Contemporary Clinical Trials 53 (2017) 36–43

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Effectiveness of adjunctive, personalised psychosocial intervention for non-response to opioid agonist treatment: Study protocol for a pragmatic randomised controlled trial☆

John Marsden [a,b,*], Garry Stillwell [a,b], Jennifer Hellier [c], Anne Marie Brown [a,b], Sarah Byford [d], Michael Kelleher [b], Joanne Kelly [e], Caroline Murphy [e], James Shearer [d], Luke Mitcheson [b]

[a] Addictions Department, Institute of Psychiatry, Psychology and Neuroscience, King's College London, United Kingdom
[b] Lambeth Addictions, South London and Maudsley NHS Mental Health Foundation Trust, United Kingdom
[c] Department of Biostatistics, Institute of Psychiatry, Psychology and Neuroscience, King's College London, United Kingdom
[d] King's Health Economics, Institute of Psychiatry, Psychology and Neuroscience, King's College London, United Kingdom
[e] King's Clinical Trials Unit at King's Health Partners, Institute of Psychiatry, Psychology and Neuroscience, King's College London, United Kingdom

ARTICLE INFO

Article history:
Received 7 September 2016
Received in revised form 25 November 2016
Accepted 3 December 2016
Available online 08 December 2016

Keywords:
Heroin
Cocaine
Opioid substitution
Psychosocial
Trial

ABSTRACT

Introduction: Opioid use disorder (OUD) is a debilitating and relapsing psychiatric disorder; opioid agonist therapy (OAT) is the front-line, evidence-supported treatment. A substantial number of patients relapse or continue to use heroin or other illicit drugs during OAT. There is considerable heterogeneity in the OAT-resistant subpopulation, with many behavioural moderators of treatment response. We have developed a personalised psychosocial intervention (PSI) targeting these individuals. A formulation-guided assessment is linked to a toolkit of motivational, cognitive/behavioural and social support techniques. Change methods have been adapted from evidence-supported psychological therapies and are idiosyncratically tailored to the need and response.
Methods: In this single-centre, 18-week, parallel group, pragmatic randomised clinical trial, we will determine the clinical and cost-effectiveness of the PSI as an adjunctive intervention during OAT, in comparison to opioid agonist treatment-as-usual. We plan to recruit 368 adults. The primary outcome measure is the proportion of participants categorised as 'responders' at the end of the intervention (defined as self-reported abstinence from heroin and cocaine with no positive biological drug tests during the 28 days prior to the endpoint). Secondary outcomes include: percentage of days abstinent from heroin and cocaine in the 28 days before follow-up; treatment retention; therapy compliance; health and social functioning; exploratory genetic biomarkers; and analyses of treatment moderation and mediation.
Conclusions: This pragmatic controlled trial determines the effectiveness and cost-effectiveness of a personalised PSI for non-responding patients during OAT. Our intervention applies motivational, cognitive/behavioural and social support techniques adapted from evidence-based therapies. Findings will inform stratified delivery of OAT.

1. Introduction

Non-medical opioid use is an important contributor to the global burden of disease [1]. Opioid use disorder (OUD) is a debilitating and relapsing psychiatric condition characterised by compulsive drug taking, despite significant adverse physical and psychosocial consequences [2]. Oral opioid agonist therapy (OAT) is the front-line medication assisted treatment, offering medical management of physiological dependence and access to medical and social care.

Systematic reviews of randomised controlled trials show that OAT is effective - with marked reductions in illicit drug use and drug injecting, and a high level of retention in treatment [3,4,5]. However, a significant minority of individuals do not stop using illicit drugs during OAT [6,7]. For example, using national data in England, we observed that between 26 and 33% of patients did not reduce heroin use after 6 months of treatment, and 3% deteriorated to more frequent levels than at admission [8].

Our work in community addiction clinics points to three OAT-resistant groups: *intermittent responders* - patients who stop or substantially reduce drug use in the first few weeks, but then relapse and cycle through periods of unsanctioned exit and re-admission; *brief responders* - patients who achieve only short periods of reduced drug use; and *poor responders* - patients who do not achieve any significant reductions in their illicit drug use, although they may stay in treatment for longer than average. Patients from these sub-populations might benefit from psychosocial interventions. However, systematic review evidence

☆ South London and Maudsley NHS Foundation Trust. Community Drug and Alcohol Team (Lorraine Hewitt House).

* Corresponding author at: Addictions Department, Box 48, Institute of Psychiatry, Psychology and Neuroscience, DeCrespigny Park, Denmark Hill, London SE5 8AF, United Kingdom.
E-mail address: john.marsden@kcl.ac.uk (J. Marsden).

http://dx.doi.org/10.1016/j.cct.2016.12.003
1551-7144/

shows that specific adjunctive psychosocial interventions to date have not been able to increase treatment retention or help patients reduce drug use [9].

