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Maintenance treatment for opioid dependence with slow-release oral morphine: a randomized cross-over, non-inferiority study versus methadone

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ABSTRACT

Aims To compare the efficacy of slow-release oral morphine (SROM) and methadone as maintenance medication for opioid dependence in patients previously treated with methadone. **Design** Prospective, multiple-dose, open label, randomized, non-inferiority, cross-over study over two 11-week periods. Methadone treatment was switched to SROM with flexible dosing and vice versa according to period and sequence of treatment. **Setting** Fourteen out-patient addiction treatment centres in Switzerland and Germany. **Participants** Adults with opioid dependence in methadone maintenance programmes (dose ≥50 mg/day) for ≥26 weeks. **Measurements** The efficacy end-point was the proportion of heroin-positive urine samples per patient and period of treatment. Each week, two urine samples were collected, randomly selected and analysed for 6-monoacetyl-morphine and 6-acetylcodeine. Non-inferiority was concluded if the two-sided 95% confidence interval (CI) in the difference of proportions of positive urine samples was below the predefined boundary of 10%. **Findings** One hundred and fifty-seven patients fulfilled criteria to form the per protocol population. The proportion of heroin-positive urine samples under SROM treatment (0.20) was non-inferior to the proportion under methadone treatment (0.15) (least-squares mean difference 0.05; 95% CI = 0.02, 0.08; $P > 0.01$). The 95% CI fell within the 10% non-inferiority margin, confirming the non-inferiority of SROM to methadone. A dose-dependent effect was shown for SROM (i.e. decreasing proportions of heroin-positive urine samples with increasing SROM doses). Retention in treatment showed no significant differences between treatments (period 1/period 2: SROM: 88.7%/82.1%, methadone: 91.1%/88.0%; period 1: $P = 0.50$, period 2: $P = 0.19$). Overall, safety outcomes were similar between the two groups. **Conclusions** Slow-release oral morphine appears to be at least as effective as methadone in treating people with opioid use disorder.

Keywords Dose–response, maintenance treatment, methadone, opioid addiction, retention rate, slow-release oral morphine.

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INTRODUCTION

Medication-assisted maintenance treatment with psychosocial support is suggested to stabilize opioid-dependent patients [1,2]. All substances with significant agonistic activity at opioid-μ-receptors, i.e. methadone, buprenorphine, codeine, diacetylmorphine and morphine, are appropriate for opioid maintenance treatment (OMT) [3], although methadone is the accepted gold standard, with established effectiveness [4]. However, methadone is limited by side effects influencing compliance, resulting in inadequate treatment retention [5,6]. A diversity of OMTs, including diacetylmorphine and morphine, is required to reach individual treatment goals [7–9]. Morphine acts as a pure agonist on opioid receptors; its mode of action differs from that of methadone and buprenorphine [10,11]. However, its inherently short elimination half-life limits its practical use regarding dispensing treatment to patients, and has resulted in the development of methadone as an

alternative [12]. Slow-release preparations of morphine that result in sustained blood concentrations for 24 hours after once-daily oral administration therefore represent an advantage over traditional morphine [13,14].

The clinical utility of slow-release oral morphine (SROM) for opioid dependence has been reported previously, and may be associated with reduced opioid craving and improved tolerability versus methadone [15–20]. However, only one of these studies was a randomized cross-over trial [18]. Advantages of SROM in patients intolerant to methadone or with inadequate withdrawal suppression [21] and those intolerant to supplementary methadone [22] have been reported. Only one study has not demonstrated any advantage of SROM over methadone [23]. The other available data are based mainly on trials in which patients were not randomized or without control, so robust evidence for the clinical utility of SROM in treating opioid dependence is lacking [24].

The objective of this study was to validate the effectiveness of SROM in opioid-dependent patients treated previously with methadone in a randomized cross-over design, aiming to show non-inferiority of SROM over methadone with flexible dosing. A non-inferiority margin of 10% was set because differences between SROM and methadone treatment were expected to be relatively small [18,25]. A cross-over design was selected, as patients to be included were already under methadone treatment and thus in a stable condition. Further, this design, rather than a parallel group design, allows repeated measurements for each patient during two treatment periods, minimizes confounding covariates and allows for higher statistical power with fewer patients [26,27]. Two endpoints were taken into account: (i) weekly urinalyses for co-consumption of heroin in the same patient independent of treatment and (ii) in-treatment retention for each treatment period.

