View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Aberdeen University Research Archive

RESEARCH REPORT

doi:10.1111/add.15394

Effectiveness of incentivised adherence and abstinence monitoring in buprenorphine maintenance: a pragmatic, randomised controlled trial

Hesham Farouk Elarabi[1,2], Mansour Shawky[1,3], Nael Mustafa[1], Doaa Radwan[1,4], Abuelgasim Elarasheed[1], Ahmed Yousif Ali[1], Mona Osman[5], Ahmed Kashmar[1], Helal Al Kathiri[1], Tarek Gawad[1,6], Ayman Kodera[1], Mohammed Al Jneibi[1], Abdu Adem[7], Amanda J. Lee[8] & John Marsden[2]

National Rehabilitation Centre, Abu Dhabi, United Arab Emirates,[1] Addictions Department, Division of Academic Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK,[2] Department of Neuropsychiatry, Faculty of Medicine, Assuit University, Egypt,[3] Faculty of Medicine, Institute of Psychiatry, Ain Shams University, Egypt,[4] World Health Organization, Eastern Mediterranean Regional Office, Cairo, Egypt,[5] Faculty of Medicine, Cairo University, Egypt,[6] Department of Pharmacology and Therapeutics, College of Medicine and Health Sciences, Khalifa University, P.O.Box 127788, Abu Dhabi, United Arab, Emirates[7] and Medical Statistics Team, University of Aberdeen, UK[8]

ABSTRACT

Background and Aim Buprenorphine (BUP) maintenance treatment for opioid use disorder (OUD) begins with supervised daily dosing. We estimated the clinical effectiveness of a novel incentivised medication adherence and abstinence monitoring protocol in BUP maintenance to enable contingent access to increasing take-home medication supplies. **Design** Two-arm, single-centre, pragmatic, randomised controlled trial of outpatient BUP maintenance, with during-treatment follow-ups at 4 weeks, 8 weeks, 12 weeks and 16 weeks. **Setting** Inpatient and outpatient addictions treatment centre in the United Arab Emirates. **Participants** Adults with OUD, voluntarily seeking treatment. **Interventions** The experimental condition was 16 weeks BUP maintenance with incentivised adherence and abstinence monitoring (I-AAM) giving contingent access to 7-day, then 14-day, then 21-day and 28-day medication supply. The control, treatment-as-usual (TAU) was 16 weeks BUP maintenance, with contingent access to 7-day then 14-day supply. **Measurements** The primary outcome was number of negative urine drug screens (UDS) for opioids, with non-attendance or otherwise missed UDS, imputed as positive for opioids. The secondary outcome was retention in treatment (continuous enrolment to the 16-week endpoint). **Findings** Of 182 patients screened, 171 were enrolled and 141 were randomly assigned to I-AAM (70 [49.6%]) and to TAU (71 [50.4%]. Follow-up rates at 4 weeks, 8 weeks, 12 weeks and 16 weeks were 91.4%, 85.7%, 71.0%, 60.0% respectively in I-AAM and 84.5%, 83.1%, 69.0%, 56.3% in TAU. By intention-to-treat, the absolute difference in percentage negative UDS for opioids was 76.7% (SD = 25.0%) in I-AAM versus 63.5% (SD = 34.7%) in TAU (mean difference = 13.3%; 95% CI = 3.2%–23.3%; Cohen's d = 0.44; 95% CI = 0.10–0.87). In I-AAM, 40 participants (57.1%) were retained versus 33 (46.4%) in TAU (odds ratio = 1.54; 95% CI = 0.79–2.98). **Conclusions** Buprenorphine maintenance with incentivised therapeutic drug monitoring to enable contingent access to increasing take-home medication supplies increased abstinence from opioids compared with buprenorphine maintenance treatment-as-usual, but it did not appear to increase treatment retention.

Keywords abstinence, adherence, buprenorphine, effectiveness, opioid use disorder, therapeutic drug monitoring.

Correspondence to: Hesham Farouk Elarabi, Institute of Psychiatry, Psychology and Neurosciences - King's College London, Addiction Sciences Building, 4 Windsor Walk, Demark Hill, London, Denmark Hill, SE5 8AF, United Kingdom. E-mail: hesham.elarabi@kcl.ac.uk

Submitted 27 August 2020; initial review completed 19 October 2020; final version accepted 23 December 2020

INTRODUCTION

Opioid use disorder (OUD) is a global public health problem associated with a high disease burden [1]. Retention-oriented medication maintenance treatment with methadone or buprenorphine (BUP), or combined BUP and naloxone, are the first-line pharmacotherapies. Patients who engage in OUD treatment have a marked

© 2021 The Authors. *Addiction* published by John Wiley & Sons Ltd on behalf of Society for the Study of Addiction.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

reduction in overdose mortality and use of opioids [2,3]. However, many patients struggle to adhere to treatment and discontinue prematurely. In a systematic review of four randomised controlled trials (RCT) and 63 observational studies (294 592 participants in total), the median retention rate was approximately 57% at 12 months [4]. Non-adherent patients are substantially more likely to relapse to opioid use [5].

Driven by safety concerns, national clinical guidelines for OUD maintenance treatment recommend that patients should receive all, or the majority of their medication, by supervision for several months, with access to take-home supplies (to a typical maximum of 14-days at a single dispensing event) granted to those who can attend and take their medication as directed [6,7]. Clinicians favour access to unsupervised dosing for adherent patients [8,9] and it would appear that most patients endorse this as well [10]. Some patients believe supervised dosing is stigmatising and this may motivate the decision to leave treatment [11].

Typically, prescription adherence during OUD maintenance treatment is monitored through a combination of non-attendance alerted by the dispensing pharmacy and monitoring of point-of-care urine drug screening (UDS) at the clinic. The UDS is a qualitative test that gives an indication of recent medication use (at a level of detection sensitivity) but it cannot show whether the prescribed dose has been taken as prescribed. There have been several clinical effectiveness studies of supervised and unsupervised dosing. A meta-analysis of six such studies in methadone, BUP and combined BUP and naloxone maintenance (four RCTs and two prospective observational cohort studies; 7999 participants in total) judged that there was insufficient evidence for a robust difference in retention (relative risk = 0.99, 95% CI = 0.88–1.12); or endpoint abstinence (67% vs 60%); or medication diversion (5% vs 2%) [12]. However, the quality of these studies was rated as 'low–very low', thus further evidence is likely to change this conclusion.

