Pilot randomised controlled trial of community pharmacy administration of buprenorphine versus methadone

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Abstract

Objectives  The established regime for opiate substitute prescribing for drug misusers is daily methadone administered under supervision in community pharmacies. Buprenorphine has recently been introduced as an alternative. However there is a lack of evidence of the effectiveness of buprenorphine maintenance therapy (BMT) in the UK treatment setting. This study aimed to assess methods for a randomised controlled trial (RCT) and the feasibility of pharmacy-based supervised self-administration (SSA) of buprenorphine compared to methadone.

Setting  Specialist substance misuse service, general practices and community pharmacies in Aberdeen, Scotland.

Method  The design was a pilot RCT. Opiate-dependent drug misusers, newly referred for maintenance treatment were randomised to receive BMT or methadone maintenance therapy (MMT). Clients and pharmacists were interviewed at baseline and at the end of a 12-week intervention period. Clients completed the quality of life measure EQ-5D. Pharmacy activities were timed.

Key findings  Twenty-one opiate-dependent clients were recruited (BMT = 11, MMT = 10). Recruitment levels improved as the trial progressed. Clients’ treatment preferences were evident. Withdrawals occurred early with BMT. Clients found SSA of buprenorphine acceptable, but found daily administration more manageable than three times weekly. Pharmacists found the dispensing of buprenorphine to be an acceptable role, but felt less certain of ensuring against diversion with buprenorphine than they were with methadone. Pharmacy activities associated with buprenorphine took longer than those associated with methadone (mean = 7 min 25 s versus mean = 3 min 27 s, respectively).

Conclusion  Recruitment to a trial comparing MMT to BMT for opiate-dependent clients within a UK treatment setting is feasible. Clients and pharmacists found buprenorphine acceptable.

Introduction

Methadone maintenance therapy (MMT) is endorsed for opiate dependence in the UK in a primary care setting, and is well supported by research evidence.1,2 Being potentially lethal in overdose and subject to diversion, daily-supervised self-administration of methadone (SSAM) is recommended.1 In Scotland, SSAM occurs almost exclusively in community pharmacies.

Buprenorphine is an alternative maintenance therapy. As a partial agonist, it has a ceiling on its agonist effect and therefore, if taken on its own, is relatively safe in overdose.3 It binds strongly to opiate receptors, relieving withdrawal symptoms and blocking other opiates. It has a long duration of action, allowing three times weekly dosing. This could relieve pressure on pharmacies as well as benefit clients.

Research evidence has demonstrated buprenorphine maintenance therapy (BMT) to be an effective treatment for opiate dependence.4,5 However, its effectiveness, relative to MMT, remains unclear.2 BMT and MMT appear similar in terms of reduction in illicit drug use,6-10 retention in treatment,6,7,10 withdrawal severity,10-12 and quality of life.12 Where methadone has appeared more effective, this has been attributed to non-equivalent dose
comparisons,\textsuperscript{2} and/or slow induction on buprenorphine.\textsuperscript{13} The majority of trials have employed fixed-dose comparisons (not reflecting clinical practice where flexible dosing is employed), have been inadequately powered to make a meaningful comparison, and have all taken place outside the UK.\textsuperscript{14} The evidence for practical, primary care-based treatment is limited.

Buprenorphine has been licensed for use in opiate dependency in the UK since 1999. Uptake of its use has been slow,\textsuperscript{13,16} which may be due to the following reasons: a lack of evidence of the effectiveness of BMT in the UK;\textsuperscript{2} its cost relative to methadone;\textsuperscript{15,16} concerns about supervising the sublingual absorption of buprenorphine tablets; and in Scotland in particular, a history of intravenous abuse of buprenorphine in the 1980s and early 1990s when the drug was licensed as the analgesic Temgesic.\textsuperscript{17,18}

The limitations of previous studies identify the need for a UK, community-based, flexible dose, definitive randomised controlled trial (RCT) of BMT versus MMT. This paper reports on a pilot RCT, conducted to inform the design of a subsequent, multicentred study. A secondary aim was to test the feasibility of dispensing and managing buprenorphine in the pharmacy. An open labelled design was chosen to facilitate alternate day dosing as an option in the BMT arm. Previous research has demonstrated alternate-day dosing to be acceptable under blinded conditions,\textsuperscript{13} but the full benefits or otherwise of clients requiring fewer treatment visits can only be investigated in an open trial.

