Pharmacological maintenance treatments of opiate addiction

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For people seeking treatment, the course of heroin addiction tends to be chronic and relapsing, and longer duration of treatment is associated with better outcomes. Heroin addiction is strongly associated with deviant behaviour and crime, and the objectives in treating heroin addiction have been a blend of humane support, rehabilitation, public health intervention and crime control. Reduction in street heroin use is the foundation on which all these outcomes are based. The pharmacological basis of maintenance treatment of dependent individuals is to minimize withdrawal symptoms and attenuate the reinforcing effects of street heroin, leading to reduction or cessation of street heroin use. Opioid maintenance treatment can be moderately effective in suppressing heroin use, although deviations from evidence-based approaches, particularly the use of suboptimal doses, have meant that treatment as delivered in practice may have resulted in poorer outcomes than predicted by research. Methadone treatment has been 'programmatic', with a one-size-fits-all approach that in part reflects the perceived need to impose discipline on deviant individuals. However, differences in pharmacokinetics and in side-effects mean that many patients do not respond optimally to methadone. Injectable diamorphine (heroin) provides a more reinforcing medication for some 'nonresponders' and can be a valuable option in the rehabilitation of demoralized, socially excluded individuals. Buprenorphine, a partial agonist, is a less reinforcing medication with different side-effects and less risk of overdose. Not only is it a different medication, but also it can be used in a different paradigm of treatment, office-based opioid treatment, with less structure and offering greater patient autonomy.

Introduction

Opioid maintenance treatment is a well-established modality of treatment for heroin addiction. Since the 1960s, maintenance on methadone has been the most common medical treatment of heroin addiction internationally. In the last two decades, buprenorphine has also been used as maintenance treatment for heroin addiction, and there has been a resurgence of interest in prescribing pharmaceutical heroin.

A recent estimate is that there were between 15.2 and 21.1 million people abusing or dependent on opioids worldwide [1]. Age-adjusted mortality among heroin users is high, at 1–3% per annum [2]. Among younger heroin users, overdose is the commonest cause of death, with suicide and violence also contributing to mortality [3]. The injecting of street drugs, and sharing of needles, is a major route of transmission of blood-borne viruses, notably hepatitis C and human immunodeficiency virus, and as addicts and former addicts age, deaths due to liver disease,

acquired immunodeficiency syndrome and a variety of medical conditions become more common [4].

For many years in the UK, prescribing of pharmaceutical heroin was the commonest approach to treating dependence on opioids, a situation which pertained until the 1960s. The rationale for such prescribing was straightforward; it was a humane response to people who found themselves in a predicament. However, successive social changes since the 1960s changed the context and response to heroin addiction, as the UK began to suffer some of the problems that had been evident in the USA for several decades, where heroin use had been concentrated among marginalized, urban youth. Once a black market in heroin (or other opioid) becomes established in a population, there is a slow but steady recruitment of new users, drawn predominantly from socially excluded, disaffected young people, who have often been involved in crime and delinquency prior to using heroin [5]. Dependence on heroin – and other drugs – exacerbates any pre-existing adjustment difficulties and entrenches the addict's social

exclusion and involvement in crime. Superimposed on this pattern of recruitment have been cyclical 'epidemics' of heroin use, which are periods of rapid recruitment of new users, often 'middle-class' users, during times when heroin has become plentifully available [6].

Given the strong association with social problems and deviance, it is unsurprising that opioid maintenance treatment has had somewhat blurred objectives, ranging from humane support, through rehabilitation of socially excluded individuals and public health intervention to reduce blood-borne virus transmission, to a programme to control deviance and reduce crime. Lack of clarity around the objectives of treatment, and therefore how to evaluate effectiveness, has been a persistent feature of treatment of heroin addiction [7]. Associated with this lack of clarity, there has been a proliferation of models of treatment, with differing objectives and differing outcomes. This review summarizes evidence for the effectiveness of prescribing methadone, buprenorphine and diamorphine and analyses the factors that contribute to better outcomes.

Methadone maintenance treatment

Among people seeking treatment for heroin addiction, the course of addiction tends to be a chronic, relapsing one [8], often involving multiple episodes and differing modalities of treatment [9]. The duration of methadone treatment has been demonstrated to be a linear, nonthreshold predictor of outcome, with better outcomes from longer treatment [10], and retention is regularly used in research studies as a proxy measure of outcome. Those patients who have ceased heroin use and have established supports (such as stable housing, employment, a stable relationship, affiliation with a support group) have a better prospect of sustaining abstinence after leaving treatment, but relapse is still common [11, 12].

