we aim to compare the safety and efficacy of OT with methadone for medication-assisted treatment of opioid use disorder for the first time.

2 | MATERIALS AND METHODS

This protocol paper is prepared based on the Fifth Amendment of the primary protocol. More information is available in Data S1 and at two ICMJE recognized registry databases of clinical trials (ClinicalTrials.gov: NCT02502175; IRCT.ir: IRCT201506261556N78).

2.1 | Hypothesis and objectives

The primary objective was to determine if opium tincture is as equally effective as methadone for retaining patients with opioid use disorder in medication-assisted treatment using flexible patient-centered dosing strategy. Our primary hypothesis is that OT is as equally effective as methadone for retaining participants in medication-assisted treatment with opioid use disorder. Our secondary objective is to compare OT and methadone in terms of other health-related outcomes including adverse events, craving, withdrawal symptoms, abstinence from illicit use of drugs, physical health, psychological health, cognitive function, quality of life, cost-effectiveness, and patient satisfaction (Table 1).

2.2 | Research design

In this Phase 3 multicenter, parallel group, double-blind, noninferiority randomized clinical trial (Food and Drug Administration, 2016), patients with opioid use disorder were randomized to receive either opium tincture or methadone using a patient-centered flexible dosing strategy for 12 weeks, complying with the Iranian National Protocol For Medication-Assisted Treatment of Opioid Use Disorder. The Clinical Research Ethics Board of the University of British Columbia (UBC-CREB; H15-00220) and Tehran University of Medical Sciences Ethics Committee (TUMS-EC; 28099) approved the study. DaruPakhsh Pharmaceutical company provided methadone and opium tincture at a discounted price (one third of the real price, contract No: 139281). The Iran National Science Foundation (Grant No. 93045481), Tehran

University of Medical Sciences (Grant No. 28099), and AJA University of Medical Sciences (2/12/95) funded the study.

2.3 | Sampling, eligibility, and recruitment

Recruitment centers were primarily four private outpatient medication-assisted treatment clinics located in major cities in Iran: Sari and Tehran in the north, Isfahan in the center, and Shiraz in the south. The Tehran center dropped out due to an inability to recruit participants. We later added a rural center in Sari. To achieve the target sample size, brochures and flyers were distributed in community outreach, general and mental hospitals, nongovernmental organization (NGO)-run communities, colleges and universities, drop-in centers, and specialized clinics for treatment of participants with HIV and hepatitis C. In addition, flyers were posted on the billboard of bus/subway and local stores as well as in the above mentioned places. The recruitment period was from July 2017 to January 2018.

Participants provided informed consent before any study-related procedure. It was required that eligible participants be willing and able to adhere to the treatment protocol based on their consent and assessment by the experienced physician at each clinic. Participants were selected from patients with opioid use disorder based on the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-V) criteria (American Psychiatric Association, 2013). Female participants of childbearing age were included only if they agreed to use an acceptable method of contraception approved by the research physician during the study follow-up period.

Participants were excluded if they met any of the following criteria: active participation in another treatment program for opioid use disorder within the last 14 days before inclusion in this study; severe hepatic impairment; hypersensitivity to methadone, opium, or their ingredients; pregnancy; severe chronic respiratory disease; head injuries and raised intracranial pressure; biliary tract disease; and consumption of monoamine oxidase inhibitors within the last 14 days prior to the study.

2.4 | Randomization, allocation concealment, and blinding

Participants were randomized with a 1:1 allocation ratio to methadone or OT treatment arms using stratified randomization block technique with block sizes of 2 and stratification on sex (female/male ratio = 1/9). This stratification is based on gender distribution of the population with opioid-dependence in Iran according to the results of the Iranian Mental Health survey in 2011 (Rahimi-Movaghar et al., 2014). Sealed Envelope Ltd., 2015 created the blocked randomization list (<https://www.sealedenvelope.com/simple-randomiser/v1/lists> [Accessed 17 June 2017]; seed number: 276524980879508). A randomization list was uploaded on the trial website (metopitrial.ir). The clinic pharmacist logged in to the trial website, which assigns each participant to a unique randomization code and retrieved the intervention arm when dispensing the medications. The pharmacist was the only person aware of both allocation label and randomization code of each participant. The patients, investigators, treatment team (except pharmacist),

and assessors were only aware of the randomization code for each participant, but not the allocation label or randomization tables. An essence was added to methadone syrups to make them similar to opium tincture in terms of smell, color, and taste. No biological test that could potentially unbind the treatment was planned in this study. Randomization and allocation concealment would be broken in emergency situations at the discretion of the responsible physician.

