

# Strategies for the Treatment of Pain in the Context of Alcohol and Substance Use Disorders

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## Abstract

The Psychiatric Consultation Service at Massachusetts General Hospital sees medical and surgical inpatients with comorbid psychiatric symptoms and conditions. During their twice-weekly rounds, Dr Stern and other members of the Consultation Service discuss the diagnosis and management of hospitalized patients with complex medical or surgical problems who also demonstrate psychiatric symptoms or conditions. These discussions have given rise to rounds reports that will prove useful for clinicians practicing at the interface of medicine and psychiatry.

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Ms B had a history of hypertension, osteoarthritis, major depressive disorder, chronic back pain following a work-related accident, and a severe AUD (with a history of withdrawal seizures and delirium tremens). Moreover, she had multiple admissions to short-term inpatient detoxification programs for the management of alcohol withdrawal and had completed an involuntary treatment program for an AUD 6 months earlier. She had an individual counselor and psychiatrist, who prescribed oral naltrexone (50 mg/d) and acamprosate (666 mg 3 times/d) for the management of her AUD as well as gabapentin (600 mg 3 times/d) for pain. She had an excellent response to the injectable formulation of naltrexone (Vivitrol), with 3 months of abstinence from alcohol. However, she was reluctant to restart monthly Vivitrol due to concerns about the potential of needing opioid agonists for pain control. In the past year, Ms B visited the emergency department 11 times because of severe pain, and she was prescribed 3–5-day courses of oxycodone for her pain.

Have you been challenged by caring for a patient with acute or chronic pain in the context of an alcohol use disorder (AUD) or a substance use disorder (SUD)? Have you been uncertain whether abstinence from substance use is required before pain is treated or whether the dosages of analgesics need to be raised for those with an SUD? Have you struggled to decide on whether to fill “lost prescriptions” or to set firm limits on acceptable behaviors? If you have, the following case vignette and discussion should prove useful.

## CASE VIGNETTE

Ms B, a 37-year-old woman, was found unresponsive on a sidewalk due to a respiratory arrest that led to a cardiac arrest. Emergency medical technicians administered naloxone and performed cardiopulmonary resuscitation; then, she was transferred to the hospital for further management. Her blood alcohol level was 367 mg/dL, and her urine toxicology was positive for fentanyl.

## DISCUSSION

### How Can AUDs and SUDs Be Diagnosed?

Screening tests for SUDs are recommended by the Centers for Disease Control (CDC) in their Clinical Practice Guideline for Prescribing Opioids for Pain<sup>1</sup>; these tests include the Alcohol Use Disorders Identification Test<sup>2</sup> and the Drug Abuse Screen Test.<sup>3</sup> Even single-item screeners (eg, “How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?”) have been able to identify illicit substance use and prescription misuse in primary care settings.<sup>4</sup> Among individuals who screen positive, a diagnosis of an AUD, opioid use disorder (OUD), cannabis use disorder, or another SUD can be made through a clinical interview that establishes the presence of the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition,

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## Clinical Points

- Screening tests (eg, the Alcohol Use Disorders Identification Test and Drug Abuse Screen Test) for substance use disorders are recommended by the Centers for Disease Control in their clinical practice guidelines for prescribing opioids for pain.
- Contemporary algorithms for the treatment of pain place a greater emphasis on the minimization of opioid use and incorporation of alternative modalities (such as acupuncture, chiropractic care, massage therapy, nonopioid medications, and mindfulness-based therapies) into pain management algorithms.
- When prescribing opioids for pain control, prescription monitoring programs should be checked, regular urine toxicology screening should be conducted, and patients with an opioid use disorder should receive US Food and Drug Administration–approved medication (eg, methadone or buprenorphine) and a referral for counseling.

Text Revision (*DSM-5-TR*) criteria (which include spending a great deal of time getting, using, or recovering from the substances' effects; having cravings for the drug; using the substance despite its adverse effects on physical and mental health; developing tolerance to the drug's effects; and developing withdrawal symptoms upon discontinuing use of the substance).<sup>5</sup>

In addition to physiological tolerance and withdrawal symptoms, the *DSM-5-TR* criteria center around behavioral patterns that an individual has developed, which indicate impaired control (eg, using more than intended, difficulty reducing, or stopping use), engagement in risk-taking behaviors (eg, using in situations that would be physiologically hazardous), and impairment of function due to their use (eg, failing to complete major obligations and recurrent issues in relationships). Of note, for prescribed medications (eg, opioids and benzodiazepines), there is a potential for the development of tolerance and withdrawal, so that these criteria do not count toward an SUD diagnosis.

Recent diagnostic systems have moved away from using categorical distinctions of “abuse” and “dependence”; instead, they reflect the severity of an SUD along a continuum. Endorsement of 2 to 3 criteria indicates a mild severity, 4 to 5 indicates a moderate severity, and 6 or more criteria indicates a severe SUD.<sup>6</sup> SUDs are often chronic and recurrent. Accordingly, diagnostic specifiers indicate the stage of recovery. Individuals are designated as being in early remission when they no longer meet the criteria for 90 consecutive days and in sustained remission when they no longer meet the criteria for 12 consecutive months. Further modifiers indicate if recovery status has been achieved in a controlled setting, such as a residential program, or while on maintenance therapy, such as methadone or suboxone.

## How Is Pain Often Treated in the Context of an AUD or SUD?

Pain management in individuals with an AUD or SUD presents unique challenges and opportunities due to the interplay among the brain's pathways for pain and reward and the efficacy of analgesic approaches. Integrating the World Health Organization (WHO) analgesic ladder with contemporary algorithms, given the current opioid epidemic, involves the incorporation of complementary and alternative medicine strategies, use of over-the-counter (OTC) medications, and interventions into a comprehensive and inclusive framework.<sup>7</sup> The WHO analgesic ladder for pain management was initially designed for the treatment of cancer-related pain, but it is also applicable to pain from other causes. It was comprised of 3 steps: use of nonopioid analgesics for mild pain; weak opioids, with or without nonopioid analgesics for moderate pain; and potent opioids for severe and/or persistent pain. In addition, adjuvants (such as antidepressants, anticonvulsants, and topical therapies) were used in combination with analgesics to enhance pain relief. Contemporary algorithms place a greater emphasis on the minimization of opioid use and the incorporation of alternative modalities (such as acupuncture, chiropractic care, massage therapy, and mindfulness-based therapies) into pain management algorithms.<sup>8,9</sup> A comprehensive pain management plan should prioritize individualized care, multidisciplinary approaches, patient education, and shared decision-making. It should also address the psychosocial aspects of pain, including mental health support, social determinants of health, and lifestyle modifications. Newer models of the WHO analgesic ladder have reimaged its steps as bidirectional or with additional steps that include the use of integrative medicine therapies, minimally invasive interventions, nerve blocks, epidurals, patient-controlled analgesia, and spinal cord stimulators.<sup>8,9</sup>

Pharmacologic and nonpharmacologic pain interventions for acute and chronic pain should be guided by a comprehensive assessment of pain. The Brief Pain Inventory is a useful multidimensional questionnaire that provides a framework for the assessment of the quality and intensity of pain.<sup>10</sup> It characterizes past attempts at pain relief, the quality and severity of pain, and the cause of pain.<sup>10–14</sup> The characteristics and use of OTC medications (including acetaminophen, aspirin, nonsteroidal anti-inflammatory drugs [NSAIDs], OTC medications [such as S-adenosylmethionine, magnesium oxide, and capsaicin], as well as adjuvant medications) are presented in Table 1.<sup>13</sup> In addition, a list of the US Food and Drug Administration (FDA)–approved indications for a variety of pain conditions, as well as the off-label evidence (when available), problematic side effects, and precautions needed for use in those with

Table 1.

