INTRODUCTION

Increased opioid prescribing for the management of chronic noncancer pain has been accompanied by an increase in opioid abuse. A 2007 US government survey found that 14 percent of adults engaged in nonmedical use of pain relievers during their lifetime, including nearly 2 percent who reported inappropriate use of oxycodone. These data reflect abuse rates among individuals who were prescribed analgesic medications legitimately and those who obtained them illegitimately. Given widespread abuse, it is not surprising that many primary care physicians are concerned about the risk of opioid abuse and lack confidence in how to minimize that risk. For example, it has been shown that implementation of a urine drug monitoring protocol may decrease the rate of substance abuse in opioid-treated patients by 50 percent, yet the majority of physicians who prescribe opioids do not routinely conduct urine drug monitoring, and most prescribers have difficulty interpreting urine drug monitoring results accurately.

For prescribers, potential strategies to reduce prescription opioid abuse include implementation of the recommendations of clinical guidelines on the use of opioids; appropriate use of formulations.
designed with impediments to abuse; and compliance with legislative and regulatory measures addressing prescription drug abuse, such as the US Food and Drug Administration (FDA) long-acting opioid Risk Evaluation and Mitigation Strategies (ERLA opioid REMS),\(^\text{10}\) Washington State Guidelines on Opioid Dosing,\(^\text{11}\) and the Florida State Law on Controlled Substance Prescribing.\(^\text{12}\) We compiled a list of nine distinct strategies for minimizing abuse and responding to aberrant drug-related behaviors:

1. conducting a thorough patient assessment (history and physical);
2. assessment of the risk for substance abuse;
3. use of controlled-substance agreements;
4. selection of an appropriate opioid and careful dose titration;
5. observance of an opioid dose ceiling for most patients;
6. use of formulations designed with impediments to tampering;
7. compliance monitoring (eg, pill counts and urine screening);
8. adherence to practice guidelines; and
9. compliance with regulatory and legal measures.

Given the prevalence of opioid prescribing and opioid abuse, it is important to determine whether the effectiveness of these recommended strategies is substantiated by clinical outcomes research. We performed a systematic review to identify and grade the level of evidence of data in support of potential strategies for minimizing abuse potential and responding to aberrant drug-related behaviors in opioid-treated patients.

**SEARCH METHODS**

**Strategy**

Searches of PubMed under nine general headings (detailed below) related to minimizing opioid abuse risk and addressing aberrant drug-related behavior were performed on January 18, 2013, for English language clinical trials and practice guidelines published in the past 5 years. Results obtained were reviewed to identify citations relevant to assessing the effectiveness of strategies for minimizing abuse risk and addressing aberrant drug-related behavior. We consulted current pain society guidelines from the United States and Canada on opioid therapy for chronic noncancer pain, which summarizes thorough literature reviews on these topics, and we also reviewed the literature to identify articles published more than 5 years ago.\(^\text{6,7}\)

**Individual searches**

Search 1, regarding patient assessment, used the search terms, “initial examination OR initial screening OR baseline screening OR initial medical assessment OR medical history AND (opioid OR buprenorphine OR codeine OR fentanyl OR hydrocodone OR hydromorphone OR morphine OR oxymorphone) AND (abuse OR addict OR misuse OR dependence OR overdose OR death OR fatal).” This search identified 74 citations, of which eight were found to be relevant.

Search 2, regarding risk assessment, used the search terms, “current opioid misuse measure OR opioid risk tool OR screener and opioid assessment for patients with pain revised OR SOAPP-R OR risk assessment tools OR risk of abuse AND (opioid OR buprenorphine OR codeine OR fentanyl OR hydrocodone OR hydromorphone OR morphine OR oxymorphone) AND (abuse OR addict OR misuse OR dependence OR overdose OR death OR fatal).” This search identified 122 citations, of which eight were found to be relevant.

Search 3, regarding controlled-substance agreements, used the search terms, “contract OR agreement AND (controlled substance OR opioid OR buprenorphine OR codeine OR fentanyl OR hydrocodone OR hydromorphone OR morphine OR oxymorphone) AND (abuse OR addict OR misuse OR dependence OR overdose OR death OR fatal).” This search identified 31 citations, of which three were found to be relevant.

Search 4, regarding dose titration, used the search terms, “dose escalation OR dose titration OR increasing dose AND (opioid OR buprenorphine OR codeine OR fentanyl OR hydrocodone OR hydromorphone OR morphine OR oxymorphone) AND (abuse OR addict OR misuse OR dependence OR overdose OR death OR fatal).” This search identified 34 citations, of which one was found to be relevant.
Search 5, regarding dose ceiling, used the search terms, “opioid AND high dose AND abuse” and identified 42 citations, of which five were found to be relevant upon manual review.

Search 6, regarding formulations designed with impediments to abuse, used the search terms, “abuse deterrent OR abuse resistant OR crush resistant OR tamper resistant OR opioid antagonist OR naloxone OR naltrexone OR aversive OR aversion OR niacin OR prodrug AND (opioid OR buprenorphine OR codeine OR fentanyl OR hydrocodone OR hydroxymorphine OR morphine OR oxycodone OR oxymorphone OR Acurex OR Embeda OR Remoxy OR Oxecta OR Egalet OR Suboxone OR TQ-1015 OR COL-003) AND (abuse OR addict OR misuse OR dependence OR overdose OR death OR fatal).” This search identified 604 citations, of which six were found to be relevant upon manual review.

