The ASAM/AAAP

CLINICAL PRACTICE GUIDELINE ON THE

Management of Stimulant Use Disorder

ASAM American Society of Addiction Medicine

AAP American Academy of Addiction Psychiatry

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Clinical Practice Guideline on the
Management of Stimulant Use Disorder

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The American Society of Addiction Nursing

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Executive Summary

Purpose

The American Society of Addiction Medicine (ASAM) and the American Academy of Addiction Psychiatry (AAAP) developed this *Clinical Practice Guideline on the Management of Stimulant Use Disorder* (hereafter referred to as the Guideline) to provide evidence-based strategies and standards of care for the treatment of stimulant use disorders (StUDs), stimulant intoxication, and stimulant withdrawal, as well as secondary and tertiary prevention of harms associated with stimulant use.

Background

Rates of StUDs are rising, as are stimulant potency and rates of stimulant use in combination with opioids. These factors have contributed to overdose death rates increasing three-fold for cocaine and twelve-fold for other stimulants—including methamphetamine, amphetamine, and prescription stimulants—in the past ten years.[1]

Beyond overdose deaths, StUD can cause a range of serious and long-term health problems, including cardiac, psychiatric, dental, and nutritional complications. Injection stimulant use increases the risk of contracting human immunodeficiency virus (HIV), viral hepatitis, and other infectious diseases such as infective endocarditis. The stable or rising availability of stimulants, low prices, and potential contamination of stimulants with high potency synthetic opioids such as fentanyl and other components such as levamisole are expected to exacerbate risks.

Taken together, these factors have propelled StUD and stimulant use to an urgent health crisis. This Guideline aims to assist clinicians in treating individuals with StUD (including adolescents and individuals who are pregnant), as well as individuals experiencing stimulant intoxication or withdrawal, and individuals who are at high risk of developing StUD.

Key Takeaways

This Guideline focuses on the identification, diagnosis, treatment, and promotion of recovery for patients with StUD, stimulant intoxication, and stimulant withdrawal. It also includes recommendations related to screening for risky stimulant use and secondary and tertiary prevention of StUD. Recommendations that address general practice for all substance use disorders (SUDs) are not included, with a few exceptions. The following are seven key takeaways of this Guideline:

1. Contingency management (CM) has demonstrated the best effectiveness in the treatment of StUDs compared to any other intervention studied and represents the current standard of care. CM can be combined with other psychosocial interventions and behavioral therapies, such as community reinforcement approach (CRA) and cognitive behavioral therapy (CBT) (See Recommendations 5-6).
2. Pharmacotherapies, including psychostimulant medications, may be utilized off-label to treat StUD (See Recommendations 9-20).
    - When prescribing controlled medications, clinicians should closely monitor patients and perform regular ongoing assessment of risks and benefits for each patient.
    - Psychostimulant medications should only be prescribed to treat StUD by:
        - physician specialists who are board certified in addiction medicine or addiction psychiatry; and
        - physicians with commensurate training, competencies, and capacity for close patient monitoring.
3. Co-occurring conditions—including but not limited to attention-deficit/hyperactivity disorder (ADHD), depression, anxiety, eating disorders, and

other SUDs—are common in patients with StUD. Any co-occurring psychiatric disorders or SUDs should be treated concurrently alongside StUD with care coordination (See Recommendations 21-25).

- Evidence supports the use of pharmacotherapy, including psychostimulant medication, to treat ADHD in individuals with co-occurring StUD.
- Some pharmacotherapies that can be considered to treat StUD off-label have demonstrated efficacy in treating common co-occurring psychiatric disorders and SUDs and can be given additional consideration.

4. Clinicians should provide adolescents and young adults who use stimulants with the same treatment, harm reduction, and recovery support services (RSS) as adults in a developmentally responsive manner (See the Adolescent and Young Adult Section).
5. Acute stimulant intoxication can result in several life-threatening complications that include but are not limited to cardiovascular complications (eg, acute coronary syndrome [ACS], hypertensive emergency, myocardial infarction [MI]), hyperthermia, and acidosis, among others. These acute issues should be addressed immediately in an appropriate level of care (See Recommendations 55-72).
6. Treating symptoms of stimulant withdrawal may help supporting ongoing treatment engagement (See the Stimulant Withdrawal section).
    a. Post-acute symptoms of stimulant withdrawal—which include depression, anxiety, insomnia, and paranoia—can last for weeks to months. It is important to assess for and treat these symptoms to reduce the risk for decompensation and return to stimulant use.
7. Secondary and tertiary prevention strategies should be used to reduce harms related to overdose risk, risky sexual practices, injection drug use, oral health, and nutrition (See Recommendations 79-92).

Summary of Recommendations

Treatment of Stimulant Use Disorder Recommendations

Assessment Recommendations

Initial Assessment Recommendations

1. When assessing patients for StUD, the first clinical priority should be to identify any urgent or emergent biomedical or psychiatric signs or symptoms, including acute intoxication or overdose, and provide appropriate treatment or referrals (*Clinical consensus, Strong Recommendation*).

Comprehensive Assessment Recommendations

2. After first addressing any urgent biomedical or psychiatric signs or symptoms, patients should undergo a comprehensive assessment that includes:
    a. assessment for StUD based on diagnostic criteria (eg, current *DSM*; *Clinical consensus, Strong Recommendation*);
    b. a StUD-focused history and physical examination (*Clinical consensus, Strong Recommendation*);
    c. a mental status exam to identify co-occurring psychiatric conditions, such as signs and symptoms of psychoses, ADHD, mood disorders, cognitive impairment, and risk of harm to self or others (*Clinical consensus, Strong Recommendation*); and
    d. a full biopsychosocial assessment (*Clinical consensus, Strong Recommendation*).
3. Clinicians treating StUD should conduct routine baseline laboratory testing (*Clinical consensus*, *Strong Recommendation*).
    a. Clinicians should conduct other clinical tests as necessary based on each patient's clinical assessment findings (*Clinical consensus, Conditional Recommendation)*.
4. When evaluating patients with long-term or heavy stimulant use, clinicians should exercise:
    a. an elevated degree of suspicion for cardiac disorders (*Clinical consensus, Conditional Recommendation)*,
    b. a lower threshold for considering ECG testing based on findings of the history and physical exam (*Clinical consensus, Conditional Recommendation)*,
    c. a lower threshold for considering creatine kinase (CK) testing for rhabdomyolysis based on findings of the history and physical exam (*Clinical consensus, Strong Recommendation*), and
    d. an elevated degree of suspicion for renal disorders (*Clinical consensus, Conditional Recommendation)*.

