

## **Buprenorphine induction and stabilisation in the treatment of opiate dependence**

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### *Summary*

Many early trials of buprenorphine in opiate dependence used fixed doses and slow induction protocols. However, more recent data show that subjects requiring higher doses need to be stabilised more rapidly. Analysis of ten trials suggests a relationship between days taken to reach a 6 mg buprenorphine tablet equivalent dose and retention of subjects at 4 weeks. Recent US studies show that dosage can be stepped up quickly, e.g. 8 mg on Day 1, 16 mg on Day 2. Maintenance dosage should then be adjusted to meet patients' clinical needs; fixed dose studies ignore the breadth of buprenorphine's effective dose range.

**Key Words:** Buprenorphine - Methadone - Opiate  
Dependence - Induction - Dosing

### **Introduction**

Evidence on the use of buprenorphine in the treatment of opiate dependence is the subject of increasing debate amongst both physicians and policy-makers.

The introduction of a new medication in the context of existing therapeutic approaches, in this case predominantly methadone, naturally leads to caution regarding change. This paper summarises what is known regarding induction with buprenorphine as compared to methadone, and the associated outcomes in terms of stabilisation and maintenance.

It discusses the findings and implications of three recent meta-analyses, and reviews the underlying trial evidence. In particular, we have explored the relationship between speed of induction and rates of retention in treatment.

### **Meta-analyses**

West et al <sup>(40)</sup> analysed data from nine trials comparing buprenorphine with methadone using urinalysis as the common outcome measure. The results indicated a non-significant superiority for methadone. However, the heterogeneity in effect sizes led to a focused test being undertaken on four studies that provided data on subjects' previous experience with methadone maintenance programmes. This gave a significant result ( $p < 0.01$ ) in favour of buprenorphine's efficacy in preventing illicit opiate usage.

West et al <sup>(40)</sup> comment that "for all practical purposes" buprenorphine and methadone can be used with equal success, but that there are other aspects that may influence clinicians' choice of treatment. These include the superior safety profile of buprenorphine and its milder withdrawal syndrome. The authors also comment on the high degree of variability in the findings of individual studies.

Barnett et al <sup>(4)</sup> compared data from five randomised clinical trials of maintenance treatment, i.e. the use of buprenorphine as a substitute for heroin, with retention in treatment as the primary outcome measure. Reduction in opiate use was also measured by means of urinalysis.

Barnett et al <sup>(4)</sup> found that, for retention in treatment and urinalysis, 8-12 mg/day buprenorphine was superior to 20-35 mg/day methadone but not as effective as 50-80 mg/day methadone. However, they also found that the differences in effectiveness were small by comparison with the wide variation in outcomes achieved in different treatment programmes.

They concluded that the observed difference in effect between the two treatments might be attributable to the dose used and to other features of study design. In particular, in the three fixed dose studies which found methadone to be more effective than buprenorphine <sup>(32)(18)(19)</sup> all the authors suggested that higher doses of buprenorphine may have been needed.

The third recent meta-analysis, by Farre et al <sup>(11)</sup>, focused primarily on methadone studies but included the same five buprenorphine studies as Barnett et al <sup>(4)</sup> plus one additional study by Strain et al <sup>(34)</sup>.

Farre et al <sup>(11)</sup> classified maintenance doses of buprenorphine of  $>8$ mg per day as "high dosage", and found a non-significant difference between this and high dose methadone in terms of both positive urines and retention in treatment. Their data indicate that both methadone and buprenorphine show a dose-response relationship. They also conclude that buprenorphine has certain other advantages over methadone, including alternate day dosing, the possibility of less social stigma, only mild withdrawal symptoms following abrupt discontinuation and a theoretically lower risk of overdose.

The focus of all three meta-analyses was on relatively early studies of buprenorphine

in which the drug was fitted to the known optimal conditions for methadone induction, at a time when the optimal conditions for buprenorphine were unknown. By contrast, current treatment guidelines such as the Australian National Clinical Guidelines<sup>(23)</sup> [www.health.gov.au](http://www.health.gov.au)) provide for a much more rapid rate of induction of buprenorphine.

For those involved in running treatment programmes outside the conditions of a clinical trial it is important to recognise that dosing schedules for buprenorphine have changed from those used in the early trials as more experience with the drug has been generated and the implications of its different pharmacology have become better understood.