METHODS

Patient population

Patients were recruited between July 2007 and August 2010 at four out-patient treatment centres in Switzerland and 10 in Germany. All patients with a diagnosis of opioid-dependence according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, text revision (DSM-IV 4.9) were eligible. Independent adults (age ≥18 years) participating in a methadone maintenance programme for ≥26 weeks with a permanent residence were eligible for inclusion. Other inclusion criteria were: methadone dose of ≥50 mg/day at time of inclusion, capability to act responsibly and no intention of dose reductions aiming for abstinence during the trial. Women were required to have a negative urine pregnancy test prior to initial dose of study medication and every 4 weeks during the study and, if of child-bearing potential, were required to use hormonal contraception. Patients were excluded if they had acute somatic illnesses or other clinically significant somatic disorders, serious unstable mental health problems, known contraindications for opioids, pending imprisonment at the time of inclusion, baseline QTc-interval >450 msec or long QT-syndrome or were pregnant/breastfeeding. Treatment-naive patients or patients unsatisfied with pre-treatment due to insufficient control of drug-seeking and/or tolerability were also excluded.

The protocol and informed consent forms were reviewed and approved by the national and regional ethics committees and national health authorities competent for the respective trial sites. The study was conducted according to the Declaration of Helsinki, the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice, the European Union Clinical Trials Directive 2001/20/EC and relevant national narcotics laws.

Study design

This was a multiple-dose, open-label, randomized, cross-over, non-inferiority study. At study entry, patients were randomized to receive one of two sequences of treatment with methadone oral solution or SROM for 11 weeks per period. To minimize the potential for withdrawal symptoms, there was no wash-out period. Instead, each period consisted of a 1-week adjustment phase followed by a 10-week treatment phase with the study drug. During the 10-week treatment phase, flexible dosing was permitted depending on a patient's individual needs. The total duration was 47 weeks: 22 weeks with a two-way cross-over followed by 25 weeks of extension with SROM treatment. This publication reports the findings from the cross-over phase. Results from the extension phase will be submitted for separate publication.

Assignment to treatment was printed onto individualized case report forms (CRFs) per patient and site and used by increasing order of patient number per site. Selection for a sequence-group was determined by a computer-generated randomization list with a 1:1 ratio of test and reference treatment and permuted blocks of six without stratification factors (SPSS version 15.0.1.; SPSS, Inc., Chicago, IL, USA). The randomization sequence was checked based on the day of randomization.

SROM was provided as capsules (Bard Pharmaceuticals, Cambridge, UK; Mundipharma Gesellschaft m.b.H., Vienna, Austria); daily doses were prepared using the appropriate number of capsules containing 60, 120 or 200 mg morphine sulphate. Methadone solution was provided in Switzerland as 1% solution (Amino AG,

Neuenhof, Switzerland) and in Germany as 0.5% solution (Eptadone oral solution; Molteni Farmaceutici, Scandicci, Italy). Methadone oral solution and SROM capsules were administered orally once daily. Methadone was switched to SROM in a ratio of 1:6–1:8 of the previous methadone dose. SROM was switched to methadone in a ratio of 8:1–6:1 of the previous SROM dose. During treatment phases, supervised intake of study medication was scheduled for at least 3 days per week.

Study assessments

The primary efficacy end-point was the proportion of positive urine samples per patient and per treatment for co-consumption of heroin. Weekly urine samples were collected. To fulfil criteria for random urine sampling, based on a Mersenne Twister random number generator taking into account the take-home schedule for each week (statistical package SPSS version 15.0.1), each CRF contained a pre-defined schedule indicating the 2 working days per week on which urine samples had to be collected and shipped for analysis. Each trial site used a different random number seed [28]. Staff members at the trial sites were not permitted to disclose the schedule of urine sampling to patients.

