Quality of Life in Opioid Replacement Therapy: A Naturalistic Cross-Sectional Comparison of Methadone/Levomethadone, Buprenorphine, and Diamorphine Patients

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Keywords

Methadone · Diamorphine · Buprenorphine · Quality of life · Opioid replacement therapy

Abstract

Background: Research on quality of life (QoL) of chronically ill patients provides an opportunity to evaluate the efficacy of long-term treatments. Although it is established that opioid replacement therapy is an effective treatment for opioid-dependent patients, there is little knowledge about physical and psychological functioning of QoL for different treatment options. **Objectives:** Altogether, 248 opioid-dependent patients receiving substitution treatment with either methadone/levomethadone ($n = 126$), diamorphine ($n = 85$), or buprenorphine ($n = 37$) were recruited in 6 German therapy centers. **Methods:** Sociodemographic data were collected. QoL – physical and psychological functioning – for different substitutes was assessed using the *Profile of the Quality of Life in the Chronically Ill* (PLC) questionnaire. **Results:** Patient groups were similar regarding age and duration of opioid dependence. Employment rate was significantly higher ($p < 0.005$, $\phi = 0.22$) in the buprenorphine group (46%) compared to methadone (18%). Dosage adjustments were more

frequent ($p < 0.001$, $\phi = 0.29$) in diamorphine (55%) than in methadone (30%) or buprenorphine (19%) patients. Buprenorphine and diamorphine patients rated their physical functioning substantially higher than methadone patients ($p < 0.001$, $\eta^2 = 0.141$). Diamorphine patients reported a higher psychological functioning ($p < 0.001$, $\eta^2 = 0.078$) and overall life improvement ($p < 0.001$, $\eta^2 = 0.060$) compared to methadone, but not compared to buprenorphine patients (both $p > 0.25$). **Conclusion:** Measurement of important QoL aspects indicates significant differences for physical and psychological functioning in patients receiving the substitutes methadone/levomethadone, diamorphine, and buprenorphine. This could be relevant for the differential therapy of opioid addiction.

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Published by S. Karger AG, Basel

Introduction

Dependence on opioids is one of the most frequent substance-related disorders worldwide [1]. Of an estimated 2.1 million opioid-dependent individuals in the USA, approximately 17% receive opioid replacement therapy [2]. In Germany, almost 80,000 of the estimated 166,000

opioid-dependent individuals receive opioid replacement therapy [1, 3], which represents about 48% of the opioid-dependent population. Opioid replacement therapy is today considered the most effective treatment for opioid-dependent patients [4]. However, often existing accompaniments of opioid dependence, such as psychiatric comorbidities, infectious diseases, and psychological distress and stigmatization, can render the treatment largely challenging and often require a multidimensional approach to therapy [5–8]. In Germany, the most commonly used substitutes are methadone (41%), levomethadone (34%), and buprenorphine (23%) [9]. While buprenorphine and levomethadone are increasingly used in therapy, methadone substitution has been declining since the turn of the millennium [9, 10]. Intravenous application of diamorphine as an opioid replacement treatment is limited in its use (1%). It is only prescribed in specialized outpatient clinics in 10 German cities [9] and has been recognized as a legal treatment method in substitution therapy for severely dependent patients since 2009 after a lengthy legal discernment process [11]. A summary of the results of international studies on diamorphine treatment suggests that diamorphine-assisted treatment might be superior to methadone-assisted treatment in terms of patients' health development, illegal drug use, high-risk injection behavior, and delinquency [12–14]. Treatment improvements were observed in nonresponding patients in methadone therapy, who then benefited more from diamorphine therapy [15, 16]. Primary goals of the substitution-based treatment of opioid-dependent patients are health stabilization as well as personal, social, and family functioning [17, 18], and thus an increase in essential quality of life (QoL) characteristics of the patients. Compared to untreated opioid users, the QoL of patients with opioid replacement therapy is increased by the treatment [19, 20]. However, in contrast to conventional substitutes such as methadone or buprenorphine, there are only few studies on QoL under diamorphine-assisted substitution. Karow et al. [21] investigated diamorphine patients versus methadone patients in terms of health-related QoL. Diamorphine patients were found to have a higher health-related QoL than methadone patients. When comparing diamorphine patients with patients with conventional opioid replacement therapy, it should be considered that different treatment conditions may exist, such as stricter requirements, supervised dosing, or frequency of presence in the facility in diamorphine treatment, which may affect patient perception of their treatment [22]. QoL studies with methadone and buprenorphine substitution suggest that both have simi-

