

Misuse of and dependence on opioids

Study of chronic pain patients

Meldon Kahan, MD, CCFP, FRCPC Anita Srivastava, MD, MSC, CCFP Lynn Wilson, MD, CCFP, FCFP
Douglas Gourlay, MD, FRCPC Deana Midmer, RN, EDD

ABSTRACT

OBJECTIVE To review the evidence on identifying and managing misuse of and dependence on opioids among primary care patients with chronic pain.

QUALITY OF EVIDENCE MEDLINE was searched using such terms as “opioid misuse” and “addiction.” The few studies on the prevalence of opioid dependence in primary care populations were based on retrospective chart reviews (level II evidence). Most recommendations regarding identification and management of opioid misuse in primary care are based on expert opinion (level III evidence).

MAIN MESSAGE Physicians should ask all patients receiving opioid therapy about current, past, and family history of addiction. Physicians should take “universal precautions” that include careful prescribing and ongoing vigilance for signs of misuse. Patients suspected of opioid misuse can be treated with a time-limited trial of structured opioid therapy if they are not acquiring opioids from other sources. The trial should consist of daily to weekly dispensing, regular urine testing, and tapering of doses of opioids. If the trial fails or is not indicated, patients should be referred for methadone or buprenorphine treatment.

CONCLUSION Misuse of and dependence on opioids can be identified and managed successfully in primary care.

RÉSUMÉ

OBJECTIF Examiner les données scientifiques concernant l'identification et la prise en charge de l'usage abusif d'opiacés et de la dépendance à leur endroit chez des patients en soins de première ligne souffrant de douleur chronique.

QUALITÉ DES PREUVES Une recension a été effectuée dans MEDLINE à l'aide des expressions en anglais «usage abusif d'opiacés» et «toxicomanie». Les quelques études sur la prévalence de la dépendance aux opiacés dans les populations de première ligne se fondaient sur une étude rétrospective de dossiers médicaux (preuves de niveau II). La plupart des recommandations portant sur l'identification et la prise en charge de l'usage abusif d'opiacés reposaient sur l'opinion d'experts (preuves de niveau III).

PRINCIPAL MESSAGE Les médecins devraient demander à tous les patients traités aux opiacés s'ils ont actuellement ou s'ils ont eu un problème de dépendance, ou s'il y a des antécédents familiaux de ce problème. Les médecins devraient prendre des «précautions universelles», notamment prescrire avec prudence et surveiller constamment les signes d'usage abusif. S'ils soupçonnent un usage abusif d'opiacés chez leur patient, ils peuvent faire l'essai d'une thérapie structurée aux opiacés pour une période de temps limitée, si le patient n'obtient pas d'opiacés d'autres sources. L'essai devrait comporter une administration passant d'une fois par jour à une fois par semaine, des analyses d'urine régulières et la diminution des doses d'opiacés. Si l'essai échoue ou n'est pas indiqué, un traitement à la méthadone ou au buprénorphine devrait être recommandé.

CONCLUSION Il est possible, dans les soins de première ligne, d'identifier et de prendre en charge avec succès l'usage abusif d'opiacés et la dépendance à leur endroit.

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Cet article a fait l'objet d'une révision par des pairs.

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In a recent national survey, 35% of Canadian family physicians reported that they would never prescribe opioids for moderate-to-severe chronic pain, and 37% identified addiction as a major barrier to prescribing opioids.¹ This attitude leads to undertreatment and unnecessary suffering.²

Physicians' concerns about patients' becoming dependent on opioids, however, are legitimate. The prevalence of opioid misuse is increasing, and untreated dependence can result in loss of productivity, family disruption, depression, overdose, and suicide.³⁻⁵ Family physicians must be able to prescribe opioids safely and effectively, and at the same time must identify and manage opioid misuse and dependence in their practices.

Quality of evidence

MEDLINE was searched using such terms as "opioid misuse" and "addiction." The few studies on the prevalence of opioid dependence in primary care populations were based on retrospective chart reviews (level II evidence). Observational studies have documented a high prevalence of opioid misuse in certain primary care patient populations, although the population prevalence is unknown. Most recommendations regarding identification and management of opioid misuse in primary care are based on expert opinion (level III evidence). Screening instruments for detecting opioid dependence have not yet been fully validated in primary care. Level I evidence indicates that primary care physicians can manage opioid dependence safely and effectively with methadone or buprenorphine therapy.

