Journal of Pharmacological Sciences xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Pharmacological Sciences

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

Full Paper

Switching opioid-dependent patients in substitution treatment from racemic methadone, levomethadone and buprenorphine to slow-release oral morphine: Analysis of the switching process in routine care

Cinzia Baschirotto [a, b], Kirsten Lehmann [a, *], Silke Kuhn [a], Jens Reimer [a, c], Uwe Verthein [a]

[a] Centre for Interdisciplinary Addiction Research, University Medical Center Hamburg-Eppendorf, Martinistr. 52, D-20246, Hamburg, Germany
[b] University of Florence, Department of Psychiatry, AOU Careggi, Florence, Italy
[c] Gesundheit Nord, Bremen, Germany

ARTICLE INFO

Article history:
Received 15 February 2020
Received in revised form
5 June 2020
Accepted 10 June 2020
Available online xxx

Keywords:
SROM
Slow-release oral morphine
Switching process
Substitution treatment
OST

ABSTRACT

Since 2015 slow-release oral morphine (SROM) is approved for opioid substitution treatment (OST) in Germany. The SROMOS study (efficacy and tolerability of slow-release oral morphine in opioid substitution treatment) evaluates the efficacy and safety of SROM in routine care. This article describes the switching process from racemic methadone, levomethadone and buprenorphine to SROM.

Between July 2016 and November 2017 180 patients in 23 study centers in Germany were included in the prospective, non-interventional, naturalistic observational study. Patients were already in OST and switched from a previous medication to SROM. The switching process was analyzed during a period of fourteen days.

Data were available for 169 participants. The switching process had a different progression depending on premedication and pre dosage. On the fourteenth day of SROM treatment patients switched from racemic methadone took an average dosage of 922.2 mg/day, from levomethadone 801.0 mg/day and from buprenorphine 626.7 mg/day. Average conversion ratio racemic methadone to SROM was 1:11.8, levomethadone to SROM 1:17.4 and buprenorphine to SROM 1:58.0.

This study provides the first data on the switching process from buprenorphine to SROM. Average dose ratio racemic methadone to SROM on the fourteenth day of treatment was considerably higher than recommended in the prescribing information.

1. Introduction

Opioid substitution treatment (OST) is the most recognized drug treatment for opioid dependence worldwide.[1–3] A multitude of clinical studies and evaluation programs prove its effectiveness in reducing illicit opioid use, drug-related mortality and transmission of the blood-borne viruses human immunodeficiency virus (HIV), hepatitis C (HCV) and hepatitis B (HBV). OST also improves physical and psychological health and quality of life and promotes social functioning and reintegration.[2,4–14]

Medications with mu-receptor agonist activity suitable for OST include racemic methadone, levomethadone, buprenorphine (alone or in combination with naloxone), dihydrocodeine, diacetylmorphine and slow-release oral morphine (SROM). Methadone is prescribed to 63% of all OST patients in Europe. A further 35% is treated with buprenorphine.[3] Extensive literature shows the efficacy of methadone and buprenorphine.[15–20] However, side effects may influence the patient's compliance and decrease the retention rate.[21] Some patients treated with methadone experience increased sweating, constipation, dry mouth, insomnia, decreased libido, difficulty in achieving orgasm, painful joints and bones and general malaise.[21,22] Furthermore, methadone may not be indicated

* Corresponding author. Fax: +49 (0)40 7410 55121.
E-mail addresses: cinziabaschirotto@hotmail.com (C. Baschirotto), k.lehmann@uke.de, k.lehmann@isd-hamburg.de (K. Lehmann), skuhn@uke.de (S. Kuhn), reimer@uke.de (J. Reimer), u.verthein@uke.uni-hamburg.de (U. Verthein).

Peer review under responsibility of Japanese Pharmacological Society.

https://doi.org/10.1016/j.jphs.2020.06.004

in case of prolongation of the electrocardiographic QTc interval[23–25] and in case of simultaneous treatment with other drugs that induce or inhibit the cytochrome P450 enzymes, as this may impact plasma methadone levels and cause withdrawal or sedation.[6,26] Methadone's effectiveness and tolerability can also be limited for special populations as end-stage liver disease patients,[6] rapid metabolizers[27,28] and patients with atypical pharmacodynamics response.[21]

Possible side effects of a buprenorphine substitution treatment are headache, constipation, sleep disorders and anxiety.[29] Furthermore, patients under buprenorphine describe a “clear state of consciousness”, expressed as a “feeling of clarity” in mind, a sensation that is far from the sedation resulting from the use of other opioids.[30] This can make buprenorphine a suitable drug for patients with particular features as strong motivation, stable living conditions or low psychiatric co-morbidity.[31,32]

Higher retention in treatment leads to better results and is the key of the success of OST.[6,33] Given that patients respond differently to drugs, it is crucial to increase the pharmacological options balancing side effects and effectiveness.[34,35] In this context, SROM can be a useful alternative, and it may help to reach a larger number of patients[35] and to reduce the gap between who might benefit from OST and who receive it.[36,37]

SROM is a mu-opioid receptor agonist which formulation enables a slow and continuous release that guarantees steady blood levels over 24 h[38–40] and allows its use as a once-daily drug in OST.[41] Comparable effectiveness to methadone could be determined in the randomized cross-over trials of Eder et al.[36] and Beck et al.[42,37–41] Thus, SROM represents a valuable alternative to methadone (and other substances) for the treatment of opioid-dependent patients[43] especially for those who are intolerant[44] or responding poorly to methadone[41] experiencing inadequate withdrawal suppression.[45]

SROM was first approved for use in OST in Austria in 1998.[32] Since April 2015 it is authorized in Germany. The SROMOS study (efficacy and tolerability of slow-release oral morphine in opioid substitution treatment) investigates the use of SROM under routine clinical conditions in Germany in terms of effectiveness and safety. In this article, the switching process of patients in OST from methadone, levomethadone and buprenorphine to SROM will be analyzed to describe the duration of the medication switch and conversion ratios.

