Retention rate and substance use in methadone and buprenorphine maintenance therapy and predictors of outcome: results from a randomized study

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Abstract

This was a 6-month, randomized, flexible-dose study comparing the effects of methadone (Meth) and buprenorphine (Bup) on retention rate and substance use in a sample of 140 opioid-dependent, primarily heroin-addicted, patients who had been without opioid substitution therapy in the 4 weeks prior to the study. The major aims were to compare the efficacy of Bup and Meth in a flexible dosing regimen and to identify possible predictors of outcome. There were no major inhomogeneities between treatment groups. All patients also received standardized psychosocial interventions. Mean daily dosages after the induction phase were 44–50 mg for Meth and 9–12 mg for Bup. Results from this study indicate a favourable outcome, with an overall retention rate of 52.1% and no significant differences between treatment groups (55.3% vs. 48.4%). Substance use decreased significantly over time in both groups and was non-significantly lower in the Bup group. Predictors of outcome were length of continuous opioid use and age at onset of opioid use, although these were only significant in the Bup group. Mean dosage and other parameters were not significant predictors of outcome. Overall, the results of this study give further evidence that substitution treatment is a safe and effective treatment for drug dependence. Meth and Bup are equally effective. Duration of continuous opioid use and age at onset were found to have predictive value for negative outcome. The intensity of withdrawal symptoms showed the strongest correlation with drop-out. Future studies are warranted to further address patient profiles and outcome under different substitution regimens.

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Key words: Buprenorphine, drug dependence, methadone, outcome, substitution.

Introduction

The prevalence of use of opioids, including heroin, has markedly increased over the last few decades; the prevalence is ~0.4% in the population aged 15–64 yr (United Nations Office for Drug Control, 2005). Long-term studies among opioid addicts indicate a low abstinence and high mortality rate (Hser et al., 2001; Hulse et al., 1999). According to recent data, 27–38% of drug users die within 20 yr of starting regular drug use (Termorshuizen et al., 2005). Substitution treatment with opioid agonists such as methadone (Meth) is one of the major treatment options for patients, with proven efficacy in reducing opioid consumption and criminal behaviour, lowering rates of HIV/HBV infection and increasing retention rate and social functioning (Newman, 1987; Plomp et al., 1996; Sullivan et al., 2005; West et al., 2000). Meth is a synthetic µ-opioid receptor agonist with pharmacological activity similar to morphine. A number of clinical studies and meta-analyses found that, overall, Meth treatment significantly reduces the excess mortality associated with opioid use (Caplehorn et al., 1996; Dolan et al., 2005; Fugelstad et al., 1995; Langendam
et al., 2001; Mattick et al., 2004; Maxwell et al., 2005). Meth is also a cost-effective treatment in opioid dependence (Barnett, 1999).

More recently, buprenorphine (Bup) has been introduced into clinical practice as an alternative treatment. Bup is a weak, partial μ-opioid agonist and a κ-opioid receptor antagonist. Its unique profile includes a ceiling effect on agonist activity and slow dissociation from the μ-opioid that decreases toxicity and risk for overdose (Davids and Gastpar, 2004; Vormfelde and Poser, 2001). The drug undergoes extensive first-pass metabolism and is therefore administered sublingually. Bup was found to decrease craving and to block withdrawal symptoms in opioid-dependent patients, thus qualifying as an alternative to Meth (Ling et al., 1998; Pani et al., 2000). A number of studies have shown Bup also to be effective in substitution treatment (Amass et al., 2000; Bickel et al., 1999; Montoya et al., 2004; meta-analysis by West et al., 2000), although in some studies the retention rate was lower than in patients receiving Meth (meta-analysis by Barnett et al., 2001). There is some but limited evidence that patients receiving Bup are more likely to stay drug-free (West et al., 2000). Indirect comparison of data from cross-sectional studies suggested that mortality may be lower with Bup than with Meth, a finding supported by data from post-mortem studies (Pirnay et al., 2004; Soyka et al., 2005).

