Treatment practices and perceived challenges for European physicians treating opioid dependence

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Summary

This survey investigated the current practices and challenges of physicians treating opioid dependence in Germany, France, Italy and the UK. Doses favoured in Europe appeared to conflict with recommended best practice, with low mean methadone and buprenorphine maintenance doses reported (44.3 and 9.5 mg, respectively). Mean time to buprenorphine maintenance doses was longer than recommended at 14.4 days. Respondents also rated diversion and misuse management as their most difficult challenge in treating opioid dependence. These data suggest that prescribing practices are likely to increase this problem, as well as impeding treatment success by decreasing compliance and retention.

Key Words: Maintenance treatment; pharmacotherapy; diversion; misuse; induction; dosing; methadone; buprenorphine

1. Introduction

It is now widely accepted among healthcare professionals that opioid dependence is a chronic relapsing condition that is treatable, and that long-term comprehensive care leads to the best outcomes (41).

Maintenance pharmacotherapy has long been established as an important component in the treatment of this condition and methadone in particular has accumulated several decades of clinical experience. Methadone’s pharmacological potential for overdose and diversion necessitated the development of highly regulated treatment systems most often based on daily supervised dosing in specialist addiction centres. This treatment delivery model has been the ‘gold standard’ since the 1970s and continues to form the basis for much of current opioid-dependence treatment in Europe despite the emergence of new medications, such as buprenorphine and buprenorphine/naloxone (bup/nx), with substantially different pharmacological characteristics.

Political pressures have led to marked geographical differences in the treatment options available and the restrictions under which physicians are allowed to treat patients. Where some opioid users can access treatment just by walking into a local physician’s office (eg, France) or drug treatment clinic (eg, Italy, Spain and the UK), others are required to remain on waiting lists for many months or even years (eg, Greece) or undergo detoxification for all other drugs before being allowed maintenance therapy (eg, Norway).

Variation in the amount of training available to physicians and the availability of national clinical guidelines can exacerbate such differences. For example, doctors wishing to treat opioid users in Germany face a mandatory training
course of 56 hours, whereas in France any physician is allowed to prescribe buprenorphine with no additional training. Also, the vast majority of treatment in France is provided in doctors’ offices, whereas 95% of treatment in Italy takes place in specialist clinics.

Inappropriate dosing of opioid pharmacotherapies can put patients at risk of significant complications. Excessive opioid doses can lead to overdose and/or death, whereas prescribing doses that are too low can limit the potential for success and expose patients to the myriad of harms associated with continued illicit drug use.

This study aimed to shed some light on the attitudes of physicians in four large European countries relating to specific aspects of opioid-dependence treatment, how this translates into real-world clinical practice, and the overall impact on the quality of care that opioid-dependent patients are receiving.

2. Methods

2.1 Physician surveys

A structured online questionnaire was developed and circulated to physicians in Italy, Germany, France and the UK in February 2010. The survey was estimated to take about 25 minutes, and respondents received a fee of €20 for completing it. Data for 300 respondents (75 per country) were collected anonymously. The survey was stopped in each country after the quota of respondents who met the inclusion criteria was filled. An additional 246 entries did not meet the inclusion criteria and 82 more submissions were incomplete. Survey data were collated and analysed in the SPSS statistical package.

2.2 Inclusion criteria

Physicians were restricted to those specialising in addiction medicine, emergency medicine, general practice, internal medicine, neurology, pain, psychiatry/psychology or rheumatology. They were required to have at least 2 years of experience in prescribing methadone and/or buprenorphine to an average of 20 or more opioid-dependent patients per month. To ensure representation of all maintenance pharmacotherapies in the survey results, at least half of the doctors from each country prescribed buprenorphine (including bup/nx) to at least 20% of their patients.

2.3 Exclusion criteria

Respondents with less than 2 years or over 35 years experience in their field were excluded.

2.4 Survey overview

Physicians responding to the survey were asked to report the proportion of their patients who received maintenance pharmacotherapy versus those who underwent short-term detoxification. They also submitted the average dose of methadone and/or buprenorphine on day 1 of induction, the average final maintenance dose and the average time taken to reach that dose. They were also asked to rate the difficulty they experienced in 10 different aspects of opioid-dependence treatment on a scale of 1 (easiest) to 7 (most difficult) and to subjectively estimate the extent of medication diversion and misuse in their local area. These findings as well as the physicians’ goals for treatment are discussed herein.

The survey also contained questions about the components of a high-quality treatment programme and the areas of improvement that the respondents identified in their individual countries. These results are not discussed here.