Search 7, regarding compliance monitoring, used the search terms, “urine testing OR urine screening OR urine toxicology OR urine analysis OR urinalysis AND (opioid) AND (abuse OR addict OR misuse OR dependence OR overdose OR death OR fatal).” This search identified 115 references, of which 12 were found to be relevant.

Search 8, regarding compliance with clinical guidelines, used the search terms, “treatment guidelines OR practice guidelines OR guideline adherence OR protocol adherence OR guidance AND (opioid OR buprenorphine OR codeine OR fentanyl OR hydrocodone OR hydroxymorphine OR morphine OR oxymorphine OR oxycodone OR oxymorphone OR Acurex OR Embeda OR Remoxy OR Oxyxalta OR Egalet OR Suboxone OR TQ-1015 OR COL-003) AND (abuse OR addict OR misuse OR dependence OR overdose OR death OR fatal).” This search identified 44 references, of which two were found to be relevant.

Search 9, regarding legal and regulatory measures, used the search terms, “legislation OR law OR regulation OR regulatory OR prosecution OR penalty OR ‘risk evaluation and mitigation’ OR ERLA opioid REMS AND (opioid OR buprenorphine OR codeine OR fentanyl OR hydrocodone OR hydroxymorphine OR morphine OR oxymorphine) AND (abuse OR addict OR misuse OR dependence OR overdose OR death OR fatal).” This search identified 111 references, of which five were found to be relevant.

Levels of evidence

The articles identified using this search strategy were graded on a scale adapted from the Oxford Centre for Evidence-Based Medicine (CEBM) Levels of Evidence (Table 1). Articles with level 1 (strong) evidence include systematic reviews of randomized, controlled clinical trials (RCTs) and individual RCTs with a narrow confidence interval; level 2 (moderate to strong) evidence includes systematic reviews of cohort studies, individual cohort studies, and low-quality RCTs. Level 3 (weak to moderate) evidence includes systematic reviews of case-control studies and individual case control studies, and level 4 (weak; incorporating CEBM levels 4 and 5) evidence includes case series and expert opinion without an explicit critical appraisal, or statements based on physiology, bench research, or first principles.

Table 1. Levels of evidence

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Type of evidence</th>
<th>Quality designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SR of RCTS</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>RCT with narrow CI</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>SR of cohort studies</td>
<td>Moderate to strong</td>
</tr>
<tr>
<td></td>
<td>Cohort study</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low-quality RCT</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>SR of case control studies</td>
<td>Weak to moderate</td>
</tr>
<tr>
<td></td>
<td>Case control study</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Case series</td>
<td>Weak</td>
</tr>
<tr>
<td></td>
<td>Bench research</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Expert opinion</td>
<td></td>
</tr>
</tbody>
</table>

*Level 4 included Oxford Center for Evidence-Based Medicine levels 4 and 5. CI, confidence interval; RCT, randomized controlled trial; and SR, systematic review.

ABERRANT DRUG-RELATED BEHAVIOR DEFINED

Aberrant drug-related behaviors include any behavior that suggests nonmedical use of a drug and/or addiction. Common opioid-related aberrant drug-related behaviors typically fall within several categories, as summarized in Table 2. These categories include efforts to obtain opioids for misuse from sources other than the patient’s doctor. Research has shown that many patients steal or are given opioids by family members or friends with legitimate prescriptions and that opioids are also...
often diverted or stolen from pharmacies, medical practices, drugmakers, and addiction treatment centers. Patients may also attempt to obtain opioids by asking for frequent dosage increases or complaining of lost prescriptions. Evidence that a patient is not taking his prescribed opioid is also an aberrant drug-related behavior, potentially indicating that the patient is diverting the opioid.

### Strategies to Prevent and Identify Aberrant Drug-Related Behaviors

Our review of the literature evaluated nine basic strategies for preventing and identifying aberrant drug-related behaviors (Table 3). Levels of evidence for these strategies are presented below.

#### Patient Assessment

Guidelines published in the United States and Canada recommend a thorough medical history and physical examination to establish the pain diagnosis, assess general medical condition and psychiatric status, and prior history of abuse. These recommendations are based on weak to moderate evidence that the strongest risk factors for current abuse are a history of abuse and psychiatric conditions.

As noted in US guidelines, a well-established and documented diagnosis of pain is essential before initiating opioid therapy. Factors to consider include the cause and severity of pain, its effects on function and quality of life, and prior treatment with opioids or nonopioid analgesics. These considerations are part of the risk versus benefit assessment regarding therapeutic choices which may indicate that, on balance, opioid therapy may not be appropriate for a given patient.

Level 2 evidence suggests that patients with a history of substance abuse have a higher risk of current abuse and that the majority of opioid abusers also have a history of abusing nonopioid substances, such as alcohol, nicotine, and other legal and illegal drugs. Level 2 evidence suggests that it is important to identify psychiatric conditions known to be frequently comorbid with substance abuse, such as depression, anxiety, bipolar disorder, and posttraumatic stress disorder. Several personality disorders (PDs) have also been associated with risk of substance abuse, including conduct disorder in adolescence, schizotypal PD, passive-aggressive PD, and borderline PD. Level 2 evidence also suggests that a history of physical or sexual abuse is associated with an increased risk of substance abuse, and that individuals who have contemplated or attempted suicide are also at increased risk.

In a study of 1,408 patients treated for opioid...
abuse, two thirds of women and a little more than half of men had been treated for a psychiatric disorder (e.g., depression, anxiety, and bipolar disorder) within the prior 12 months. Depression, anxiety disorders, and bipolar disorder are among the psychiatric diagnoses that may be neglected in the primary care setting, which means that abuse risk in the subset of these patients for whom opioids may be indicated may be underestimated.