Is there a better way to monitor adherence during BUP maintenance and help patients receive increasing take-home supplies? One promising set of procedures is therapeutic drug monitoring (TDM). TDM is defined as the 'quantification and interpretation of drug concentrations in blood to optimize pharmacotherapy' [13]. Clinical applications involve repeated measurements of the plasma concentration of a medicine to reach a dose that is well tolerated, minimises the risk of adverse drug reactions and achieves the desired effect. Unlike UDS, TDM can provide a precise indication that medication has been taken as directed. Two decades ago, TDM was predicted to become the standard-of-practice for OUD maintenance pharmacotherapy [14]. However, TDM has not been implemented to any significant extent, and there have been no trials applying TDM procedures during BUP maintenance.

Accordingly, this study is a contribution toward closing this gap. As a precursor, we optimised a laboratory quantification method for BUP monitoring, demonstrating that this was feasible during routine clinical operations [15]. Including TDM procedures, we developed a novel incentivised medication adherence and abstinence monitoring (I-AAM) protocol. The aim of I-AAM was to enable BUP dose-optimised patients who could provide ongoing evidence of adherence and abstinence from opioids, access to increasing take-home supplies of their medication. The aim was to estimate the clinical effectiveness of BUP maintenance with I-AAM versus BUP maintenance treatment-as-usual (TAU).

METHODS

Setting

The study was done at the inpatient and outpatient service of the National Rehabilitation Centre (NRC), Abu Dhabi, United Arab Emirates (UAE). The NRC is the only national provider of BUP maintenance treatment in the UAE. The centre receives referrals from metropolitan Abu Dhabi with 50% of patients attending from other cities and remote areas. In the UAE, heroin, morphine and tramadol are the most common illicit and non-medical prescription opioids reported by populations with OUD. Locally, BUP is not available at community retail pharmacies, so medication is dispensed by the NRC's outpatient pharmacy.

The NRC commenced BUP maintenance treatment in 2002. Patients who took their medication as directed and were abstinent from opioids received up to 14-days take-home supply (this limit set by the centre's dispensing policy). A decade later, and in the context of anecdotal reports of BUP diversion and non-adherent dosing behaviours among some patients, the NRC suspended treatment for people with no treatment history of BUP maintenance, although granting maintenance treatment to new patient episodes enrolled in this study.

Design

This was a single-centre, two-arm, open-label, parallel group, pragmatic RCT of BUP I-AAM (the experimental group) versus BUP TAU (the control group) during 16-weeks of outpatient maintenance treatment. During-treatment follow-ups were at 4 weeks, 8 weeks, 12 weeks and 16 weeks. The NRC's Institutional Review Board approved the protocol (NRC/2/2014). The study was retrospectively registered with the ISRCTN registry (number ISRCTN416 45 723) and the study protocol was published [16]. In this article, methods and findings are reported by Consolidated Standards of Reporting Trials (CONSORT)

© 2021 The Authors. *Addiction* published by John Wiley & Sons Ltd on behalf of Society for the Study of Addiction.

[17]. Medication management and other participant materials can be access on the Open Science Framework (https://osf.io/t9rp4/quickfiles).

The study was conducted in accordance with the ethical principles of the World Medical Association's Declaration of Helsinki for research involving human subjects, good clinical practice and the Abu Dhabi Department of Health's guidelines for medical research. Study participants received study medication without charge and did not receive any compensation for completing research measures. After participants completed the study, they continued to receive BUP maintenance according to their preference and clinic policy.

Contingent on evidence of adherence (attendance and contrasting BUP measured and concentrations) and abstinence (from opioids by UDS), participants allocated to the I-AAM condition had access to increasing take-home supplies of BUP. Dispensing increased from 7 days, to 14 days, to 21 days to a maximum of 28 days supply. Participants allocated to TAU had no blood testing for BUP concentration measurement and had access to a 7 days then 14 days maximum.

An online randomisation service (www.randomization.com) was used to allocate participants to the two groups (1:1; no stratification). Given the open-label design, it was not feasible to mask participants and study investigators. A planned, exploratory health economic analysis will be reported elsewhere.

Inpatient withdrawal management and BUP stabilisation

At the NRC, medically supervised opioid withdrawal and BUP dose induction is done at an onsite inpatient programme before outpatient treatment. During inpatient stay, dose stabilisation was carried out with the objective of settling on a maintenance dose that was personalised for each participant informed by signs and symptoms of opioid withdrawal and their feedback.

Outpatient maintenance medication treatment

Participants were maintained on BUP-naloxone (4:1) sublingual film formulation (Suboxone; Indivior; BUP herein). This product was developed to limit risk of diversion and dissuade injection. All medication was bought commercially. The outpatient maintenance treatment endpoint was 16 weeks (112 days). This was pragmatic and judged reasonable to estimate clinical benefit. During treatment, all participants were offered general counselling and case management support.

For each scheduled clinic visit, the participant was asked to return opened medication packaging and take a UDS test. We used commercial point-of-care UDS product (https://www.cliawaived.com). The test cup was configured to detect morphine (detection limit 300 ng/mL), heroin (6-acetylmorphine 20 ng/mL), codeine (100 ng/mL), propoxyphene and hydrocodone (300 ng/mL), tramadol (200 ng/mL), oxycodone (100 ng/mL), fentanyl (1000 ng/mL) and BUP (10 ng/mL). With the exception of BUP, all test results were required to be negative for the UDS to be recorded 'opioid negative'. All positive opioid test results were confirmed by gas chromatography tandem mass spectrometry.

Study participants

Participants were adults (18 years and over). All had current OUD and voluntarily seeking treatment (Table 1 shows the inclusion and exclusion criteria). Consecutive referrals were screened in person and all participants provided their informed written consent. All adverse events were reviewed by the senior investigators and the data monitoring committee.

Study procedures

After enrolment, participants were admitted to the NRC's onsite inpatient service for up to 4 weeks for medically supervised withdrawal, BUP induction and dose stabilization. As soon as they were comfortable, participants completed a structured interview recording demographic characteristics and baseline measures. Each participant was administered BUP daily under supervision at the same time. In an effort to personalise each participant's dosing

Table 1 Participant inclusion and exclusion criteria.