**Medications for Pain in Those With an AUD OR SUD**

Medications and FDA indications	Mechanism of action	Typical dose	Indication/evidence	Common side effects	Serious reactions	Caution/other information
<b>Non-narcotic medications</b>						
<b>Acetaminophen</b>	COX inhibitor	325–1,000 mg every 4–6 h PRN maximum 1 g every 4 h and 4 g/d from all sources	Mild pain, fever	Headache, nausea or vomiting, rash	Anaphylaxis, hepatotoxicity, renal tubular necrosis, nephropathy, anemia, thrombocytopenia	Caution in the setting of hepatic disease, chronic alcohol use, renal impairment, hypersensitivity
<b>Aspirin</b>	COX inhibitor, reduces prostaglandin and thromboxane A2 synthesis, anti-inflammatory, affects platelet aggregation	325–650 mg every 4–6 h PRN, maximum 4 g/d	Mild pain, arthritis, fever	Nausea, vomiting, abdominal pain, constipation or diarrhea, dizziness, tinnitus, hyperuricemia, ecchymosis	Blood cell dyscrasias, anaphylaxis, angioedema, bleeding, GI bleeding and perforation, ulcer, nephrotoxicity, hepatotoxicity, Reye syndrome	GI bleeding, G6PD deficiency, uncontrolled HTN, pregnancy starting at 30 wk gestation, alcohol use, renal or hepatic impairment, gout
<b>NSAIDs (ibuprofen, naproxen, celecoxib, meloxicam, Voltaren, indomethacin, others)</b>	Blocks prostaglandin synthesis through COX-1 and COX-2 inhibition	Oral, gel, topical patch	Mild-to-moderate pain, fever, osteoarthritis, rheumatoid arthritis, others	Dyspepsia, nausea, abdominal pain, rash, pruritus, ecchymosis, dizziness, AST or ALT elevation	GI bleeding and perforation, edema, HTN, congestive heart failure, stroke, thrombotic events, renal impairment, nephritis, nephrotic syndrome, chronic kidney disease, SJS, TEN	Renal impairment, interactions with numerous medications <sup>12</sup>
<b>Lidocaine - Postherpetic neuralgia</b>	Blockade of voltage-gated sodium channels leading to reversible block of action potential propagation	Various dosing, maximum 4.5 mg/kg/dose, 300 mg/total dose; patch, regional, infiltration, peripheral, or central nerve block	Arrhythmias; local, regional, and spinal anesthesia	Tremor, confusion, hypotension, lightheadedness, dizziness, nausea, vomiting, anxiety, hallucinations, drowsiness, lethargy	CNS toxicity, seizures, respiratory or cardiac arrest, bradycardia, heart block, arrhythmia, hypotension, anaphylaxis	Cardiac impairment, elderly, caution in renal impairment, hepatic impairment, antiarrhythmic, lowers seizure threshold, bradycardia
<b>Capsaicin topical - Diabetic neuropathy, neuropathic pain with postherpetic neuralgia</b>	Exact mechanism unknown, selectively binds TRPV1 receptors, degenerates cutaneous nociceptive neurons, substance P depletion	Cream 0.025%, 0.075%, apply TID to QID	Musculoskeletal pain	Burning, erythema, hyperalgesia	Severe burns, neurotoxicity	Avoid use on skin that is damaged, broken, or irritated
<b>Over-the-counter agents</b>						
<b>S-adenosyl-methionine (SAME)</b>	DNA methylation	200 mg by mouth BID up to 800 mg by mouth BID, TID dosing	Treatment-resistant depression (TRD), pain disorders, chronic fatigue syndrome, osteoarthritis, low back and knee pain, fibromyalgia, cognition, dementia	Nausea, diarrhea, dry mouth, headache, anxiety, restlessness, insomnia	Mania	Generally viewed as safe
<b>Magnesium oxide</b>	Inhibits calcium influx via NMDA receptor blockade	Oral, IV, intrathecal 400 mg by mouth QHS	Headache prevention, perioperative and postoperative pain, dysmenorrhea, neuropathic pain, postherpetic neuralgia, neuropathy	Diarrhea, GI upset, weakness, nausea, and vomiting		Generally viewed as safe

(continued)

Table 1 (continued).

Medications and FDA indications	Mechanism of action	Typical dose	Indication/evidence	Common side effects	Serious reactions	Caution/other information
<b>Antidepressants</b>						
<b>TCAs</b>						
<b>Amitriptyline</b> - Depression	Tertiary amine TCA inhibits serotonin and norepinephrine reuptake	10–25 mg by mouth QHS, up to 150 mg by mouth QHS	Off label: diabetic neuropathy, migraine headache prophylaxis, postherpetic neuralgia, fibromyalgia	Sedation, nausea, vomiting, constipation, dry mouth, blurry vision, palpitations, tachycardia, weight gain, rash, urinary retention	HTN, syncope, arrhythmias, QTc prolongation, MI, stroke, tardive dyskinesia, blood cell dyscrasias, hallucinations, psychosis, mania, depression, suicidality, serotonin syndrome, transaminitis, paralytic ileus, withdrawal symptoms if abruptly discontinued	Can monitor for therapeutic drug levels, efficacy may take weeks, ECG if cardiac disease, suicidality, behavioral changes, CYP2D6 (primary) 1A2, 2C19, active metabolites including nortriptyline
<b>Nortriptyline</b> - Depression	Secondary amine TCA Active metabolite of amitriptyline	10–25 mg by mouth QHS, up to 150 mg by mouth QHS	Off label: chronic pain, neuropathy, postherpetic neuralgia	Sedation, nausea, vomiting, constipation, dry mouth, blurry vision, palpitations, tachycardia, weight gain, rash, urinary retention, increased appetite, tachycardia, confusion, restlessness	HTN, syncope, arrhythmias, QTc prolongation, MI, stroke, tardive dyskinesia, blood cell dyscrasias, hallucinations, psychosis, mania, depression, suicidality, serotonin syndrome, transaminitis, paralytic ileus, withdrawal symptoms if abruptly discontinued	Similar cautions and monitoring as amitriptyline; lower sedation, hypotension, and anticholinergic side effects compared with tertiary amines (amitriptyline)
<b>SNRIs</b>						
<b>Duloxetine</b> - MDD, GAD - Diabetic neuropathy - Fibromyalgia - Chronic musculoskeletal pain	SNRI	20–30 mg by mouth daily, up to 60 mg by mouth BID, often dosed BID for pain disorders	Off label: chemotherapy-induced peripheral neuropathy and stress urinary incontinence	Headache, nausea, weight loss, abdominal pain, somnolence, fatigue, nausea, vomiting, dizziness, sexual dysfunction, agitation, elevated blood pressure, urinary hesitancy, ALT or AST elevation	Withdrawal syndrome, mania, depression, suicidality, serotonin syndrome, seizures, SIADH, liver enzymes, hypotension, bleeding, SJS, EM, hyponatremia	Doses >60 mg/d are rarely more effective for depression; creatinine clearance <30, hepatic disease, cirrhosis, abrupt withdrawal, elderly
<b>Venlafaxine</b> - MDD, GAD, social anxiety disorder, panic disorder	SNRI also inhibits dopamine reuptake	75–225 mg by mouth/d, typical dose 150 mg ER by mouth/d	Off label: migraine prophylaxis, diabetic neuropathy, fibromyalgia, PTSD, OCD, ADHD, premenstrual dysphoric disorder	Headache, nausea, constipation, diarrhea, weight loss, sexual dysfunction, decreased libido, abnormal dreams	Hypomania/mania, suicidality, serotonin syndrome, SIADH, bleeding, blood cell dyscrasias, SJS, TEN, EM, hyponatremia, seizures, HTN, arrhythmia, QT prolongation, Torsades de pointes, pancreatitis, hepatotoxicity, withdrawal syndrome	Doses >225 mg may increase blood pressure; liver CYP2D6 (primary) 3A4, active metabolite desvenlafaxine
<b>Desvenlafaxine</b> - MDD	SNRI and dopamine reuptake	50–100 mg by mouth/d, maximum 200 mg by mouth/d	Off label: neuropathic pain, moderate-to-severe menopausal vasomotor symptoms	Headache, nausea, constipation, dry mouth, diarrhea, weight loss, sexual dysfunction, decreased libido, abnormal dreams, hyperlipidemia, anxiety, vertigo, yawning	EPS, SIADH, HTN, serotonin syndrome, mania, hypomania, depression exacerbation, suicidality, hypersensitivity reaction, SJS, glaucoma, seizures, SIADH, hyponatremia, withdrawal syndrome	CYP3A4 (minor)

(continued)

Table 1 (continued).