2.5 | Treatment interventions

After obtaining informed consent, participants who fulfilled the eligibility criteria were invited for Baseline Visit. In this visit, participants were assessed using several assessment batteries in a structured clinical interview and then randomized into either opium tincture (10 mg/ml) or methadone (5 mg/ml) treatment arms. Both treatments were manufactured by DaruPakhsh.co, Tehran, Iran, in accordance with instructions provided by the World Health Organization on Good Manufacture Practice. The essence was added to the methadone syrup after strict laboratory evaluations for stabilization and lack of interaction with other ingredients. Also, the volume of the essence-contained methadone syrups was controlled during production, not to be different from normal methadone syrups in terms of concentration of active ingredients. Medications were monitored regularly by the pharmacist at each center. Patients received their treatment based on patient-centered flexible dosing strategy using the following flow-charts where one unit of medication is equal to 1 ml (10 mg) of opium tincture or 0.5 ml (2.5 mg) of methadone (Figure 1). The treatment would be discontinued in case the participant voluntarily chose not to continue, or the research physician decided to discontinue the treatment based on predefined criteria discussed in the safety section.

All the relevant assessments, treatments, and laboratory tests were free of charge for all participants. Furthermore, all the participants received routine psychological therapies provided by the psychologist at the clinic based on an individual's need. Also, participants received concomitant prescription medications other than opioids on a need basis according to the physician's opinion and instructions. The type, duration, and reason for all the psychological therapies and prescribed medications were documented.

2.6 | Outcomes, instruments, and timeline

Table 2 and Figure 2 represent the study schedule as well as participants' flow throughout the study. In brief, patients had 30 visits during the 12 weeks from the point they started their treatment. Table 1 demonstrates study outcomes as well as methods for their assessment.

2.6.1 | Primary outcome

Retention in treatment

Retention in treatment is defined as participating in a certain proportion of scheduled treatment sessions to receive their medications. Because frequencies of visits were different in various stages of the study, we had to set the cut-off for each stage separately. A previous study had defined retention in treatment as receiving treatment for 10 out of the last 14 (71.4%) days of follow-up period

TABLE 1 Secondary outcomes, method of measurement, and analysis

Measures	Tool	Description of tool	Main reference	Application in Iranian population	Method of Analysis
Illicit drug use	Self-report and urine toxicology	Self-reports for all drugs, and urine toxicology for methamphetamines, THC, and cocaine will be applied using ABON 5 Panel Multidrug Urine Test Kit	Company		Regression method
Craving	Visual Analogue Scale (VAS) (0–10)	Marking on a 10-cm line in proportion to their craving from 0 (<i>no craving</i>) to 10 (<i>the highest level of craving</i>)	Wewers & Lowe, 1990		Regression method
Withdrawal	Subjective Opioid Withdrawal Scale (SOWS)	A self-administered scale containing 16 symptom items, each on a scale of 0 (<i>not at all</i>) to 4 (<i>extremely</i>)	Handelsman et al., 1987	Assadi, Hafezi, Mokri, Razzaghi, & Ghaeli, 2004; Kheirabadi, Ranjesh, Maracy, & Salehi, 2008	Regression method
Physical health	Opiate Treatment Index (OTI)	A structured interview designed to provide a measure of the effectiveness of drug treatments through six outcomes, including drug use, HIV risk-taking behavior, social functioning, criminality, health status, and psychological functioning. We only use the health section of the OTI, which is composed of items addressing signs and symptoms in major organ systems as well as injection-related health problems, and is designed to give an indication of the subject's current state of health, especially in relation to those areas within which the individual drug user usually develops problems	Darke, Hall, Wodaki, Heather, & Ward, 1992	Esmaili, Ziaddin, Nikraves, Baneshi, & Nakhah, 2014; Azizi, Borjali, & Golzari, 2010	Regression method
Psychological health	Symptom Checklist-90-Revised (SCL-90-R)	A 90-item, brief, multidimensional checklist designed to assess psychopathology and psychological distress using nine primary symptom dimensions: somatization, obsessive compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. It is then expressed through three intensities: Global Severity Index, Positive Symptom Distress Index, and positive symptom total	Derogatis, 1996	Noorbala, Ramezanzadeh, Abedinia, Yazdi, & Jafarabadi, 2007; Bagheriyazdi, Bolhari, & Shahmohammad, 1994	Regression method
Severity of substance use problem	Addiction Severity Index-5th (ASI-5th)	A semi-structured interview consisted of 200 items designed to address recent and lifetime problems in substance users in seven domains: medical status, employment and support, drug use, alcohol use, legal status, family/social status, and psychiatric status. The final score is calculated based on the manual in a range of 0–1	McLellan et al., 1992	Ahmadi, 2002, 2003	Regression method
Cognitive function	Montreal Cognitive Assessment (MoCA)	A brief screening measure designed to identify cognitive impairment using a one-page 30-point test format. Assessment domains include short-term memory, visuospatial abilities, executive function, attention, concentration, language, and orientation	Nasreddine et al., 2005	Emsaki, Molavi, Chitsaz, Abtahi, & Asgari, 2011	Regression method
Quality of life	World Health Organization Quality of Life-BREF (WHOQOL-BREF)	Field Trial Version provides a short form quality of life assessment that includes 26 questions, among which 24 items come from the 24 facets contained in WHOQOL-100, and two other items represent overall quality of life and general health. Also, Quality-Adjusted Life-Month (QALM) and Quality-Adjusted Life-Year (QALY) will be calculated based on the WHOQOL-BEF	World Health Organization, 1996	Nejat, Montazeri, Holakouie Naieni, Mohammad, & Majdzadeh, 2006; Jahanlou & Karami, 2011	Regression method