Behavioral Treatment Recommendations

5. Contingency Management (CM) should be a primary component of the treatment plan in conjunction with other psychosocial treatments for StUD (*High certainty, Strong Recommendation*).
6. The following three interventions have the most supportive evidence and are preferred alongside CM:

a. Community Reinforcement Approach (CRA) (*Low certainty, Conditional Recommendation)*,

b. Cognitive Behavioral Therapy (CBT) (*Moderate certainty, Strong Recommendation*), and

c. the Matrix Model (*Moderate certainty, Conditional Recommendation)*.

Technology-Based Interventions Recommendations

7. Clinicians can consider offering evidence-based behavioral interventions delivered via digital therapeutics or web-based platforms as add-on components to treatment for StUD, but they should not be used as standalone treatment (*Low certainty, Strong Recommendation*).
8. Clinicians should consider using telemedicine to deliver behavioral treatment for StUD to patients who may face challenges accessing in-person care (*Moderate certainty, Strong Recommendation*).

Pharmacotherapy Recommendations

Non-Psychostimulant Medication Recommendations

Cocaine Use Disorder: Bupropion Recommendations

9. For patients with cocaine use disorder, clinicians can consider prescribing bupropion to promote cocaine abstinence (*Low certainty, Conditional Recommendation)*.
    a. Clinicians can give bupropion additional consideration for patients with co-occurring tobacco use disorder (TUD), as this medication can also reduce nicotine/tobacco use (*Low certainty, Conditional Recommendation)*.
    b. Clinicians can give bupropion additional consideration for patients with co-occurring depressive disorders, as this medication can also treat depression (*Low certainty, Conditional Recommendation)*.

Cocaine Use Disorder: Topiramate Recommendations

10. For patients with cocaine use disorder, clinicians can consider prescribing topiramate to reduce cocaine use (*Low certainty, Conditional Recommendation)*.
    a. Clinicians can give topiramate additional consideration for patients with co-occurring alcohol use disorder (AUD), as this medication can also reduce alcohol consumption (*Low certainty, Conditional Recommendation)*.

Amphetamine-Type Stimulant Use Disorder: Bupropion Recommendations

11. For patients with amphetamine-type stimulant (ATS) use disorder with low- to moderate-frequency (ie, less than 18 days per month) stimulant use, clinicians can consider prescribing bupropion to promote reduced use of ATS (*Low certainty, Conditional Recommendation)*.
    a. Clinicians can give bupropion additional consideration for patients with co-occurring TUD, as this medication can also reduce nicotine/tobacco use (*Low certainty, Conditional Recommendation)*.
    b. Clinicians can give bupropion additional consideration for patients with co-occurring depressive disorders, as this medication can also treat depression (*Low certainty, Conditional Recommendation)*.

Amphetamine-Type Stimulant Use Disorder: Bupropion and Naltrexone Recommendations

12. For patients with ATS use disorder, clinicians can consider prescribing bupropion in combination with naltrexone to promote reduced use of ATS (*Moderate certainty, Conditional Recommendation)*.
    a. Clinicians can give this combination additional consideration for patients with co-occurring AUD, as naltrexone can also reduce alcohol consumption (*Moderate certainty, Conditional Recommendation)*.
    b. Clinicians can give this combination additional consideration for patients with co-occurring TUD, as bupropion can also reduce nicotine/tobacco use (*Moderate certainty, Conditional Recommendation)*.
    c. Clinicians can give this combination additional consideration for patients with co-occurring depressive disorders, as bupropion can also treat depression (*Moderate certainty, Conditional Recommendation)*.

Amphetamine-Type Stimulant Use Disorder: Topiramate Recommendations

13. For patients with ATS use disorder, clinicians can consider prescribing topiramate to reduce use of ATS (*Low certainty, Conditional Recommendation)*.
    a. Clinicians can give topiramate additional consideration for patients with co-occurring AUD, as this medication can also reduce alcohol consumption (*Low certainty, Conditional Recommendation)*.

Amphetamine-Type Stimulant Use Disorder: Mirtazapine Recommendations

14. For patients with ATS use disorder, clinicians can consider prescribing mirtazapine to promote reduced use of ATS (*Low certainty, Conditional Recommendation)*.

a. Clinicians can give mirtazapine additional consideration for patients with co-occurring depressive disorders, as this medication can also treat depression (*Low certainty, Conditional Recommendation)*.

Psychostimulant Medication Recommendations

General Psychostimulant Medication Recommendations

15. Recommendations related to the prescription of psychostimulant medications to treat StUD are only applicable to:
    a. physician specialists who are board certified in addiction medicine or addiction psychiatry; and
    b. physicians with commensurate training, competencies, and capacity for close patient monitoring *(Clinical consensus, Strong Recommendation)*.
16. When prescribing psychostimulant medications for StUD, clinicians should maintain a level of monitoring commensurate with the risk profile for the given medication and patient. Monitoring may include pill counts, drug testing, more frequent clinical contact, and more frequent prescription drug monitoring program (PDMP) checks *(Clinical consensus, Strong Recommendation)*.

Cocaine Use Disorder: Modafinil Recommendations

17. For patients with cocaine use disorder and without co-occurring AUD, clinicians can consider prescribing modafinil to reduce cocaine use and improve treatment retention (*Low certainty, Conditional Recommendation)*.

Cocaine Use Disorder: Topiramate and Extended-Release Mixed Amphetamine Salts Recommendations

18. For patients with cocaine use disorder, clinicians can consider prescribing a combination of topiramate and MAS-ER to reduce cocaine use and cocaine craving (*Moderate certainty, Conditional Recommendation)*.
    a. Clinicians can give this combination additional consideration for patients with co-occurring AUD, as topiramate can also reduce alcohol consumption (*Moderate certainty, Conditional Recommendation)*.
    b. Clinicians can give this combination additional consideration for patients with co-occurring ADHD, as MAS-ER can also reduce ADHD symptoms (*Moderate certainty, Conditional Recommendation)*.

Cocaine Use Disorder: Amphetamine Formulation Recommendations

19. For patients with cocaine use disorder, clinicians can consider prescribing a long-acting amphetamine formulation psychostimulant to promote cocaine abstinence (*Low certainty, Conditional Recommendation)*.
    a. Clinicians can give long-acting amphetamine formulation psychostimulants additional consideration for patients with co-occurring ADHD, as these medications can also reduce ADHD symptoms (*Low certainty, Conditional Recommendation)*.
    b. When prescribing a long-acting amphetamine formulation psychostimulant, clinicians can consider dosing at or above the maximum dose approved by the FDA for the treatment of ADHD to effectively reduce cocaine use (*Low certainty, Conditional Recommendation)*.

