Chapter 7
Medications for Substance Use and Relapse Prevention

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Introduction

Adolescent- and young adult-onset substance use disorders (SUDs) are associated with elevated morbidity and mortality [1, 2]. Early identification and successful treatment of youth with SUDs have the potential to alter developmental trajectories and improve long-term health outcomes. Evidence-based psychosocial interventions represent the primary treatment modality recommended for youth with SUD [1]. A number of evidence-based psychosocial interventions have demonstrated short-term efficacy and effectiveness for treatment of SUDs in youth. These interventions generally result in a modest reduction in substance use on average, but with significant individual differences in treatment response across adolescents [2]. Many youth that initiate substance use treatment, even when evidence-based interventions are applied, drop out prior to treatment completion, do not substantially reduce their substance use, or relapse within 6 months of treatment engagement. Thus, a significant minority of youth with an SUD who present for treatment fail to improve on traditional study outcomes with current "gold-standard" treatments.

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Recent clinical research priorities have focused on developing novel treatment strategies that enhance treatment response and improve functional outcomes in both adolescents and adults [1, 2]. One treatment strategy that has demonstrated effectiveness in adult SUDs has been to combine evidence-based psychosocial interventions with adjunctive pharmacotherapy. A growing body of evidence suggests that medications for addiction treatment (MAT, formerly known as medication-assisted treatment) improve treatment outcomes in adults with opioid, alcohol, and tobacco use disorders [2]. In contrast to the ample research in adults, few studies have been completed in youth. Here, we review the scientific literature on clinical studies of pharmacotherapies and MAT for SUDs in adolescents and young adults.

Significance of Developmental Differences in SUD Interventions for Youth

Developmental differences in biological, mental, and social processes exist between adults and adolescents and carry implications for psychosocial and pharmacologic SUD interventions [1–3]. During adolescence, the neural circuitry involved in cognitive control, motivation, and emotion processing undergoes staggered maturational shifts leading to a developmentally "sensitive period" of imbalanced circuit function reflected in a relatively "weak" top-down cognitive regulation system and a relatively "strong" bottom-up emotion reactivity and reinforcement system [3]. (These development considerations are discussed in greater depth in Chap. 2: "Developmental Perspectives and Risk Factors for Substance Use.") Age-related differences in hepatic function, metabolic enzyme activity, and neurotransmitter system function also exist and result in adolescent versus adult differences in pharmacokinetics and pharmacodynamics for commonly misused substances, as well as psychotropic medications [2, 3].

Categories of Pharmacological Treatments

Medications used in the treatment of addictive disorders generally target one of the three SUD-related domains: (a) acute withdrawal symptoms and syndromes as part of detoxification, (b) reduction of cravings and substance use as part of maintenance SUD treatment, or lastly (c) overdose prevention as part of emergency management of high-risk individuals [4]. A number of medications have been approved by the US Food and Drug Administration (FDA) for the treatment of SUDs in adults. To date, buprenorphine is the only addiction medication that is FDA-approved for use in adolescents, and it is only approved for ages 16 and older [2]. While scientific evidence suggests that other addiction medications may improve outcomes (see Table 7.1), the use of these medications to treat SUD in adolescents is considered "off-label."

Table 7.1 Substance use disorder pharmacotherapies with limited safety, tolerability, and efficacy data in adolescents and young adults

Substance use disorder	Medication target			Level of evidence[a]
	Withdrawal/ detoxification	Maintenance or cessation aids	Overdose prevention	
Opioids	Buprenorphine, buprenorphine-naloxone	Buprenorphine, buprenorphine-naloxone		Grade B (level 2 evidence)
	Methadone	Methadone		Grade C (level 3 evidence)
	Clonidine			Grade B (level 2 evidence)
		Oral naltrexone or long-acting injectable extended-release naltrexone		Grade C (level 3 evidence)
			Intranasal or intramuscular naloxone	Grade C (level 3 evidence)
Alcohol	Benzodiazepines			Grade C (level 3 evidence)
		Oral naltrexone or long-acting injectable extended-release naltrexone		Grade C (level 3 evidence)
		Disulfiram		Grade C (level 3 evidence)
		Ondansetron		Grade C (level 3 evidence)
		Topiramate		Grade C (level 3 evidence)
Tobacco		Nicotine replacement therapy (patch, gum, lozenge, nasal spray, or inhaler)		Nicotine patch, grade B (level 2 evidence); nicotine gum and nasal spray, grade C (level 3)
		Bupropion-sustained release		Grade B (level 2 evidence)
		Varenicline		Grade B (level 2 evidence)
Cannabis		*N*-acetylcysteine		Grade B (level 2 evidence)
	Gabapentin	Gabapentin		Grade C (level 3 evidence)