lar positive effects on the course of treatment [23–25]; however, the retention rate was found to be better with methadone treatment than with buprenorphine [4, 26, 27]. With a comparison to patients' misuse of opioids in the substitution therapy, no difference between the individual replacement opioids (methadone, buprenorphine, and buprenorphine-naloxone) was discovered, so that the particular patient features are to play an important role for substitution treatment aims [28]. For example, there is an increased abuse of opiates in patients with psychiatric comorbidities such as attention-deficit/hyperactivity disorder [29]. Research on QoL is of increasing relevance, not only because it is associated with patient's remission in opioid replacement treatment [30], but also with treatment quality and success [31–33].

The main aim of the present research is to compare the substitutes methadone/levomethadone, buprenorphine, and diamorphine on 2 important aspects of QoL, since such comparisons of the 3 substitution medicaments have so far received only little attention. Therefore, the 2 subscales physical and psychological functioning of the Quality of Life Questionnaire in the Chronically Ill (PLC [34]) were assessed. The subscale physical functioning includes questions about resilience and coping with everyday tasks, capacity of performance, and physical constraints. The subscale psychological functioning measures relaxation, sleeping behavior, appetite, and social and personal enjoyment qualities. Because main aims of opioid replacement therapy are to improve personal, social, and family functioning, as well as the reintegration into everyday life [18, 35], these 2 subscales, physical and psychological functioning of QoL, are used to represent those key objectives.

Methods

Participants

A total of 248 individuals participated in the study. The survey took place in 6 medical institutions with addiction care in Berlin, Hamburg, and Bavaria in 2018. Patients had to be at least 18 years of age and at least 6 months in treatment. Diamorphine patients ($n = 85$) were surveyed in 2 outpatient clinics in Berlin and Hamburg. These patients were either treated exclusively with diamorphine or with diamorphine in combination with levomethadone or extended-release morphine. Methadone/levomethadone patients ($n = 126$) were recruited in 2 outpatient clinics and a general practice in Berlin. For the purposes of simplified notation, the term levomethadone has been subsequently omitted, so that both methadone and levomethadone patients are included under the term methadone patients. Buprenorphine patients ($n = 37$) were also recruited in the 2 outpatient clinics in Berlin and in 2 general practitioner practices in Berlin and Bavaria. The practice staff of-

ferred the patients the questionnaire on a voluntary and anonymous basis in a survey period of 4–12 weeks. The entire study project was preapproved by the Ethics Committee of the Medical School Hamburg. Due to the voluntariness and complete anonymity of study participation, a declaration of consent of the patients was not required, what has been approved by the Ethics Committee of the Medical School Hamburg. The questionnaires were sealed by the patients in an opaque envelope and collected in a nontransparent box. As compensation, they received sweets for their participation. The survey was approved by the Institutional Review Board of the MSH Medical School Hamburg.

Measures

Sociodemographic and clinical data were measured via self-report. Investigated clinical features included *opioid prescribed for replacement therapy, duration of maintenance treatment, current and previous dosage, frequency of daily medication intake, rules for take-home medication, duration of drug dependency, and current employment status*. The subscales physical and psychological functioning, which each contained eight 5-step Likert scale items (ranging from *not at all* to *very much*), were assessed using the PLC Questionnaire – Quality of Life Questionnaire for the Chronically Ill [34]. Additionally, the perceived improvement in life through substitution treatment in general was asked on a 5-step Likert scale (ranging from *not at all* to *very much*): *How much has my life improved through substitution therapy with the current substitute*. Furthermore, a 5-level Likert scale (0–4) was also used to ask how frequently and intensively patients would evaluate their co-use of illegal drugs and their consumption of alcohol (I never co-use illicit drugs–I co-use illicit drugs daily).

Procedure

In the outpatient clinics and practices, the questionnaires were made available to the patients for voluntary participation. The participants were informed about the anonymity and voluntariness of study participation, as well as about the procedure, by the briefed practice personnel. Patients were invited to complete the questionnaire in a separate room. After an agreed period between 4 and 12 weeks, the box and the questionnaires were collected from the outpatient clinics.