Inclusion criteria
1. Aged 18 and above (no upper limit)
2. Current diagnosis of OUD
3. Voluntarily seeking BUP maintenance treatment
4. Resident in the UAE
5. Evidence of stable accommodation
Exclusion criteria
1. Benzodiazepine use in excess of 20 mg/day daily diazepam equivalent in the past 28 days
2. Known naloxone or BUP hypersensitivity
3. Pregnancy
4. Hepatic impairment (elevation of liver function tests three times normal)
5. Suicide attempt in past 12 months
6. Involvement in criminal justice system, which is likely to result in arrest and incarceration
7. Uncontrolled severe mental or physical illness judged to compromise safety
8. Mini Mental State Examination score <17 (indicating cognitive dysfunction)

OUD = opioid use disorder; UAE = United Arab Emirates; BUP = buprenorphine.

© 2021 The Authors. *Addiction* published by John Wiley & Sons Ltd on behalf of Society for the Study of Addiction.

interval, those who consumed illicit opioids by an injection (or with a body mass index of 30 and polysubstance use) commenced daily dosing. Those with prescription OUD were recommended to receive alternate-day dosing (i.e. every 48 hours). Our protocol also included the option for this patient group to attempt stabilisation with thrice-weekly dosing (to the dose maximum of 32 mg/day). Alongside patient preference, clinical signs and symptoms (using the Clinical Opiate Withdrawal Scale [COWS]) [18]; pupil reflexes (https://www.neuroptics.com) and craving using the Minnesota Cocaine Craving Scale adapted for opioids (MCCS-O; scored: 0–100%) [19] informed decisions about commencing, achieving a dosing interval or reverting to a more frequent dosing interval.

When the participant was comfortably stable on the same BUP dose for 2 weeks, we assumed BUP's steady-state concentration had been achieved. An on-site laboratory, computed the BUP elimination rate (EL.R) from three blood samples; the first drawn 30 minutes before administration of the participant's BUP dose (to estimate the BUP trough concentration), the second drawn after 40 minutes (peak concentration), and the third after 48 hours before the next BUP dose (for a second trough concentration to confirm steady-state concentration if replicated). The inpatient episode was then judged completed once the EL.R had been calculated and the participant had a COWS score of 0–4 (no active opioid withdrawal). Before transfer to the outpatient programme, a member of the study team accessed the randomisation service and the participant was allocated to the I-AAM or TAU condition.

I-AAM procedure and take-home dosing schedule

1 For the first 5 days of BUP maintenance treatment, the participant was asked to attend the clinic daily for supervised dosing and to take a UDS test at each visit (or a minimum of three UDS). If they adhered (i.e. all doses taken, at least three negative UDS and all UDS positive for BUP), participants were dispensed with two doses to take that weekend and a 7-day supply. They were given instructions on how to take their medication (i.e. daily, alternate-day and thrice weekly regimens) and asked to return to the clinic 1 week later.
2 If participants returned as directed, reported following their prescription, and gave an opioid negative UDS that was positive for BUP, they were dispensed with a 14-day supply. Participants were asked to not take their BUP dose on the day of their next appointment because this was given by the dispensing pharmacy. On arrival, they were given their dose of BUP, they took a UDS and had a blood sample drawn. A pharmacokinetic model was applied to predict BUP concentration [15]. If the UDS confirmed abstinence for opioids and was positive for BUP, the participant was given a further 14-day supply (with same directions) and asked to return to the clinic 2 weeks later.
3 On return to the clinic, the procedure was repeated and the predicted BUP concentration (estimated from the previous visit) was contrasted with the BUP concentration on the day. If the concentration difference was <20% and the UDS was negative, participants were given a 21-day supply and asked to return 3 weeks later. As a safety measure, participants given a 21-day supply were contacted randomly and asked to attend for UDS and blood testing.
4 On return to the clinic, and with evidence of continued adherence and clinical benefit (i.e. difference in BUP concentration <20%; UDS negative), participants were given a 28-day supply and asked to return 1 month later for a further monthly supply. Adherence and abstinence were then randomly monitored every other month to the endpoint.

Those not adhering to the above procedure at the outset or for the requirements of the 7-day supply were held at a 5-day supervised dosing requirement pending evidence of adherence and abstinence. Those receiving 14 days who were non-adherent or non-abstinent were 'reset' to receive a 7-day supply. Those receiving a 21-day and 28-day supply that were non-adherent or non-abstinent were reset to a 14-day or 21-day supply, respectively. At any point, a participant who was non-adherent and non-abstinent was held in a 5-day supervised dosing and UDS testing regimen. During this process, patients discussed their scores on the COWS (weeks 1–4), and MCCS-O (weeks 1–4 and 5–8), and pupil reflexes (weeks 5–8 and 13–16) and asked if they wanted their dose adjusted.

TAU procedure and take-home dosing schedule

1 In the first 5 days of maintenance, participants were asked to attend the clinic at least once for supervised BUP dosing and to take a UDS at each visit. Between visits participants were dispensed with take-home doses. If they adhered (i.e. all doses taken, all UDS-negative and all UDS-positive for BUP), they were dispensed with a 7-day supply including 1 dose to take on each day of weekend. Participants were given instructions on how to take their medication (i.e. daily, alternate-day and thrice weekly regimens) and asked to return to the clinic 1 week later.
2 If participants returned, reported following their prescription, and provided an opioid negative UDS that was positive for BUP, they were dispensed with a 14-day take-home supply.

Participants who did not adhere to the above procedure at the outset or for the requirements of the 7-day supply, were held in 5-day supervised dosing (with 2 take-home doses for the weekend) until there was evidence of abstinence.

© 2021 The Authors. *Addiction* published by John Wiley & Sons Ltd on behalf of Society for the Study of Addiction.

At any point, a participant who was non-adherent and non-abstinent was reset to 5-day supervised dosing and UDS testing. During treatment, there was discussion of withdrawal symptoms, craving and dose adequacy, as described above for the experimental group.

Table S1 summarizes the Interventions under each arm.

Outcome measures

The primary outcome was the number (percentage) of scheduled and biochemically verified (UDS and laboratory confirmed) tests negative for opioids during 16 weeks of outpatient BUP maintenance treatment. Conservatively, non-attendance for scheduled UDS was recorded as positive for opioids [20]. The secondary outcome measure was retention in outpatient treatment, defined as completion of 16 weeks of treatment (with no more than three missed consecutive clinic appointments).