3. Results

3.1 Treatment practices

European physicians treating opioid dependence reported that an average of 61.4% of their patients received maintenance treatment and 38.6% underwent short-term detoxification. Three in five physicians prescribed either methadone or buprenorphine maintenance to at least 60% of their opioid-dependent patients (Figure 1). UK doctors maintained 69.9% of their patients on pharmacotherapy, significantly higher than in other countries (p <0.05).

Physicians rated six different goals of opioid-dependence treatment on a 1–5 scale according to how important they were considered in an effective treatment programme (Table 1).

3.2 Dosing practices

The mean reported induction dose of methadone was 31.3 mg. The average day 1 dose of buprenorphine prescribed was 8.7 mg. However, these means mask considerable variability in the doses prescribed. Buprenorphine tended to be inducted at low doses with 58% of physicians prescribing less than 8 mg of buprenorphine on the first day, 48% prescribing 4 mg or less and more than a quarter (27.3%) prescribing 2 mg or less (Figure 2a). Low dosing was also reported in methadone induction with 24% giving their patients less than 15 mg on day 1 (Figure 3a). There was also a marked degree of high dosing in methadone induction, with one in five doctors giving initial doses of 50 mg or higher and 4% routinely prescribing 100 mg or more on day 1 (Figure 3a).

The mean maintenance doses were 44.3 mg for methadone and 9.5 mg for buprenorphine. In total, 41% of patients were receiving less than 40 mg of methadone (Figure 3b) or 8 mg of buprenorphine (Figure 2b) per day on average.

Methadone patients reached their maintenance dose in an average of 16.7 days. Furthermore, 21.3% were stabilised in less than 7 days (Figure 3c). Only 13.4% of patients ar-
Physicians
0% 1–19% 20–39% 40–59% 60–79% 80–99% 100%

30
defined at their buprenorphine maintenance dose in 3 days or less, while over half took longer than 7 days and a quarter (26.5%) took at least 15 days (Figure 2c). There was also a large variation between the countries in the number of days physicians took – averaging between 9.3 in Germany and 21.5 in France – to get their buprenorphine patients to their target dose (Table 2).

Dosing practices were largely similar across the four countries but national differences did emerge in some areas (Table 2). Italian physicians inducted patients on an average of 41.9 mg of methadone or 12.9 mg of buprenorphine, significantly higher than all the other countries (p <0.05). By contrast, methadone maintenance doses in Italy were significantly lower than the European average at 31.8 mg (p <0.05). In Germany, the average times taken for methadone and buprenorphine patients to reach their maintenance doses were 9.3 days and 6.9 days, respectively – significantly faster than their European counterparts (p <0.05).

3.3 Physician challenges

Survey respondents overwhelmingly regarded the quality of care that patients in their country currently receive as less than optimal. On a scale of 1–5, where 5 represents optimal care, only 3.7% gave their country’s treatment system the highest rating, while 18.4% felt that the quality of care in their country was less than adequate (1–2 out of 5). Italian and German physicians were the most pessimistic, with 100% and 98.7%, respectively, giving their country’s treatment less than 5. Ratings from the UK and France were 94.7% and

Table 1. The importance of various treatment objectives to the quality and effectiveness of opioid-dependence treatment.

<table>
<thead>
<tr>
<th>How important do you think the following patient objectives are in determining the quality and effectiveness of a treatment programme?</th>
<th>Mean score</th>
<th>Very important (5)</th>
<th>Not important (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvements in patient’s quality-of-life</td>
<td>4.3</td>
<td>46%</td>
<td>0%</td>
</tr>
<tr>
<td>Abstinence from street drugs</td>
<td>4.3</td>
<td>46%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Optimisation of ORT dosing for each patient</td>
<td>4.1</td>
<td>27%</td>
<td>0%</td>
</tr>
<tr>
<td>Minimising harm</td>
<td>4.0</td>
<td>37%</td>
<td>1%</td>
</tr>
<tr>
<td>Strict compliance with treatment programme conditions</td>
<td>4.0</td>
<td>28%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Achieving a completely drug-free life (including ORT)</td>
<td>3.6</td>
<td>24%</td>
<td>4%</td>
</tr>
</tbody>
</table>
92%, respectively. Measuring withdrawal severity, titrating to a therapeutic maintenance dose and understanding side-effects and drug–drug interactions were rated as the easiest aspects of treatment (Table 3). Induction also ranked among the easier aspects of treatment provision despite the disparity of induction practices reported. Identifying diversion and misuse and transferring between opioids were reported as the most challenging activities by the survey respondents, with between one-third and one-fifth of doctors finding them very difficult (1–2 out of 7).

