Risk Factors for Opioid-Use Disorder and Overdose

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Opioid analgesics are recognized as a legitimate medical therapy for selected patients with severe chronic pain that does not respond to other therapies. However, opioids are associated with risks for patients and society that include misuse, abuse, diversion, addiction, and overdose deaths. Therapeutic success depends on proper candidate selection, assessment before administering opioid therapy, and close monitoring throughout the course of treatment. Risk assessment and prevention include knowledge of patient factors that may contribute to misuse, abuse, addiction, suicide, and respiratory depression. Risk factors for opioid misuse or addiction include past or current substance abuse, untreated psychiatric disorders, younger age, and social or family environments that encourage misuse. Opioid mortality prevalence is higher in people who are middle aged and have substance abuse and psychiatric comorbidities. Suicides are probably undercounted or frequently misclassified in reports of opioid-related poisoning deaths. Greater understanding and better assessment are needed of the risk associated with suicide risk in patients with pain. Clinical tools and an evolving evidence base are available to assist clinicians with identifying patients whose risk factors put them at risk for adverse outcomes with opioids. (Anesth Analg 2017;125:1741–8)

Opioids are recognized as necessary and legitimate agents to treat pain but are associated with significant risks to patients and society that include misuse, abuse, diversion, addiction, and overdose deaths. Deaths related to prescribed opioids (excluding nonmethadone synthetic opioids such as fentanyl and tramadol) exceeded 15,000 in 2015.[1]

Policymakers have responded to the crisis with a national focus on reducing opioid prescribing, strengthening regulatory controls, and enacting stringent prescribing guidelines.[2] These and other measures appear to be having the desired effect of driving down dispensed prescriptions for opioids, which dropped for 2 straight years, falling 2.7% in 2015 and 1.7% in 2016, as reported by the Quintiles IMS Institute.[3] Unfortunately, misuse and substance-use disorders (SUDs) involving opioids have not fallen in tandem, and the needs of patients in pain receive inadequate attention.[4] Cost-effective and available alternative options for pain relief remain out of reach for too many pain sufferers, and federal funding for pain research has steadily declined.[5]

The impact of chronic pain varies, but some people experience severe pain every day: Responses to the Functioning and Disability Supplement of the 2012 National Health Interview Survey led to estimates that 126.1 million US adults experienced some pain during the previous 3 months.[6] Of those, 25.3 million adults (11.2%) suffered every day and 23.4 million (10.3%) reported "a lot" of pain. Those who reported the highest levels of pain had worse health status, used more health care services, and suffered the most disability. Mortality risk also rises with pain intensity, duration, and frequency of interference with daily activities as shown in a large cohort study of older pain sufferers (≥50 years).[7]

Comprehensive, multidisciplinary care is best for chronic pain, and opioids, although not to be considered first-line therapeutics, do reduce pain and restore function for some patients.[8] Prevalence statistics of opioid-use disorders (OUDs) in patients treated with therapeutic opioids vary widely due to inconsistent criteria and methodology used in studies.[9] Multiple studies have put the number of addicted, opioid-treated patients from 1% to 5% or even lower[8–11]—but much depends on the methodology and definitions used. A systematic review that included 38 studies of opioid-treated patients with chronic pain found that misuse averaged between 21% and 29%, and addiction averaged between 8% and 12%.[12] Other research has put the prevalence of OUDs closer to 35% in opioid-treated patients,[13] but the parallel to addiction is uncertain. A rational interpretation of the data is that more people use opioids for legitimate medical reasons than abuse or misuse them. However, the high quantity of opioids prescribed translates to a heavy weight in adverse health and societal consequences when addiction or poisoning mortality do occur,[4] including harm to people who take opioids without being prescribed them. This article discusses strategies to minimize risks and improve therapeutic outcomes with prescribed medications commonly used in pain management, which, in addition to opioids, include antidepressants, anxiolytics, sleep aids, and other controlled substances.

DEFINITIONS RELATED TO OPIOID USE AND MISUSE

Table 1 contains definitions related to opioid use and misuse used in this manuscript. It is important to define terms given that appropriate clinical actions differ per category.

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The criteria for OUDs from the Diagnostic and Statistical Manual of Mental Disorders (5th edition)[16] include withdrawal and tolerance, which may occur in a person with or without OUD as determined by the context of use (Table 2). Definitions that describe substance misuse are distinct from expected physiological effects of medical opioids that include tolerance and physical dependence. Tolerance with long-term use and withdrawal with abrupt cessation are normal human reactions to opioids and call for optimal management of the patient's analgesic treatment. Inadequate pain relief can itself trigger drug abuse relapse. As a subset of SUDs, OUDs from mild to severe may be present when a person craves or continues use and is unable to stop, even when physical, psychological, social, occupational, and other difficulties arise (Table 2).