Amphetamine-Type Stimulant Use Disorder: Methylphenidate Formulations Recommendations

20. For patients with ATS use disorder, clinicians can consider prescribing a long-acting MPH formulation to promote reduced use of ATS (*Low certainty, Conditional Recommendation)*.
    a. Clinicians can give long-acting MPH formulations additional consideration for patients with moderate or higher frequency of ATS use at treatment start (ie, 10 or more days per month; *Low certainty, Conditional Recommendation)*.
    b. Clinicians can give long-acting MPH formulations additional consideration for patients with co-occurring ADHD, as these medications can also reduce ADHD symptoms (*Low certainty, Conditional Recommendation)*.
    c. When prescribing a long-acting MPH formulation, clinicians can consider dosing at or above the maximum dose approved by the FDA for the treatment of ADHD to effectively reduce ATS use (*Low certainty, Weak Recommendation)*.

Co-occurring Disorders: General Guidance Recommendations

21. Clinicians should treat both StUD and co-occurring disorder(s) concurrently (*Very low certainty, Strong Recommendation*).
22. Clinicians should use an integrated behavioral treatment approach that addresses both conditions when available (*Very low certainty, Strong Recommendation)*. Otherwise, clinicians should tailor recommended behavioral therapy for StUD (eg, CM, CBT, CRA) to address possible interactions between a patient's StUD and co-occurring disorder(s) (*Very low certainty, Strong Recommendation*).

23. Symptoms of psychosis or mania should be treated with indicated pharmacotherapy (*Moderate certainty, Strong Recommendation*).
    a. If stimulant-induced psychosis or mania is suspected, clinicians should consider a gradual taper off antipsychotic medication after a period of remission of psychotic symptoms (*Moderate certainty, Strong Recommendation*).
24. When developing a treatment plan for symptoms of depression, anxiety, insomnia, and/or attentional problems observed during periods of stimulant use or withdrawal, clinicians should:
    a. consider pharmacotherapy based on symptom severity and duration, even if symptoms are stimulant induced (*Very low certainty, Strong Recommendation*); and
    b. consider whether the patient's clinical presentation follows the expected time course of stimulant-induced symptoms given the phase of use (ie, active use, waning intoxication, acute withdrawal, post-acute withdrawal, post-withdrawal abstinence) or are present at other times (*Very low certainty, Strong Recommendation*).
25. Clinicians initiating treatment for StUD in a patient with a preexisting co-occurring diagnosis should:
    a. review the patient's existing treatment plan, ideally in coordination with the patient's existing treatment provider(s) (*Clinical consensus, Strong Recommendation*); and
    b. continue current medications as appropriate (*Clinical consensus, Strong Recommendation*), with consideration for safety in the context of the patient's potential continued use of stimulants and other substances (*Clinical consensus, Strong Recommendation*).

Concurrent Management of StUD and ADHD Recommendations

26. For patients with co-occurring StUD and ADHD, clinicians should address ADHD symptoms as part of the treatment of StUD (*Low certainty, Strong Recommendation)*. Clinicians should consider:
    a. prescribing psychostimulant medications to manage ADHD when the benefits of the medication outweigh the risks (*Low certainty, Strong Recommendation)*,
    b. prescribing non-stimulant medications to manage ADHD when the benefits of psychostimulant medications do not outweigh the risks (*Low certainty, Strong Recommendation)*, and
    c. behavioral approaches (*Low certainty, Strong Recommendation)*.

27. When prescribing psychostimulant medications to a patient with co-occurring StUD and ADHD, clinicians should consider:
    a. using extended-release formulations (*Clinical consensus, Strong Recommendation)*; and
    b. maintaining a level of monitoring commensurate with the risk profile for the given medication and patient—monitoring may include pill counts, drug testing, more frequent clinical contact, and more frequent PDMP checks (*Clinical consensus, Conditional Recommendation)*.
28. For adolescent and young adult patients with co-occurring StUD and ADHD, clinicians should additionally consider:
    a. arranging for a parent, health professional (eg, trained school nurse), or other trusted adult to directly observe administration of the medication, especially if using a short-acting formulation (*Clinical consensus, Strong Recommendation)*; and
    b. counseling families on the importance of safely storing and restricting access to controlled medications (*Clinical consensus, Conditional Recommendation)*.

Population-Specific Considerations Recommendations

Adolescents and Young Adults Recommendations

Adolescent and Young Adult Assessment and Treatment Planning Recommendations

29. Clinicians should avoid routine drug testing to screen adolescents and young adults for StUD (*Clinical consensus, Strong Recommendation)*.
    a. When considering drug testing in patients under the age of 18, clinicians should ask patients for permission to test, even if parental/guardian consent was given, unless obtaining assent is not possible (eg, loss of consciousness; *Clinical consensus, Strong Recommendation)*.
30. Clinicians should pay particular attention to signs or symptoms of ADHD and eating disorders in adolescent and young adult patients (*Clinical consensus, Strong Recommendation)*.
31. If available, clinicians should refer adolescent and young adult patients to age-specific treatment and support programs to address identified biopsychosocial needs (*Clinical consensus, Strong Recommendation)*.

Adolescent and Young Adult Treatment Recommendations

32. When treating adolescents and young adults for StUD, clinicians should:

a. consider delivering behavioral interventions that have been demonstrated to be effective in the treatment of other SUDs in adolescents and young adults (eg, CM, CBT, CRA, family therapy) and in the treatment of StUDs in adults (eg, CM, CBT, CRA; *Low certainty*, *Strong Recommendation)*;

b. use an adolescent- and young adult-specific treatment model (eg, adolescent CRA [A-CRA]) or tailor existing treatments to be developmentally responsive (*Moderate certainty, Strong Recommendation)*;

c. use peer-age groups for behavioral treatment in group formats when possible and avoid incorporating adolescents and young adults into group behavioral treatment with older adults (*Very low certainty, Strong Recommendation)*;

d. consider treating adolescents and young adults with StUD with the off-label pharmacotherapies detailed in the Pharmacotherapy section when the developmentally contextualized benefits outweigh the harms (*Very low certainty, Weak Recommendation)*;

e. counsel parents/guardians to not conduct home drug tests to assess stimulant use in adolescents and young adults without the oversight of a trained clinician (*Clinical consensus, Strong Recommendation)*;

f. recognize that involvement of family members is often beneficial in the treatment of adolescents and young adults with SUDs and involve family members and/or trusted adults when appropriate (*Clinical consensus, Strong Recommendation)*;

g. be familiar with state laws on adolescents' ability to consent to treatment when treating minors under age 18; in some states, minors can proceed with treatment without involvement of a parent or legal guardian in their care, whereas in other states, parental/guardian consent may be required before proceeding with some or all aspects of treatment (*Clinical consensus, Strong Recommendation)*; and

h. understand that while parental/guardian consent is not required for treatment of young adults, clinicians should initiate a conversation with the young adult patient about whether their treatment plan might be enhanced by involving a trusted adult (*Clinical consensus, Strong Recommendation)*.

