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ORIGINAL ARTICLE

Patients' Perceptions of Opioid Replacement Therapy: a Comparison of Diamorphine and Methadone/ Levomethadone

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Abstract
Diamorphine was first legalized as a novel treatment option for heroin dependence in Germany in 2009. Today, specialized clinics in ten German cities provide diamorphine to heavily addicted patients. As the medical and societal context of diamorphine-assisted therapy is evolving, continued research into patients' perceptions of opioid replacement therapy remains important. From February 2018 to June 2018, we conducted a survey study of outpatients on maintenance treatment with either diamorphine ($n = 85$) or methadone/levomethadone ($n = 126$). Patients were asked to complete a self-report questionnaire querying, besides socio-demographic information, the study participant's satisfaction with the substitute drug, relapse with illicit drugs, patterns of craving, and alcohol consumption. Duration of opioid dependence did not differ significantly between groups. Patients on diamorphine were approximately 3 years younger than patients on methadone/levomethadone. They also had a higher frequency of daily intake of their substitute drug and had had their dosage adjusted more often during the preceding 6 months. Still, diamorphine patients reported greater satisfaction with their substitute drug in tandem with significant reductions in relapse-related behaviors and cravings. While the most common relapse reported by patients on methadone replacement was heroin relapse (68%), most instances of illicit drug use in the diamorphine group involved cocaine (48%). Although self-reported alcohol consumption did not differ significantly between groups, a higher percentage of diamorphine patients than methadone patients endorsed decreased alcohol consumption since entering therapy. Taken together, these findings point to meaningful differences between diamorphine and methadone/levomethadone in opioid replacement therapy.

Keywords Diamorphine · Heroin · Methadone · Opioid replacement therapy · Opioid dependence

Methadone replacement therapy was first introduced in Germany in 1987 after lengthy and contentious debate (Michels et al. 2007). Today, it is widely accepted as an evidence-based mainstay in the treatment of heroin dependence (Mattick et al. 2003). The overall number of opioid-dependent persons in Germany in 2016 was estimated to be around 170,000 (Kraus et al. 2019). Of these, 94,381 patients received opioid substitution treatment and had been entered into the Federal Institute for Drugs and Medical Devices (BfArM) substitution registry

(Kraus et al. 2019). The number of these registered patients receiving opioid-assisted therapy has remained relatively stable over the last decade (BfArM 2018).

The German Model project on heroin-assisted therapy found that, compared with patients on methadone maintenance, opioid-dependent patients receiving supervised injected heroin showed greater improvements in physical and mental health in tandem with a decrease in illicit drug use (Haasen et al. 2007). In 2009, the German parliament (Bundestag) voted to institute diamorphine therapy as a new treatment option for severe opioid use disorder, albeit on a quite limited scale. At present, pure synthetic heroin (i.e., diamorphine) is legally provided to patients by specialized clinics in ten medium to large German cities. This so-called diamorphine program is tailored for heavily opioid-dependent patients who have been dependent for at least 5 years with mainly intravenous use. The ratio of patients on diamorphine to patients on methadone/levomethadone is currently 1:75 (BfArM 2018). Further research is needed to evaluate the current state and implementation of diamorphine-assisted treatment in Germany.

The World Health Organization (WHO) has called for research into patient satisfaction with drug abuse treatment with a view to improving the delivery of services (Marsden et al. 2019). Broadly speaking, multiple factors may impact a patient's experience such as the size of a service (Pascoe 1983), waiting times (Sitzia and Wood 1997), organizational characteristics (Greenley and Schoenherr 1981), professional experience of staff, and specific protocols for the delivery of care (Wettach et al. 2000). General instruments developed for assessing treatment satisfaction in mental health care may not be well suited to capture specific issues related to substance use treatment (Marsden et al. 2000). This has resulted in some efforts to devise questionnaires to score patient satisfaction in addiction treatment programs (Marsden et al. 2000). However, literature on patient satisfaction during opioid replacement therapy has so far remained scant (Dampz et al. 2012; Strada et al. 2019). In particular, a vicious cycle of perceived stigmatization, negative affective states, and low quality of life has been described (Frischknecht et al. 2011). The subjective experiences of patients may also provide new insights into the differential roles of particular substitute opioids in aiding recovery.