Most patients do not wish to remain indefinitely in treatment. People remain for variable periods, often cycling in and out of episodes of treatment [13]. It is not possible to be definitive about how long an individual should remain in treatment. The appropriate duration of treatment depends on the severity of the individual's problems and the extent of their supports. It ranges from months to indefinite maintenance.

Treatment of heroin addiction does not fit an acute care paradigm, with the objective of cure, but is better conceptualized as the management of a chronic condition [14]. The objectives of long-term management are reduced risk of death and disease, improvement in mental health and outlook, and restoration of impaired social role. These objectives are most likely to be achieved if patients stop or markedly reduce their use of street heroin and other drugs [15]. In suppressing use of street heroin, pharmacological maintenance treatment is more effective than short-term treatment or no treatment [16]. Methadone treatment attracts

and retains in treatment more heroin users than drug-free approaches [9, 16]. The result of suppression of heroin use is a reduction in the risk of death, because of entry into treatment, with the protective effect lasting while people remain in treatment [17], in conjunction with availability of clean needles and syringes, a reduction in risk of blood-borne virus transmission [18], reduction in involvement in crime [19] and subjective improvement in quality of life [20].

However, while these reassuring data support methadone treatment as an effective intervention in reducing the harm associated with heroin addiction, methadone as delivered in practice often deviates from models of treatment demonstrated to be effective [21, 22]. Broad claims about the 'effectiveness' of methadone treatment obscure the fact that, as delivered in practice, methadone treatment is not always effective. It is therefore useful to analyse the mechanism of action by which treatment can produce beneficial outcomes.

Suppression of withdrawal

Drug use starts out as pursuit of euphoric and reinforcing effects of drugs, but dependent drug use appears to be in large part driven by avoidance of withdrawal [23]. Methadone is a long-acting drug, and the appeal of methadone treatment for dependent heroin users is that a daily dose of methadone will abolish withdrawal, freeing them from compulsive drug use and allowing them to resume normal interests and activities [20].

There is consistent evidence from studies of patients on methadone that failure to suppress withdrawal is associated with worse outcomes. Up to one-third of heroin users metabolize methadone sufficiently rapidly that when given methadone once daily, they experience low-grade withdrawal symptoms in the latter half of the dosing interval [24]. Patients with rapid metabolism are more likely to experience withdrawal dysphoria, low mood and craving, to persist in heroin use and to misuse other drugs despite receiving methadone [24, 25]. Increasing the daily methadone dose in these subjects is unlikely to be effective, because withdrawal symptoms are not predicted by the absolute blood or central nervous system concentration of methadone, but the rate at which the concentration is falling [25].

Recent studies have underlined the importance of methadone pharmacology and made the picture more complex. The methadone formulations supplied in most jurisdictions is racemic methadone. Individual differences in metabolism can contribute to different ratios of *R*- to *S*-methadone, and higher proportions of *S*-methadone are associated with depression and symptoms of withdrawal [26, 27].

The foundation of maintenance treatment is suppression of withdrawal; without this, maintenance treatment is unlikely to be effective. Many factors may contribute to the fact that some people in methadone treatment persist in ongoing use of street drugs, and therapeutic drug

monitoring is potentially valuable in identifying those patients in whom rapid methadone clearance means that alternative medications may be more effective. This is particularly relevant given the documented interindividual variation in methadone metabolism [28]. However, therapeutic drug monitoring has never been widely employed in methadone treatment. This in part reflects the 'one-size-fits-all' approach to treatment, in which patients have no choices about medication. Until the last decade, there was no alternative approved drug besides methadone in many jurisdictions, meaning that there was little point in identifying those who were failing to respond. More importantly, as will be discussed in the section headed 'Non-pharmacological factors in maintenance treatment', there has been a widespread assumption that pharmacology is relatively unimportant in dealing with complex behavioural problems, with clinicians placing greater importance on counselling, programme rules and other nondrug elements in treatment. Many practitioners, confronted with the daily disorder in a methadone clinic, have assumed that part of the role of treatment structure was to discipline deviant individuals, and offering alternative medications may have seemed to be an indulgence.

