

Addressing misuse and diversion of opioid substitution medication: guidance based on systematic evidence review and real-world experience

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ABSTRACT

Background Opioid dependence treatment, comprising opioid substitution treatment (OST) and psychosocial intervention, is accepted to improve outcomes in opioid addiction for both the individual and public health. OST medication such as methadone or buprenorphine may be misused or diverted. This results in failure to recover from addiction, increased crime and the spread of blood-borne viruses. Worldwide, attempts to address misuse and diversion have been proposed and implemented with varying impact.

Methods A structured, expert-led process recommended the most impact. As an initial step, a broad range of strategies were defined, and a systematic review of published literature identified 37 highly relevant sources of evidence. Experts reviewed this evidence and ranked the list of strategies for effectiveness and ease of implementation, based on their clinical experience.

Results/Conclusions Three groups of strategies to address misuse or diversion are defined, depending on impact (effectiveness and ease of implementation). Preferred strategies include the promotion of access to treatment and the use of product formulations less likely to be misused. However, additional data and innovative approaches to address this complex problem are needed.

Keywords diversion, misuse, opioid addiction, opioid substitution treatment (OST), strategy, treatment outcomes

Introduction

Opioid dependence is a chronic condition resulting in serious negative consequences to the individual and society. Untreated opioid dependence harms the individual and society through increased mortality, increased risk of blood-borne virus (BBV) transmission associated with injecting drug use, poor social functioning, loss of economic productivity and criminal justice expenditure.¹ There are effective interventions for opioid dependence: the best treatment outcomes are achieved with a comprehensive multidisciplinary

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approach, by integrating health- and social-care strategies. This includes opioid substitution treatment (OST) and psychosocial interventions that are delivered on an individualized personal basis.² OST has made an impact in reducing harm associated with opioid dependence (overdose deaths, crime) and in limiting the spread of BBVs.³ However, OST medicines can be diverted or misused for recreational, self-medication or other purposes due to their agonist properties.

Diversion is defined as the intentional transfer of a controlled drug from legitimate distribution and dispensing into illegal channels.⁴ Misuse is defined as the use of a medication other than as directed or as indicated, whether wilful or unintentional, and whether resulting in harm or not.⁵ Although recent attempts to understand the prevalence of misuse and diversion have been made,⁶ the problem has yet to be well defined. Misuse and diversion of OST medication negatively impact treatment outcomes and the community as a whole, through adverse impacts on public health and crime. First, mortality rates are increased compared with the general population, and individuals are put at risk of BBV through continued injecting drug use.^{7,8} Misuse and diversion result in poor adherence to recommended treatment.⁹ Beyond the individual, children may be put at significant risk, including that of accidental ingestion, by parents misusing OST medication.¹⁰ Demand for diverted OST medications causes an increase in associated crime, such as thefts from pharmacies and from homeowners.¹¹ Significant costs to society result from this increase in crime, also including expenditure associated with medical treatment of overdose, complications and associated illnesses such as BBV.¹²

A working group of experts in the management of opioid dependence was convened to review evidence and determine recommended strategies to address misuse and OST diversion. The aim of this review is to assess the evidence of effectiveness of specific strategies to address misuse and diversion while maintaining access to therapy. The framework for approaching this problem assesses a broad set of potential strategies by considering overall impact, derived from effectiveness and ease of implementation.

Method

A PubMed literature search was performed, covering the period from January 2005 to January 2015, to identify sources of evidence reporting effectiveness of strategies to address diversion or misuse of buprenorphine- and methadone-containing medications. The search terms used were 'methadone', 'buprenorphine', 'opioid substitution', 'opioid maintenance' or 'medication assisted' and 'misuse' or 'diversion', in the title or abstract. The initial search identified 610

publications. Two independent reviews of the initial literature search results were conducted, classifying publications based on examination of their titles and abstracts. Studies were considered relevant if they included evaluation or discussion of strategies to limit misuse or diversion. Thirty-seven studies of strategies to limit misuse and diversion were identified.

To add evidence from real-world experience to that identified in the systematic literature review, the opinion of experts in the treatment of opioid dependence was assessed. Nine experts from the UK, Germany, Spain, Norway, Finland and Italy were invited to provide clinical experience from day-to-day practice managing the care of opioid addiction and express their opinion of strategies to address misuse and diversion. This was initially assessed via a pilot online survey focussed on evaluating possible strategies to address the problem, identified in the literature review, with the aim to generate an overall consensus on recommended strategies as discussed in a meeting. Nine experts rated various measures to address misuse and diversion for effectiveness and ease of implementation, on a scale of 1–5, where 1 was the least effective or feasible and 5 was very effective or feasible. Assessments of effectiveness and ease of implementation were combined as weighted averages in a composite score of impact.