**Methods**

**Participants and setting**

Opiate-dependent clients, newly referred to NHS Grampian Substance Misuse Service (SMS), considered clinically suitable for maintenance treatment, were invited to participate. Exclusion criteria were: clients aged <18 years; pregnant women or breastfeeding mothers; hypersensitivity to buprenorphine or any component of the tablet; severe respiratory insufficiency; acute alcohol or delirium tremens; severe and enduring mental illness or any other significant chronic medical illness (according to the medical judgement of the SMS); inability to give informed consent. Three community pharmacies participated. They were purposively selected from pharmacy volunteers in Aberdeen with over 20 methadone clients to include urban and city centre locations, different pharmacy types and to be within reasonable travelling distance of the specialist clinic. All pharmacies had considerable experience in dealing with opiate-dependent clients.

**The intervention**

Clients attending the SMS were assessed for eligibility by the clinic nurse. Eligible clients were given study information to take away. At the following visit, clients were given an opportunity to ask questions about the study before deciding whether to take part. There was no ‘fast tracking’ for individuals agreeing to participate. Those who declined received the standard treatment (MMT). Those agreeing gave their written consent to the nurse. Nurses were asked to maintain a log of approaches made to patients, and refusals. Figure 1 maps the protocol implemented following recruitment. Randomisation to receive either buprenorphine sublingual tablets or methadone liquid (control) was carried out independently by the researchers. Treatment allocation was non-blinded. The intervention period was 12 weeks. Clients in the buprenorphine arm were asked to refrain from opiates for 24 h prior to commencing treatment under existing local procedures. Doses were tailored according to individual need and in line with national guidelines,\textsuperscript{1} with induction doses for buprenorphine of 2–4 mg and for methadone of 20–40 mg. These doses were altered to address withdrawal symptoms or toxicity, as appropriate. Clients in the buprenorphine arm were titrated in increments of 2–4 mg over 2–5 five days at the specialist clinic. The SMS base was the setting for this stage, as there is a need for people to have access to emergency services when being titrated on buprenorphine, as those with a high baseline opiate level may experience sudden withdrawal. Once titrated, participants attended their allocated pharmacy to self-administer their buprenorphine six times per week under pharmacist supervision. After a period of 6 weeks, they were given the option of receiving their treatment three times a week, still under pharmacist supervision. Clients randomised to methadone were titrated by the SMS and received their doses under supervision in a community pharmacy, in accordance with an agreed service specification derived from the locally negotiated contract. Take-home doses were dispensed for Sundays when pharmacies were closed. Dose alterations were made weekly in increments of 5–10 ml, over approximately 6 weeks.

**Data collection**

Structured interviews, consisting of open questions, were conducted with clients at baseline and after 12 weeks of treatment. Interviews were tape recorded and transcribed. In addition, at both time points demographic details, level of involvement with crime and the EQ-5D quality of life meas-

![Figure 1](IJPP%2014(4).book%20Page%20244%20Monday%20November%2013%202006%205%2049%20PM)
ure were collected. The EQ-5D was chosen, as it is short, holistic and has been widely validated in many areas of health. The baseline schedule included: previous experience of treatment; perceptions and concerns about the allocated treatment. At 12 weeks it included: general wellbeing; illicit drug use; and experience of treatment.

