The Role of Supervision of Dosing in Opioid Maintenance Treatment

James Bell, MD, FRACP, FACHAM, National Addiction Centre, London
The role of supervision of dosing in opioid maintenance treatment

James Bell, MD, FRACP, FAcChAM, National Addiction Centre, London

Background

The role of supervised administration (also referred to as “direct observation of treatment”), in opioid maintenance treatment (methadone and buprenorphine), received very little attention prior to the 1990s. In the United States, from the early 1970s, concern over diversion of methadone, and overdose fatalities from use of diverted methadone, had led to detailed regulations stipulating that most doses should be taken with direct observation (Jaffe & O’Keeffe, 2003). There were detailed restrictions on availability of take-home doses of methadone. It was not until studies in the early 1990s confirmed the effectiveness of buprenorphine as a suitable medication in treating opioid dependence that the issue of relaxing controls on supervision of dosing began to be seriously considered. The critical issues leading to this reappraisal were (1) the lower risk of fatal overdose associated with buprenorphine, and (2) the need to expand access and to minimize costs of treatment. Led by NIDA, there were moves to expand access to treatment in the United States by allowing office-based treatment with a new medication, combination buprenorphine-naloxone. Clinical trials in developing this drug ran in parallel with political moves to change regulation of treatment. This culminated in passage of the Drug Abuse Treatment Act, 2000, which allowed medical practitioners in office based practice to treat opioid dependent patients without direct observation of dosing. The only medications approved for this purpose have been buprenorphine and combination buprenorphine-naloxone (Jaffe & O’Keeffe, 2003).

While the United States was embarking on the process of legal changes to allow the use of buprenorphine without supervision, there was an abrupt and dramatic expansion of high dose buprenorphine treatment in France, beginning in 1994. In France, most people received prescriptions, without direct observation of dosing, and as the number of people in buprenorphine treatment escalated, the number of fatal opioid overdoses in France dropped sharply (Auriacombe et al, 2001). However, while France and the US were expanding access to treatment without supervision, in the UK change in the opposite direction was occurring. In the early 1990s, methadone treatment in the UK involved prescribing methadone tablets (and occasionally methadone ampoules), with very little supervision of dosing, but by the end of the decade there had been a substantial shift towards more supervised dosing with methadone liquid (Strang et al, 2007). This change was driven by concerns over the high rate of deaths due to methadone diverted from people in receipt of prescriptions to people not in treatment.

The changes in the UK, France and USA, focus attention on the costs and benefits of supervision of medication. This review will investigate two key questions:

1. The extent to which supervision of dosing reduces diversion and the harms associated with diversion. For the purpose of this review, “diversion” is defined broadly, as both inappropriate use of medication by those for whom it has been prescribed, and use by people for whom the medication has not been prescribed.

2. Whether supervision of doses enhances or reduces the effectiveness of treatment, both for individuals in treatment and as a public health measure.
Methodology

The methodology employed in this review was to undertake a literature search, using as key words “direct observation of dosing”, “take-away doses”, “methadone and contingency management”, “methadone and mortality”, “methadone and buprenorphine and diversion”, “medical maintenance”, seeking articles relevant to the issue of supervision of doses.

Diversion is difficult to quantitate, and is either measured indirectly, or possibly unreliably by self-report. There are no controlled trials providing evidence on this issue, but a very large number of descriptive and observational studies, and a small number of studies involving historical or geographical comparisons. On the issue of efficacy of unsupervised treatment, there are three controlled trials comparing retention under different levels of supervision of dosing, one of which does not report methodology nor any statistical analysis; and three reports of observational studies with historical controls, measuring either retention or heroin use. The mixed data that is available did not lend itself to pooling results across studies.

There is a more extensive literature on the use of take-home doses in contingency management, and some descriptive studies of patients’ views of supervision.

1. Diversion

There is an extensive literature, much of it case series, documenting harm associated with diversion of opioids. However, there is more systematic data, particularly data on overdose fatalities, available from 3 settings. These settings are the UK, 1986-2006; Australia, 1996-2006; and USA, from mid 1990s. In addition, data on buprenorphine diversion and associated harms is reviewed.

United Kingdom

Analyses of changes in methadone prescription rates and overdose mortality in the United Kingdom during the 1990s suggest a substantial impact of increasing the level of supervision of methadone treatment. In the early 1990s, it was estimated that there were over 185,000 opiate misusers in the U.K. Treatment had poor penetration, but was expanding; 17,266 patients were receiving methadone in 1992, a little more than twice the number receiving methadone 3 years earlier (Farrell et al, 1998). However, as treatment expanded, the number of methadone-related deaths rose. Between 1974-1992, the number of heroin overdose deaths rose from 7 in 1974 to 90 in 1992, and the number of fatal overdoses involving methadone rose from 26 to 240; these findings could not simply be explained by the increase in opiate misuse or improved reporting methods (Neeleman & Farrell, 1997). In each year between 1989 and 1992, death due to overdose usually resulted from diverted methadone being taken by someone for whom it had not been prescribed. Farrell et al (1998) reported that in 1989, notified addicts not prescribed methadone were 6.4 (95% CI 2.6-18.7) times more likely to die of methadone overdose than notified addicts who were prescribed methadone.

As a result of concern over diversion, the department of health proposed that there should be an increase in the level of supervision of treatment, particularly early in treatment (DOH, 1996). In 1999 the United Kingdom Departments of Health published "Drug Misuse and Dependence – Guidelines on Clinical Management" (DOH, 1999). These guidelines formalised the recommendations of 1996, recommending that in order to ensure compliance and reduce diversion new prescriptions of methadone should be taken under daily supervision for a minimum of three months. Subsequently, as demonstrated by Morgan et al (2006), there
was a dramatic reduction in methadone poisoning in the UK. Methadone-related deaths were between 12-13 per thousand methadone patient years between 1993-1997, but subsequently dropped sharply between 1997 and 2004, reaching 3.1 per thousand patient years in 2004. During the same period, participation in methadone treatment expanded. Police seizures of illicit methadone dropped after 1998, in parallel with the dropping rate of methadone-related fatalities. In a commentary on these findings, Zador and colleagues (2006) point out that the critical change during these years was a marked increase in supervision of methadone administration, from no supervision in England in 1995 to 36% of doses supervised in 2005.