PAIN ASSESSMENT

Pain, which is recognized as a biopsychosocial experience,[17] contains elements not only of clinical significance but of meaningfulness to the patient. The need is to assess how severe the patient's pain is and whether that pain is likely to respond to the selected treatment modalities. Comprehensive multidisciplinary care is optimal for chronic pain treatment. If pain is severe to the point of interfering with function and daily activities, and patients gain greater mobility and quality of life with opioids, then individualized clinical decision-making should occur. Patients themselves are usually the most reliable source of information about their own pain—its location, intensity, effects on their physical functioning, and quality of life. However, widely used pain scales that ask patients to rate their pain from 0 to 10 may mean different things to different people. Newer systems such as the Stanford-developed and implemented Collaborative Health Outcomes Information Registry offer the opportunity for greater depth in pain evaluation by using item banks that capture many physical, psychological, and social functioning domains.[18]

Pain management providers are to conduct a careful risk–benefit analysis and to document the rationale, therapeutic regimen, and course of therapy for each patient, as called for in the education component of the US Food and Drug Administration's risk evaluation and mitigation strategy for extended-release and long-acting opioids.[19] The same procedures apply with short-acting opioids, and the effects of pain and adjuvant medications on the patient's analgesia, possible aberrant drug-seeking behaviors, side effects, family, work, and social life, mood, and daily activities all form questions for follow-up.

Patients whose lives are worsened during the course of opioid therapy—even though they do have physical pain—may not be using opioids primarily for reasons of pain control but to blunt emotional pain, for euphoric effects, to self-medicate psychiatric conditions, or compulsively because of addiction. Such uses subvert the intended result of pain relief and pose great dangers to the individual and, ultimately, to society.

RISK FACTORS FOR MISUSE, ABUSE, AND ADDICTION

Types of medication misuse and abuse occur in patients and nonpatients for various reasons that include the following:[20]

Table 1. Definitions Related to Use and Misuse of Opioid Analgesics

Term	Definition	Source
Misuse	Use of a medication (for a medical purpose) other than as directed or indicated, whether willful or unintentional, and whether harm results or not	Katz et al (2007)[14]
Abuse	Any use of an illegal drug or the intentional self-administration of a medication for a nonmedical purpose such as altering one's state of consciousness, for example, getting high	Katz et al (2007)[14]
Addiction	A primary, chronic disease involving brain reward, motivation, memory, and related circuitry that can lead to relapse and progressive development, and that is potentially fatal if left untreated; markers include craving and continued use despite adverse outcomes	Smith, (2012)[15] Katz et al (2007)[14]
Tolerance	A state of adaptation in which exposure to the drug results in diminution of its effects over time	Katz et al (2007)[14]
Physical dependence	Engenders abstinence syndrome when the drug is abruptly stopped	Katz et al (2007)[14]

Table 2. Criteria[a] for Opioid-Use Disorders From the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

1. Opioid taken in larger amounts or over a longer period than intended
2. Persistent desire or unsuccessful efforts to cut down or control opioid use
3. A lot of time spent obtaining, using, or recovering from the effects of the opioid
4. Craving or a strong desire to use opioids
5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home
6. Continued use despite persistent or recurring social or interpersonal problems caused or exacerbated by opioid use
7. Stopping or reducing important social, occupational, or recreational activities due to opioid use
8. Recurrent use of opioids in physically hazardous situations
9. Continued use despite knowledge of having persistent or recurrent physical or psychological problems cause or worsened by opioid use
10. Tolerance as defined by either a need for markedly increased amounts to achieve intoxication or desired effect or by markedly diminished effect with continued use of the same amount (does not apply when used appropriately under medical supervision)
11. Withdrawal manifesting as either characteristic syndrome or the substance is used to avoid withdrawal (Does not apply when used appropriately under medical supervision)

Data were derived from Saunders.[16]

[a]A minimum of 2–3 criteria is required for a mild substance-use disorder diagnosis, while 4–5 is moderate, and 6–7 is severe. Opioid-use disorder is specified instead of substance-use disorder, if opioids are the drug of abuse.

- Misunderstanding between the patient and provider
- Unauthorized self-medication of pain, mood, or sleep problems
- Desire to avoid symptoms of abstinence syndrome
- Desire for euphoria or other psychoactive reward
- Compulsive use due to addiction
- Illegal diversion for the financial gain

Before treating chronic pain with opioid therapy, a clinician should assess patients for risk of an OUD to set the appropriate level of clinical monitoring. Some of the risk factors for behaviors that might indicate an OUD include the following[10,13,21–26]:

- Nonfunctional status due to pain
- Exaggeration of pain
- Unclear etiology for pain
- Young age
- Smoking
- Poor social support
- Personal history of substance abuse
- Family history of substance abuse
- Psychological stress
- Psychological trauma
- Psychological disease
- Psychotropic substance use
- Focus on opioids
- Preadolescent sexual abuse
- History of legal problems
- History of substance-abuse treatment
- Craving for prescription drugs
- Mood swings
- Childhood adversity

Stress because of pain that is uncontrolled can also lead to opioid misuse or abuse in a patient with no other risk factors. In addition, mental and emotional pain from histories of childhood or adult trauma, despair within economically depressed communities, binge use and thrill-seeking behavior, and social environments that encouraged illicit substance use—all these factors and more—potentially contribute to adverse outcomes and therapeutic failure with opioid therapy.[27]

OVERDOSE MORTALITY RELATED TO OPIOIDS

Risk factors for overdose death related to medical and nonmedical opioid use encompass age, comorbid mental and medical disorders, a history of SUD (perhaps the strongest factor), and sources of psychological and social stress.[26,28–34] They include the following:

- Middle age
- History of substance abuse, including prescription and illicit drugs and alcohol
- Comorbid mental and medical disorders
- High opioid dose (particularly with added benzodiazepines)
- Methadone use
- Benzodiazepine coprescribing
- Antidepressant coprescribing
- Unemployment
- Polysubstance abuse
- Opioid naïvety
- Recent release from prison
- Recent release from abstinence-based addiction treatment
- Sleep apnea
- Heart or pulmonary complications (eg, respiratory infections, asthma)
- Pain intensity (eg, elevated, low, moderate, moderate–severe, severe)

In 1 study, medical examiner narratives in death investigations revealed histories of substance abuse for over half of overdose decedents and a history of chronic disease, chronic pain, or a mental disorder for over a third of decedents.[31] The same study emphasized that, although oxycodone and methadone were the opioids most frequently mentioned in opioid-related deaths, all opioids are potentially lethal in overdose, particularly in combination with other drugs.[31] The danger of polydrug poisoning is a frequently underappreciated risk with opioid therapy for pain.

People with severe pain often suffer from depression, anxiety, sleep disorders, and other psychiatric and medical comorbidities that occur alongside pain.[28,29,31,32] Comorbid medical and psychiatric conditions contribute complexity to the therapeutic regimen as medications used to treat some of these disorders, such as anxiolytics and antidepressants, may also depress breathing and compound risk for unintentional overdose.[32,35]

Known risk factors for fatal and nonfatal respiratory events with opioids form the basis of the Risk Index for Overdose or Serious Opioid-induced Respiratory Depression (RIOSORD). A version of the RIOSORD showed excellent (nearly 90%) predictive accuracy in a Veterans Administration case–control analysis of close to 9000 veteran patients[36] and was subsequently validated in the commercial insurance records of a nonveteran population of approximately 18 million medical users of prescription opioids.[32] The tool generates a risk index to predict the likelihood of an overdose or opioid-induced respiratory depression (OIRD) with medical opioids. Table 3 shows the risk factors found to be most predictive of an adverse event in the large population of commercially insured, opioid-treated patients.[32] The RIOSORD is designed for incorporation into the electronic health record and to facilitate individualized, point-of-care decision-making to mitigate opioid risk.[32,36]

The following factors were found to be strong or moderate predictors of OIRD[32]:

Strong Predictors

- SUD diagnosis in previous 6 months (single strongest predictor)
- Bipolar disorder or schizophrenia
- Cerebrovascular disease
- Renal disease
- Heart failure
- Nonmalignant pancreatic disease
- Concurrent benzodiazepine or antidepressant prescription

Moderate Predictors

- Recurrent headache
- Chronic pulmonary disease
- Sleep apnea
- Extended-release and long-acting opioid formulations
- Daily morphine equivalence dose (MED) ≥100 mg

Fentanyl, morphine, and methadone were the opioids most strongly associated with OIRD, which was more likely in people 55 years and older and in those with high health care utilization in previous 6 months, including 1 or more emergency department visits or hospital admissions.

It should be noted that the presence of an antidepressant was a stronger predictor of OIRD than an opioid dose level ≥100 mg MED. In a previous study, overdose risk was not appreciably increased until 200 mg MED unless a benzodiazepine was also present.[31] This suggests the need to study other possible contributors to overdose risk along with dose, such as reasons the higher dose was indicated, intractable pain, mood disorders, and posttraumatic stress.

Table 3. Factors Associated With Serious Opioid-Induced Respiratory Depression[a,b]

Covariate	Odds Ratio (95% Confidence Interval)
Demographic	
Age group, y	
18–34 (reference)	
35–54	1.05 (0.95–1.15)
55+	1.16 (1.04–1.29)
Male	1.03 (0.95–1.11)
US census region	
Northeast (reference)	
Midwest	1.20 (1.08–1.33)
South	1.09 (0.99–1.23)
West	1.39 (1.23–1.58)
Clinical	
Individual CCI comorbidities	
Heart failure	2.06 (1.74–2.44)
Peripheral vascular disease	0.91 (0.72–1.14)
Cerebrovascular disease	2.52 (2.18–2.92)
Chronic pulmonary disease	1.72 (1.56–1.89)
Serious autoimmune rheumatologic disease	1.47 (1.23–1.77)
Chronic hepatitis/cirrhosis	1.39 (0.96–2.00)
Warfarin treatment	0.79 (0.66–0.95)
Renal disease with renal impairment	2.17 (1.83–2.57)
Any malignancy, including leukemia and lymphoma	1.09 (0.93–1.29)
Skin (pressure) ulcers	1.50 (1.18–1.90)
Metastatic solid tumor	0.95 (0.73–1.23)
Other selected comorbidities	
Non–pain-related	
Substance-use disorder	12.74 (11.46–14.16)
Bipolar disorder/schizophrenia[c]	2.85 (2.44–3.32)
Sleep apnea	1.33 (1.16–1.52)
Cardiovascular disease	0.98 (0.81–1.20)
Nonmalignant pancreatic disease	2.07 (1.56–2.75)
Skin infections/abscesses	1.14 (1.00–1.30)
Pain-related	
Recurrent headache	1.73 (1.57–1.90)
Active traumatic injury	1.53 (1.41–1.65)
Prescription drugs	
Opioids	
By active ingredient	
Hydrocodone	1.30 (1.20–1.41)
Oxycodone	1.32 (1.19–1.45)
Hydromorphone	1.50 (1.38–1.64)
Morphine	2.93 (2.49–3.43)
Fentanyl	3.72 (3.10–4.46)
Methadone	2.80 (2.22–3.51)
Tramadol	1.19 (1.08–1.31)
By formulation[d]	
Not ER/LA (reference)	
ER/LA	1.73 (1.51–1.99)
By route	
Nonoral (reference)	
Oral	1.90 (1.54–2.34)
Maximum prescribed daily MED, mg/d	
<100 (reference)	
≥100	2.04 (1.87–2.24)
Selected nonopioid drugs	
Benzodiazepines	2.35 (2.18–2.54)
Antidepressants	2.19 (2.03–2.36)
All-cause health care utilization	
≥1 ED visit	1.52 (1.41–1.65)
≥1 d of hospitalization	1.12 (1.02–1.23)