2. Materials and methods

The SROMOS study was carried out as a non-interventional naturalistic observational study using Case Report Forms (CRFs) for physicians and patients. The patients were recruited between July 2016 and November 2017 in 23 outpatient addiction treatment centers in Germany. Only opioid-dependent patients were included in the study. The patients already had to be in OST as outpatients in addiction clinics or general practitioners’ practices. The decision to switch to SROM had to be unaffected by the study inclusion. Thus there was no interference in the setting of the standard medical care. The morphine used for treatment in this study was morphine sulfate, in the form of hard capsules, slow-release, available in four dosages: 30 mg, 60 mg, 100 mg and 200 mg.

The inclusion criteria were diagnosis of opioid dependence (F11.2) according to ICD-10, minimum age of 18 years, being in OST with an agonist for substitution approved drug and having a previous unsatisfactory treatment course in terms of physical and/or mental health problems or impairments (e.g. persistent heroin craving, debilitating side effects). Other inclusion criteria were the willingness to switch from the previous substitution drug to SROM and the ability to understand the study conditions and to participate in the assessments and interviews. Exclusion criteria were hypersensitivity or intolerance to morphine sulfate, ileus, acute abdomen, and already being in substitution treatment with SROM.

The study began with the baseline questioning and the documentation of the general health status (anamnesis and medical findings) of the patients. Physicians further stated the previous medication and mentioned the reasons for switching to an alternative opioid. Afterwards, the patients were converted from their previous substitution drug to SROM. The dose of the substitution medication was documented daily during every visit for the first 14 days of treatment until the switching process was completed, and the patient had reached a stable SROM maintenance dose.

The change in mental impairment is the key criterion for effectiveness in this study. It was measured using the Global Severity Index (GSI) of the standardized Brief Symptom Inventory-18 (BSI-18), according to Franke et al.[46] Data were collected at baseline and after 3, 6 and 12 months.

Any event occurring during the course of the study that affected the patient's well-being was defined as an adverse event (AE), regardless of whether a causal relation to SROM was suspected. AEs were coded according to the 27 categories of the system organ classes (SOC) of the Medical Dictionary for Regulatory Activities (MedDRA®, version 20.1).

The study was completed after 12 months or with the patient's previous withdrawal from SROM treatment. After completion of the study, treatment continued as needed. The participation (or termination) in the observational study did not influence on the treatment conditions and their further course. Patients received an expense allowance of EURO 30 for six data assessments within a one-year study duration. In the event of premature dropout, the amount was reduced accordingly.

On the bases of the first results of the SROMOS study, the analysis described in this article systematically examines the switching process of opioid-dependent patients in substitution treatment from racemic methadone, levomethadone and buprenorphine to SROM. The switching process was analyzed during 14 days. After these two weeks, all the patients had completed the switching process to SROM. The research plan was designed to allow a detailed daily description of the switching process from the former substitution agent to SROM. We did not intervene in the course of treatment at any time and merely observed the switching process and routine care during the study.

No wash-out of previous medication is required when patients were pre-treated with racemic methadone; thus, SROM can be given one to the other day with an additional few days to titrate up.[47] Dose equivalents for patients who have already been pre-treated with racemic methadone are available.[42,48] For the conversion from buprenorphine to SROM, only experiences from Austria exist[49] but as yet no clinical data have been published. Following the pharmacological treatment principle, the most important aim of OST is to reduce opioid consumption and associated behaviours. An adequate conversion ratio to administer a sufficient dosage of SROM is clinically significant to avoid withdrawal symptoms and heroin cravings.

The present analysis determines the average conversion ratios from racemic methadone, levomethadone and buprenorphine to SROM and evaluates the switching process under real care conditions to derive practical conclusions.

Descriptive statistics were used to describe the study population. Statistical analyses were performed with IBM SPSS Statistic Version 22.

All patients were informed about the objectives, nature, extent and risks of the study in an understandable way and expressed written consent to participate in the study. Participation in the

Please cite this article as: Baschirotto C et al., Switching opioid-dependent patients in substitution treatment from racemic methadone, levomethadone and buprenorphine to slow-release oral morphine: Analysis of the switching process in routine care, Journal of Pharmacological Sciences, https://doi.org/10.1016/j.jphs.2020.06.004

study was voluntary, and the patient could withdraw his or her study consent at any time. The study was financially supported by Mundipharma GmbH (Germany).

3. Results

3.1. Sample description

For this analysis, valid data of 169 patients (out of 180 patients included in the study) were available. The switching process for 11 patients was not appropriately documented, or they left SROM treatment during the first two days. The patients were predominantly male (74.6%). The average age was 44.1 years, with a range of 20–62 years. On average, the patients had been opioid-dependent for 22.5 years, had undergone an OST for 7.1 years, and had been in treatment for 5 years at the current practice or clinic (Table 1).

Thirty patients (17.8%) were previously treated with racemic methadone. They took an average dosage of 92.2 mg/day. The majority of patients was earlier in OST with levomethadone (N = 99, 58.6%) with an average dose of 48.7 mg/day. 34 patients (20.1%) took buprenorphine with an average dosage of 12.6 mg/day. 6 patients were in OST with other medications: two patients took dihydrocodeine, two tramadol, one morphine (other preparation than SROM), and one patient received diamorphine.

The majority of patients lived in stable conditions. 35.5% had stable work/employment or were studying or in training.