Induction of tolerance

A dose of medication sufficient to provide respite from withdrawal is necessary, but not sufficient, for effective maintenance treatment. Doses of methadone of 30–50 mg day⁻¹ block withdrawal for 24 h in the majority of dependent heroin users, but these doses are not adequate for effective maintenance treatment. Heroin use is a powerfully reinforcing and motivating factor that shapes the behaviour and consciousness of people who have been addicted. In the first months of treatment, people maintained on low doses of methadone tend to continue injecting. By increasing the daily methadone dose, patients' tolerance to opioids is progressively increased, and high tolerance attenuates the individual's response to injected heroin, tending to extinguish the habit. Experimental studies demonstrate that high-dose methadone makes heroin administration less reinforcing, leading to reduction in self-administration [29, 30].

These laboratory findings have been confirmed in clinical trials. A pooled review of randomized controlled trials concluded that high doses (60–100 mg day⁻¹) were more effective in producing abstinence from nonprescribed opioids as detected by urine testing than were medium (40–60 mg) doses [relative risk = 1.59 (1.16, 2.18)] or low doses (<40 mg) [relative risk = 1.51 (0.63, 3.61)] [31].

Methadone treatment is based on inducing a higher level of tolerance than occurs during use of street drugs, and if the level of tolerance is raised too rapidly, toxicity results. During induction into methadone treatment, methadone doses need to start low and be increased slowly to avoid fatalities in the first 1–2 weeks of treatment. Once in treatment, a high level of tolerance protects

against overdose, but on leaving treatment tolerance falls, and there is a sharp rise in risk of death in the month after leaving treatment [9, 32].

Diamorphine

In the 1990s, concern over methadone 'nonresponders' – people who persist in injecting heroin despite being in methadone treatment – led Swiss researchers to undertake an observational study of injectable diamorphine (pharmaceutical heroin). Following positive results of that study, since 1998 there have been several randomized trials comparing injectable heroin with oral methadone [33–37]. All were based on the assumption of injectable heroin as second-line treatment, mostly offered to people who had 'failed' methadone treatment.

A Cochrane review concluded that among methadone treatment failures, provision of injectable heroin retained patients better in treatment than did methadone and reduced use of illicit drugs, but exposed participants to a substantially greater risk of adverse events related to study medication [38].

To minimize diversion and ensure safety, diamorphine treatment is highly structured, with no provision of unsupervised ('take-home') medication. The target population is people who have not responded to, or engaged with, other modalities of treatment. A 'poor level of functioning' in physical/medical, psychological and/or social domains was specified as an inclusion criterion in several studies. Most patients attend twice daily to inject heroin and to receive a dose of oral methadone alongside injectables, in order to provide adequate suppression of withdrawal throughout the day.

There are two hypotheses for why diamorphine may work where methadone has failed.

- 1 Some individuals tolerate methadone poorly – whether due to side-effects or to poor control of withdrawal symptoms – and may experience better symptom control from diamorphine.
- 2 Some individuals seek a more reinforcing drug than methadone. Access to diamorphine may be one of the few motivating factors for some long-term addicts who have become demoralized and lost the expectation of experiencing other rewards in life.

Analysis of the published reports provides some insights into why diamorphine may be useful as a treatment option. People randomized to receive injectable heroin reported less use of street heroin than those randomized to methadone, but the 'methadone nonresponders' who were randomized to methadone showed marked improvement compared with baseline. In one Swiss trial, more than half the subjects initially randomized to oral methadone declined the option of transferring to diamorphine when the 6 months of randomized treatment was completed; they had become

methadone responders [36]. This is probably because once enrolled in the trial, subjects received better quality, protocol-driven treatment, with adequate doses and monitoring of continued drug use and quality of life.

It appears incontrovertible that all patients should receive good-quality treatment, delivered 'per-protocol', with clear objectives, adequate doses, monitoring of response and adjustment of treatment if required. However, some patients do not comply with protocol-driven treatment. People who have few alternative rewards in their life and who want the option of continuing to use drugs in addition to prescribed opioid maintenance treatment medication often resist higher doses, attend erratically, and drop out if required to attend daily for supervised administration. For some of these methadone 'nonresponders', the prospect of eventual access to prescribed diamorphine in the Swiss trial appears to have been sufficient incentive for them to comply with 6 months of quality methadone treatment and to respond. It seems reasonable to conclude that one function of diamorphine is to act as an incentive to unmotivated addicts to comply with treatment by providing a more rewarding drug, or even merely the possibility of a more rewarding drug.