### 3.4 Diversion and misuse of medication

There was considerable concern over misuse and diversion reported by responding physicians, with 70.3% agreeing that it is a significant issue and that physicians themselves have a responsibility to address it (rating 4–5 out of 5). Responses were similar across the four countries, although concern was highest in Italy at 78.7%. Using the same scale, 65% agreed that prescribing formulations with the lowest misuse potential was essential for reducing diversion and misuse. French
Table 3. Doctors rated the difficulty they experienced with 10 aspects of treatment on a scale of 1–7, with 7 representing the easiest tasks and 1 the most difficult.

<table>
<thead>
<tr>
<th>How easy do you find the following... (7 = Very easy, 1 = Difficult)</th>
<th>Mean score</th>
<th>Very easy (6 or 7)</th>
<th>Very difficult (1 or 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measuring withdrawal severity based on physical signs</td>
<td>4.2</td>
<td>16.7%</td>
<td>9.0%</td>
</tr>
<tr>
<td>Understanding the safety, side-effects and drug–drug interactions of the different pharmacotherapies</td>
<td>4.1</td>
<td>12.7%</td>
<td>11.3%</td>
</tr>
<tr>
<td>Titrating therapeutic maintenance doses</td>
<td>4.1</td>
<td>12.0%</td>
<td>9.3%</td>
</tr>
<tr>
<td>Smooth induction onto methadone</td>
<td>3.9</td>
<td>10.3%</td>
<td>14.3%</td>
</tr>
<tr>
<td>Smooth induction onto buprenorphine or buprenorphine/naloxone</td>
<td>3.9</td>
<td>8.3%</td>
<td>14.0%</td>
</tr>
<tr>
<td>Building an open relationship with patients so they will talk about their drug use, cravings and problems</td>
<td>3.8</td>
<td>11.0%</td>
<td>19.0%</td>
</tr>
<tr>
<td>Selecting the most suitable pharmacotherapy for each patient</td>
<td>3.8</td>
<td>9.3%</td>
<td>17.7%</td>
</tr>
<tr>
<td>Switching buprenorphine patients to buprenorphine/naloxone</td>
<td>3.6</td>
<td>7.7%</td>
<td>19.0%</td>
</tr>
<tr>
<td>Transfers between the different pharmacotherapies</td>
<td>3.4</td>
<td>4.3%</td>
<td>22.7%</td>
</tr>
<tr>
<td>Detecting and responding to misuse and diversion with the patient</td>
<td>3.1</td>
<td>3.0%</td>
<td>33.0%</td>
</tr>
</tbody>
</table>
doctors felt significantly more strongly about this than the other countries, with 77% agreeing that the prescribing of the least divertible medications is essential (p <0.05).

When asked how prevalent diversion or misuse of medication was in their local area, 72% of doctors said diversion was a ‘huge’ or ‘significant’ problem while 52% said the same about medication misuse (Figure 4).

4. Discussion

4.1 Limitations

This survey has uncovered a wide range of treatment practices among European doctors treating opioid-dependent patients, a proportion of which are at odds with clinical evidence and treatment guidelines around the world. While the data have revealed much about how European doctors currently practice, it should be noted that the dosing data are self-reported recollections from the physicians themselves rather than a review of physician prescribing records. Questions on the prevalence of diversion and misuse were also subjective, so do not necessarily reflect the exact extent of the problem in any of the four countries.

4.2 Treatment modalities

Despite the advantages of long-term pharmacotherapy over abstinence-oriented treatment in retaining patients and reducing drug use and its associated harms (5, 9, 13, 18, 21, 27, 31), these findings suggest that as much as 39% of patients across Europe are still receiving detoxification rather than long-term treatment. Clinical evidence suggests that between 60 and 72% of detoxified patients can be expected to relapse to drug use within 1 year (14). They are also subject to further risks compared to maintenance patients. For example, medication-assisted treatment reduces opioid-related mortality by about eight-fold (5) and non-fatal overdoses are also reduced by maintenance therapy but not by detoxification (9). Patients who undergo single detoxification episodes do not alter behaviours that put them at risk of contracting HIV (27). Even among maintenance patients, HIV prevalence and infection rates are inversely correlated to the duration of treatment (31). Long-term treatment leads to improved outcomes including lower illicit substance use, fewer psychiatric problems and an enhanced quality of life (23), while detoxification is associated with substantial psychological distress (21).

