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

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Practice-oriented review of what we know about the diversion (to other people) and misuse (mainly by injecting) 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 illustrating 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 others. Buprenorphine and, according to an Australian study, especially the combination product with naloxone, will often be shared with friends without money changing hands.

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 other opioids. 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...
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How to control diversion and misuse

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restrictions on the duration of benzodiazepine prescribing helped reduce misuse. Availability (and co-prescribing), diversion, and misuse, warrant increased attention, as in France where benzodiazepines and alcohol augment the respiratory depressant effects of buprenorphine and the recent data reveals a significant relationship between a decline in heroin overdose deaths after the 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

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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 opioid 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.

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 there 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 how they know 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 opioid misuse, and 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 providing them with an opportunity for diversion and misuse, but how well has not been researched. Random medication counts can also help identify diversion and misuse, 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.

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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.

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 prescribers 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.

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\text{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.}
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\text{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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\text{Last revised 19 February 2015. First uploaded 13 February 2015}
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