**Reassessment of risk during treatment.**
Guidelines for safe, effective opioid use recommend that regular reassessments should be conducted to identify evidence of behavioral or physical changes that may result from therapy, but again, this recommendation is supported by weak evidence. Aberrant drug-related behaviors such as those outlined in Table 2 may emerge with continued treatment, and persistent use and/or withdrawal symptoms may mean that the patient has become dependent on their opioid. Level 4 evidence suggests that clinicians should also regularly reassess the painful condition and document findings. Requests for increased opioid doses may reflect drug seeking, but it may also signal an increase in pain due to progression of the painful condition. Inadequate pain relief can precipitate behaviors described earlier: requests for more medication, attempts to obtain medication from other sources, taking doses higher than those prescribed and then running out. As stated earlier, level 4 evidence suggests that abuse risk changes over time, making repeat assessments an appropriate precaution, although the value of reassessment for preventing aberrant drug-related behaviors has not been demonstrated.

**Risk assessment**

**Assessment at initiation of opioid therapy.**
There are currently several validated screening tools for assessment of pretreatment opioid abuse risk, including the Current Opioid Misuse Measure (COMM), Opioid Risk Tool (ORT), Screener and Opioid Assessment for Patients with Pain–Revised (SOAPP-R), and Prescription Drug Use Questionnaire. However, as stated in US and Canadian guidelines, only weak evidence supports the utility of these instruments for identifying patients at risk of opioid abuse. Level 2 evidence suggests that risk factors included in screening tools vary between populations in ways that the screening tools do not pick up. For example, in a survey of older patients (n = 163) with chronic pain (level 2 evidence), risk factors for abuse included higher pain severity, lower

### Table 3. Identifying and preventing aberrant drug-related behaviors

<table>
<thead>
<tr>
<th>Risk-reduction strategy</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient assessment</strong></td>
<td></td>
</tr>
<tr>
<td>Medical history and examination to determine legitimate analgesic needs prior to treatment</td>
<td>2</td>
</tr>
<tr>
<td>Assessment for psychiatric comorbidity</td>
<td>2</td>
</tr>
<tr>
<td>Reassessment of analgesic needs and psychiatric comorbidities during treatment</td>
<td>4</td>
</tr>
<tr>
<td><strong>Assessment of abuse risk</strong></td>
<td></td>
</tr>
<tr>
<td>Validated screening tools (COMM, SOAPP-R, and ORT) to identify current or past drug abuse or heightened risk of abuse</td>
<td>4</td>
</tr>
<tr>
<td><strong>Treatment agreement/contract</strong></td>
<td></td>
</tr>
<tr>
<td>Define appropriate opioid use</td>
<td>Lack of evidence</td>
</tr>
<tr>
<td>Establish compliance monitoring protocols</td>
<td>Lack of evidence</td>
</tr>
<tr>
<td>Agree on steps to be taken in response to signs of opioid misuse</td>
<td>Lack of evidence</td>
</tr>
<tr>
<td><strong>Opioid selection and titration</strong></td>
<td></td>
</tr>
<tr>
<td>Start with low-potency opioids</td>
<td>2-3</td>
</tr>
<tr>
<td>Use long-acting formulations</td>
<td>4</td>
</tr>
<tr>
<td>Start with a low dose and titrate slowly</td>
<td>4</td>
</tr>
<tr>
<td>Observe a dose ceiling for most patients</td>
<td>1-2</td>
</tr>
<tr>
<td>Use tamper-resistant opioid formulations</td>
<td>1-4</td>
</tr>
<tr>
<td><strong>Compliance monitoring, including</strong></td>
<td></td>
</tr>
<tr>
<td>Urine drug screening</td>
<td>2-4</td>
</tr>
<tr>
<td>Pill and patch counts</td>
<td>2-4</td>
</tr>
<tr>
<td>Feedback from pharmacies or caregivers</td>
<td>2-4</td>
</tr>
<tr>
<td>Continuous physician-patient communication</td>
<td>2-4</td>
</tr>
<tr>
<td>Adherence with treatment guidelines</td>
<td>Lack of evidence</td>
</tr>
<tr>
<td>Compliance with regulatory and legal measures</td>
<td>Lack of evidence</td>
</tr>
</tbody>
</table>

COMM, Current Opioid Misuse Measure; ORT, Opioid Risk Tool; and SOAPP-R, Screener and Opioid Assessment for Patients with Pain–Revised.
disability scores, and depression. Problems with alcohol were not associated with increased risk. Risk factors such as alcohol are included in screening tools such as the SOAPP-R and ORT, but variability of risk according to age is not addressed in these assessments.6

Level 2 evidence suggests that there are also sex-specific factors that modify the importance of specific risk factors addressed in available screening tools. In an analysis of 29,906 patient assessments at 220 addiction treatment centers (level 2 evidence), men were more likely than women to abuse opioids at age ≥54 years; be manual laborers; have a history of incarceration; drink to intoxication >3 times weekly; or use marijuana, heroin, hallucinogens, or more than one substance. Women were more likely than men to live with children; be professionals or in management; use benzodiazepines or amphetamines; have medical or psychiatric problems; or have a history of suicide attempts, depression, anxiety, or emotional, physical, or sexual abuse.22 As with age, assessment tools such as the COMM or SOAPP-R do not capture sex-related differences for specific risk factors.