It is assumed that methadone-related deaths of people not in treatment provide a proxy measure of the extent of diversion of methadone, as do police seizures of illicit methadone. These UK reports provide a picture of increasing deaths due to methadone as unsupervised treatment expanded, followed by impressive reduction in risk of death as, in the face of continued expansion of treatment, supervision was introduced. A quite modest increase, to 36% of all doses being supervised, was associated with a 75% reduction in deaths.

In addition to these lines of evidence, two comparative studies have been reported suggesting the benefit of supervised dosing with methadone in reducing diversion and methadone-related deaths. Weinrich and Stewart (2000), noting the pending availability of office based treatment in the USA, reported on experience in the UK, comparing the efficacy and safety of two Scottish primary care-based opioid agonist treatment programs. This naturalistic study was based on differences between programs in the cities of Edinburgh and Glasgow. The Glasgow program required supervised consumption of methadone in community pharmacies for the first year. The programs were estimated to have achieved similar levels of penetration (60% to 80% of injection drug users in Edinburgh, and 41% to 73% of those in Glasgow were enrolled in methadone maintenance in 1998-1999). Mean doses were Edinburgh 61 mg, and Glasgow, 54 mg. The Glasgow program experienced significantly fewer methadone-related deaths than Edinburgh in 1997 (17 vs 30 deaths; P<.0001). The authors concluded that diversion of methadone, and methadone overdose fatalities, had been reduced by the Glasgow policy requiring supervised consumption in community pharmacies in the first year.

A subsequent analysis comparing Edinburgh and Glasgow was reported by Roberts and Hunter (2004). The authors reported that the number of Glasgow pharmacies where supervised consumption of doses of methadone on the premises took place increased from 20% (43/212) in 1994 to 80% (173/215) in 2003. The number of patients visiting the pharmacies increased from an estimated 2800 in 1997/8 to 6300 in 2003. The Scottish Drug Misuse database showed that in 2002 Glasgow had a higher level of persons reported to the database and the higher level of prescribing of methadone than was the case in Edinburgh, but a lower level of persons reported as using illicit methadone. Edinburgh had a much lower level of supervised consumption of methadone than Glasgow. The study also noted that despite the continuing increase in the amount of methadone prescribed, methadone deaths in Strathclyde (the police area covering Glasgow and the West of Scotland) had decreased since 1996.

Hunter and Roberts also identified a different sort of harm associated with diversion – public antipathy towards substitution treatment when it is perceived to be causing problems. They reported that one reason for supervised consumption of methadone in Glasgow was previous experience of an unstructured and unsupervised system in the late 1970s-early 1980s, when public opinion became extremely antagonistic to methadone as a treatment modality. Supervised consumption was introduced because “Great caution was thus required to gain acceptance of its reintroduction as a treatment option. To this day there is still a high level of
public resistance to the concept that methadone is the drug of choice for the treatment of opiate dependence.”

1.2 Australia

As methadone treatment expanded rapidly through the 1990s in Australia, there was an increase in methadone-related deaths. About 2/3 of deaths associated with MMT occurred as a consequence of diversion of methadone to persons not in treatment (Sunjic & Zador, 1999). The source was primarily takeaway doses; a study in Sydney found that there was a very active black market in methadone, and the source was almost entirely (88%) diverted takeaway doses (Darke et al, 1995). A subsequent study from Darke et al (2002) reported that diversion of drugs to the black market rose in proportion to the degree to which treatment without direct observation was available (Darke et al, 2002).

An analysis of jurisdical differences in policy regarding “take-home” doses of methadone reported that those Australian jurisdictions with restrictive policies around takeaway doses had the lowest reported incidence of methadone injecting (Ritter et al, 2005). However, other factors also influenced whether IDUs were likely to inject methadone. In one state with restrictive takeaway policies, there was a high incidence of methadone injecting reported. In that state, there was almost no heroin available, and there had not been for many years. Respondents in that state frequently identified methadone as their preferred drug, whereas in jurisdictions with greater availability of heroin, heroin was overwhelmingly the preferred drug. The authors concluded that where heroin is not available, and prescription opioids are the drugs of choice, there is a greater pressure to divert unsupervised doses (Ritter et al, 2005).

Further evidence for the impact of drug markets came in Australia in 2001, when there was an abrupt and sustained drop in supply of heroin. Following this “heroin drought”, monitoring of drug trends indicated that illicit use and injection of buprenorphine rose disproportionately to the increase in numbers of people being prescribed buprenorphine (Kinner & Fisher, 2003).

In the Australian context, there was also information that in the State of NSW, where methadone diversion was greatest, an audit of prescribing practices revealed widespread lack of compliance with prescribing guidelines. In particular, several practitioners were identified who were prescribing more than the maximum number of takeaway doses per week, for more than 50% of their patients. This excessive prescribing of doses for unsupervised consumption was particularly observed in practitioners working in office-based practice (Hailstone, 2005).

This problem had been noted in the USA early in the expansion of methadone treatment, when, as noted by Jaffe et al (2003), “…there was no practical mechanism to prevent their misuse as a cover for profit-oriented prescribing of methadone”.

1.3. USA

Recent systematic monitoring data emerging from the United States provides a different aspect of diversion. Media reports of methadone-associated deaths in Maine, Florida, and North Carolina prompted investigations into this problem. All three states had per capita distribution of methadone tablets through pharmacies exceeded the national average (Centre for Substance Abuse Treatment, 2006). In North Carolina, the number of deaths associated with methadone increased five-fold from 1997 through May 2001, for a total of 198 cases over that five-year period. When the source of the methadone could be determined (in about half the cases), physician prescription orders were identified in 75 percent, with the rest
obtained from non-medical sources (e.g., prescribed to a relative/friend, obtained at a party, or “street purchase”). Only four percent of the decedents were participating in addiction treatment at or near the time of death, and OTPs were considered an unlikely source of the methadone involved in the fatal cases.

