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▶ Buprenorphine/naloxone for opioid dependence: clinical practice guideline.

Handford C. et al.
[Ontario, Canada] Centre for Addiction and Mental Health, 2011.

Though tailored for Canada, these guidelines from an internationally respected centre offer valuable guidance to clinicians in Britain and elsewhere on a form of the main alternative to methadone for the maintenance treatment of addiction to heroin and allied drugs, one whose greater safety counterbalances greater cost.

The following account broadly reproduces the document's summary with the addition (because discontinuation is not dealt with in the summary) of the section from the main text on tapering stable patients.

These Canadian guidelines provide clinical recommendations for the initiation, maintenance and discontinuation of buprenorphine/naloxone maintenance treatment for opioid dependence in Ontario. The focus is on the combination product (marketed as Suboxone) because this is the only sublingual buprenorphine product available in Canada for maintenance treatment. The addition of naloxone is intended to deter injection because if taken in this way the naloxone is active and could precipitate withdrawal in people dependent on drugs like heroin and methadone. The buprenorphine is the active ingredient which by substituting for the opiate-type drugs the patient is dependent on is intended to safeguard them from harm related to injecting and the use of illegally acquired drugs, stabilise their lives, and to bring them in to a setting where their addiction can be treated.

The guidelines were developed by a multidisciplinary committee, including specialists in addiction medicine, family medicine and pharmacy, who had available to them the results of a systematic review of the literature which formed the evidence base for the guidelines. Recommendations were assigned levels of evidence depending on the methodological rigour of the supporting studies, and grades which reflect the level of evidence plus clinical expertise.

The background to the guidelines is that opioid dependence is an increasing clinical and public health problem in Canada, yet only an estimated 25% of people dependent on

opioids are enrolled in a methadone programme. Methadone uptake is limited by issues of access, especially in non-urban areas, as well as patient disinterest. Due in part to its demonstrated effectiveness and safety in the primary care setting, buprenorphine/naloxone has the potential to improve access to evidence-based treatment for opioid dependence.

Selecting buprenorphine maintenance treatment

• Buprenorphine/naloxone is an effective medication for the maintenance treatment of opioid dependence. It improves outcomes compared to detoxification and, with the exception of retention in treatment, appears to be of equal efficacy compared to methadone.

Clinical assessment

• Contraindications to initiation of buprenorphine/naloxone are:
− allergy to buprenorphine/naloxone;
− pregnancy (for buprenorphine/naloxone combination product specifically);
− severe liver dysfunction;
− acute severe respiratory distress;
− paralytic ileus;
− decreased level of consciousness;
− inability to provide informed consent.
• Exercise caution if baseline liver enzymes are elevated above 3−5 times the upper limit of normal.
• The clinical assessment will include the establishment of the diagnosis of opioid dependence, an estimation of degree of the patient's physical dependence on opioids and their level of psychosocial functioning, an appreciation of other concurrent medical and psychiatric diagnoses and an understanding of the patient's treatment goals. Urine drug testing and a small but important selection of other laboratory tests are also essential components of the assessment.

Preparation

• Ensure a clinical assessment has resulted in a diagnosis of opioid dependence, a urine drug test has been interpreted and is positive for opioids, and that there has been a consideration of the contraindications to initiating buprenorphine/naloxone.
• Ensure the patient has provided informed consent to buprenorphine maintenance treatment, is aware of the possible long-term nature of this treatment and has been made aware of other treatment options. A written consent and treatment agreement may be useful.
• Ensure that there are no concurrent substance use disorders, psychiatric illnesses or medical disorders that should be stabilised prior to induction of buprenorphine/naloxone.
• Inform the patient how long to remain abstinent from opioids to maximise the likelihood of beginning their induction in satisfactory withdrawal to minimise the likelihood of precipitated withdrawal during the induction.
• Ensure the patient has no plans to drive a vehicle or operate heavy machinery during the early induction period.