The Cochrane database indicates that both drugs are effective in treatment of opioid withdrawal and maintenance treatment, especially in combination with psychosocial treatment (Amato et al., 2004; Gowing et al., 2006; Mattick et al., 2004). In a recent and extensive systematic review of Meth and Bup for the management of opioid dependence, Connock et al. (2007) concluded that both drugs are effective. Most of the studies included in this analysis had a fixed-dose design and only a few a flexible-dose design. The retention rate in studies using flexible dosing was somewhat superior with Meth compared with Bup but there was no significant difference in opioid use.

In a review based on five Cochrane reviews of substitution maintenance treatments for opioid dependence (52 studies, 12,075 participants), Amato et al. (2005) concluded that Meth treatment is effective but also recommended that future clinical trials should collect data on a broad range of health outcomes and recruit participants from heterogeneous practice settings and social contexts to increase generalizability of results.

Very few randomized clinical studies have addressed the role of individual characteristics in the prediction of outcome with Meth or Bup treatment (Connock et al., 2007). We report data from a randomized clinical study, funded by the German Ministry of Health, that compared the effects of Meth and Bup in an outpatient and primary-care setting. The major aims were to compare the efficacy of Bup and Meth in a flexible-dose regimen and identify possible predictors of outcome.

**Method**

**Design**

This was a 6-month, randomized, prospective, intention-to-treat clinical study comparing the effects of Bup and Meth on retention rate, consumption of drugs, withdrawal symptoms and side-effects. Patients were also treated with standardized psychotherapeutic interventions consisting of 18 group sessions and/or an individually defined combination of activation of resources and coping with social conflicts.

The psychosocial treatment was planned for 6 months. A flexible dosing design was used. In case of unsatisfactory outcome or side-effects, a switch from Bup to Meth and vice versa was permitted.

Inclusion criteria were opioid dependence, a history of heroine abuse and minimum age of 18 yr; exclusion criteria were acute psychosis and any regular substitution treatment or any regular psychosocial treatment in the month prior to treatment.

The study protocol and informed consent was approved by the ethics commission of the University of Munich.

**Subjects**

A total of 140 subjects, who were admitted for treatment of opioid dependence to one of six outpatient clinics in Bavaria were included. Recruitment did not involve advertisements nor payments.

Each patient was informed about the study by the physician and also received written information about the study. Participation was completely voluntary, patients were assured that they would not receive any disadvantage in their medical care if they declined to participate. After signing a letter of consent to participate, patients were randomly assigned to the substitution drug. Seventy-six patients received Meth and 64 Bup.

**Measures**

Withdrawal symptoms were assessed with the Opiate Withdrawal Scale (OWS; Bradley et al., 1987), which
consisted of 32 symptoms that had to be rated on a four-point scale (none, mild, moderate, severe). The OWS was applied daily for the first 7 d (days 0–6) and afterwards on a weekly basis (weeks 1–26). The first 7 d (days 0–6) were analysed separately as an induction phase.

The staff of the respective substitution outpatient clinic (physicians or nurses) completed a questionnaire to assess the dosage and side-effects; questionnaires were completed daily for the first 7 d and then on a weekly basis for 26 wk. The questionnaire asked about 18 possible side-effects which have been reported to occur during substitution treatment with Meth or Bup.

Urine analyses to screen for concomitant use of opioids, cocaine, cannabis, amphetamines, barbiturates and benzodiazepines were performed weekly from weeks 1 to 26, but not from days 0 to 6. Alcohol use was assessed with a breathalyzer.

A structured interview, the EuropASI (Gsellhofer et al., 1999), was used to assess patient characteristics. This instrument measures a severity profile for each of the following areas: medical, economic, alcohol, drug, legal, family/social and psychiatric status. We used the composite scores in our analyses because they are less dependent on subjective ratings. Other data were not analysed in this study.

**Statistical analysis**

Statistical analyses were performed using SPSS statistical software, version 12.0 (SPSS Inc., Chicago, IL, USA), and included both descriptive statistics and inference statistical procedures.

Treatment group differences were evaluated using analysis of variance (one-way ANOVA) or t test for continuous variables and χ² test for categorical variables. For treatment × time effects, data were analysed with a two-factor repeated-measures ANOVA. A Kaplan–Meier survival analysis (log-rank test) was used to evaluate treatment retention. Binary logistic regression analyses (forward stepwise) were used to determine prediction variables for drop-out from treatment. Correlations were measured by non-parametric correlations (Spearman’s ρ). The two-tailed level of significance was p < 0.05.