Medications and FDA indications	Mechanism of action	Typical dose	Indication/evidence	Common side effects	Serious reactions	Caution/other information
<b>Milnacipran</b> - Fibromyalgia	SNRI	12.5 mg by mouth/d x 1, then 12.5 mg by mouth BID x 2 d, then to 50 mg by mouth BID over 1 wk, maximum 200 mg/d	Off label: MDD	Headache, nausea, constipation, dry mouth, dizziness, weight loss, sexual dysfunction, decreased libido, ALT or AST elevated, paresthesias, tremor, chest discomfort, urinary retention, urinary hesitancy	EPS, SIADH, HTN, serotonin syndrome, mania, hypomania, depression, exacerbation, suicidality, SJS, EM, cardiomyopathy, bleeding, hepatotoxicity, withdrawal syndrome	<i>Avoid in AUD or alcohol abuse</i> , hepatic impairment; creatinine at baseline, BP/HR at baseline; CrCL <50; avoid in chronic liver disease
<b>Antiepileptic medications</b>						
<b>Topiramate</b> - Seizure disorders - Migraine headache prophylaxis	Carbonic anhydrase inhibitor; positive allostatic modulator at GABA <sub>A</sub> receptors, increases chloride ion influx; GABA-mediated inhibition; AMPA/kainate	Dosage titration and varying doses from 50 mg up to 300 mg by mouth daily	Off label: AUD, cocaine use disorder, tobacco use disorder, PTSD, binge-eating disorder, weight loss	Brain fog/cognitive impairment bilateral upper and lower extremity paresthesia, hypoesthesia, weight loss, somnolence, fatigue, ataxia, taste changes, visual disturbances, nystagmus, tremor, anxiety, nervousness, depression, paresthesias, dysesthesias	Nephrolithiasis, metabolic acidosis, osteoporosis, osteomalacia, hyperammonemia, SJS, TEN, EM, may decrease effectiveness of oral contraceptives, folate deficiency, major congenital malformations	Creatinine at baseline, bicarbonate, signs and symptoms of depression, behavioral changes, suicidality. Consider use in patients with chronic migraine headache, comorbid PTSD, binge-eating disorder, and to promote weight loss
<b>Gabapentin</b> - Partial seizures - Postherpetic neuralgia	Modulates GABAergic activity on voltage-gated calcium channels	300 mg by mouth TID or 600 mg by mouth TID	Off label: pain disorders: fibromyalgia, neuropathy/neuralgia AUD, postacute protracted alcohol withdrawal (with anxiety and insomnia), moderate to severe menopausal vasomotor symptoms	Dizziness, somnolence, fatigue, peripheral edema, weight gain	Depression, suicidality, allergic reactions including SJS, TEN, EM, angioedema	Creatinine at baseline, signs and symptoms of depression, behavioral changes, suicidality; consider use in patients with comorbid pain disorders or alcohol withdrawal anxiety and insomnia, abuse potential
<b>Pregabalin</b> - Diabetic neuropathy - Fibromyalgia - Seizures	Binds to presynaptic voltage-gated calcium channels and decreasing calcium influx, decreasing release of excitatory neurotransmitters	Various dosing for IR and ER form; suggested starting dose for neuropathic pain is 50 mg by mouth TID, increasing to 300 mg/d within 1 wk of starting	Off label: chronic pain, GAD, social anxiety, bipolar disorder, insomnia, restless leg syndrome	Dizziness, somnolence, blurred vision, nausea, headache, constipation, impaired coordination, decreased platelets	Depression, suicidality, SJS, thrombocytopenia, rhabdomyolysis, abuse potential, withdrawal syndrome	Avoid in alcohol use, abuse potential; CrCL <30, renal impairment, angioedema, CNS depressant risk; structurally like GABA but does not bind to GABA receptors
<b>Valproate</b> - Migraine headache prophylaxis - Bipolar disorder - Seizures	Inhibits voltage-gated sodium channels	250–500 mg twice daily for migraine prophylaxis	Off label: diabetic peripheral neuropathy, postherpetic neuralgia, agitation and aggression related to traumatic brain injury	Headache, nausea/vomiting, sedation, blood cell dyscrasias, dyspepsia, abdominal pain, diarrhea, weight gain, transaminitis, blurry vision, tremor	Hepatotoxicity, pancreatitis, hyponatremia, pancytopenia, allergic reactions including SJS, TEN, anaphylaxis, psychosis, hallucinations, suicidality, hyperammonemia	Caution for use in those on lamotrigine or cross-tapering due to risk of serious skin reactions (SJS and TEN)

(continued)

Table 1 (continued).

Medications and FDA indications	Mechanism of action	Typical dose	Indication/evidence	Common side effects	Serious reactions	Caution/other information
<b>Carbamazepine</b> - Neuropathy - Neuralgia	Blocks voltage-gated sodium channels; exact mechanism unknown in trigeminal neuralgia	200–400 mg twice daily, max 1,200 mg daily	Off label: restless leg syndrome, bipolar disorder, seizure disorder	Nausea/vomiting, constipation, dizziness, ataxia, HTN, hyponatremia, dry mouth, pruritus, blurry vision, tremor, rash, HTN, tremor, hyponatremia, speech disturbance	Suicidality, male infertility, serious dermatologic reactions, anaphylaxis, blood cell dyscrasias, aplastic anemia, hyperammonemia, agranulocytosis, SIADH, hepatotoxicity, arrhythmia, AV block, syncope, SJS, TEN, EM, syncope, angioedema, pancreatitis	CYP1A2, 2C8, 3A4 (primary); many cytochrome interactions and inducer CYP3A4 inhibition; caution in those with elevated AST/ALT
<b>Oxcarbazepine</b> - Partial seizures	Blocks voltage-sensitive sodium channels, exact mechanism unknown	300–1,200 mg by mouth BID, starting with 300 mg by mouth BID and increasing by 300 mg daily every 3 d as tolerated	Off label: neuropathy/neuralgia, trigeminal neuralgia, bipolar disorder	Dizziness, sedation, ataxia, headache, confusion, nausea, abdominal pain, diarrhea, constipation, rash, hyponatremia, somnolence, fatigue	Suicidality, SIADH, anaphylaxis, SJS, TEN, EM, pancreatitis; hematologic side effects are rare	10-keto derivative of carbamazepine; causes fewer rashes and is typically better tolerated than carbamazepine; hyponatremia may be more common in oxcarbazepine; may decrease efficacy of oral contraceptives
<b>Lamotrigine</b> - Bipolar I disorder maintenance - Seizure disorders - Lennox-Gastaut syndrome	Selectively inhibits voltage-gated sodium channels, stabilizes presynaptic neuronal membranes, inhibits presynaptic glutamate and aspartate release	Start 25 mg daily, increase by 25 mg/d weekly, usual dose 100 mg daily migraine prophylaxis, up to 200–400 mg daily divide daily to BID, valproate inhibits the metabolism of lamotrigine	Off label: migraine with aura prophylaxis, diabetic neuropathy, fibromyalgia, bipolar depression, mood stability in personality disorders	Dizziness, vertigo, headache, ataxia, nausea, vomiting, blurry vision, diarrhea, constipation, dyspepsia, abdominal pain, xerostomia, amenorrhea, rash, fatigue, tremor, fever, anxiety, mood lability, edema, impaired concentration, irritability, depression	Suicidality, worsening depression, severe rash, SJS, TEN, angioedema, severe or life-threatening hypersensitivity reaction, blood cell dyscrasias, aseptic meningitis, hepatic failure, arrhythmia, tubulointerstitial nephritis	Caution in pregnancy: possible risk of teratogenicity, CrCl <50, renal impairment, hepatitis impairment, heart failure, arrhythmia or cardiac disease, Cr at baseline, ECG at baseline in patients over age 60 y
<b>Lacosamide</b> - Adjunctive therapy of seizure disorders	Stabilizes voltage-gated sodium channels	Start 50 mg by mouth BID x 3 wk, may increase by 100 mg/d/wk, up to 100–200 mg by mouth BID	Off label: diabetic neuropathy	Dizziness, vertigo, headache, ataxia, nausea, blurry vision, nystagmus, diarrhea, tremor, depression, somnolence, pruritis	Suicidality, psychosis, hypersensitivity, SJS, TEN, blood cell dyscrasias, abuse potential ECG PR prolongation, AV block, bradycardia, ventricular arrhythmia, atrial fibrillation	<i>Avoid alcohol use, abuse potential</i> CrCl <30, mild-moderate hepatic impairment: decrease maximum dose by 25%; avoid severe impairment, cardiovascular disease, cardiac conductivity
<b>Opioid pain medications</b>						
<b>Tramadol</b> - Pain moderate to severe, acute, and chronic	μ-opioid receptor agonist, also SNRI	Start: IR: 25 mg by mouth in the morning, up to 50–100 mg by mouth every 4–6 PRN  Chronic: 100–300 mg ER by mouth daily	Off label: depression, premature ejaculation	Dizziness, headache, nausea, vomiting, diarrhea, constipation, dyspepsia, pruritis, flushing, insomnia, xerostomia	Suicidal ideation, risk of seizures especially at high doses and when co-prescribed other serotonergic medications and antidepressants, or general anesthetic, serotonin syndrome, sleep apnea, anaphylaxis, SJS, TEN, hypotension, syncope, QT prolongation	<i>Abuse potential, misuse</i> , alcohol or drug intoxication, risks with concomitant use with benzodiazepines or other CNS depressants, serotonin syndrome, neonatal opioid withdrawal Avoid when the CrCl <30, MAO inhibitor within 2 wk, cardiac disease, QT prolongation, ventricular arrhythmia, seizure risk, head injury