Levels of evidence

Level I: At least one properly conducted randomized controlled trial, systematic review, or meta-analysis

Level II: Other comparison trials, non-randomized, cohort, case-control, or epidemiologic studies, and preferably more than one study

Level III: Expert opinion or consensus statements

Dr Kahan is Medical Director of the Addiction Medical Service at St Joseph's Health Centre in Toronto, Ont, and Head of the Alcohol Clinic at the Centre for Addiction and Mental Health. **Dr Srivastava** is a staff physician at St Joseph's Health Centre and a clinical researcher at the Centre for Addiction and Mental Health. **Dr Wilson** is Chief of the Department of Family Medicine at St Joseph's Health Centre. **Dr Gourlay** is an Addiction Consultant in the Wasser Pain Clinic at Mount Sinai Hospital in Toronto. **Drs Srivastava, Gourlay, and Kahan** are also staff physicians at the Centre for Addiction and Mental Health. **Ms Midmer** is a researcher in the Department of Family and Community Medicine at the University of Toronto.

Key concepts

Substance dependence (addiction). Dependence occurs when patients find the psychoactive effects of a drug so reinforcing that they have difficulty controlling their use of the drug. Addiction is characterized by the four Cs: loss of **C**ontrol over use, continued use despite knowledge of harmful **C**onsequences, **C**ompulsion to use, and **C**raving. The reinforcing effects of opioids range from a mild "mood leveling" to profound euphoria.

Physical dependence. Dependence involves 2 related phenomena, tolerance and withdrawal. Tolerance occurs when patients must take more of the drug over time to achieve the same effect. Tolerance is due to compensatory changes in the number and sensitivity of central nervous system receptors. Tolerance to the analgesic effects of opioids develops slowly; tolerance to their mood-altering effects begins within days.

Physical symptoms of withdrawal include myalgia, and cramps and diarrhea. Psychological symptoms include anxiety, craving, and insomnia. Objective signs include lacrimation, acute rhinitis, yawning, sweating, chills, and piloerection. These signs are most evident several days after high doses of opioids are discontinued. Withdrawal peaks 2 to 3 days after last use, and physical symptoms largely resolve by 5 to 10 days after last use, although insomnia and dysphoria can last for months afterward. Opioid withdrawal does not have medical complications except during pregnancy when it can induce spontaneous abortion, premature labour, and neonatal withdrawal.

Opioid misuse. Opioid misuse (or aberrant drug behaviour) refers to opioid use that is not medically sanctioned, such as dose escalation, running out of the drug early, bingeing on opioids, or crushing controlled-release tablets. While opioid misuse can result from opioid dependence, it can also reflect inadequately treated pain, patients' attitudes toward medication, and other factors.

Potential for abuse. Level II evidence suggests that oxycodone has a greater risk of abuse than morphine.⁶⁻⁸ Controlled-release opioids have a slower onset of action and in theory have lower abuse potential than short-acting opioids (although they can be easily converted into immediate-release by crushing the tablets). The abuse potential of a drug is dose-related^{9,10}; controlled-release preparations contain larger doses of opioids than acetaminophen-opioid preparations.

Pseudoaddiction. This is said to occur when patients with inadequately treated pain exhibit drug-seeking behaviour similar to that of true addicts. Consensus opinion (level III evidence) suggests that this behaviour resolves with reasonable dose increases. True addictive behaviour remains the same or worsens.¹¹ One study

found that patients with inadequate pain relief were no more likely to misuse opioids than those with adequate pain relief,¹² suggesting that pseudoaddiction is an uncommon reason for opioid misuse.

Prevalence

The reported prevalence of opioid dependence among chronic pain patients varies among clinical settings. A review of studies conducted in tertiary care pain clinics found that prevalence ranged from 3% to 19% or more.^{13,14} Other studies, generally of older patients attending specialty clinics, found rates of 1% to 3%.¹⁵ In 3 retrospective chart reviews in primary care clinics, 7% to 31% of charts documented opioid misuse,^{16,17} and drug abuse was diagnosed in 6% of these patients.¹⁸ The true prevalence of prescribed opioid misuse is unknown. In the Health Care for Communities Study in the United States, which involved 14 000 patients,¹⁹ those taking prescription opioids had 4 times the risk of problems with use of prescribed and illicit drugs and of mood and anxiety disorders the other participants had. These studies must be interpreted with caution because opioid misuse is not synonymous with opioid dependence. A detailed diagnostic assessment of opioid users found that non-addicted patients frequently misuse opioids.²⁰