84 patients (55.6%) had at least one ongoing psychiatric comorbidity. The most frequent diagnosis was of the affective spectrum (N = 52), followed by anxiety disorders (N = 20). 58.5% of the patients were positive for hepatitis C antibodies, and 24.4% had an active HCV infection. The prevalence of HIV infection was 2.5%.

Table 2 shows the reasons for the switch of substitution medication. The treating physicians were asked to give the reasons for changing the substitution agent to SROM (multiple answers were possible) and also to identify the main reason for the switch. The main and most stated reason for starting SROM treatment was a better-expected effect in suppressing heroin craving. Other often indicated reasons were better-expected tolerability and an

Table 1
Sociodemographic and clinical characteristics (N = 169).

Variables	Percentage or Mean (±SD)
Sex	
Male	74.6%
Female	25.4%
Age (in years)	44.1 (±8.8)
Years of opioid dependence	22.5 (±9.8)
Duration of OST (in years)	7.1 (±7.0)
Duration of OST at current practice/clinic (in years)	5.0 (±5.9)
Substitution medication	
Racemic methadone	17.8%, mean dosage 92.2 (±35.8) mg
Levomethadone	58.6%, mean dosage 48.7 (±22.5) mg
Buprenorphine	20.1%, mean dosage 12.6 (±5.2) mg
Others	3.6%
Nationality	
German citizens	94.7%
Different nationality	5.3%
Migration background	
Immigrated to Germany	4.8%
Child of migrants	7.1%
No migration background	88.1%
Relationship	
Single	62.5%
In a relationship, not living together	8.9%
In a relationship, living together	28.6%
Having children	38.2%
Housing situation	
Live in their own apartment	82.2%
Stay at relative's home	6.5%
Stay temporarily at a friend's home	3.0%
Live in assisted housing	4.7%
Live in dormitories, hotels or hostels	3.6%
Employment	
Work full-time	18.9%
Work part-time	13.6%
Occasional jobs	6.5%
Study or training	3.0%
Retired	10.1%
Run a household	3.6%
Are unemployed	42.4%
Comorbidities	
Previous physical comorbidities	85.8%
Previous mental comorbidities	66.9%
Ongoing physical comorbidities	60.4%
Ongoing mental comorbidities	55.6%
HCV status (N = 164)	
Anti-HCV negative	34.1%
Anti-HCV positive/RNA negative	34.1%
RNA positive	24.4%
Unknown	7.3%
HIV positive (N = 163)	2.5%

Please cite this article as: Baschirotto C et al., Switching opioid-dependent patients in substitution treatment from racemic methadone, levomethadone and buprenorphine to slow-release oral morphine: Analysis of the switching process in routine care, Journal of Pharmacological Sciences, https://doi.org/10.1016/j.jphs.2020.06.004

Table 2
Reasons for the change of the substitution medications (multiple entries, N = 169).

Reasons for the change of the substitution medications	percentage	main reason (rank)
Better (expected) effect in suppressing heroin craving	54.4	1
Better (expected) tolerability	51.5	4
Unsatisfying previous course of treatment/wish to try the new drug	40.8	5
Better (expected) effect on mental comorbidity	38.5	2
Strong side effects under the previous substitution medication	30.2	3
Too strong sedation under the previous substitution medication	13.0	
Greater therapeutic range	10.7	
Morphine is generally the most suitable substitution medication	8.3	
Better/easier handling	7.1	
Less interaction with other concomitant medication	5.9	
Prolongation of QTc interval under the previous substitution medication	5.3	
Better feasible personalized dose adjustment	4.7	
Other	10.1	

unsatisfying previous course of treatment associated with the wish to try the new substitution agent.

3.2. Duration of the switching process and dosage of slow-release oral morphine

The results on the switching process based on 163 patients with complete data sets previously treated with racemic methadone, levomethadone or buprenorphine. The patients previously treated with other substitution drugs (n = 6, see above) is too small to allow meaningful assertions; thus, they were excluded from this analysis. The switching process was analyzed during a period of 14 days. After these two weeks, all the patients completed the switching process to SROM.

Table 3 shows the switching process from racemic methadone, levomethadone and buprenorphine to SROM. The majority (76.9%) of the patients could be switched “from one day to the next”, that means that the previous medication was stopped and SROM was started the next day.

23 patients (76.7%) previously treated with racemic methadone were switched from one day to the next. These patients were previously treated with an average dose of 89.8 mg/day racemic methadone. For 23.3% of the patients, the switching process took up to 9 days, as the prescribing doctors decided to titrate down the original medication and at the same time to titrate up SROM. These patients previously took an average dose of 100.0 mg/day methadone (T = 0.478, P = 0.647). 72 of the patients (72.7%) previously treated with levomethadone were switched from one day to the next. Their average dose was 45.3 mg/day levomethadone. 27.3% of the patients took from 1 to 13 days to complete the switching process. They were previously treated with, on average 57.6 mg/day levomethadone (T = 2.473, P = 0.015). 88.2% of the patients (N = 30) previously treated with buprenorphine completed the switching process from one day to the next. They previously received an average dose of 12.4 mg/day buprenorphine. For 11.8% of the patients, the switching process took one day longer. These patients were previously in OST, with an average dose of 14.0 mg/day buprenorphine (T = 0.923, P = 0.389).

The patients previously treated with methadone started with an average SROM dose of 673.9 mg/day. On the fourteenth day, these patients reached an average dose of 922.2 mg/day. The patients previously treated with levomethadone started with 591.9 mg/day and achieved an average dose of 801.0 mg/day. And the patients previously treated with buprenorphine increased their SROM dose from, on average, 453.3 mg/day up to 626.7 mg/day on day 14 (Table 3, Fig. 1).