Pregnant and Postpartum Patients Recommendations

Pregnant and Postpartum Patients Assessment Recommendations

33. Clinicians should incorporate additional elements into the comprehensive assessment of StUD for patients who are pregnant, including:

a. providing referrals to prenatal care providers if not already established (*Low certainty, Strong Recommendation)*, and

b. reviewing eligibility criteria for locally available programs that specifically address biopsychosocial needs related to pregnancy and parenting (eg, childcare, WIC programs; *Low certainty, Strong Recommendation)*.

34. Coordination of prenatal care and treatment of StUD is encouraged (*Low certainty, Strong Recommendation)*.

35. When screening for acute issues, complications, and sequalae associated with stimulant use in patients who are pregnant, clinicians should pay particular attention to factors that impact pregnancy and fetal development (*Low certainty, Strong Recommendation)*.

36. Since the ramifications of a positive drug test result for patients who are pregnant may be more severe than the general populations, before conducting drug testing in patients who are pregnant, clinicians should:

    a. know their state's requirements on mandatory reporting and ramifications of reporting (*Clinical consensus, Strong Recommendation)*;

    b. weigh the potential benefits with the risks of utilizing drug testing in this population (*Clinical consensus, Strong Recommendation)*; and

    c. obtain informed consent, unless there is immediate clinical need and obtaining consent is not possible (eg, loss of consciousness; *Clinical consensus, Strong Recommendation)*.

Pregnant and Postpartum Patients Treatment Recommendations

37. Risk versus benefit to the fetus or infant should be considered when medications are used to manage StUD, stimulant intoxication, or stimulant withdrawal (*Very low certainty, Strong Recommendation)*.

38. Wherever possible, clinicians should incorporate psychosocial treatments targeted toward meeting the additional needs of patients who are pregnant (*Clinical consensus, Strong Recommendation)*, including:

    a. Parent-focused treatment modalities (eg, parenting skills training; *Clinical consensus, Strong Recommendation)*, and

    b. family-based treatment modalities (*Clinical consensus, Strong Recommendation)*.

39. Clinicians should consider CM to incentivize attendance at prenatal appointments, if feasible, in addition to usual targets (eg, stimulant abstinence; *Low certainty, Strong Recommendation)*.

40. Clinicians should consider providing additional treatment support around the time of birth, as the postpartum period may be a time of increased stress and risk of return to stimulant use (*Very low certainty, Conditional Recommendation)*.

Breastfeeding Recommendations

41. Clinicians should educate patients who use stimulants on the risks of use while breastfeeding and counsel patients not to breastfeed if they are actively using stimulants (except as prescribed; *Very low certainty, Strong Recommendation)*.

Additional Population-Specific Considerations Recommendations

Sexual Orientation and Gender Identity Recommendations

42. Clinicians should consider referring sexual and gender minoritized (SGM) patients with StUD to SGM-affirming programs when their history and/or behavior suggest they may not be comfortable fully participating in a general population setting (eg, distress related to their identities, difficulties discussing drug-related sexual activities, inner conflicts, trauma histories) (*Low certainty, Strong Recommendation)*.

Patients Involved in the Criminal and/or Legal Systems Recommendations

43. Initiation of treatment for StUD is recommended for individuals in the criminal and/or legal systems, including within jails and prisons (*Clinical consensus, Strong Recommendation)*.

Patients Experiencing Homelessness or Unstable Housing Recommendations

44. For patients experiencing homelessness, housing insecurity, food insecurity, and/or poverty, clinicians might consider:
    a. providing case management services or a referral to a case manager or other appropriate service provider(s) who can help the patient navigate health and social safety net resources (*Clinical consensus, Strong Recommendation)*; and
    b. providing a referral to a recovery residence based on the patient's needs (*Clinical consensus, Strong Recommendation)*.

Stimulant Intoxication and Withdrawal Recommendations

Assessment and Diagnosis Recommendations

Initial Assessment Recommendations

45. The clinical examination should first identify any acute concerns and complications of stimulant intoxication or withdrawal that would indicate the patient requires a higher level of care (*Clinical consensus, Strong Recommendation)*. This includes an assessment of hyperadrenergic symptoms, including tachycardia, hypertension, hyperthermia, and agitation (*Clinical consensus, Strong Recommendation)*.
46. The initial clinical examination when evaluating for suspected stimulant intoxication or withdrawal should include (*Clinical consensus, Strong Recommendation)*:
    a. a clinical interview (as feasible),
    b. physical examination,
    c. observation of signs and patient-reported symptoms,
    d. review of any available collateral information, and
    e. a safety assessment of the patient's risk of harm to self and others.

Comprehensive Assessment Recommendations

47. Stimulant intoxication and withdrawal are primarily diagnosed based on the patient history and physical examination, as well as findings from any clinical, diagnostic, and/or toxicology testing (*Clinical consensus, Strong Recommendation)*.
48. If some elements of the medical workup are not available in given a setting, the results from a basic assessment of vital signs and focused mental status evaluation should be used to determine the urgency of further medical evaluation or referral for more comprehensive medical evaluation (*Clinical consensus, Strong Recommendation)*.
49. Clinical testing should be based on presenting signs and symptoms and should include a complete blood count (CBC), a comprehensive metabolic panel (CMP), LFTs, markers for muscle breakdown (eg, CK, lactate [in cases of muscle breakdown and acidosis]) or cardiac injury (eg, CK, troponin; *Clinical consensus, Strong Recommendation)*.
50. When analyzing CBC results for patients with cocaine intoxication or withdrawal, clinicians should be alert to neutrophil levels, as levamisole is a common adulterant in the cocaine supply and can cause immunosuppression—in particular, neutropenia—and small vessel vasculitis (*Clinical consensus, Conditional Recommendation)*.

Toxicology Testing Recommendations

51. In patients presenting with stimulant intoxication or withdrawal, clinicians can use toxicology testing to:
    a. inform clinical thinking regarding the differential diagnosis, along with other clinical information (*Clinical consensus, Strong Recommendation)*; and
    b. identify substance use that could produce drug–drug interactions when considering pharmacotherapy to manage signs and symptoms of stimulant intoxication or withdrawal (*Clinical consensus, Conditional Recommendation)*.
52. Clinicians should consider the possibility of novel psychoactive stimulants if stimulant intoxication is suspected but presumptive testing is negative (*Clinical consensus, Conditional Recommendation)*.