Data were derived from Zedler et al.[32] Model performance: *C* statistic = 0.91.
Abbreviations: CCI, Charlson comorbidity index; ED, emergency department; ER/LA, extended-release/long-acting; MED, morphine equivalent dose.
[a]A serious prescription opioid-related respiratory or central nervous system (CNS) depression event was defined as a listed opioid poisoning or external cause code occurring within 61 day of a listed (1) CNS or respiratory adverse effect code or (2) mechanical ventilation or critical care code. All primary and nonprimary codes were considered.
[b]The multivariable logistic regression model includes all variables retained at a *P* value of <.10 as well as all variables considered to be confounders (ie, removal from the model resulted in a 20% or greater change in parameter estimates for 1 or more of the other variables). All of these variables are presented in this table and summarize the output from the model in which they were simultaneously tested.
[c]Bipolar disorder and schizophrenia were combined into 1 variable, "bipolar disorder/schizophrenia," for multivariable modeling.
[d]Missing opioid formulation (ER/LA), route, and MED information were analyzed in the reference group in regression modeling. Sensitivity analyses were conducted to examine the impact of this and found no appreciable difference between such models relative to those in which the missing data were excluded.

Suicide Risk

Painful conditions are known to be associated with suicide risk.[37] Patients within a chronic pain population are at an elevated risk for suicide ideation and attempts.[38,39] Frequent correlates of pain (eg, stress, social problems, psychiatric issues such as depression, and substance abuse) add risk for intentional overdose or suicide.[38,40,41] So does pain itself, as Hassett et al[40] wrote in a review of risk factors for suicide mortality: "In all likelihood, there are aspects of chronic pain itself that add uniquely to an individual's suicide risk profile." There is overlap but also distinction in the risk factors associated with suicide in the general population and the risk factors in people with chronic pain (Table 4).

National statistics analysis assigns manner-of-death categories of accident, suicide, homicide, or undetermined to poisoning deaths related to prescription opioids; however, evidence suggests that suicides may be misclassified and undercounted.[42,43] It is possible that deaths counted

Table 4. Suicide Risk Factors in General and Chronic Pain Populations

General	Chronic Pain
• Family history of suicide	• Pain severity
• Personal history of attempted suicide	• Pain type: back pain, fibromyalgia, migraine headache
• Anxiety disorders (eg, PTSD)	• Pain catastrophizing
• Major depressive disorder	• Perception of disability
• Substance abuse	• Access to analgesics
• Feelings of isolation	• Poor sleep
• Hopelessness and helplessness	• Desire to escape from pain
• Significant loss/grief	• Avoidance
• Abuse in childhood	• Problem-solving deficits
• Access to weapons/substances	

Data were derived from Hassett et al.[40]
Abbreviation: PTSD, posttraumatic stress disorder.

as unintentional or intent undetermined were actually the result of intentional overdoses, in which an excess amount of opioid is ingested in an attempt to halt distress.[43,44] Inadequately treated pain is a risk factor for intentional overdose.[37,38,40] Because severe pain is a risk factor for suicide, it is logical that severe pain is also a risk factor for a passively awaited overdose. Recognizing that death from drug self-intoxication may be passively awaited is important for prevention, as factors associated with suicide and other adverse outcomes with opioids are also risk factors for passively awaited deaths.

DIVERSION

Diversion is the intentional removal of a medication from legal dispensing and distribution channels. Examples of diversion include forged prescriptions, pharmacy robberies, patients selling their own drugs on the street, theft of patients' drugs by family members or others, and patients taking doses other than those prescribed.[45]

Factors that may indicate risk for diversion within a pain clinic setting include but are not limited to the following[46]:

- A positive family history of drug abuse
- A personal history of criminal behavior
- The age group 35–44 years
- Divorce (increased risk of having medications stolen)
- Financial strain (increased risk of lost or stolen medications)

Surveys indicate that family and friends are the most common source of diverted opioids.[47] Diversion in a clinical scenario may be difficult to identify, and research indicates diverters who pose as patients may easily deceive physicians.[48]

IN CLINICAL PRACTICE

Assessment Tools (Misuse, Abuse, Addiction)