Note: Buprenorphine (approved for ages > 16 years) is the only current FDA-approved medication for the treatment of substance use disorders in adolescents

[a]Levels of evidence presented are based on the US Preventative Services Task Force Strength of Recommendation Taxonomy approach to grading evidence in the medical literature. Levels of evidence include level 1, good-quality, patient-oriented evidence including systematic reviews, meta-analyses, and well-designed randomized controlled trials with consistent findings; level 2, limited-quality patient-oriented evidence including lower-quality/less consistent systematic reviews, meta-analyses, or clinical trials as well as cohort and case-control series; and level 3, other evidence in the form of consensus guidelines, disease-oriented evidence, and case series. These levels of evidence are used to determine a strength of recommendation grade, which includes A (good-quality, patient-oriented evidence), B (limited-quality, patient-oriented evidence), C (other evidence), and no recommendation

Medications to Treat Acute Withdrawal Syndromes

Many youth with SUDs report acute and/or protracted withdrawal symptoms upon cessation of alcohol and other drugs. While adolescents, on average, experience less intense withdrawal compared to adults, youth who do experience withdrawal symptoms are at elevated risk for poor treatment outcomes and persistent drug use. As such, providers should assess for withdrawal symptoms and syndromes in all youth presenting with SUDs. Based upon the drug the patient is withdrawing from, the severity of withdrawal symptoms, and/or other risk factors, providers may consider using a medication to treat the acute withdrawal syndrome.

Opioid Withdrawal Syndrome

Opioid withdrawal (OW) is the only acute withdrawal syndrome for which controlled studies have been completed in adolescent samples. This syndrome is often accompanied by anxiety, restlessness, bone or joint aches, lacrimation (tearing), rhinorrhea (runny nose), mydriasis (dilated pupils), yawning, tremor, abdominal cramping, diarrhea, tachycardia (elevated heart rate), and diaphoresis (sweating). The onset and duration of symptoms depend on the half-life of the opioid. For short-acting opioids such as heroin, symptoms often peak within 48–72 h and resolve within 7 days. However, some symptoms such as insomnia and irritability may persist beyond this time period.

Buprenorphine-naloxone, a mu-opioid receptor partial agonist, has been shown to effectively reduce OW symptoms across three controlled studies in adolescents [5, 6]. Please refer to Case 4 in Section IV for further details on buprenorphine and how it may be used in clinical practice. Clonidine, an alpha-2-agonist and non-opioid detoxification medication, has also been shown to be effective at reducing OW symptoms [5]. Marsch and colleagues compared the efficacy of clonidine and buprenorphine, as part of a 28-day outpatient opioid detoxification protocol, in a double-blind, randomized controlled trial [5]. Clonidine and buprenorphine were both effective at reducing OW symptoms, but compared to the clonidine group, youth in the buprenorphine arm had fewer opioid-positive urines and were more likely to remain in treatment and initiate a non-agonist maintenance treatment.

Given these findings, buprenorphine should be the detoxification agent of choice in youth with moderate-to-severe OUD and has shown to be effective in outpatient and inpatient settings. For youth and families of youth with less severe OUD or those that are interested in non-opioid detoxification medications, clonidine has also reduced withdrawal symptoms, but is associated with poorer treatment engagement compared to buprenorphine [5].

Alcohol Withdrawal Syndrome

Alcohol withdrawal syndrome (AWS) is rare in adolescents. Presenting symptoms may include anxiety, tremor, diaphoresis, elevated blood pressure, nausea/vomiting, headache, auditory/visual hallucinations, or in rare cases in adolescents, seizures. To date, no controlled studies have examined pharmacotherapy interventions for AWS in adolescents. Any individual presenting with an alcohol use disorder (AUD) should be evaluated for AWS. Clinical guidelines for AWS in youth are modeled after best practices in adults. Benzodiazepines are currently the first line of pharmacotherapy for treatment of AWS in adults. Consensus guidelines suggest that adolescents with severe AUD who present with moderate-to-severe AWS should be treated with benzodiazepines in inpatient treatment settings [7].