Induction

- Patient presents in moderate opioid withdrawal to the physician's office as early in the day as possible.
- After an assessment to establish the severity of opioid withdrawal, the physician prescribes an initial induction dose of 2–4mg of buprenorphine/naloxone (though it could be as high as 6mg), to be administered sublingually.
- The ingestion of the dose is observed by a pharmacist or other health care professional to ensure the tablet has dissolved completely.
- Consideration is given to reassessing the patient one hour after the dose to assess for precipitated withdrawal.
- If necessary, the patient is reassessed after approximately three hours to assess effectiveness of the initial dose and consider prescribing an additional observed dose (to a maximum of 8mg total on the first day). If after this re-assessment the prescriber is unsure about the need for another buprenorphine/naloxone dose, the prescriber may also consider prescribing one or two 2mg tablets of buprenorphine/naloxone for the patient to take home on that first induction day in case withdrawal symptoms emerge later in the evening (not exceeding 8mg total on the first day).
- The prescriber either asks to see the patient the next day or writes a prescription for observed once-daily dosing of buprenorphine/naloxone for the next one to two days for the total amount taken by the patient on day one. At the follow-up appointment the patient is assessed for the effectiveness of the dose and any side effects. The patient is made aware they can present for reassessment earlier than the suggested day if they are feeling the dose is very inadequate or they are having side effects from the dose.
- At each follow-up visit, the buprenorphine/naloxone dose is titrated, generally by 2–4mg at a time, until an optimal maintenance dose is reached. An optimal dose is one where, among other things, the patient is free of opioid withdrawal symptoms for the full 24-hour dosing interval without experiencing intoxication or sedation from the medication.

Maintenance

- Once at the maintenance dose and more clinically stable, patient visits become gradually less frequent. Even a highly stable patient should be assessed at least every 12 weeks. Visits will again be more frequent during periods of instability.
- At follow-up visits, patient clinical stability is ascertained using the clinical assessment and urine drug testing.
- Areas to cover at follow-up visits include: adequacy of the dose and side effects, substance use, psychiatric symptoms, employment, social relationships, and participation in counselling/mutual aid groups.
- Once the patient is at a stable maintenance dose, consideration can be given to alternate-day dosing (ie, double the dose on Monday, Wednesday and Friday and a single dose on Sunday).
- Patients should not receive a dose of buprenorphine/naloxone if they appear intoxicated or sedated upon presenting for their dose.
- The prescriber should have a structured approach to missed doses.
- The prescriber should have a structured approach to deciding about initiating and increasing the number of take-home doses once the patient achieves clinical stability.

Take-home doses

- Prescribing of take-home doses of buprenorphine/naloxone is a therapeutic intervention with benefits and risks.

• Take-home doses should not be initiated until the patient exhibits features of clinical stability. Exercise caution if patient has recently been suicidal, is injecting, is cognitively impaired or has unstable housing.
• Generally, tighter boundaries should be loosened as the patient displays increased clinical stability rather than tightening initially looser boundaries in response to instability.
• There should be a gradual increase in the number of weekly take-home doses up to a suggested maximum of one to two weeks of consecutive take-home doses dispensed between observed doses.
• Health Canada states that all doses are to be observed, with the exception of weekends and holidays, for at least the first two months on buprenorphine/naloxone. If the prescriber feels that a patient is eligible for additional regular take-home doses earlier than two months, this should be justified in the clinical record and the patient needs to have explicitly consented to this 'against label' prescription.
• When about to receive their first take-home dose(s), all patients should be made aware of the risks to themselves, their family and the public.
• Take-home doses should be reduced or eliminated in response to a loss of clinical stability. If high levels of take-home doses are eliminated all at once and if misuse or diversion of the take-home doses is suspected, the prescriber should strongly consider reducing the buprenorphine/naloxone dose by 25–50%. This would reduce the likelihood of opioid toxicity once the patient starts ingesting their buprenorphine/naloxone doses on a daily basis.

Adverse events and safety

• Buprenorphine's partial mu agonist pharmacodynamic properties suggest that there is less risk of overdose and short-term mortality compared to full mu agonists such as methadone. Population-level studies appear to consistently and robustly support that hypothesis.
• There is evidence that this medication can be prescribed as safely and effectively by appropriately trained or experienced practitioners in a primary care clinic as it can be in a clinic which specialises in prescribing opiate-type drugs in the treatment of addiction.
• Risk of harm with buprenorphine does still exist, including the risk of injecting the drug, so practitioners must be systematic and thorough in their approach to diagnosing opioid dependence, determining eligibility for buprenorphine/naloxone and inducting and maintaining patients on buprenorphine/naloxone maintenance therapy.