The prevalence of prescription opioid misuse appears to be increasing. The Drug Abuse Warning Network in the United States reported a 7-fold increase in oxycodone-related emergency department visits from 1996 to 2002.^{10,11} A national surveillance system involving addiction experts confirmed that opioid abuse increased in the United States from 2002 to 2004, with oxycodone showing the greatest increase.²¹

Risk factors for opioid dependence include youth; current, past, or family history of substance abuse; concurrent psychiatric disorders; and a childhood history of sexual abuse. Studies of the positive or negative predictive value of these risk factors have had inconsistent results.^{12,22,23}

Identifying opioid misuse and dependence

Universal precautions.²⁴ Physicians should take a careful baseline history of substance use on all patients, inquiring about current and past use of opioids, alcohol, benzodiazepines, cocaine, cannabis, and other drugs, as well as about history of previous treatment for substance abuse and family history. Physicians should routinely use treatment agreements, titrate opioid doses cautiously, and watch for signs of misuse.

Screening Screening instruments have not yet been shown in prospective studies to predict accurately which primary care patients suffering pain will become addicted to opioids.²⁵ Several instruments are currently under development.^{26,27} Two brief screening instruments, the Opioid Risk Tool²⁸ and the CAGE test,²⁹ can be

administered in primary care settings, although further validation research is needed (Tables 1 and 2).

Table 1. Opioid Risk Tool: Check box if factor applies (0–3 points—low risk, 4–7 points—moderate risk, ≥8 points—high risk).

FACTOR	MALE PATIENTS	FEMALE PATIENTS
Family history of substance abuse		
• Alcohol	<input type="checkbox"/> 3 points	<input type="checkbox"/> 1 point
• Illegal drugs	<input type="checkbox"/> 3 points	<input type="checkbox"/> 2 points
• Prescription drugs	<input type="checkbox"/> 4 points	<input type="checkbox"/> 4 points
Personal history of substance abuse		
• Alcohol	<input type="checkbox"/> 3 points	<input type="checkbox"/> 3 points
• Illegal drugs	<input type="checkbox"/> 4 points	<input type="checkbox"/> 4 points
• Prescription drugs	<input type="checkbox"/> 5 points	<input type="checkbox"/> 5 points
Age between 16 and 45	<input type="checkbox"/> 1 point	<input type="checkbox"/> 1 point
History of preadolescent sexual abuse	<input type="checkbox"/> 0 points	<input type="checkbox"/> 3 points
Psychiatric disease		
• Attention deficit disorder, obsessive-compulsive disorder, bipolar disorder, schizophrenia	<input type="checkbox"/> 2 points	<input type="checkbox"/> 2 points
• Depression	<input type="checkbox"/> 1 point	<input type="checkbox"/> 1 point

Table 2. CAGE test: Two or more positive responses indicate misuse or dependence and suggest patients need further assessment.

In the past have you ever:
C —tried to Cut down or Change your pattern of drinking or drug use?
A —been Annoyed or Angry because of others' concern about your drinking or drug use?
G —felt Guilty about the consequences of your drinking or drug use?
E —had a drink or used a drug in the morning (as an "Eye-opener") to decrease hangover or withdrawal symptoms?

Clinical features of opioid dependence. We do not know which opioid misuse behaviour most reliably predicts opioid dependence (Tables 3,³⁰ 4, and 5).³⁰ Some behaviour, such as injecting or crushing tablets and buying opioids on the street, is probably more predictive than other behaviour.²⁰ Such behaviour tends to be hidden from physicians.

Opioid misuse can be grouped into several categories: unsanctioned use (running out early, bingeing); altering the route of delivery (injecting, crushing tablets);

Table 3. Behaviour suggesting opioid dependence

BEHAVIOUR LESS SUGGESTIVE OF DEPENDENCE
Hoarding drugs during periods of reduced symptoms
Acquisition of similar drugs from other medical sources
Aggressive complaining about the need for higher doses
Unapproved use of the drug to treat another symptom
One or two unsanctioned dose escalations
Requesting specific drugs
Reporting psychiatric effects not intended by the physician
BEHAVIOUR MORE SUGGESTIVE OF DEPENDENCE
Selling prescription drugs
Prescription forgery
Concurrent abuse of related illicit drugs
Recurrent losses of prescriptions
Many unsanctioned dose escalations
Stealing or borrowing drugs from others
Obtaining prescription drugs from nonmedical sources
Injecting oral formulations