Urine samples were analysed by a central laboratory (University Hospital Basel, Switzerland) under blinded conditions for 6-monoacetyl-morphine (6-MAM) and 6-acetylcodeine (6-A-cod), using liquid chromatography–mass spectrometry (LCMS) [29]. A urine sample was deemed positive if the 6-MAM and/or 6-A-cod concentrations exceeded 10 ng/ml. For each patient the extent of heroin use was defined as proportions and calculated by dividing the number of the patient's heroin-positive urine samples by the number of their weekly urine samples selected for urinalysis per cross-over period. Urine samples were also analysed semiquantitatively by immunoassay (CEDIA® and DRI®; Thermo Fisher Scientific Inc., Fremont, CA, USA) for benzodiazepines, cannabinoids, cocaine and adulterations. Further, the extent of self-reported use of heroin, cocaine, alcohol, cannabis and benzodiazepines per period was assessed by calculating the average number of days of reported consumption during the cross-over period. Patients received a weekly monetary compensation of €15 for providing urine samples, and were assured that the results of their urinalyses had no adverse consequences. Safety during the study was monitored by recording all adverse events (AEs) as well as by periodic evaluation of vital signs and physical examinations.

Statistical methods

This was a non-inferiority trial, assuming that the extent of heroin use based on urinalyses would not differ between maintenance treatment with SROM or methadone. Non-inferiority was concluded if the two-sided 95% confidence intervals (CI) were below a 10% non-inferiority margin in the per protocol (PP) population. In order to secure the highest possible quality of data, stringent criteria were set for the PP population, and included only those patients who completed each of the two cross-over treatment periods (11 weeks) within a specified time-frame of ≥70 days and ≤84 days, who had urinalyses for ≥9 of 11 weeks per cross-over period and no discontinuation of study medication for more than 5 consecutive days. For each cross-over period, the mean [least-square (LS) mean] and 95% CI of individual proportions of heroin-positive urine samples were calculated. Considering the cross-over design, the primary analysis was performed by analysis of variance (ANOVA) with fixed factors for treatment, period, sequence and subject nested within sequence. However, in this analysis, including the sequence effect allows only a limited assessment of the carry-over effect. Therefore, the extent of an unequal carry-over effect for each treatment was tested by adding the proportion of heroin-positive urine samples of both periods for each patient and comparing those by a two-sample *t*-test (Welch *t*-test). To confirm the robustness of non-inferiority, analyses were also performed on the results from the intent-to-treat (ITT) population [27,30]. Dose effects were analysed (LS mean) by considering quartiles of average daily doses of treatment and the corresponding proportions of heroin-positive urine samples.

The sample size was calculated based on testing for non-inferiority within a cross-over design. Sixty-four PP patients per sequence (a total of 128 PP patients) were required to conclude, with a power of 80% and a one-sided significance level of 2.5%, that SROM is non-inferior to methadone (pre-specified non-inferiority margin of 10%) determined by the proportion of heroin-positive urine samples per patient. Assuming that up to 40% of patients would not be eligible for the PP population, the necessary sample size to achieve the power of 80% was calculated to be 215 patients (SAS®, version 9.1.3; SAS Institute, Cary, NC, USA).

The incidence, severity and relationship to study drug of adverse events (AEs) was reported for each treatment. *P*-values were calculated from a logistic regression model (with treatment as fixed factor) using generalized estimating equations (GEE).

RESULTS

Two hundred and seventy-six patients were enrolled; 141 (51.1%) were randomized to the treatment sequence morphine/methadone (group 1) and 135 (48.9%) to the treatment sequence methadone/morphine (group 2)