**Results**

**Patient characteristics**

Patient characteristics are shown in Table 1. Sixty-six per cent of the subjects were male. Thirty-one per cent of the subjects lived with a partner, 13.6% alone and 11% with a parent. Forty-four per cent were unemployed. Fifty-four per cent had finished school and 6% had no school education. The mean age at the onset of continuous use of opioids was 16.35 yr (S.D. = 10.21 yr). On average, the subjects used opioids 77.3 times (S.D. = 75.2) during the last 6 months before the study began.

Comparisons of baseline demographic and social characteristics, age at commencement of continuous use of opioids, frequency of substance use in the 6 months prior to the study, number of suicide attempts and EuropASI profiles revealed no significant differences between groups.

Patients in the Bup group were significantly older (mean = 31.2 yr, S.D. = 8.6 yr) than those in the Meth group [mean = 27.9 yr, S.D. = 9.6 yr; t(137.45) = −2.17, p = 0.03]. When age was taken as a covariate in the variance analyses, it did not have any influence on the results.

ASI composite scores (medical status, employment status, drug use, psychiatric status) did not differ significantly between the groups at baseline.

Concerning psychiatric comorbidities, 12 patients suffered from affective disorders (4 Meth, 8 Bup), eight patients from a personality disorder (6 Meth, 2 Bup) and four from an anxiety disorder (2 Meth, 2 Bup). There was no significant difference between the two treatment groups. Regarding physical impairments, there were significantly more patients in the Meth group (n = 30) who suffered from chronic hepatitis C than in the Bup group (n = 14, χ²(2) = 7.03, p = 0.03).

The most common route of administration of opioids during the last month before the start of substitution treatment was the i.v. route in both groups (55% Meth, 56% Bup). This may explain the relatively high rate of hepatitis C infections. Seventeen per cent of the patients in the Meth group and 13% in the Bup group sniffed or smoked the substance. In each group only three patients indicated a mainly oral application of opioids such as Meth.

In total, 61.4% (n = 86) of the patients indicated that the opioid they used was never prescribed by a physician. Only four patients reported that they started to use opioids because of a medical prescription. It is unknown whether the remaining 50 patients were prescription opiate abusers or heroin abusers. Because of the young age at commencement of continuous opioid use (mean 16.35 yr) we may assume that most of them started to consume illegally and conclude that our sample consists primarily of heroin addicts. At start of treatment, 22 patients received concomitant medication, mainly...
ibuprofen, interferon and asthmatics (two patients each). There was no concomitant psychotropic medication.

**Treatment retention and reasons for drop-out**

Drop-out was defined as premature termination of substitution treatment in the respective institution for any reason. Three patients changed substitution substance from Meth to Bup, and eight patients from Bup to Meth.

In the following analysis, the patients who changed substitution drug are included in the group to which they were allocated at the start of treatment. A change in substitution drug was therefore not considered to be a drop-out in these cases.
Overall, 52.1% \((n = 73)\) of the patients completed the 26-wk study. The completion rate in the Meth group was 55.3% \((n = 42)\) and in the Bup group 48.4% \((n = 31)\). A Kaplan–Meier survival analysis found no significant difference in the retention rate between the groups (log-rank test, \(p = 0.42\)). Figure 1 shows the retention rate for both treatment groups throughout the 26-wk study period.

On average, patients in the Meth group \((n = 76)\) remained in treatment for 19.3 wk \((\text{S.D.} = 1.1 \text{ wk})\) and patients in the Bup group \((n = 64)\) for 18.6 wk \((\text{S.D.} = 1.2 \text{ wk})\).

If the patients who changed substitution drug during the study are excluded from the analysis, the retention rate is the same in both groups (53.7% for the Meth group and 53.6% for the Bup group; \(p = 0.91\)).

In both substance groups, there was a significant, positive correlation between drop-out and the severity of withdrawal symptoms, the severity of side-effects and the frequency of positive urine screenings for all drugs and for opioids, but not between drop-out and mean dosage (see Table 2). Of all included variables, the severity of withdrawal symptoms had the highest correlation with drop-out in both the Meth \((r = 0.70, p = 0.00)\) and the Bup group \((r = 0.56, p = 0.00)\).