Results

Evidence from published studies or guidelines

The identified relevant publications provided an overview of the current understanding of strategies to address misuse and diversion of OST. Review of this limited published evidence supporting potential strategies provided an initial view of the advantages and limitations of various strategies.

First, supervising consumption of OST medication in patients identified as being the most likely to misuse or divert their medication has been assessed in the literature. A prescription drug monitoring programme has been implemented in France, and was observed to reduce diversion without limiting access to treatment.¹³ In Florida, USA, a survey of pharmacists called for a similar system to decrease diversion and doctor shopping.¹⁴ Two comparisons relating levels of misuse and diversion to dosing supervision found that less strictly supervised, community-based dosing correlated with higher levels of misuse and diversion in North America and in six Australian states.^{15,16} However, a limitation to the effectiveness of dosing supervision was identified by two studies,^{17,18} finding that retention in treatment was greater, including for unstable subjects, when patients were unsupervised and allowed take-home doses of their medication.¹⁸

There are studies describing the use of abuse-deterrent formulations of OST medication. Crushing mono-buprenorphine

tablets has been suggested as a method to prevent diversion, and this has been found not to alter serum buprenorphine levels, absorption time or withdrawal symptoms in patients: effectiveness in addressing misuse or diversion is not clear.¹⁹ Electronic medicine dispensers reduced diversion of buprenorphine/naloxone (BNX) by 16% in a Finnish study.²⁰ Capsules containing liquid methadone were evaluated for potential for misuse and diversion by a study, which found that 28.6% of patients surveyed reported availability of these capsules on the street. 7.3% of these patients had tried to solubilize the capsules and 19.5% had tried to snort them.²¹ An American study of buprenorphine misusers revealed a preference for the tablet formulation over the film, although all formulations were sometimes misused or diverted.²²

As an alternative to abuse-deterrent formulations, mechanical deterrence or the addition of an antagonist such as naloxone may be used to limit misuse by injection. A study by Comer *et al.*²³ determined that BNX had less potential to be abused intravenously than mono-buprenorphine or heroin; furthermore, a literature review found that no BNX dose was misused more than placebo and recommended BNX as the best abuse-deterrent option.²⁴ The combination of methadone with naloxone was assessed by Bell *et al.*,²⁵ and a 50 : 1 combination was found to be comparable with methadone alone for treating symptoms of withdrawal.

Other strategies to address misuse and diversion are based on the doctor–patient interaction. Doctors and other health-care practitioners involved in OST treatment may be educated to counsel patients to reduce misuse and diversion. A US survey of physicians found that most had limited training in treating addiction; knowledge and practice behaviours improved following continuing medical education and this was recommended for all physicians involved in OST.²⁶ In Germany, a survey of patients and OST-accredited physicians found that access to treatment was inadequate, particularly outside of major cities. To increase access to treatment, additional support and training was recommended to increase physician participation in OST and awareness and utilization of recommended strategies to reduce misuse and diversion.²⁷ Supporting the value of training, a physician survey found that physicians who took more steps to limit misuse and diversion of buprenorphine had more experience and more medical training.²⁸ However, Bell²⁹ found that clinical prescribing guidelines including strategies to prevent misuse and diversion were often not adhered to and recommended regular clinical audits to enhance compliance with guidelines.

OST patients may receive incentives to engage in monitoring to demonstrate that they are not misusing their medication: a study by Tacke *et al.*³⁰ showed that compliance monitoring by microchip led to a reduction in diversion in

~25% of patients. Furthermore, this monitoring was well accepted by patients and was found to increase adherence to treatment.

One strategy that is not supported by the literature is limiting access to treatment. A US study found that the most robust risk factor for buprenorphine misuse was an inability to access treatment.³¹ Comparing opioid prescribing and overdose mortality in the USA and the UK, one factor contributing to the larger market for illicit prescription opioids in the USA was the greater difficulty in accessing treatment.³²

In some countries, clinical guidelines attempt to address the problem of misuse and diversion with recommendations for treatment providers.