3.3. Dose ratio of the previous substitution treatment to SROM

On the first day of the switch from racemic methadone to SROM, the physicians choose an average dose ratio of 1–8.3 (Table 4). On the 14th day of treatment with SROM, the average dose ratio methadone to SROM was 1–11.8. The switch from levomethadone started at an average ratio of 1–13.8 and reached 1 to 17.4 on day 14. The average dose ratio buprenorphine to SROM was 1–42.3 on the first day and increased to 1 to 58.0 on the 14th day.

Fig. 2 shows the relationship between the conversion ratios of racemic methadone and methadone-equivalent of levomethadone and buprenorphine to SROM. Levomethadone was divided by two, and buprenorphine was divided by five. Since no scientific evidence

Table 3
Switching process from racemic methadone, levomethadone and buprenorphine to slow-release oral morphine (SROM), average daily doses in mg.

Days	Racemic Methadone (N = 30)		Levomethadone (N = 99)		Buprenorphine (N = 34)	
	Racemic Methadone (±SD) [N]	SROM (±SD)	Levomethadone (±SD) [N]	SROM (±SD)	Buprenorphine (±SD) [N]	SROM (±SD)
1	88.6 (±50.1) [7]	673.9 (±188.1)	41.9 (±17.2) [27]	591.9 (±244.0)	14.0 (±2.8) [4]	453.3 (±190.7)
2	38.0 (±36.3) [5]	758.3 (±181.6)	39.3 (±11.8) [16]	653.4 (±277.7)	0.0 (±0) [0]	547.3 (±184.4)
3	46.7 (±30.6) [3]	755.6 (±202.5)	37.5 (±13.8) [15]	682.4 (±282.9)	0.0 (±0) [0]	553.9 (±187.9)
4	50.0 (±14.1) [2]	841.8 (±217.9)	34.2 (±14.0) [15]	701,3 (±304.2)	0.0 (±0) [0]	605.5 (±177.6)
5	43.3 (±20.8) [3]	822.2 (±217.2)	34.6 (±13.2) [13]	715.5 (±300.5)	0.0 (±0) [0]	596.4 (±192.0)
6	30.0 (±14.1) [2]	855.7 (±233.1)	35.0 (±11.6) [12]	718.3 (±300.8)	0.0 (±0) [0]	586.1 (±209.6)
7	30.0 (±0.0) [1]	867.8 (±243.5)	35.5 (±12.0) [11]	736.7 (±300.2)	0.0 (±0) [0]	611.9 (±181.9)
8	20.0 (±0.0) [1]	877.9 (±236.6)	23.4 (±10.4) [5]	765.1 (±296.0)	0.0 (±0) [0]	605.6 (±195.8)
9	10.0 (±0.0) [1]	891.7 (±249.3)	21.0 (±7.4) [5]	767.6 (±293.1)	0.0 (±0) [0]	599.4 (±205.4)
10	0.0 (±0.0) [0]	908.7 (±261.9)	21.3 (±8.5) [4]	770.1 (±304.0)	0.0 (±0) [0]	608.5 (±201.4)
11	0.0 (±0.0) [0]	915.3 (±250.8)	21.7 (±10.4) [3]	770.4 (±313.9)	0.0 (±0) [0]	610.0 (±200.3)
12	0.0 (±0.0) [0]	915.3 (±250.8)	27.5 (±3.5) [2]	785.5 (±315.7)	0.0 (±0) [0]	603.6 (±200.5)
13	0.0 (±0.0) [0]	915.3 (±250.8)	30.0 (±0.0) [1]	788.6 (±314.2)	0.0 (±0) [0]	618.8 (±205.0)
14	0.0 (±0.0) [0]	922.2 (±261.0)	0.0 (±0.0) [0]	801.0 (±321.8)	0.0 (±0) [0]	626.7 (±213.3)

Please cite this article as: Baschirotto C et al., Switching opioid-dependent patients in substitution treatment from racemic methadone, levomethadone and buprenorphine to slow-release oral morphine: Analysis of the switching process in routine care, Journal of Pharmacological Sciences, https://doi.org/10.1016/j.jphs.2020.06.004

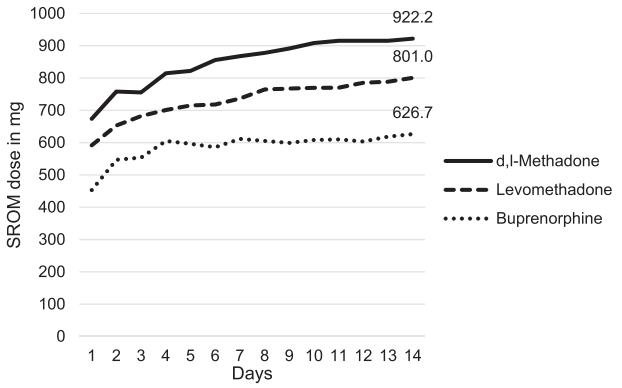

Fig. 1. Dosage of slow-release oral morphine over the first 14 days of treatment.

Table 4
Dose ratio of the previous substitution drug to slow-release oral morphine (1:x).