Against this background, we contend that an idiosyncratic approach has the best chance of success. Our conceptualisation of addiction treatment unites three constructs: the severity of addiction symptoms, health and social problem complexity, and the patient's personal recovery strengths. We have shown than in the day-to-day operation of addiction clinics these constructs predict treatment response: patients with higher ratings of addiction and concurrent problem complexity are more likely to be using heroin or cocaine at follow-up, and those with more personal strengths are more likely to have achieved stable abstinence [10]. We have designed the current study to produce results that can be generalized and applied to routine practice settings. In this protocol paper, we describe the rationale, methods, analyses, strengths and limitations for a pragmatic randomised controlled trial (RCT) of personalised psychosocial intervention (PSI) during OAT to help patients abstain from heroin and cocaine (Addiction Recovery Clinic Trial [the ARC Trial]).

2. Methods

2.1. Study design

The ARC Trial is a single-centre, 18-week, parallel-group, pragmatic RCT of standard care OAT plus PSI, compared to standard care OAT. It has been designed to conform to the CONSORT guideline extension for such trials [11], and the Template for Intervention Description and Replication (TIDierR) checklist for reporting interventions [12].

The study is registered (ISRCTN number: 69,313,751) and will be conducted according to the ethical principles of the Declaration of Helsinki (1996), with all members of the study team trained in accordance with Good Clinical Practice. Participant materials, study protocol and clinical research forms have been reviewed and approved by the London-Bromley Research Ethics Committee (reference: REC 13/LO/0640; granted 05.06.2013; first participant enrolled on 07.06.2013).

2.2. Study aims

Among patients who have received six or more weeks of OAT and are currently using illicit heroin or cocaine[1], the primary aim of the study is to determine the effectiveness and cost- effectiveness (see Section 2.13.5) of OAT with a 12-week, adjunctive PSI to help patients abstain from heroin and cocaine. The comparison condition is OAT with standard case management (the treatment-as-usual condition; TAU).

The secondary aims of the trial are to estimate the effectiveness of the PSI as evidenced by self-reported heroin and cocaine use, treatment retention, intervention adherence, craving response for heroin and cocaine, quality adjusted life years, and may include description of longer-term criminal offending and mortality. There will be exploratory analyses of treatment moderation and mediation using clinical measures, and targeted analyses of genetic biomarkers of treatment response.

2.3. OAT treatment, setting and study population

Current United Kingdom (UK) clinical guidelines recommend the following front-line oral opioid agonist medications: methadone (mu opioid receptor (μOR) agonist: 60-120 mg/day during the post-induction maintenance phase); and buprenorphine (partial μOR: 12-32 mg/day during maintenance; also available as a 4:1 buprenorphine-naloxone formulation).

[1] In the UK illicit opioid using population, the smokeable base form of cocaine [colloquially known as *crack*] rather than the powder version is most commonly available.

The trial will be conducted at a specialist National Health Service (NHS) community addiction treatment centre in London operated by South London and Maudsley NHS Mental Health Foundation Trust. The centre admits ~15 patients per month into OAT. This is delivered by a multi-disciplinary team including psychiatry, psychiatric nursing, psychology and social work specialties. OAT patients are assigned to a member of the clinical team (known as a *keyworker* in the UK treatment system) for case co-ordination, general counselling and support.

The study population are adults with clinically confirmed opioid use disorder (OUD; DSM-IV [2]) who have been enrolled in oral methadone, or oral buprenorphine, or oral buprenorphine-naloxone OAT at the centre for at least six weeks and are classified as non-responders (operationally defined for the trial as continuing [or relapsing] to use heroin or cocaine use, with biological verification of recent drug use).

We plan to recruit 368 adults. The study is estimated to take 3.5 years to complete, as follows: participant recruitment to month 30; clinical data collection completed by month 36; and data management and analysis completed by month 42.

2.4. Patient eligibility and enrolment

Participant inclusion and exclusion criteria for the study are summarised in Table 1.

Keyworkers will refer patients to the ARC Trial research team based at the centre. Electronic patient records will also be used to identify potential participants. At a screening visit (~30 min to complete), a brief medical and social history will be recorded, including OAT medication

Table 1
Participant inclusion and exclusion criteria.

Inclusion criteria:
In order for a participant to be enrolled into the study they must fulfil all of the following inclusion criteria:
(a) Aged 18 ≥ years (no upper limit, but usually <60 years);
(b) Current diagnosis of OUD;
(c) Enrolled in oral methadone, buprenorphine or buprenorphine-naloxone treatment for 6 ≥ weeks;
(d) Self-reported use of heroin and/or cocaine (verified by urine drug screen toxicology test);
(e) Voluntarily seeking continued treatment and able to attend the clinic as required in the protocol;
(f) Stable accommodation;
(g) Able to communicate verbal understanding of study material and protocol in English;
(h) Possession of a personal phone and ability to nominate at least one locator individual to assist with arranging research appointments.
Exclusion criteria
Otherwise eligible individuals will be excluded from the trial for any of the following:
(a) Clinically significant physical health conditions that may compromise safety or study conduct;
(b) Suicide planning (past 30 days) or suicide attempt (past six months);
(c) Clinically significant or uncontrolled mental health problems (including but not limited to psychosis, bipolar disorder, schizoaffective disorder) and/or history or evidence of organic brain disease or dementia that may compromise safety or compliance with the study protocol;
(d) Current legal proceedings which are likely to result in imprisonment or relocation outside of the centre's catchment area;
(e) Participation in a SUD treatment intervention study in past six months.