Level 4 evidence suggests that additional risk factors such as legal problems, a history of victimization, mental and physical health status, and geographic location are risk factors that are not captured in standard screeners and may be subject to change over time.35 Level 4 evidence also suggests that a majority of clinicians will comply with implementation of a uniform protocol for assessing abuse risk at the beginning of treatment, provided that the assessment tools are concise, are clinically relevant, and suit the time constraints of practice.42

Controlled-substance agreements

United States guidelines7,9,40 fall short of recommending a controlled-substance agreement. However, they do cite level 4 evidence (expert opinion) that a controlled-substance agreement may help clarify the treatment plan with the patient, patient’s family, and other clinicians involved in the patient’s care. Level 4 evidence suggests that controlled-substance agreements may contain stipulations that patients may only get opioids from one pharmacy and fill prescriptions at one pharmacy, more frequent prescribing of smaller amounts of opioids, compliance monitoring protocols, and a list of aberrant drug-related behaviors that may prompt discontinuation of therapy. Canadian guidelines recommend that physicians and patients should enter into a controlled-substance agreement, citing weak evidence from several small trials but no randomized controlled trials. Level 1 evidence suggests that clinicians instructed in the use of controlled-substance agreements will use them15 and that identification of aberrant drug-related behaviors may lead to discontinuation of the agreement.39,43 However, evidence is lacking that these agreements reduce the frequency of aberrant drug-related behavior.

Level 2 evidence from a survey of 84 physician/patient pairs found that most clinicians entered into controlled-substance agreements with only a minority of their patients who were prescribed opioids, and that physicians were more likely to do so if the patient was considered to be at high risk of substance abuse. Approximately 40 percent of patients whose physicians reported they had a controlled-substance agreement in place reported that they were unaware of it; roughly one third of patients reported uncertainty about having a controlled-substance agreement in place regardless of whether their physician reported that one was in place.44 Hence, the value of these agreements may be limited by a lack of communication and consistency in their use.

Initial opioid selection and dose titration

First-line opioids. Canadian guidelines suggest that opioid therapy should start with a lower potency opioid, such as codeine or tramadol, which have been shown in some studies to have lower attractiveness for abuse and lower rates of abuse relative to the frequency with which they are prescribed compared with oxycodone, hydromorphone, and hydrocodone (level 2-3 evidence).6 United States guidelines say little about individual selection of opioids.7,9 In the United States, hydrocodone is both the most commonly prescribed first-line opioid and the most commonly abused opioid; however, it should be noted that although the total quantity of hydrocodone abused is large compared with other opioids, the proportion of all hydrocodone prescriptions that are diverted to abuse is low (level 2 evidence).45

High potency opioids. When low potency opioids prove ineffective, Canadian guidelines recommend a trial of a high-potency opioid, such as morphine, hydromorphone, oxycodone, or oxymorphone.6 The Canadian guidelines cite level 2 evidence that oxycodone, hydromorphone, and
perhaps hydrocodone have greater abuse liability compared with morphine, based on data from a large US population health surveillance database. They also cite level 1 evidence that oxycodone has more positive subjective effects compared with equianalgesic doses of morphine and level 2 evidence that oxycodone, hydromorphone, and hydrocodone have similar abuse liability.6

United States guidelines state that there is insufficient evidence to prefer the use of a long-acting formulation over a short-acting formulation for chronic pain on the basis of efficacy or safety considerations.7,9 However, Canadian guidelines recommend that older patients be prescribed long-acting opioids for reasons of treatment compliance and because these have more stable pharmacokinetics and pharmacodynamics, citing only level 4 evidence (expert opinion).6 With respect to mitigating the risk of opioid abuse, it must be remembered that extended-release (ER) formulations contain larger amounts of opioid compared with immediate-release (IR) formulations, potentially making them attractive for abusers who tamper with tablets by crushing them to accelerate oral release or facilitate intranasal use, or by dissolving them in a liquid to create a solution for intravenous abuse.46

**Dose titration.** Guidelines recommend that opioid treatment should begin as a time-limited trial with a small initial dose that is titrated slowly. Canadian guidelines recommend initial dosages equivalent to 5-10 mg of morphine four times daily, with incremental increases of 5-10 mg/wk. The preferred dose will result in a ≥2-point reduction in subjective pain rating on a 10-point scale and/or a similar improvement in function.

Level 4 evidence suggests that this method of slow, gradual titration might prevent administration of unnecessarily high opioid doses.6 During titration, opioids should be prescribed in small amounts (eg, weekly rather than monthly) to allow the clinicians to gauge response with each increase and watch for signs of aberrant drug-related behavior.47

Although this is intuitive, a single 135-patient study of veterans prescribed opioids for chronic pain found no difference in the occurrence of aberrant drug-related behaviors between patients held on a stable dose and those using a more liberal dose-escalation strategy (level 1 evidence).48 The present literature search found no published data supporting the value of slow, gradual titration as a means of preventing misuse.