The main aim of the present report is therefore to comparatively explore patients' subjective views of opioid replacement therapy with either diamorphine or methadone/levomethadone. Our survey focuses on patient satisfaction with the substitute drug, relapse behaviors, craving, and alcohol consumption behaviors.

Materials and Methods

Survey Participants

A total of 211 patients took part in this survey, which was conducted between February 2018 and June 2018. All participants were aged 18 years or older. In brief, patients on diamorphine replacement therapy ("diamorphine patients," $n = 85$) were recruited from two specialized diamorphine outpatient clinics located in the German federal states of Berlin and Hamburg. The patients receiving methadone/levomethadone replacement ("methadone patients"; $n = 126$) were recruited from two outpatient addiction clinics and from one general practice (GP) surgery in the federal state of Berlin. Eligibility criteria for patients and protocols for the delivery of care did not differ between services located in Hamburg and Berlin. Diamorphine patients were either treated with diamorphine exclusively or with a combination

of diamorphine and either levomethadone or extended release morphine. All patients included in this survey had been on maintenance therapy for at least 6 months. Patients were approached by practice staff and invited to participate in the study. Patients were informed that participation in the survey was entirely voluntary and that their responses would be anonymous. Completed surveys were collected in a box in reception to protect anonymity. Additionally, survey forms from Berlin and Hamburg were lumped together and shuffled before analysis. The project had been pre-approved by the institutional review board of the MSH Medical School Hamburg.

Measures

Socio-demographic and clinical data were collected through self-report. Clinical characteristics queried included, among other items, duration of maintenance treatment and opioid prescribed for maintenance treatment, current and past dosages, frequency of drug intake per day, duration of drug addiction, and current work situation. For the purposes of this study, we designed a measure to capture the patient's view of opioid replacement (Table 1). This 16-item self-report questionnaire, termed the "Patients' View of Opioid Replacement Therapy" (PORT), covers the following dimensions: satisfaction with opiate substitute (items 1–5), relapse with illicit drugs (items 6–10), participants' perceived intensity of craving (items 11–13), and alcohol consumption (items 14–16). All items, with the exception of questions 10 and 16, are rated on a 0–4 Likert scale ranging from "not at all/never" to "very much/very frequently" or from "not at all satisfied" to "very much satisfied." Questions 10 and 16 have categorical answer options. Indirect response options ranging from "not at all/never" to "very much/very frequently" are less emotionally charged and show a higher correlation with behavioral outcomes (Ware and Hays 1988). Direct questions such as the question in item #1 of the PORT scale are clearly related to the theoretical construct being assessed and were therefore used to complement the scale (Dampz et al. 2012).

Statistical Analyses

Statistical analyses were performed using IBM SPSS 25.0. Values are presented as mean ± standard deviation (SD) or as median and confidence interval (CI) as appropriate. Comparisons between groups were performed using Mann-Whitney *U* test or chi-square test. Cohen's *d* was used as a measure of effect size. Cronbach's alpha was used to assess the internal consistency of the PORT scale and of its four dimensions.

Results

Socio-demographic and clinical characteristics of the survey sample are given in Table 2. Briefly, diamorphine patients were slightly younger than methadone patients. The frequency of drug intake per day was higher in diamorphine patients. Also, there had been more dose adjustments over the preceding 6 months in diamorphine patients than in methadone patients. Duration of treatment had been longer in patients on methadone substitution.