In Australia and the UK, buprenorphine dosing is generally supervised, with inspection of the mouth to ensure complete dissolution, and tablets may be broken up to reduce the potential for diversion.^{33,34} In Australia, take-home doses may be prepared to reduce potential for diversion, e.g. by diluting methadone or prescribing a BNX film rather than the tablet formulation, which is no longer available.³⁵ If OST medication is continually diverted, patients may be discharged from treatment.³⁵

In Canada, doctors involved in OST are encouraged to consider prescribing products with a lower potential for misuse and diversion.³⁶ Physicians must explain the risks of misuse and diversion and the patient's responsibility to store and use their dose safely, and take-home methadone dosing is only permitted for patients considered not to be a significant risk for overdose, misuse or diversion; no active addiction or mental illness; prescriptions from one physician only and no reported misuse or diversion.³⁷

In New Zealand, prescribers may request that methadone is diluted with water or consumed in front of a pharmacist, or that buprenorphine tablets be crushed, to prevent diversion.³⁸ In the USA, opioid dependence treatment programmes must have a 'Diversion Control Plan' that assigns specific responsibilities to staff to control diversion: this should include monitoring of diversion.³⁹ Take-home dosing is only available on days when the clinic is closed or for patients considered to be at a low risk of diversion (stability, no criminality, no recent misuse or illicit drug use).³⁹

Evidence from real-world experience

To better assess strategies to address misuse and diversion, expert opinion was consulted. Nine leading experts from across Europe were asked, via a pilot online survey, to rate various measures (Table 1) to address misuse and diversion for effectiveness and ease of implementation. Experts were asked to evaluate strategies on a scale of 1–5 for effectiveness and ease of implementation, and weighted averages are

Table 1 Real-world experience assessment of strategies to address OST misuse and diversion

Number	Strategy	Effectiveness	Ease of implementation
1	Supervise consumption in those most likely to misuse or divert	High	High
2	Restrict take-home for formulations that could put children at risk through unintentional exposure	High	High
3	In products prone to injection misuse, such as opioids, require mechanical deterrence or the addition of an antagonist to limit the problem	High	High
4	Restrict take-home for formulations most subject to misuse and diversion	High	Intermediate
5	Provide extended take-home treatment only for patients accepting abuse-deterrent formulations	High	High
6	Increase healthcare practitioner education to counsel those in treatment to reduce misuse and diversion	High	High
7	Change the formulation of products to make it harder to misuse, reducing value for diversion	High	High
8	Promote the development of product formulations that are more difficult to divert	High	Intermediate
9	Use only the least divertible formulations in controlled settings (e.g. prisons)	Intermediate	High
10	Restrict access market wide to specific products that are most commonly misused or diverted	Intermediate	Low
11	Increase treatment levels and access to treatment for all	Intermediate	High
12	Incentivize service users to engage in monitoring to show that they are not engaging in misuse	Lower	High
13	Increase reimbursement to healthcare providers showing reductions in frequency of misuse and diversion	Lower	Intermediate
14	Increase criminal penalties for misuse and diversion	Lower	Lower
15	Limit access to treatment to those less likely to misuse or divert	Lower	Lower

displayed. Assessments of effectiveness and ease of implementation were combined in a composite score of impact. Ranked scores for effectiveness and implementation were compared to describe overall impact. Strategies assessed as having higher effectiveness with higher ease of implementation were grouped as preferred higher impact options. Strategies with intermediate effectiveness or ease of implementation were grouped in a second tier. Strategies with lower scores were grouped as ‘not recommended over other options’.

The analysis (Fig. 1 and Table 1) defines three groups of strategies: recommended higher impact, other important strategies and strategies not recommended relative to other options.

Recommended higher impact strategies:

- Supervise consumption in those most likely to misuse or divert
- Restrict take-home for formulations that could put children at risk through unintentional exposure
- In products prone to injection misuse, such as opioids, require mechanical deterrence or the addition of an antagonist to limit the problem
- Provide extended take-home treatment only for patients accepting abuse-deterrent formulations
- Increase healthcare practitioner education to counsel those in treatment to reduce misuse and diversion
- Change the formulation of products to make it harder to misuse, reducing value for diversion