### Dose ceiling

Both 2009 US7 and 2011 Canadian6 guidelines state that doses above a morphine-equivalent (MED) 200 mg/d are considered high, with the Canadian guidelines surpassing the US guidelines by stating that the 200-mg MED should be the ceiling dose for most patients. Subsequent guidelines published in 2012 by the American Society of Interventional Pain Physicians (ASIPP) state that daily MED doses >90 mg are to be considered high.49 MED conversions for available opioids can be calculated using several online resources, including the Practical Pain Management Opioid Calculator,50 the GlobalRPh calculator,51 and the Johns Hopkins Opioid Conversion Program calculator.52

A systematic review (level 2 evidence) of 62 trials of high-potency opioids presented in the most recent Canadian guidelines found that for most patients, the preferred dose was well below 200-mg/d MED.6 Doses above 200 mg/d are considered high-dose therapy in both US7 and Canadian6 guidelines for the use of opioids. The Canadian guidelines recommend careful reassessment of patients approaching this “watchful dose.”47 As stated, the most recent US guidelines set the threshold for high-dose therapy much lower, at >90 mg/d MED.49

This is consistent with level 1 evidence that higher doses have been associated with an increased risk of overdose and mortality.53-56 In response to this increase, the state of Washington imposed a 120-mg/d MED ceiling on opioid prescriptions.11 Level 2 evidence demonstrated that imposition of this ceiling was accompanied by a 50 percent reduction opioid-related mortality in the state.57

### Formulations designed with impediments to abuse

Patients who abuse ER opioids may manipulate them to accelerate opioid release from ingestion (eg, by chewing) or to alter the route of delivery to increase the rate of release from the tablet, which typically involves crushing of the tablet for insufflation or dissolving it in a solvent for intravenous use (level 3 evidence).46 Rapid onset of effect is an important factor increasing the attractiveness of an opioid for abuse (level 3 evidence).58 Increasingly, ER opioids are being reformulated to incorporate physical or chemical impediments to these types of
tampering (Table 4). Oxycodone CR,60 oxymorphone ER,61 and tapentadol ER are each formulated with hardened matrices designed to resist crushing and to turn into a viscous gel when immersed in fluids, making it difficult to either snort or inject the product. A formulation of oxycodone IR with potentially aversive ingredients is designed to cause mucosal irritation if the product is insufflated; however, the prescribing information does not disclose which ingredient(s) cause the aversive effects.62 Morphine ER with sequestered naltrexone is designed so that its opioid effects will be neutralized by naltrexone if it is crushed.63-65 This product was approved and then withdrawn from the market owing to issues related to the stability of the formulation.66 These formulations are not discussed in current guidelines, which were published before any of these formulations received clinical approval or had data supporting their value for preventing abuse. However, early evidence of level 1-4 quality suggests that these formulations may be less easily tampered with and therefore less attractive for abuse than older formulations.

The value of reformulated oxycodone CR, the first tamper-resistant formulation to reach the market, consists of a level 1 randomized, placebo-controlled trial67 and level 2 postmarketing data.60,68,69 In 19 healthy recreational drug users,68 reformulated oxycodone CR was associated with lower drug-liking scores compared with oxycodone IR. Oxycodone CR had to be administered at twice the dose to achieve drug-liking scores similar to oxycodone IR. Oxycodone CR and oxycodone IR produced similar drug-liking scores when the tamper-resistance mechanism was defeated by crushing the tablet.

An analysis of data from the National Addictions Vigilance Interventions and Prevention Program (NAVIPPRO) surveillance network on 140,496 patients entering substance abuse treatment found that oxycodone CR abuse declined by 30 percent during the 20 months after introduction of the reformulated tablet. Reductions in the proportion of oxycodone CR abusers who did so by smoking, insufflating, or injecting declined by approximately one-third to one half.68 However, during the period that abuse of oxycodone CR declined, the abuse of oxymorphone ER and buprenorphine increased, suggesting that prescription opioid abusers switched to products that were easier to abuse.68 Similarly, a survey of 2,566 opioid-dependent patients entering treatment facilities found that a decrease in oxycodone CR abuse after its reformulation was paralleled by an increase in abuse of prescription opioids not formulated to resist tampering and in abuse of heroin (level 2 evidence).70

Level 4 evidence, consisting of bench top laboratory experiments and expert opinion, supports the value of reformulated oxymorphone ER61 for deterring tampering. In laboratory experiments, oxymorphone ER tablets could not be crushed with professional pill crushers or a hammer and could not be successfully dissolved in a variety of solvents.61 In two studies enrolling experienced recreational drug abusers, participants attempted to crush or dissolve oxymorphone ER tablets using implements and solvents of their choice but were not allowed to consume any drug.71 Less than 10 percent of participants obtained particles they would be willing to snort, while efforts to dissolve the tablets yielded <2 percent of active drug in an injectable form. Seventy-two percent of participants stated they would pay less for reformulated oxymorphone ER compared with the previous oxymorphone ER tablet, and 28 percent stated they would pay nothing for it.71

The abuse liability of oxycodone IR with potentially aversive ingredients was evaluated in a randomized, controlled trial (level 1 evidence) in which 40 experienced recreational drug abusers attempted to crush

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Tamper-resistance strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>OxyContin® (oxycodone controlled release)</td>
<td>Matrix resists crushing</td>
</tr>
<tr>
<td>Opana® ER (oxymorphone extended release)</td>
<td>Forms a viscous gel on dissolution that is difficult to inject</td>
</tr>
<tr>
<td>Nucynta® ER (tapentadol extended release)</td>
<td>Sequestered antagonist is released if the product is crushed or dissolved, neutralizing opioid effects</td>
</tr>
<tr>
<td>Embeda® (morphine/naltrexone controlled release)</td>
<td>Aversive ingredients cause mucosal irritation if the product is crushed and abused intranasally</td>
</tr>
</tbody>
</table>

Table 4. Currently available opioids with tamper-resistant features59
oxycodone IR with aversive ingredients and conventional oxycodone IR tablets and then insufflate the tampered tablets. Subjects gave the oxycodone IR with aversive ingredients lower scores for drug liking and willingness to use it again compared with the standard oxycodone IR tablet. Subjects who attempted to insufflate the powder from the crushed oxycodone IR with aversive ingredients experienced nasal burning and discomfort, and more than 50 percent could not completely insufflate the entire contents of a tablet. Although not mentioned in this study, the inability to snort to the entire contents could be related partly to the mass of the 11-mm diameter oxycodone IR tablet with aversive ingredients compared with the common 6-mm diameter oxycodone IR tablets without aversive ingredients. Approximately 30 percent of subjects said they would not be willing to use oxycodone IR with aversive ingredients again, whereas only 5 percent stated they would not use oxycodone IR again.