We used the PORT questionnaire (Table 2) to capture the survey participants' perceptions of key aspects of opioid replacement therapy (Table 1). The 14 Likert items of the PORT questionnaire demonstrated sufficient internal consistency for the total scale (Cronbach's

Table 1 The Patient's View on Opioid Replacement Therapy (PORT) Questionnaire

Categories	Items
Satisfaction	*1. How satisfied am I with the substitute drug?* *2. How good does my body feel with the substitute drug?* *3. How good does my mood feel with the substitute drug?* *4. How good do I feel overall with the substitute drug?* *5. How much has my life improved as a result of the current replacement therapy?*
Relapse	*6. How many times have I relapsed over the last 6 months?* *7. How often do I think about relapsing?* *8. How many relapses did I have with the current substitute drug over the entire period of replacement therapy?* *9. How much does the substitute drug help me not to relapse?* *10. In case of a relapse during replacement therapy, I most often relapsed with: (please tick the appropriate box or complete the answer)* □ *Heroin* □ *Cocaine* □ *Benzodiazepines* □ *Pregabalin* □ *Fentanyl* □ *Tilidine* □ *Tramadol* □ *Oxycodone* □ *Cannabis* □ *Speed (i.e., amphetamines)* □ *Ecstasy (i.e., MDMA)* □ *Crystal Meth (i.e., methamphetamine)* □ *polydrug use* □ *other, namely .....*
Cravings	*11. How often do I experience cravings?* *12. When I experience cravings, how strong do they feel?* *13. How much does the substitute drug help me cope with cravings?*
Alcohol	*14. How often do I consume alcohol?* *15. If / when I consume alcohol, how much do I drink?* *16. Since entering opioid replacement therapy, I drink* □ *more alcohol* □ *less alcohol* □ *same amount of alcohol*

alpha = 0.79) and sufficient to excellent internal consistencies for the four subscales (satisfaction, Cronbach's alpha = 0.91; relapse, Cronbach's alpha = 0.82; cravings, Cronbach's alpha = 0.75; alcohol consumption, Cronbach's alpha = 0.87).

Table 3 summarizes survey participants' responses. Diamorphine patients reported greater satisfaction with their substitute drug along with reduced relapse-related behaviors and reduced cravings. Illicit drug use differed significantly between groups (χ^2 (10, $N = 195$) = 51.46, $p < .001$). By far, the most common relapse in participants on methadone replacement therapy was heroin relapse. In contrast, most instances of illicit drug use in the diamorphine group involved cocaine (Fig. 1a). In addition, cannabis use was more prevalent among diamorphine patients than among methadone patients (Fig. 1a). Self-reported alcohol consumption did not differ between diamorphine patients and methadone patients (Table 3). However, significant

Table 2 Socio-demographic and clinical characteristics of survey participants

	Methadone $N = 126$	Diamorphine $N = 85$	Total $N = 211$	
1. Age, mean (*SD*)	46.12 (*10.65*)	43.20 (*9.65*)	44.94 (*10.34*)	U (126,85) = 4416*
2. Gender, *N* (%)				
Male	85 (68%)	67 (79%)	152 (72%)	χ^2 (1, $N = 210$) = 3.83, $p = .051$
Female	41 (32%)	17 (20%)	58 (28%)	
Missing values	–	1	1	
3. Duration of maintenance treatment, *N* (%)				
6–24 months	17 (13%)	26 (31%)	43 (20%)	χ^2 (2, $N = 211$) = 9.46**
> 24 months	109 (87%)	59 (69%)	168 (80%)	
Missing values	–	–	–	
4. Frequency of medication intake per day, *N* (%)				
Once a day	99 (79%)	18 (21%)	117 (55%)	χ^2 (2, $N = 209$) = 69.37***
Multiple times a day	26 (21%)	66 (78%)	92 (44%)	
Missing values	1	1	2	
6. Duration of drug dependence, *N* (%)				
0–5 years	1 (1%)	1 (1%)	2 (1%)	χ^2 (4, $N = 210$) = 8.07, $p = .089$
5–10 years	20 (16%)	6 (7%)	26 (12%)	
10–20 years	36 (29%)	17 (20%)	53 (25%)	
> 20 years	68 (54%)	61 (72%)	129 (61%)	
Missing values	*1*	–	*1*	
7. Current work situation, *N* (%)				
Full-time job	6 (5%)	10 (12%)	16 (7%)	χ^2 (5, $N = 207$) = 6.43, $p = .267$
Part-time work	17 (14%)	14 (17%)	31 (15%)	
Unemployed	52 (41%)	33 (39%)	85 (40%)	
Retired	46 (37%)	22 (26%)	68 (32%)	
Incapacitated	3 (2%)	4 (5%)	7 (3%)	
Missing values	2	2	4	
8. Dosage changes in last 6 months, *N* (%)				
None	88 (70%)	37 (44%)	125 (59%)	χ^2 (3, $N = 210$) = 28.77***
Dose increase	22 (17%)	12 (14%)	34 (16%)	
Dose decrease	15 (12%)	21 (25%)	36 (17%)	
Both dose increase and decrease	1 (1%)	14 (17%)	15 (7%)	
Missing values	–	*1*	*1*	