In a nonrandomized heroin programme in Switzerland with experience of treating more than 2000 patients, 70% of patients had left treatment by 6 years, of whom 60% transferred to methadone treatment (and 40% to drug-free treatment). Thus, even without exposure to a mandatory period of optimized methadone treatment, over time more than 40% of formerly 'nonresponding' patients receiving diamorphine had transferred to methadone treatment. For many patients, it appears that diamorphine treatment can serve as a transitional step in social reintegration [39].

Even with quality treatment, a proportion of patients on methadone persist in street heroin use, and in these individuals diamorphine is a potential second-line treatment. It is a highly structured, demanding treatment, often involving attendance twice daily, and is much more expensive to deliver than is methadone treatment. It is unclear what proportion of heroin users might be appropriate for this modality. In persisting methadone nonresponders, it seems appropriate to investigate methadone pharmacokinetics, to identify those with more rapid metabolism and less effective withdrawal suppression. In rapid metabolizers, a trial of an alternative agent, such as slow-release oral morphine, may be indicated before moving to the diamorphine. A research priority is to investigate whether alternative oral medications, such as slow-release oral morphine, may be effective in people with rapid methadone clearance and a poor response to methadone treatment.

Buprenorphine

Unlike full opioid agonists, such as methadone or morphine, buprenorphine has a high affinity for the μ

opioid receptor. It also acts on κ , δ and ORL-1 receptors, some of these properties being shared with its main active metabolites, norbuprenorphine, buprenorphine-3-glucuronide and norbuprenorphine-3-glucuronide. At low doses, it is a potent agonist; 1 mg subcutaneous buprenorphine produces similar subjective effects (euphoria and sedation) to 30 mg subcutaneous morphine [40]. Buprenorphine, however, has a pharmacological profile described as 'partial agonist', with a flattened dose-response curve [41] due to its low intrinsic activity. This ceiling effect limits the maximal opioid activity of buprenorphine and reduces the risk of respiratory depression due to overdose. Postmarketing studies have confirmed that buprenorphine is associated with a significantly lower risk of overdose deaths than is methadone [42].

A Cochrane review of data from randomized controlled trials concluded that buprenorphine was statistically significantly superior to placebo in retaining heroin users in maintenance treatment, and in doses >8 mg was effective in suppressing heroin use. Low doses of buprenorphine ($2\text{--}4$ mg day⁻¹) were not effective in suppressing heroin use. Comparisons with methadone have been reported as showing that methadone was more effective than buprenorphine in retaining patients in treatment [43].

A double-blind, double-dummy randomized controlled trial provided the most likely explanation for the shorter retention in buprenorphine treatment. Buprenorphine-maintained subjects experienced more withdrawal and less positive reinforcement from their medication than did subjects receiving methadone [44], suggesting that buprenorphine is a less reinforcing drug and suppresses withdrawal less completely. Even on 16 mg day⁻¹ of buprenorphine, some subjects experience low-grade withdrawal symptoms during buprenorphine maintenance [45], with perhaps the compensation that withdrawal after stopping buprenorphine is less severe than withdrawal on stopping methadone.

The usual pattern of participation in treatment by heroin addicts is that people cycle through multiple, brief episodes of methadone treatment [13] and cycle through differing modalities of treatment [9]. Consistent with the poor retention observed in clinical trials, observational studies indicate that patients cycle in and out of buprenorphine treatment more much rapidly than methadone treatment [32], and while in treatment, attendance is often irregular. Continuous participation in treatment is associated with better outcomes (in terms of reducing the likelihood of re-entering treatment within 12 months) than repeated shorter episodes [9, 13]. The critical question is whether poorer retention compromises the public health benefit and individual health benefit of buprenorphine treatment.