The five exploratory outcome measures (end-of-study group comparison), were; The Addiction Severity Index-Lite—drug use sub-scale (ASI-Lite) [21], the nine-item Patient Health Questionnaire (PHQ-9) [22], the Generalized Anxiety Disorder scale (GAD-7) [23], the Barratt Impulsivity Scale (BIS-11) [24] and the Work and Social Adjustability Scale (WSAS; score range = 0–40; higher scores reflecting more social impairment attributed to OUD) [25]. No changes were made to the outcomes after the trial commenced.

Statistical analysis

To guide the target sample size, we used a measure of sustained (3-week) abstinence between treatment and comparison groups in a meta-analysis of incentivised OUD treatment (44% vs 23%; OR 1.96) [26]. With type I error at 5%, and a 15% increase in the sample to offset withdrawal attrition, we estimated that 182 participants (91 in each group) would give 80% statistical power for detection of a treatment effect.

The analysis was done by intention-to-treat in Stata 15 (Statacorp 2017). The primary outcome was analysed as the absolute difference in the percentage of negative UDS tests for opioids, reporting the mean and SD for each group, the mean difference on this measure with a 95% CI; and the Cohen's *d* effect size with a 95% CI.

There were two sensitivity checks: (1) an adjusted treatment effect estimated by a bootstrapped Poisson regression (incident rate ratio [IRR]) with the following covariables: age, baseline ASI-Lite drug use, and (2) time (days) to discontinuation or completion of treatment. We also calculated the primary outcome as a complete case measure using only observed (non-imputed) UDS data. The secondary outcome measure was analysed by Odds Ratio (OR) and Kaplan-Meier test. Exploratory outcomes were analysed by group mean difference at the study endpoint. The incidence of all adverse events was reported for both study groups.

RESULTS

Characteristics of the participants

The first participant was enrolled on 15 September 2014 and the last follow-up contact was on 16 September 2016. The trial database was locked on 19 January 2017. A total of 182 patients were screened for eligibility and 171 were enrolled into the study. Thirty participants (17.5%) withdrew before randomisation and 141 (82.4%) were randomised (70 [49.6%] to the I-AAM group and 71 [50.4%] to the TAU group. Figure 1 shows the study profile and reasons for exclusion. We were unable to extend the participant recruitment phase because of restrictions on the time permitted for the study.

On admission to the inpatient service, the majority of participants received daily dosing at the outset, with just four accepting our recommendation for alternate-day dosing. A single participant was inducted onto thrice-weekly dosing. The two groups were well-balanced on demographic and clinical characteristics (upper section of Table 2). After randomisation, all participants were transferred to commence BUP maintenance at the outpatient clinic. In the first week, 16 participants left treatment (six in the I-AAM group and ten in the TAU group).

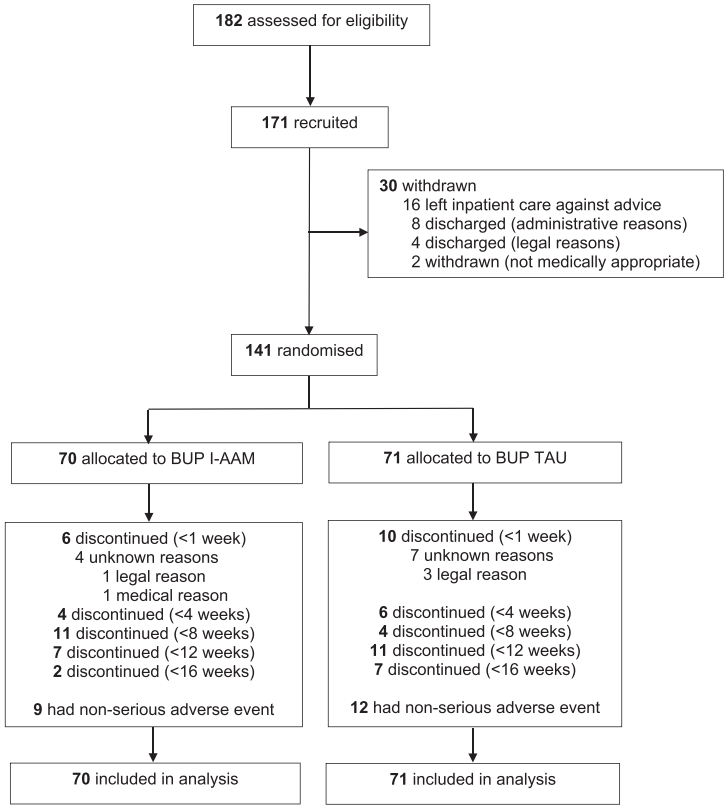
Between randomisation and the endpoint, a total of 30 (42.9%) participants in the I-AAM group and 38 (53.5%) participants in the TAU group discontinued treatment. All participants agreed to take UDS, provide blood samples, return opened BUP packaging and all consented for their data to be used for the analysis. Follow-up rates at 4 weeks, 8 weeks, 12 weeks and 16 weeks were 91.4%, 85.7%, 71.0%, and 60.0%, respectively, in the I-AAM group and 84.5%, 83.1%, 69.0% and 56.3%, respectively, in the TAU group.

BUP maintenance treatment

Table 2 (lower section) shows the mean BUP dose for the participants retained at each follow-up week and their access to take-home supplies. On average, the BUP dose was 15 mg/day in the I-AAM group and 16 mg/day in the TAU group at each follow-up. Almost all study participants remained on their stabilisation dose during maintenance (138/141; 97.9%).

Three participants increased their dose, as follows: after 3 weeks, a participant in the I-AAM group reported distressing craving and informed by measures of pupil reflexes (particularly measures of maximum pupil

© 2021 The Authors. *Addiction* published by John Wiley & Sons Ltd on behalf of Society for the Study of Addiction.



Note:

BUP I-AAM, BUP maintenance with incentivised adherence and abstinence monitoring;

BUP TAU, BUP maintenance treatment-as-usual.

Figure 1 Study profile

diameter) their dose was increased from 14–16 mg/day; a TAU participant—with a long history of tramadol use—reported opioid withdrawal symptoms in the second week of treatment and dose was increased from 12–14 mg/day; the other participant—a member of the TAU condition—had presented for treatment with severe OUD involving intravenous use of morphine and tramadol—reported craving and withdrawal symptoms during the second week of treatment and dose was increased from 12–16 mg/day.