Medications for Maintenance SUD Treatment

Opioid Use Disorder Pharmacotherapies

Opioid maintenance pharmacotherapy can broadly be categorized into agonist (buprenorphine and methadone) and antagonist (naltrexone) treatments. OUD pharmacotherapy should always be provided in conjunction with psychosocial interventions. The intensity of clinical management and consideration for MAT in adolescents should be based on the severity of opioid use and the presence of negative prognostic factors such as intravenous drug use, overdose risk, co-occurring psychiatric disorders, and prior failed psychosocial treatments [2]. Treatment of youth with mild-to-moderate severity OUD and few negative prognostic factors should involve medically assisted detoxification for OWS when indicated, followed by psychosocial interventions. Adolescents with severe OUD or multiple negative prognostic factors usually require higher-intensity treatment (e.g., inpatient/residential care) and are more likely to benefit from adjunctive OUD pharmacotherapy [6, 8]. Indeed, the American Academy of Pediatrics now recommends that adolescents with severe OUD routinely receive MAT.

How long youth with OUD should remain on maintenance pharmacotherapy is unclear. Growing evidence from naturalistic studies support the use of MAT with buprenorphine, methadone, and naltrexone in young adults with OUD [9]. Conversely, few pharmacotherapy trials have been completed in adolescents and none for longer than 12 weeks. The potential harms of long-term agonist-based maintenance treatment for adolescent OUD have not yet been studied [10]. For providers considering OUD pharmacotherapy in adolescents, the possible negative effects of chronic opioid agonism on brain development must be weighed against the risk for overdose and impact on brain development of persistent versus intermit-

tent street opiate/opioid use. More research is needed to clarify the efficacy and safety of long-term agonist treatment in this population.

Methadone

Methadone maintenance treatment (MMT) is currently FDA-approved for individuals under 18 with OUDs that have had two or more treatment failures of drug-free detoxification followed by psychosocial interventions [10]. In practice, this restriction, combined with the poor availability of methadone maintenance programs who accept individuals under 18, has resulted in exceptionally few adolescents who receive methadone for OUD treatment. To date, no controlled studies examining MMT for the treatment of adolescent OUD exist. Much of the literature that has informed MMT guidelines in youth is older (1970s) and used naturalistic or observational study designs.

Buprenorphine

Buprenorphine, a partial agonist of the mu-opioid receptor, is FDA-approved for OWS and maintenance OUD treatment in individuals 16 years or older. A multisite randomized clinical trial completed through the NIDA Clinical Trials Network (CTN) in adolescents and young adults (n = 152) examined 2-week short-term buprenorphine-naloxone detoxification (detox group) versus 8-week extended medication-assisted therapy with buprenorphine-naloxone [6]. The results of the study showed that compared to the detox + counseling group, the group receiving buprenorphine-naloxone maintenance pharmacotherapy and counseling had more opioid-negative urines during active treatment, but that after discontinuing the buprenorphine-naloxone, youth in the maintenance group quickly relapsed, and there were no group differences in opioid outcomes at 12-month follow-up. This study converges with the adult OUD literature and suggests that continued maintenance treatment with buprenorphine-naloxone may be crucial to sustain opioid abstinence in youth.

Naltrexone

Naltrexone, a mu-opioid receptor antagonist, blocks the rewarding effects of opioids. It is available in daily oral (oral naltrexone) and monthly injectable (extended-release naltrexone [XR-naltrexone]) formulations. One study to date, a single open-label prospective case series, has examined XR-naltrexone for the treatment of adolescent and young adult OUD. The results of this study indicated that XR-naltrexone was well-tolerated and associated with clinical improvement in youth with OUD. In addition, it demonstrated the feasibility of using XR-naltrexone as part of an OUD outpatient treatment for youth [11].

Alcohol Use Disorder Pharmacotherapies

Advancement of pharmacotherapies for AUD in adults has expanded the treatment options beyond behavioral therapy. In adults naltrexone, acamprosate, and disulfiram are FDA-approved for the treatment of AUD. Please refer to Case 6 in Section IV for further details on these medications and how they may be used in clinical practice.

