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▶ A review of buprenorphine diversion and misuse: the current evidence base and experiences from around the world.

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Journal of Addiction Medicine: 2014, 8(5), p. 299–388.

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Practice-oriented review of what we know about the diversion (to other people) and misuse (mainly by injecting it) of buprenorphine used in the treatment of opiate dependence, featuring extended, practical guidance on how to identify and respond to these life-threatening behaviours as a therapeutic challenge rather than a disciplinary issue.

SUMMARY This review collated published evidence about buprenorphine misuse and diversion, and the unintended consequences for patients, providers, and societies. It was accompanied in the same journal issue by an article taking the form of a case conference about how to deal with a patient apparently misusing and diverting buprenorphine medication.

Buprenorphine is a drug prescribed to opiate-addicted patients for the same purposes as methadone – to substitute for more damaging opiates like heroin generally obtained illegally without a prescription. As buprenorphine prescribing has increased, so too have concerns about the drug's diversion and misuse, the former defined as unauthorised rerouting or misappropriation of prescription medication to someone other than the intended patient, the latter, as taking medication in a manner, by a route, or at doses, other than those prescribed. In the case of buprenorphine tablets intended for sublingual (dissolving under the tongue) administration, injecting, snorting, or smoking would constitute misuse. Also available is sublingual buprenorphine film ▶ illustration below.

Due to limited opiate-type effects and its potential to precipitate withdrawal in people dependent on opiate-type drugs, buprenorphine is less attractive to potential misusers than heroin or methadone. Combining it with naloxone in products such as Suboxone is intended to make it less attractive still by precipitating withdrawal in opiate-dependent users if the product is injected rather than taken as intended.

Diversion of buprenorphine should be set in the context of the widespread practice of patients 'sharing' medicines of various kinds with other people. Buprenorphine and, according to an Australian study, especially the combination product with naloxone, will often be shared with friends without money changing hands.

Key points

Buprenorphine is prescribed to opiate-addicted patients for the same purposes as methadone, to substitute for illegally obtained opiates like heroin.

It is less likely than methadone to be injected and to lead to overdose deaths, especially when combined with naloxone to deter injecting. Deaths do happen however, especially when the drug is taken with other CNS depressant drugs, including alcohol and benzodiazepines.

Diversion to people other than the patient and misuse by injecting are not uncommon, and in some circumstances (eg, lack of supervised consumption and large take-home supplies) can become very common.

These behaviours risk the patient's and other people's welfare and undermine the effectiveness of addiction treatment, but should be considered part and parcel of the problem being treated rather than as a disciplinary issue.

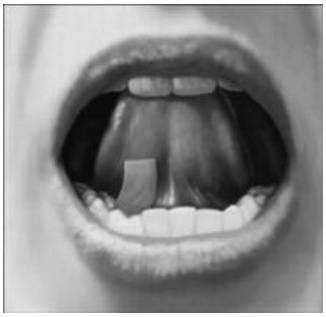
They can be indentified and responded to by prescribers in ways which do not punish patients or heighten risk due to their leaving or being discharged from treatment.

Prescribing the combination product with naloxone, individualised supervision and dosing regimens, and understanding how/why that individual patient might divert or misuse their medication, can help prevent these happening.

Main findings

Misuse by injection

Buprenorphine injecting been reported around the world, involving individuals both in and out of treatment. Generally it is less common than for drugs like heroin and methadone with full opiate-type effects and less common (but by no means eliminated) when the buprenorphine has been combined with naloxone.



For example, in the USA, 6% of patients seeking treatment for their use of prescribed opioids said they had injected buprenorphine "to get high", but 37% had injected other prescription opioids. A monitoring system found that in the past month 46% of people starting treatment for opioid use problems had injected buprenorphine but just 16% the combined naloxone product. In Australia too, fewer opiate substitution patients (but about the same proportion as injected oral methadone) injected the naloxone product at least weekly (7%) than injected pure buprenorphine (13%). In France 5% and 10% of opiate substitution patients at specialist clinics admitted injecting generic and brand name buprenorphine respectively.

The sole study (conducted in Australia) to investigate injecting of buprenorphine/naloxone film found few injected this frequently (among

patients in opioid addiction treatment, 3%; among injectors not in treatment, 1%), and that frequent injecting was more common with buprenorphine/naloxone tablets and more so pure buprenorphine, the latter engaged in by 6% of the out-of-treatment sample and 11% of patients.

Rarely has buprenorphine been found to be injected more often than heroin, methadone, or other full-action opioids, but due to special circumstances, this has been the case in some countries. In Finland it was due to heroin shortages and the buprenorphine was generally smuggled in from aborad. Patients were primarily treated with lofexidine and withdrawal protocols; mortality rates were high, similar to those among primary heroin users. After the naloxone combination product became available, a survey of needle exchange attendees found 15% injected it daily, compared to 74% injecting pure buprenorphine. These numbers may have partly reflected poor access to opioid maintenance treatment in Finland.