(Continues)

TABLE 1 (Continued)

Measures	Tool	Description of tool	Main reference	Application in Iranian population	Method of Analysis
Client satisfaction	Treatment Perception Questionnaire (TPQ)	A 10-item scale for assessment of patients' satisfaction in an addiction treatment program in two domains: Perception of the clients towards the nature and extent of their contact with the program staff, and aspects of the treatment service and its operation and rules and regulations. Items are scored on a Likert scale of 1 (<i>strongly agree</i>) to 5 (<i>strongly disagree</i>)	Marsden et al., 2000	Ali et al., 2005	Regression method
Childhood trauma	Childhood Trauma Questionnaire (CTQ)	A standardized, retrospective 28-item self-report inventory that measures the severity of different types of childhood trauma. It contains five clinical subscales each composed of five-item scores on a Likert scale of 1 (<i>never</i>) to 5 (<i>very often</i>): emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect. The measure also includes a three-item minimization/denial subscale indicating the potential underreporting of maltreatment. These three items are dichotomized as 0 (<i>never</i>) or 1 (<i>all other responses</i>) and summed up	Bernstein & Fink, 1998	Naqavi, Mohammadi, Salari, & Nakhiae, 2011	Regression method
Stages of change	University of Rhode Island Change Assessment Scale (URICA)	A 32-item measure with four subscales measuring the stages of change in an interview or self-report format: precontemplation, contemplation, action, and maintenance. Items are scored on a Likert scale of 1 (<i>strong disagreement</i>) to 5 (<i>strong agreement</i>). Subscale scores are combined arithmetically to yield a second-order Readiness to Change score at entrance to treatment	DiClemente, Schlundt, & Gemmell, 2004; McConaughy, Prochaska, & Velicer, 1983	Ghannadiasl, Mahdavi, & AsghariJafarabadi, 2014; Jafari, Shahidi, & Abedin, 2012	Regression method
Cost-effectiveness	Substance Abuse Services Cost Analysis Program (SASCAP)	Cost per QALM and QALY will be calculated using SASCAP and the methodology applied by Vanagas, Padaiga, and Bagdonas (2010) for cost-utility analysis for each treatment arm	Zarkin, Dunlap, & Homs, 2004; Vanagas et al. (2010)		Regression method

(Oviedo-Joekes et al., 2009). So, we set 70% of the visits at each stage after rounding them up as the cut-off for retention in treatment. So, participants who attend a minimum of four (out of six) visits in the first 3 days, six (out of nine) visits from day 4 to 14, four (out of six) visits from day 15 to 28, and six (out of nine) visits in the next 8 weeks were considered "retained in the treatment." This outcome has been consistently used in several previous trials in a medication-assisted treatment of opioid use disorder (Mattick, Breen, Kimber, & Davoli, 2009).

2.6.2 | Secondary outcomes

Key secondary outcomes are craving, withdrawal symptoms, abstinence from illicit use of drugs, physical health, psychological health, cognitive function, severity of problems related to substance use, client satisfaction, and cost-effectiveness. Behavioral stages of change and childhood traumatic experiences were measured at baseline. Table 1 summarizes the measured outcome, measurement instruments, and the methods of analysis.