Interviews were conducted with pharmacists at the start of the study, to assess their expectations and concerns regarding buprenorphine dispensing and its supervised self-administration (SSA). Experiences were assessed, similarly, at 12 weeks. The total time associated with dispensing and SSA (including record keeping) of methadone and buprenorphine was monitored, using pharmacist self-reported data over the course of a week, and by non-participant observational methods. For both timings, a stop-watch and standardised data collection form were used.

Analyses

Quantitative data were not analysed. The purpose of administering the questionnaires was to assess their suitability for use in a larger, appropriately powered trial. Retention rates and timings of pharmacy activities are presented for each group. Responses from interview narratives were systematically coded, and themes identified.

Ethical approval

Grampian Research Ethics Committee granted their approval of this research following a full appraisal of the purpose and proposed methods of this research. When the trial concluded, participants could continue with their randomised treatment. Those allocated to BMT could change to the standard treatment (MMT) if preferred.

Results

Recruitment and retention

Figure 2 maps the course of participants during the trial period. Twenty-one clients were recruited over a 5-month period, and were randomised to receive MMT (n=10) or BMT (n=11). All MMT participants completed the induction period. Four participants in the BMT arm withdrew either prior to (n=3) or during (n=1) the induction period (delay in treatment initiation due to the clinic being full (n=1), failure to meet the required opiate abstinence (n=2), and withdrawal symptoms at day two (n=1)). At 12 weeks, 11 participants remained in treatment (MMT n=6, BMT n=5). Six participants had either voluntarily withdrawn from, or been discharged from, treatment (MMT n=4, BMT n=2). Of the five remaining BMT clients, two received their drug treatment three times a week, and three, six times a week. The mean daily dose for clients receiving methadone was 36 mg (standard deviation SD = 11 mg), and for buprenorphine 12 mg (SD = 4 mg).

Seven of 22 nurses completed recruitment logs, showing that 15 of 38 clients had agreed to participate (39%). Recruitment did not occur uniformly during the study period. During months one and two, two clients were recruited, during month three, four were recruited, in month four, eight were recruited, and in month five, seven were recruited.

All client participants (n=21) were interviewed before the intervention. Following the intervention, 10 of 11 clients remaining in treatment were interviewed (five methadone, five buprenorphine). The eleventh did not respond to repeated invitations. Pharmacists from all three pharmacies were interviewed at baseline and 12 weeks.

The EQ-5D was fully completed by all participants at baseline, and by those remaining in treatment at follow up. Table 1 shows the mean times of pharmacy activities. Activities associated with dispensing SSA of buprenorphine took longer.

Table 1 Mean times in seconds per patient by therapy type (95% confidence interval)

<table>
<thead>
<tr>
<th>Activity</th>
<th>BMT; recordings = 26; mean (SD)</th>
<th>MMT; recordings = 26; mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supervised self-administration (s)</td>
<td>315 (197)</td>
<td>78 (47)</td>
</tr>
<tr>
<td>Dispensing (s)</td>
<td>64 (21)</td>
<td>56 (9)</td>
</tr>
<tr>
<td>Other activity (s)</td>
<td>49 (85)</td>
<td>17 (44)</td>
</tr>
<tr>
<td>Documentation in CD(^d) register (s)</td>
<td>Not applicable</td>
<td>67 (35)</td>
</tr>
<tr>
<td>Total time (s)</td>
<td>445 (268)</td>
<td>207 (35)</td>
</tr>
</tbody>
</table>

*Pharmacist self-reported data and researcher-observed data combined.
\(^d\)Buprenorphine maintenance therapy.
\(^c\)Methadone maintenance therapy.
\(^d\)Controlled drugs.
Client expectations: methadone

There was ambivalence among those randomised to receive methadone: there was relief to be receiving treatment, but concerns that methadone would be more addictive than heroin. The following quote illustrates commonly expressed perceptions:

“I’ve been told that it [methadone] rots your teeth, it seeps into your bones, it’s harder than heroin to come off. That’s the bad side of it. The good sides of it are that you don’t have to take any heroin if you’re stabilised on methadone and likewise there won’t be any crime or things like that.” (Female, 26 years)

Client expectations: buprenorphine

For those randomised to BMT there was positive feeling about trying buprenorphine. Clients described feeling ‘excited’ (male, 25 years) and ‘elated inside’ (male, 42 years) regarding the prospect, though some concerns were expressed, including fears that one might accidentally swallow the tablet and lose the therapeutic effect.