During treatment, 18 participants in the I-AAM group (29.0%) were determined to be non-adherent to BUP and non-abstinent. All were reset to 5-day supervised dosing. Among 62 participants in the I-AAM group who received at least one 14-day supply of medication, a total of 109 blood samples were drawn with 37 samples estimated to have BUP concentrations outside the 20% range for adherence (33.9% non-adherent). In the TAU group, 20 participants (28.2%) were able to receive no more than a total of 7-day take-home doses, and 51 (71.8%) received no more than a 14-day take-home supply.

In the I-AAM group, among 62 participants who received at least 2 weeks take-home supply, 109 blood samples were drawn (mean 1.8 [SD 0.77] per participant). The non-adherence rate was 34% (i.e. 37 samples had BUP concentrations outside the 20% range). Eighteen participants in the I-AAM group (29.0%) were evaluated as BUP non-adherent and non-abstinent and were reset to 5-day directly supervised dosing.

In the TAU group, 20 participants (28.2%) received no more than 7-day take-home doses, and 51 (71.8%) received no more than 14-day take-home doses. There was no statistically significant difference in the mean number of scheduled UDS: 16.2 (SD = 9.0) in the I-AAM group versus 14.1 (SD = 8.9) in the TAU group (P value = 0.10).

During treatment, participants in both groups returned opened BUP packaging to the pharmacy very sporadically. Patients failing to return opened packaging were reminded to do so, but full compliance was rare. In the group of participants completing the 16 weeks of maintenance treatment, 1 participant in the I-AAM group was fully adherent according to TDM data and remained abstinent; 17 (42.5%) were adherent, but not abstinent. Among the non-adherent, 18 (45.0%) were also non-abstinent, and 4 (10.0%) were abstinent.

© 2021 The Authors. *Addiction* published by John Wiley & Sons Ltd on behalf of Society for the Study of Addiction.

Table 2 Participant characteristics (n = 141).

Characteristic	*I-AAM (n = 70)*	*TAU (n = 71)*
Demographic and clinical characteristics at baseline	30.4 (8.70)	27.7 (7.30)
Age, years		
Sex, male	69 (98.6%)	70 (98.6%)
Married	36 (51.4%)	46 (63.3%)
Employed, full or part-time	28 (40.0%)	21(29.6%)
Resident in metropolitan Abu Dhabi	36 (52.8%)	30 (42.2%)
Heroin/morphine OUD	55 (78.6%)	55 (77.5%)
Prescription/mixed OUD	15 (21.4%)	16 (22.5%)
Duration of OUD, median years	9.9 (5.7–17.3)	8.9 (5.4–14.7)
MCCS-O, maximum intensity in week before admission	88.6% (23.7%)	83.9% (31.5%)
ASI (drug use scale score)	0.2 (0.1–0.4)	0.2 (0.1–0.4)
PHQ-9	12.9 (6.6)	13.6 (6.9)
GAD-7	10.0 (4.0–15.0)	10.0 (5.0–15.0)
WSAS	22.1 (9.8)	24.2 (9.2)
Inpatient withdrawal and stabilisation (ng/mL)		
BUP trough concentration after 2 weeks—mean	1.73 (1.47)	1.81 (2.47)
EL.R before transfer to outpatient treatment—median	0.05 (0.03–0.09)	0.05 (0.02–0.10)
Maintenance treatment week—BUP dose (mg/day)[a]		
Week 1	14.51 (4.63)	15.71 (3.60)
Week 4	14.68 (4.58)	15.60 (3.51)
Week 8	15.08 (4.50)	15.72 (3.52)
Week 12	15.02 (4.57)	15.72 (3.58)
Week 16	14.75 (4.45)	15.36 (3.22)
Take-home supplies (total dispensing events)		
No more than 7 days	1 (1)	20 (20)
No more than 14 days	55 (402)	51 (387)
No more than 21 days	7 (81)[b]	–[d]
No more than 28 days	1 (8)[c]	–[d]

I-AAM = BUP maintenance treatment with incentivised adherence and abstinence monitoring; TAU = BUP maintenance treatment-as-usual; OUD = opioid use disorder; MCCS-O, Minnesota Cocaine Craving Scale, adapted for opioids, maximum intensity in week before admission (0–100%); PHQ-9 = Patient Health Questionnaire; GAD-7 = Generalized Anxiety Disorder; WSAS = Work and Social Adjustability Scale; ASI-Lite = Addiction Severity Index; EL.R = elimination rate (ng × mL/hr − 1). Numbers in parentheses = SD, interquartile range, or as shown. [a]All participants enrolled at follow-up. [b]Five participants were dispensed this supply once and two each received this supply twice. [c]This participant received two successive 21-day supply before the single 28-day supply. [d]Prohibited under local treatment system policy.

Table 3 Summary of scheduled and imputed urine drug screen tests and primary outcome measure (n = 141).

Measure	*I-AAM (n = 70)*	*TAU (n = 71)*
UDS testing		
A. Mean number of scheduled UDS (SD)	16.2 (9.0)	14.1 (8.9)
B. Mean number of UDS positive for opioids (SD)	1.0 (1.8)	1.9 (3.2)
C. Mean number of UDS, missed, imputed positive (SD)	2.3 (2.4)	2.2 (2.4)
Efficacy		
Primary outcome measure[a]	76.7% (25.0%)	63.5% (34.7%)
Mean difference (95% CI)	13.3% (3.2%–23.3%)	
d (95% CI)	0.44 (0.10–0.87)	

I-AAM = incentivised adherence and abstinence monitoring; TAU = treatment-as-usuale; UDS, urine drug screen. [a]Computed as A − B + C)/(A × 100) (SD).

Primary outcome

Although the obtained sample was smaller that was targeted (post-study sample size calculation using the expected effect and obtained sample size indicated that statistical power was 75%), there was a statistically significant effect for the I-AAM condition on the primary outcome (Table 3).

For the two sensitivity analyses, I-AAM effectiveness (including age, baseline ASI-Lite drug use and time to discontinuation or completion of treatment) was observed (adjusted IRR = 1.15; 95% CI = 1.02–1.32), and using

© 2021 The Authors. *Addiction* published by John Wiley & Sons Ltd on behalf of Society for the Study of Addiction.