Tapering stable patients

• Buprenorphine/naloxone maintenance treatment is generally considered a long-term treatment with no predetermined end point. That said, there will be patients for whom a taper off of buprenorphine/naloxone maintenance has been agreed upon by the patient and prescriber.
• Ideally, patients taper off of buprenorphine/naloxone maintenance while drug-free, functioning well and with ongoing psychosocial support. In some circumstances patients may choose to taper off under less than ideal circumstances (eg, ongoing drug use or ongoing social instability).
• Regardless of the clinical circumstances, buprenorphine/naloxone should be tapered gradually, perhaps by 2mg per week initially, and the taper rate adjusted based on the patient's experience of the taper.
• Throughout the taper patients should be monitored carefully for withdrawal, cravings,

and lapses to drug use. If clinical stability is lost during the taper, re-titration of the buprenorphine/naloxone dose should be recommended to the patient.

FINDINGS Though tailored for Canada, these guidelines from an internationally respected centre offer valuable guidance to clinicians in Britain and elsewhere. Uniquely they focus on the buprenorphine/naloxone product rather than buprenorphine, but the recommendations are usually appropriate to both. Realistically they admit that the anti-injection properties of the combination product – its main claim to being preferred to alternatives – are not 100%. Non-dependent opioid abusers, they say, still get a 'buzz' from injecting the product as do some patients maintained on buprenorphine/naloxone, and there is substantial evidence that the combination product finds an illicit market. Such considerations are important, because they mean that if supervised consumption is thought necessary at least initially to prevent buprenorphine being diverted on to the illicit market, the same is true of the combination product. This undermines its anticipated advantages as a medication potentially prescribed widely from GP's surgeries in regimens which reduce supervision costs and the restrictions supervision places on patients' working and family lives. However, buprenorphine with or without naloxone lends itself to being taken every other day, meaning that even if supervision is thought necessary, the attendance burden is halved compared to methadone.

An international review and UK guidance have contrasted the virtues of methadone versus buprenorphine. Like the featured guidance, these found little in the research to indentify who would do best on one drug or the other. The Findings analysis tentatively offered the indications that buprenorphine possibly helps depressed patients more than those not suffering depression, while patients dependent on large doses of opiates may find it inadequate because there is a ceiling beyond which higher doses do not augment opiate-type effects. Patients who value the 'wrapped in cotton wool' feeling typical of heroin may prefer methadone, while those who value a clearer mind might prefer buprenorphine.

Britain's National Institute for Health and Clinical Excellence suggests that when for an individual the medications are equally appropriate, methadone might take precedence because it costs less and on average extends the benefits of being in treatment. With the emphasis in Britain shifting from retention to treatment exit and concern over recently increased numbers of methadone-involved overdose deaths, buprenorphine with or without naloxone could find a greater profile, especially if the cost savings of alternate day dosing, less need to supervise consumption, and primary care rather than clinic-based treatment, are fully realised to counter the greater cost of the drug and the greater time required for each supervised consumption.

For other guidelines offering advice on buprenorphine maintenance run this search on the Findings site.

This draft entry is currently subject to consultation and correction by the study authors and other experts.

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Guidance for the use of substitute prescribing in the treatment of opioid dependence in primary care DOCUMENT 2011

Risk of death during and after opiate substitution treatment in primary care: prospective observational study in UK STUDY 2010

Pharmacotherapies for the treatment of opioid dependence: efficacy, cost-effectiveness and implementation guidelines REVIEW 2009

Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence DOCUMENT 2009

Mortality prior to, during, and after opioid maintenance treatment (OMT): a national prospective cross-registry study STUDY 2008

Preventing unauthorised use of medications prescribed for the treatment of opiate addiction NOTES 2010

International review and UK guidance weigh merits of buprenorphine versus methadone maintenance REVIEW 2008

The SUMMIT Trial: a field comparison of buprenorphine versus methadone maintenance treatment STUDY 2010

QT interval screening in methadone maintenance treatment: report of a SAMHSA expert panel REVIEW 2011

Maintenance treatment with buprenorphine and naltrexone for heroin dependence in Malaysia: a randomised, double-blind, placebo-controlled trial STUDY 2008