The mounting evidence of serious problems associated with prescription drug diversion places the issue of structured treatment, including varying degrees of supervised dosing, on the agenda of doctors in primary care and generalist health settings. There is clear and increasing evidence of harm associated with prescription drug diversion. Paulozzi (2006) used data from the Drug Abuse Warning Network to document this rising problem. He reported that the number of reports of opioid analgesics nearly doubled between 1997 and 2002; methadone, oxycodone, and unspecified opioid analgesics accounted for 74.3% of the increase. Oxycodone reports increased 727.8% (from 72 to 596 reports). By 2002, opioid analgesics were noted more frequently than were heroin or cocaine.

A recent US study investigated new entrants to methadone treatment, and confirmed that there is an increasing number of people whose primary drug of dependence is a prescribed opioid (Rosenblum et al, 2007). They surveyed methadone clinics, oversampling from more rural areas, where prescription drug dependence was thought to be common. Thirty-eight percent of entrants to treatment reported they were primarily dependent on prescription opioids. About 40% of entrants, both those primarily dependent on heroin, and those primarily dependent on prescription opioids, reported chronic pain. Being away from large cities (“low urbanicity”) was a predictor for prescription opioid misuse. The most frequent source of prescribed opioids were dealer, friend or relative, or doctor’s prescription. Internet or forged prescriptions were uncommon. Prescription opioid dependence was particularly common in the age group 18-25.

These reports, a small selection of many reports on prescription drug diversion, are cited to document two issues. Firstly, diversion from methadone treatment programs, which rely on supervised doses and strict criteria as to who should receive takeaway doses, is contributing substantially less to the illicit opioid market, and to mortality, than diversion of unsupervised opioids prescribed for pain. Secondly, diverted pain medication is creating a new cohort of opioid-dependent people. This data makes clear that it is no longer valid, if it ever was, to make rigid distinctions between prescribing opioids for treatment of pain, and prescribing for treatment of dependence. This has led some authors to recommend “universal precautions” – including urine testing, and at times daily dispensing of medication - in prescribing opioids, whether for pain or for treatment of established dependence (Kahan et al, 2006). The precaution of supervising administration may be seen as a behavioural strategy, not only to minimize the temptation to sell drugs to the black market, but also to reduce the risk of inappropriate use by people with impaired control over drugs.

1.4 Buprenorphine diversion

There is considerable evidence that buprenorphine is susceptible to diversion and misuse, and can result in harms. Three patterns of abuse have been identified.

First, buprenorphine may be, by virtue of its availability, a primary drug of abuse. In certain cities or countries where buprenorphine has been readily available, and where heroin availability is low, buprenorphine has been the most frequently used drug of abuse - usually crushed and injected (Robinson, 1993; Lavelle, 1991; Frischer, 1992). There is recent evidence that massive diversion of buprenorphine from France has contributed to an extensive black market in some other European countries, where injected buprenorphine has
become the primary drug of abuse. It has been reported that the availability of diverted buprenorphine led to an 80% increase in the number of injecting opioid dependent people in Georgia between 2003-2006 (Parfitt, 2006). This not only represents a public health problem of contributing to addiction and morbidity associated with injecting, but also creates public antipathy towards buprenorphine treatment.

Secondly, buprenorphine may be used as a “fall back” drug, a drug to be used when other drugs (mainly heroin) are unavailable. In this situation it is usually injected, but may be taken sublingually (O’Connor, 1988; Chowdhury, 1990).

Thirdly, patients receiving buprenorphine as maintenance treatment for addiction may abuse the drug in two ways – by injecting take home doses, and by selling take-home medication to people not in treatment. In France, the only country with extensive experience of high-dose buprenorphine substitution treatment, where buprenorphine treatment is delivered without supervised administration, there has been a substantial amount of injecting of buprenorphine (Obadia et al, 2001). A report on the French experience with buprenorphine (Bouchez, 1998) indicated that pharmacists reported selling injecting kits along with dispensing buprenorphine on 30% of occasions.

Despite the evidence of diversion, there is also impressive evidence of the safety of buprenorphine. Following the introduction of buprenorphine in France in 1995, an estimated 60,000 patients were treated each year. It was estimated that about half the 150,000 estimated opioid-dependent people in France received treatment in the five years following expansion of buprenorphine treatment. Between 1994-1999, the number of fatal opioid overdoses dropped progressively, from 564 in 1994 to 120 in 1999 (Auriacombe, 2004). The massive increase in people in treatment was presumably a major factor reducing overdose mortality. In addition, the reduction in deaths is consistent with the hypothesis that diversion of buprenorphine, with its substantially lower risk of fatal overdose, might actually reduce the risk of fatal overdose, and have a net public health benefit, allowing individuals not in treatment to manage withdrawal symptoms in relative safety.

There is little systematic documentation of harms associated with buprenorphine injection, making risks difficult to quantify. Some fatal overdoses have occurred. Tracqui (1998) reported on overdoses associated with the use of buprenorphine in France. 29 cases of overdose presenting to the University Hospitals of Strasbourg were examined retrospectively, along with an examination of 20 cases of fatal overdose, mostly identified through forensic records. 13 of the 29 overdose cases were receiving prescribed buprenorphine; the remainder obtained the drug on the black market. The authors comment that monitoring was very lax, and 4 of the 13 subjects being prescribed buprenorphine were described as “medical nomads”, obtaining prescriptions from multiple practitioners. The authors identified intravenous use of buprenorphine as a risk for toxicity. Ten of the fatal overdose cases had used the buprenorphine intravenously.