Four of five remaining methadone clients interviewed at 12 weeks reported using heroin. Clients reported using heroin when it was felt the methadone dose was too low to ease withdrawal symptoms:

“The methadone I was getting was getting me half by and then I was having to use illicit drugs to get me through the day altogether.” (Male, 28 years)

Three methadone clients reported involvement in crime since starting treatment. All clients reported methadone treatment as being beneficial. The main benefit was to relieve the pressure of having to seek out heroin. Some clients described improved general wellbeing:

“My meth is making me feel good and I want to get up and do things . . . because I am feeling normal.” (Female, 24 years)

At three months, two of five remaining buprenorphine clients reported using heroin. Both had transferred to a three times weekly regime. Use was associated with the longest gap between treatment days. Participants commented that the dose had not been altered adequately to accommodate this.

All reported no involvement in crime since starting treatment. Clients reported benefits from BMT:

“This is better. Methadone, you get a hit with methadone. You get that little high and a buzz. This you don’t. You just feel okay so you feel you’re back to the world.” (Male, 42 years)

One client found the alternate-day dosing confusing. At three months, three clients had either remained on or reverted to daily maintenance treatment. Two remained on three times weekly treatment. Fears that the tablet might accidentally be swallowed were unmet. One participant described making repeated attempts to meet the required abstinence before successfully commencing BMT:

“I couldn’t cope with it like by the end of Sunday night before starting on the Monday. So by Sunday night I would end up just going and getting something and that happened twice so third time lucky. I went and stayed with my mum and dad, and I managed to do it.” (Female, 28 years)

Pharmacists’ experience and views

At baseline, pharmacists correctly anticipated that supervision would take longer for buprenorphine. At follow-up it was noted that dissolution time varied among clients and did not correspond to dose. They noted spending more time talking with buprenorphine clients:

“Obviously you have to wait longer but it is quite a good chance to speak to the patient, find out how they are getting on.” (Pharmacist 2)

Five minutes was considered a long time to wait with a client. One pharmacist reported that they would wait for the first minute, then go and do other work, and then return to check the client.

Pharmacists saw greater potential for leakage with buprenorphine than with methadone, as they felt it was easier to know when methadone had been consumed:

“I think you’d have to have a bigger bond of trust with the clients than with methadone [where] it’s easier just to see what’s going on.” (Pharmacist 1)

Pharmacists reported that administering and supervising buprenorphine was an acceptable role, and that buprenorphine had a future place in the treatment of opiate dependence.

The patients like it. Although the dosage is a bit up and down I think once you get the proper dose it will be good.” (Pharmacist 2)

Discussion

Main findings

Invaluable lessons have been learned in this pilot, which will help inform the development of a subsequent RCT to compare BMT with MMT. For example, recruitment for a trial comparing MMT and BMT for opiate-dependent clients is feasible. It also provides an indication of pharmacy time involved, which will help inform practice issues and remuneration. Significant challenge relates to trial recruitment: 15 of 22 nurses did not submit a log of clients approached, and it has not been possible to measure the total number of clients assessed for eligibility. As UK-based treatment for opiate dependence is largely community based, via ‘shared care’ schemes, points of contact for client recruitment will be dispersed among substance misuse nurses who have a role of gatekeepers to treatment. As a result, in any subsequent trial, a large number of nurses would be involved in recruitment. This study has highlighted the need for continuous input from the trial team in order to maintain recruitment. Although there is a lack of evidence regarding which strategies are effective in improving recruitment to trials, for a subsequent trial to be successful, local trial co-ordinators working within participating services, where they can keep the profile of the research raised, is viewed to be crucial.
National guidance for buprenorphine induction advocates the first dose be delayed by at least 8 h from the last heroin use.\(^{22}\) Local clinical practice with buprenorphine detoxification (authors, GR and AR) is based on 24-h abstinence, so this was applied in this study. The rate of successfully initiating treatment might have been improved if a shorter abstinence period was used, while also ensuring time is adequate to avoid precipitated withdrawals.