In Malaysia the problem arose when financial incentives for general practitioners to prescribe and dispense buprenorphine resulted in generous take-home supplies for the treatment of addiction. There were no requirements for prescribers to be trained and no practice guidelines. After (along with practitioner training and registration of patients) in 2006/7 buprenorphine was withdrawn and replaced by buprenorphine/naloxone, the proportion of patients with experience of injecting these products who did so daily fell from 63% for buprenorphine to 34% for buprenorphine/naloxone.

Why is buprenorphine injected?

Studies reported above suggest that no particular type of health care or addiction treatment system is immune from buprenorphine injecting. Just like heroin, medications can become available to the illicit market through importation, and their use is more common when access to opioid maintenance treatment is inadequate, blocked, and/or stringently controlled. When provider incentives encourage this, the Malaysian experience shows that providing substantial take-home supplies of buprenorphine to opioid addiction patients can result in widespread injecting.

Asked why they inject the drug, patients commonly mention self-treatment of withdrawal or addiction, but also use for euphoric/pleasurable effects; these are not mutually exclusive. Though patient accounts can mimic the medical reasons for which the medication is prescribed, so too do the reasons many give for injecting heroin. The fact that these drugs may be used stave off withdrawal and feel 'normal' does not make their misuse by injecting desirable or safe, but may be a sign of the need for improved access to and/or expansion of treatment.

One French study associated buprenorphine injecting among addiction patients being prescribed the medication with their having a history of injecting, current cannabis use, and having no salary. Ongoing heroin use was associated with *not* injecting the medication, probably because such injecting can precipitate withdrawal. This result also suggests patients were diverting their medication on order to obtain their preferred opioid, heroin.

Another French study followed up buprenorphine patients for six months after they had been in treatment for at least three months. Over those six months buprenorphine injecting was more likely when patients felt their dose inadequate (the typical dose was 6mg), had a history of feeling suicidal, and had been injecting longer.

Consequences of buprenorphine misuse and diversion

France illustrates the risks of buprenorphine but also that overall these are less than for the alternatives. There buprenorphine became widely prescribed in addiction treatment, primarily by general practitioners. Training, supervised dosing, urine drug testing, and counselling were not required, and in one study, in 43% of cases buprenorphine was prescribed with benzodiazepines. Reports of deaths involving buprenorphine followed. Frequently the deceased had been injecting and there were toxicological signs of recent benzodiazepine use, suggesting these factors heightened risk. Other countries too have reported concomitant use of benzodiazepines and/or alcohol heighten the risk of fatal overdose. Despite these risks, in France during 1994–1998, death rates per patient associated with buprenorphine were a third those for methadone, and between 1995 and 1999 the number of drug overdose deaths decreased by 79% while addiction treatment with buprenorphine and methadone increased by more than 95%.

In the United States between 2002 and 2013, 464 deaths involved sublingual buprenorphine products (including generics), of which 91% involved naloxone combination products. However (for non-generics only), it can be estimated that the combination naloxone product was 49 times more frequently prescribed than buprenorphine alone, suggesting that the greater number of deaths involving these products does not mean that per dose they are less safe.

A particular concern are deaths of children. In the USA in 2009, buprenorphine/naloxone accounted for just 2.2% of all retail opioid prescriptions, but caused nearly 1 in 10 emergency admissions for drug ingestion involving children under six years of age, more than any other single medication. The combination film product seems much less likely to feature in such incidents. It is important for buprenorphine patients to realise that the medication can be deadly for children. Physicians should discuss the need for safe storage with all patients, not just those living with children, because children may take medication prescribed not just to their parents but to other family and friends.

However, overall in the USA the safety profile of buprenorphine seems superior to that of methadone, featuring in proportionately many fewer drug diversion reports and poison centre calls. As in France, recent data reveals a significant relationship between a decline in heroin overdose deaths after the approval and implementation of buprenorphine treatment in Baltimore City, an area with particularly high rates of heroin abuse and heroin-related deaths.

Benzodiazepines and alcohol augment the respiratory depressant effects of buprenorphine and the combination is associated with many buprenorphine-involved deaths. This means benzodiazepine availability (and co-prescribing), diversion, and misuse, warrant increased attention, as in France where restrictions on the duration of benzodiazepine prescribing helped reduce misuse.

Buprenorphine-related deaths should be set in the context of the fact that death rates are very high generally among untreated opioid-dependent persons, and that the number of deaths involving full-action opioid analgesics is markedly higher.