Despite the widespread prescribing of unsupervised buprenorphine in France, it appears that the drug has limited appeal to people not in treatment. Auriacombe (2004) cites a report that in a sample of 50 IDUs presenting for in-patient detoxification, 18% were positive for buprenorphine, 80% were positive for heroin, and 72% for benzodiazepines. Another study cited in the same article reported on the use of buprenorphine by individuals who were interviewed while they were accessing clean syringes from syringe exchange programs, vending machines, or community pharmacies. In this intravenous drug-using population, 57% reported that they injected buprenorphine at least once over the past six months. Sixty percent
of those having used buprenorphine intravenously at least once reported being regular injectors of heroin and-or cocaine, but injecting buprenorphine only occasionally. The remaining 40% of buprenorphine injectors - 24% of the total sample – reported having injected buprenorphine exclusively over the past six months; most of these subjects reported that they were in buprenorphine treatment.

This limited data suggests that in an environment in which there is availability of heroin, a minority of people use buprenorphine. However, among people prescribed buprenorphine without supervision, injecting of the drug is not rare.

In France, most buprenorphine is prescribed, without supervision of dosing. However, even in jurisdictions where buprenorphine is given supervised, diversion occurs. Reported illicit use and injecting of buprenorphine in the Australian State of Victoria has occurred since the introduction of the drug in 2000. In 2005, most (85%, n=128) of the Melbourne respondents in a national survey of injecting drug users reported lifetime use of buprenorphine, and 63% (n=94) reported using this drug illicitly in the last six months (Jenkinson et al, 2005).

1.4.1 Summary- weighing up the harms and benefits of unsupervised buprenorphine

In France, a rapid expansion of treatment using unsupervised buprenorphine was associated with a substantial drop in fatal overdoses. To the extent that this expansion of treatment capacity was only possible without supervision, unsupervised dosing may have an important public health role. The basis on which lack of supervision may have contributed to the expansion is that cost may have prohibited the development of supervised programs, and that supervised programs may have deterred many people from participating. Data could not be found providing evidence in relation to these plausible hypotheses.

There have been harms associated with the buprenorphine program in France, of which the most serious appears to be massive diversion to jurisdictions in which buprenorphine has become the primary drug of misuse. There has also been diversion and injection of buprenorphine within France, although the extent to which this causes harm is not defined. Although there have been case reports of harm associated with buprenorphine injection, there is no systematic documentation of the harm resulting from injection of medication designed for sublingual route.

1.5 Measures to reduce diversion - Clinical Guidelines

Clinical guidelines for methadone treatment in the USA, Australia and the UK (Federal Register, 2001; Henry-Edwards, 2003; DOH, 1999) recommend initial supervision, patient selection, and ongoing monitoring, as the critical measures in prescribing. During the initial phase of supervised dosing (2-3 months), patients’ response to treatment (either methadone or buprenorphine) is assessed. Those who achieve “stability” (generally assessed by measures such as employment, cessation of injection, not using cocaine or amphetamines, not dependent on alcohol or benzodiazepines) are progressively allowed increasing availability of unsupervised doses. Ongoing monitoring of treatment is required, and if a patient becomes destabilized, they may be returned to supervised dosing.

As has been noted above, recommendations based on initial supervision, and supervision of unstable patients, appeared to result in a marked reduction in methadone diversion in the UK.

There is some evidence from France that stability criteria contained in guidelines correlate with less likelihood of injecting buprenorphine. A French survey of people in buprenorphine treatment found two variables which were independently significantly associated with
injecting buprenorphine; being unemployed, and having used cocaine, crack or cannabis
undertook a survey of patients in methadone and buprenorphine treatment in a variety of
treatment settings. Among 339 respondents, 25.7% reported having injected drugs and 15.3%
had injected the substitution drug. Injection was more common among buprenorphine-
maintained individuals (40.1%) than among users on methadone (15.2%) (p < 0.01)
(probably reflecting the greater level of supervision of methadone administration). In the
buprenorphine group, injection was related independently to social situation, as measured by
housing (unstable versus stable housing, OR = 4.3; 95% CI = 1.6-11.5), but this was not the
case in the methadone group. Interestingly, the risk of injection increased with buprenorphine
dosage (high/low dosage OR = 6.2; 95% CI = 2.0-19.7), but this association was not observed
in the methadone group.

In summary, it would appear that there is some limited support for higher supervision of
people who are less stable – specifically, unemployed, lack stable housing, using multiple
drugs, or continuing to inject drugs.

1.5.1 Alternate formulations

The third method of minimizing diversion is through the use of alternate preparations less
susceptible to diversion and misuse.

The preparation buprenorphine-naloxone is designed to minimize risks of diversion and
misuse by precipitating withdrawal if injected by opioid-dependent individuals. Stoller et al
(2001) tested 4:1 ratio buprenorphine-naloxone in subjects maintained on 40mg/day of oral
hydromorphone. Subjects underwent challenges with IM buprenorphine at 1,2,4,8,16mg (all
4:1 with naloxone). Challenges were also performed with mono buprenorphine 8mg, and
10mg IM hydromorphone. 10 subjects participated. Salient findings were that:

- Buprenorphine 8mg IM produced euphoric effects, similar to IM hydromorphone
- Bup 8mg sl was indistinguishable from placebo
- Buprenorphine-naloxone given IM produced dose-dependent antagonism. From 4-
  16mg this differed significantly from placebo. There was a bell-shaped response in
terms of intoxication and drug liking – at low and high doses there were few “good”
effects, maximal good effects were reported in mid-range. All “good effects” scores
with combination product were lower than with IM buprenorphine mono.

This study confirms that buprenorphine is a reinforcing drug, and that its reinforcing
properties are reduced by combination with naloxone. However, in opioid users not currently
neuroadapted, injected combination buprenorphine/naloxone produces opioid-like actions
without precipitated withdrawal (Strain et al, 2000). Similarly, in people maintained on
sublingual buprenorphine, injection of the combination product is unlikely to precipitate
withdrawal (Eissenberg, 1996).