### **Treatment Induction and Dosing Studies**

The phenomenon of matching the buprenorphine induction protocol to that for methadone in clinical trials stems from the traditional concerns regarding safety in the treatment of opioid addiction. In particular, the well-established evidence that increasing the dose of methadone too quickly can lead to fatalities<sup>(6)(17)(38)(41)</sup> has understandably encouraged a cautious approach.

To the present authors' knowledge, there have been no fatalities reported during induction onto buprenorphine. Unlike methadone, buprenorphine is a partial agonist at the mu-opiate receptor, and there is consequently a ceiling on its ability to cause respiratory depression. The agonist effect of buprenorphine has been studied at sublingual doses of 2-32 mg and intravenous doses of 2-16 mg in non-dependent individuals and a plateau reached in both cases which is below the threshold for potentially fatal respiratory depression<sup>(39)(37)</sup>.

There is other strong evidence of buprenorphine's safety<sup>(20)(30)</sup> including its superiority over methadone in overdose<sup>(3)</sup>. In dosing regimen studies, patients have received up to four times their normal daily dose without experiencing any additional opioid agonist effects compared to their daily dose<sup>(28)</sup>.

There is now also compelling evidence that the step-up dosing in the induction phase can be much more rapid with buprenorphine than with the traditional five to seven day or longer protocol (depending on final dose) used with methadone<sup>(14)(16)</sup>. In a one-year US clinical trial, 472 heroin subjects safely received 8 mg buprenorphine on the first day of the induction protocol and then proceeded to a dose of 16 mg on Day 2<sup>(13)</sup>. In the open label flexible dosing phase of this study, the dose could be adjusted up to 24 mg per day, depending on the needs of the patient. This induction schedule is in marked contrast to those used in many studies in the EU, such as that reported by Pani et al<sup>(26)</sup> in which it took 7 days to reach a dose of 8 mg of buprenorphine.

The safety issues associated with rapid induction of buprenorphine were considered by Di Petta et al<sup>(8)</sup> in a recent study of 650 subjects in Italy. Subjects transferred from heroin were induced with 32mg buprenorphine on Day 1, this dosage remaining constant over the first five days. Patients transferred from methadone were induced with doses reaching 32 mg (for the lowest dose methadone subjects) to 24-56 mg (for

Table 1: Dosage Regimes in Selected Trials of Buprenorphine Induction and Maintenance		
Trial	Buprenorphine Induction Schedule	Buprenorphine Maintenance Dosage
Studies included in Barnett et al <sup>(4)</sup>		
*Johnson et al <sup>(15)</sup>	3 mg, 6 mg and 11 mg on Days 1, 2 and 3	11 mg fixed dose from Day 3 to the end of Week 17
*Kosten et al <sup>(18)</sup>	3 mg on Day 1 and gradually increased to 9 mg during the first 2 weeks	3 or 9 mg fixed dose for 24 weeks
*Strain et al <sup>(34)</sup>	3 mg, 6 mg, 9 mg and 11 mg on Days 1, 2, 3 and 4	11 mg fixed dose for 3 weeks, then flexible dosing up to 23 mg to the end of Week 16
*Ling et al <sup>(19)</sup>	3 mg, 6 mg and 11 mg on Days 1, 2 and 3	11 mg fixed dose from Day 3 to Week 52
*Schottenfeld et al <sup>(33)</sup>	1 mg, 3 mg and 6 mg or 6 mg, 11 mg and 17 mg on Days 1, 2 and 3	6 or 17 mg fixed dose from Day 15 to the end of Week 24
Additional studies included in West et al <sup>(40)</sup>		
Eder et al <sup>(10)</sup> – (interim data) superseded by Fischer et al <sup>(12)</sup> – (full data)	2 mg, 4 mg, 6 mg and 8 mg on Days 1, 2, 3 and 4	Individual stable doses determined during induction maintained for 24 weeks
Uehlinger et al <sup>(36)</sup> superseded by Petitjean et al <sup>(27)</sup>	4 mg on Days 1-3. Flexible dose titration from Day 4 to 8 mg on Day 4, up to 12 mg by Day 8, and up to 16 mg by Day 15	Individual stable doses determined during induction maintained during Days 22 - 42
Additional study included in Farre et al <sup>(11)</sup>		
*Strain et al <sup>(35)</sup>	3 mg, 6 mg, 9 mg and 11 mg on Days 1, 2, 3 and 4	11 mg fixed dose for 3 weeks, then flexible dosing up to 23 mg to the end of Week 16
Other studies		
*Ling et al <sup>(20)</sup>	3 mg, 6 mg, 11 mg, 17 mg and 23 mg on Days 1, 2, 3, 4 and 5 (according to randomised fixed dose group). 2 mg control group received this dose throughout the study	1 mg, 6 mg, 11 mg and 23 mg fixed doses from end of induction to end of Week 16
Ling et al <sup>(21)</sup>	8 mg, 12 mg, 16 mg and 24 mg on Days 1, 2, 3 and 4	Open flexible dosing of up to 24 mg tablet