Statistical Analyses

Statistical analyses were performed with IBM SPSS 25.0. Mean $\pm$ standard deviation, standard error, and confidence interval are reported. A one-way ANCOVA calculation was used to compare the substitution groups on the subscales physical and psychological functioning of the PLC, controlling for relevant variables such as sociodemographic characteristics. Variance homogeneity of both subscales was tested using the Levene test (all $p > 0.05$). Kolmogorov-Smirnov tests and Q-Q plots showed that the PLC scales are normally (psychological functioning) or almost normally (physical functioning) distributed. Nonetheless, there is a rather strong robustness of the ANCOVA against violations of normality [36] in the light of the used sample size. The effect size in the main effect of ANCOVA is indicated by the partial eta square (η^2). Testing for multicollinearity of the independent variables resulted in tolerance values of 0.910–0.994 (VIF values of 1.006–1.099) for the variables substitute, employment status, duration of addiction, duration of treatment, dose course, take-home medication, substitution intake frequency, and gender. These calculated VIF values

consequently provide no indication of multicollinearity. Depending on the scale level (metric/nominal), further comparisons between the groups were performed using one-way ANOVA with partial eta square (η^2) as effect size, or χ^2 test with phi (ϕ) as effect size. Cronbach's alpha was used to calculate the internal consistency of the scales. Correlations between variables were calculated using a correlation analysis by Pearson or, respectively, Spearman, depending on the distribution of the variables.

Results

Sociodemographic Analysis of the Sample

As shown in Table 1 depicting sociodemographic data, no significant difference between the substitution groups was found for the variable age ($F[2, 247] = 2.14, p = 0.119, \eta^2 = 0.017$) and duration of dependency. A comparison of the 3 groups in terms of gender showed a significant difference ($p < 0.05; \phi = 0.19$). Buprenorphine patients had a higher proportion of women than diamorphine patients ($p < 0.005$) while methadone patients did not differ significantly from buprenorphine ($p = 0.134$) or diamorphine ($p = 0.051$) patients. When comparing the 3 groups in terms of treatment duration, there was a significant difference ($p < 0.005, \phi = 0.19$). Methadone patients reported significantly more often that they have been in treatment for >2 years than diamorphine patients ($p < 0.01$). Buprenorphine patients did not differ significantly from methadone ($p = 0.413$) or diamorphine ($p = 0.182$) patients. When comparing the 3 groups in regard to the employment status, a significant difference was observed ($p < 0.005, \phi = 0.22$). Buprenorphine patients were significantly more likely to be in employment than methadone patients ($p < 0.005$). Diamorphine patients differed significantly neither from methadone patients ($p = 0.087$) nor from buprenorphine patients ($p = 0.057$) in terms of their employment status. A comparison of the 3 substitute groups concerning the dose course of the last 6 months of treatment showed a significant difference ($p < 0.001, \phi = 0.29$). Diamorphine patients had significantly more dose adjustments than methadone patients ($p < 0.001$) and buprenorphine patients ($p < 0.001$). Methadone patients and buprenorphine patients did not differ significantly ($p = 0.179$). Buprenorphine patients reported to receive take-home prescription significantly more often than methadone patients ($p < 0.05, \phi = 0.20$). Note that take-home prescription for diamorphine is not allowed because of legal restrictions [37]. The substitution groups showed a significant difference in the frequency of daily intake of their medication ($p < 0.001, \phi = 0.57$). For diamorphine, a multiple daily use was reported sig-

Table 1. Sociodemographic distribution of the sample and χ^2 test for mean value difference