An observational study from Australia compared the risk of dying over several years following entry to a first

episode of methadone or buprenorphine treatment. It confirmed a reduced risk of death while in treatment, and that on leaving an episode of either methadone or buprenorphine treatment, the risk of death by overdose rose sharply. The potential implication of cycling in and out of treatment is an increased risk of death, but this was not observed. Consistent with previous studies, the study found markedly shorter retention in buprenorphine treatment and more out-of-treatment time in those initially entering buprenorphine treatment, but a nonsignificantly lower risk of death in the years after entry to treatment (6.7 per 1000 person-years for buprenorphine and 8.3 per 1000 person-years for methadone; relative risk = 0.80, 95% confidence interval 0.56–1.16, $P = 0.11$) [32]. It thus appears that intermittent participation in buprenorphine treatment is at least as effective in reducing risk of death as is participation in methadone treatment.

Retention is a proxy outcome, a predictor of benefits such as less drug use, reduced risk of overdose, better social reintegration and lower risk of relapse, rather than an end in itself. Prolonged treatment is unappealing to consumers, who refer to methadone as 'liquid handcuffs'. The most plausible explanation for people dropping out of buprenorphine treatment is the simple one; they can. As a less reinforcing drug, and possibly with milder withdrawal than methadone, consumers find it easier to cease buprenorphine. Viewed from this perspective, buprenorphine offers consumers greater autonomy. Buprenorphine is an alternative pharmacological agent, but prescribed through office-based practice as occurs in France and the USA, may also be thought of as a different paradigm of treatment, with less structure and offering greater patient autonomy.

Most heroin users enter treatment at a time of crisis, when their drug use and/or their lives are 'out of control', and many are keen to leave treatment once they have regained sufficient control of their circumstances. Some abstain from heroin for periods (in treatment and after leaving), while some engage in controlled use of heroin while in treatment or after leaving; many of those who leave will re-enter treatment if and when heroin use threatens to go out of control. Buprenorphine treatment allows patients to leave treatment more easily, and ready access to buprenorphine may well provide people with a sense of greater control and autonomy than is available through methadone treatment.

Such autonomy is not optimal treatment for all heroin addicts. People with complex problems of social exclusion, mental and physical health problems and lack of access to nondrug rewards in life require more structure and incentives than can be provided in office-based treatment, as well as a more reinforcing medication to maintain their engagement. Methadone appears to be a more effective treatment than buprenorphine for the majority of heroin users entering treatment, as illustrated in a randomized trial comparing initiation into treatment using methadone

or buprenorphine, with more people eventually remaining in methadone treatment [46].

The availability of a drug with lower risk of overdose has permitted the development of a new model of maintenance treatment. In France and the USA, methadone is delivered in highly structured and regulated treatment programmes, with most doses taken under direct observation, but high-dose buprenorphine is delivered by prescription, from office-based settings. In addition to providing less institutionalized, more acceptable treatment to consumers, the critical advantage of treatment without direct observation of dosing is cost, because the expense of daily observed treatment is a major cost factor in delivering treatment [47]. This is particularly relevant in developing countries, in many of which there has been a rapid increase in opioid addiction, and where buprenorphine treatment can be provided at low cost [48].

Diversion

Heroin addiction occurs in the setting of a black market, and there is a latent demand and potential for diversion of maintenance medication to people not in treatment. Diversion of medication prescribed for management of addiction is an inevitable concomitant of such treatment; as prescribing increases in a jurisdiction, overdose deaths (a marker of diversion) increase [49]. Effective measures to reduce diversion include the administration of doses under direct observation, restricting unsupervised doses to people who meet criteria of stability, and dispensing take-home methadone in dilute form, reducing the likelihood that it will be injected.

Although safer in overdose, buprenorphine is a drug that has been widely misused, and the provision of buprenorphine without supervised administration risks considerable diversion. A pharmacological approach to minimizing intravenous misuse has been to issue combination medications of an opioid agonist with naloxone, a pure antagonist which is not absorbed orally. The rationale is that taken orally or sublingually, the naloxone has only trivial bioavailability. However, if the medication is crushed and injected, the presence of naloxone attenuates the opioid effect, and in dependent subjects precipitates withdrawal. This is the rationale behind Suboxone®, a combination of buprenorphine and naloxone in a 4:1 ratio, designed to deter intravenous use. There is conflicting evidence of the effectiveness of adding naloxone to buprenorphine to make the drug less susceptible to intravenous misuse. The addition of naloxone appears to reduce, but does not abolish, intravenous misuse [50].