Client expectations are also an issue. Clients were aware of their treatment allocation, and interview data revealed disappointment among those randomised to MMT, and satisfaction among those randomised to BMT. There were commonly held negative perceptions of methadone. Questions are raised regarding the ethics of meeting or disappointing study participants’ expectations. Motivation to take part in RCTs often relies on an otherwise unavailable, novel intervention holding a perceived benefit to prospective participants. It is important that study information given to clients emphasises the lack of clear evidence regarding the relative benefits of the two treatments, so as to minimise this effect.

This study has indicated the levels of attrition that might be expected in a subsequent trial, particularly during the initiation of buprenorphine. Considerable attrition was observed before induction. The required opiate abstinence prior to treatment proved difficult and unmanageable by some. Other research has highlighted an association with attrition and the initial two weeks of BMT.\(^{13}\) This may partly be due to an initial dysphoric effect,\(^{23}\) or could be an indication that starting doses are not adequate. Royal College of General Practitioners’ guidelines on prescribing methadone in primary care recommend a range of 60–120 mg methadone.\(^{24}\) The average range in this pilot fell below this at 36 mg. The recommended range for buprenorphine is 12–24 mg,\(^{22}\) indicating that the average dose in the pilot (12 mg) was at the lower end. This could explain why participants were supplementing their treatment. An important finding for a future trial is therefore that adequate doses of MMT and BMT are used in order to make a meaningful comparison. Subtherapeutic doses could be responsible for the difficulties encountered by some BMT participants in coping with the three times weekly administration. As the doses and titration procedures used in this pilot were in keeping with normal practice in the Grampian Area, the study also highlights the issue of the delay, often inherent, in services putting evidence into practice. This raises issues for managing trials in real practice.

### Feasibility issues

Pharmacy-based SSA of buprenorphine was acceptable to both clients and pharmacists. Although attrition rates were similar for BMT and MMT, there was a tendency for attrition in the BMT arm to occur before or during the induction process. In particular, the requisite abstinence from opiates prior to the initial dose of buprenorphine proved too difficult for some. Clients managed daily administration of BMT better than three times weekly. Illicit opiate use among BMT clients was associated with withdrawal symptoms experienced during the longest gap between treatment days. Altering the buprenorphine dose appropriately could overcome this.

Pharmacists’ found dispensing and supervising buprenorphine acceptable. Although the time for SSA of buprenorphine was longer than for methadone, they supported the use of buprenorphine because of its perceived benefits. The potential for partial (inadequate) supervision, and the difficulty of ensuring the dose was consumed were highlighted.

### Strengths and weaknesses

A combination of methods, including the collection of quantitative data through questionnaires and timing observations, as well as an exploration of experiences through open-ended questions in interviews, was used in this study. This enabled a comprehensive picture of the experiences of participants, and assessed methods for a future trial. The study had some limitations. These included the biases inherent in self-reported data, the small numbers, and those lost to follow up.

### Conclusion

It is feasible to recruit and randomise patients in a trial comparing MMT to BMT for opioid-dependent clients within a Scottish primary care-based treatment setting. However, the findings should be of interest to people conducting clinical trials in similar settings in other countries. Administration of buprenorphine in the community pharmacy setting was acceptable to both clients and pharmacists. Induction processes need to be refined, and the impact of being in the ‘preferred group’ needs to be explored. This pilot has provided invaluable information for a proposed multicentred trial, and has indicated the feasibility of SSA of buprenorphine in community pharmacies.

### References