N number of subjects, *U* Mann-Whitney *U* test, χ^2 chi-square test

*$p < .05$; **$p < .005$; ***$p < .001$

differences emerged in survey participants' self-reported changes in alcohol use once opioid replacement therapy had been initiated (χ^2 (10, $N = 195$) = 51.46, $p < .001$). The percentage of participants who endorsed increased alcohol consumption since entering opioid replacement therapy was significantly higher ($p < .001$) in the methadone group than in the diamorphine group. At the same time, significantly more ($p < .001$) diamorphine patients than methadone patients reported decreased alcohol consumption since entering opioid replacement therapy (Fig. 1b).

Discussion

Heroin use disorder represents a highly complex medical, societal, and economic challenge. There are patently no easy solutions, and progress will most likely be incremental. Also, a

range of stakeholders beyond the individual patient have to be considered who rightfully expect to be involved in the development of policies surrounding opioid abuse and treatment (Volkow et al. 2019). Nevertheless, with these caveats in mind, exploring the experiences, attitudes, and behaviors of patients on opioid substitution may be genuinely impactful.

The aim of this multicenter survey was to explore, from the patient's point of view, differences in the effectiveness of two substitute drugs, i.e., diamorphine and methadone/levomethadone, in the German setting of outpatient drug treatment services. While methadone has been relatively widely available as a treatment option in Germany since 1992 (Kassenärztliche Bundesvereinigung 1992), diamorphine treatment for heroin dependence was only introduced in 2009 (Deutscher Bundestag 2009). Still today, only a tiny fraction of opioid-dependent patients receive diamorphine as a prescription medication in Germany.

This study has several important limitations, which should be noted at the outset. The "PORT" questionnaire has not been previously validated. As this was an anonymous survey, we were also not able to objectively control for relapse with illicit drugs or alcohol. Moreover, to keep the questionnaire simple, the survey did not allow respondents to list more than one illicit drug as the most frequently used illicit drug. While these factors may have resulted in some skewing of our findings, the simplicity of the PORT questionnaire (i.e., Likert scale, lack of open questions, etc.) may also have allowed patients with somewhat impaired cognitive status before or after drug intake to participate in this study. In addition, considering the strict eligibility criteria for diamorphine treatment, another crucial advantage of our anonymous survey design should not go unmentioned: research in social psychology strongly suggests that strict anonymity rather than confidentiality is most effective in eliciting truthful answers to sensitive questions (Ong and Weiss 2000).