How to control diversion and misuse

From the above it is clear that buprenorphine misuse and diversion are common. When they occur within treatment, they indicate that patients are not adhering to the prescribed medication regimen. For all medical disorders, non-adherence impedes the effectiveness of treatment. In opiate substitution treatments, it is associated with relapse to illicit opioid use. To prevent relapse, one must pay attention to medication adherence. Each clinical visit should include assessment of misuse and diversion, handled as aspects of the patient's problem substance use and addressed therapeutically rather than punitively.

A punitive, 'no tolerance' approach to diversion and misuse with automatic discharge from treatment is highly unlikely to help patients, because untreated opioid addiction is characterised by relapse, illness and death. Good treatment benefits both individuals and public health, even when patients are unable to sustain an end to all drug use, injecting and criminal activity. This does not imply that prescribers must accept and do nothing about medication misuse and diversion, or continue to prescribe buprenorphine to patients who are passing it to others rather than taking it themselves. Rather, the point is that treatment can be beneficial even if the ideal outcome is not attained. The goal is to evaluate treatment benefits and harms for each patient, individualising the treatment plan to minimise harms while not foregoing benefits.

Once providers understand the context and circumstances giving rise to a patient's diversion or misuse, practical solutions can be formulated. For instance, patients who encounter drug dealers at the pharmacy which dispenses their prescription and are induced to sell their medication can change pharmacies and be directed to financial help. For patients unable to escape from drug-addicted social networks, it may help to discuss how to hide the fact that they have medication.

Patients may not disclose medication misuse and diversion, but this may be indicated by various signs ▸ panel right. Among these are urine drug testing to check whether medication has been taken, though patients could skip medication for several days and still produce a urine screen positive for buprenorphine. Random medication counts can also help identify diversion and misuse, but how well has not been researched.

Checklist to detect diversion and misuse

Talk Explain to each patient what diversion and misuse are, ask for examples from their experience, discuss potential triggers, develop strategies to combat these, at each visit ask about occurrences or close calls of medication diversion and misuse, discuss openly throughout treatment.

Examine Look for non-healing or fresh track marks or signs of intranasal use of buprenorphine or of other substances possibly traded for buprenorphine. Note patients reporting severe withdrawal in the absence of objective symptoms.

Listen Repeated requests for early re-prescriptions because of various reasons.

Monitor Missing appointments, incorrect medication tablet/film counts, no buprenorphine and/or norbuprenorphine in urine tests, unexpected medical problems for a patient believed to be in recovery (eg, abscesses), unexplained prescription records or multiple prescriptions from different providers.

Collaborate Feedback from pharmacist about unusual behaviour such as appearing intoxicated or being accompanied by someone overly interested in the medication, or exchange of something in a car park or waiting area. Counsellor or reliable family members say the patient is in contact with old drug-using friends or not adhering to their medication regimen.

Prescribers can also set up their practice to help minimise misuse and diversion and respond effectively when it occurs. Patients seeking medication to sell on the street may be deterred if it is explained from the start that treatment entails multiple aspects such as assessment and monitoring and frequent visits until stable, and perhaps too that longer-duration prescriptions will only be provided in line with objective evidence of stability. To avoid unintentional diversion, all patients could be advised on safe storage, for example, in a locked box and not in kitchens and bathrooms or other common areas where medication could easily be 'borrowed' or stolen.

Given lower abuse liability, the combined naloxone formulation should be preferred for non-pregnant patients. Patients who request a buprenorphine-only formulation require careful assessment and documentation of the individual risks and benefits (eg: Is no treatment the alternative? Is this patient likely to inject the medication?), and the development of a plan for monitoring diversion and misuse, and switching if indicated to the naloxone formulation.

In the USA, the maximum recommended dose is 24mg daily. Over this, prescribing is 'off-label', and physicians should document a rationale for surpassing this dosage, recording how they knew lower doses were inadequate. No studies to date have found higher doses produce superior results, and most patients stabilise on between 8 and 24mg daily. Dosing should be flexible and incremental, according to published practice guidelines and taking into account both the evidence base and the individual patient's response to medication. Providers should avoid sub-therapeutic dosing, which fails to prevent withdrawal and enables patients still to feel 'high' from 'on-top' illicit opioid use, but also avoid supra-therapeutic dosing, which may allow patients to share or sell some of their medication while still having enough for themselves. Also to be avoided is providing large drug supplies to unstable patients, providing them with an opportunity for diversion and misuse.

When diversion and misuse are suspected or confirmed, potential responses include practical solutions individualised to the patient, but also more frequent clinic and/or counselling visits, smaller supplies of unsupervised medication, and initiation of or increase in the frequency of supervised consumption. Dosing under supervision three times a week rather than daily reduces the burden on the clinic without compromising treatment outcomes. Observed ingestion at the clinic, pharmacy, or by a trusted non–drug-user who lives with or nearby the patient can also be considered, and promoted by network therapy. However, it is critical to avoid choosing helpers in an abusive or exploitative relationship with the patient.