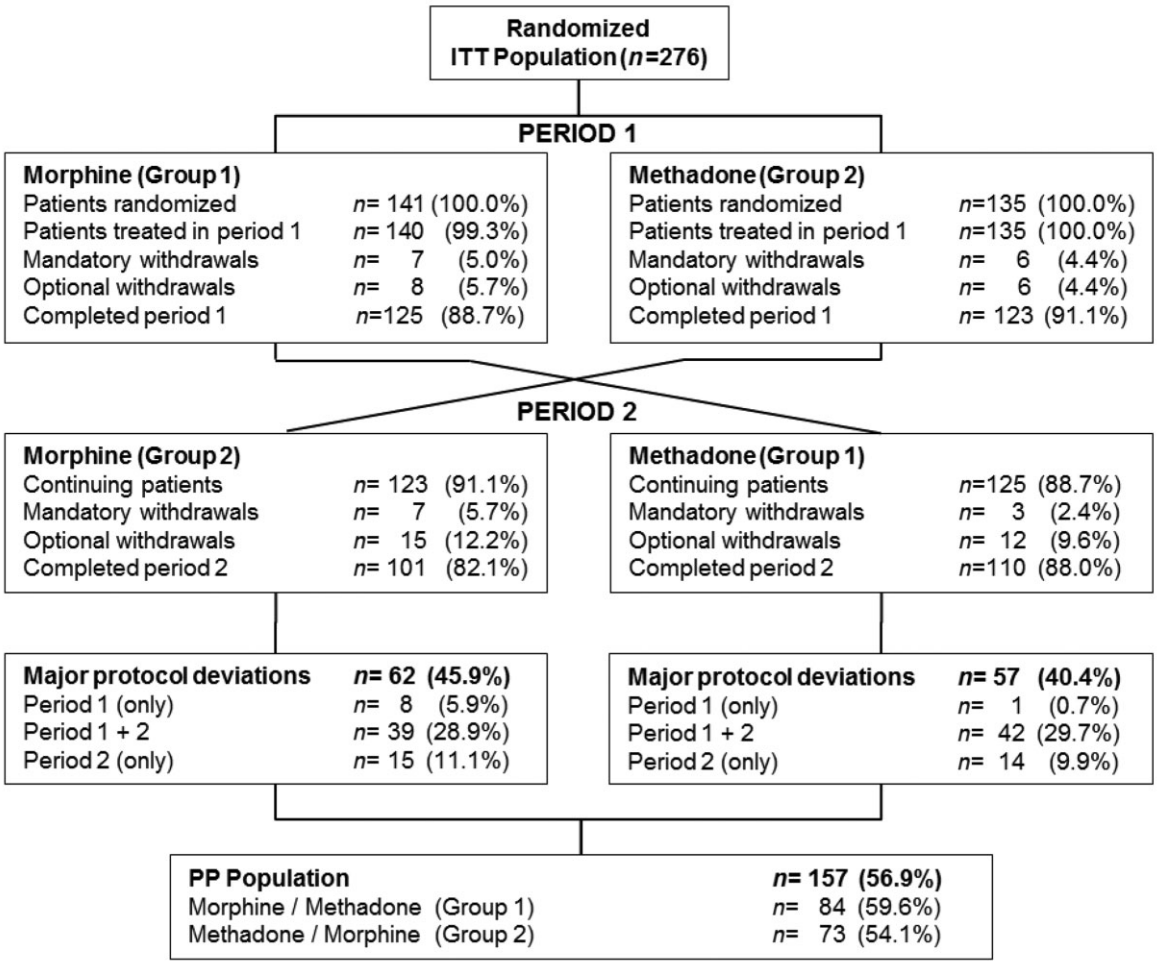

Figure 1 Randomization of patients and treatment completion per period

(ITT population). The 22-week cross-over phase was completed by 110 patients (78.0%) in group 1 and 101 patients (74.8%) in group 2 ($P = 0.5312$, χ^2 test) (Fig. 1). Retention in treatment was high under both treatments between periods and sequences: SROM 88.7% (group 1, period 1; 95% CI = 82.2%, 93.4%; $n = 125/141$) and 82.1% (group 2, period 2; 95% CI = 84.2%, 88.4%; $n = 101/123$); methadone 91.1% (group 2, period 1; 95% CI = 85.0%, 95.3%; $n = 123/135$) and 88.0% (group 1, period 2; 95% CI = 81.0%, 93.4%; $n = 110/125$). Differences per period were similar (period 1: χ^2 test, $P = 0.4989$, period 2: χ^2 test, $P = 0.1933$). In the ITT population women had a lower retention in treatment than men ($P = 0.0350$); there was no association between psychiatric comorbidities and retention in treatment ($P = 0.0644$).