Although not currently available, the potential abuse-deterrence of morphine ER with sequestered naltrexone is supported by level 1 evidence. In an RCT conducted in a controlled environment, experienced opioid abusers assigned lower drug liking scores and reported feeling less high after receiving intravenous morphine plus naltrexone compared with intravenous morphine without naltrexone. Conversely, a level 1 study of oxycodone combined with low-dose naltrexone was not associated with reduced abuse potential compared with oxycodone alone.

Collectively, it would appear that data support the potential for tamper-resistant opioids to have a meaningful positive effect on the problem of opioid abuse. However, the evidence also suggests that the introduction of tamper-resistant opioids has been followed by abusers switching to prescription opioids that are more easily abused, as well as potentially more dangerous substances, such as heroin. It would be speculative to consider whether requiring all opioids to have tamper-resistant formulations would substantially reduce opioid abuse or be accompanied by increased misuse of illegal opioids, which may be more dangerous.

Compliance monitoring

Urine screening is perhaps the most objective tool for monitoring and documenting treatment compliance (level 4 evidence). Other compliance monitoring tools include pill and patch counts, feedback from pharmacy and caregivers, prescription drug monitoring programs (PDMPs) established by US states, and regular physician-patient interaction as a means of follow-up, referral, and discharge.

United States guidelines published jointly by the American Pain Society and American Academy of Pain Medicine in 2009 reported that there is no reliable evidence to support the efficacy of any of these monitoring techniques for detecting, preventing, or modifying aberrant opioid-related behaviors. However, the subsequent ASIPP guidelines state that the evidence for compliance monitoring is good. The Canadian guidelines cite a prospective 100-subject study in which urine drug screening identified substance abuse in 16 percent of opioid-treated patients, and a subsequent study of the same population in which a monitoring protocol that combined urine screening with pill counts, treatment agreements, and patient education reduced substance abuse by 50 percent (level 1 evidence). Level 2 evidence suggests that urine screening will identify opioids in many patients with chronic pain and distinguish between overuse and underuse. However, a systematic review (level 1 evidence) determined that there is relatively weak evidence to support the usefulness of urine drug screening conducted in conjunction with a controlled-substance agreement for reducing the occurrence of opioid misuse. In other words, evidence is stronger that screening identifies misuse than that it prevents or modifies misuse.

Results from a survey of 99 physicians (level 2 evidence) indicated that the majority had a poor understanding of how to interpret urine drug screening results, but that a majority also felt confident about interpreting results; indeed, among male respondents there was an inverse relationship between competence and confidence in one’s interpretation skills. This suggests not only that physicians lack the expertise to conduct urine testing but also that many physicians lack self awareness that a knowledge gap exists. Recognizing the lack of guidelines for urine drug monitoring, an international panel convened to formulate recommendations about how to effectively monitor patients.

State-run PDMPs have been implemented to track patient prescriptions of opioids and other abusable substances, allowing physicians to monitor prior efforts to obtain opioids and prior use. In 2004, the US General Accounting Office noted (level 4 evidence) that the 15 PDMPs implemented as of 2002 differed in their purposes and methodologies, but that these programs appeared to deter diversion and
of patients). The screening protocol identified 47 percent of patients as having low risk, 52 percent moderate risk, and 1 percent high risk for opioid misuse. However, during the 4-month follow-up period, many patients with evidence of aberrant drug-related behaviors were improperly categorized as being low risk. These data suggest that clinicians may lack adequate understanding of how to interpret compliance-monitoring results or may not appreciate the relevance of abnormal findings to opioid abuse. For example, did the clinicians consider any recreational drug use (eg, urine positive for cocaine) to be aberrant drug-related behavior for a patient prescribed opioids for chronic pain and not exclusively misuse of opioids?

**Guideline recommendations on responding to aberrant drug-related behaviors.** Patients exhibiting signs of misuse or a high risk of abuse may be classified in 1 of 4 categories: 1) patients with a high risk of addiction (eg, history); 2) patients with suspected opioid misuse of intact tablets obtained from a physician, without addiction or abuse of other substances; 3) patients who are suspected of misusing opioids obtained from nonmedical sources, tampering with opioid tablets, and/or being addicted to or misusing other substances; and 4) patients with current opioid addiction (level 4 evidence). Responses to aberrant drug-related behaviors suggestive of abuse in patients in these categories are listed in Table 5.