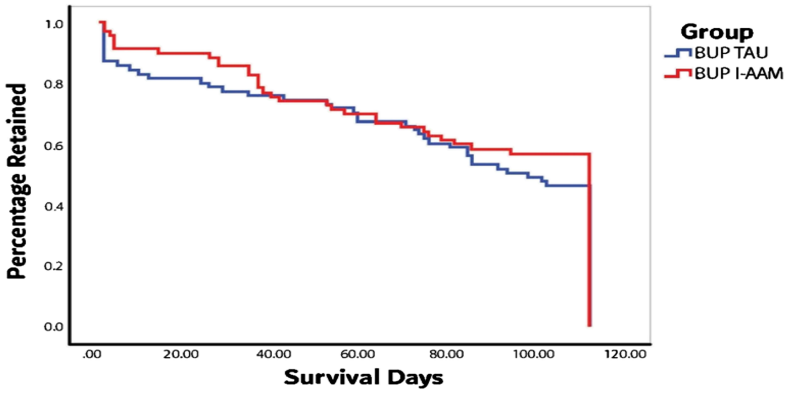


Figure 2 Survival analysis for retention over 16 weeks (log-rank *P* value = 0.26). BUP = Buprenorphine; I-AAM = incentivised adherence and abstinence monitoring; TAU = treatment-as-usual. [Colour figure can be viewed at wileyonlinelibrary.com]

observed UDS data only, the percentage of UDS negative for opioids was 90.5% (SD = 19.8%) in the I-AAM group and 71.8% (SD = 36.7) in the TAU group (mean difference 18.7%; 95% CI = 8.9–28.5; *d* = 0.63; 95% CI = 0.29–0.97). There was no statistically significant difference in the mean number of scheduled UDS tests (16.2 [SD = 9.0] in the I-AAM group versus 14.1 [SD = 8.9] in the TAU group; *P* value = 0.10).

Secondary outcome

Forty participants (57.1%) in the I-AAM group were retained continuously in maintenance treatment to the endpoint versus 33 participants (46.4%) in the TAU group (OR = 1.54; 95% CI = 0.79–2.98). The I-AAM group was retained for a mean of 81.7 days (SD = 42.3), and TAU participants were retained for a mean of 76.6 days (SD = 39.9; mean difference 5.1 days; 95% CI = −8.6–18.8). Figure 2 displays a survival chart for time-to-discontinuation by group (log rank test *P* value = 0.26).

Exploratory outcomes

End-of-study group differences on the exploratory outcome are shown in the article's supplementary material (Supporting information Table S2). There was an I-AAM effect on the WSAS indicating less social impairment associated with OUD at the endpoint (a 6-point mean difference; Cohen's *d* = 0.53; 95% CI = 0.19–0.87).

Adverse events

There were no serious adverse events requiring hospitalisation and there was a similar profile of adverse events in both groups (Supporting information Table S3). The adverse event with the highest reported incidence was sweating. This was rated severe by three participants in the I-AAM group and four participants in TAU group and judged to have a possible association with BUP.

DISCUSSION

In the I-AAM group, slightly more participants achieved dispensing of 14 days supply compared with TAU (55 vs 51). Within the I-AAM group, a minority achieved dispensing supplies above this; seven receiving dispensing of 21 days supply and one attaining maintenance dispensing of 28 days supply. In terms of the primary outcome, there was significant variability between the two groups, but we believe that the I-AAM condition was associated with a clinically important effect. There was a single exploratory outcome on the WSAS suggested that I-AAM participants had the additional benefit of fewer social problems attributed to OUD.

Although the randomisation procedure did not include any stratification, the sensitivity including patient demographic, baseline drug use and time in treatment showed an adjusted treatment effect that was statistically significant. Furthermore, comparison of the conservatively imputed versus observed primary outcome measure (13.3% vs 18.7%, respectively), suggests that true effect for I-AAM is bracketed within these two estimates. Nevertheless, there remains considerable scope to increase clinical effectiveness. Among participants in the I-AAM group who completed 16 weeks of treatment, 22 (55%) were completely adherent. This is comparable to an Australian surveillance study, where a third of patients enrolled in BUP-naloxone maintenance did not adhere and 34 (85%) of those who stayed in treatment did not abstain from opioids [27].

In the present study, I-AAM was not significantly associated with a higher rate of completion for the 16-week active treatment period or duration of enrolment (57% vs 46%). These rates are comparable with other studies of BUP maintenance. For example, in a United States dose comparison trial over 16 weeks of BUP maintenance, completion rates were 52% for patients receiving 8 mg/day, and 61% for those allocated to 16 mg/day [28]. Another United States trial of 17 weeks of maintenance treatment reported a 58% completion for patients receiving higher-doses of 16–32 mg/day [29].

© 2021 The Authors. *Addiction* published by John Wiley & Sons Ltd on behalf of Society for the Study of Addiction.

Study limitations

Our findings must be considered in the light of several limitations. First, the sample was 23% smaller than planned so the analyses had reduced statistical power by 5%. The study took longer to complete than we envisaged because of a lower rate of recruitment. During the recruitment phase there was a reduction in opioid use in the UAE and an increase in amphetamine-type stimulant use [30]. This may have reduced OUD treatment demand.

Second, the sample was almost exclusively male, with just two female participants. We had no control over the referral process, and it remains an important priority to study sex as a factor in OUD treatment delivery and outcomes [31].

Third, the BUP induction and stabilisation was done in an inpatient facility that is typically available in the healthcare systems in UAE and states in the Eastern Mediterranean, but dose induction is most commonly done in an outpatient setting elsewhere. A 24-hour medically supervised setting makes it more convenient to collect blood samples, but our discontinuation rate in this phase of the study (30/171; 17.5%) was comparable to the discontinuation rate reported for an 8-day outpatient study in Australia (14% for patients assigned to BUP for withdrawal management) [32]. We contend that where outpatient services are based in locations with reasonably good local transport options, collection of three blood samples for BUP EL.R should be acceptable to most patients.

Clinical and research importance of the findings

The I-AAM protocol included a quantitative TDM procedure (BUP plasma concentration criterion) to monitor adherence. TDM procedures to inform changes in maintenance dosing were rarely used with the majority of the group remaining on their stabilisation dose. We also found that almost all participants accepted daily dosing.