The problem of diversion is not restricted to drugs prescribed in opioid maintenance treatment. The development of a black market in opioid drugs prescribed for pain has become a public health problem in several jurisdictions, particularly the USA. Commonly, diverted drugs

intended for oral use are crushed, dissolved and injected to obtain maximal intoxication. New formulations combining naloxone with opioids have been marketed in recent years. The addition of naloxone has been marketed as being to reduce constipation in people prescribed opioids. However, the addition of naloxone also potentially reduces the risk of intravenous misuse and the black market value of such formulations.

Misuse of drugs other than heroin during maintenance treatment

While high opioid tolerance blocks the effects of street opioids for patients on methadone or diamorphine maintenance, and μ receptor occupancy blocks response to street heroin in patients on buprenorphine, opioid maintenance therapy is not effective in suppressing use of other classes of drug. Few people entering treatment for heroin addiction use only heroin. Multiple drug use is usual, and an adequate dose of methadone or buprenorphine is not effective in suppressing use of drugs such as cocaine, cannabis, alcohol and benzodiazepines. Many people in treatment continue to seek the reinforcing effects of these drugs, and this is one of the critical limitations of opioid maintenance treatment.

A recent Cochrane review suggested that there was potential benefit of maintenance prescribing to treat concomitant cocaine use among people in opioid maintenance treatment [51]; however, there is limited experience with this approach. There is even less evidence and less clinical consensus on how to respond to alcohol misuse or to use of cannabis or benzodiazepines. In particular, patients who report that they are dependent on benzodiazepines or need benzodiazepines to sleep provoke diverse responses. The major risks involved in prescribing are that benzodiazepines may contribute to cognitive impairment, to risk of sleep apnoea and risk of overdose, and that prescribed drugs will be diverted to the black market. Many practitioners prescribe benzodiazepines along with methadone, whereas others consider that the risks outweigh any potential benefits.

Nonpharmacological factors in maintenance treatment

Opioid maintenance treatment is a pharmacological treatment, but it is not only a pharmacological treatment. People who have lost control of their drug use and their lives need structure and support, and freedom from the compulsion to use heroin is often merely a first step. Many heroin users have significant mental health, physical health and social adjustment problems that predate their addiction and impede their recovery [52].

However, despite (or perhaps because of) a vast literature on the subject, it is not easy to state definitively what constitutes optimal treatment. For example, although it is widely assumed that psychological interventions are an essential part of treatment, a recent Cochrane review of psychosocial treatments as an adjunct to methadone treatment found that such interventions did not improve outcomes in terms of retention, nonprescribed opioid use, psychiatric symptoms, compliance or depression [53]. This was true overall for psychosocial interventions, and true for specific interventions, such as contingency management.

Although there is limited evidence or clinical consensus regarding what constitutes optimal treatment, there is more evidence on factors contributing to poor-quality treatment.

The first factor is financial. Delivering treatment 'per protocol' costs more and delivers better outcomes [22]. Where there is a latent demand for treatment, it is possible to establish minimal structure (less supervision and monitoring of patients), thereby reducing costs. In the case of methadone, such inadequate treatment, far from causing consumers to complain, they are often quite happy. In those jurisdictions in which 'for profit' prescribing has flourished, there have been suggestions that care has at times been inadequate [54]. Governments too are keen to minimize expenditure, and cost-cutting in delivery of treatment is not restricted to private practitioners.

As in other areas of health care, maintenance treatment needs quality standards and clinical audit to ensure that treatment is delivered appropriately. However, there is consistent evidence from many jurisdictions that clinical guidelines and quality standards have been somewhat ineffective in preventing deviation from evidence-based care. This is most apparent in the use of subtherapeutic doses of medication, even among patients who persist in heroin use while in treatment.

Inadequate methadone doses are the second factor contributing to poor-quality treatment. This widespread problem was documented in the USA two decades ago [55], and remains an issue in the UK. A recent UK survey found that the mean methadone dose was 56 mg day⁻¹ [56]; a subsequent study reported that across England more than 60% of patients in treatment reported heroin use within the preceding month [57]. This subtherapeutic dosing is not occurring out of ignorance, because widely promoted clinical guidelines in the UK recommend methadone doses in the range 60–100 mg day⁻¹ [58].