Day	Racemic Methadone	Levomethadone	Buprenorphine
1	8.3	13.8	42.3
2	9.1	15.0	51.5
3	9.7	15.7	52.1
4	10.5	16.0	56.4
5	10.5	16.4	56.2
6	11.2	16.5	54.7
7	11.4	16.9	58.3
8	11.6	17.0	56.8
9	11.7	17.1	55.7
10	11.6	17.2	56.0
11	11.7	17.2	56.9
12	11.7	17.3	55.7
13	11.7	17.3	57.1
14	11.8	17.4	58.0

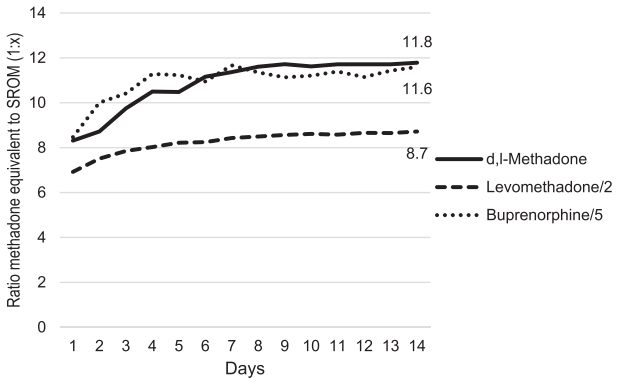

Fig. 2. Relationship between the conversion ratios of racemic methadone equivalent, levomethadone/2 and buprenorphine/5 to slow-release oral morphine (SROM) over the first 14 days of treatment.

for a generally accepted methadone equivalent dose exists for buprenorphine the dose ratio of 1–5 buprenorphine to SROM was taken from the Austrian consensus statement from 2010.[49] According to Fig. 2, the increase in the dose ratio is similar for racemic methadone and buprenorphine. Based on methadone equivalent, the dose ratio for levomethadone is lower.

3.4. Adverse events after switching to SROM

At the time of this analysis a total of 51 AEs were documented in 24 patients (14.2%). Of all AEs, 26 (51.0%) in 13 patients were reported within the first four weeks, indicating that these events occurred as a result of switching the substitution medication. In this article, only AEs are described for which data were available and which occurred within the first four weeks after switching to SROM. A detailed analysis of all adverse reactions (AEs as well as adverse drug reactions - ADRs) will be carried out in another publication on the main results of the SROMOS study.

Overall, 61.5% of all observed AEs were assessed as strong in terms of severity, while 38.5% were considered to be moderate. In 3.9% of the cases, an assessment was not available due to missing data. A majority (61.5%) of all AEs had a possible, probable or certain causal link with SROM. An unlikely causality was reported for 30.8%. No causal link between SROM and the occurrence of the AE was documented in only 3.9% of all AEs. In 3.9% of the cases, no information could be provided. Patients could not recover from most of the AEs (46.2%). However, 34.6% were able to recover fully, but for 7.7%, this recovery was associated with health consequences for the patients, including the consequences of accidents and withdrawal symptoms. For 11.5%, no information could be given on the outcome of the AEs. In the narrow majority of patients, several, in one person up to five, AEs occurred (53.9%) within four weeks after switching to SROM. Only one AE was reported in 46.2%.

The documented AEs encoded in the SOCs were examined with regard to their frequency of occurrence. The most frequently documented AEs were classified as psychiatric disorders (26.9%). These mainly included withdrawal symptoms such as craving, perspiration or nausea. The second most common documented events are gastrointestinal disorders such as diarrhoea or vomiting (19.2%). These symptoms were also found in the category of psychiatric disorders but were explicitly listed as withdrawal symptoms. If the symptom was mentioned exclusively, it was coded as SOC gastrointestinal disorders. General disorders such as pain or dizziness followed in third place (15.4%).

4. Discussion

The sociodemographic characteristics of the sample indicate that the life expectancy of patients in OST has increased during the past years. 28.4% of the patients in our study are 50 years and older. The patients have been opioid-dependent for more than 22 years on average. A recent representative study of more than 2000 patients in substitution treatment in Germany found comparable results.[50]

Although the patients in our sample presented an unsatisfactory OST course in terms of physical and/or mental health problems or impairments (e.g. persistent heroin craving, debilitating side effects) they have undergone a substitution treatment for more than 7 years on average, most of the time in the same practice or clinic. Therefore it is to be expected that many patients are well known to the treating physicians.

The data indicates a relatively stable social situation of the patients. Four-fifths live in their own apartment, more than one-third work full or part-time. This is even a higher rate than in the randomized study of Falcato et al.[51] that investigated the self-reported craving under methadone and SROM treatment, in which almost a quarter of the patient was employed.

The prevalence of HCV antibodies in our sample (58.5%) is slightly lower to the prevalence found among PWID in 2014 in Hamburg (67.7%) and 2013 in others German cities (Frankfurt on the Main 64.5%, Cologne 66.5%, Hanover 73.0% and Munich 62.2%)[52] as well as to the estimated worldwide anti-HCV prevalence in PWID (60%–80% in 26 countries, higher than 80% in a further 12 countries worldwide).[53]

The majority of the patients in this study was previously in OST with levomethadone. One-fifth of the patients took buprenorphine and only 17.8% racemic methadone. This does not accurately reflect the situation of substitution treatment in Germany. The report of

Please cite this article as: Baschirotto C et al., Switching opioid-dependent patients in substitution treatment from racemic methadone, levomethadone and buprenorphine to slow-release oral morphine: Analysis of the switching process in routine care, Journal of Pharmacological Sciences, https://doi.org/10.1016/j.jphs.2020.06.004

the German substitution register 2018 (data from July 2017) shows that the majority was treated with racemic methadone (40.9%) and just 34.0% with levomethadone. It is though noteworthy that the percentage of patients treated with levomethadone in Germany has been steadily rising for more than 10 years. The percentage of patients who received buprenorphine in this study is similar to that reported in the substitution register 2018.[54]