2.7 | Setting and personnel

The trial centers were private outpatient centers that fulfilled the personnel and equipment requirements set by national guidelines. Each center had a director, one full-time general practitioner, one full-time psychologist, one full-time pharmacist, and one secretary. They were equipped with outpatient as well as basic emergency care facilities. All research physicians had at least 5 years of experience in treatment of patients with opioid use disorder. Also, clinical psychologists were experienced and/or trained in the implementation of assessment batteries used in this study.

2.8 | Quality assurance, data collection, monitoring, and confidentiality

At each study center, the staff were trained by investigators on the Tri-council Policy Statement 2 and Ethics Code of Iran, as well as for appropriate methods of assessment, completion of case report forms (CRF), and data management procedures using face to face lectures

FIGURE 1 Dosing strategy for treatment with opium tincture or methadone in patients with opioid use disorder, where one unit of medication is equal to 1 ml of opium tincture or 0.5 ml of methadone. (a) Day 1, morning; (b) day 1, afternoon; (c) day 2–3; and (d) day 4–84

and role playing with the staff. Independent entities at the data center reviewed confirmed CRFs, and would contact the clinics for clarification if incomplete or inaccurate data were found in CRFs.

Data were collected on paper (i.e., CRF). Paper documents are kept in a locked place in the clinic office with authorized access. Electronic data were entered into a safely secured, encrypted, and password-protected database with regular synching and back-ups. All documents will be kept in the treatment center for 25 years after completing the study, after which paper forms will be shredded and electronic data will be permanently deleted.

A unique study code not derived from or related to the information about the individual was used on all study documents except randomization lists, consent form, and screening log. This code cannot be translated to identify the individual and investigators or their institutions could not use or disclose the unique study code for other purposes or disclose the mechanism for re-identification. Participant medical information obtained during the study is confidential and disclosure to third parties is prohibited. No identifying participant information, including names, will be disclosed in reports, publications, or presentations. At the participant's written request, medical information may be given to his/her personal physician.

Access to data and associated documentation will be permitted only if user agrees to use the data for research purpose, commit to confidentiality principles, and destroy the data after completing the analyses. Principal investigator, coinvestigators and clinic staff in Iran will have direct access to paper forms.

2.9 | Consent, safety, and adverse events

Trained staff were responsible for obtaining informed written consent at each study site. Screened participants received paper consents with full details, including but not limited to potential adverse events, potential benefits, timelines and procedures, and contact information of responsible bodies in accordance to the guidelines by the UBC-CREB and TUMS-EC. Participants were provided with adequate time, could discuss any issue regarding the consent with the clinic physician, and were free to withdraw their consent at any time during the trial without affecting their relationship with the healthcare providers.

Any untoward medical occurrence in a subject without regard to the causal relationship to the study is defined as an adverse event (AE). AEs were recorded according to the spontaneous reports by the patients/caregivers/clinic personnel, clinical examination, monthly lab tests, and a comprehensive checklist which was used to capture all events, their severity, and their relatedness to the study procedures by the clinic physician from the baseline visit throughout all subsequent visits. The physician followed AEs until resolution, stabilization, or study end, and serious study-related AEs are followed beyond study end as long as the participant is alive and affected. AEs are included in the reports to the Data Safety Monitoring Board (DSMB), as well as investigators and ethics committees at sponsor institutions. The reports will follow the regulations set by the Iranian Ministry of Health Adverse Drug Reporting Center.

TABLE 2 Schedule of study procedures

Activity/ Assessment	2 (screening /consent)	1 (screening)	0 (baseline /randomization)	T1 (visits 1–6 twice daily/day 1–3)	T2 (visits 7–14 daily/day 4–14)	T3 (visits 15–21 on even days/day 15–28)	T4 (visit 22/day 29)	T5 (visit 23–25 weekly/day 30–56)	T6 (visit 26/day 57)	T7 (visit 27–29 weekly/day 58–84)	T8 (visit 30/day 85)
Informed consent	X										
Clinical eligibility screening	X										
Paraclinical eligibility screening		X									
Randomization		X									
Clinical evaluations:											
Demographics		X									
History		X									
Physical examinations		X									
URICA			X				X		X		X
CTQ			X				X		X		X
SCL-90			X				X		X		X
VAS craving			X				X		X		X
SOWS			X				X		X		X
OTI			X				X		X		X
MoCA			X				X		X		X
ASI			X				X		X		X
WHoQOL-BREF			X				X		X		X
Extra program costs			X				X		X		X
SASCAP											
Adverse events				X							
TPQ					X				X		
Paraclinical evaluation:											
BS			X								X
CBC			X								X
Electrolytes			X								X
RFT			X								X
LFT			X								X
Lipid profile			X								X