In order to understand how this situation has arisen, it is helpful to trace the evolution of ideas about maintenance treatment. Dole and Nyswander proposed a 'medical' model of treatment, in which methadone was medication for treating an acquired disease. Many people delivering treatment rejected this explanation, preferring a 'psychotherapeutic' paradigm and discounting the importance of methadone as medication. This view was summarized by Avram Goldstein, a seminal researcher in the evolution of

methadone treatment in the USA, who argued that doses above 50 mg were essentially equivalent, and that 'interpersonal transactions' were the central challenge in rehabilitation [59]. The psychotherapeutic paradigm was even more dominant in the UK, where it was considered that the prescription of opioids served merely as the lure to attract drug misusers into the treatment services. In the words of one of the leading UK addiction specialists at the time, 'regular contact between the addict and the doctor ... gives the opportunity for a relationship to be built up which may eventually lead to the addict requesting to be taken off the drug' [60].

Motivation is central to addictive disorders. Heroin users enter treatment only if they perceive it as offering some advantage, and it is an accurate insight to recognize that methadone is a lure, offering respite from withdrawal and from the rigours of addicted lifestyle (just as diamorphine is a lure for patients not responding to methadone). The critical difference between the 'psychotherapeutic' and 'medical' theories lay in their understanding of what constituted 'treatment'. In one view, medication was primarily important as a way of promoting engagement. For Dole, medication was the foundation of treatment. Evidence supports Dole's contention that medication is central to the effectiveness of methadone treatment, yet as delivered in practice much treatment appears to adhere to the psychotherapeutic paradigm.

In fact, Dole and Nyswander's model of treatment embraced more than medication. They identified three critical components of treatment [61]. The first element was the clear sense that addiction was a disease, and that the objective of treatment was management of the disease through use of medication. The second element was the importance of the therapeutic relationship, and the need for practitioners delivering treatment to believe in the possibility of positive change. The third element was the critical importance of change in attitude and identity that occurs on entering treatment; a process characterized by Marie Nyswander as the transition 'from drug addict to patient'. Freed from the compulsion to use drugs, and treated with respect and dignity, the patient is helped to develop a new sense of themselves.

These central elements of treatment laid out four decades ago by Dole and Nyswander – optimism, attitude change, and the clear objective of stopping use of street heroin – are some of the key elements being rediscovered under the rubric of the 'recovery agenda' [62].

The notion of a transition in identity is central to managing drug dependence. Interviews with addicts in and out of treatment suggest that the 'addict identity' is an exciting one, a free spirit, alienated, unbound by conventional expectations. In contrast, the patient in treatment is perceived by street heroin users as having given up the struggle and surrendered his autonomy [63]. This perspective contributes to the ambivalence about being in treatment experienced by many heroin users. So to does patients'

fear that they risk becoming 'more addicted' by taking high-dose methadone [64]. A common result is for people to enter treatment but remain on a low dose of methadone that is sufficient to suppress withdrawal, but low enough to allow them to continue to experience the reinforcing effects of injected heroin.

Critically, prescribing low methadone doses is not primarily a function of patient preference. Observational studies demonstrate that dose is a result of clinic policy [65]. Clinics with a metabolic paradigm employ high doses, whereas clinics with more psychological orientation to treatment employ low doses. Clinicians in low-dose clinics find patients expressing a preference for low doses, in part because lack of a clear pharmacological rationale for treatment fosters patients' ambivalence about taking methadone.

Establishing a therapeutic relationship requires structure, with clearly defined protocols, programme rules, mutual expectations between therapist and patient, and agreed objectives of treatment [66]. Heroin users are a diverse group, with different supports and problems, and treatment objectives other than suppression of heroin use should be individualized. Monitoring of drug use (including use of urine testing), minimizing risk, and monitoring side-effects and mental and physical health form the basic 'structure' of treatment and the context in which the therapeutic alliance can develop. Without such a defined structure, interaction between patient and clinician becomes a matter of power and conflict (or worse, a ritual without clear purpose or direction).

A review of differing approaches to psychotherapy suggested that all forms of therapy also require a rationale, conceptual scheme or myth that provides a plausible explanation for the patient's symptoms, and the particular rationale needs to be accepted by the client and by the therapist (but need not be 'true') [67]. Dole's theory of a metabolic disease requiring replacement therapy with methadone served as a therapeutic myth to explain methadone treatment. Subsequent research on the neurobiology of addiction has provided more plausible evidence for the notion of addiction as a brain disease, and a rationale for maintenance therapy in controlling chronic withdrawal and the risk of relapse. The first step to a more effective psychological treatment to support maintenance treatment is for clinicians and patients to accept that maintenance treatment is primarily pharmacological.