The extent to which this combination product will reduce diversion is uncertain. It is difficult
in research trials to monitor the extent of diversion of medication. It becomes more possible
when the drug is registered and in widespread use, as surveys may then begin to produce
reliable indicators of the extent of diversion. Such studies are under way in several
jurisdictions.
Summary of key findings and strength of evidence regarding diversion

Making treatment accessible, affordable, and attractive to potential consumers needs to be balanced against the need to minimize diversion. A degree of diversion is inevitable, even in the best-run treatment programs. It is also inevitable that there will be doctors, who either for profit or out of misguided beliefs, prescribe inappropriately, and thereby contribute to diversion (Jaffe & O’Keeffe, 2003).

Several authors have suggested that an excessive “historical” preoccupation with minimizing diversion has distorted treatment practice, particularly in the USA (e.g., Rhoades, 1998). It has been suggested that the harm associated with diversion has been exaggerated, and there is some support for this claim. Drugs diverted from treatment services goes primarily to people who are already opioid dependent (Spunt et al., 1986). An Australian study on methadone-related deaths found that most fatalities associated with diverted methadone occurred in people who were established heroin users (Sunjic & Zador, 1999).

However, there is substantial evidence from a wide range of settings that diversion is an integral risk in prescribing opioids, whether in management of dependence or management of pain. A recent literature review from the UK (Fountain et al., 2000) investigated the extent and nature of the black market in diverted pharmaceuticals. The authors concluded that the black market in diverted drugs was substantial, and involved a large number of individuals, each diverting small amounts of their own prescribed drugs. Major motives for selling prescribed drugs were to raise funds to buy other, preferred, drugs and/or to pay for a private prescription. Drug users in treatment were reported to exploit the variations in prescribing practice—such as how much 'take-home' medication they are allowed and whether tests are conducted to ascertain if they are using it themselves—and divert their prescribed drugs.

Diversion of prescribed opioids has been associated with three serious adverse consequences—fatal overdose, an increased incidence of addiction (particularly in jurisdictions where heroin is scarce), and compromising the public acceptance of treatment programs. In addition, there is an ill-defined issue of harm due to injecting drugs intended for oral or sublingual administration.

While buprenorphine diversion is not clearly associated with an increased risk of fatal overdose than diversion of methadone (and may even contribute to reducing risk), it is not free of harm. To the extent that the diversion of buprenorphine contributes to increasing the prevalence of dependence on opioids, compromises public acceptance of treatment, and diminishes the effectiveness of treatment, diversion is a public health problem. To the extent that buprenorphine substitutes for use of heroin or other opioid drugs, diversion to the black market may be reducing overdose risks. There is no definitive data weighing up these different harms and benefits, in part because the extent of diversion and misuse depends on local factors—notably, availability of other opioid drugs.

Key findings on diversion

1. The potential harms associated with diversion to people not in treatment are
   - fatal overdose
   - contributing to the supply of illicit drugs and dependence
• loss of community acceptance of treatment programs.

(Multiple observational studies).

2. Supervision of dosing reduces the risk of diversion of opioid drugs (Multiple observational studies). Circumstantial data from Scottish studies suggests that introduction of supervised dosing in the first 3 months of treatment was associated with a marked reduction in diversion.

3. Supervision of methadone dosing reduces the risk of fatal overdose due to diversion. (Multiple observational studies.) In the UK, in the context of new clinical guidelines, an increase from 0-36% of supervised methadone doses (primarily due to initial supervision) was associated with a reduction of 2/3 in the rate of methadone-related deaths.

4. Some of the factors associated with the increased likelihood of diversion of methadone or buprenorphine to the black market are low availability of heroin, jurisdictional policies allowing multiple take-home doses, greater cost of paying for treatment, and low levels of doctors’ compliance with guidelines. (Multiple observational studies)

5. Patients with unstable housing, multiple drug use, poor and inconsistent attendance, appear to be at greater risk of injecting prescribed medication than stable patients (observational studies).

6. Buprenorphine-naloxone without supervision may have a lower risk of diversion, although the extent to which this occurs remains to be defined in different settings. In places with high availability of heroin or other full agonist drugs, buprenorphine-naloxone diversion is likely to be less of a problem than in settings where other opioids are scarce. Based on the French experience, and the fact that naloxone will not readily reverse buprenorphine, the group most likely to inject the combination product are those being prescribed it for unsupervised use. (Laboratory and observational studies)

7. Diversion of opioids prescribed for pain is a greater problem in some jurisdictions than diversion from opioid treatment programs (multiple observational studies).

2. Efficacy

Some authors have suggested potential therapeutic benefits from observed dosing. These included the belief that daily attendance brings people into contact with services (McLellan et al, 1993). Also suggestions that structure was valuable early in treatment, to reduce risks of misuse of prescribed medication, making treatment as experienced by the patient safer (Bell, 1998). However, there is little data to support these speculations.

This is a critical topic, as the strongest evidence supporting the effectiveness of maintenance treatment comes from randomised-control studies, and these have all involved supervision. The initial placebo-controlled trials supporting methadone (Dole et al, 1969; Newman & Whitehill, 1979; Gunne & Grondblaht, 1981) involved supervision. Subsequent trials comparing methadone and buprenorphine also involved supervised dosing (Johnson et al, 1992; Kosten et al, 1993; Strain et al, 1994; Ling et al, 1996; Fischer et al, 1999; Johnson et al, 2000; Mattick et al, 2003). Placebo-controlled trials demonstrating the effectiveness of buprenorphine involved supervised dosing (Johnson et al, 1995; Kakko, 2003), and, in at least one case, supervised dosing and payments for people to attend during the randomised phase (Fudala et al, 2003).
2.1 Comparisons of supervised versus unsupervised treatment

There are three reported trials comparing the effectiveness of different levels of supervision, two involving buprenorphine treatment and one involving methadone.

There is one as-yet-unpublished randomised trial (Bell et al, in press), which compared retention and heroin use in 119 opioid-dependent (almost entirely heroin dependent) subjects randomly allocated to supervised dosing or to weekly dispensing of medication. All subjects received combination buprenorphine-naloxone (mean dose 12mg), and were randomised within 7-10 days of commencing treatment. They continued in their randomized condition for 3 months, after which time subjects from either group who met criteria of stability were able to receive treatment without supervision. Over three months randomised phase, retention in the two groups was almost identical (57% unsupervised, 61% supervised), and heroin use (monitored by self-report, urine tests and hair testing) was also very similar.