Our survey found that, on balance, diamorphine patients view their substitute drug more favorably than methadone patients view theirs. The main results of this investigation may be summarized as follows. (1) Self-reported satisfaction with the substitute drug was higher in the diamorphine group than in the methadone group. (2) The diamorphine group reported significantly less craving than the methadone group. (3) The diamorphine group also reported significantly less relapsing behaviors with illicit drugs than the methadone group. Importantly, the most frequent relapse reported by patients on methadone substitution was illicit "street" heroin relapse. (4) Self-reported alcohol consumption did not differ between groups. However, a significantly higher number of methadone patients indicated an increase in alcohol consumption since the start of opioid substitution treatment.

In this place, it may be well to recapitulate briefly some of the key pharmacological characteristics of diamorphine. When ingested orally, it undergoes such extensive first-pass metabolism into morphine that there are no measureable blood levels of diamorphine (Inturrisi

Table 3 Self-reported satisfaction with opioid replacement therapy, relapse behaviors, craving, and alcohol use

Category	Methadone/levomethadone			Diamorphine			Mann-Whitney *U*	Effect size
	n	Median	95% CI	*n*	Median	95% CI	*U* value, *p* value	Cohen's *d*
Satisfaction	126	2.10	2.01–2.34	85	3.40	3.15–3.42	$U = 1775$, $p < .001$	1.37
Relapse	126	1.50	1.44–1.83	85	0.75	0.70–0.99	$U = 3107$, $p < .001$	0.77
Craving	124	1.67	1.63–2.00	85	0.67	0.83–1.16	$U = 2896$, $p < .001$	0.83
Alcohol	122	1.25	1.38–1.89	83	1.00	1.06–1.52	$U = 4506$, $p = .176$	0.19*

N number of subjects, *CI* confidence interval, *U* Mann-Whitney *U* test

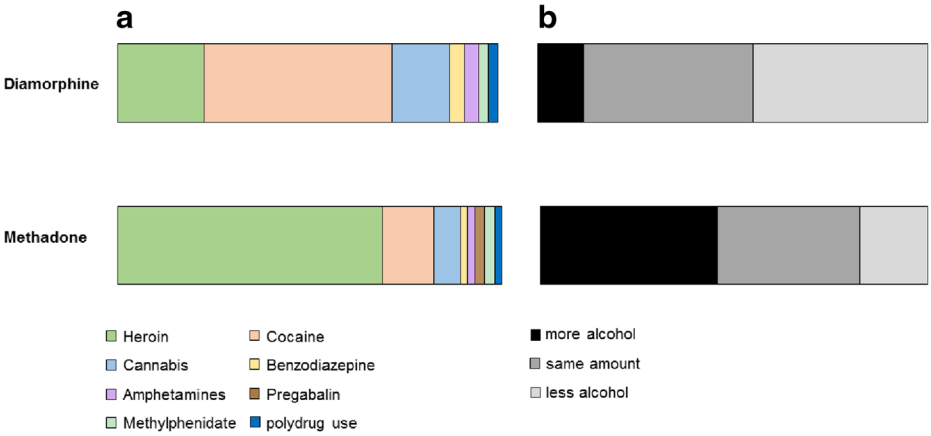

Fig. 1 Opioid substitution and self-reported illicit drug use and alcohol use. **a** Illicit drug use while on opioid maintenance treatment. All instances of illicit drug use per group represent 100%. **b** Changes in alcohol consumption after entering into opioid replacement therapy