Setting Determination Recommendations

53. Patients with severe clinical concerns or complications related to stimulant intoxication should be managed in acute care settings (*Clinical consensus, Conditional Recommendation)*.
54. Some patients with acute stimulant intoxication can be safely managed in lower acuity clinical settings if (*Clinical consensus, Conditional Recommendation)*:
    a. the patient is cooperative with care;
    b. the patient is responsive to interventions (eg, verbal and nonverbal de-escalation strategies, medications) that can be managed in the clinical setting;
    c. the patient is not experiencing more than mild hyperadrenergic symptoms or is responsive to medications that can be managed in the clinical setting; and
    d. clinicians are able to:
        i. assess for acute issues and complications of stimulant intoxication,
        ii. monitor vital signs,
        iii. assess and monitor suicidality,
        iv. monitor for worsening signs and symptoms of intoxication and emergent complications related to stimulant intoxication,
        v. provide adequate hydration,
        vi. provide a low-stimulation environment,
        vii. manage the risk of return to stimulant use, and
        viii. coordinate clinical testing as indicated.

Managing Stimulant Intoxication and Withdrawal Recommendations

Behavioral and Psychiatric Symptoms of Stimulant Intoxication Recommendations

55. Clinicians should evaluate the patient to identify causal factors for agitation and/or psychosis other than stimulant intoxication; treatment should address all underlying causes (*Clinical consensus, Strong Recommendation)*.
56. Clinicians should use verbal and nonverbal de-escalation strategies to calm patients who are agitated, delirious, and/or psychotic to support their cooperation with care (*Clinical consensus, Strong Recommendation)*.
57. Clinicians can consider treating stimulant-induced agitation or confusion with medication (*High certainty, Conditional Recommendation)*.
    a. Benzodiazepines can be considered a first-line treatment for managing stimulant-induced agitation and/or confusion (*High certainty, Conditional Recommendation)*.
58. De-escalation strategies should not delay the use of medication to manage patients who are agitated, delirious, and/or psychotic and at imminent risk for severe complications (*High certainty, Strong Recommendation)*.
59. Clinicians should treat stimulant-induced psychotic symptoms with an antipsychotic medication (*High certainty, Strong Recommendation)*.
    a. The urgency, formulation, and duration of antipsychotic pharmacotherapy should be based on etiology and symptomatology (*High certainty, Strong Recommendation)*.
    b. Clinicians should avoid the use of chlorpromazine and clozapine for stimulant-induced psychosis as these medications may place patients at increased risk for seizures (*High certainty, Strong Recommendation)*.
60. For agitation and/or psychosis that is moderate to severe or escalating, clinicians should:
    a. conduct a medical evaluation focused on identifying life-threatening medical signs and symptoms that require referral for emergent hospital workup and management (*Clinical consensus, Strong Recommendation)*, and
    b. conduct a mental status evaluation focused on evaluating the patient's danger to self and others that would require immediate referral for full psychiatric assessment and/or involuntary containment and evaluation (*Clinical consensus, Strong Recommendation)*.

61. If agitation and/or psychosis does not respond to the setting's available de-escalation and/or medication management interventions, clinicians should coordinate transition to a more intensive level of care (*Clinical consensus, Strong Recommendation)*.
    a. When possible, interventions that address agitation, confusion, delirium and/or psychosis should be initiated while arranging for transport (*Clinical consensus, Strong Recommendation)*.
62. Clinicians should monitor for progression of psychiatric symptoms, breakthrough psychosis, suicidality, and emergence of trauma-related symptoms; in particular, suicidality may increase during waning intoxication and acute withdrawal (*Clinical consensus, Conditional Recommendation)*.

Hyperadrenergic Symptoms of Stimulant Intoxication Recommendations

63. When patients present with hyperadrenergic symptoms, clinicians should provide ongoing monitoring and management of vital signs—especially heart rate and blood pressure—to prevent complications that may result from untreated sympathomimetic toxicity (*Clinical consensus, Strong Recommendation)*.
64. Clinicians should treat patients in a stimulant-induced hyperadrenergic state with GABAergic agents (eg, benzodiazepines, phenobarbital, propofol); benzodiazepines can be considered first-line treatment for this purpose (*Low certainty, Strong Recommendation)*.
65. If the hyperadrenergic state persists despite appropriate improvement in agitation and neuromuscular hyperactivity following treatment with benzodiazepines or other GABAergic agent, clinicians can consider adjunctive treatment with the following medications:
    a. A beta blocker with concomitant alpha-1 antagonism (eg, carvedilol, labetalol; *Moderate certainty, Conditional Recommendation)*.
    b. An alpha-2 adrenergic agonist (eg, dexmedetomidine for severe symptoms, clonidine for mild to moderate symptoms; *Moderate certainty, Conditional Recommendation)*.
    c. Where beta blockers are contraindicated, clinicians can consider other pharmacological options such as calcium channel blockers, alpha-1 adrenergic antagonists, alpha-2 adrenergic agonists, and nitric oxide-mediated vasodilators, with consideration of other clinically relevant signs and symptoms (*Moderate certainty, Conditional Recommendation)*.
    d. While calcium channel blockers, alpha-1 adrenergic antagonists, alpha-2 adrenergic agonists, and nitric oxide-mediated vasodilators may be most beneficial in treating hypertension and vasospasm, clinicians should be alert to

potential side effects, including poor control over tachycardia or reflex tachycardia (*Moderate certainty, Strong Recommendation)*.

66. If a patient with stimulant intoxication is experiencing a hypertensive emergency, clinicians should:

    a. use short-acting agents such as sodium nitroprusside, phentolamine, or dihydropyridine calcium channel blockers (*Very low certainty, Strong Recommendation)*;

    b. avoid long-acting antihypertensives to avoid abrupt hemodynamic collapse (*Very low certainty, Strong Recommendation)*; and

    c. use nitroglycerin if the patient exhibits signs or symptoms of cardiac ischemia (*Very low certainty, Strong Recommendation)*.

Acute Issues and Complications Recommendations

Chest Pain Recommendations

67. For patients experiencing chest pain during stimulant intoxication, clinicians should initiate treatment for the underlying intoxication with GABAergic agents (eg, benzodiazepines, phenobarbital, propofol) as long as there are no clinical contraindications (*Moderate certainty, Conditional Recommendation)*.

68. Alternative agents (eg, calcium channel blockers, vasodilators) are generally preferred for management of cardiac ischemia in patients experiencing stimulant intoxication. However, if beta blockers are used in patients with stimulant intoxication, clinicians should consider using a medication with concomitant alpha-1 antagonism (eg, carvedilol, labetalol). If an unopposed beta blocker was used in a patient who is or was recently stimulant intoxicated, clinicians should also consider providing a coronary vasodilator (eg, nitroglycerin, calcium channel blocker). For complex cases, consult with cardiology and/or medical toxicology (*Low certainty, Conditional Recommendation)*.

69. While treating underlying stimulant intoxication in patients experiencing chest pain, clinicians should concomitantly evaluate for ACS and other causes of acute chest pain in stimulant intoxication (eg, pulmonary, musculoskeletal [MSK]). Chest pain that does not fully resolve as signs and symptoms of stimulant intoxication improve should be evaluated and treated following current standards of care (*Moderate certainty, Strong Recommendation)*.