The authors have also reported a cost analysis, showing that treatment without direct observation was significantly cheaper, and therefore significantly more cost effective. The mean cost of treating the unobserved group was $AUD1663 (95% CI 1308–2017), less than for the observed group at $AUD2138 (95% CI 1713 –2562). For the unobserved group the cost of the medication comprised the largest proportion of costs. The direct costs of dosing and dispensing were larger for the observed group (mean cost of $AUD374, compared to $AUD186 for the unobserved group). These represent the costs of treatment as delivered in specialist clinics, rather than primary care settings.

Not only was unobserved treatment cheaper for the clinic delivering care, it was substantially cheaper for the individuals in treatment. The mean travel costs for 3 months treatment for observed subjects was $AUD451, compared to $AUD133 for unobserved subjects.

Despite the lower cost and presumed greater convenience of attendance, self-reported psychological symptoms (depression, anxiety and stress) and quality of life after 3 months treatment did not differ between the groups.

One limitation to the generalisability of this study is that a minority of people (131/591) who sought buprenorphine treatment at the participating centres met eligibility criteria for the study. The commonest reason for excluding patients was homelessness, on the grounds that it was unsafe to supply tablets for a week to people without stable accommodation. The other major reason was that many patients were seeking short term treatment only, and did not want to commit to maintenance.

A French study is described in Auriacombe et al (2004), in which 202 patients were assigned “quasi-randomly” to daily supervised dosing for either two weeks, three months, or six months, after which dosing was on a weekly schedule. The method of randomisation is not described, nor is any data presented on how well-matched the groups were. Results from this study showed that retention in treatment at the six-month follow-up was highest for those patients in the six-month daily supervised dosing group (80%) and lowest for those patients in the two-week daily supervised dosing group (46%). (The three-month daily supervised dosing group fell between these two [65%].) Rates of opioid-positive urine samples were lowest for the six-month daily supervised dosing group (14%), compared to the three-month daily supervised (22%) and two-week daily supervised (18%) groups. Average daily doses at the six-month assessment were similar for the three groups (7.9, 8.7, and 8.5 mg-day for the
six-months, three-month, and two-week groups, respectively). On the face of it, there appears to be a three-fold greater risk of dropping out of treatment among subjects receiving on 2 weeks of supervision, suggesting a very significant beneficial effect of supervised dosing. However, the numbers in each group are not reported, and no statistical tests of these differences in retention are reported.

Rhoades et al (1998) reported a study using methadone treatment, in which subjects were randomly allocated on two dimensions; to either 5 days per week or two days per week of supervised dosing; and to either 50mg or 80mg daily. The abstract reports that the study occurred in 150 subjects, but the text reports that 142 were consented, but patients with “emergent psychiatric comorbidity” were not randomized; 123 were randomized, and data from 107 subjects analyzed. The final numbers in each group were not reported. The authors report that at 80mg/day, there were no differences in retention between the 2 or 5 days per week attendance, with nearly 80% retained for 6 months. At the lower dose levels, in subjects asked to attend 5 days per week, retention fell to 40%. Heroin use was lower in the high dose group, and did not differ according to level of supervision. The authors concluded that fewer clinic attendances were associated with better retention.

Thus from three trials we have three conflicting results: one showing no difference in retention or heroin use, one showing benefits of supervision on both parameters, and one showing the negative effect on retention of greater levels of supervision. However, two of these three trials were consistent in finding that at adequate doses, different levels of supervision of dosing made no difference in retaining people in treatment, nor in heroin use. The third study, which appears to be a work in progress and is yet to be reported in detail, found a marked advantage of supervision in retaining patients in treatment and reducing heroin use.

In addition to these trials, there are several observational studies reported, all of which take advantage of regulatory changes to investigate the impact of different levels of supervision. In one quasi-experimental study reported from Italy, Gerra and colleagues (2003) describe outcomes when their methadone clinic was required to reduce the number of people attending daily. The 265 patients in long-term methadone treatment were allocated to receive either 0, 5 or 6 takeaway doses each week. The basis of allocation and degree of matching of the groups was not reported. Thereafter, patients with no take home doses returned 45% of urine specimens free of morphine, compared to 32% among subjects receiving 5 takeaways, and 22% clear among patients receiving 6 takeaways. The authors concluded that access to unsupervised doses contributed to poorer outcomes.

Patch (1978) reported an observational study that took advantage of a policy change in which methadone clinics in Boston were required to stop providing takeaway doses. For three months after this policy directive, discharge and readmission rates to methadone clinics increased, consistent with a negative reaction from consumers to withdrawal of takeaways. However, after 3 months, discharge and readmission rates returned to baseline, or slightly less than baseline levels. The authors concluded that while withdrawal of takeaways provoked negative reactions, availability of takeaways did not enhance retention in treatment.

A similar study with a different conclusion was reported from Italy by Pani et al (2000). The authors report on regulatory changes which saw methadone takeaways allowed, then prohibited for 2 years, then allowed again. During the initial period, patients with 6 months documented stability could attend the clinic once per week, submit a urine test, and collect a week’s supply of methadone. After the prohibition of takeaways, 211 subjects were randomly
selected for study, and a retrospective control group of 200 subjects who had been in treatment (and potentially eligible for takeaways) 12 months earlier was identified. There was a higher drop-out rate in the cohort unable to receive takeaways (19.9% vs 3.2% over 6 months), and a similar difference in proportions undergoing elective withdrawal. Pani et al concluded that takeaway doses for stable patients enhance retention in treatment.

Thus, three observational studies also provide contradictory results – one showing no difference, one a deleterious effect of supervision, and one a beneficial effect.