While short-term detoxification may be suitable for some patients, particularly those with high motivation and family support, the WHO recommended that it not be promoted as an evidence-based treatment option due to the poor associated outcomes (41). Indeed, the persistently high rates of detoxification seem to be at odds with the physicians’ stated priorities for treatment, where improvements in quality of life and abstinence from street drugs were reported as much more important than complete abstinence. One possible reason may be the influence of patients who often may not understand the chronic relapsing nature of opioid dependence and therefore have unrealistic expectations of being drug-free quickly. A lack of awareness of the available treatment options could also lead a patient to prefer detoxification. A recent study has shown that patients’ own preferences are one of the most important determinants of which treatment they receive (36).
4.3 Induction and titration

Where patients do receive maintenance treatment, the survey revealed extensive under-dosing with both methadone and buprenorphine combined with relatively fast methadone induction and slow buprenorphine induction. The principles of methadone induction have long been a low initial dose followed by slow titration to stability (‘start low, go slow’), due to the risks of respiratory depression. A range of international guidelines generally recommend an initial methadone dose of 10–30 mg and maintenance doses of 60–120 mg per day (11, 25, 32, 40). Dose increases are generally recommended to be no more than 10 mg every 3 days (or 30 mg per week) depending on the patient’s opioid tolerance. However, while the mean induction dose was close to the recommended maximum, more than half of responding physicians prescribed higher doses. Indeed, one in five respondents inducted on at least 50 mg of methadone and 4% even reported using 100 mg or more. Most methadone-related deaths occur in the first 2 weeks of treatment (6, 20, 43) and the majority of those are associated with doses of just 40–60 mg (25). This indicates that one-fifth of European methadone prescribers may routinely be putting their patients at serious risk of overdose death. The time taken to reach maintenance also appeared short given the slow dose increases recommended for maintenance. It is unclear whether this is really due to rapid dose increases or simply a function of the low maintenance doses prescribed. At the rate of increase generally cited in guidelines, a doctor could titrate from a starting dose of 10 mg to the average reported methadone dose of 44 mg in just 9–12 days.

Buprenorphine has very different pharmacological characteristics to methadone, and thus a very different recommended induction strategy. Unlike methadone, buprenorphine guidelines generally advocate reaching the target maintenance dose in 3 or 4 days at most (11, 25, 32, 40, 42). Recommended doses are 8 mg on day 1, 12–16 mg on day 2 and maintenance doses are 12–24 mg (11, 25, 32, 40, 42), with up to 32 mg being cited as necessary in some cases (11). However, buprenorphine prescribers in the four countries surveyed appear to be following the ‘start low, go slow’ induction principles of methadone treatment. Almost three-fifths of doctors prescribed less than 8 mg on day 1 and 48% prescribed 4 mg or less. Meanwhile, the average of 14.4 days to reach maintenance doses is far higher than the recommended buprenorphine induction time of 2–3 days (11, 25, 42). Such cautious induction protocols have been acknowledged as potentially leading to lower treatment retention by the Cochrane Review Panel and the UK National Institute for Clinical Excellence’s Healthcare Technical Assessment (7, 29), and the importance of rapid induction is underscored in the best practice published in more recent treatment guidelines (11, 32). Clinical data support this; trials that allow patients to reach 8 mg sooner tend to retain patients better, particularly if they achieve this level within 1–3 days (Figure 5). Studies that take longer than 3 days to reach 8 mg appear to retain fewer patients (22, 34, 35).

4.4 Maintenance dosing

Mean methadone maintenance doses were markedly lower than the advocated range in all countries and nearly three-fifths of doctors maintained their patients on less than 60 mg, with 42% prescribing less than 40 mg. Even these doses may represent an improvement in some countries. UK physicians prescribed an average of 51.3 mg of methadone, up from just 36.9 mg reported in a 2005 survey of nearly 1900 general practitioners (39). Low maintenance doses are associated with decreased treatment retention, putting patients at risk of relapse and the associated harms of drug use, including mortality (3).

Buprenorphine maintenance doses in Europe also appear to be sub-therapeutic, as trials using similar doses have shown only modest outcomes (17, 24, 38). Indeed, 58% of
European patients are being maintained on 8 mg or less per day, many on doses lower than the generally recommended day 1 dose. Low buprenorphine doses markedly reduce retention and abstinence in a range of early studies (Figure 6). The wider adoption of rapid induction protocols at therapeutic dose levels could make a considerable difference to retention rates for patients in buprenorphine therapy. A 6-month patient retention of nearly 80% has been reported using a titration strategy where patients receiving either methadone or bup/nx had their dose increased fortnightly until drug use, withdrawal symptoms and cravings were eliminated (19). In addition, bup/nx patients reached 16 mg in 2 days. This 6-month retention rate is markedly higher than that typically reported in opioid-dependence studies (28, 29).