Owing to the narrow criteria for assessing the PP population, a substantial number of patients had to be excluded from the statistical analyses [group 1: $n = 57$ (40.4%); group 2: $n = 62$ (45.9%)], due mainly to failing to comply with the 11-week duration of each cross-over period and/or failing to deliver the required number of samples for urinalyses (there were no statistically significant differences between periods and treatments with regard to exclusion of patients from the analyses). There were no differences in baseline characteristics between the PP and ITT populations (Table 1) or between patients in groups 1 and group 2.

Treatment duration in the cross-over phase was 76.8 ± 1.2 days per period for the PP population without any significant differences between sequences or periods. The mean SROM dose was 791 ± 233 mg/day, that of methadone 103 ± 30 mg/day. Methadone doses were converted to SROM at a mean ratio of 1:7.7 ± 1.3 and SROM doses to methadone at a mean ratio of 7.5 ± 2.4:1. Treatment switch was not associated with signs of overdose or opioid withdrawal in any patient. Only a few (approximately 10%) patients required dose adaptations during cross-over, primarily when treatment was switched from methadone to SROM. Patients self-administered medication on average 2.14–2.33 times per week (without any significant differences

Table 1 Baseline characteristics of patients.

	ITT population n = 276	*PP population n = 157*
Gender		
Male	225 (81.5%)	132 (84.1%)
Female	51 (18.5%)	25 (15.9%)
Age[a]	38.1 ± 7.6 (38.00)	38.9 ± 7.4 (39.00)
Body mass index (calculated)[a]	25.2 ± 4.38 (24.5)	24.77 ± 4.16 (24.3)
Civil status: single	206 (74.6%)	122 (77.7%)
Employment status: full-time job ≥70%	36 (13.0%)	12 (7.6%)
Years of prior maintenance treatment[a]	3.85 ± 4.43 (2.00)	3.58 ± 4.40 (2.00)
Pretreatment: last dose of methadone (mg/day)[a]	98.03 ± 39.95 (90.00)	92.03 ± 30.78 (90.00)
Addiction history		
EuropASI—alcohol[a]	0.12 ± 0.17 (0.03)	0.12 ± 0.18 (0.02)
EuropASI—drugs (modified)[a]	0.31 ± 0.14 (0.31)	0.31 ± 0.15 (0.31)
Age at first heroin consumption[a]	20.26 ± 5.11 (19.00)	20.53 ± 5.08 (19.00)
Patients with ongoing somatic comorbidity	218 (79.0%)	132 (84.1%)
Number of ongoing somatic comorbidities per patient	2.88 ± 1.97	2.84 ± 1.75
HIV—positive	10 (3.6%)	7 (4.5%)
Syphilis—positive	1 (0.4%)	1 (0.6%)
Hepatitis B virus—positive	140 (57.4%)	71 (51.1%)
Hepatitis C virus—positive	158 (57.7%)	105 (67.3%)
Patients with ongoing psychiatric comorbidity	191 (69.2%)	90 (57.3%)
Number of ongoing psychiatric comorbidities per patient	2.19 ± 1.20	1.82 ± 0.98
Number of comedications per patient	3.80 ± 3.52	3.98 ± 3.46

EuropASI = European Addiction Severity Index; PP = per protocol; ITT = intention-to-treat. [a]Mean ± standard deviation (median).

regarding sequences or periods). Adherence to random urine sampling criteria was very high in each sequence and period of treatment (Table 2). Fewer than 1% of urine samples were not collected, not shipped or refused to be given by the patient; 1.1% of samples were rated as manipulated.