2.2 Summary - Does supervision enhance efficacy?

The six studies described here vary significantly in methods and outcomes, and it is not meaningful to undertake a meta-analysis. Two prospective trials did reach a similar finding – at adequate doses, the level of supervision in the first 3 or 6 months of treatment did not influence retention or heroin use. Therefore, based on limited and conflicting data, it seems reasonably to conclude tentatively that the degree of supervision of dosing makes little difference to outcomes in the initial months.

However, that conclusion needs to be taken in context. Subjects in the Bell (in press) study were a minority of applicants for treatment, and they received close clinical monitoring, with weekly appointments, monthly inspection of injecting sites, weekly urine tests and three monthly hair tests for toxicology. Such intensive clinical monitoring is not generally practised outside of research studies. The importance of clinical monitoring is emphasized in an observational report from France, which found that less clinical monitoring was associated with more heroin use and more injecting of buprenorphine (Barau et al, 2001). Lack of supervision of dosing does not indicate a lack of close clinical monitoring, and, conversely, supervision of dosing does not imply good clinical monitoring. The appropriate conclusion from the available data is that in the presence of close clinical monitoring, treatment without supervision can be as effective as supervised dosing.

There has been a widespread assumption that unsupervised dosing is less expensive, and the finding that such treatment is less costly and more cost effective, although based on a single study, seems robust.

2.3 Can take-home doses enhance efficacy?

The studies cited above look at supervision as a policy issue, comparing take-away with no takeaway conditions. However, in clinical practice, availability of takeaways is contingent on people meeting criteria of stability, and in some cases is actually part of a formal contingency management (CM) program. CM is defined as providing a system of incentives and disincentives designed to make supplemental drug use less attractive, and abstinence more attractive. A review and meta-analysis (Griffiths et al, 2000) concluded that CM was effective in reducing heroin use. CM interventions included in the review were: increase or decrease in methadone dose; increase in methadone; decrease in methadone; take-home methadone; vouchers; or a mixture of reinforcers.

Six of the studies identified by Griffiths used take-home doses as a reinforcer, 2 involving doses <50mg/day, 2 involving a range of doses, and 2 involving doses >50mg/day. Three studies were non-significant, and 3 found significant advantage of providing take-home doses as a reward for subjects submitting urine tests free of morphine.

This provides grounds for using unsupervised dosing in contingency management, and is consistent with the finding that people in treatment place high value on take-away doses.
Chutuape et al (1998) surveyed methadone-maintained patients about their preferences for incentives. Responses were highly consistent across surveys and indicated that, in general, take-homes were the most preferred, followed by dose increases and then counselling; 64% of respondents placed take-home medication in their top five preferences.

No studies since 2000 were identified in which take-home doses were used in contingency management as reinforcers.

2.3.1 Effectiveness of “medical maintenance”

While there are few direct comparisons between levels of supervision, there is a small and consistent literature confirming the effectiveness and safety of “medical maintenance” - providing methadone (up to 30 days supply of medication at a time) to stable, long-term patients. Several US trials of methadone medical maintenance have demonstrated that it is effective and well-liked by patients (eg King et al, 2006; Fiellin et al, 2001; Merrill et al, 2005). Stable patients – those who have been in long-term treatment and have ceased injecting drug use – as might be expected, do well without supervision, although not clearly better than if being supervised. The common experience of these studies is that patients report improved quality of life at not having to attend a clinic regularly. Episodic dabbling in drugs, and relapse into “unstable” drug use, occur occasionally, as they do in supervised treatment (Feillin et al, 2001). The only study which reported the figures indicated that only a small proportion of subjects met eligibility (7%) criteria, and fewer actually entered treatment (Merrill et al, 2005).

A similar experience has been reported with buprenorphine-naloxone from a small Australian study which demonstrated the feasibility and acceptability of weekly dispensing of buprenorphine-naloxone (Bell et al, 2004). In this study, stable patients (who represented only 11% of the patients in treatment during the recruitment phase) reported substantial improvements in quality of life when transferred to treatment without supervision.

2.4 Does supervision deter participation?

Direct observation of treatment has shaped the culture of substitution programs (Bell et al, 2002). Clinics dosing large numbers of clients develop economical ways to deliver treatment to large numbers of people daily, but in doing so become mechanical and perfunctory systems in which patients line up to receive doses in minimal time. Most clients of methadone clinics dislike attending the clinic daily, not merely for the inconvenience, but because they dislike the ethos of methadone clinics (Bell & Zador, 2000). It is plausible that dislike of attending clinics or pharmacies for supervised dosing deters a significant proportion of people from participating in treatment.

This is difficult to investigate definitively. A recent study from USA (Finch et al, 2007) reported on a chart review from general practitioners who had prescribed buprenorphine-naloxone. The review identified 71 patients, 52% of whom had previously used heroin (the remainder being dependent on prescription opioids). Seventy percent had no prior history of substitution treatment, consistent with the hypothesis that treatment without supervision might be reaching a population unwilling to participate in supervised treatment. However, more data is required to support this proposition, as there are many reasons, independent of unsupervised dosing, why a new, office based program might attract a new clientele. Geographical access, and the stigma associated with methadone treatment, are two obvious reasons. The finding that office-based prescribing reaches a new clientele does not in itself demonstrate that supervision is a deterrent. At this stage, the possibility that treatment
without supervision may encourage a new group of patients into maintenance treatment remains to be confirmed or refuted.

2.5 Conclusions – efficacy

1. Initial supervision of dosing, in programs with adequate dosages and good clinical monitoring, does not result in worse treatment outcomes than unsupervised treatment (2 randomised trials)

2. The requirement for supervision may deter some people from participation (insufficient data).

3. Supervision makes treatment more expensive for health funders and for consumers (1 cost effectiveness trial).

4. Supervised dosing is not necessary for effective treatment in selected stable patients (multiple observational studies), but this probably represents a small proportion of people in treatment programs (2 observational studies)

5. Contingent access to unsupervised doses serves as an incentive to people to reduce the likelihood of submitting positive urine tests (multiple randomised trials).