(continued)

Table 1 (continued).

Medications and FDA indications	Mechanism of action	Typical dose	Indication/evidence	Common side effects	Serious reactions	Caution/other information
<b>Tapentadol</b> - Pain moderate to severe, acute and chronic - Diabetic peripheral neuropathic pain	$\mu$ -opioid receptor agonist, also SNRI	50–100 mg by mouth every 4–6 h PRN		Dizziness, headache, somnolence, fatigue, lethargy, nausea, vomiting, dyspepsia, constipation, diaphoresis, pruritus, insomnia, anxiety	Respiratory depression, confusion, coma, hallucinations, seizures, tachycardia, agitation, tremor, miosis, dyspnea, atrial fibrillation; risk of seizures especially at high doses and when co-prescribed other serotonergic medications and antidepressants, or general anesthetic, serotonin syndrome, sleep apnea, anaphylaxis, SJS, TEN, hypotension, syncope, QT prolongation	Abuse potential, misuse, alcohol or drug intoxication, risks with concomitant use with benzodiazepines or other CNS depressants, serotonin syndrome, neonatal opioid withdrawal Avoid when CrCl <30, hepatic impairment, MAO inhibitor within 2 wk, pulmonary impairment, seizure risk, head injury
<b>Buprenorphine + naloxone - OUD</b>	Opioid partial agonist	Dosing for OUD: dosage escalation starting with 2 mg/0.5 mg SL x 1, up to 8/2 mg SL on first day, up to 16 mg SL daily, usual maintenance dose 4 mg/1 mg–24 mg/6 mg SL daily	OUD, AUD: off label, adjunct in OUD	Headache, insomnia, anxiety, dizziness, depression, vertigo, rigors, vomiting, pain, withdrawal symptoms	Hepatotoxicity, misuse and dependency, adrenal insufficiency, respiratory depression, central sleep apnea, anaphylaxis, QT interval prolongation, withdrawal	Moderate-to-severe hepatic disease, consider buprenorphine monotherapy Consider use in patients with OUD and comorbid AUDs
<b>Muscle relaxants</b>						
<b>Baclofen (see below)</b>						
<b>Carisoprodol</b> - Musculoskeletal pain, acute	Centrally acting muscle relaxant	250–350 mg by mouth TID and QHS for up to 2–3 wk, taper gradually		Dizziness, drowsiness, headache	EM, angioedema, seizures, hypotension, syncope, blood cell dyscrasias	Abuse, dependency, withdrawal symptoms; caution renal impairment, hepatic impairment, seizure history or seizure risk, substance use history
<b>Cyclobenzaprine</b> - Muscle spasm	SNRI, centrally acting muscle relaxant	15–30 mg by mouth/d up to 3 wk		Dizziness, drowsiness, sedation, fatigue, constipation, dyspepsia, nausea, anxiety, confusion	Psychosis, seizures, stroke, myocardial infarction, arrhythmia, hypersensitivity, anaphylaxis	Caution in use with benzodiazepines or other CNS depressants, serotonin syndrome, alcohol use, myocardial infarction, hepatic impairment, elderly, cardiac conduction disturbance, arrhythmia, MAO inhibitor in 2 wk
<b>Methocarbamol</b> - Muscle spasm	Centrally acting muscle relaxant	1,000 mg by mouth QID, start 1,500 mg by mouth QID for 2–3 d, other dosing for IM or IV route		Dizziness, somnolence, nausea, vomiting, headache, hypotension, lightheadedness, urticaria, pruritus, rash	Seizures, syncope, bradycardia, anaphylaxis	Caution in use with benzodiazepines or other CNS depressants, alcohol use; seizure disorder, elderly, renal impairment
<b>Tizanidine</b> - Spasticity	Binds to central alpha-2 adrenergic receptors, centrally acting muscle relaxant	2 mg by mouth x 1, may repeat every 6–8 PRN, up to 3 doses/24 h, may increase by 2–4 mg/dose every 1–4 d, taper dose if prolonged, high dose use		Dizziness, somnolence, hypotension, nausea, vomiting, constipation, bradycardia, blurry vision, nervousness, hallucinations	Hallucinations, syncope, hepatotoxicity, bradycardia, withdrawal symptoms, SJS, anaphylaxis, exfoliative dermatitis	Caution in use with benzodiazepines or other CNS depressants, alcohol use; caution in breastfeeding, abrupt withdrawal, elderly patients, CrCl <25, hepatic impairment

(continued)

Table 1 (continued).