In the PP population, the proportion of heroin-positive urine samples under SROM was 0.2020 (95% CI = 0.1811, 0.2229) versus 0.1508 (95% CI = 0.1299, 0.1716) under methadone. Although the difference between treatments was statistically significant (0.0513; 95% CI = 0.0217, 0.0808; $P = 0.0008$), it was within the pre-specified non-inferiority margin of 10%. Thus, non-inferiority of SROM was confirmed. However, the period effect ($P = 0.0389$) and sequence effect ($P = 0.0201$) reached statistical significance. This was due to a somewhat higher (0.24 ± 0.27) but statistically significant proportion of heroin-positive urine samples from patients in group 1 and period 1 versus patients in group 2 and period 1 (10.15 ± 0.24; $P = 0.0352$); no significant differences were found in period 2 (group 1: 0.15 ± 0.23, group 2: 0.17 ± 0.25; $P = 0.6734$). Despite these differences in period 1, the test for a possible unequal carry-over effect was not significant ($P = 0.3397$) (Table 2). A tendency for a treatment centre effect was observed (effect of centre: $P = 0.0800$; interaction term of centre and treatment: $P = 0.0743$). The treatment differences of SROM versus methadone between centres were –0.0489 to 0.1709. No interaction between number of days with take-home medication and proportion of heroin-positive urine samples was found (SROM: $P = 0.0657$; methadone: $P = 0.8519$). No notable difference between the proportion of heroin-positive urine samples regarding the number of patients recruited at the centres was observed. There was no association between the proportion of heroin-positive urine samples and treatment in period 1 with respect to dose ratios after treatment switch from methadone to SROM.

Non-inferiority of SROM was also confirmed in the ITT population. The proportion of heroin-positive urine samples in patients receiving SROM was 0.2564 (95% CI = 0.2330, 0.2799) versus 0.2584 (95% CI = 0.2344, 0.2823) for methadone, a treatment difference of –0.0019 (95% CI = –0.0355, 0.0316; $P = 0.9104$). The effect of the periods was significant ($P = 0.0293$), but effects for sequence ($P = 0.1610$) and carry-over ($P = 0.5152$) were not (Table 2).

A significant ($P = 0.0003$) dose effect was observed with both treatments: the proportion of heroin-positive urine samples decreased with increasing doses (Fig. 2). Quartiles of average SROM doses correlated inversely

Table 2 Collection of urine samples and results of urinalysis.

	ITT population (n = 276)	*PP population (n = 157)*
Number of visits	5265	3454
% weeks with two randomly taken urine samples	73.2	93.9
Total number of assessable urine samples for heroin	4707 (100.0%)	3451 (100.0%)
Number of missing/not analysed urine samples for heroin	558 (11.9%)	3 (0.1%)
Number of urine samples set positive for heroin[a]	257 (5.5%)	62 (1.8%)
Number of urine samples testing heroin-positive	837 (17.8%)	553 (16.0%)
Number of urine samples testing heroin-negative	3613 (76.8%)	2836 (82.2%)
Use of heroin		
Proportion of heroin-positive urine samples per patient under morphine	0.2564 (95% CI = 0.2330, 0.2799)	0.2020 (95% CI = 0.1811, 0.2229)
Proportion of heroin-positive urine samples per patient under methadone	0.2584 (95% CI = 0.2344, 0.2823)	0.1508 (95% CI = 0.1299, 0.1716)
Difference between morphine and methadone	–0.0019 (95% CI = –0.0355, 0.0316) ($P = 0.9104$)	0.0513 (95% CI = 0.0217, 0.0808) ($P = 0.0008$)
Sequence	$P = 0.1610$	$P = 0.0201$
Period	$P = 0.0293$	$P = 0.0389$
Carry-over effect	$P = 0.5152$	$P = 0.3397$

[a]Criteria for setting a sample positive for opioids (heroin): urine sample not collected, urine sample refused by patient, urine sample manipulated. PP = per protocol; ITT = intention-to-treat; CI = confidence interval.

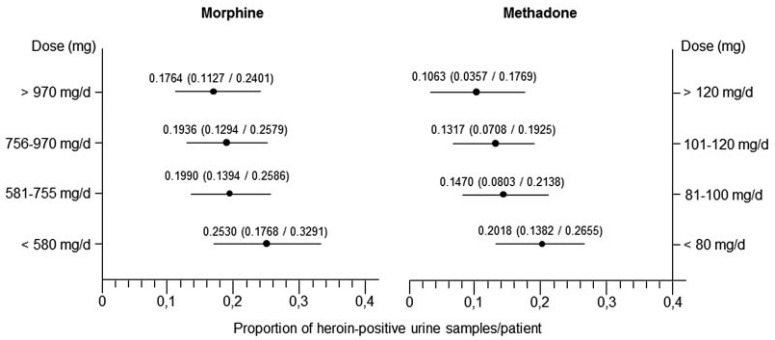

Figure 2 Dose–response: correlation of the proportion of heroin-positive urine samples and quartiles of mean daily doses (data presented as least-square means and corresponding 95% confidence interval (CI), per protocol (PP) population, $n = 157$)