It is important to consider how the primary and secondary outcomes were defined in this study. At present, there is no common outcome set for OUD pharmacotherapy trials. It is not uncommon to define the primary outcome as a count of consecutive negative UDS. This can give valuable insight into periods of stability. This was a pragmatic and study among patients who presented for treatment as usual, so we believe our findings are generalizable. Our I-AAM protocol has promise as a clinically effect method helping patients access increasing supplies of take-home medication. Relatively few participants (8/40; 20%) were able to provide evidence of sustained adherence and abstinence to receive supplies above the comparator. Overall, participants in the I-AAM condition received 20% more take-home supplies for more or equal to 7 days (492 total dispensing events vs 407 among the TAU group).

There remains a priority need to discover better ways of encouraging patients to stay in optimised treatment. Although efforts to increase retention are crucial, it should be recognised that retention is a proxy measure of clinical benefit because some patients stay in treatment but continue to use opioids. This has been observed in other treatment systems. For example, in an English national study of 12 745 patients enrolled for 12–26 weeks in OUD maintenance pharmacotherapy, 64% reported using opioids on 10 or more days in the month before follow-up [33]. One option is to include an adjunctive psychosocial intervention targeting patients who struggle to adhere or abstain [33]. Extended-release (depot injection) BUP products are now becoming increasingly available and this may reduce concerns about diversion and provide potential opportunities to apply TDM for dose optimisation during stabilisation and dose adjustment during maintenance.

Although we had direct access to a clinical toxicology laboratory, it typically took 48 hours to process blood samples and receive test results for BUP plasma levels. This was longer than anticipated and it did hamper our efforts to make timely clinical decisions with study participants. In other areas of psychiatry, there is active research and development on non-invasive technologies such as small, portable sensing or test strips for capture of capillary blood to detect antipsychotic medication concentration [34]. Rapid point-of-care diagnostics to facilitate medication adherence monitoring during BUP treatment would be welcome. Monitoring BUP plasma concentration may be added to measures of craving, drug use and withdrawal symptoms to optimise treatment as part of measurement-based care for OUD [35].

Declarations of interests

In the past 3 years, J.M. declares research grants to King's College London (KCL) from: (i) the National Institute for Health Research (NIHR) for a multi-centre RCT of acamprosate for alcohol use disorder; (ii) the NIHR Biomedical Research Centre for Mental Health at South London and Maudsley NHS Mental Health Foundation Trust (SLaM) for a pilot RCT of novel cognitive therapy for cocaine use disorder; and (iii) an unrestricted grant from Indivior to KCL and SLaM from Indivior for a multi-centre, RCT of extended-release injectable buprenorphine for OUD. He has part-time employment as Senior Academic Advisor for the Alcohol, Drugs, Tobacco and Justice Division, Health Improvement, Public Health England. He is a clinical academic consultant for the United States National Institute on Drug Abuse, Centre for Clinical Trials Network. He holds no stocks in any company. All other authors state they have no declarations of interests.

© 2021 The Authors. *Addiction* published by John Wiley & Sons Ltd on behalf of Society for the Study of Addiction.

Acknowledgements

The authors wish to thank the patients and staff at the National Rehabilitation Centre for their participation and to the NRC director general, Dr. Hamad Al Ghaferi, for his advice and support. Work on this study was included as part of H.E.'s doctoral studies and supervisor J.M. kindly acknowledge support from the Scholarship Office at the Ministry of Presidential Affairs, United Arab Emirates.

Author contributions

Hesham Elarabi: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; software; supervision; validation; visualization. **Mansour Shawky:** Data curation; investigation. **Nael Mustafa:** Data curation; investigation; project administration; validation. **Doaa Radwan:** Data curation; investigation. **Abuelgasim Rasheed:** Conceptualization; data curation; methodology. **Ahmed Yousif Ali:** Conceptualization; methodology; project administration. **Mona Osman:** Data curation; project administration; software. **Ahmad Kashmar:** Data curation. **Helal Alkathiri:** Data curation; project administration. **Tarek Gawad:** Project administration. **Ayman Kodera:** Investigation. **Mohammed Aljeneibi:** Data curation; investigation; project administration. **Abdu Adem:** Supervision. **Amanda Lee:** Formal analysis; validation. **John Marsden:** Conceptualization; formal analysis; investigation; methodology; resources; software; supervision; validation.