Naltrexone

Naltrexone, in both oral and XR formulations, has been shown to reduce the number of heavy-drinking days and relapse rates in adult AUDs. While no studies exist on the use of long-acting injectable naltrexone in adolescent AUD, two small clinical studies have examined the effects of oral short-acting naltrexone. The first study was an outpatient-based 6-week open-label pilot study. In this study, oral naltrexone was well-tolerated in adolescents with AUD and led to reductions in drinks per day (8.9 to 1.3 drinks) and alcohol-related thoughts/obsessions [12]. The second study was a randomized double-blind placebo-controlled 4-week crossover study. Compared to placebo, naltrexone was associated with reductions of heavy-drinking days and an attenuation of alcohol cravings and subjective response to alcohol during a laboratory challenge [13].

Disulfiram

Disulfiram is an aversive agent that irreversibly binds to the enzyme aldehyde dehydrogenase, resulting in accumulation of acetaldehyde when alcohol is consumed and producing aversive symptoms. One study has been completed in adolescents, a 90-day double-blind placebo-controlled study compared disulfiram (200 mg/day) to placebo in 26 adolescents receiving AUD outpatient treatment [14]. The study results indicated that disulfiram was well-tolerated and not associated with adverse events. Compared to the group receiving placebo, the disulfiram group had more cumulative days of abstinence and higher rates of sustained abstinence. However, this medication should be used with caution, given the potential severity of the disulfiram reaction when combined with alcohol. The coerced administration of this medication to individuals under the age of 18 also raises potential ethical concerns.

Topiramate

Topiramate is an FDA-approved anticonvulsant for the treatment of seizure disorders and migraines that has been studied extensively in adult AUD and shown to be associated with reductions in heavy drinking and relapse rates. Preliminary findings

from a small, 5-week, double-blind placebo-controlled study of topiramate (doses up to 200 mg/day) in heavy-drinking youth (ages 14–24 years) not enrolled in treatment indicate that it is safe and well-tolerated and may reduce drinks per week (-1.8 drinks/week) [15].

Ondansetron

Ondansetron is a selective serotonin 5-HT_3 receptor antagonist FDA-approved for the treatment of nausea and vomiting. A small ($n = 12$) open-label pilot study examined ondansetron in combination with cognitive behavioral therapy for 8 weeks in adolescents meeting DSM-IV criteria for alcohol dependence [16]. Ondansetron was well-tolerated and the participants had a significant reduction in drinks per day (-1.7 drinks). Additionally, a randomized controlled study of ondansetron in alcohol-dependent adults showed that individuals with early-onset adult AUD had a better response [17].

Acamprosate

Acamprosate, a N-methyl-D-aspartate (NMDA) receptor modulator, is approved by the FDA as a pharmacologic treatment for AUDs in individuals >18 years of age [18]. It is hypothesized to promote balance in excitatory-inhibitory neurotransmission by altering gamma-aminobutyric acid (GABA) and glutamatergic activity and, in doing so, to reduce "protracted" withdrawal symptoms and cravings [19]. It has been shown to improve alcohol-related outcomes (i.e., increase abstinence rates, reduce relapse, and reduce heavy drinking) in adult AUDs with comparable effect sizes to oral naltrexone [18]. Acamprosate has not been systematically studied in adolescents.

Cannabis Use Disorder Pharmacotherapies

There are no FDA-approved medications for the treatment of cannabis use disorder (CUD) at this time. As cannabis use modulates glutamatergic and GABAergic activity in the brain, pharmacotherapies that target these systems have shown promise as agents that aid with cannabis cessation [2, 3].

N-Acetylcysteine (NAC)

NAC is a cysteine prodrug that modulates intracellular and extracellular glutamate by way of the cysteine-glutamate exchanger. There has been one open-label and one RCT examining NAC in adolescents and young adults meeting DSM-IV criteria for cannabis dependence [20, 21]. Findings from these studies suggest that NAC is safe,

is well-tolerated, and when combined with contingency management (CM) interventions, is associated with significant reductions in cannabis use. Further support for the role of NAC for youth CUD comes from a large multisite placebo-controlled trial of NAC in adults (ages 18–50) with CUD [22]. While the main study results showed no group differences between NAC and placebo (indicating limited effect in adults), post hoc analyses, despite being underpowered, found that young adults (ages 18–21) receiving NAC compared to placebo had double the rates of abstinence (OR = 2.0, $p = 0.18$).