The most mentioned reasons for the medication switch were expected a decrease in heroin craving, expected better tolerability of the drug and unsatisfying previous course of treatment. These benefits are also remarked in the scientific literature: the advantages of the substitution treatment with SROM versus methadone are less craving for heroin, better tolerability and higher patient satisfaction.[36,43,44,48,51] When the physicians were asked to identify the main reason for the switch the expectation of a stronger suppression of heroin craving ranked first. The second main reason was the expectation of a better effect on mental comorbidity. SROM indeed appears to reduce depressive and anxiety symptoms.[36,43,48] Other important advantages of SROM versus methadone that were mentioned by the attending physicians are the absence of drug-induced QTc interval prolongation in the ECG[48] and the less interaction with other concomitant medications. This feature is particularly relevant because patients with drug use disorders show a high prevalence of comorbidities and therefore, are frequently treated with multiple drugs at the same time.[7,40] The switch from methadone to SROM could also be advantageous in patients carrying genetic variations, e.g. in CYP2C19 and who for this reason, require a high methadone dose. These patients may be treated with a comparably lower dose of slow-release morphine.[48]

In the summary of product characteristics (SmPC), the pharmaceutical company affirms that the switch from other substitution medications to morphine sulfate can be done from one day to the next. This applies to the majority of patients in the study. However, in some cases (less than one quarter) the switching process took longer. Some prescribing physicians preferred to titrate down the original substitution medication and at the same time to titrate up the dosage of SROM. Since there is not an exact equivalent dose when switching from one opioid to another, it makes sense that the prescribing doctors would be conservative in estimating the needed dose of SROM. This happened mostly when patients were previously in OST with higher medication doses.

The conversion ratio methadone hydrochloride to morphine sulfate suggested in the SmPC is 1:6 to 1:8. Similar data can also be found in the most recent European studies. In 2004 Mitchell et al. used lower conversion rates. The initial switching ratio of 1:3.5 had to be increased to relieve bland withdrawal symptoms and to reach the stable SROM maintenance dose with an average ratio of 1:4.6.[55] Eder et al. found the equivalence dose ratio racemic methadone to SROM around 1:7.75 in 2005.[36] Kastelic et al. indicated as appropriate a ratio of 1:8.[45] Bond et al. in 2012 reported an average switching rate of 1:7.5.[44] The ratio 1:6 to 1:8 was used by Beck et al. in the randomized cross-over study in 2014.[42]

The conversion ratio racemic methadone to SROM found in this study is remarkably higher than indicated in most of the recent scientific literature and also compared to the number recommended by the SmPC. The initial average dose ratio of 1:8.3 at the first switching day has increased and reached the average value of 1:11.8 on the fourteenth day. The switching process levomethadone to SROM started with an average rate of 1:13.8 and reached 1:17.4 after two weeks. Considering that methadone is a racemic mixture of equal amounts of left- and right-handed enantiomers and levomethadone is composed of only left-handed enantiomers, the dose ratio of levomethadone found in this study is considerably lower than twice the dose ratio of methadone. That confirms the hypothesis that right-handed enantiomers contained in the racemic methadone are not completely devoid of pharmacodynamic action.[56] This study provides the first data under routine care about the conversion ratio buprenorphine to SROM, which was 1:58.0 on the fourteenth day of treatment. Based on a methadone equivalent ratio of a buprenorphine dose divided by five, the conversion ratio buprenorphine to SROM is similar to the racemic methadone ratio.

This data has been analyzed for the first time and can be regarded as a standard orientation in medical practice until further research is available. With nearly a quarter of all substituted patients, buprenorphine has been on the rise in Germany for a long time for the treatment of opioid dependence. Due to its European approval in 2019 as an injection depot formulation, buprenorphine may become more important again. Throughout the European Union, 34% of substituted patients are treated with medications based on buprenorphine, and in eight countries, buprenorphine is the main substitute.[57] Thus, data on the switching process from buprenorphine to SROM is of great importance regarding the medical care of opioid-dependent people.

Some limitations of this study should be acknowledged. The study was uncontrolled and carried out in several outpatient settings. The sample is self-selected and relatively limited in number; from eleven patients, there was no sufficient data for the analyses. We must note that the study started more than 15 months after the introduction of SROM into the German market. The most urgent and motivated cases were already switched to SROM and thus not eligible for study participation.

The strength of this study lies in its design, which allows to evaluate the switching process under routine care conditions and to include patients with many comorbidities. The purpose of this analysis is indeed to analyze the switching process under real care conditions to provide useful and practical indications for prescribing physicians.

5. Conclusions

The switching processes varied depending on the previously taken drug and its dosage. More than three-quarter of patients were able to switch from one day to the next. After 14 days, all the patients in this study completed the switching process to SROM.

The average dose ratio racemic methadone to SROM on the 14th day of treatment was considerably higher than recommended in the product information. Since a significant dose−response-correlation was found in the study by Beck et al.,[42] this finding is relevant for routine practice.

The present study provides the first data on the switching process of buprenorphine to SROM. The average dose ratio buprenorphine to SROM on the 14th day of treatment was 1: 58.0.

Ethical statement

The Ethics Committee of the Chamber of Physicians in Hamburg approved the study protocol in March 2016 (No. PV5222). The study was conducted by following the Declaration of Helsinki and is registered with the German Register of Clinical Trials (DRKS, ID: DRKS00010712).

Declaration of Competing Interest

The study was conducted by the Centre for Interdisciplinary Addiction Research (University Medical Center Hamburg-Eppendorf, UKE) as an Investigator Initiated Trial (IIT) and was financially supported by the pharmaceutical company Mundipharma Deutschland GmbH & Co. KG (Frankfurt on the Main, Germany) (unrestricted educational grant). The funding body had

no role in the study design and the collection, analysis and interpretation of data.