Data from Passik et al.³⁰

Table 4. Additional clinical features of opioid dependence

Taking a high dose or a rapidly escalating dose despite stable pain condition
Past or strong family history of addiction
Only one type of opioid works
Deteriorating or poor social functioning
Binging on opioids
Reporting opioid withdrawal symptoms
Acknowledging being addicted
Currently addicted to other drugs (cocaine, benzodiazepines, cannabis, etc)
Underlying mood or anxiety disorders not responsive to treatment
Inconsistent urine drug screen results
Concern expressed by family members

accessing opioids from other sources (friends, the street, other doctors); drug-seeking behaviour (anger, harassing office staff for fit-in appointments); and reluctance to use other methods of pain management. This behaviour stems from opioid-dependent patients' need to overcome opioid tolerance, achieve desired psychoactive effects, and relieve withdrawal symptoms.

If asked, opioid-dependent patients might say that they experience withdrawal symptoms at the end of a dosing interval. They might even acknowledge that, although they use the drug for pain, they are also addicted to it. They typically experience depression, anxiety, and social isolation and often have a current, past,

Table 5. Clinical features of pain patients with and without addictions

FEATURES	NON-ADDICTED PATIENTS	ADDICTED PATIENTS
Development of tolerance to desired effect	Very slow	Very fast
Pattern of use	Scheduled	Binge
Route of administration	Oral	Oral, intravenous, or snorting
Dose	Steady and moderate for underlying pain condition	Escalating and high for underlying pain condition
Withdrawal symptoms	Infrequent, mild	Frequent, severe
Source	Family doctor	Family doctor, other doctors, or the street
Current and past history of addiction	Sometimes	Often

or strong family history of addiction.

It is sometimes difficult to distinguish patients with opioid dependence from patients with pain disorder, also known as chronic pain syndrome. Patients with pain disorder often describe their pain in dramatic terms, are prescribed high doses of opioids, focus on medications, and are depressed and socially isolated. They differ from opioid-dependent patients in that they are not usually seeking a psychoactive effect from their opioids, do not have a strong personal or family history of addiction, and generally comply with their medication schedules.

Urine testing. Physicians who regularly prescribe opioids for chronic pain should be skilled in ordering and interpreting the results of urine tests. Such drug tests can help to identify noncompliance, opioid diversion, and concurrent drug abuse (Table 6 and 7). One study showed that 21% of chronic pain patients without any evidence of drug-seeking behaviour had unauthorized drugs in their urine.^{31,32}

Assessment of suspected opioid misuse or dependence. Physicians should take a complete history of substance use and carefully inquire about mood and occupational and family functioning. Urine should be tested, and records from previous care providers should be requested. Physicians should enquire about binge use, psychoactive effects, use from other sources, withdrawal symptoms, and other features of dependence. Spouses should be interviewed, if feasible, as they will notice features of dependence long before physicians do.

Management

Physicians should manage opioid dependence as they would any other medical condition, without

defensiveness, avoidance, or anger (Table 8). Physicians can anticipate varying degrees of resistance from patients and must be comfortable with setting boundaries and saying “no.”

Management strategies described below allow patients with chronic pain to receive opioids under controlled conditions based on their level of risk of addiction. The category “suspected opioid misuse or dependence” recognizes the difficulty in diagnosing opioid dependence in patients who will not disclose their true symptoms or behaviour.

Table 6. Urine testing for drugs

INDICATIONS
<ul style="list-style-type: none"> • Baseline testing for high-risk patients • Regular testing when opioid misuse is suspected
BEFORE THE TEST
<ul style="list-style-type: none"> • Inform patients about the test • Take a careful history of medication use during the past week • Order testing for a specific drug or drug class on the laboratory requisition
TESTS DONE
<ul style="list-style-type: none"> • Laboratory will do an immunoassay if physician orders tests on a class of drugs, such as opioids and benzodiazepines • Laboratory will do chromatography if physician orders tests on specific drugs, such as oxycodone
DETECTION TIME
<ul style="list-style-type: none"> • Up to 5 days for immunoassay • 1-2 days for chromatography
LIMITATIONS
<ul style="list-style-type: none"> • Immunoassay does not distinguish between different opioids; produces false-positive results if patients have ingested poppy seeds or quinolone antibiotics; and often misses oxycodone, methadone, and fentanyl • Chromatography detects morphine when codeine has metabolized to codeine and morphine, and produces false-negative results (although it is more accurate than immunoassay)