A binary logistic regression analysis to predict drop-out by patient characteristics, with age, sex, living situation, employment status, education, psychiatric status, frequency of substance abuse during the past 6 months and age at commencement of continuous use of opioids as predicting variables, showed that age was the only significant variable at the start of continuous opioid use \((p = 0.00, \text{odds ratio} = 0.94, R^2 = 0.11)\). The younger the patients were when they began to use opioids regularly, the more likely they were to drop out of treatment. A non-parametric correlation analysis was performed separately for each group. It revealed that the correlation between age at commencement of continuous opioid use and drop-out was significant in the Bup group only \((r = 0.29, p = 0.01)\), as was the correlation between length of continuous opioid use and drop-out \((r = 0.30, p = 0.00)\).

The most frequently named reasons for drop-out were craving for drugs and concomitant use of illicit drugs (22% of patients), followed by the influence of partner (16%), doubts about the use of therapy (14%), concomitant use of medications (13%), doubts about being capable of living drug-free (11%) and being...

**Table 2.** Correlations between drop-out and severity of withdrawal symptoms, severity of side-effects, number of positive urine screenings for all drugs and for opioids and mean dosage for both treatment groups

<table>
<thead>
<tr>
<th></th>
<th>Drop-out (methadone, (n = 34))</th>
<th>Drop-out (buprenorphine, (n = 33))</th>
</tr>
</thead>
<tbody>
<tr>
<td>r</td>
<td>(0.70)</td>
<td>(0.56)</td>
</tr>
<tr>
<td>(p)</td>
<td>(0.00^{**})</td>
<td>(0.00^{**})</td>
</tr>
<tr>
<td>Severity of withdrawal symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity of side-effects</td>
<td>(0.53)</td>
<td>(0.37)</td>
</tr>
<tr>
<td></td>
<td>(0.00^{**})</td>
<td>(0.00^{**})</td>
</tr>
<tr>
<td>Number of positive urine screenings (all drugs)</td>
<td>(0.54)</td>
<td>(0.28)</td>
</tr>
<tr>
<td></td>
<td>(0.00^{**})</td>
<td>(0.02^{*})</td>
</tr>
<tr>
<td>Number of positive urine screenings (opioids)</td>
<td>(0.32)</td>
<td>(0.25)</td>
</tr>
<tr>
<td></td>
<td>(0.00^{**})</td>
<td>(0.03^{*})</td>
</tr>
<tr>
<td>Mean dosage</td>
<td>(0.10)</td>
<td>(-0.02)</td>
</tr>
<tr>
<td></td>
<td>(0.21)</td>
<td>(0.45)</td>
</tr>
</tbody>
</table>

\(* p < 0.05, ** p < 0.01.\)
confident of getting along without any therapy (11%) (see Table 3). Other reasons were doubts about the joys of a drug-free life, concomitant use of alcohol, contacts with friends, parents or children and confrontation with incriminating topics.

Six patients (4%) named side-effects of the substitution drug as the reason for drop-out; four of them were being substituted with Bup, two with Meth (see Side-effects and adverse events section below).

**Dosage**

In both treatment groups, the largest increase of dose took place in the first 7 d. The mean initial dose of the patients in the Meth group was 34.7 (s.d. = 16.1) mg on day 0. At the end of the first 7 d the mean dose of Meth had increased to 44.7 (s.d. = 20.1) mg. A further increase took place up to month 2 (mean = 49.8, s.d. = 22.6), then the mean dose decreased to 46.8 (s.d. = 25.3) mg in month 5, with a slight increase again in month 6 (mean = 49.1, s.d. = 26.7).

In the Bup group the mean initial dosage was 9.8 (s.d. = 5.5) mg on day 0 and increased to 12.1 (s.d. = 5.5) mg on day 6. Similar to the Meth group, the mean dosage then slightly decreased to 9.5 (s.d. = 4.7) mg by month 3 and increased again to 10.7 (s.d. = 5.2) mg in month 6.

There were no significant correlations between mean dosage and severity of withdrawal symptoms (r = 0.02, p = 0.43) or side-effects (r = 0.07, p = 0.30), or between mean dosage and positive urine screenings for all drugs (r = 0.06, p = 0.33) or for opioids (r = 0.19, p = 0.07).