Summary of opioid maintenance treatment

The key questions in treatment are not primarily which medication, but the degree of autonomy offered to patients, and the intensity of monitoring and supervision that different individuals require for safe and effective treatment. Patients with good social functioning (stable

housing, employment, relationships) are likely to respond to less structured, less reinforcing treatment, while people who are socially excluded and chaotic are more likely to benefit from more highly structured treatment. In terms of choice of medication, buprenorphine is least reinforcing and safest in overdose, and is the most suitable medication for less structured treatment. It allows patients greater autonomy. Patients who fail to benefit from this approach require more structured treatment, with more supervised administration. Methadone is more reinforcing and holds people better in structured treatment than buprenorphine. Diamorphine is most reinforcing, providing an incentive for patients with least motivation to participate in highly structured behavioural treatment.

Clinical guidelines in the USA [68], UK [58] and Australia [69] reflect these assumptions. In all three countries, they recommend initiating methadone treatment with supervised administration, and relaxing the requirement for supervision in patients who cease injecting drug use. In the USA, buprenorphine may be prescribed in office-based practice. In the UK, entry to diamorphine treatment is restricted to treatment nonresponders, and all diamorphine administered is directly observed.

A note on nicotine maintenance for smokers

Most smokers express the view that they would prefer to quit but experience smoking as highly addictive. About 80% of smokers report a withdrawal syndrome on stopping [70]. Nicotine replacement therapy (NRT) has been marketed as an aid to quitting smoking, by relieving nicotine withdrawal during early quitting. However, smokers go through several phases of quitting and relapsing, and some consumers use NRT as a maintenance medication. In the Lung Health Study, 31% of subjects randomized to receive NRT were still using it beyond 12 months (although they had been instructed to use it short term as an aid to quitting). After 12 months, 41% of quitters and 26% of smokers were still using NRT; 10% used gum for the entire 5 years [71]. Over half (54%) of the people using gum were intermittent smokers, who would abstain for a period, then relapse for a period.

Nicotine replacement therapy is less addictive, and very much less harmful, than smoking. The fact that it does not provide the same reinforcement as smoking is what makes it less addictive and is a key factor limiting its effectiveness as a substitute for smoking. Alternative approaches to maintenance therapy for smoking are now appearing, often referred to as smokeless tobacco, including e-cigarettes and snus (oral tobacco) [72]. The best researched of these alternative products is snus. With snus, the nicotine delivery is much closer to that of smoking and is therefore more reinforcing. Smokers who use snus as a cessation aid have a substantially higher success rate than

those who use nicotine medications, and primary snus users have a much lower rate of starting smoking than those without previous snus use [73]. Smokeless tobacco is not currently available in many jurisdictions, and there is some opposition to making it available, on the grounds that more people will become, and remain, 'addicted' to nicotine.

Like heroin users seeking treatment, most smokers enrolling in quit programmes do not succeed in quitting; among those who initially succeed, relapse is common [74]. The use of NRT by smokers has parallels with the use of buprenorphine by heroin users. Some use the medication as a short-term 'detoxification', whereas some use it as long-term maintenance. Some use it while continuing the use of their primary drug, abstain episodically and relapse episodically. Such is the chronic, relapsing nature of addiction among people seeking help for drug dependence. It is easy to recognize when observing smokers, but our perceptions of the behaviour of heroin addicts are distorted by stigma and the need to control deviance.

Nicotine replacement therapy and smokeless tobacco are better thought of as self-management than as treatment, and probably that is how buprenorphine in office-based practice should be considered, as an aid to help individuals manage their opioid addiction. Self-management is most likely to be useful for those individuals who have reasonable social supports and alternative rewards in their lives. Repeated failures at self-management, and management of people with complex problems who have lost their social connections, are indications for more structured treatment, and often for more reinforcing drugs to hold patients in that treatment. Once we accept the irrefutable fact that lapses and relapses are common, maintenance treatment for opioids or nicotine is the relatively straightforward challenge of supplying a safer, better controlled drug. What makes management of heroin addiction difficult is facilitating the slow and stuttering process of social reintegration.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: J.B. received funding support from ReckittBenckiser and Martindale Pharmaceuticals in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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