QRS Widening Recommendations

70. Cocaine has local anesthetic-like effects at sodium channels and can cause QRS widening with impairment in cardiac contractility during severe cocaine intoxication. If

these issues are identified, in addition to treating intoxication, clinicians should administer sodium bicarbonate to improve the conduction block and contractility; this will also improve metabolic acidosis if present (*High certainty, Strong Recommendation)*.

Seizure Recommendations

71. When a patient presents to the emergency department (ED) with seizures following stimulant use, full neurological workup is not necessary if the seizures are well explained by substance use or withdrawal (*Clinical consensus, Conditional Recommendation)*.
    a. When the etiology of the seizures is not well explained by stimulant use, the workup and management of seizures should proceed according to usual best practices (*Clinical consensus, Strong Recommendation)*.
72. For stimulant intoxication-related seizures or concomitant alcohol- or sedative-related seizures, clinicians should treat with benzodiazepines (*High certainty, Strong Recommendation)*.
    a. If seizures are refractory to benzodiazepines, clinicians can consider treating with either phenobarbital or propofol (*High certainty, Strong Recommendation)*.

Follow-up Recommendations

73. Clinicians should screen patients for StUD and engage them in brief interventions using motivational interviewing (MI) or motivational enhancement therapy (MET) to facilitate referral for assessment for StUD, if indicated (*Very low certainty, Conditional Recommendation)*.

Secondary and Tertiary Prevention Recommendations

Screening Recommendations

74. When general healthcare providers screen adolescents or adults for risky substance use per USPSTF guidelines,[2] they should include screening for stimulant misuse (ie, nonmedical or nonprescribed use; *Very low certainty, Strong Recommendation)*.
75. Clinicians should consider more frequent screening for stimulant misuse in patients who take prescribed psychostimulant medications (*Very low certainty, Strong Recommendation)*.
76. Clinicians should check their state's PDMP prior to prescribing psychostimulant medications (*Moderate certainty, Strong Recommendation)*.

Assessment Recommendations

77. For patients who screen positive for stimulant misuse:

a. Clinicians should conduct a focused history and clinical exam to evaluate complications of use related to route of administration and type of preparation used and provide treatment or referrals as appropriate (*Very low certainty, Strong Recommendation)*.

b. Clinicians should assess the following to determine harm reduction service and counseling needs:

i. risky patterns of stimulant use, including:

1. frequency and amount of use, including binge use (*High certainty, Strong Recommendation)*;
2. use of stimulants with no one else present (*High certainty, Strong Recommendation)*;
3. concurrent use of prescribed and nonprescribed medications and other substances, particularly opioids, alcohol, and other central nervous system depressants (*High certainty, Strong Recommendation)*;
4. history of overdose (*High certainty*, Strong Recommendation); and
5. history of stimulant-related ED visits and hospitalizations (*High certainty, Strong Recommendation)*;

ii. routes of administration, particularly injection drug use (*Very low certainty, Strong Recommendation)*; and

iii. risky sexual behaviors (*High certainty, Strong Recommendation)*.

c. Clinicians should consider asking patients about:

i. the context of their stimulant use (eg, chemsex, weight loss, academic or work performance, staying awake; *Clinical consensus, Strong Recommendation)*,

ii. trauma (*Clinical consensus, Strong Recommendation)*, and

iii. intimate partner violence (IPV; *Clinical consensus, Strong Recommendation)*.

d. Clinicians should conduct baseline laboratory testing based on clinical assessment of risk factors (see Assessment; *Clinical consensus, Strong Recommendation)*.

78. Patients who engage in nonmedical use of prescription stimulants should be evaluated for ADHD, which may also require treatment (*Clinical consensus, Strong Recommendation)*.

Early Intervention for Risky Stimulant Use Recommendations

Interventions to Reduce Risky Stimulant Use Recommendations

79. Clinicians should consider providing brief interventions to patients with any risky stimulant use using MI techniques to encourage patients to reduce or stop their use (*Very low certainty, Strong Recommendation)*.
80. Clinicians should be aware of some of the unique motivators of stimulant use and be prepared to discuss and suggest safer alternatives as part of brief interventions for stimulant use (eg, chemsex, weight loss, academic or work performance, staying awake; *Clinical consensus, Strong Recommendation)*.

Referral to Treatment for Stimulant Use Disorder Recommendations

81. For patients who screen positive for risky stimulant use, clinicians should conduct or offer referrals for comprehensive assessment and treatment for potential StUD with linkage support, including warm handoffs (*Very low certainty, Strong Recommendation)*.
82. For patients who are ambivalent about referrals for StUD assessment or treatment, clinicians should consider using interventions to enhance motivation for treatment (eg, MI, MET; *Very low certainty, Strong Recommendation)*.
83. Clinicians should consider the use of peer navigators to link patients to StUD assessment and treatment (*Low certainty, Weak Recommendation)*.

Harm Reduction Recommendations

Harm Reduction Education Recommendations

84. For patients who engage in risky stimulant use, clinicians should:
    a. offer basic harm reduction education about safer stimulant use (*Low certainty, Strong Recommendation)*,
    b. tailor harm reduction education to the patient's patterns of substance use (eg, context of use, route of administration, type of preparation; *Low certainty, Strong Recommendation)*,
    c. refer to relevant local harm reduction services as indicated based on the patient's clinical assessment (*Low certainty, Strong Recommendation)*,

d. offer harm reduction education on overdose prevention and reversal (*High certainty, Strong Recommendation)*, and

e. offer harm reduction education regarding safer sexual practices (*High certainty, Strong Recommendation)*.

Overdose Prevention and Reversal Recommendations

85. For patients who use stimulants from nonmedical sources or are socially engaged with others who do, clinicians should prescribe or distribute overdose reversal medications (eg, naloxone) or refer patients to locations where they can obtain these medications in the community (*High certainty, Strong Recommendation)*.

86. Clinicians should recommend that patients perform comprehensive drug checking, including using fentanyl test strips, every time they obtain a new batch of stimulants from nonmedical sources and review the technique for using fentanyl test strips when permitted by state law (*Moderate certainty, Conditional Recommendation)*.

87. Clinicians should consider referring individuals to local supervised consumption sites (SCS) when available (*Moderate certainty, Strong Recommendation)*.

Safer Sexual Practices and Contraception Recommendations

88. For patients who engage in risky sexual behaviors, clinicians should:

    a. offer or refer for sexually transmitted infection (STI) testing at least every 3 to 6 months or more frequently depending on the individual patient's risk (*Moderate certainty, Strong Recommendation)*;

        i. consider providing information about local STI testing services where patients can obtain free or low-cost testing (*Moderate certainty, Strong Recommendation)*;

    b. consider offering a referral to a local psychosocial sex education program or harm reduction program that addresses risky sexual behavior for additional or continuing harm reduction intervention (*Low certainty, Strong Recommendation)*; and

    c. offer condoms and lubrication or advice about where to obtain them (*Clinical consensus, Strong Recommendation)*.