Pani et al <sup>(26)</sup>	2 mg, 2 mg, 4 mg, 4 mg, 6 mg, 6 mg, 8 mg and 8 mg on Days 1-8	8 mg fixed dose for 6 months
*Johnson et al <sup>(16)</sup>	6 mg on Day 1, increasing to 11 mg on Days 2 through 7	Flexible dosing up to 46 mg (32 mg solution)
Fudala et al <sup>(13)</sup>	8 mg on Day 1, 16 mg on Day 2	4-week double blind phase: 16 mg or placebo tablet. 48 week open safety phase: flexible dosing of 4 mg - 24 mg tablet
Mattick et al <sup>(24)</sup>	Ave 3.9 mg, 4.3 mg, 4.5 mg, 5.4 mg on Days 1, 2, 3 and 4 rising to ave 6.7 mg on Day 7, 8.6 mg on Day 14	Open flexible dosing
* These studies conducted with buprenorphine sublingual solution; tablet equivalent dosages presented are based on 70% bioavailability vs solution, using conversion factor of 1.43, rounded to nearest 1mg		

the highest dose methadone subjects) by Day 5. No significant side effects relating to respiratory function, or liver or kidney function, were identified.

Table 1 summarises buprenorphine tablet-equivalent dosage schedules in each of the clinical studies included in the meta-analyses by Barnett et al <sup>(4)</sup>, West et al <sup>(40)</sup> and Farre et al <sup>(11)</sup>. Tablet-equivalent doses have been used for consistency, based on a bioavailability of 70% compared to the solution formulation <sup>(5)(25)(22)</sup>. This relative bioavailability is accepted by the US Food & Drug Administration for product labelling purposes on Subutex <sup>®</sup> tablets.

It should be noted that the paper by Eder et al <sup>(10)</sup> reported interim data and was superseded by Fischer et al <sup>(12)</sup>, and the paper by Uehlinger et al <sup>(36)</sup> was in some respects superseded by that by Petitjean et al <sup>(27)</sup>.

Six additional studies <sup>(20)(21)(26)(16)(13)(24)</sup> are also included in Table 1 for comparison. These indicate the growing body of evidence regarding more rapid rates of induction than those considered in the meta-analyses.

Figure 1 shows the relationship between speed of induction onto 4 mg per day buprenorphine solution or 6 mg per day buprenorphine tablet (Subutex<sup>®</sup>) and subject retention at 4 weeks (correlation coefficient -0.815). The figure has been compiled from published studies in which these data were presented or have been made available to the present authors. It therefore does not provide comprehensive data across all the studies cited in Table 1. Nevertheless, the available data suggest that more patients will drop out from treatment the longer the period taken for induction onto buprenorphine.

A 4 mg dose of buprenorphine solution (approximately 6 mg tablet equivalent) is recognised as one that will hold patients in treatment. In particular, this was demonstrated in the study by Schottenfeld et al <sup>(32)</sup> in which 94% of subjects in the 12 mg