United States and Canadian guidelines recommend that for patients assessed to have an elevated risk of addiction or misuse, prescribing precautions may include small quantities dispensed at short intervals, avoiding popular drugs of abuse, performing frequent urine testing and pill counts, and level 4 evidence suggests consideration of a tamper-resistant opioid. Guidelines cite weak-to-moderate evidence to recommend that patients with suspected opioid misuse should be administered opioids in a structured trial that includes avoidance of short-acting or parenteral formulations and even more frequent dispensing and monitoring; patients who fail a structured opioid trial, tamper with their opioid, are addicted to other substances, and/or acquire opioids from illegal sources may require referral to a specialty pain clinic for a structured trial of methadone or buprenorphine and formal addiction counseling; patients with current addiction to opioids or other legal or illegal drugs warrants

Compliance with pain management guidelines

**Does compliance with clinical guidelines mitigate risk of opioid abuse?** Although current US and Canadian guidelines include recommendations for a multimodal approach to pain management and the use of compliance monitoring (eg, urine toxicology), there have been few publications on the impact of these strategies on reducing the frequency of aberrant drug-related behaviors. A literature search for articles evaluating the effects of multimodal therapy on the risk of opioid abuse and the frequency of aberrant drug-related behaviors identified no articles. Level 3 evidence suggests that many clinicians do not routinely perform appropriate compliance monitoring in opioid-treated patients to assess whether the opioids are being taken as prescribed or to look for evidence of recreational drug use.

A 2011 study (level 1 evidence) of physicians treating 1,487 patients with moderate to severe chronic pain at 281 primary care treatment centers evaluated physician compliance with pain management guidelines through patient assessment and regular reassessment, controlled-substance agreements, validated risk-screening tools, and three compliance monitoring techniques: cards for obtaining/tracking prescriptions, pill counts, and urine drug screening. The investigators reported a rate of compliance of only 48 percent (64 percent of physicians complied with the protocol in 75 percent
discontinuation of opioid therapy, often accomplished with a trial of methadone or buprenorphine.\textsuperscript{6,7,14} Level 2 evidence suggests that the structured opioid trial may resolve aberrant drug-related behaviors in some patients. For example, a retrospective chart review examined outcomes in 195 patients exhibiting aberrant drug-related behaviors who were referred to a specialized “Opioid Renewal Clinic” for structured therapy that included frequent visits, heightened monitoring, adherence to a treatment agreement, opioids prescribed in small amounts, counseling, and education. At 1 year, 89 (45.6 percent) patients resolved their aberrant drug-related behaviors, whereas 106 (54.4 percent) were discharged from the program. Reasons for program discharge included persistence of aberrant drug-related behaviors and unwillingness to accept referral for addiction treatment (n = 61; 31.3 percent), acceptance of addiction treatment (n = 20; 10.2 percent), and inability to follow the structured protocol (n = 25; 12.8 percent).\textsuperscript{87} These results suggest that structured opioid therapy was useful for improving treatment compliance in patients identified to have aberrant drug-related behaviors and to identify patients whose risk of misuse was of such concern that opioid therapy was discontinued.

The value of methadone and buprenorphine for patients who are abusing or addicted to opioids has been documented and deserves discussion. Methadone is a pure opioid that has been around for decades and is considered effective as an analgesic (level 4 evidence)\textsuperscript{88} and for opioid detoxification (level 1 evidence).\textsuperscript{89} However, abuse of methadone can occur even with the strict supervision usually maintained in specialized clinics (eg, by taking several days’ dose at once or obtaining extra doses illegally), leading to a high rate of methadone overdose deaths (level 2 evidence).\textsuperscript{90}

Buprenorphine has proven effective as an analgesic in patients with chronic pain (level 1 evidence),\textsuperscript{91,92} and formulations combining buprenorphine with naloxone have shown reduced abuse liability compared with buprenorphine (level 1 evidence).\textsuperscript{93,94} Buprenorphine/naloxone has shown good efficacy for patients undergoing opioid detoxification (level 1 evidence).\textsuperscript{95-97} Of the two agents,
buprenorphine appears to be associated with more rapid resolution of withdrawal symptoms and a higher rate of complete opioid withdrawal, with less risk of abuse. In a survey of opioid abusers, buprenorphine was abused by approximately 20 percent of opioid abusers for whom it was prescribed, which is less frequent than the corresponding rate for methadone.

Legal and regulatory measures

The US FDA has mandated an ER and long-acting (LA) opioid analgesics risk evaluation and mitigation strategy (ERLA opioid REMS) to be funded and developed by pharmaceutical companies, which includes a medication guide for the opioid and patient education materials to be made available through prescribers. The impact of ERLA opioid REMS on opioid abuse risk has not been measured. However, an FDA advisory committee asked to comment on their value offered several criticisms (level 4 evidence). Committee members noted that medication guides are not likely to have a major impact on abuse rates because many drug companies already routinely offer medication guides and most physicians know the risks associated with opioids. Additional mandatory physician education is not required as part of an ERLA opioid REMS. It was observed that opioids are not abused primarily by people who obtain them via prescription, and that implementation of ERLA opioid REMS is unlikely to reduce abuse by individuals who obtain their opioid from a relative, friend, or other source. On the basis of these limitations, the advisory committee concluded that ERLA opioid REMS as currently conceived are unlikely to significantly reduce abuse. Recommendations for improving them included mandatory prescriber training, use of tamper-resistant prescription pads, and the development of prospective methods for obtaining data about opioid abuse.

Physician surveys (level 4 evidence) suggest that the ERLA opioid REMS may improve patient education and help reduce abuse but may also place demands on physicians that make them less likely to prescribe opioids. For example, in a survey of physicians who currently prescribe opioids (level 4 evidence), nearly half stated that they would discontinue prescribing a specific opioid if doing so meant they were required to provide patient education about it. Forty-four percent stated they would discontinue prescribing that same opioid if it meant they would be required to enroll in a 2-hour training session about it. These results suggest that imposition of even modest requirements on physicians may serve as more of a deterrent to legitimate prescribing than it would be to patient abuse.