Patients at high risk of opioid dependence. Patients with a history or strong family history of addiction should be asked to sign specific treatment agreements and should be monitored regularly with urine tests. Physicians should avoid prescribing opioids (such as oxycodone and hydromorphone) with a higher potential for abuse. Doses well below 300 mg/d of morphine (or equivalent) should be adequate in almost all cases. Particularly at the beginning of therapy, physicians should prescribe small doses and schedule frequent follow-up visits, and patients should bring their medications in for pill or patch counting. The approach taken with these patients is similar to that described below for opioid misusers (structured opioid therapy), but might not be as stringent depending on patients’ degree of risk.

Currently dependent on nonopioid drugs. Opioids are, in most cases, contraindicated in patients currently addicted to other drugs. Alcohol, benzodiazepines, and opioids are a dangerous combination. Cocaine users sometimes sell their opioids to pay for cocaine. Actively addicted patients should be referred for formal addiction treatment.

Suspected opioid misuse or dependence. Several experts in the field (level III evidence) have suggested a time-limited trial of structured opioid therapy for patients suspected of opioid misuse or dependence who have pain that warrants opioid treatment.^{11,27,33} If the trial fails, options include an integrated pain and addiction treatment program,³⁴ if available, or treatment with methadone or buprenorphine.

Structured opioid therapy. A trial of structured opioid therapy is indicated for chronic pain patients suspected of opioid misuse who are not currently addicted to other substances, do not acquire opioids from other sources,

Table 7. Interpretation of urine drug-screening results among patients receiving oxycodone

RESULT	LIKELY INTERPRETATION	ACTION
Immunoassay negative for opioids	Immunoassay often misses oxycodone	Request testing for oxycodone specifically, and laboratory will do chromatography
Immunoassay positive for opioids	Could indicate oxycodone, another opioid, poppy seeds, or quinolone antibiotics	Request testing for oxycodone specifically, and laboratory will do chromatography
Chromatography positive for oxycodone	Expected result	
Chromatography positive for oxycodone and morphine	Patient has taken codeine, morphine, or heroin in addition to oxycodone	Assess patient for opioid misuse
Chromatography negative for oxycodone	Patient has not taken oxycodone in the past 1-2 days	Before testing, take a history of recent oxycodone use. Patient might have missed 1-2 days for an innocent reason. Assess patient for non-compliance and diversion
Immunoassay or chromatography positive for cocaine	Patient has used cocaine in the last few days	Patient might be addicted to cocaine. Consider referral for opioid agonist treatment

Table 8. Management of suspected opioid misuse or dependence

TYPE OF PATIENT	MANAGEMENT
At high risk of opioid misuse (has past or strong family history)	Use opioids after an adequate trial of nonopioid treatment Prescribe small amounts and do pill counts Carry out regular urine testing Avoid opioids with high potential for abuse Keep dose below 300 mg/d of morphine (or equivalent)
Currently addicted to nonopioid drugs	Opioids are usually contraindicated; refer for formal treatment
Suspected of opioid misuse and <ul style="list-style-type: none"> • has organic pain, • gets opioids only from family physician, • takes opioids only orally (no injecting or crushing tablets), and • has no current addiction to cocaine, alcohol, or other drugs 	Trial of structured opioid therapy involving: <ul style="list-style-type: none"> • frequent dispensing (daily, alternate days, twice weekly), • regular urine testing (1-4 times monthly), • pill or patch counts, • switching patient to sustained-release preparations, • avoiding parenteral use and short-acting agents, • being cautious with patient's current opioid or with oxycodone or hydromorphone, and • tapering if dose is higher than 300 mg/d of morphine (or equivalent)
Suspected of opioid misuse and <ul style="list-style-type: none"> • structured opioid trial fails, • patient is not eligible for structured opioid trial (injecting or crushing tablets, addicted to other drugs, acquiring opioids from other sources), or • patient meets criteria for opioid dependence 	Methadone or buprenorphine treatment consisting of: <ul style="list-style-type: none"> • daily supervised dispensing, • gradual introduction of take-home doses, • frequent urine drug screens, and • counseling and medical care

and do not inject or crush opioid tablets. Patients should be asked to sign revised treatment agreements that specify the type and dose of opioid, the frequency of dispensing and of urine tests, and other components of care. Opioids should be dispensed daily, weekly, or biweekly for patients who frequently run out early. Urine testing should be obtained as often as weekly, depending on patients' patterns of misuse and the reliability of their self-reports. Pill and patch counting should be done routinely.