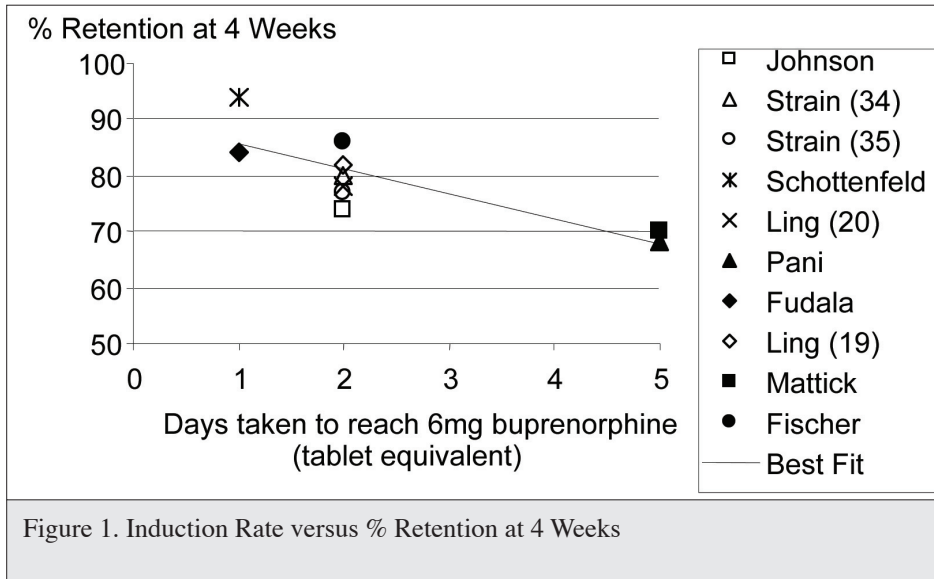


Figure 1. Induction Rate versus % Retention at 4 Weeks

buprenorphine group remained in treatment after 4 weeks; these patients received 4 mg solution per day for Days 1-7.

The study reported by Ling et al <sup>(20)</sup> was a large scale double-blind trial in the USA of four different dosage groups receiving buprenorphine. The group following the most rapid induction protocol to achieve the highest dose of 16 mg solution comprised 181 subjects who received 2 mg on Day 1, 4 mg on Day 2, 8 mg on Day 3, 12 mg on Day 4 and 16 mg on Day 5. Of these subjects, 110 (61%) completed the full 16 week protocol, compared to 52% and 51% completion rates for the 8 mg and 4 mg groups respectively. There were no deaths in any of the study groups and none of the adverse medical events reported were found to be dose-related.

Although the induction schedules reported in the two studies by Ling et al <sup>(20, 21)</sup> cited in Table 1 are rapid in comparison to the early EU studies, they are relatively slow in comparison to that used by Fudala et al <sup>(13)</sup> and the now accepted faster induction options in use in Australia which provide for dosage of up to 24 mg per day by Day3 <sup>(23)</sup> and [www.health.gov.au](http://www.health.gov.au)). There is thus mounting evidence of the benefits of more rapid induction with buprenorphine.

Restraining the induction protocol for buprenorphine to match the relatively slow protocol for methadone, and focussing on fixed maintenance dose studies, risks a bias in comparative trials that favours methadone. This fact has been commented on in some of the study reports and needs to be appreciated when trial results are being reviewed by decision-makers in drug addiction programmes.

## **Stabilisation & Maintenance Studies**

Because of the comparison problems associated with matching a buprenorphine to a methadone induction protocol, buprenorphine's effectiveness in the stabilisation and maintenance phase needs to be considered separately from that in the induction phase.

A good example of where this is necessary in interpreting the trial data is the study reported by Mattick et al<sup>(24)</sup>. The rate of induction onto buprenorphine in this study was matched to the slower rate of methadone induction, resulting in more buprenorphine subjects dropping out early in the trial. However, this was a flexible dose study in which the dose of buprenorphine tablet (Subutex®) or methadone was titrated to the clinical needs of the subject, and amongst those who received adequate daily doses of either drug at around 10 days and remained in the trial, there were no differences in rates of retention in treatment following stabilisation.

Mattick et al<sup>(24)</sup> also found that, in the first 6 weeks (including induction) there were no differences between buprenorphine and methadone with regard to reductions in opioid use, measured by urine toxicology, or heroin craving, measured on a visual analogue scale.

A key finding was that the effective dose range of buprenorphine was quite broad with some subjects being adequately maintained on 4 mg (tablet) per day while others required up to 24 mg per day. The mean daily dose was 10.9 mg/day at end of Week 6.

In the second part of this study, during a 7 week period where alternate day dosing of buprenorphine was compared with daily methadone administration, the effectiveness of buprenorphine was maintained with no differences in the percentages of opiate-free urines or retention in treatment compared to the methadone group. The mean equivalent daily dose of buprenorphine during this alternate day dosing period was comparatively stable, ranging from 10.8 to 11.2 mg per day.

Similarly, Petitjean et al<sup>(27)</sup>, in a double-blind flexible dosing study conducted in Switzerland comparing buprenorphine with methadone, found the mean stabilisation dose of buprenorphine to be 10.5 mg at six weeks. Comparable reductions were reported in opioid-positive urines ( $p=0.759$ ) and heroin craving ( $p=0.735$ ) for buprenorphine and methadone.