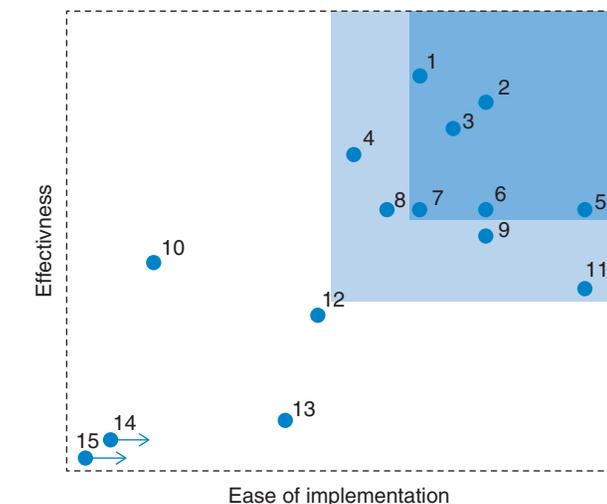


Fig. 1 Real-world evidence: impact of strategies to address OST misuse and diversion (numbers in figure refer to listed strategies in Table 1). Dark blue: higher impact strategies; light blue: intermediate impact strategies; white: lower impact strategies.

Other important strategies:

- Restrict take-home for formulations most subject to misuse and diversion
- Promote the development of product formulations that are more difficult to divert
- Use only the least divertible formulations in controlled settings (e.g. prisons)

- Restrict access market wide to specific products that are most commonly misused or diverted
- Increase treatment levels and access to treatment for all

Strategies with lower impact compared with other options, not recommended as initial options:

- Incentivize service users to engage in monitoring to show that they are not engaging in misuse
- Increase reimbursement to healthcare providers showing reductions in frequency of misuse and diversion
- Increase criminal penalties for misuse and diversion
- Limit access to treatment to those less likely to misuse or divert

Discussion

Main findings of this study

Experts in the field of opioid addiction treatment recommend, based on published evidence and clinical experience, that misuse and diversion of OST medicines such as buprenorphine and methadone be addressed through supervision of dosing/restriction of take-home doses for those most likely to misuse or divert their medicine and the use of abuse-deterrent forms. Restricting access to treatment is strongly not recommended.

What is already known on this topic

Some of these recommended strategies have already been implemented or are under consideration in countries around the world, but alignment of policies in different countries could not only improve and standardize care worldwide but also potentially limit problems such as the trafficking of diverted OST medicines internationally. An example of the success of such alignment is Finland and Estonia, where after the removal of mono-buprenorphine from the market in Finland, the use of the drug continued to be a problem due to drug tourism to Estonia.⁴⁰ In response, Estonia made legislative changes to restrict mono-buprenorphine, with success in reducing drug tourism. Mono-buprenorphine in Finland now frequently comes from other countries, such as Sweden,⁴¹ highlighting the importance of international cooperation to reduce misuse and diversion.

It is important to understand motivations for misuse and diversion, to best design and implement methods of prevention. For instance, if self-medication may motivate misuse, then a review of dosing for each individual could reduce misuse. Diversion of medication may be motivated by the desire of OST patients to help friends or family; increasing access to treatment and taking measures to reduce the stigma of treatment could decrease this type of diversion.

What this study adds

This analysis provides useful guidance in addressing misuse and diversion, which is of concern for many policymakers and treatment administrators. A review of both published and real-world evidence of effectiveness and ease of implementation of strategies to address misuse and diversion has identified strategies recommended to address these problems and ultimately improve both public health and the care of people with opioid dependence.

Limitations of this study

Given the limited evidence base describing strategies to address misuse and diversion, it is concluded that more research is required to better characterize OST medicine misuse and diversion and understand what strategies may prevent misuse and diversion while facilitating access to treatment and improving treatment outcomes. It may be of value to understand how ease of obtaining treatment in rural or urban areas impacts misuse and diversion, for example.

Conclusion

OST misuse and diversion present a significant problem for policymakers, healthcare practitioners, patients and other people involved in opioid dependent treatment, negatively impacting individual treatment outcomes and recovery from addiction as well as having wider negative effects on the public.

Addressing this issue is a complex problem; in this literature review and summary of expert opinion, strategies to prevent misuse and diversion are considered and evaluated for effectiveness and ease of implementation. Strategies deemed effective by published studies and expert real-world experience include supervision of dosing and the use of abuse-deterrent formulations. Limiting access to treatment is not supported by studies, and expert opinion recommends increasing treatment accessibility to decrease illicit use of prescription or other opioids, which may be diverted. However, further studies are required to more precisely define the impact that strategies to address misuse and diversion could have.

Authors' contributions

All authors were involved in the study design, had full access to the survey data and analyses, and interpreted the data, critically reviewed the manuscript and had full control, including final responsibility for the decision to submit the paper for publication.

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Conflict of interest

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