Patients suspected of abusing a specific opioid should, in general, be switched to a different opioid. Oxycodone and hydromorphone should be used with caution. Tapering is indicated if the opioid dose is well above 300 mg/d of morphine. Tapering can improve patients' mood and pain³⁵ because the cycle of intoxication and withdrawal is less extreme once they have been stabilized at a lower dose. Tapering should be done with scheduled doses of controlled-release opioids, if possible. A suggested tapering schedule involves reductions of 10% every 2 to 4 weeks, slowing to reductions of 5% once a dose of one third of the initial dose is reached.³⁶ The end point of successful tapering is either abstinence or a moderate scheduled dose that provides effective analgesia with minimal withdrawal symptoms. Patients who remain noncompliant with the trial after 1 to 3 months should be referred for opioid agonist treatment.

Opioid agonist treatment. Treatment with methadone or buprenorphine is indicated for patients who have failed a trial of structured opioid therapy or were

ineligible for such a trial because they injected drugs, acquired opioids from other sources, or had active addiction. Patients receiving opioid agonist treatment must meet the criteria for opioid dependence.

Opioid agonist treatment consists of daily supervised dosing, gradual introduction of take-home doses, frequent urine tests, and medical follow up and counseling. Methadone is an oral opioid with a slow onset and long duration of action. In appropriate doses it relieves symptoms of withdrawal and cravings for 24 hours without inducing sedation or euphoria. Methadone maintenance is highly effective in reducing drug use and its consequences (level I evidence).³⁷⁻⁴¹ Buprenorphine, soon to be available in Canada as Subutex® and Suboxone®, is a sublingual partial opioid agonist. Buprenorphine has level I evidence of effectiveness^{42,43} and can be prescribed safely and effectively by primary care physicians.⁴⁴⁻⁴⁷ While buprenorphine might be less effective than high doses of methadone, it can be titrated more quickly and has a lower risk of overdose.^{48,49}

Conclusion

Opioid misuse and dependence can be detected through careful assessment of patients, vigilance for opioid misuse, and urine testing. If opioid misuse or dependence is suspected, physicians could consider a trial of structured opioid therapy provided patients are not injecting opioids, crushing opioid tablets, or acquiring opioids from other sources. If the trial fails or is not indicated, patients should be referred for opioid agonist treatment with methadone or buprenorphine. 

Competing interests

Dr Gourlay has received honoraria from Ligand Pharmaceuticals, Janssen-Ortho, Purdue Pharma, and Cephalon.

Correspondence to: Dr Meldon Kahan, Centre for Addiction and Mental Health, 33 Russell St, Toronto, ON M5S 2S1; telephone 416 535-8501, extension 6019; fax 416 530-6160; e-mail meldon_kahan@camh.net or kahanm@stjoe.on.ca

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EDITOR'S KEY POINTS

- Family doctors are in the difficult position of trying to address legitimate needs for pain control and concerns about patients misusing opioids.
- The exact prevalence of opioid misuse in primary care is unknown, but misuse appears to be increasing as reflected in the increasing number of emergency department visits related to drug abuse.
- Risk factors for opioid misuse include younger age; current, past, or family history of substance abuse; concurrent psychiatric disorders; and childhood sexual abuse.
- Managing patients at higher risk for misuse includes insisting on treatment contracts, structured prescribing, and urine testing, and when these fail, referring patients for methadone or buprenorphine treatment.

POINTS DE REPÈRE DU RÉDACTEUR

- Les médecins de famille vivent le dilemme de répondre à des besoins légitimes de contrôle de la douleur et à des préoccupations entourant l'usage abusif d'opiacés par leurs patients.
- La prévalence exacte de l'usage abusif d'opiacés en soins de première ligne n'est pas connue, mais elle semble à la hausse si on en juge par le nombre accru de visites à l'urgence reliées à la toxicomanie.
- Au nombre des facteurs de risque d'usage abusif d'opiacés figurent un plus jeune âge, des antécédents familiaux ou des problèmes passés ou présents de toxicomanie, des troubles psychiatriques simultanés et des abus sexuels durant l'enfance.
- La prise en charge des patients à risque plus élevé d'usage abusif comporte l'insistance sur un contrat de traitement, des ordonnances structurées et des analyses d'urine. En cas d'échec, il faut recommander un traitement à la méthadone ou à la buprénorphine.

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