with the number of urine samples testing positive for 6-MAM (Pearson's correlation coefficient: –0.1941; $P = 0.0149$) and 6-A-cod (Pearson's correlation coefficient: –0.1709; $P = 0.0323$). Similar effects were confirmed for methadone: an inverse correlation was found between quartiles of average daily methadone doses with urine samples tested positive for 6-MAM (Pearson's correlation coefficient –0.2225; $P = 0.0051$) and 6-A-cod (Pearson's correlation coefficient: –0.1868; $P = 0.0192$). The magnitude of dose effect was 0.49 for SROM and 0.71 for methadone (Cohen's *d*, comparing the first and the fourth dose quartiles of the PP population).

In the PP population 12 (8%) patients received prescribed benzodiazepines, but 75 (47.7%) patients used non-prescribed benzodiazepines in both cross-over periods, according to urinalyses. No differences between period and sequences of treatment were found for the number of patients and the extent of co-consumed benzodiazepines (proportion of benzodiazepine-positive urine samples: SROM 0.32 ± 0.41; methadone 0.35 ± 0.42; $P = 0.0642$). No significant differences between treatments were observed in the self-reported use (proportion of days with use per period) of heroin, cocaine or benzodiazepines. In addition, the proportions of urine samples that were positive for cannabis, cocaine or benzodiazepines were not significantly different between treatments. Self-reported cocaine and benzodiazepines use correlated strongly with urinalysis results. However, self-reported use of heroin was lower than the proportion of positive urine samples (Table 3).

Overall, safety profiles of SROM and methadone by ICH criteria were similar (Table 4), with no statistical differences between treatments in incidence of AEs, their severity or causality. One patient died under methadone treatment due to intentional multiple drug overdose. The detailed safety outcomes, considering preferred terms as stated by investigators from this study, will be submitted for separate publication.

Table 3 Individual proportion of positive urine samples and self-reported use of heroin, cocaine and benzodiazepines per treatment [per protocol (PP) population; $n = 157$].

	Proportion of positive urine samples		*Proportion of self-report*			
Variable	*Methadone*	*Morphine*	*Methadone*	*Morphine*	*Pearson correlation coefficient*	*P-value*
Heroin	0.15 ± 0.23	0.20 ± 0.26	0.08 ± 0.15	0.08 ± 0.15	0.4465	<0.0001
Cocaine	0.13 ± 0.27	0.15 ± 0.27	0.03 ± 0.10	0.03 ± 0.08	0.7716	<0.0001
Benzodiazepines	0.39 ± 0.43	0.36 ± 0.42	0.10 ± 0.21	0.11 ± 0.23	0.5745	<0.0001

Table 4 Summary of safety data [intention-to-treat (ITT) population].

	Morphine (n = 262)	*Methadone (n = 260)*	*P-value*
Patients with at least one AE [*n* (%)]	212 (81%)	205 (79%)	0.6172
Number of AEs	879	830	
Patients with at least one related AE [*n* (%)]	154 (59%)	147 (57%)	0.5979
Number of related AEs	534	467	
Patients with at least one serious AE [*n* (%)]	8 (3%)	11 (4%)	0.1175
Number of serious AEs	13	21	
Patients with at least one related serious AE [*n* (%)]	1 (0%)	2 (1%)	0.3191
Number of related serious AEs	1	5	
Patients who died [*n* (%)]	0 (0%)	1 (0%)	NA

AE = adverse event; NA = not applicable.