Injection Drug Use Recommendations

89. For patients who inject stimulants, clinicians should:

a. provide or refer for harm reduction education on safer injection practices and include information specific to the patient's stimulant(s) and preparation(s) of choice (eg, safer acid pairings for crack cocaine injection; *Low certainty, Strong Recommendation)*, and

b. provide or refer for safe injection supplies and harm reduction services (*Moderate certainty, Strong Recommendation)*.

HIV Preexposure Prophylaxis Recommendations

90. Clinicians should offer HIV preexposure prophylaxis (PrEP) to patients who use stimulants and are at increased risk for HIV, including those who:

    a. engage in risky sexual behaviors (*High certainty, Strong Recommendation)*,

    b. access postexposure prophylaxis (PEP) regularly (*High certainty, Strong Recommendation)*, and/or

    c. inject drugs (*High certainty, Strong Recommendation)*.

Oral Health Recommendations

91. People who use stimulants are at high risk of dental complications, such as poor dentition, dental carries, abscesses, and subsequent malnutrition. Clinicians should:

    a. encourage patients who use stimulants to maintain good oral hygiene and receive regular dental care (*High certainty, Strong Recommendation)*, and

    b. offer referrals to dental care providers if needed (*High certainty, Strong Recommendation)*.

Nutrition Recommendations

92. People who use stimulants may experience appetite suppression and go for long periods without appropriate nutrition, placing them at high risk for nutritional deficits such as malnutrition, cachexia, and sequalae involving specific vitamin deficiencies. Clinicians should:

    a. inquire about diet, nutrition, and food security (*Clinical consensus, Strong Recommendation)*; and

    b. encourage patients who use stimulants to eat nutritious food (*Clinical consensus, Conditional Recommendation)*.

Introduction

Purpose

The American Society of Addiction Medicine (ASAM) and the American Academy of Addiction Psychiatry (AAAP) jointly developed this *Clinical Practice Guideline on the Management and Treatment of Stimulant Use Disorders* (hereafter referred to as the Guideline) to provide information on evidence-based strategies and clinically informed standards of care for the treatment of stimulant use disorder (StUD), stimulant intoxication, and stimulant withdrawal. The Guideline also addresses secondary and tertiary prevention of harms associated with stimulant use. This document draws on existing empirical evidence and clinical judgment with the goal of improving the quality of care for people with StUD.

Background

Overdose deaths involving stimulant drugs—including cocaine, methamphetamine, amphetamine, and prescription stimulants—have risen precipitously over the past decade.[1] Between 2012 and 2021, the rate of overdose deaths involving cocaine more than tripled from 1.4 per 100 000 in 2012 to 7.3 in 2021, increasing on average by 21% per year.[1] Over the same period, deaths involving methamphetamine, amphetamine, and prescription stimulants increased more than 12-fold from 0.8 per 100 000 in 2012 to 10.0 in 2021.[1] The precipitous increase in novel and designer drugs (eg, cathinones, amphetamines) in the market complicates the clinical picture.[3]

While the rate of cocaine use has been relatively flat, rates of cocaine use disorder, methamphetamine use, and methamphetamine use disorder are rising.[4–7] In addition, there has been a large increase in the risk from use due to the increasing potency of illicit stimulants and the increasing use of stimulants in combination with opioids, which can increase toxicity.[8] A growing number of people with opioid use disorder (OUD) are using stimulants intentionally.[9] Others may be unaware that the stimulants they use are contaminated with fentanyl or other opioids.[10]

In 2021, 50% of all overdose deaths in the US involved stimulants,* 23% involved cocaine, and 30% involved psychostimulants (primarily methamphetamine). Beyond the mortality

* Per *International Classification of Diseases*, 10th Revision (*ICD-10)* underlying cause-of-death codes for cocaine and psychostimulants with abuse potential (T40.5 and T43.6, respectively) in CDC WONDER.

risk, StUD can also lead to long-term health problems, including cardiac, pulmonary, psychiatric, dental, nutritional, and dermatologic issues, as well as cognitive impairment.[11] Further, injection stimulant use puts people at risk for infectious diseases, including human immunodeficiency virus (HIV) and viral hepatitis, as well as other infectious complications such as infective endocarditis.[11]

The most recent *National Drug Threat Assessment* from the US Drug Enforcement Administration (DEA) reported stable or rising availability and potency and low prices for cocaine and methamphetamine that are expected to exacerbate these trends.[8] To address this urgent issue, ASAM and AAAP convened a committee of experts to jointly develop a clinical practice guideline (CPG) for the prevention and treatment of StUD.

Scope of Guideline

This Guideline focuses on the management of StUD, including the identification, diagnosis, treatment, and promotion of recovery for patients with StUD, stimulant intoxication, and stimulant withdrawal. It also includes recommendations related to screening for risky stimulant use and secondary and tertiary prevention of StUD. With a few exceptions, recommendations that address general practices for all substance use disorders (SUDs) are not included.

A glossary of terms used in the Guideline can be found in Appendix A. A summary of abbreviations and acronyms can be found in Appendix B.

Intended Audience

The intended audience of this Guideline comprises clinicians—including behavioral health professionals, physicians, nurse practitioners, physician assistants, nurses, and pharmacists—who provide treatment for StUD, stimulant intoxication, or stimulant withdrawal in specialty addiction treatment settings and nonspecialty settings such as primary care offices, emergency departments (EDs), and hospitals. Some recommendations only apply to specific settings (eg, EDs, non-acute care settings) as indicated in the section narrative. The Guideline may also be useful for healthcare administrators, insurers, and policymakers.

Qualifying Statement

This Guideline is intended to aid clinicians in their clinical decision-making and patient management. It strives to identify and define clinical decision-making junctures that meet

the needs of most patients in most circumstances. Clinical decision-making should consider the quality and availability of expertise and services in the community wherein care is provided. The recommendations in this Guideline reflect the consensus of an independent committee (see Methodology) convened by ASAM and AAAP beginning in March 2021. This Guideline will be updated regularly as clinical and scientific knowledge advances.

Prescribed courses of treatment described in this Guideline are most effective if the recommendations are followed as outlined. Because lack of patient understanding and adherence may adversely affect outcomes, clinicians should make every effort to promote the patient's understanding of and adherence to prescribed and recommended treatment services.