	Methadone (N = 126)	Diamorphine (N = 85)	Buprenorphine (N = 37)	χ^2 (df)	p value	ϕ value
Age mean (SD)	46.12 (10.65)	43.20 (9.65)	46.08 (11.84)		0.12	
Gender,* N (%)						
Male	85 (68)	67 (79)	20 (54)	χ^2 (2) = 8.60	<0.05	0.19
Female	41 (32)	17 (20)	17 (46)			
Missing values	–	1	–			
Duration of maintenance treatment,* N (%)						
6–24 months	17 (13)	26 (31)	7 (19)	χ^2 (2) = 9.20	<0.05	0.19
>24 months	109 (87)	59 (69)	30 (81)			
Missing values	–	–	–			
Frequency of medication intake per day,** N (%)						
Once a day	99 (79)	18 (21)	31 (84)	χ^2 (2) = 81.25	<0.001	0.57
Multiple times a day	26 (21)	66 (78)	6 (16)			
Missing values	1	1	–			
Take-home privileges,* N (%)						
No take-home medication	35 (28)	85 (100)	3 (8)	χ^2 (1) = 6.40	<0.05	0.20
Take-home medication	89 (71)	– (0)	34 (92)			
Missing values	2	–	–			
Duration of drug dependence, N (%)						
0–5 years	1 (1)	1 (1)	2 (5)	χ^2 (6) = 11.16	0.084	0.21
5–10 years	20 (16)	6 (7)	4 (11)			
10–20 years	36 (29)	17 (20)	9 (24)			
>20 years	68 (54)	61 (72)	22 (60)			
Missing values	1	–	–			
Current work situation,* N (%)						
In employment	23 (18)	24 (28)	17 (46)	χ^2 (2) = 11.85	<0.005	0.22
Unemployed, retirement	103 (82)	61 (72)	20 (54)			
Missing values	–	–	–			
Dosage changes in the last 6 months,** N (%)						
Stable dose	88 (70)	37 (44)	30 (81)	χ^2 (2) = 20.60	<0.001	0.29
Dose adjustments	38 (30)	47 (55)	7 (19)			
Missing values	–	1	–			

SD, standard deviation; N, number of subjects; ϕ , effect size by phi value; p value, significance level of 0.05; χ^2 , χ^2 value of cross tabulation; df, degrees of freedom. * Significant difference. ** Highly significant difference.

nificantly more often than for methadone ($p < 0.001$) and buprenorphine ($p < 0.001$). Methadone patients did not differ significantly from buprenorphine patients ($p = 0.538$).

QoL – Physical and Psychological Functioning

For PLC subscales physical and psychological functioning, good internal consistencies were obtained (physical functioning: Cronbach's alpha = 0.85; psychological functioning: Cronbach's alpha = 0.80). A one-way ANCOVA between the 3 substitution groups on physical functioning was conducted, controlling for those variables for which substantial group differences were observed (gender, treatment duration, employment status,

dose course, take-home medication, and substitution intake frequency), as outlined above. There was a highly significant difference in physical functioning between the substitution groups, $F(2, 232) = 12.64$, $p < 0.001$, $\eta^2 = 0.141$. Bonferroni-adjusted post hoc test showed that diamorphine patients scored significantly higher ($p < 0.001$) than methadone patients. Buprenorphine patients scored significantly higher ($p < 0.001$) than methadone patients. Between diamorphine and buprenorphine patients, no difference could be detected ($p = 0.719$). Table 2 shows the means and confidence intervals of the substitution medication groups of the subscale of physical functioning.

A one-way ANCOVA between the 3 substitution groups on psychological functioning was applied, again

Table 2. Mean values and confidence intervals of physical functioning, psychological functioning, and overall life improvement of substitute groups

	N	Mean (SD)	SE	95% CI, LL–UL
<i>Physical functioning**</i>				
Methadone	114	1.79 (0.64)	0.07	1.65–1.92
Buprenorphine	31	2.45 (0.63)	0.13	2.20–2.70
Diamorphine	80	2.30 (0.76)	0.09	2.12–2.49
<i>Psychological functioning**</i>				
Methadone	123	2.18 (0.65)	0.06	2.05–2.31
Buprenorphine	31	2.37 (0.60)	0.12	2.14–2.61
Diamorphine	84	2.68 (0.64)	0.09	2.51–2.86
<i>Life improvement**</i>				
Methadone	126	2.69 (1.19)	0.10	2.49–2.89
Buprenorphine	37	3.09 (0.91)	0.18	2.73–3.45
Diamorphine	84	3.38 (0.76)	0.15	3.09–3.67

N, number of subjects; SD, standard deviation; SE, standard error; CI, confidence interval; LL, lower limit; UL, upper limit. *Significant difference; **highly significant difference.

controlling for those variables with substantial group differences as described above. There was a highly significant difference between the substitution groups, $F(2, 235) = 4.55$, $p < 0.001$, $\eta^2 = 0.078$. Bonferroni-adjusted post hoc test showed that diamorphine patients scored significantly higher ($p < 0.001$) than methadone patients in psychological functioning. Between the diamorphine and the buprenorphine group, no difference could be observed ($p = 0.296$). Also, no significant difference was found between the methadone and buprenorphine groups ($p = 0.245$). Table 2 shows the means and confidence intervals of the substitution groups of the subscale psychological functioning.