Medications and FDA indications	Mechanism of action	Typical dose	Indication/evidence	Common side effects	Serious reactions	Caution/other information
<b>Emerging medications or medications of interest/concern</b>						
<b>Baclofen</b> - Muscle relaxant used to treat spasticity	GABA <sub>B</sub> receptor antagonist	Begin with 5 mg by mouth TID, titrating up 5–10 mg/d every 3 d, most trials 30–80 mg by mouth daily	Antispasmodic, muscle spasms and pain in multiple sclerosis, AUD, hiccups - Approved for AUD treatment in France	Drowsiness, dizziness, confusion, headaches, urinary frequency, fatigue	CNS depression, respiratory depression, ataxia, depression, hallucinations, autonomic dysregulation	Creatinine at baseline
<b>Cannabis</b>	Cannabinoid		Off label: cancer pain, neuropathic pain, seizure disorder, muscle spasticity, appetite stimulation, treatment of nausea/vomiting			Caution in use with benzodiazepines or other CNS depressants, alcohol use, opioid use, or in those with alcohol use disorder or substance use disorder
<b>Cannabidiol</b>	Cannabinoid	2.5 mg/kg/dose twice daily up to 20 mg/kg/d	Rare pediatric seizure disorders	Somnolence, diarrhea, decreased appetite, and weight loss, vomiting, abdominal discomfort, gastroenteritis, fever, fatigue, insomnia, decreased platelets, increased eosinophils, sialorrhea	Hepatotoxicity, CNS depression, respiratory failure	Liver enzymes, total bilirubin, depression and suicidality, behavioral changes *Limited evidence of efficacy and low quality

Abbreviations: ALT = alanine aminotransferase, AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, AST = aspartate aminotransferase, AUD = alcohol use disorder, BID = twice daily, CNS = central nervous system, COX = cyclooxygenase, EM = erythema multiforme, ER = extended release, GABA = γ-aminobutyric acid, GI = gastrointestinal, HTN = hypertension, IM = intramuscular, IR = immediate release, IV = intravenous, NSAID = nonsteroidal anti-inflammatory drug, OUD = opioid use disorder, PRN = as needed, QHS = every night, QID = 4 times/d, SIADH = syndrome of inappropriate antidiuretic hormone secretion, SJS = Stevens–Johnson syndrome, SL = sublingual, SNRI = serotonin-norepinephrine reuptake inhibitor, TCA = tricyclic antidepressant, TEN = toxic epidural necrosis, TID = 3 times daily.

AUDs or SUDs, and medications used for pain relief in individuals with AUDs or SUDs are provided in Table 1. Recent research has highlighted nonopioid interventions for pain management, their sites of action in the brain and pain pathways, and the potential benefits of personalized and integrated approaches that use multimodal interventions (eg, cognitive-behavioral therapy [CBT], hypnosis, and neuromodulation) with transcranial magnetic stimulation or transcranial direct stimulation, anticonvulsants, antidepressants, NSAIDs, botulinum toxin, capsaicin, and lidocaine.<sup>11</sup>

When choosing a medication for use in those with acute or chronic pain who might have an AUD or SUD, prescribers should consider whether an underlying comorbid medical condition (such as liver disease, hepatitis C, or gastrointestinal [GI] bleeding) is present that might predispose an individual to complications when used with acetaminophen or NSAIDs. Concerns regarding pharmacologic interventions are listed in the context of drug misuse or withdrawal and synergistic central nervous system (CNS) depression (see Table 1). Moreover, many nonopioid medications with serotonergic properties (eg, selective serotonin reuptake inhibitors

[SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs], tricyclic antidepressants [TCAs], ondansetron, and promethazine) and opioid medications (eg, buprenorphine, tramadol, and tapentadol) may lead to a serotonin syndrome. Certain medications (such as milnacipran, pregabalin, lacosamide, tramadol, tapentadol, and most muscle relaxants) should be avoided by individuals who are taking benzodiazepines, other CNS depressants, or medications with a high potential for misuse or in those with an AUD.

Two medications not FDA approved (gabapentin and topiramate) for treatment of AUDs may benefit those with an AUD (see Table 1 for dosing and additional information on both). Gabapentin is FDA approved for the treatment of postherpetic neuralgia and has been beneficial in several pain disorders; there is also evidence for its use in those with AUD.<sup>15</sup> Evidence suggests considering use in patients with comorbid AUD, mood symptoms, anxiety, and insomnia.<sup>15</sup> Gabapentin should be used with caution in patients who are taking sedatives/hypnotics (eg, benzodiazepines or phenobarbital), as their effects are synergistic. However, gabapentin can be misused.<sup>11,15</sup> Topiramate is FDA



approved for migraine prophylaxis and has been useful in AUDs, cocaine use disorder, posttraumatic stress disorder (PTSD), binge-eating disorder, and weight loss.<sup>15</sup> Several other antiepileptic medications have analgesic properties worth noting. Although valproate has shown some benefit in heavy drinking, elevated liver enzymes may also serve as a source of concern, and significant side effects limit its usefulness. However, it remains useful in pain disorders and is FDA approved for migraine headache prophylaxis and is used off label for diabetic neuropathy and postherpetic neuralgia. Similarly, carbamazepine is FDA approved for the treatment of neuropathy and neuralgia; however, it has been associated with the metabolic induction of many medications, blood cell dyscrasias, and elevating liver function tests. Oxcarbazepine has off-label evidence for use in neuropathy, neuralgia, and trigeminal neuralgia, and it may be better tolerated than carbamazepine; however, hyponatremia may be more common with its use than with carbamazepine. Several medications (such as oxcarbazepine) should be prescribed with care in women of childbearing age due to their potential interactions with oral contraceptives or their risk of teratogenicity (with valproate, lamotrigine, and topiramate). Tramadol is a  $\mu$ -opioid agonist that also exhibits serotonergic activity, so that coprescription with SSRIs and SNRIs increases the risk for serotonin syndrome. Furthermore, both tramadol and tapentadol can lower the seizure threshold, particularly when used at higher doses. Cases of seizures have been reported when tramadol and tapentadol have been used in combination with TCAs, SSRIs, general anesthetics, morphine, or ondansetron. When considering use of muscle relaxants for muscle spasms, clinicians should be concerned about their potential for misuse. In addition, cyclobenzaprine has serotonergic properties, which raises the risk for serotonin syndrome when it is prescribed along with other serotonergic medications, including ondansetron. Baclofen, a muscle relaxant, has been approved for AUD treatment in France. It acts as a  $\gamma$ -aminobutyric acid ( $GABA_B$ ) agonist that has off-label evidence for the management of musculoskeletal pain and pain associated with multiple sclerosis. Finally, tizanidine is often used in the SUD population for detoxification purposes, as well as to minimize OUD withdrawal symptoms given its  $\alpha$ -adrenergic properties that are similar to clonidine. It is generally considered safer and a better alternative to more sedating muscle relaxants; however, it may be associated with significant risks (see Table 1).

Many patients use cannabis for pain relief, but supporting evidence is limited. While several randomized controlled trials have explored the use of cannabis for the treatment of cancer-related pain, the evidence for its use is not robust.<sup>16</sup> The use of medical cannabis to manage chronic nonmalignant pain raises safety

concerns due to the lack of high-quality evidence in this area; moreover, it may exacerbate underlying addiction issues or lead to a heightened risk of substance use, and it has generated concerns about its use when combined with benzodiazepines, other CNS depressants, alcohol, or opioids. Additionally, chronic cannabis use is associated with tolerance and withdrawal symptoms when discontinued. Cannabinol and cannabidiol have limited psychoactive effects, so they may have less potential for addiction, but more research is needed on how effective they are in reducing pain.

### Which Nonpharmacologic Treatments Facilitate Successful Treatment?

Patients often face barriers to the initiation or maintenance of treatments that could improve their health, functioning, or quality of life. These barriers can be external, such as insurance limitations or geographic distance to treatment facilities, or internal, such as fear, uncertainty, or lack of confidence in one's own ability to make or sustain the change. For individuals with chronic pain and an SUD, these barriers are often circular. For instance, Stumbo and colleagues<sup>17</sup> found that engagement in treatment for OUD was commonly precluded by patients' fear of uncontrolled pain. Accordingly, motivational interviewing has been incorporated into care models for chronic pain, SUDs, and their combination to help overcome the motivational barriers that can impede treatment adherence.<sup>18,19</sup> Motivational interviewing is a collaborative, patient-centered method of communication that explores ambivalence, elicits change-oriented self-talk, and enhances intrinsic motivation for behavioral change.<sup>20</sup> It can be used as a stand-alone intervention to help broach the topic of change or as an adjunctive therapeutic approach to an existing care plan. Motivational interviewing techniques emphasize the collaborative identification of goals that are consistent with a patient's values. They also help patients to engage with their own reasons or needs, which make attempting change worthwhile, and to aid in the formulation of realistic, achievable plans for change that inspire confidence and hope. Importantly, while clinicians help to guide the conversation, patients have the ultimate say on decision-making.