**Concomitant drug use**

Rates of concomitant use of opioids, benzodiazepines, cocaine and all drugs, including opioids, cannabis, amphetamines, cocaine, barbiturates and benzodiazepines, are shown in Figure 2. In the rate of all drugs every patient was included with at least one positive urine sample. Results are shown for the first 2 wk together, then monthly for both groups (Meth, Bup). Missing urine screenings were not counted as positive samples.

In both treatment groups the rates of opioid-positive urine screenings decreased significantly from the first 2 wk to month 6 [F(6) = 6.26, p = 0.00]. There was also a significant decrease in the use of benzodiazepines [F(6) = 6.74, p = 0.00] and of all drugs [F(6) = 13.46, p = 0.00] over the same period. However, the concomitant use of cocaine remained relatively stable over time [F(6) = 1.59, p = 0.15].

In the first 2 wk of the study, 64% of the subjects (n = 90) had at least one positive urine analysis but by the end of the study the percentage had decreased to 34% (n = 48). As can be seen in Figure 2, there was a clear drop between month 2 (61% positive urine screenings) and month 3 (42% positive urine screenings).

There was no significant difference in the percentage of positive urine analyses for opioids, benzodiazepines, cocaine or all drugs between the groups and there were also no significant interaction effects. However, the Bup group had a lower overall concomitant drug use than the Meth group, although the difference was not significant, and a statistical trend towards a lower consumption of benzodiazepines [F(1) = 3.59, p = 0.06].

After opioids and benzodiazepines, cannabis was the third most frequently used drug. The percentage of patients with a positive cannabis result decreased from 25.0% in the first 2 wk to 17.6% in month 6 in the Meth group, and from 17.5% to 12.3% in the Bup group. Again, this decrease over time was significant in both groups [F(6) = 2.33, p = 0.03].

Overall, there were eight positive (6 Meth, 2 Bup) and 45 negative breathalyzer tests (26 Meth, 19 Bup). The concomitant use of alcohol was not automatically tested by physicians and only checked if there was clinical evidence for an alcohol use disorder.

**Withdrawal symptoms**

On the first day of substitution the most frequent withdrawal symptoms were perspiration (60.7% of all patients), followed by rhinorrhea (56.5%), fatigue (55.0%), restlessness (55.0%), sleeplessness (52.9%), loss of appetite (52.9%), sensation of cold (51.4%), hot and cold shivers (50.7%) and weakness (50.7%).

Table 3. Most frequently named reasons for drop-out (n = 64)

<table>
<thead>
<tr>
<th>Reasons for dropout</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Craving for drugs</td>
<td>31</td>
<td>22</td>
</tr>
<tr>
<td>Concomitant use of illicit drugs</td>
<td>31</td>
<td>22</td>
</tr>
<tr>
<td>Family/partner</td>
<td>23</td>
<td>16</td>
</tr>
<tr>
<td>Lack of motivation</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td>Concomitant use of legal drugs</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td>Doubts about being capable of leading a drug-free life</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Being confident about getting along without therapy</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Side-effects</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>
When the OWS scores were summed to assess the overall severity of withdrawal symptoms, it was found that withdrawal symptoms decreased significantly in the first 7 d $[F(6) = 14.7, p = 0.00]$. As Figure 3 shows, in the first 7 d the mean OWS scores of the Meth group were slightly lower than those of the Bup group. However, this difference did not reach statistical significance $[F(1) = 1.25, p = 0.27]$. From weeks 1 to 26 there was a further significant decrease in the mean OWS scores in both groups $[F(25) = 16.03, p = 0.00]$ and a significant interaction effect $[F(25) = 2.40, p = 0.00]$ between time and substitution drug. The withdrawal symptoms were more severe in the Bup group in the first 7 d and at week 1 whereas after week 12 the Meth group showed more withdrawal symptoms.

The long-term withdrawal states have to be interpreted carefully, as the percentage of concomitant drug use remains relatively high throughout the study. In the Meth group 45 patients were still in treatment at month 6. Twenty-seven (60%) of them had at least one positive urine analysis in this month, mostly for benzodiazepines and opioids. In the Bup group, 16/31 patients (52%) had at least one positive urine analysis in the last month of the trial, mostly for opioids.