Uwe Verthein received speaker's honoraria from Mundipharma Deutschland GmbH & Co. KG and travelling expenses from Camurus GmbH and Mundipharma Deutschland GmbH & Co. KG. Jens Reimer participates in the speaker's bureaus of Camurus GmbH, Hexal AG, Indivior PLC and Sanofi-Aventis Deutschland GmbH. Kirsten Lehmann received a reimbursement of travel expenses as well as the absorption of participation fees and accommodation costs from pcm scientific. The other authors declare no conflicts of interest.

References

1. United Nations Office on Drugs and Crime. *World drug report 2018*. 2018.
2. United Nations Office for Drug Control and Crime Prevention. *World drug report 2000*. 2000.
3. European Monitoring Centre for Drugs and Drug Addiction. *European drug report. Trends and developments. Luxembourg*. 2018.
4. World Health Organization. *United Nations office on drugs and crime, joint United Nations programme on HIV/AIDS. Substitution maintenance therapy in the management of opioid dependence and HIV/AIDS prevention: position paper*. 2004.
5. European Monitoring Centre for Drugs and Drug Addiction. *European drug report*. Luxembourg: Trends and developments; 2013.
6. Bart G. Maintenance medication for opiate addiction: the foundation of recovery. *J Addict Dis*. 2012;31(3):207–225.
7. Connery HS. Medication-assisted treatment of opioid use disorder: review of the evidence and future directions. *Harv Rev Psychiatr*. 2015;23(2):63–75.
8. Degenhardt L, Randall D, Hall W, Law M, Butler T, Burns L. Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: risk factors and lives saved. *Drug Alcohol Depend*. 2009;105(1–2):9–15.
9. Gowing L, Farrell MF, Bornemann R, Sullivan LE, Ali R. Oral substitution treatment of injecting opioid users for prevention of HIV infection. *Cochrane Database Syst Rev*. 2011;8:CD004145.
10. Gronbladh L, Ohlund L, Gunne L. Mortality in heroin addiction: impact of methadone treatment. *Acta Psychiatr Scand*. 1990;82(3):223–227.
11. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev*. 2009;3:CD002209.
12. O'Connor P. Methods of detoxification and their role in treating patients with opioid dependence. *J Am Med Assoc*. 2005;294(8).
13. Soyka M, Kranzler H, van den Brink W, Krystal J, Moller H, Kasper S. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of substance use and related disorders. Part 2: opioid dependence. *World J Biol Psychiatr: Off J World Federation Soc Biolo. Psychiatr.*. 2011;12(3):160–187.
14. Torrens M, San L, Martinez A, Castillo C, Domingo-Salvany A, Alonso J. Use of the Nottingham Health Profile for measuring health status of patients in methadone maintenance treatment. *Addiction*. 1997;92(6):707–716.
15. Brugal MT, Domingo-Salvany A, Puig R, Barrio G, Garcia de Olalla P, de la Fuente L. Evaluating the impact of methadone maintenance programmes on mortality due to overdose and aids in a cohort of heroin users in Spain. *Addiction*. 2005;100(7):981–989.
16. Connock M, Juarez-Garcia A, Jowett S, et al. Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation. *Health Technol Assess*. 2007;11(9).
17. Lavignasse P, Lowenstein W, Batel P, et al. Economic and social effects of high-dose buprenorphine substitution therapy. Six-month results. *Ann Med Interne*. 2002;153(3 Suppl), 1S20-26.
18. Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev*. 2004;3:CD002207.
19. Sees K, Delucchi K, Masson C, et al. Methadone maintenance vs 180-day psychosocially enriched detoxification for treatment of opioid DependenceA randomized controlled trial. *J Am Med Assoc*. 2000;283(10).
20. Ward J, Mattick R, Hall W. The effectiveness of methadone maintenance treatment: an overview. *Drug Alcohol Rev*. 1994;13(3):327–335.
21. Dyer KR, White JM. Patterns of symptom complaints in methadone maintenance patients. *Addiction*. 1997;92(11):1445–1455.
22. Kreek MJ. Medical safety and side effects of methadone in tolerant individuals. *J Am Med Assoc*. 1973;223(6):665–668.
23. Ehret G, Desmeules J, Broers B. Methadone-associated long QT syndrome: improving pharmacotherapy for dependence on illegal opioids and lessons learned for pharmacology. *Expet Opin Drug Saf*. 2007;6(3):289–303.
24. Ehret G, Voide C, Gex-Fabry M, et al. Drug-induced long QT syndrome in injection drug users receiving methadone: high frequency in hospitalized patients and risk factors. *Arch Intern Med*. 2006;166(12):1280–1287.
25. Krantz M, Lewkowiez L, Hays H, Woodroffe M, Robertson A, Mehler P. Torsade de pointes associated with very-high-dose methadone. *Ann Intern Med*. 2002;137(6):501–504.
26. Schlatter J, Madras J, Saulnier J, Poujade F. Drug interactions with methadone. *Presse Med*. 1999;28:1381–1384.
27. Holmstrand J, Anggard E, Gunne L. Methadone maintenance: plasma levels and therapeutic outcome. *Clin Pharmacol Therapeut*. 1978;23(2):175–180.
28. Tennant Jr F. Inadequate plasma concentrations in some high-dose methadone maintenance patients. *Am J Psychiatr*. 1987;144(10):1349–1350.
29. World Health Organization. *Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence*. 2009.
30. Fischer G, Jagsch R, Eder H, et al. Comparison of methadone and slow-release morphine maintenance in pregnant addicts. *Addiction*. 1999;94(2):231–239.