Further, as mentioned previously, non-narcotic interventions for pain management, including CBT and mindfulness-based therapies, are increasingly used to successfully treat co-occurring chronic pain and SUDs. These interventions help individuals build awareness of the antecedents and consequences of their substance misuse or other maladaptive pain management behaviors. They also teach strategies to disrupt the "autopilot" nature of use behavior and to develop healthier means of responding to cravings and triggers.<sup>15</sup>

Table 2.

**Useful Screening Tests, Clinical Practice Guidelines, and Consensus Statements**

Screening Tests	
<b>Alcohol Use Disorders Identification Test</b>	Screening test that can help identify those with hazardous drinking or active AUD.
<b>Drug Abuse Screening Test (DAST-10)<sup>3</sup></b>	Screens for multiple SUDs and assesses problems related to substance use. The DAST-10 has the strongest psychometrics and is widely used in primary care settings.
<b>Opioid Risk Tool<sup>23</sup></b>	Brief, self-report screening tool to assess risk for opioid misuse among individuals who are prescribed opioids for the treatment of chronic pain.
<b>Screener and Opioid Assessment for Patients with Pain<sup>24</sup></b>	Easy-to-use questionnaire to help determine how much monitoring an individual on long-term opioid therapy might require. Evaluation of the risk for overdose and developing an OUD.
<b>Brief Pain Inventory<sup>10</sup></b>	Multidimensional questionnaire for the assessment of the quality and intensity of pain.
Clinical Practice Guidelines and Consensus Statements	
<b>CDC Clinical Practice Guideline for Prescribing Opioids for Pain<sup>1</sup></b>	Available at <a href="https://www.cdc.gov/mmwr/volumes/71/rr/rr7103a1.htm">https://www.cdc.gov/mmwr/volumes/71/rr/rr7103a1.htm</a>
<b>American Society of Addiction Medicine Consensus Statement on the Appropriate Use of Drug Testing in Clinical Addiction Medicine</b>	Available at <a href="https://www.asam.org/quality-care/clinical-guidelines/drug-testing">https://www.asam.org/quality-care/clinical-guidelines/drug-testing</a>

Abbreviations: AUD = alcohol use disorder, OUD = opioid use disorder, SUD = substance use disorder.

### What Are the Risks and Challenges Associated With Using a Potentially Addictive Medication in Someone With an SUD and the Risks of Not Treating Them?

Approximately 15 million Americans have an AUD, while roughly 116 million US adults experience chronic pain.<sup>21</sup> Maleki and colleagues<sup>21</sup> noted a bidirectional relationship between having an AUD and chronic pain, with AUDs being more prevalent among those with chronic pain, while noting alcohol's pain-relieving effects, which may contribute to the risks associated with co-occurring opioid use. In addition, brain changes associated with chronic AUDs can lead to chronic neuropathic pain.<sup>21</sup> The relationship among alcohol misuse, chronic pain, and opioid use is complex and influenced by multiple factors (such as genetics, the environment, and social factors).<sup>21</sup> When providing care to individuals with co-occurring pain and an SUD, a holistic, team-based approach, which prioritizes dignity and respect, is crucial to minimize the risk of relapse. Opioids should not be withheld from individuals in significant pain when they are indicated. Individuals with an OUD and co-occurring pain are often undertreated for a variety of reasons. Concerns about the adverse effects of coprescribing short-acting and long-acting opioids (like methadone), the addictive potential of opioids, and labeling the requests of those with uncontrolled pain as "drug-seeking behaviors" can lead to the inadequate treatment of pain by health care professionals.<sup>22</sup> Actively involving patients, those in their support network, and specialists in pain management and addiction can help mitigate the risk for relapse or the escalation of alcohol or substance use, while providing empathic, integrated, holistic approaches.<sup>22</sup>

When concern arises for OUDs in individuals who are prescribed an opioid, it may be challenging to distinguish among inadequate control of pain, tolerance to a medication, and an SUD.<sup>23</sup> Signs that may herald an OUD include frequent requests for early refills, requests for specific medications, and reports from a state prescription monitoring program that lists prescriptions from multiple providers. Those who are diagnosed with an OUD should be offered the full spectrum of nonpharmacologic and nonopioid therapies for pain. Individuals who are already taking prescription opioids should be transitioned to medications for OUD that have analgesic properties, such as buprenorphine or methadone.<sup>23</sup> Screening tools, such as the Opioid Risk Tool, to predict aberrant behaviors in opioid-treated patients and the Screener and Opioid Assessment for Patients with Pain may help in the evaluation of the risks for developing an OUD and a drug overdose (see Table 2).<sup>23–25</sup> Risk mitigation strategies for chronic opioid treatment emphasize goals of care, structure through frequent visits, a shorter duration for refills, urine toxicology screening, patient agreements, and use of prescription drug monitoring programs.<sup>25</sup> In addition, it is wise to focus on decreasing the risk of overdose through discussions with patients, including the use of sedating medications and substances, and providing naloxone education and prescription.<sup>25</sup>

### Are Opioids Used for Pain Control Contraindicated in Those With an AUD or SUD?

Managing pain (either acute or chronic) in those with an SUD creates challenges. One such concern centers around the risk of prescribing an opioid to those with a

concurrent SUD; given the reluctance to prescribe opioids, pain is often undertreated.<sup>26</sup>

Challenges in pain management differ for acute and chronic pain. In a person with an OUD, tolerance to opioids often requires use of higher opioid doses to achieve adequate relief from pain. When medications (such as methadone and buprenorphine) are prescribed for an OUD, supplemental doses of opioid analgesics should be provided (for the shortest possible period) and tapered if their use is required for longer than several days. Both methadone and buprenorphine are FDA approved for pain management; however, methadone cannot be prescribed solely for OUD by a provider outside of a methadone maintenance treatment program clinic. Distinctions between methadone (a full opioid agonist) and buprenorphine (a high-affinity partial agonist) are such that patients on buprenorphine who present with acute pain may need higher doses of short-acting full-agonist opioids to overcome buprenorphine's high-affinity strong binding to the  $\mu$ -opioid receptors. In contrast, patients on methadone require more careful monitoring due to the risk of iatrogenic overdose related to the addictive effects of full-agonist opioids.

Physicians often choose between providing adequate pain control and the risks of medication misuse (and its attendant harmful consequences).<sup>27</sup> Unfortunately, chronic pain can lead to dysphoria, which tends to increase the risk of substance misuse. In addition, since alcohol has analgesic properties,<sup>28</sup> some individuals with chronic pain drink alcohol as a form of self-medication. However, chronic heavy alcohol use is associated with hyperalgesia.<sup>29–31</sup> Chronic opioid exposure in the context of having an OUD has also been linked to hyperalgesia.<sup>32,33</sup> Conversely, chronic pain may also elevate the risk of developing an OUD.<sup>34,35</sup>

Despite its challenges, treatment of chronic pain improves outcomes in those with SUDs. Nonopioid management of chronic pain is preferred and should be a first-line approach. In addition to standard precautions when prescribing opioid agents for chronic pain,<sup>36</sup> a comprehensive approach to patients with an SUD is needed. Several instruments have been developed to guide the treatment of patients with chronic pain and SUDs,<sup>37,38</sup> which provide guidance for prescribing opioids to patients with a history of addiction.

It is crucial to perform a thorough risk assessment and engage in careful discussions that outline treatment agreements (with frequent visits and shorter prescriptions, regular toxicology screening, and, most importantly, referral to SUD services including individual counseling, group therapy, and recovery coaches). In addition, careful screening of patients with chronic pain and referral to psychiatric care, when appropriate, is needed.<sup>39</sup>

In 2022, the CDC updated its clinical practice guideline for prescribing opioids for pain control.<sup>1</sup>

Recommendations include checking prescription monitoring programs, conducting regular urine toxicology screening, offering naloxone, and avoiding or exercising caution when prescribing opioids in concert with other sedatives, such as benzodiazepines. Patients with an OUD should receive FDA-approved medication (eg, methadone or buprenorphine) and a referral for counseling.