Table 4 shows the withdrawal symptoms that were estimated as most severe on the four-point rating scale during the first 7 d. Perspiration and sleeping problems were the symptoms with the highest intensity, followed by loss of appetite, restlessness, sensation of cold, rhinorrhoea, hot and cold shivers and tiredness. The only significant differences between the groups were found for sensation of cold ($p = 0.01$) and rhinorrhoea ($p = 0.03$), both with a higher mean in the Bup group.

**Responder analysis**

Analysis of the reduction of withdrawal symptoms at the individual level showed that 60.3% of the patients...
on Meth and 70.2% of those on Bup were positive responders in the first 7 d, i.e. they showed a decrease in severity of withdrawal symptoms from day 0 to day 6. We defined positive responders as those showing a reduction in the overall OWS score of $\geq 3$ from day 0 to day 6. A total of 17.6% of the patients in the Meth group and 21.1% in the Bup group had no responder reaction (non-responders), which was defined as a reduction in the OWS score of $\geq 2$ from day 0 to day 6.

The percentage of negative responders, defined as subjects with an increase in the OWS score of $\geq 3$ from day 0 to day 6, was 15% in the Meth group and 5% in the Bup group. This difference just failed to reach significance $[\chi^2(1) = 3.44, p = 0.06]$.

Table 5 shows the comparison between the average dose of positive responders and negative responders (including non-responders) on day 0 and day 6 separately for each substance group. In both treatment groups the positive responders had a higher starting dose and thereafter a larger increase in the average dosage than the group of negative and non-responders.

### Side-effects and adverse events

The difficulty in measuring side-effects is that they can hardly be discriminated from withdrawal symptoms. Most of the symptoms can occur simultaneously as a side-effect or as a withdrawal symptom. Side-effects occur within a certain time after the beginning of intake of the substance and can be of temporary nature only and disappear later. It makes sense to compare the side-effects at different time-points, e.g. at weeks 1, 4 and 12.
Table 6. Side-effects in both treatment groups by number (percentage) of subjects who indicated them

<table>
<thead>
<tr>
<th>Side-effect (week 1)</th>
<th>Buprenorphine (n = 64)</th>
<th>Methadone (n = 76)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perspiration</td>
<td>18 (28.1)</td>
<td>27 (35.5)</td>
<td>0.35</td>
</tr>
<tr>
<td>Sensation of cold</td>
<td>15 (23.4)</td>
<td>18 (23.7)</td>
<td>0.97</td>
</tr>
<tr>
<td>Akathisia</td>
<td>13 (20.3)</td>
<td>19 (25.0)</td>
<td>0.51</td>
</tr>
<tr>
<td>Headache</td>
<td>13 (20.3)</td>
<td>11 (14.5)</td>
<td>0.50</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>11 (17.2)</td>
<td>17 (22.4)</td>
<td>0.25</td>
</tr>
<tr>
<td>Dysphoria</td>
<td>11 (17.2)</td>
<td>11 (14.5)</td>
<td>0.66</td>
</tr>
<tr>
<td>Tiredness</td>
<td>10 (15.6)</td>
<td>17 (22.4)</td>
<td>0.31</td>
</tr>
<tr>
<td>Obstipation</td>
<td>9 (14.1)</td>
<td>10 (13.2)</td>
<td>0.88</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (10.9)</td>
<td>5 (6.6)</td>
<td>0.36</td>
</tr>
<tr>
<td>Fear</td>
<td>6 (9.4)</td>
<td>9 (11.8)</td>
<td>0.64</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>6 (9.4)</td>
<td>2 (2.6)</td>
<td>0.09</td>
</tr>
<tr>
<td>Euphoria</td>
<td>4 (6.3)</td>
<td>4 (5.3)</td>
<td>0.80</td>
</tr>
<tr>
<td>Pupil dilatation</td>
<td>4 (6.3)</td>
<td>5 (6.6)</td>
<td>0.79</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (4.7)</td>
<td>2 (2.6)</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Table 6 displays the side-effects separately for the Bup and the Meth groups in week 1. There was no significant difference between the groups in the frequency of any of the listed symptoms either in week 1 or in week 4. The most frequent side-effects in the Bup group were perspiration, sensation of cold, akathisia and headache. In the Meth group the most frequent symptoms were perspiration, akathisia, sensation of cold, drowsiness and tiredness. In week 12 significantly more patients substituted with Bup reported headache than did those with Meth \( x^2 (1) = 5.16, p = 0.02 \).