After a careful risk–benefit analysis, if the clinician determines that a trial of opioid therapy is necessary, assessment for potential misuse, abuse, or addiction is warranted. After initiation of an opioid trial, a decision to continue to prescribe an opioid should be based on a therapeutic benefit that is usually measured by functional improvement or decreased pain. Risk factors that may predict problems with managing opioid intake have been used to construct clinical tools to assign patients to risk categories to determine the type and intensity of follow-up measures. Patients may change risk categories over time. Most clinical and medicolegal guidelines contain the expectation that pain management providers will assess patients for current substance misuse and pertinent risk factors before prescribing opioids for chronic pain.[2,49–52] Several opioid-specific screening tools are available. They include the initial and revised Screener and Opioid Assessment for Patients in Pain,[22,26] the Diagnosis, Intractability, Risk, Efficacy Score,[53] and the author's Opioid Risk Tool (Table 5).[10] However, none has been fully validated in a variety of clinical settings. The tool that correctly identifies most patients with potential drug abuse problems has high sensitivity but may have high false-positives. Clinicians should choose the tool that fits with their clinical practice and apply it—or a less formal set of questions incorporating known risk factors—consistently. Such assessment methods are generally chosen by evaluating the length of the assessment tool, the time available, and the level of clinician expertise within the clinic. Assessment is treated as routine during interactions with patients to encourage patient openness and willingness to share honest information.

Assessment usually helps clinicians place patients into a risk category to facilitate monitoring according to test results or other clinical signs. Patients whose scores indicate low risk may still develop OUDs; conversely, people stratified as high risk, although an opioid may not be an optimal treatment, will not necessarily develop an OUD or problematic drug-related behaviors. Monitoring tools such as the Current Opioid Misuse Measure are useful for following patient progress.[54,55] In addition to assessing patients for the risk of problematic opioid use, it is important to watch for comorbid mental disorders and to provide treatment, including comanagement with mental-health and substance-abuse specialists, as necessary.

An initial urine test to detect current medications and other licit or illicit substances can also help start communication between patient and provider, guide treatment decisions, and enable the clinician to advocate on the patient's behalf.[19,20] If presented up front to patients as a routine, consensual part of medical care, with a full explanation of why it is important—as a diagnostic tool providing objective documentation of compliance with a mutually agreed on treatment plan and goals of care—it is more likely to be accepted by patients. An initial check of the state prescription-monitoring database is also advised when available.[19] The literature is incomplete as to whether prescription database checks or urine drug testing affect the incidence of OUDs or overdoses.

Highest-risk patients usually have a history of drug abuse or are actively abusing drugs yet are simultaneously experiencing pain. A history of drug abuse is not a sure sign that a patient will abuse again, although it may mean treating the patient with more care and, perhaps, seeking comanagement from an addiction specialist. Such patients are often best managed on nonopioid or nonpharmacologic alternatives, such as physical rehabilitation, behavioral therapies, and lifestyle change if possible.[20] If pain is so severe that opioids are necessary, safety measures may include the

prescribing of lower doses in combination with alternative therapies, careful control of supply of medications, medication choices with less rewarding properties (eg, buprenorphine, tapentadol), and stringent measures such as frequent visits and smaller quantities dispensed.[20]

Clinicians who initiate trials of opioid medications should document all treatment decisions and patient discussions in the medical record. They may also need to use exit strategies. Good clinical practice includes preparation to humanely taper opioids when necessary and to initiate alternatives or refer to professionals in substance-abuse, mental-health, or alternative pain treatment fields as appropriate.

Suicide Assessment

Clinicians should screen patients regularly for suicidal thoughts and plans[40] and be aware that the following factors may heighten risk[56]:

- Age >45 years
- Woman
- Positive history of suicide attempts
- Low social support
- Divorce
- Active mental disorders
- Active substance abuse
- Unemployment
- Endorsement of specific suicide plan
- Access to means (eg, lethal supply of prescription medications)
- Alcohol dependence
- High pain intensity
- Long pain duration
- Insomnia
- Migraine, back pain, abdominal pain, generalized pain

If a patient is at high risk for suicide but has no current plan or intent, clinical safety measures include limiting opioid

Table 5. Comparison of Risk Assessment Tools for Aberrant Drug-Related Behaviors in Chronic Opioid Therapy

Tool	No. Items	Indications in Chronic Opioid Therapy	Minutes to Complete	Validated (n)
SOAPP[26]	5, 14, 24	Initial visit, best for high-risk populations	5–10	14-item version: (396)
SOAPP-R[22]	24	Initial visit, primary care	5	(283)
ORT[10]	5	Initial visit, stratifies as low, moderate, high risk	1	Preliminary in 1 pain clinic: (185)
DIRE[53]	7	Initial visit, assesses suitability for chronic opioid therapy	2	Retrospective: (61)

Abbreviations: DIRE, Diagnosis, Intractability, Risk, Efficacy; ORT, Opioid Risk Tool; SOAPP, Screener and Opioid Assessment for Patients in Pain; SOAPP-R, Revised Screener and Opioid Assessment for Patients in Pain.