31. Clark N. High dose buprenorphine may be an effective interim treatment for long term heroin users waiting for drug-assisted rehabilitation. *Evid Base Ment Health*. 2003;6(3):30.
32. Kraigher D, Jagsch R, Gombas W, et al. Use of slow-release oral morphine for the treatment of opioid dependence. *Eur Addiction Res*. 2005;11(3):145–151.
33. Timko C, Schultz NR, Cucciare MA, Vittorio L, Garrison-Diehn C. Retention in medication-assisted treatment for opiate dependence: a systematic review. *J Addict Dis*. 2016;35(1):22–35.
34. White JM, Lopatko OV. Opioid maintenance: a comparative review of pharmacological strategies. *Expet Opin Pharmacother*. 2007;8(1):1–11.
35. Woody GE. New horizons: sustained release morphine as agonist treatment. *Addiction*. 2005;100(12):1758–1759.
36. Eder H, Jagsch R, Kraigher D, Primorac A, Ebner N, Fischer G. Comparative study of the effectiveness of slow-release morphine and methadone for opioid maintenance therapy. *Addiction*. 2005;100(8):1101–1109.
37. Socías M, Wood E. Evaluating slow-release oral morphine to narrow the treatment gap for opioid use disorders. *Ann Intern Med*. 2018;168(2):141–142.
38. Broomhead A, West R, Eglinton L, et al. Comparative single-dose phannacokinetics of sustained-release and modified-release morphine sulfate capsules under fed and fasting conditions. *Clin Drug Invest*. 1997;13(3):162–170.
39. Hagen NA, Thirlwell M, Eisenhoffer J, Quigley P, Harsanyi Z, Darke A. Efficacy, safety, and steady-state pharmacokinetics of once-a-day controlled-release morphine (MS Contin XL) in cancer pain. *J Pain Symptom Manag*. 2005;29(1):80–90.
40. Trescot AM, Datta S, Lee M, Hansen H. Opioid pharmacology. *Pain physician. Opioid Special Issue*. 2008;11:133–153.
41. Mitchell TB, White JM, Somogyi AA, Bochner F. Comparative pharmacodynamics and pharmacokinetics of methadone and slow-release oral morphine for maintenance treatment of opioid dependence. *Drug Alcohol Depend*. 2003;72(1):85–94.
42. Beck T, Haasen C, Verthein U, et al. Maintenance treatment for opioid dependence with slow-release oral morphine: a randomized cross-over, non-inferiority study versus methadone. *Addiction*. 2014;109(4):617–626.
43. Verthein U, Beck T, Haasen C, Reimer J. Mental symptoms and drug use in maintenance treatment with slow-release oral morphine compared to methadone: results of a randomized crossover study. *Eur Addiction Res*. 2015;21(2):97–104.
44. Bond AJ, Reed KD, Beavan P, Strang J. After the randomised injectable opiate treatment trial: post-trial investigation of slow-release oral morphine as an alternative opiate maintenance medication. *Drug Alcohol Rev*. 2012;31(4):492–498.
45. Kastelic A, Dubajic G, Strbad E. Slow-release oral morphine for maintenance treatment of opioid addicts intolerant to methadone or with inadequate withdrawal suppression. *Addiction*. 2008;103(11):1837–1846.
46. Franke GH, Ankerhold A, Haase M, et al. [The usefulness of the Brief Symptom Inventory 18 (BSI-18) in psychotherapeutic patients]. *Psychother Psych Med*. 2011;61:82–86.
47. Mundipharma GmbH. *[Prescribing information Substitol® 30/60/100/200 mg hard capsules, retarded]*. 2018.
48. Hämmig R, Kohler W, Bonorden-Kleij K, et al. Safety and tolerability of slow-release oral morphine versus methadone in the treatment of opioid dependence. *J Subst Abuse Treat*. 2014;47(4):275–281.
49. Haltmayer H. [Addiction medicine in research and practice]. *ÖÄZ.*. 2010;4:36–49.
50. Strada L, Schmidt CS, Rosenkranz M, et al. Factors associated with health-related quality of life in a large national sample of patients receiving opioid substitution treatment in Germany: a cross-sectional study. *Subst Abuse Treat Prev Pol*. 2019;14(1):2.
51. Falcato L, Beck T, Reimer J, Verthein U. Self-reported cravings for heroin and cocaine during maintenance treatment with slow-release oral morphine compared with methadone: a randomized, crossover clinical trial. *J Clin Psychopharmacol*. 2015;35(2):150–157.
52. European Monitoring Centre for Drugs and Drug Addiction. *Statistical Bulletin 2018 - drug-related infectious diseases: infectious diseases > Notifications > HCV*; 2018. http://www.emcdda.europa.eu/data/stats2018/drid_pt. Accessed October 9, 2019.
53. Nelson P, Mathers B, Cowie B, et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. *Lancet*. 2011;378(9791):571–583.
54. *Bundesinstitut für Arzneimittel und Medizinprodukte. [Report on the Substitution Register]*. 2018.
55. Mitchell TB, White JM, Somogyi AA, Bochner F. Slow-release oral morphine versus methadone: a crossover comparison of patient outcomes and acceptability as maintenance pharmacotherapies for opioid dependence. *Addiction*. 2004;99(8):940–945.
56. Davis A, Inturrisi C. D-methadone blocks morphine tolerance and N-Methyl-DAspartate-Induced hyperalgesia. *J Pharmacol Exp Therapeut*. 1999;289(2):1048–1053.
57. *European monitoring Centre for drugs and drug addiction (EMCDDA)*. Lisbon: European Drug Report: Trends and Developments; 2019.

Please cite this article as: Baschirotto C et al., Switching opioid-dependent patients in substitution treatment from racemic methadone, levomethadone and buprenorphine to slow-release oral morphine: Analysis of the switching process in routine care, Journal of Pharmacological Sciences, https://doi.org/10.1016/j.jphs.2020.06.004