When the side-effect ratings on the four-point rating scale were summed to give an overall severity score, side-effects were found to decrease significantly from day 0 to day 6 \( F(6) = 17.99, p = 0.00 \), and then from week 1 to week 26 \( F(25) = 11.56, p = 0.00 \). There were no significant differences in severity score between the groups.

Four patients in the Bup group and two in the Meth group dropped out because of side-effects. The patients on Bup suffered most frequently from tiredness, dizziness, perspiration and nausea, the patients on Meth from obstipation.

In the Bup group, one patient suffered from an epileptic seizure of unknown cause. Seven patients in the Bup group and two in the Meth group had to be detoxified in hospital for drug dependence. One patient in the Bup group had to be treated in hospital for unknown reasons. Besides these no major adverse events occurred.

**Discussion**

Drug dependence is a ‘chronic relapsing disorder’ (O’Brien, 1994). Abstinence-oriented interventions are effective but may work only in a subgroup of motivated patients with stable living conditions and adequate social support (Flynn et al., 2003; review by van den Brink and Haasen, 2006).

Currently, substitution treatment with opioid agonists is widely accepted as a first-line treatment for many patients with opioid dependence (White and Lopatko, 2007). Both Meth and Bup have been reported to be effective in the treatment of opioid dependence but studies have produced mixed results on outcome (retention rate, drug use) and safety (mortality) (Connock et al., 2007).

This was a randomized trial to compare the effects of Meth and Bup in the treatment of opioid dependence and to identify possible predictors of outcome using a flexible-dose design reflecting real-world practice. Mean doses used in this study were moderate for both Meth (44–50 mg) and Bup (9–12 mg).

With respect to individual characteristics, since the inclusion criteria allowed no substitution treatment for 4 wk before the study our patients may represent a more chronic group than those included in other randomized trials (Connock et al., 2007).

In brief, the data from this study did not show any significant differences in outcome between Meth and Bup, although the retention rate was slightly higher in the Meth group (55.3% vs. 48.4%) if the change in substitution substance remained unconsidered. If these patients were excluded, the retention rate was almost equal (53.7% vs. 53.6%). Drug use was slightly lower in the Bup group. Since there were no baseline inhomogeneities between treatment groups, except for hepatitis C prevalence and age, the main result is that both drugs were equally effective in the treatment of opioid dependence. The retention rate was within the range of or higher than that found in other studies (Farre et al., 2002; Gerra et al., 2004; Vigezzi et al., 2006; West et al., 2000). Connock et al. (2007) reported an average retention on treatment with Bup of 44% after 24 wk for flexible dosing studies. A few older studies had indicated a somewhat higher retention rate on Meth compared to Bup (Fischer et al., 1999; Kosten et al., 1993; Mattick et al., 2003, 2004). Different dosages may play a significant role in this respect.
Unlike other studies (Vigezzi et al., 2006), in our study the retention rate for Meth or Bup was not better with a higher daily dosage (> 50 mg Meth, 8 mg Bup). There was less benzodiazepine use in the Bup group, although this did not quite reach significance; there were no other differences between treatment groups with respect to substance use. Concerning adverse events, a seizure occurred in the Bup group and more patients had to be detoxicated in hospital in the Bup group than in the Meth group (7 vs. 2). Only six patients dropped out because of side-effects. Although side-effects are difficult to distinguish from withdrawal symptoms in drug dependence, there were no significant differences between Meth and Bup and no unusual side-effects were recorded.

