Primary care management of opioid use disorders

Abstinence, methadone, or buprenorphine-naloxone?

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Abstract

Objective To advise physicians on which treatment options to recommend for specific patient populations: abstinence-based treatment, buprenorphine-naloxone maintenance, or methadone maintenance.

Sources of information PubMed was searched and literature was reviewed on the effectiveness, safety, and side effect profiles of abstinence-based treatment, buprenorphine-naloxone treatment, and methadone treatment. Both observational and interventional studies were included.

Main message Both methadone and buprenorphine-naloxone are substantially more effective than abstinence-based treatment. Methadone has higher treatment retention rates than buprenorphine-naloxone does, while buprenorphine-naloxone has a lower risk of overdose. For all patient groups, physicians should recommend methadone or buprenorphine-naloxone treatment over abstinence-based treatment (level I evidence). Methadone is preferred over buprenorphine-naloxone for patients at higher risk of treatment dropout, such as injection opioid users (level I evidence). Youth and pregnant women who inject opioids should also receive methadone first (level III evidence). If buprenorphine-naloxone is prescribed first, the patient should be promptly switched to methadone if withdrawal symptoms, cravings, or opioid use persist despite an optimal buprenorphine-naloxone dose (level II evidence). Buprenorphine-naloxone is recommended for socially stable prescription oral opioid users, particularly if their work or family commitments make it difficult for them to attend the pharmacy daily, if they have a medical or psychiatric condition requiring regular primary care (level IV evidence), or if their jobs require higher levels of cognitive functioning or psychomotor performance (level III evidence). Buprenorphine-naloxone is also recommended for patients at high risk of methadone toxicity, such as the elderly, those taking high doses of benzodiazepines or other sedating drugs, heavy drinkers, those with a lower level of opioid tolerance, and those at high risk of prolonged QT interval (level III evidence).

Conclusion Individual patient characteristics and preferences should be taken into consideration when choosing a first-line opioid agonist treatment. For patients at high risk of dropout (such as adolescents and socially unstable patients), treatment retention should take precedence over other clinical considerations. For patients with high risk of toxicity (such as patients with heavy alcohol or benzodiazepine use), safety would likely be the first consideration. However, the most important factor to consider is that opioid agonist treatment is far more effective than abstinence-based treatment.

EDITOR'S KEY POINTS

- Canada is now the leading per capita user of prescription opioids in the world, and rates of addiction and overdose are correspondingly high. Family physicians are often called upon to recommend treatment options for patients dependent on prescription opioids, but there is uncertainty about which option to recommend for which patient populations.
- Opioid agonist treatment is far more effective than abstinence. Method of ingestion, type of opioid, and patient life stage, health status, social situation, and preferences should be taken into consideration when choosing the appropriate opioid agonist treatment.
- As with other chronic conditions, opioid addiction is best managed in a primary care setting: physicians should initiate buprenorphine-naloxone treatment or refer for methadone treatment when appropriate, and specialized clinics should refer buprenorphine-naloxone patients back to primary care when they are stable.

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Canada is now the leading per capita user of prescription opioids in the world,[1] and rates of addiction and overdose are correspondingly high.[2-4] In 2010, 510 people died from an opioid-related overdose in Ontario, making it a leading cause of death in younger adults.[5] Most fatal overdose cases in Ontario had received an opioid prescription within the previous 3 weeks,[6] and many if not most Canadian family physicians will have opioid-dependent patients in their practice.[7]

Case description

C.J. is a 21-year-old woman who has been in your practice since childhood. Her mother, also your patient, has an alcohol use disorder. C.J. comes to your office asking for a refill of hydromorphone and some lorazepam, saying that they have been prescribed to her from a clinic near her house for migraines and neck spasms. She is vague about the doctor's name and cannot give you any information to help in obtaining medical records. On examination you note that she has lost weight and has track marks on her arms, and results of a urine drug screen are positive for hydromorphone, morphine, and cannabis. With further history from C.J. and collateral history from her mother, you diagnose her with an opioid substance use disorder.

Physicians have 3 main treatment options to offer their opioid-dependent patients: abstinence-based treatment, buprenorphine-naloxone, or referral to a methadone clinic. Methadone and buprenorphine are opioids with a slow onset and long duration of action. In the appropriate dose, they relieve withdrawal symptoms and cravings for 24 hours without causing sedation or euphoria.

This review is intended as a guide for choosing the appropriate treatment option for specific patient subgroups. Its recommendations build on other recently released guidelines.[8]

Sources of information

We reviewed the literature separately for buprenorphine-naloxone and methadone. Using PubMed, we searched specifically for evidence comparing the medications on efficacy and safety, and on adverse effects. We searched for comparative studies in specific subpopulations, including heroin users, prescription oral opioid users, adolescents, and pregnant women. Both observational and interventional studies were included in the review. Through consensus we applied levels of evidence (**Box 1**) to each recommendation.