Moreover, there were significant negative correlations between physical functioning and severity of co-use of illicit drugs ($r = -0.274$, $p < 0.001$) and alcohol consumption ($r = -0.204$, $p < 0.001$). Also, between psychological functioning and the self-reported intensity of illicit substance co-use ($r = -0.328$, $p < 0.001$) and alcohol consumption ($r = -0.191$, $p < 0.001$), highly significant negative correlations were detected.

Overall Life Improvement

A one-way ANCOVA between the 3 substitution groups on overall life improvement was conducted and again controlling for the abovementioned with substantial group differences. There was a highly significant difference between the 3 substitution groups, $F(2, 228) =$

5.57 , $p < 0.001$, $\eta^2 = 0.060$. Bonferroni-adjusted post hoc test showed that diamorphine patients scored significantly higher ($p < 0.001$) than methadone patients. There was a statistical trend suggesting that buprenorphine patients scored higher ($p = 0.052$) than methadone patients. Between the diamorphine and the buprenorphine group, no difference could be observed ($p = 0.381$). Table 2 shows the means of *overall life improvement* of the 3 substitution groups. Figure 1 illustrates the means of the 3 substitute groups in terms of physical and psychological functioning and perceived improvement in life through substitution treatment. Between the perceived overall life improvement and self-reported co-use of illicit drugs ($r = -0.586$, $p < 0.001$) and alcohol consumption ($r = -0.229$, $p < 0.001$), highly significant moderate correlations have been found.

Discussion

The aim of the present study was to compare self-reported physical and psychological functioning as well as the perceived improvement in life as a result of the substitution therapy in patients receiving either methadone/levomethadone, buprenorphine, or diamorphine as a substitute. For a correct interpretation of the data, it is important to point out that in a substantial number of patients who received diamorphine, also levomethadone

Fig. 1. Physical and psychological functioning and overall life improvement in substitution therapy. Mean values of methadone, buprenorphine, and diamorphine patients of the dimensions of the QoL report.

or extended-release morphine was prescribed as a bridging therapy in order to prolong intervals between diamorphine injections. Between the 3 treatment groups, significant differences for certain sociodemographic parameters, for example, gender, treatment duration, employment rate, dose course, take-home medication, and substitution intake frequency, were observed: in the buprenorphine group, the proportion of women was higher than in diamorphine- or methadone/levomethadone-treated patients. Average treatment duration in diamorphine patients was shorter compared to methadone; however, possible previous treatments with other substitutes were not recorded in this survey. There was no significant difference in the duration of drug dependence between the 3 treatment groups. Buprenorphine patients more often had take-home privileges than methadone patients. Because in Germany take-home prescription of diamorphine is not permitted [37], the proportion of take-home prescriptions for diamorphine was 0%. However, diamorphine-treated patients could also receive take-home prescriptions with other oral substitutes [38]. As expected, methadone/levomethadone and buprenorphine generally were taken once daily according to their long half-life time [39, 40] while most diamorphine patients needed multiple dosages per day because of the short duration of action [39, 40]. Therefore, it is interesting that despite of the need of multiple doses per day, 28% of the patients with diamorphine therapy but only 18% of methadone-treated patients reported to be in employment, which however did not reach statistical significance at the conventional significance threshold ($p = 0.087$). With 46%

employment rate, buprenorphine patients were significantly more often employed than patients with methadone as a substitute. Dose adjustments, which are usually an indicator for patient instability, were found to be more frequent in the diamorphine group than in methadone- or buprenorphine-treated patients. In the present study population, diamorphine patients were allowed to choose their daily dose themselves. Therefore, patients could vary using diamorphine as a self-medication for psychological stress situations, as it was previously described by Khantzian [41]. In this sense, dose changes in diamorphine-treated patients must not necessarily be interpreted as a sign of instability, but rather as an expression of a self-determined option to react to ups and downs in daily life and phases of changing symptom intensity of psychiatric comorbidity. This is in line with previous findings that the extent to which patients can determine their substitution dose themselves is an important quality parameter for the assessment of substitution therapy from the patient's perspective [22, 42, 43].