Regular and timely urine toxicology screening is useful when prescribing opioids for patients with an SUD. Results of the urinary toxicology screens can inform the selection and dose of an opioid medication, especially with agents that suppress respiratory drive (such as alcohol, benzodiazepines, and other sedatives). Of note, xylazine, an  $\alpha_2$ -adrenergic agonist used as a sedative in veterinary medicine, is increasingly present in illicit drugs in the United States and is often in the system at the time of opioid overdose deaths.<sup>1,40</sup> Health care providers should be aware that not all substances routinely appear on toxicology screens; therefore, clinicians should be familiar with the limitations of urine toxicology screens available and order confirmatory testing when indicated.

### Can Methadone or Buprenorphine Be Used for Those With Chronic Pain and an SUD?

Fortunately, buprenorphine and methadone are promising options for pain control in people with an SUD.<sup>41</sup> Buprenorphine might be preferred due to its ceiling effect on respiratory suppression. There is also some evidence that buprenorphine might be associated with reduced levels of alcohol consumption.<sup>42,43</sup> However, there are also reports of fatal poisonings when alcohol and buprenorphine have been combined, especially when it is inhaled or injected intravenously. In a meta-analysis comparing methadone to buprenorphine for the treatment of OUDs, methadone was better for retention in treatment.<sup>44</sup> Among secondary outcomes, buprenorphine was associated with reduced use of cocaine, fewer cravings and less anxiety, and higher treatment satisfaction. People receiving methadone had fewer hospitalizations and less alcohol use.

Specific concerns have arisen when CNS depressants (such as alcohol and benzodiazepines) are used in patients being treated with opioids (due to their risk of inducing respiratory depression and death). About one-third of patients on medication for opiate use disorders (MOUD) have an AUD; therefore, careful screening of patients for excessive alcohol use is needed, as is timely referral to a withdrawal management program if indicated.<sup>45,46</sup> The FDA recommends that medications not be withheld for the treatment of OUD in patients taking a CNS sedative, but patient education on the risks of coadministration is needed. With attention paid to proper precautions,

Table 3.

**Common Medications and Causes of False-Positive (and False-Negative) Urine Toxicology<sup>a</sup>**

Amphetamines	Benzodiazepines	Cannabis	Cocaine	Opioids	Phencyclidine
Amantadine	Oxaprozin	Cannabidiol (CBD) oil	Coca leaf tea	Dextromethorphan	Dextromethorphan
Bupropion	Sertraline	Efavirenz	Topical anesthetics with cocaine	Diphenhydramine	Diphenhydramine
Chlorpromazine	Alprazolam (false negative)	Hemp seed oil	Salicylates (false negative)	Poppy seeds	Ibuprofen
Desipramine	Clonazepam (false negative)	NSAIDs		Quetiapine (positive for methadone)	Ketamine
Labetalol		Pantoprazole		Quinine	Meperidine
Metformin		Synthetic cannabinoids (eg, K2/Spice) (false negative)		Quinolone antibiotics	Tramadol
Ofloxacin				Rifampin	Venlafaxine
Phentermine				Verapamil	
Phenylephrine				Semisynthetic and synthetic opioids (false negative)	
Pseudoephedrine					
Ranitidine					
Selegiline					
Trazodone					
Venlafaxine					
MDMA					

Synthetic cathinones “bath salts”  
(stimulant-like effect, false negative)

<sup>a</sup>Based on Argoff et al<sup>48</sup> and Algren and Christian.<sup>49</sup>

Abbreviations: MDMA = 3,4-methylene-dioxymethamphetamine, NSAID = nonsteroidal anti-inflammatory drug.

prescribing opioids to patients with an SUD can be successful and improve their quality of life.<sup>47</sup>

### Should Screening Tests/Blood Levels Be Obtained to Assess Adherence With the Treatment Regimen?

Experts in pain management, addiction medicine, primary care, pharmacotherapeutics, and toxicology have developed consensus recommendations for urine drug monitoring (UDM) in patients with chronic pain who are prescribed opioids.<sup>48</sup> Argoff and colleagues<sup>48</sup> recommended the use of definitive UDM testing that includes quantitative confirmatory tests, such as gas chromatography/mass spectrometry, to assess baseline opioid use and misuse in individuals with chronic pain who are considered for opioid treatment, as well as for ongoing monitoring of patients receiving opioids for chronic pain. In addition, they advocated for a comprehensive approach to the assessment and risk stratification that is based on a variety of factors (such as history of an SUD or a psychiatric disorder), as well as on use of validated tools to assess for opioid misuse and use disorder and checking prescription drug monitoring programs and previous UDM results, when available.<sup>48</sup> They highlighted the variability of UDM in those

prescribed opioids for chronic pain in advocating for standardized guidance. Additionally, the authors<sup>48</sup> noted that point-of-care immunoassays should be used for initial UDM screening that can provide rapid results at a low cost; however, they can yield false-positive results due to cross-reactivity and false-negative results from drug concentration cutoffs. Further, some opioids and benzodiazepines are not detected well by immunoassays.<sup>48</sup> False-negative and false-positive urine drug screens are commonly seen with many psychotropics (see Table 3).<sup>48,49</sup>

Similarly, in those with an SUD, the American Society of Addiction Medicine Consensus Statement on the Appropriate Use of Drug Testing in Clinical Addiction Medicine provides a comprehensive guideline for optimizing the use of toxicology screening within the context of addiction medicine (see Table 2). It outlines a framework for integrating urine toxicology screening into clinical practice as a valuable tool for assessing and managing SUDs.<sup>50</sup> Jarvis and colleagues<sup>50</sup> highlighted the importance of using drug testing as part of a comprehensive assessment and treatment process; they considered factors such as an individual's history of an AUD or SUD, medical and psychiatric comorbidities, treatment goals, and risk for relapse. The document

**Table 4.**  
**Resources for Information on SUDs**

Resource	Information	Website
<b>American College of Academic Addiction Medicine (ACAAM)</b>	ACAAM's website offers an educational portal, weekly National Addiction Medicine Didactic Curriculum, and an online community to connect, collaborate, and educate peers.	<a href="https://www.acaam.org">https://www.acaam.org</a>
<b>American Society of Addiction Medicine (ASAM)</b>	Committed to improving access to high-quality, evidence-based addiction prevention and treatment with clinical practice guidelines, the <i>Journal of Addiction Medicine</i> , textbooks, patient resources, and education.	<a href="https://www.asam.org">https://www.asam.org</a>
<b>National Harm Reduction Coalition</b>	A nationwide advocacy organization with the goal of promoting the health and dignity of individuals and communities affected by drug use. The online resource center covers a wide variety of harm reduction topics, including how to access naloxone.	<a href="https://harmreduction.org/">https://harmreduction.org/</a>
<b>National Institute on Alcohol Abuse and Alcoholism (NIAAA)</b>	A federal agency with the mission to "generate and disseminate fundamental knowledge about the effects of alcohol on health and well-being, and apply that knowledge to improve diagnosis, prevention, and treatment of alcohol-related problems, including alcohol use disorder, across the lifespan."	<a href="https://www.niaaa.nih.gov/">https://www.niaaa.nih.gov/</a>
<b>National Institute on Drug Abuse (NIDA)</b>	A federal agency whose mission is to "advance science on drug use and addiction and to apply that knowledge to improve individual and public health."	<a href="https://nida.nih.gov/Opioids and Pain Management">https://nida.nih.gov/Opioids and Pain Management</a> <a href="https://nida.nih.gov/nidamed-medical-health-professionals/opioids-pain-management">https://nida.nih.gov/nidamed-medical-health-professionals/opioids-pain-management</a>
<b>Substance Abuse and Mental Health Services Administration (SAMHSA)</b>	An agency within the US Department of Health and Human Services that "leads public health efforts to advance the behavioral health of the nation and improve the lives of individuals living with mental and substance use disorders and their families."	<a href="https://www.samhsa.gov/">https://www.samhsa.gov/</a>
<b>SAMHSA In Brief: Treating Sleep Problems of People in Recovery from Substance Use Disorders</b>	Excellent reference on assessment and treatments for sleep problems in patients with SUDs with links to additional web resources.	<a href="https://store.samhsa.gov/sites/default/files/sma14-4859.pdf">https://store.samhsa.gov/sites/default/files/sma14-4859.pdf</a>
<b>Massachusetts Consultation Services for Treatment of Addiction and Pain (MCSTAP)</b>	Within Massachusetts, MCSTAP offers real-time phone consultation on safe prescribing and managing care for adults with chronic pain, SUD, or both. Consultation is free for all patients statewide, regardless of insurance.	<a href="https://www.mcstap.com/">https://www.mcstap.com/</a>
<b>Providers Clinical Support System (PCSS)</b>	Funded by SAMHSA, offers a national training and clinical mentoring project for the treatment of OUD.	<a href="https://pcssnow.org/">https://pcssnow.org/</a>
<b>Boston University SCOPE (Safer/Competent Opioid Prescribing Education) of Pain</b>	A program that consists of online activities, monthly live national webinars, resources, and supplemental, focused content to extend the knowledge of pain in health care settings.	<a href="https://www.scopeofpain.org">https://www.scopeofpain.org</a>
<b>FindTreatment.gov</b>	Free and anonymous resources for treatment facilities in the United States can be found for substance use and/or mental health.	<a href="https://findtreatment.gov/">https://findtreatment.gov/</a>