References

1. Peacock A., Leung J., Larney S., Colledge S., Hickman M., Rehm J., *et al*. Global statistics on alcohol, tobacco, and illicit drug use: 2017 status report. *Addiction* 2018; **113**: 1905–26.
2. White M., Burton R., Darke S., Eastwood B., Knight J., Millar T., *et al*. Fatal opioid poisoning: a counterfactual model to estimate the preventive effect of treatment for opioid use disorder in England. *Addiction* 2015; **110**: 1321–9.
3. Mattick R., Breen C., Kimber J., Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev* 2014; **2**: 1–70.
4. O'Connor A., Cousins G., Durand L., Barry J., Boland F. Retention of patients in opioid substitution treatment: a systematic review. *PLoS ONE* 2020; **15**: e0232086; https://doi.org/10.1371/journal.pone.0232086
5. Tkacz J., Severt J., Cacciola J., Ruetsch C. Compliance with buprenorphine medication-assisted treatment and relapse to opioid use. *Am J Addict* 2012; **21**: 55–62.
6. Ajayi T. Drug misuse and dependence: UK guidelines on clinical management - Department of Health (England) and the devolved administrations, Department of Health (England), the Scottish government, welsh assembly government and Northern Ireland executive, 2007, 128 pp. *Psychiatric Bulletin* 2008; **32**: 360–360.
7. US substance Use and Mental Health Services Administration (SAMHSA), Federal Guidelines for Opioid Treatment Programs. Rockville: MD: US Department of Health and Human Services [online]. 2015. Available at: https://store.samhsa.gov/system/files/pep15-fedguideotp.pdf (Accessed on 4th of April 2020)
8. Lofwall M., Walsh S. A review of buprenorphine diversion and misuse. *J Addict Med* 2014; **8**: 315–26.
9. Schuman-Olivier Z., Connery H., Griffin M., Wyatt S., Wartenberg A., Borodovsky J., *et al*. Clinician beliefs and attitudes about buprenorphine/naloxone diversion. *Am J Addict* 2013; **22**: 574–80.
10. Griffith J., Rowan-Szal G., Roark R., Simpson D. Contingency management in outpatient methadone treatment: a meta-analysis. *Drug Alcohol Depend* 2000; **58**: 55–66.
11. Gerra G., Saenz E., Busse A., Maremmani I., Ciccocioppo R., Zaimovic A., *et al*. Supervised daily consumption, contingent take-home incentive and non-contingent take-home in methadone maintenance. *Prog Neuropsychopharmacol Biol Psychiatry* 2011; **35**: 483–9.
12. Saulle R., Vecchi S., Gowing L. Supervised dosing with a long-acting opioid medication in the management of opioid dependence. *Cochrane Database Syst Rev* 2017; **4**(4): 1–39.
13. Hiemke C., Bergemann N., Clement H., Conca A., Deckert J., Domschke K., *et al*. Consensus guidelines for therapeutic drug monitoring in Neuropsychopharmacology: update 2017. *Pharmacopsychiatry* 2018; **51**: 9–62. https://doi.org/10.1055/s-0043-116492
14. Wolff K., Strang J. Therapeutic drug monitoring for methadone: scanning the horizon. *Eur Addict Res* 1999; **5**: 36–42; https://doi.org/10.1159/000018961
15. Elarabi H., Hasan N., Marsden J., Radwan D., Adem A., Almamari S., *et al*. Therapeutic drug monitoring in buprenorphine/naloxone treatment for opioid use disorder: clinical feasibility and optimizing assay precision. *Pharmacopsychiatry* 2020; **53**: 115–21. https://doi.org/10.1055/a-1083—6842
16. Elarabi H., Alrasheed A., Ali A., Shawky M., Hasan N., Gawad T. A., *et al*. Suboxone treatment and recovery trial (STAR-T): study protocol for a randomised controlled trial of opioid medication assisted treatment with adjunctive medication management using therapeutic drug monitoring and contingency management. *J Addict* 2019. https://doi.org/10.1155/2019/2491063; **2019**: 1–11.
17. Schulz K., Altman D., Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010; **8**: 18–27.
18. Wesson D., Ling W. The clinical opiate withdrawal scale (COWS). *J Psychoactive Drugs* 2003; **35**: 253–9.
19. Halikas J. A., Kuhn K. L., Crosby R., Carlson G., Crea F. The measurement of craving in cocaine patients using the Minnesota cocaine craving scale. *Compr Psychiatry* 1991; **32**: 22–7.
20. McPherson S., Barbosa-Leiker C., Burns G., Howell D., Roll J. Missing data in substance abuse treatment research: current methods and modern approaches. *Exp Clin Psychopharmacol* 2012; **20**: 243–50.
21. Cacciola J., Alterman A., McLellan A., Lin Y., Lynch K. Initial evidence for the reliability and validity of a "lite" version of the addiction severity index. *Drug Alcohol Depend* 2007; **87**: 297–302.
22. Kroenke K., Spitzer R., Williams J. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001; **16**: 606–13.

© 2021 The Authors. *Addiction* published by John Wiley & Sons Ltd on behalf of Society for the Study of Addiction.

23. Spitzer R., Kroenke K., Williams J., Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med* 2006; **166**: 1092–7.
24. Patton J. H., Stanford M. S., Barratt E. S. Factor structure of the Barratt impulsiveness scale. *J Clin Psychol* 1995; **51**: 768–74.
25. Mundt J. C., Marks I. M., Shear M. K., Greist J. H. The work and social adjustment scale: a simple measure of impairment in functioning. *Br J Psychiatry* 2002; **180**: 461–4.
26. NICE. Drug misuse in over 16s: psychosocial interventions [online]. 2007. Available at: psychosocial-interventions-2007-nice-guideline-cg51–2555119693/chapter/surveillance-decision. (accessed 17 May 2020).
27. Larance B., Degenhardt L., Lintzeris N., Bell J., Winstock A., Dietze P., *et al*. Post-marketing surveillance of buprenorphine-naloxone in Australia: diversion, injection and adherence with supervised dosing. *Drug Alcohol Depend* 2011; **118**: 265–73.
28. Ling W., Charuvastra C., Collins J., Batki S., Brown L., Kintaudi P., *et al*. Buprenorphine maintenance treatment of opiate dependence: a multicenter, randomized clinical trial. *Addiction* 1998; **93**: 475–86.
29. Johnson R., Chutuape M., Strain E., Walsh S., Stitzer M., Bigelow G. A comparison of Levomethadyl acetate, buprenorphine, and methadone for opioid dependence. *N Engl J Med* 2000; **343**: 1290–7.
30. Al Ghaferi H., Ali A., Gawad T., Wanigaratne S. Developing substance misuse services in United Arab Emirates: the National Rehabilitation Centre experience. *BJPsych Int* 2017; **14**: 92–6.
31. Jones H., Fitzgerald H., Johnson R. Males and females differ in response to opioid agonist medications. *Am J Addict* 2005; **14**: 223–33.
32. Lintzeris N., Bell J., Bammer G., Jolley D. J., Rushworth L. A randomized controlled trial of buprenorphine in the management of short-term ambulatory heroin withdrawal. *Addiction* 2002; **97**: 1395–404.
33. Marsden J., Eastwood B., Bradbury C., Dale-Perera A., Farrell M., Hammond P., *et al*. Effectiveness of community treatments for heroin and crack cocaine addiction in England: a prospective, in-treatment cohort study. *Lancet* 2009; **374**: 1262–70.
34. Kalaria S., Kelly D. Development of point-of-care testing devices to improve clozapine prescribing habits and patient outcomes. *Neuropsychiatr Dis Treat* 2019; **15**: 2365–70. https://doi.org/10.2147/NDT.S216803
35. Marsden J., Tai B., Ali R., Hu L., Rush A., Volkow N. Measurement-based care using DSM-5 for opioid use disorder: can we make opioid medication treatment more effective? *Addiction* 2019; **114**: 1346–53.

Supporting Information

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

Table S1: Summary of study procedures by arm
Table S2: Exploratory outcomes at study endpoint by group (n = 141)
Table S3: Adverse events during BUP maintenance treatment over 16-weeks by severity likelihood of association and group (n = 141).

© 2021 The Authors. *Addiction* published by John Wiley & Sons Ltd on behalf of Society for the Study of Addiction.