Table 6. CIP-Based RIOSORD

Question[a]	Points for "Yes" Response
In the past 6 mo, has the patient had a health care visit (outpatient, inpatient, or ED) involving any of the following health conditions?[b]	
Substance-use disorder (abuse or dependence)? (this includes alcohol, amphetamines, antidepressants, cannabis, cocaine, hallucinogens, opioids, and sedatives/anxiolytics)	25
Bipolar disorder or schizophrenia?	10
Stroke or other cerebrovascular disease?	9
Kidney disease with clinically significant renal impairment?	8
Heart failure?	7
Nonmalignant pancreatic disease (eg, acute or chronic pancreatitis)?	7
Chronic pulmonary disease (eg, emphysema, chronic bronchitis, asthma, pneumoconiosis, asbestosis)?	5
Recurrent headache (eg, migraine)	5
Does the patient consume:	
Fentanyl?	13
Morphine?	11
Methadone?	10
Hydromorphone?	7
An extended-release or long-acting formulation of any prescription opioid?[c]	5
A prescription benzodiazepine?	9
A prescription antidepressant?	8
Is the patient's current maximum prescribed opioid dose 100 mg morphine equivalents per day? (include all prescription opioids consumed on a regular basis)	7
Total point score (maximum = 146)	

Data were derived from Zedler et al.[32]

Abbreviations: CIP, commercially insured health plan claims database; ED, emergency department; ER/LA, extended-release/long-acting; RIOSORD, Risk Index for Overdose or Serious Opioid-Induced Respiratory Depression.

[a]This questionnaire is intended to be completed and interpreted by a health care professional. It is not a replacement for clinical judgment and is intended to guide and inform clinical decision-making in patients who are treated with opioids.

[b]The condition does not have to be the primary reason for the visit, but it should be entered in the chart or electronic health record as one of the reasons or diagnoses for the visit.

[c]ER/LA formulation and certain opioid active ingredients were significantly and independently associated with the likelihood of overdose in the model. As such, ER/LA and each active ingredient are included and scored as independent factors in the risk index. For example, a fentanyl ER formulation or methadone receives RIOSORD risk points for both the active ingredient and the ER/LA formulation. A short-acting fentanyl receives points for the active ingredient only. ER/LA risk points are counted only once, regardless of the number of ER/LA opioid products that the patient consumes.

dose, quantity, and duration, avoiding concomitant central nervous system (CNS) depressants, initiating psychotherapy or regular psychiatric care, teaching coping skills to minimize catastrophizing and kinesiophobia, encouraging cognitive–behavioral treatment of sleep disorders, obtaining contact information for psychiatric emergency situations, and reassessing frequently, while remembering that suicide may be passive (eg, awaiting death) in patients with intractable pain.[44]

Sleep Apnea Assessment

Sleep apnea is a risk factor for respiratory depression with high-dose methadone (>50 mg/d) or other opioids (>150 mg/d MED), and in patients with a predisposition.[57] Consider a sleep study for high-risk patients and possible inpatient evaluation of opioid therapy safety.

Benzodiazepines With Opioids

Coprescribing of benzodiazepines and opioids is not recommended unless no alternative to the combination is possible.[35] In cases when the combination is essential, the lowest possible dose of both medications should be used and stringent follow-up and referral for addiction or mental-health management as needed are necessary.[35] Relative contraindications to the opioid/benzodiazepine combination include the following[35]:

- History of SUD with short periods of remission, absent or poor recovery program, abuse history involving benzodiazepines, opioids, alcohol, and other CNS depressants
- Mood, anxiety, or thought disorders
- Personality disorders
- Medical comorbidities that include morbid obesity, sleep-disordered breathing, chronic obstructive pulmonary disease, and hepatic or renal dysfunction
- Older adults at elevated risk of falls

Clinicians should be aware of risk factors for unintentional or intentional overdose mortality. Consider use of the RIOSORD as a tool (Tables 6 and 7) to assess for the risk of a serious opioid-related respiratory depression event in patients treated with medical opioids.

High Dose

Recent opioid-prescribing guidelines have proposed daily opioid MED ceilings to reduce risks associated with long-term opioid therapy.[2,51] It is important to remember that dose alone may not be sufficient to judge risk to a patient, that danger may also occur at lower doses, that patients differ genetically in opioid response necessitating individualized therapy, and that additional risks arise from coadministration of benzodiazepines and other CNS depressants and mental-health issues.[58]

SUMMARY

A number of biologic, psychiatric, and social risk factors are associated with opioid-related harm. Tools are available to assist with clinical decision-making and follow-up. Regardless of which tool or other process is selected, clinicians need knowledge of factors that may contribute to an OUD, worsening of psychiatric disease, suicidality, or unintentional overdose mortality risk in a patient with pain. Research indicates that a recent diagnosis of SUD is possibly the top predictor of overdose and overdose mortality. A thorough evaluation of substance abuse and psychiatric history should take place before opioids are initiated or continued for chronic pain. No clinical steps can prevent all harm in pain management, but harm should be reduced if clinicians are vigilant.

Table 7. CIP-based RIOSORD: Probability by Risk Class of Experiencing Serious Opioid-Induced Respiratory Depression

Risk Index Score[a]	Average Predicted OIRD Probability in Next 6 mo (95% CI), %
0–4	1.9 (1.9–1.9)
5–7	4.8 (4.8–4.9)
8–9	6.8 (6.8–6.8)
10–17	15.1 (15.1–15.3)
18–25	29.8 (29.7–30.0)
26–41	55.1 (54.8–55.4)
≥42	83.4 (83.2–83.7)

Abbreviations: CI, confidence interval; CIP, commercially insured health plan claims database; OIRD, opioid-induced respiratory depression; RIOSORD, Risk Index for Overdose or Serious Opioid-induced Respiratory Depression.

[a]Interpretation example: a patient with a RIOSORD score of 30 is predicted to have a 55% chance, on average, of experiencing a life-threatening opioid emergency such as an overdose or serious respiratory depression within the 6 months after the RIOSORD score is calculated.