Type of evidence. Conclusions about treatment retention rates for methadone versus buprenorphine-naloxone are based on randomized trials and systematic reviews; conclusions about safety are based on animal studies, preclinical human studies, and population-based studies. The recommendations about patients at high risk of treatment dropout are based on clinical trials, systematic reviews, and observational studies conducted in heroin users. Recommendations about oral prescription opioid users and about specific populations (adolescents and pregnant women) are based on observational studies and a few small randomized trials.

Box 1. Levels of evidence

Level I: Multiple large randomized controlled trials and systematic reviews
Level II: 1 or 2 small randomized controlled trials
Level III: Cohort and case-control studies
Level IV: Consensus

Main message

Recommendations are based primarily on differences between the 3 treatments—methadone, buprenorphine-naloxone, and abstinence—in safety and treatment retention. Treatment retention is a critically important treatment outcome; heroin users who drop out of treatment have higher rates of overdose deaths and arrests than those who remain in treatment.[9-13]

We have organized our comparisons of the 3 treatments into several patient categories: method of ingestion and type of opioid, life stage, health status, and social factors (rural community, job requiring alertness). Clinical factors favouring methadone versus buprenorphine-naloxone are summarized in **Box 2**.

Box 2. Clinical factors in prescribing methadone versus buprenorphine-naloxone

Factors favouring methadone include the following:
- Injection opioid use
- Pregnant or adolescent injection opioid users
- Other risk factors for treatment dropout (eg, unstable housing, lack of social support, concurrent mental illness)
- Previous treatment dropout with buprenorphine or adverse effects

Factors favouring buprenorphine-naloxone include the following:
- Oral prescription opioid use
- At risk of methadone toxicity (eg, elderly; heavy alcohol users; those with cardiac or respiratory compromise, at risk of QT prolongation, or taking benzodiazepines or atypical antipsychotics)
- In a rural community without methadone access
- Previous treatment dropout with methadone or adverse effects
- Job requiring alertness (eg, driving or operating machinery)
- Sexually active men at low risk of treatment dropout
- Requiring regular primary care for screening, health maintenance, or a chronic medical or psychiatric illness

Method of ingestion and type of opioid

Injection opioid users: Both methadone and buprenorphine-naloxone are recommended over abstinence-based treatment for patients who inject heroin or other opioids (level I evidence). Controlled trials, systematic reviews, and epidemiologic studies have clearly demonstrated that both methadone and buprenorphine-naloxone treatment are associated with higher treatment retention rates[14,15] and markedly reduced rates of opioid use, mortality, health care use, and crime in heroin users, compared with patients receiving placebo, no treatment, abstinence-based psychosocial treatment, or medical detoxification.[14,16-20] Residential treatment programs have very high reported relapse rates,[15] and patients who attend an abstinence-based program have a higher risk of fatal overdose than waiting-list controls do because of loss of tolerance.[21]

Methadone is recommended over buprenorphine-naloxone for injection opioid users (level I evidence). Systematic reviews of controlled trials have concluded that buprenorphine-naloxone was less effective than methadone for retaining heroin users in treatment.[22]

This is likely because buprenorphine is a partial opioid agonist, whereas methadone is a potent full μ-opioid agonist and is therefore more effective at relieving withdrawal symptoms and cravings.

If buprenorphine-naloxone is used first in injection opioid users, it should be titrated rapidly to an optimal dose and the patient should be switched to methadone immediately if withdrawal symptoms, cravings, or opioid use persist (level II evidence). One controlled trial found that the retention rate for methadone was similar to that for buprenorphine-naloxone followed by immediate transfer to methadone for patients who experienced persistent cravings or opioid use.[23]

Oral prescription opioid users: Buprenorphine-naloxone or methadone maintenance is recommended over abstinence-based treatment in oral prescription opioid users (level II evidence). Controlled trials and observational studies have demonstrated that buprenorphine-naloxone maintenance has statistically significantly higher treatment retention rates than tapering and abstinence for oral prescription opioid users. In a controlled comparison of buprenorphine-naloxone maintenance and tapering in oral prescription opioid users, treatment retention at 14 weeks was 66% in the buprenorphine-naloxone maintenance group compared with only 11% in the tapering group.[24] Other studies support this finding.[25,26]

If tapering is attempted, tapers of 4 weeks or longer are more effective than 1- or 2-week tapers.[27] On completion of the taper, patients should be given take-home naloxone and counseling on overdose prevention, and should be offered immediate access to buprenorphine-naloxone maintenance treatment if they experience persistent withdrawal symptoms, cravings, or relapse.