Abbreviations: OUD = opioid use disorder, SUD = substance use disorder.

also provided guidance on the frequency, timing of drug testing, frequency of testing based on stage of treatment, risk for relapse, and progress in achieving goals in a personalized approach. The consensus document also reviewed the different testing available (including toxicologic testing of urine, oral fluid, and other laboratory-based tests to detect a range of substances). They further recommended drug testing in addition to other interventions such as counseling, medication-assisted treatment, and psychosocial support that may be best provided by addiction professionals.

### How Effective Are Alcoholics Anonymous and Narcotics Anonymous for AUD and SUDs?

Mutual-help groups, also known as mutual-aid, peer support, or self-help groups, are free, widely available, and effective for helping individuals reduce heavy drinking, achieve abstinence from substances, and sustain long-term remission from SUDs.<sup>51–53</sup> Mutual-help participation has also been linked to increased rates of outpatient treatment completion among individuals from historically marginalized groups who are in recovery from a primary OUD.<sup>54</sup> These groups support recovery

through several mechanisms, including facilitating self-awareness and perspective taking, forming stabilizing and supportive bonds, developing coping skills, engaging in interesting and rewarding activities, and fostering hope and confidence in one's ability to change.<sup>55</sup>

A wide array of mutual-help options is available (encompassing a variety of spiritual and secular philosophies, as well as a range of specialty subgroups [eg, women's groups; lesbian, gay, bisexual, transgender, queer or questioning, or another diverse gender identity; black, indigenous, and other people of color, military and first responder, and young adult communities]). Accordingly, individuals are encouraged to try different options and engage in the group or groups with which they feel a sense of cohesion.<sup>56,57</sup> Individuals who become actively involved in their chosen peer-support community (through weekly attendance, volunteering, working with a sponsor, or having a home group) tend to have more positive outcomes.<sup>58</sup> Platforms, such as *In the Rooms* ([www.intherooms.com](http://www.intherooms.com)), provide streamlined access for locating in-person and online mutual-help meetings.

Among the mutual-help options, 12-step programs, such as Alcoholics Anonymous (AA) and Narcotics Anonymous (NA), have the most well-established evidence base for benefitting individuals with abstinence goals. These groups have comparable success rates to clinical care when paired with 12-step facilitation,<sup>51</sup> and individuals with primary SUDs other than AUD benefit similarly from NA or AA participation.<sup>59</sup> The literature around 12-step experiences for patients prescribed MOUD is more complex due to negative attitudes toward MOUD in some 12-step settings. Overall, research indicates that 12-step participation benefits this subgroup of individuals, and some studies have linked 12-step participation with improved adherence among individuals prescribed buprenorphine/naloxone.<sup>60</sup> However, a recent study<sup>61</sup> of 12-step participants highlighted ways in which stigmatizing beliefs can manifest in some 12-step groups (eg, refusing to sponsor people using MOUD) and strategies that health care providers and prospective participants can use to help prepare for or mitigate potential stigma when engaging in 12-step programs.

For patients seeking alternatives to 12-step groups, secular options, such as SMART Recovery, LifeRing, and Women for Sobriety, have been accumulating empirical support, with studies showing comparable abstinence outcomes to AA for individuals with AUD.<sup>53</sup> Moreover, the themes or mechanisms of change associated with 12-step engagement occur at equal rates in both 12-step and non-12-step groups.<sup>55</sup> Less research exists on the benefits of mutual-help groups for individuals with harm-reduction goals (eg, patients interested in safer use

practices or in reducing use rather than abstinence from all substances). However, there is early support for peer-operated recovery community centers, which have been associated with improved quality of life and decreased psychological distress.<sup>62</sup> Based on the philosophy that there are multiple recovery pathways, recovery community centers provide a range of psychosocial supports, including social activities, nondenominational all-recovery peer support groups, and connection to housing, education, volunteer, and employment opportunities.

### Where Can Patients Obtain Specialty Consultation, Support, and Treatment?

Several professional and government agencies provide valuable resources for learning more about SUDs and/or the management of comorbid pain and substance use. Sleep problems in individuals with pain disorders and SUDs are common. The Substance Abuse and Mental Health Services Administration, *In Brief: Treating Sleep Problems of People in Recovery from Substance Use Disorders*<sup>63</sup> is an excellent summary with additional web resources to help with guidance. These resources are included in Table 4. In addition, free and anonymous resources for treatment facilities in the United States can also be found for substance use and/or mental health through FindTreatment.gov (<https://findtreatment.gov/>).

### What Happened To Ms B?

Once Ms B recovered and was medically stable, she was started on oral buprenorphine for pain control. The opioid receptor antagonist naltrexone was discontinued prior to buprenorphine induction. Gabapentin was tapered off, and acamprosate was continued for the management of her AUD. She was transitioned to subcutaneous extended-release buprenorphine 2 weeks after her hospital discharge. She completed an intensive outpatient program for SUDs, attended AA meetings, and was connected to a recovery coach.

## CONCLUSION

It is crucial to perform a thorough risk assessment and to engage in careful discussions that outline treatment agreements (with frequent visits and shorter prescriptions, regular toxicology screening, and, most importantly, referral to SUD services, including individual counseling, group therapy, and recovery coaches). In addition, careful screening of patients with chronic pain and referral to psychiatric care, when appropriate, is needed.

Fortunately, buprenorphine and methadone are promising options for pain control in people with

an SUD. Nevertheless, regular and timely urine toxicology screening is useful when prescribing opioids for patients with an SUD. Results of the urinary toxicology screens can inform the selection and dose of an opioid medication, especially when agents that suppress respiratory drive (such as alcohol, benzodiazepines, and other sedatives) are being used.

Since about one-third of patients on MOUDs have an AUD, careful screening of patients for excessive alcohol use is needed, as is timely referral to a withdrawal management program, if indicated. Mutual-help groups, also known as mutual-aid, peer support, or self-help groups, are free, widely available, and effective for helping individuals reduce heavy drinking, achieve abstinence from substances, and sustain long-term remission from SUDs. Moreover, several professional and government agencies provide valuable resources for learning more about SUDs and/or the management of comorbid pain and substance use.

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