There are a number of flexible-dose studies comparing the efficacy of Meth to Bup, with mixed results (Fischer et al., 1999; Johnson et al., 2000; Lintzeris et al., 2004; Mattick et al., 2003; Petitjean et al., 2001; Strain et al., 1994a,b). A pooled analysis of these studies suggested a significantly superior retention with Meth treatment compared with Bup, while there was no difference in the level of opioid use. The dose used plays an essential role in this respect. In contrast to our findings, at high doses Meth (> 50 mg) was found to be more effective than fixed-dose Bup (> 8 mg), while a lower fixed dose of Meth and a higher fixed dose of Bup were found to be equally effective (Connock et al., 2007). The rate of opioid and cocaine use in Bup-treated patients was found to be lower in some previous studies (Gerra et al., 2004; Giacomuzzi et al., 2003).

Allocation of opioid-dependent patients to different therapies or medications according to patients’ profiles remains a difficult task. In this study, duration of continuous opioid use and age at onset were predictors for negative outcome but only in the Bup group. The intensity of withdrawal symptoms showed the strongest correlation with drop-out in both substance groups, followed by the intensity of side-effects and the number of positive urine screenings. This indicates the special relevance of withdrawal symptoms for negative outcome.

Other individual characteristics such as EuropASI scores or dosage failed to show any correlation with outcome. The length of opioid use may indicate a more severe course of opioid dependence, independent of the substitution drug used, but future studies may address the question whether more chronic patients might benefit from Meth than from Bup treatment.

Very few randomized studies have addressed the role of individual characteristics in the prediction of outcome in substitution treatment (Connock et al., 2007). In most studies patients with significant medical or psychiatric comorbidity were excluded. Lintzeris et al. (2004) identified three non-randomized trials that examined the impact of individual characteristics on treatment outcomes. Gerra et al. (2004) studied predictors of outcome in patients entering a 12-wk Meth or Bup treatment programme and reported that in the Meth group treatment retention and opioid use was influenced by Meth dose and level of psychosocial functioning at intake but not by psychiatric comorbidity or drug use history, while in the Bup group treatment outcome was better in individuals with a high level of depression at intake. The other parameters, including Bup dose, were unrelated to outcome.

Piorier et al. (2004) reported that treatment outcome in Bup was better in patients with a higher psychopathological EuropASI score, low disinheritance and boredom susceptibility scores, no alcohol dependence, no family history of addiction or mood disorder, and duration of opioid dependence < 10 yr. The authors did not find any correlation between patients’ sociodemographic characteristics and outcome. Schottenfeld et al. (1998) did not find a correlation between levels of psychopathology at intake and outcome in Meth and Bup patients, in contrast to an observational study by Gerra et al. (2004) who reported a better treatment response in Bup but not Meth patients with a history of depression.

Several limitations must be addressed. First, the sample size in this study was adequate but we cannot rule out that significant differences between treatment groups may have been shown in larger samples. Second, setting effects may be of relevance. Although in most studies there were no differences in treatment outcome in patients treated in specialist centres or primary-care settings (Fiellin et al., 2001; Gibson et al., 2003; King et al., 2002), one study reported a better outcome for the primary-care group (O’Connor et al., 1998). Third, as mentioned above, withdrawal symptoms may be difficult to distinguish from side-effects or toxic effects in opioid dependence. Results related to such symptoms must be discussed with caution since there is a high intercorrelation between these groups of symptoms, both of which basically rely on subjective responses. Fourth, for outcome evaluation more domains have to be considered. For example, van den Brink et al. (2003) in a study about medical prescription of heroin defined patients as responders when they showed at least 40% improvement in at least three domains (physical, mental, social) at the end of the treatment compared with baseline.
From our study several implications for clinical practice can be derived. The non-significant differences in retention rate, withdrawal symptoms and side-effects indicate that Meth and Bup are equally effective as substitution drugs. Results suggest that more chronic patients with a longer history of heroin addiction may benefit from a substitution with Meth, as duration and young age at beginning of opioid use are negative predictors for outcome in the Bup group. However, this requires more detailed study. Furthermore, this study underscores the importance of withdrawal symptoms for outcome, as they have a high correlation with drop-out.

In conclusion, our randomized trial gives further evidence that substitution treatment is a safe and effective treatment in opioid dependence. Future studies are warranted to further address the role of patient profiles, different settings and substitution regimens on treatment outcome, thus allowing a better allocation of patients to treatment according to distinct symptom profiles.

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Statement of Interest

Professor Soyka has worked as a consultant for Sanofi and Essex Pharma, Forrest Laboratories, and Alkermes Inc.

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