It is important to remember that supervised dosing does not eliminate diversion and misuse. Like liquid methadone, buprenorphine tablets can be held in cheeks and taken out of the mouth if there is a brief lapse in supervision. The film product should be harder to divert because it dissolves more quickly and is 'stickier' than the tablet. However, a recent study found it was removed from the mouth as often as the tablet, perhaps because it was not placed directly into the mouth, or a dry mouth or overlapping films impeded adherence to the inside of the mouth.

If universally required, daily supervised dosing may pose a barrier to treatment entry and limit the extension of treatment due to increased costs and storage and dispensing requirements, exacerbating

the problems of untreated addiction. However, supervised dosing may be helpful for patients who do not have safe storage options or would benefit from the increased structure and clinic contact that supervised dosing can provide. One study found that supervising buprenorphine dosing three times a week as opposed to just once only modestly diminished patient satisfaction and made no difference to treatment retention, opioid use, or medication adherence. However, some patients may require an alternative treatment setting or pharmacotherapy, such as methadone.

The authors' conclusions

Buprenorphine diversion and misuse seem to be common among opioid-addicted individuals, but the frequency of use of diverted medication, route of misuse, and consequent harms, are influenced by various factors. These include the pharmacological profile of the particular buprenorphine formulation, physical dependence status of the individual, individual experience with route of drug use, availability of buprenorphine or alternative opioids in the environment, and public policies regarding opioid addiction treatment services.

Deaths involving buprenorphine have occurred around the globe, most commonly in combination with central nervous system depressants, but in the United States, deaths involving buprenorphine are far fewer than deaths involving methadone and other full-action opioid analgesics. Importantly, epidemiological data from France and the United States shows that as buprenorphine maintenance treatment expanded, there was an overall decrease in drug overdose deaths, so measures to minimise diversion and misuse must not undermine the positive patient and public health benefits gained by expanded treatment access.

FINDINGS COMMENTARY UK guidance on addiction treatment advises supervised consumption of buprenorphine normally for the first three months of treatment and until the patient is stable, and says supervision "provides the best guarantee that a medicine is being taken as directed". UK medication guidelines say usual doses range from 12–24mg daily but up to 32mg if indicated. Some patients do need the higher dose to avoid continued illegal opiate use.

Very few buprenorphine-related deaths have been identified by a UK-wide national reporting system. Though since the year 2000 these have been on an upward trend, up to 2012 they peaked at 13 in 2011, before falling in 2012 to 8 out of a total of 865 drug misuse deaths. Deaths may be curbed by the rapid uptake of the combined buprenorphine and naloxone formulation, the number of dispensed prescriptions for which increased by over 28% between 2012/13 and 2013/14.

In this context it worth reiterating the featured review's caution that measures to minimise diversion and misuse must not be so onerous for patient or clinic that they undermine the extension of treatment to the greatest number of opiate-dependent patients. Untreated heroin addiction is in general a greater threat to health than diversion and misuse arising from buprenorphine-based treatment.

Crushing tablets to prevent diversion

Apart from the anti-diversion tactics suggested in the featured review, in the UK the pharmacy profession has endorsed and extended its insurance to the 'off-label' practice of crushing buprenorphine tablets before patients dissolve the drug under the tongue, reducing the barrier of the extra time required to ensure a tablet has fully dissolved, and making it harder to 'palm' the dose or remove it from the mouth. Crushing is mentioned as an option in UK guidance on the treatment of drug dependence.

However, the practice contravenes the product licence, impeding its widespread implementation. Guidelines for England on pharmacy services for drug users stipulate that this unlicensed use of the medicine requires multiple local approvals, possibly extension of indemnity insurance for the pharmacist, and the permission of both prescriber and patient.

Though it has face validity, there is little well controlled research demonstrating that crushing achieves its objectives. Crushing has been widely implemented in Australia and was made mandatory at the pharmacy of a large treatment service, which found concerns that the powder might be inhaled or swallowed were not in practice a problem, and that many patients preferred the shortened supervision time. The latter advantage was confirmed by authors from the same centre in a controlled study which found absorption time of buprenorphine/naloxone tablets on average halved by crushing. A survey of experienced buprenorphine-dispensing pharmacies in the Australian state of Victoria found those which crushed the tablets reported fewer instances of diversion, though these are not entirely eliminated.

See these notes for more on how to prevent diversion of methadone and buprenorphine.

Thanks for their comments on this entry in draft to pharmacist Bob Dunkley based in northern England. Commentators bear no responsibility for the text including the interpretations and any remaining errors.

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