Buprenorphine-naloxone is preferred over methadone for socially stable oral prescription opioid users (level IV evidence). We could find only one trial directly comparing methadone to buprenorphine-naloxone for oral opioid users; in this trial, methadone had a lower risk of dropout than buprenorphine-naloxone did (odds ratio of 0.38).[28] Despite this, we suggest buprenorphine-naloxone over methadone in this population. Several non-randomized cohort studies have demonstrated that prescription opioid users have reasonably good treatment retention rates with primary care–based buprenorphine-naloxone treatment (59% to 65%).[29,30] Buprenorphine-naloxone is safer than methadone,[31-33] and the severe consequences of treatment dropout (overdose, imprisonment, etc) are probably less common in socially stable (eg, employed, stable housing) oral prescription opioid users (although research on this is also lacking). The risk of dropout can likely be mitigated by switching patients immediately to methadone if they do not fully respond to buprenorphine-naloxone.[23]

Life stage

Adolescents: Methadone or buprenorphine-naloxone are recommended over abstinence-based treatments for adolescents (level II evidence). One randomized trial demonstrated that buprenorphine-naloxone maintenance was more effective than buprenorphine-naloxone tapering for opioid-dependent adolescents.[34] Some physicians suggest that tapering to abstinence with buprenorphine-naloxone is more effective than tapering with methadone, but this has not been confirmed.

Methadone is recommended over buprenorphine-naloxone for adolescents who inject opioids (level III evidence). If buprenorphine-naloxone is used first, the patient should be switched immediately to methadone if opioid use or withdrawal persist (level IV evidence). Observational studies found that methadone had better treatment retention than buprenorphine-naloxone in adolescent heroin users.[35,36] For example, in a retrospective chart review, those taking methadone were retained in treatment for an average of 354 days, compared with 58 days for patients taking buprenorphine.[35] Socially stable adolescents who use prescription opioids orally should receive buprenorphine-naloxone first (level IV evidence).

Pregnant women: Pregnant injection opioid users should receive methadone first (level II evidence). If buprenorphine-naloxone is used, the patient should be switched immediately to methadone if opioid use or withdrawal persist (level II evidence). A Cochrane review of 3 controlled trials comparing methadone with buprenorphine in pregnant opioid-dependent women found that treatment retention was higher in the methadone group, although the difference did not quite reach statistical significance (risk ratio of 0.64, 95% CI 0.41 to 1.01, 223 participants).[37] In the MOTHER (Maternal

Opioid Treatment: Human Experimental Research) trial, which was the largest trial (175 participants), 33% of the women taking buprenorphine dropped out of treatment versus 18% of the women taking methadone.[38] The neonates of mothers treated with buprenorphine had shorter hospital stays and required less morphine compared with neonates of mothers taking methadone. However, neonatal abstinence syndrome is treatable and is not associated with long-term consequences. In contrast, treatment dropout can have devastating consequences, such as loss of child custody or death from overdose.

However, socially stable pregnant oral prescription opioid users should receive buprenorphine first, as they are at lower risk of treatment dropout (level IV evidence). Pregnant women taking buprenorphine-naloxone should be switched to buprenorphine alone without naloxone; the safety of naloxone in pregnancy has not been confirmed, although preliminary evidence has found that it is safe.[39-42]

The elderly: Buprenorphine-naloxone is preferred over methadone in elderly patients (level III evidence). There has been little published research on methadone or buprenorphine-naloxone use in the elderly. Methadone is considerably more potent than buprenorphine-naloxone and, therefore, should be used with caution in the elderly, who are at greater risk of opioid-related falls and other adverse events than younger patients.[43-47]

Health status

Patients requiring regular primary care: For patients who would benefit from regular primary care, buprenorphine-naloxone prescribed in a primary care setting is recommended over methadone or buprenorphine-naloxone prescribed in specialized clinics (level II evidence). Several controlled trials and observational studies have demonstrated that buprenorphine-naloxone treatment prescribed in an office or primary care setting is as effective as buprenorphine-naloxone prescribed in a specialized addiction setting.[22,48,49] Furthermore, opioid-addicted patients are more likely to receive screening, health maintenance, and chronic disease management if they receive buprenorphine-naloxone from a primary care clinic.[48,50]

Patients at high risk of methadone toxicity: Buprenorphine-naloxone is recommended for patients at high risk of methadone toxicity and overdose (level III evidence). Observational studies have consistently demonstrated that buprenorphine-naloxone has a substantially lower risk of fatal overdose than methadone does, particularly during the first few weeks of dose titration.[31-33,51] Risk factors for methadone overdose include lung or heart disease, heavy alcohol consumption, concurrent use of benzodiazepines and possibly other sedating drugs, older age, and lower opioid tolerance (nondaily opioid use, codeine addiction, recent cessation of opioid use). For this reason, buprenorphine-naloxone is recommended over methadone in mentally ill patients who are taking benzodiazepines or atypical antipsychotics (level IV evidence).