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DISCLOSURES

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REFERENCES

1. Rudd RA, Seth P, David F, Scholl L. Increases in drug and opioid-involved overdose deaths—United States, 2010-2015. *MMWR Morb Mortal Wkly Rep*. 2016;65:1445–1452.
2. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *MMWR Recomm Rep*. 2016;65:1–49.
3. Lowes R. Message heard? Pain med prescribing down second year in row. *Medscape*. May 4, 2017. Available at: http://www.medscape.com/viewarticle/879514. Accessed September 18, 2017.
4. Lynch ME, Katz J. 'One size fits all' doesn't fit when it comes to long-term opioid use for people with chronic pain. *Canad J Pain*. 2017;1:2–7.
5. Kroenke K, Cheville A. Management of chronic pain in the aftermath of the opioid backlash. *JAMA*. 2017;317:2365–2366.
6. Nahin RL. Estimates of pain prevalence and severity in adults: United States, 2012. *J Pain*. 2015;16:769–780.
7. Smith D, Wilkie R, Croft P, McBeth J. Pain and mortality in older adults: the influence of pain phenotype. *Arthritis Care Res (Hoboken)*. 2017 [Epub ahead of print].
8. Noble M, Treadwell JR, Tregear SJ, et al. Long-term opioid management for chronic noncancer pain. *Cochrane Database Syst Rev*. 2010;CD006605. doi: 10.1002/14651858.CD006605.pub2.
9. Minozzi S, Amato L, Davoli M. Development of dependence following treatment with opioid analgesics for pain relief: a systematic review. *Addiction*. 2013;108:688–698.

10. Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the opioid risk tool. *Pain Med*. 2005;6:432–442.
11. Fleming MF, Balousek SL, Klessig CL, Mundt MP, Brown DD. Substance use disorders in a primary care sample receiving daily opioid therapy. *J Pain*. 2007;8:573–582.
12. Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, van der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. *Pain*. 2015;156:569–576.
13. Boscarino JA, Rukstalis MR, Hoffman SN, et al. Prevalence of prescription opioid-use disorder among chronic pain patients: comparison of the DSM-5 vs. DSM-4 diagnostic criteria. *J Addict Dis*. 2011;30:185–194.
14. Katz NP, Adams EH, Chilcoat H, et al. Challenges in the development of prescription opioid abuse-deterrent formulations. *Clin J Pain*. 2007;23:648–660.
15. Smith DE. The process addictions and the new ASAM definition of addiction. *J Psychoactive Drugs*. 2012;44:1–4.
16. Saunders JB. Substance use and addictive disorders in DSM-5 and ICD 10 and the draft ICD 11. *Curr Opin Psychiatry*. 2017;30:227–237.
17. Institute of Medicine Committee on Advancing Pain Research, Care, and Education. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*. Washington, DC: National Academies Press (US); 2011.
18. Carriere J, Darnall B, Kao M, Mackey S. (489) An examination of the roles of perceived injustice and pain acceptance on pain interference and pain intensity in patients with chronic pain: a Collaborative Health Outcomes Information Registry (CHOIR) Study. *J Pain*. 2016;17:S97.
19. Stanos S. Evolution of opioid risk management and review of the classwide REMS for extended-release/long-acting opioids. *Phys Sportsmed*. 2012;40:12–20.
20. Savage SR. What to do when pain and addiction coexist. *J Fam Pract*. 2013;62:S10–S16.
21. Atluri SL, Sudarshan G. Development of a screening tool to detect the risk of inappropriate prescription opioid use in patients with chronic pain. *Pain Physician*. 2004;7:333–338.
22. Butler SF, Fernandez K, Benoit C, Budman SH, Jamison RN. Validation of the revised Screener and Opioid Assessment for Patients with Pain (SOAPP-R). *J Pain*. 2008;9:360–372.
23. Dunbar SA, Katz NP. Chronic opioid therapy for nonmalignant pain in patients with a history of substance abuse: report of 20 cases. *J Pain Symptom Manage*. 1996;11:163–171.
24. Friedman R, Li V, Mehrotra D. Treating pain patients at risk: evaluation of a screening tool in opioid-treated pain patients with and without addiction. *Pain Med*. 2003;4:182–185.
25. Savage SR. Assessment for addiction in pain-treatment settings. *Clin J Pain*. 2002;18(suppl 4):S28–S38.
26. Akbik H, Butler SF, Budman SH, Fernandez K, Katz NP, Jamison RN. Validation and clinical application of the Screener and Opioid Assessment for Patients with Pain (SOAPP). *J Pain Symptom Manage*. 2006;32:287–293.
27. Szalavitz M. The feds are about to stick it to pain patients in a big way. *Vice*. 2017.
28. Webster LR, Cochella S, Dasgupta N, et al. An analysis of the root causes for opioid-related overdose deaths in the United States. *Pain Med*. 2011;12(Suppl 2):S26–S35.
29. Porucznik CA, Johnson EM, Sauer B, Crook J, Rolfs RT. Studying adverse events related to prescription opioids: the Utah experience. *Pain Med*. 2011;12(Suppl 2):S16–S25.
30. *Substance Abuse and Mental Health Services Administration: SAMHSA Opioid Overdose Prevention Toolkit. HHS Publication No. (SMA) 13–4742*. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2013.
31. Dasgupta N, Funk MJ, Proescholdbell S, Hirsch A, Ribisl KM, Marshall S. Cohort study of the impact of high-dose opioid analgesics on overdose mortality. *Pain Med*. 2016;17:85–98.
32. Zedler BK, Saunders WB, Joyce AR, Vick CC, Murrelle EL. Validation of a screening risk index for serious prescription opioid-induced respiratory depression or overdose in a US Commercial Health Plan Claims Database. *Pain Med*. 2017 Mar 6 [Epub ahead of print].
33. Binswanger IA, Stern MF, Deyo RA, et al. Release from prison–a high risk of death for former inmates. *N Engl J Med*. 2007;356:157–165.
34. Anderson K. Death after treatment for heroin dependence. *Pro Talk: a rehabs.com community*.
35. Reisfield GM, Webster LR. Benzodiazepines in long-term opioid therapy. *Pain Med*. 2013;14:1441–1446.
36. Zedler B, Xie L, Wang L, et al. Development of a risk index for serious prescription opioid-induced respiratory depression or overdose in Veterans' Health Administration Patients. *Pain Med*. 2015;16:1566–1579.
37. Ilgen MA, Kleinberg F, Ignacio RV, et al. Noncancer pain conditions and risk of suicide. *JAMA Psychiatry*. 2013;70:692–697.
38. Stenager E, Christiansen E, Handberg G, Jensen B. Suicide attempts in chronic pain patients. A register-based study. *Scand J Pain*. 2013;5:4–7.
39. Fishbain DA, Lewis JE, Gao J. The pain suicidality association: a narrative review. *Pain Med*. 2014;15:1835–1849.
40. Hassett AL, Aquino JK, Ilgen MA. The risk of suicide mortality in chronic pain patients. *Curr Pain Headache Rep*. 2014;18:436.
41. Cheatle MD, Wasser T, Foster C, Olugbodi A, Bryan J. Prevalence of suicidal ideation in patients with chronic noncancer pain referred to a behaviorally based pain program. *Pain Physician*. 2014;17:E359–E367.
42. Rockett IR, Hobbs GR, Wu D, et al. Variable classification of drug-intoxication suicides across US States: a partial artifact of forensics? *PLoS One*. 2015;10:e0135296.
43. Stone DM, Holland KM, Bartholow B, et al. Deciphering suicide and other manners of death associated with drug intoxication: a Centers for Disease Control and Prevention Consultation Meeting Summary. *Am J Public Health*. 2017;107:1233–1239.
44. Madadi P, Persaud N. Suicide by means of opioid overdose in patients with chronic pain. *Curr Pain Headache Rep*. 2014;18:460.
45. Cicero TJ, Kurtz SP, Surratt HL, et al. Multiple determinants of specific modes of prescription opioid diversion. *J Drug Issues*. 2011;41:283–304.
46. Walker MJ, Webster LR. Risk factors for drug diversion in a pain clinic patient population. *J Opioid Manag*. 2012;8:351–362.
47. Setnik B, Roland CL, Goli V, et al. Self-reports of prescription opioid abuse and diversion among recreational opioid users in a Canadian and a United States city. *J Opioid Manag*. 2015;11:463–473.
48. Jung B, Reidenberg MM. Physicians being deceived. *Pain Med*. 2007;8:433–437.
49. Chou R, Fanciullo GJ, Fine PG, Miaskowski C, Passik SD, Portenoy RK. Opioids for chronic noncancer pain: prediction and identification of aberrant drug-related behaviors: a review of the evidence for an American Pain Society and American Academy of Pain Medicine clinical practice guideline. *J Pain*. 2009;10:131–146.
50. Rolfs RT, Johnson E, Williams NJ, Sundwall DN; Utah Department of Health. Utah clinical guidelines on prescribing opioids for treatment of pain. *J Pain Palliat Care Pharmacother*. 2010;24:219–235.
51. Washington State Agency Medical Directors' Group. *Interagency Guideline on Prescribing Opioids for Pain*. 3rd ed. Olympia, WA: Agency Medical Directors' Group; 2015.
52. Department of Veterans Affairs, Department of Defense. VA/DoD clinical practice guideline for opioid therapy for chronic pain. 2017.
53. Belgrade MJ, Schamber CD, Lindgren BR. The DIRE score: predicting outcomes of opioid prescribing for chronic pain. *J Pain*. 2006;7:671–681.
54. Butler SF, Budman SH, Fanciullo GJ, Jamison RN. Cross validation of the current opioid misuse measure to monitor chronic pain patients on opioid therapy. *Clin J Pain*. 2010;26:770–776.
55. Butler SF, Budman SH, Fernandez KC, et al. Development and validation of the current opioid misuse measure. *Pain*. 2007;130:144–156.
56. Tang NK, Crane C. Suicidality in chronic pain: a review of the prevalence, risk factors and psychological links. *Psychol Med*. 2006;36:575–586.
57. Webster LR. Eight principles for safer opioid prescribing. *Pain Med*. 2013;14:959–961.
58. American Academy of Pain Medicine. AAPM comments to the CDC on the proposed 2016 guideline for prescribing opioids for chronic pain. January 12, 2016. Available at: http://www.painmed.org/press/position-statements/. Accessed September 15, 2017.