Topiramate

One controlled trial has examined the efficacy of topiramate in conjunction with motivational interviewing for the treatment of heavy cannabis-using youth (ages 15–24) [23]. The topiramate group experienced greater side effect burden and higher dropout rates compared to the placebo group. Considering the poor tolerability and inconsistent effect on cannabis use outcome measures, topiramate likely does not have a role in the treatment of adolescent CUDs.

Gabapentin

Gabapentin modulates the GABAergic system and represents a potential pharmacotherapy for CUD. While no studies have been completed in adolescents, a randomized, double-blind, placebo-controlled clinical trial in adults (ages 18–65) that included young adults found that patients receiving gabapentin experienced a greater reduction in the number of days of marijuana use and greater reductions in withdrawal symptoms and cravings than the placebo group [24].

Tobacco Use Disorder Pharmacotherapies

Meta-analyses in adults with tobacco use disorders (TUDs) have shown that medications in conjunction with evidence-based psychosocial interventions are more effective for smoking cessation than either medication or psychosocial intervention alone. Adolescent tobacco cessation studies have shown promising results but generally reported more mixed findings [2, 25].

Nicotine Replacement Therapy (NRT)

NRT is an agonist-based harm reduction pharmacotherapy approach that is FDA-approved for individuals aged 18 and older for smoking cessation. Although these agents can be prescribed to individuals under 18, they cannot be sold legally to a

minor over the counter. The use of NRT (monotherapy or combined) is associated with increased likelihood of abstinence and tobacco cessation in adults when compared with placebo. To date, five studies including a total of 728 subjects have examined NRT for the treatment of tobacco cessation in adolescents [25, 26]. These findings collectively suggest that nicotine patch, but not nicotine gum or nasal spray, has short-term efficacy for tobacco cessation in adolescents, but relapse after discontinuation of NRT is a significant concern. In practice, the nicotine patch is typically prescribed to provide a basal amount of nicotine throughout the day to reduce cravings, and in addition, the short-acting nicotine lozenges, gum, nasal spray, and inhaler are also prescribed for breakthrough cravings.

Sustained-Release Bupropion (Bupropion SR)

Bupropion is a nicotinic receptor antagonist and dopamine and norepinephrine reuptake inhibitor. The sustained-release (SR) formulation of bupropion is FDA-approved for tobacco cessation in adults. To date, bupropion has been examined for adolescent tobacco cessation in 4 randomized controlled trials including a total of 688 subjects [25, 27, 28]. Cumulatively these studies suggest that bupropion SR (300 mg/day dosing) improves tobacco abstinence in adolescents with TUDs, especially when combined with psychosocial interventions and CM.

Varenicline

Varenicline is an α4β2 nicotinic receptor partial agonist. It works by modulating dopaminergic neurotransmission to counteract nicotine withdrawal symptoms (nicotinic agonism) and reducing smoking reinforcement (nicotinic antagonism). The medication received FDA approval for smoking cessation in adults in 2006. Only one trial of varenicline for adolescent smoking cessation has been published. This was an 8-week RCT comparing varenicline with bupropion (bupropion XL) for adolescent smoking cessation. Both groups demonstrated reductions in number of cigarettes per day [28]. There were no statistically significant between-group differences on any of the outcome measures, given the sample size the study was underpowered. At the time of approval, the FDA originally added a black box warning label for varenicline and bupropion for depression and suicidality. In 2016, after subsequent studies and post-market surveillance showed that the risk for depression and suicidality was lower than initially believed, the FDA removed the warning label for varenicline [29].

In summary, providers may consider NRT, bupropion SR, or varenicline to aid tobacco cessation in adolescent smokers who fail to respond to psychosocial interventions. Studies from adults suggest that combination therapy (i.e., varenicline plus nicotine replacement therapy or bupropion plus nicotine replacement therapy)

is more effective than monotherapy. Combination therapy has not yet been thoroughly studied for adolescents under 18.