Buprenorphine-naloxone is preferred for patients at high risk of QT prolongation (level III evidence). Methadone has been shown to prolong QT intervals and cause torsades de pointes, especially at higher doses (200 to 300 mg).[52] Buprenorphine does not affect the QT interval.[53]

Patients who experience intolerable adverse effects with one medication should be switched to the other (level IV evidence). Both methadone and buprenorphine-naloxone occasionally cause severe side effects such as nausea and sedation. If the side effect does not respond to dose adjustment or other interventions, the patient should be switched to the other medication. Methadone is more likely to cause erectile dysfunction than buprenorphine-naloxone is[54-56]; therefore, buprenorphine-naloxone might be preferred in sexually active men at low risk of treatment dropout.

Social factors

Rural communities: Buprenorphine-naloxone is preferred over abstinence-based treatment in communities where methadone is unavailable (level IV evidence). Methadone treatment is not feasible in many isolated communities, as they generally lack a methadone prescriber, a pharmacy open 7 days per week, and emergency services. Buprenorphine-naloxone is emerging as an effective and feasible alternative to methadone treatment in these communities.[57-59]

Work and family responsibilities: Buprenorphine-naloxone is preferred over methadone in patients whose work or family responsibilities make it very difficult to attend the pharmacy daily (level IV evidence). Methadone programs dispense methadone, with its high risk of overdose, under daily supervision during the first few months of treatment. Buprenorphine-naloxone can safely be dispensed as take-home doses earlier on in treatment if the patient is at low risk of diversion. A qualitative study found that patients preferred flexible take-home schedules.[60]

Buprenorphine-naloxone is preferred for patients whose work requires mental alertness (level III evidence). Preclinical studies and a randomized trial have demonstrated that patients taking buprenorphine-naloxone perform better than those taking methadone on cognitive tests and on psychomotor tasks related to driving.[61-65]

Case resolution

You start C.J. on buprenorphine-naloxone. She states that she is continuing to have withdrawal and to use hydromorphone despite your increasing her to a maximal dose; after 2 months she stops treatment. At her next visit you refer her to the local methadone clinic. After 3 months of taking methadone, her withdrawal

symptoms have resolved, her mood has improved, and she has completely stopped using hydromorphone. She continues to use lorazepam (from another source) on occasion, and you counsel her on the risks of mixing benzodiazepines with opioids.

Conclusion

Unlike most other medical conditions, opioid-addicted patients, their families, and addiction treatment programs often have strong preferences for one treatment over another.[66] However, while physicians must respect patients' choices, they also have a responsibility to inform patients on what the evidence states about the risks and benefits of different treatment options. Thus, physicians should inform patients that methadone or buprenorphine-naloxone are more effective than abstinence-based treatments and have a lower risk of overdose. The physician should also educate patients who choose abstinence about overdose prevention strategies and should provide urgent access to methadone or buprenorphine-naloxone if they relapse.

There is a need for comprehensive policy change to ensure that all Canadians have access to evidence-based treatment. Most provinces have finally allowed buprenorphine as a general benefit on the public drug formulary (British Columbia, Alberta, Ontario, and Newfoundland and Labrador, as well as Non-Insured Health Benefits and Correctional Services) but some provinces require special authorization (Saskatchewan, New Brunswick) and in others it can only be prescribed as a second-line agent after methadone (Manitoba, Quebec, Nova Scotia, Prince Edward Island). Provincial medical colleges generally require physicians to have received training in prescribing, and Alberta has mandatory training. Moreover, many publicly funded abstinence-based programs refuse admission to patients taking methadone or buprenorphine-naloxone. Taken together, these policies cause unnecessary death and disability by blocking access to safe, inexpensive, and effective treatments, especially for patients living in rural communities and those who cannot afford to pay for medications.

As with other chronic conditions, opioid addiction is best managed in a primary care setting: physicians should initiate buprenorphine-naloxone treatment or refer for methadone treatment when appropriate, and specialized clinics should refer buprenorphine-naloxone patients back to primary care when they are stable.

Opioid agonist treatment is far more effective than abstinence. Individual patient characteristics and preferences should be taken into consideration when choosing which opioid agonist treatment to use first. Methadone is more likely to retain patients in treatment but has a higher risk of overdose than buprenorphine-naloxone. In cases where patients are at high risk of dropout (such as adolescents and socially unstable patients), treatment retention should take precedence over other clinical considerations. For patients with high risk of toxicity (such as patients with heavy alcohol or benzodiazepine use), safety would likely be the first consideration. However, the most important factor to consider is that opioid agonist treatment, whether it is methadone or buprenorphine-naloxone, is far more effective than abstinence-based treatment.

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Contributors
All authors contributed to the literature review and interpretation, and to preparing the manuscript for submission.

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None declared

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