(Continues)

TABLE 2 (Continued)

Activity/ Assessment	2 (screening /consent)	1 (screening)	0 (baseline /randomization)	T1 (visits 1–6 twice daily/day 1–3)	T2 (visits 7–14 daily/day 4–14)	T3 (visits 15–21 on even days/day 15–28)	T4 (visit 22/day 29)	T5 (visit 23–25 weekly/day 30–56)	T6 (visit 26/day 57)	T7 (visit 27–29 weekly/day 58–84)	T8 (visit 30/day 85)
Urine toxicology			X				X		X		X
Viral: HBV, HCV, HIV			X								
Pregnancy			X				X		X		X
Treatment with either methadone or OT											
Treatment/ Study termination											

Optimally at the end of week 12, but possibly at any visit based on the predefined conditions.

Note. ASI, Addiction Severity Index; BS, blood sugar; CBC, complete blood count; CTQ, Childhood Trauma Questionnaire; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LFT, liver function tests; MoCA, Montreal Cognitive Assessment; OT, opium tincture; OTI, Opiate Treatment Index; RFT, renal function tests; SASCAP, Substance Abuse Services Cost Analysis Program; SCL-90-R, Symptom Checklist 90 revised; SOWS, Subjective Opioid Withdrawal Scale; T, time period; TPQ, Treatment Perception Questionnaire; URICA, University of Rhode Island Change Assessment Scale; VAS, visual analogue scale; WHOQoL-BREF, World Health Organization Quality of Life-Biomedical Research and Education Facility.

The research physician might decide to discontinue the treatment because of adverse reactions to study medications, a serious change in medical status which threatens patient's safety if the treatment was continued, violence against treatment team members without convincing evidence of mental illness like psychosis or delirium, or criminal behavior with resultant imprisonment during the study period. Early termination of treatment and data collection could occur in case a participant withdrew his/her consent to participate. In any of the abovementioned cases, the relationship between the healthcare team and the patient would not be affected, but the participant would receive information on alternative options to continue his treatment out of the study. In addition, data concerning treatment discontinuation or termination of participation were recorded in full, including the reason and the number of the session for such a decision.

Also, participants were informed about financial costs associated with their participation in the study that are paid by the sponsors, and their potential options to continue their self-paid treatment after the trial period. Investigators would hold the responsibility for any costs for medical treatment incurred as a result of a study-related injury. Patients will have access to the investigators through the contact information provided in the consent forms for at least 5 years after the trial is completed.

2.10 | Feasibility

Feasibility review was conducted after recruitment of first 60 patients. The interim analysis was carried out once and reported to the DSMB. Accordingly, the DSMB could make decision on any necessary changes to the ongoing protocol concerning patients' safety or data integrity after discussing the issue with investigators. Recommendations would be made to principal investigators regarding continuation, modification, or termination of the trial in case of serious safety concerns or devaluation of clinical equipoise that justified the initiation of the trial.

2.11 | Sample size

The sample size was calculated using the FDA guidelines for noninferiority clinical trials using a fixed margin (95%–95%) approach (Food and Drug Administration, 2016). To calculate the active control effect, data was obtained from a Cochrane systematic review in which, retention in treatment with methadone has been compared with placebo. The meta-analysis of the four new studies has yielded a pooled 95% confidence interval for retention ratio of methadone to placebo of 4.44 [3.26, 6.04] (Mattick et al., 2009). The lower bound of the above confidence interval, that is, 3.26 was selected as M1, which yields a treatment effect of 2.26. A very conservative clinical noninferiority margin, that is, M2 equal to 1.25 (11% of M1) was chosen. To calculate the sample size, we assumed retention rate for participants in medication-assisted treatment with methadone to be 77.7% at 3 months based on a systematic review of retention in treatment among participants in medication-assisted treatment in low-income and middle-income countries (Feelemyer, Des Jarlais, Arasteh, Abdul-

FIGURE 2 Flow diagram of patients with opioid use disorder in clinical trial of medication assisted treatment with opium tincture or methadone

Quader, & Hagan, 2014). Using the following formula (Zhong, 2009), and assuming a power of 90% and Type I error is set at 5%, the total sample size was calculated to be 240 participants, 120 in each group.