The contribution of the sociodemographic and treatment-relevant variables to the differences observed between the substitution groups regarding the QoL dimensions was controlled in the ANCOVA model. Mean self-reported physical function was significantly higher in patients who received buprenorphine or diamorphine than in patients with methadone treatment. Psychological functioning was reported highest in the diamorphine group and lowest in the methadone/levomethadone group, and the buprenorphine group was in between. However, the difference between diamorphine and bu-

prenorphine was not statistically significant. Similarly, the methadone and buprenorphine group did not significantly differ with regard to the QoL dimension psychological functioning. The reported perceived improvement in life as a result of the substitution therapy was highest with diamorphine substitution, followed by buprenorphine treatment, and lowest in methadone/levomethadone therapy, although there was no statistically significant difference between diamorphine and buprenorphine substitution. The results of this study suggest that diamorphine treatment, often combined with other substitutes according to the individual needs of the individual patient, as outlined above, is superior to methadone/levomethadone treatment with respect to physical functioning, psychological functioning, and overall life improvement. Therefore, the results of the present study support previous findings that diamorphine as a substitute can be superior to methadone/levomethadone in specific subgroups such as patients with high-risk injection behavior or with co-consumption of illicit substances, delinquency [12, 13], general health status [38, 44], and patients with psychiatric comorbidities [45–47]. The fact that diamorphine substitution seems to be particularly useful for patients with challenging treatment is also supported by the circumstance that in Germany, patients who are considered for diamorphine therapy must meet certain criteria for this form of therapy, which are at least 5 years of predominantly intravenous substance use and at least 2 failed therapy attempts in the past [11]. Despite these unfavorable preconditions, the results of the diamorphine-treated patients are remarkable. Moreover, because diamorphine therapy has been shown to be beneficial for patients with psychiatric comorbidities, which has already been identified as an inclusion criterion for diamorphine therapy [46], such patients may be selected more often for diamorphine as a substitute. Current research suggests the effectiveness of diamorphine which is able to reduce psychiatric symptoms, also due to its specific psychopharmacological properties [45–47]. Although no conclusions can be drawn about the causal direction of the correlation, it is still evident that there is a mutual influence on QoL and important treatment parameters, such as patients' high-risk co-use of illegal substances and alcohol consumption in opioid replacement therapy. In a comparative study on patients' opioid replacement treatment perception, it was found that patients under diamorphine therapy constated co-using illicit drugs less and experience less craving than patients under methadone treatment [48]. As one of the most prominent substitution therapy goals, reducing health-

endangering co-consumption of illicit substances ideally leads to a prognostically favorable course of therapy.

According to our results, the strength of buprenorphine may lie in physical functioning, that is, the ability to perform activities of daily living. This is particularly evident from the high rate of employment with 46% of patients in this group who report to be employed. In comparison with methadone/levomethadone, physical functioning in the buprenorphine group was significantly better. Note that diamorphine compared to buprenorphine substitution revealed similar results. It is already known that buprenorphine as a partial agonist is less sedative than full agonists such as methadone or diamorphine [49–51]. Clarity of thought, increased concentration and cognitive performance is maintained stronger under buprenorphine therapy [52–55]. Beyond that it provides an antidepressant effect that has been observed even in treatment-resistant patients [56, 57]. These factors may have contributed to the superiority of buprenorphine over methadone in terms of physical and psychological functioning.

Potential adverse factors of the diamorphine injection therapy in contrast to conventional oral therapies, for example, shorter half-life of the diamorphine medication, high-frequency multiple daily presence in the therapy facilities and resulting limitation of the patients' everyday life, and more complicated and stricter handling of the treatment by intravenous intake, may be compensated by other advantages of this form of treatment. Long attendance times in the therapy facilities and inflexibility regarding the dosage of the substitute are known as negative treatment factors [42, 58]. By the option to use a bridging substitute in addition to diamorphine, for example, extended-release morphine or methadone, patients get more autonomy and self-determination to organize professional and social life. Therefore, this potentially significant impact of the co-substitute would be very worth focusing on in future studies. Although questions were provided in the survey to collect information on additional prescribed bridging substitutes, the majority of the participants unfortunately did not answer them, so there is a lack of data in this regard.