A number of published studies have reported that the efficacy of buprenorphine is not compromised when buprenorphine is dosed on alternate days with double the established daily dose, or three times a week, with double, double and three times the established daily dose, respectively<sup>(1)(7)(2)(33)</sup>. Johnson et al<sup>(16)</sup> found that three times per week dosing of buprenorphine was equivalent to high dose methadone, and both regimes were superior to low dose methadone.

Petry et al<sup>(28)</sup> found that, in a comparison of four different buprenorphine dosing regimes, 86% of subjects preferred double-every-other day or triple-every-third day dosing to daily dosing; retention in treatment and urinalysis were not compromised in these less than daily dosing schedules. Importantly, there were no increased agonist

effects or adverse events when dosing at up to four times the 8 mg daily dose (i.e. 32 mg, which is the maximum daily dose supported by the current safety data).

Less than daily dosing of buprenorphine is of significant benefit in countries or clinics where supervised dosing is mandatory - and therefore has an obvious cost benefit in favour of buprenorphine compared with daily methadone. Doran et al<sup>(9)</sup> argued that the possibility of thrice weekly dosing with buprenorphine would be likely to reduce the small cost difference between buprenorphine maintenance and methadone maintenance which arises from the time taken for supervised dosing.

## **Conclusions**

Randomised trials comparing methadone and buprenorphine should be viewed as comparisons between a medication which is widely used and understood, and a newer therapy which has had understandable restrictions placed on it in its early days.

Comparisons undertaken to date have compared the well-known “gold standard” usage of methadone with early experimental and cautious buprenorphine dosing schedules. However, a slow induction with buprenorphine will tend to lead to inadequate dosing in the first days of treatment and a higher early drop-out rate than would be the case with a more rapid induction protocol.

Moreover, the use of fixed doses in trials does not reflect clinical reality, in which each patient is titrated to a dose that is clinically right for that individual. Data from flexible dosing studies such as that reported by Mattick et al<sup>(24)</sup> show that, in practice, the dosage needs of different patients in order to achieve stabilisation are very varied. This is ignored by trials using fixed dose regimes.

For the introduction of buprenorphine into treatment programmes, rapid induction and attainment of a maintenance dose, for example with dose increments of 4 mg to 8 mg per day, should be considered. Once patients are stabilised on buprenorphine, the evidence suggests that effectiveness is comparable between buprenorphine and methadone<sup>(27)(24)</sup>. However, with buprenorphine the risk associated with overdosing appears to be greatly reduced. In addition, buprenorphine offers the flexibility of dosing three times a week, every other day or every third day. These schedules are often preferred by patients over daily dosing and do not compromise rates of retention in treatment<sup>(29)</sup>.

In the flexible dosing studies conducted to date, there is a close similarity in terms of mean maintenance doses of buprenorphine tablet; 10.5 mg in Switzerland<sup>(27)</sup>, 10.9 mg and 10.8-11.2 mg in Australia<sup>(36)(24)</sup> and approximately 11-12 mg tablet equivalent in the USA<sup>(34)</sup>.

These mean dosages underline the point that a fixed or maximum dose of 8mg or less (11 mg tablet equivalent), as used in four of the five studies analysed by Barnett et al<sup>(4)</sup> and four of the six studies analysed by Farre et al<sup>(11)</sup>, is likely to lead to a number of patients being under-dosed, with a negative impact on retention in treatment.

The other meta-analysis reported by West et al<sup>(40)</sup> concluded that for practical purposes

buprenorphine and methadone are equally effective, but that buprenorphine's superior safety profile and milder withdrawal effects might influence the choice of treatment.

The limitations of the present review include the fact that comprehensive data to compare induction rates with retention in treatment across all the studies included in the three meta-analyses were not available to this review's authors. Other differences between the studies such as levels of counselling, subjects' prior methadone experience and other drug use, might also have influenced the results. Nevertheless, the findings are indicative of an important issue.

A key area for further research is therefore to establish a true comparison of methadone induction (over 7-14 days) with buprenorphine (over 2-4 days) in terms of both efficacy and safety. This has to be integrated with the already available evidence on maintenance before any robust conclusions can be drawn regarding the overall effectiveness and cost-effectiveness of buprenorphine in routine practice.

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