Remarkably, although the dosing practices revealed by these data diverge from best practice guidelines in many countries, titrating to therapeutic maintenance doses was rated as one of the easiest aspects of treatment by physicians. Induction on to methadone and buprenorphine were also not identified as a difficult area even though a proportion of physicians appear to follow induction protocols that could lead to drop-out in their buprenorphine patients and potential fatalities in their methadone patients.

Possible explanations for these deviations from best practice in Europe are that prescribers may be under-dosing with methadone due to a fear of overdose while those using buprenorphine may be erroneously following the ‘start low, go slow’ practices advised with methadone because they are unaware of buprenorphine’s distinctive safety profile as a partial mu-opioid agonist. Since early research with buprenorphine tended to use lower doses (30), it is also possible that clinical practice has yet to completely align with currently recommended best practice. Some mistrust of patients claiming to need higher doses may also be a factor, particularly as patients who feel they are under-dosed may inject their treatment or seek additional prescriptions from other doctors (ie, ‘doctor shopping’) (12). A vicious circle, where doctors become even more fearful of giving higher doses, may result.

4.5 Misuse and diversion

As well as the implications for patient retention, low and slow dosing of buprenorphine can be a driver for diversion and misuse. In a survey of 298 patients receiving take-home buprenorphine in France, 70% of those using illicit buprenorphine reported doing so to supplement inadequate dosing by their physician. Low dosing also emerged as the second-highest risk factor for misuse of prescribed buprenorphine (37). Thus, the dosing practices revealed in this research, may also contribute to the level of diversion and misuse reported, although the data are purely subjective.

Concern over the diversion and misuse of medication is already high among survey respondents; 72% thought that diversion is a problem in their area and 52% felt the same about patients misusing their own medication. Although 70% felt it was their responsibility to address diversion and misuse, this was rated as the most difficult area of opioid-dependence treatment. Only 3% reported being very confident in this area while 33% of respondents found it very difficult.

![Figure 6. Higher maintenance doses of buprenorphine tend to produce higher patient retention and increased abstinence from illicit opioids. The Joint Probability Score is a measure of the likelihood of patients remaining in treatment and being drug-free. Reproduced with the kind permission of Professor Walter Ling (personal communication).](image-url)
This presents additional challenges for physicians, as all four countries allow the prescribing of take-home buprenorphine and methadone, although the restrictions under which this is possible vary widely.

The common response to diversion and misuse in many countries is to require supervised dosing. However, mandatory supervision appears to not correlate well with overall rates of diversion and misuse (1, 10, 16, 33, 37), can be a drain on limited treatment resources and may further serve to restrict patients’ quality of life. Improving dosing practices to more closely match internationally accepted guidelines would be an important first step in addressing diversion and misuse given the that inadequate dosing appears to be a noteworthy risk factor (2, 8). Treatment options such as volume-expanded methadone and bup/nx may also be useful in this regard, and the evidence suggests that they can make a marked difference to diversion rates (4, 10, 15, 25). In total, 65% of physicians surveyed agreed that the prescribing of the least divertible medications is essential.

5. Conclusions

These results paint a troubling picture of opioid-dependence treatment in Europe. Prescribing practices are widely divergent from the clinical evidence base, with widespread non-therapeutic induction and maintenance dosing. Excessively slow buprenorphine induction times are also common. Evidence suggests that these practices may lead to diversion and misuse of medication, poor retention in treatment, and ultimately a lower quality of patient care. Indeed, the overwhelming majority of physicians in this survey felt that the that inadequate dosing appears to be a noteworthy risk factor (2, 8). Treatment options such as volume-expanded methadone and bup/nx may also be useful in this regard, and the evidence suggests that they can make a marked difference to diversion rates (4, 10, 15, 25). In total, 65% of physicians surveyed agreed that the prescribing of the least divertible medications is essential.

References


39. STRANG J., SHERIDAN J., HUNT C., KERR B.,
Contributors

JB designed the questionnaire, contributed to the design of the study and drafted the manuscript. SR contributed to the design of the questionnaire, implemented the survey and analysed the data. AP conceived of the study, contributed to the design of the questionnaire and the drafting of the manuscript.

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Conflict of Interest

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