$$N = 2 \times \left[\frac{Z_{1-\alpha} + Z_{1-\beta}}{M_2} \right]^2 \times P \times (1 - P) \left[\frac{Z_{1-\alpha} + Z_{1-\beta}}{M_2} \right]^2 \times$$

$$P \times (1 - P) = 2 \times \left[\frac{1.65 + 1.28}{15.75} \right]^2 \times 77.7 \times$$

$$(1 - 77.7) 2 \times \left[\frac{1.65 + 1.28}{15.75} \right]^2 \times 77.7 \times (1 - 77.7) = 120.$$

Due to limitation of resources for continuing the trial, we decided to adjust the sample size with the power of 80%, which yielded a sample size of 174:

$$N = 2 \times \left[\frac{Z_{1-\alpha} + Z_{1-\beta}}{M_2} \right]^2 \times P \times (1 - P)$$

$$= \left[\frac{1.65 + 0.84}{15.75} \right]^2 \times 77.7 \times (100 - 77.7) = 87.$$

Given the existing resources, clinics agreed to continue the recruitment up to a sample size of $N = 204$, which surpasses the power of 80% but did not reach the power of 90% as set initially.

2.12 | Statistical analysis

Analyses will be based on both intent-to-treat and per-protocol methods. A confidence interval procedure will be conducted to evaluate whether the upper bound of 95% confidence interval of the retention ratio of methadone to OT passes the noninferiority margin, that is, 1.25. Multiple Imputation by Chained Equations will be used for missing data when comparing score changes between the two

treatment arms. Outliers will be identified based on the distribution of outcomes and will not be included in further analysis unless confirmed for accuracy of data collection and entry. Sensitivity analyses will be used to address the impact of missing data on conclusions (Committee for Medicinal Products for Human Use, 2009). The comparison between the two arms will be further adjusted for additional interventions, such as psychological or concomitant prescription medications in the multivariate analysis. Also, the regression models will evaluate the effects of baseline variables on the outcomes of interest.

2.13 | Dissemination of results

After completion of data collection and confirmed accuracy of data by the DSMB and the auditing committee, investigators will analyze the complete data set and prepare the final reports in accordance with the approved protocol, as well as later amendments. The reports will be provided to all the related committees and boards as well as principal investigators and consultant statistician to be reviewed. Public communication of the results will be in the form of journal articles, conference abstracts, and update of the clinical trial registries.

3 | RESULT

A total of 204 participants, 128 in Sari-urban, 52 in Sari-rural, 15 in Shiraz, and 9 in Isfahan were randomized equally to two arms. Results of this clinical trial are to be reported after final analysis.

4 | DISCUSSION

This is the first study to assess the safety and efficacy of OT for medication-assisted treatment of opioid use disorder compared with methadone, the most widely administered treatment for this condition. Results of previous studies on OT in patients with opioid use disorder were inconclusive (Nikoo et al., 2016).

This study is also subject to some limitations. First, we stratified our sample based on the age and gender distributions of patients with opioid dependence in Iran, with men to women ratio of 9:1 and almost half the sample selected from patients with age range of 30–39 years old, which may be different from other countries (United Nations Office on Drugs and Crime, 2010). Second, although we used every effort to make the two treatments similar, patients might be able to guess the treatment they receive based on the characteristics that is different between OT and methadone, such as the timing and intensity of resultant euphoric effect. Third, providing free medication and care might increase the retention in treatment in both groups compared with usual treatment settings.

Among the strengths of this study are a large enough sample size and the comprehensive battery of assessments with repeated measurements. Furthermore, this clinical trial is unique in that it provides a potential basis for estimation of conversion ratio between methadone and opium tincture for treatment of opioid use disorder. In more details, because the scant evidence on optimum dosing strategy for OT in opioid use disorder is not as firm as the buck of evidence for methadone, we primarily considered each 1 mg of methadone approximately equal to 4 mg of opium in terms of analgesic effects based on the available literature of pain research; however, knowing that effectiveness of medications on alleviating symptoms and retaining patients in treatment during withdrawal phase in opioid use disorder is different from physical pain conditions, further strong evidence is needed for estimation of a reliable conversion ratio and dosing for OT. The patient-centered flexible dosing strategy in this study provides a mean for comparison of required mean dose of medication between OT and methadone treatment arms. This in turn serves as a basis for both practice with OT in patients with opioid use disorder and future similar studies.

DECLARATION OF INTEREST STATEMENT

The design, management, analysis, and reporting of the study are entirely independent of the financial sponsors. Authors of this manuscript declare that they have no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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