In the participating diamorphine outpatient clinics, common rooms and offers of social interaction, such as cooking together, are provided. Considering the substantial amount of time patients spend in the facilities, such possibilities maybe regarded as an additional valuable resource for improving the QoL of the patients, which should be investigated also in future studies as an influencing factor. In this context, it is necessary to note

that there might be an effect of the participating institution characteristics on the parameters to be measured, for example, the size of the institution, quantity of patients, or the frequency and nature of doctor-patient contact. A prerequisite for the participation of the institutions in the present study is the agreement to keep the institution's name, as well as the nature and further characteristics, completely anonymous. For ethical and legal reasons, it is therefore not possible to incorporate characteristics of the institutions in the statistical analysis.

As a limitation of the study, the lack of registration of the response rates of the clinics, which was not recorded due to the anonymous survey, should be mentioned. The anonymous data collection, on the other hand, has the advantage that socially desirable answers can be decreased [59]. As further potential limitation, the size of the sample of test persons of the survey is to be mentioned. Recruitment of this specific target cohort proves to be challenging due to limited patient compliance and commitment to survey participation. However, a post hoc power analysis using G*Power [60] showed that with our minimal sample size of $N = 135$ and 3 patient groups and given an α of 0.05 and a statistical power ($1 - \beta$ error probability) of 0.80, we could detect effect sizes of $f = 0.20$. The voluntary participation may also result in a selection effect among patients to the point that physically and cognitively less impaired patients may be more likely to participate in the survey. In addition, a sociodemographic similarity in terms of the age and duration of drug addiction of the samples can be observed, which may indicate a comparability of the groups. However, the different framework conditions of substitution therapies must be taken into account, which may play a role in the perception of the quality of treatment. As mentioned above, diamorphine patients must meet criteria for severe dependence [11] so that this group of patients may be more severely impaired than the 2 groups receiving conventional substitution therapies. The nonrandomized distribution of the volunteers needs to be considered as a limitation of the study. As mentioned above, in order to receive diamorphine treatment in Germany, patients must have had at least 2 failed therapy attempts in the past. However, the multicenter survey attempted to counteract the distortion effects of the characteristics of the individual clinics. Although the potential influence of some very important variables was controlled, a possible impact of further variables on QoL, not collected in the present study, cannot be excluded.

Conclusion

In summary, the results of this study on opioid-dependent patients point to advantages of diamorphine and buprenorphine over methadone treatment in terms of physical and psychological functioning as central dimensions of QoL. Although the results need to be further examined and replicated in future studies, they may provide an impetus for the practical implementation of substitutes and for further research in the field of QoL under substitution-assisted therapy.

Acknowledgements

The authors would like to thank the practice staff for their assistance and support in data collection. They would like to thank all participants for their cooperation and participation in this study.

Statement of Ethics

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. The study project was preapproved by the Ethics Committee of the MSH Medical School Hamburg (Project No. EK-MSH-2018-01-2017). Based on the completely anonymous data survey, an informed patient consent was waived with the approval of the MSH Ethics Committee.

Conflict of Interest Statement

Stephanie P.E. Guillery, Sören Enge, and Golo Kronenberg report no conflicts of interest. Rainer Hellweg has received honoraria from AstraZeneca, 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.

Funding Sources

First author Stephanie P.E. Guillery was supported by a travel stipend by the Berlin Society of Psychiatry and Neurology.

Author Contributions

S.G.: design, organization, conceptualization and development of study project, data processing and interpretation of the results, writing, and revision of the manuscript. R.H.: organization and conceptualization of study project and interpretation of the results. G.K.: data processing and interpretation of the results, writing,

and supervision of the study. U.B.: data processing and interpretation of the results, subject recruitment, and writing. H.K.: organization, conceptualization and development of the study project, and interpretation of the results. S.E.: organization, conceptualization and development of the study project, data processing and interpretation of the results, revision, and supervision of the study.

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