Medications for Opioid Overdose

Opioid overdose deaths in adolescents (aged 15–19) have more than tripled from 1999 to 2007 and in 2015 were 2.4 per 100,000 [30]. To address this public health crisis, the intranasal formulation of naloxone is increasingly available from pharmacies and handed out in communities. An intramuscular formulation is also available but less commonly used in most communities. Naloxone is an opioid antagonist and overdose rescue agent that can be prescribed for patients with OUDs and concerned family members to be administered by laypersons in the community if they observe an opioid overdose. No trials have been completed in adolescents or young adult samples. Still, clinicians who treat youth with OUDs should strongly consider prescribing intranasal naloxone and providing education and training to patients and concerned family members about the signs/symptoms of opioid intoxication and what to do in the event of a suspected overdose [25, 31].

Medications to Treat Co-occurring/Comorbid Psychiatric Conditions

To date, controlled studies of pharmacotherapies have been completed for depression, bipolar disorder, and attention deficit/hyperactivity disorder (ADHD) in youth with SUDs [2]. For additional details, refer to Chap. 5: "Co-occurring Mental Health Disorders."

Conclusions

Based upon the high morbidity and mortality related to alcohol and drug use in adolescents, providers should aggressively treat youth SUDs. Findings from early controlled studies have been mixed, but suggest that medications approved to treat SUDs in adults are generally safe and well-tolerated in youth. In some adolescents, especially those who have failed to improve with psychosocial treatment alone, there may be a role for adjunctive pharmacotherapy (see Table 7.2). The strongest evidence to date exists for pharmacotherapies targeting opioids, alcohol, tobacco, and cannabis use disorders. When using these medications, providers should monitor patients closely for side effects and efficacy and when possible coordinate with parents and family members to enhance medication adherence.

Table 7.2 Core principles for medications for addiction treatment in adolescent and young adult substance use disorders

	Core principles
1.	A broad range of psychotropic medications with different mechanisms of action and side effect profiles appear to be well-tolerated and not associated with increased side effect burden in youth who are actively using alcohol and other drugs
2.	There may be a role for adjunctive pharmacotherapies in specific subgroups of adolescents with substance use disorders for the treatment of withdrawal symptoms and cravings and to aid in relapse prevention by reducing the reinforcing effects of drugs. These medications may improve outcomes when combined with psychosocial interventions
3.	Providers should consider adjunctive pharmacotherapies in youth with mild-to-moderate SUDs who have failed to achieve abstinence within the first 4–6 weeks of psychosocial interventions alone
4.	Providers should consider adjunctive pharmacotherapies in youth with SUDs who have high severity substance use problems or other negative prognostic factors such as (1) co-occurring psychiatric disorders, (2) intravenous drug use, (3) history of overdoses or near overdoses, and (4) frequent risky behaviors while intoxicated that place them at high risk for injury or death (e.g., driving under the influence of alcohol or drugs, unprotected sexual intercourse, accidents)
5.	Providers should obtain information on the client's past response to medications, contraindications, adherence, and drug-to-drug interactions between medication and commonly used substances
6.	Medication-related psychoeducation with the patient and family should address the risks vs. benefits, possible side effects of a medication, and alternative treatments. These risks and benefits should be weighed against the risks of continued substance use
7.	The family's willingness to monitor the patient's medication adherence can improve treatment outcomes

Take-Home Points

- Adding pharmacotherapies to evidence-based psychosocial interventions may be an effective enhancement strategy in adolescents and young adult with substance use disorders (SUDs).
- Compared to extensive treatment research in adult SUDs, relatively few controlled pharmacotherapy trials have been conducted in adolescents and young adults with SUD.
- Medications that are FDA-approved to treat addictive disorders in adults have generally been shown to be safe and well-tolerated in youth with SUD who are actively using alcohol or other drugs.
- Buprenorphine is the only medication with an FDA-approved indication for the treatment of adolescent SUDs, specifically for opioid use disorders.
- "Off-label" addiction medications that have shown promise in controlled trials in youth include nicotine replacement therapy and bupropion for tobacco use disorders and *N*-acetylcysteine for cannabis use disorders.

- Providers considering a pharmacotherapy trial in youth with SUDs should use the adolescent's addiction severity, initial response to psychosocial treatment, risk for negative outcomes (i.e., overdose and injuries/accidents), and presence of co-occurring psychiatric disorders to guide clinical decision-making.

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Suggested Reading

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