In absence of federal prescribing regulations to curb abuse, individual US states have begun enacting legislation to restrict opioid prescribing. For example, Washington state has limited the allowable MED to ≤120 mg/d. Florida has passed legislation setting standards of practice for opioid prescribers and placing penalties, some of them criminal, on physicians and pharmacists who inappropriately prescribe opioids. Under the Florida law, law enforcement officials would be able to access prescribing records without a warrant. As with ERLA opioid REMS, it would seem possible that the proposed legal penalties might do more to limit willingness to prescribe opioids legitimately than to curb abuse and that abuse among individuals who do not obtain opioids by prescription would be unaffected. Level 2 evidence shows that the imposition of an opioid dose ceiling in Washington state was followed by a 50 percent reduction in opioid-related mortality. This decline in mortality was associated with more than a one-third reduction in the total number of opioid prescriptions.

CONCLUSIONS

Given the recognized growth in prescription opioid abuse, physicians prescribing opioids for legitimate chronic pain indications for which chronic opioid therapy may be an appropriate option need to prevent, detect, and manage aberrant drug-related behaviors that may indicate opioid misuse and abuse. Guidelines for the use of opioids state that minimizing the risk of opioid abuse requires clearly defined treatment plans and expectations about the course of treatment, careful opioid selection and titration, regular compliance monitoring, and a prespecified protocol for addressing signs of opioid misuse. Guidelines also state that use of a multimodal therapeutic approach that includes counseling, physical rehabilitation, relaxation techniques, and lifestyle modification may allow for reduced opioid consumption or opioid discontinuation for patients deemed to be at high risk of abusing their medication. The quality of evidence used...
to support previously published guideline recommendations is generally weak or moderate and has not been supported by additional high-level evidence since their publications. However, the cumulative weight of evidence suggests that routine monitoring during treatment, use of structured opioid therapy, and appropriate opioid selection may decrease the risk of abuse in patients requiring ongoing analgesia. Moreover, there is evidence to suggest that a lack of uniform methodologies with respect to patient assessment, use of controlled-substance agreements, and compliance monitoring may limit their effectiveness, leading to preliminary efforts to formalize abuse-risk management practices. However, there is modest evidence that efforts on the part of regulatory bodies and legislators to reduce risk may decrease physician willingness to prescribe opioids legitimately.

An important development since the publication of US and Canadian guidelines for the safe and effective use of opioids is the introduction of the first opioid formulations designed to be tamper-resistant. Initial epidemiology of abuse data suggests that abuse of specific opioid products declined after they were reformulated to resist certain types of tampering, but overall rates of opioid abuse have been unaffected with substance abusers simply selecting more easily abused alternative products. However, clinicians must be clear that these formulations will probably not deter abuse of intact tablets, and their use may actually have the unintended consequence of prompting a migration of abusers to other drugs and more dangerous substances, such as heroin.

Nevertheless, despite the limitations of current strategies for preventing opioid abuse, it is essential that clinicians use all available tools to prevent and detect aberrant drug-related behaviors during opioid therapy in the hope that their combination will prevent as much opioid abuse as possible. As regulators, legislators, and other interested parties consider implementing their own strategies to limit prescription opioid drug abuse, it will also be essential to ensure that their efforts do not compromise effective pain management and thereby increase suffering.

Given the risks associated with opioid abuse, the general lack of level 1 evidence supporting the use of risk-mitigation tools must be taken in the appropriate context. The Declaration of Helsinki states that clinical research in which a percentage of subjects are denied treatment (eg, a placebo group) should be reserved for conditions for which no proven therapy exists or situations in which denial of therapy will not lead to permanent or serious harm. With opioid therapy, the absence of data from randomized controlled trials assessing available strategies to prevent and identify aberrant drug-related behaviors is likely to persist because a control group cannot be ethically exposed to opioids without the best available precautions. Retrospective data collected from large populations of patients will have to be sufficient to support the use of available risk-mitigation strategies for patients facing the risks associated with exposure to highly abusable substances. Therefore, it is the position of the present paper that all patients seen in clinical practice be treated using these strategies because they are supported by common sense; they do not introduce new risks into treatment; and the likelihood of addiction, abuse, or other serious adverse outcomes would otherwise be too great.

ACKNOWLEDGMENTS

The authors thank Dr. Lynn Wilson, Associate Professor and Department Chair, Department of Family and Community Medicine, University of Toronto, Toronto, ON, Canada, who reviewed and helped provide direction for this manuscript. Editorial support for this manuscript was provided by Jeffrey Coleman, MA, and Robert Gatley, MD, of Complete HealthCare Communications, Inc. (Chadds Ford, PA), with funding from Endo Pharmaceuticals Inc. (Malvern, PA).

Conference presentations: This information was presented as a poster at the College on Problems of Drug Dependence, June 9-14, 2012, in Palm Springs, CA, and at the International Conference on Opioids, June 10-12, 2012, Boston, MA.

Charles E. Argoff, MD, Professor of Neurology, Albany Medical College, Albany, New York.
Meldon Kaban, MD, Associate Professor, Women’s College Hospital, University of Toronto, Toronto, Ontario, Canada.
Edward M. Sellers, MD, President and Principal, DL Global Partners, Toronto, Ontario, Canada.

REFERENCES