DISCUSSION

This is the first confirmatory clinical trial comparing SROM and methadone as adequate OMT in a 'real-world' situation. The non-inferiority of SROM to methadone regarding illicit heroin use and concomitant drug consumption was shown in this robustly designed trial using an established comparator and outcomes relevant to maintenance out-patient treatment under daily practice conditions [4,31]. The proportion of heroin-positive urine samples per patient was selected as the efficacy-related end-point because the use of heroin was expected to be more relevant in a cross-over study than an outcome of retention in treatment. Regarding urinalyses, two aspects were considered: (i) urine samples were collected and selected for analysis according to a two-way randomization procedure depending on relevant regulations for take-home medication; and (ii) urine samples were analysed by LCMS, a more sensitive method than immunoassay [32,33]. The effect on retention rate was estimated to be relatively modest in clinically stable patients with ≥26 weeks of ongoing methadone maintenance treatment. Other efficacy results will be submitted for subsequent publication.

Stringent criteria were set for the PP population to enhance the quality of individual data for statistical analyses. Equal duration of treatment periods and equal numbers of urine samples taken during cross-over were selected as the main criteria for a patient's inclusion in the PP population. The statistical analysis was based on a pre-defined non-inferiority margin of 10%, a strict margin for clinical trials in patients with multiple morbidities [34–38]. Although a 5% difference in the proportion of heroin-positive urine samples in favour of methadone was found, the 95% CI were within the 10% non-inferiority margin.

The impact of the observed sequence regarding the proportion of heroin-positive urine samples in period 1 and group 1 in the PP population cannot be explained on clinical grounds, especially as there were no differences between groups at baseline, or centre or treatment interactions. A carry-over effect can definitively be excluded, and no differences between treatments were found when analysing the proportion of heroin-positive urine samples from the ITT population, confirming the robustness of the results.

Furthermore, retention in treatment was high and without any differences between periods or sequences of treatment. In addition, a dose effect was shown for SROM as well as for methadone in terms of decreasing proportions of heroin-positive urine samples with increasing doses. This is in full agreement with a parallel group methadone dose–response study [39]. This study also confirms that SROM has the same general safety profile as methadone.

Limitations

Although a possible limitation, the cross-over design with no wash-out period was considered appropriate. A double-blind, double-dummy design was deemed inappropriate for two reasons. Retention rates in studies comparing methadone and buprenorphine with flexible dosing are identical, independent of open or double-blind methods [25]. The intrinsic pharmacological differences of morphine and methadone mean that patients are experienced in perceiving specific drug effects, either from prior illicit consumption or from previous maintenance treatment, so that blinding of study medications would not have a meaningful impact on the overall results of a study of OMT [40–42]. Included patients were assumed to be stable (average maintenance for more than 3 years and 90 mg dose of methadone/day at baseline), further justifying the cross-over design [26,43]. An actual wash-out period with no treatment would have been inappropriate for this study, as any interruption of OMT would have led to withdrawal symptoms. The chosen design also allowed repeated measurements in individual patients under different treatments.

Although not assessed specifically in this study, misuse of opioid substitution medicines is of general concern [44]. According to a recent review of published literature on methadone and buprenorphine, motives for, as well as the extent of, misuse depend largely upon the individual's symptom control and treatment status [45]. However, the incidence of misuse varies significantly on a regional geographic basis, and is influenced by prescribing regulations and treating-physicians' specific preferences for a particular medicine. Regarding misuse of SROM, no clear definite conclusions can be drawn from data published to date, despite licensing for OST in some European countries. In a recent survey, levels of misuse ranged from 5 to 51% across 10 European countries [46]; the greatest misuse was observed in Austria (49%) and Denmark (51%), where the main medications are SROM and methadone, respectively. However, no single risk factor for misuse was identified in the survey and one or several factors may have contributed, including, but not limited to, drug formulation, utilization of psychosocial support, duration of treatment, levels of dosing supervision and patient satisfaction with treatment. Safety concerns related to the misuse of SROM have also been discussed by Beer *et al.* [47], who postulated that morphine preparations were abused more frequently than other OST preparations, but did not provide data contextualizing the incidence of abuse or the number of subjects at risk.

This study supports previous publications suggesting the potential of SROM as a valuable option to adapt OMT more effectively to the needs of patients.

Clinical trial registration

Registration number and name of trial registry—EudraCT no.: 2008-002185-60, Swissmedic no.: 2007DR3124, NIH Study code: NCT01079117.

Declaration of interests

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