et al. 1984). Its two acetyl moieties confer to it high lipophilicity. Accordingly, a comparison of blood-brain border penetration of an intracarotid bolus of codeine, diamorphine, morphine, and methadone showed that the uptake of diamorphine exceeded, by far, the uptake of all other opioids (Oldendorf et al. 1972). Swift transit into the brain is believed to underlie the strongly habit forming and euphoria-inducing qualities of intravenous heroin. By contrast, oral methadone is characterized by a much more gradual onset of action and a much longer half-life, resulting in low abuse liability and reward effect (Kreek et al. 2010). It therefore makes sense that methadone patients reported more intense cravings for heroin than diamorphine patients. In consequence, a much higher percentage of methadone patients disclosed illicit concomitant heroin use. This observation reinforces earlier findings of a randomized controlled trial of heroin-assisted treatment conducted in seven German cities (Haasen et al. 2007). This 12-month open-label trial, which enrolled 1015 heroin-dependent participants, yielded strong evidence indicating that diamorphine-assisted treatment is superior in patients with persistent intravenous heroin use while on methadone maintenance (Haasen et al. 2007). Moreover, participants receiving diamorphine maintenance reported greater improvement in health-related quality of life than participants on methadone maintenance (Karow et al. 2010). Along the same lines, an analysis of data from the North American Opiate Medication Initiative (NAOMI) revealed higher satisfaction in those participants receiving medically prescribed injectable diamorphine than those randomized to oral methadone (Marchand et al. 2011). A recent meta-analysis of six randomized controlled trials conducted in five European countries and Canada likewise concluded that diamorphine-assisted therapy may be an effective way of treating heroin dependence not amenable to standard treatment (Strang et al. 2015). In particular, the authors found a greater reduction in the use of illicit heroin in patients receiving prescription diamorphine compared with control groups (Strang et al. 2015). Also noteworthy, a recent Berlin-wide anonymous survey of patients under opioid services found that approximately 40% of those on conventional maintenance would prefer to transfer into diamorphine substitution (Bald et al. 2013). Importantly, despite a higher opioid dose in terms of "methadone equivalents," these patients reported more frequent use of illicit drugs than patients not desiring to switch to diamorphine maintenance therapy (Bald et al. 2013). Finally, a positive association between patient satisfaction during methadone replacement therapy and treatment

retention has been demonstrated, highlighting the great clinical relevance of this variable (Kelly et al. 2011).

The patient sample surveyed in this study was relatively large. Moreover, patients were recruited from several outpatient clinics. Notwithstanding this, because of the strict anonymity governing this study, we were not able to calculate a response rate. We also do not know how many methadone patients may have applied for diamorphine-assisted therapy unsuccessfully in the past. Socio-demographic and clinical characteristics of diamorphine patients and methadone patients were relatively similar and, overall, appear to be plausible also in the context of previous studies, as outlined above. Specifically, the two groups did not differ in regard to current work situation and duration of opioid addiction (Table 2). As was to be expected, the frequency of diamorphine use per day was higher than the frequency of methadone intake. Dose adjustments during the previous 6 months were also more frequent in the diamorphine group than in the methadone group (Table 2). If anything, our study suggests that patients in the diamorphine group had a more complex clinical course than patients on standard methadone maintenance.

To summarize, this German survey study provides further evidence that, under the right circumstances, diamorphine therapy may offer certain advantages over conventional opioid replacement. Greater satisfaction with the substitute drug together with self-reported significant reductions in relapse-related behaviors and cravings tally with findings from clinical trials indicating that diamorphine-assisted therapy may improve retention, decrease illicit drug use, and enhance physical and mental health.

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Compliance with Ethical Standards

The project had been pre-approved by the institutional review board of the MSH Medical School Hamburg.

Ethical Standards The authors assert that all the procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, revised in 2008.

Conflict of Interest Stephanie P. E. Guillery, Sören Enge, and Golo Kronenberg report no conflict of interest. Rainer Hellweg has received honoraria from AstraZeneka, Janssen-Cilag, Lundbeck, Merz, Novartis, Otsuka, Pfizer, and Servier. Ulrich Bohr has received honoraria from AbbVie Deutschland GmbH & Co. KG, Bristol-Myers Squibb GmbH & Co KGaA, GILEAD Sciences GmbH, Janssen-Cilag GmbH, MSD Sharp & Dohme GmbH, Sanofi-Aventis Deutschland GmbH, and ViiV Healthcare GmbH. Hagen Kunte has received honoraria from Bayer, Biogen, Genzyme, Merck, Novartis, Roche, and Teva.

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