3. Consumer views

An English study sought views of patients seeking methadone maintenance in an area which had introduced supervised consumption as the norm (Stone & Fletcher, 2003). Patients considered that supervision was important at the commencement of methadone treatment and for chaotic individuals who were still actively engaged in illicit street drug use. They were keen to see movement away from supervision when good progress was made and an individual had objectively demonstrated that they were refraining from street drug use, complying with appointments and making positive life-style changes. Service users felt aggrieved at being put on to supervision if they had been using their medication responsibly. Consumers generally reported that in order to prevent black market leakage, only those who had proved themselves trustworthy should be given unsupervised methadone. However, some individuals reported increased heroin use because they were no longer able to split the dose of methadone.

Zisowitz (2005), in a conference presentation, reported consumer responses when a methadone clinic for the first time allowed 3-day a week dosing for unemployed patients, and extended weekend take-homes available to those in MMT for only 3 months. A significant minority of patients were reluctant to accept the take-home privileges, and numbers were reported to have relapsed to drug use shortly after gaining them.

An English study investigated attitudes of professionals and consumers towards supervision of dosing (Cox, 2002). The great majority of all three categories of professional respondents (physicians, pharmacists, and community drug workers) indicated that they were in favour of or very much in favour of community pharmacist supervision. In contrast, the majority of patients indicated that they objected or strongly objected to the supervision.

These three reports are not as inconsistent as might initially appear, and can be synthesized into a range of views recognising that there are strengths and weaknesses of supervision from
consumer perspectives. These are neatly summarized in a Scottish study, conducted shortly after the local program had moved towards increased supervision of dosing (Neale, 1999).

Reasons for disliking daily visits to the pharmacy included inconvenience (particularly if one is at college or working), dislike of everyone getting to know your business, the cost of daily travel to the pharmacy, difficulties in arranging going away on holiday, and problems attending when one does not feel well. Reasons for liking daily dispensing included a fear of not being able to manage a greater supply on one’s own, and a belief that daily dispensing decreases the incidence of people selling and abusing their drugs. Additionally, some felt that the trip to the pharmacy was useful in making sure that they ventured out for some exercise. Although many individuals stressed that they personally preferred not to be supervised, several reported that they actually wanted the arrangement. A large number of interviewees reported being indifferent to supervision, although some qualified this with ‘as long as it is private’ or ‘as long as the shop is empty’. A small number also felt that they had needed supervision in the beginning, but did not require it now. The main advantage of not being supervised was that take-home doses afforded individuals greater control over their medication, particularly the timing of consumption and the level of dosage taken. The main reason given for not wishing to be supervised was the unpleasant experience of taking the medication in a public place. For most, supervision was considered embarrassing, an infringement of privacy or degrading. Some were afraid of bumping into family, friends or neighbours, and a minority simply found it inconvenient.

When asked to evaluate supervised consumption more generally (that is, in terms of whether they thought that the practice was on balance positive or negative rather than in terms of whether they personally would prefer it), the interviewees were far more likely to describe supervision as beneficial and useful rather than as pointless or harmful. A much greater number of users viewed supervised consumption as a positive than as a negative condition. The advantages of supervision related mainly to its potential for preventing abuse of the substitute prescribing system. Additionally, there was some recognition that supervision assisted some individuals in sticking to the programme and protected others from the dangers of illicit drug use, particularly overdose and injecting. A substantial number of individuals recommended that supervision should always be a condition of receiving a prescription. Others, however, pointed out that supervision was not suitable for everyone or that an individual’s need or desire for supervision was susceptible to change over time.

The author concluded that drug users do not generally consider substitute drugs to be just like any other medication. Rather, supervision plays a part in the overall delivery of treatment. It appears that consumers recognise supervision is part of the “structure” of treatment, a component of treatment just as counselling or medical care are components. As with other components, the requirement for highly structured treatment, notably daily supervision of doses, differs between individuals, and changes within individuals over time (Bell, 1998).

**Conclusion - the role of supervision of dosing**

The data on diversion and overdose deaths consistently suggests that supervision early in methadone treatment, and perhaps throughout treatment in selected patients, reduces risk of fatal overdose to people not in treatment. Initiating treatment with supervised dosing, assessing response to treatment, and subsequently allowing unsupervised doses to patients who demonstrate stability, appears to have a substantial effect in reducing diversion, probably does not diminish efficacy, and has support from consumers. The key elements of
“stability” appear to include housing, employment, not being dependent on multiple drugs, and ceasing injecting after entering treatment.

The data do not allow a firm conclusion as to whether it is on balance more beneficial to initiate buprenorphine treatment with supervision of dosing. The benefits of making treatment more accessible, affordable and possibly more attractive to consumers need to be balanced against risk of less effective treatment, creation of a black market, and community antagonism.

Taking a broader perspective, the critical issue is not a crude policy decision between supervised or unsupervised treatment, but is answering more specific questions – who requires supervised dosing, and how patients should be monitored to determine suitability for unsupervised doses. The benefit of expanding treatment by making it less expensive needs to be balanced against the cost of delivering adequate treatment quality. Patients doing well in highly structured, well-resourced trials of unsupervised dosing do not predict that people will do well in unstructured, under-resourced treatment. In addition, treatment needs to be tailored to individuals needs. Patients with severe psychological and social problems were excluded from trials, on the assumption that safety required supervision of dosing. People with severe problems are those most likely to divert medication, and may well require supervision for prolonged periods.

References


Bell J, Dru A, Fischer B, Levit S, & Sarfraz, MA (2002) Substitution therapy for heroin addiction Substance Use and Misuse 37 (8-10); 1145-1174


Centre for Substance Abuse Treatment (2004) Methadone associated mortality; report of a National Assessment US Dept of Health and Human Services, Substance Abuse and Mental Health Services Administration

Chowdhury, AN, and Chowdhury, S (1990) Buprenorphine abuse; report from India. British Journal of Addiction, 85; 1349-50


Jaffe J & O’Keeffe C (2003) From morphine clinics to buprenorphine; regulating opioid agonist treatment of addiction in the United States Drug and alcohol dependence 70; S3-S11