Patients should be informed of the risks, benefits, and alternatives to a particular treatment and should be active parties to shared decision-making whenever feasible. ASAM and AAAP recognize that there are challenges to implementation of this Guideline in certain settings, particularly in relation to the availability of contingency management (CM) and community reinforcement approaches (CRAs) in various communities and settings. However, this Guideline aims to set the standard for best clinical practice by providing recommendations for the appropriate care of all patients with StUD in diverse settings. In circumstances in which the Guideline is being used as the basis for regulatory or payer decisions, the goal should be improvement in quality of care. Recommendations in this Guideline do not supersede any federal or state regulations.

Methodology†

Overview of Approach

ASAM's Quality Improvement Council (QIC) provided oversight for the development of this Guideline. The recommendations were developed by the Clinical Guideline Committee (CGC), which was composed of 14 members: 7 (including 1 chair) appointed by ASAM's Board of Directors and 7 (including 1 chair) appointed by AAAP's Board of Directors. One member from ASAM (Dr. Rawson) resigned prior to completion of the consensus process, leaving the CGC with thirteen total members.

Nine subcommittees were formed on Intoxication and Withdrawal, Behavioral Treatment, Pharmacotherapy, Co-occurring Disorders, Adolescents and Young Adults, Pregnant and

† The methodology used for this Guideline was not based on the *ASAM Clinical Practice Guideline Methodology* (published fall 2023).

Postpartum Patients, Secondary and Tertiary Prevention, Technology-Based Interventions, and Other Population-Specific Considerations. CGC members met in biweekly subcommittee meetings to draft recommendation statements.

The CGC was assisted by a technical team from the Institute for Research, Education and Training in Addictions (IRETA). IRETA supported the systematic literature review, quality of evidence rating, development of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) evidence profiles and recommendations, and initial drafting of the Guideline document.

A panel of seven patients was convened with assistance from Faces & Voices of Recovery (FAVOR) and Young People in Recovery (YPR) to provide feedback to the CGC at various stages of development, including determining the importance of outcomes to consider when weighing the harms and benefits of interventions. Unfortunately, the patient panel was not engaged to the degree initially hoped; only one patient panel member attended the scheduled meetings. We surmised that the patient panel may have found it intimidating to interact with professional medical societies. In response, we developed an anonymous survey to collect input that FAVOR and YPR disseminated to their membership; however, we received few responses. When the draft Guideline was sent out for public comment, it was sent to these and other patient advocacy organizations, but no feedback was received. The CGC recognizes that new strategies are required to effectively engage with patient stakeholders in this work. ASAM and AAAP will continue to iteratively explore new strategies for patient engagement in the development of CPGs.

All members of the QIC, Board of Directors, and CGC, as well as external reviewers of the Guideline, were required to disclose all current relevant relationships with industry and other entities that may represent actual, potential, or perceived conflict of interest. These disclosures are summarized in Appendix D. In general, if significant conflicts of interest are identified, committee members with significant disclosures of interest are asked to recuse themselves from voting on any relevant recommendation statements that presents a potential conflict. None of the disclosures from the CGC were deemed to present significant conflicts of interest in relation to the recommendation statements. Disclosures of interest for members of ASAM's QIC and Board of Directors and AAAP's Executive Committee were reviewed and no significant conflicts of interest were identified.

Table 1 broadly summarizes the scope and key questions developed by the CGC (see Table 1). More details about PICOS for each clinical question can be found in the EtD tables supplemental document.

Table 1. Management of Stimulant Use Disorder Scope and Key Questions Components (PICOS)

Population	Individuals with StUD (including adolescents and pregnant individuals) Individuals experiencing stimulant intoxication and/or withdrawal Individuals at high risk for developing StUD
Interventions	Pharmacotherapy for StUD (Non-stimulant medications; stimulant medications) Behavioral treatment for StUD (Contingency Management, Cognitive Behavioral Therapy; Community Reinforcement Approach) Intoxication and Withdrawal Management approaches Secondary and Tertiary Prevention strategies
Comparisons	Treatment as Usual
Outcomes	Stimulant abstinence Stimulant use reduction Other substance use Treatment retention/attrition Adverse events Risky behavior reduction
Timing	Any timing
Setting	Outpatient substance use treatment Residential substance use treatment Prenatal clinics General medical settings Emergency departments Hospital

GRADE Methodology

The Guideline was developed using the GRADE Evidence to Decision (EtD) framework for producing recommendations in health care.[12] GRADE provides a systematic, transparent approach to developing recommendations based on scientific evidence and the clinical

judgment of experts. The GRADE process encompasses systematic review of clinical evidence and its quality, consideration of existing guidelines, expert committee consensus, stakeholder comment and reconciliation, and document development.

Literature Review

A systematic literature review was conducted to support the GRADE evidence profiles used as part of the Guideline's development process. The literature review focused on identifying high-quality systematic reviews and meta-analyses, as well as new research published since the completion of those systematic reviews. The first stage of the literature review focused on locating existing systematic reviews, clinical guidelines, and gray literature on the management and treatment of StUD. The second stage of the literature review focused on locating primary research on topics for which moderate- to high-quality systematic reviews were not available and primary research released since the publication of high-quality systematic reviews. The third stage of the literature review used targeted literature searches to identify research on clinical questions identified by the CGC (see Appendix E). These searches were limited to a ten-year period.

Titles, abstracts, and full texts were reviewed by two independent senior members of the research team for inclusion in the literature review.

Supplemental literature searches were also conducted at the request of the CGC after completion of the initial literature review during the recommendation development process. These searches generally dropped the ten-year restriction, or terms were broadened to include other substances or populations with mixed SUDs that could be generalized to patients with StUD. Titles, abstracts, and full texts were reviewed by one senior member of the research team. CGC members were also permitted to request that a particular research document be included in an evidence profile.

Systematic Reviews and Meta-Analyses

A search for systematic reviews, clinical guidelines, and meta-analyses was conducted in the PubMed and PsycInfo literature databases on June 1, 2021. All text fields were searched, and the search was limited to articles published about humans in the prior ten years and available in English. Where authors or recommending bodies had published updates of an analysis or guideline, only the most recent version was included.

Primary Literature Search

A primary literature search was conducted in PubMed and PsycInfo on August 11, 2021. This search aimed to identify original research on topics for which high-quality reviews were not available and capture literature released after the publication of high-quality systematic reviews using a title, abstract, and keyword field search. All clinical study designs with random and nonrandom assignments were included, but case studies were excluded. If an article reflected a secondary analysis of data from a relevant study, the original report was included in the literature review.

Gray Literature Search

An internet search for gray literature was conducted during June 2021 that targeted published and unpublished clinical guidelines related to the management of StUD. The search followed the process suggested by the National Academy of Medicine (NAM) for searching gray literature.[13] The search was not limited by publication date; however, where recommending bodies had published updated guidelines, only the most recent versions were included.

Literature Extraction

Meta-analysis, systematic review, and individual study methods were extracted by one member of the research team. The quality of the meta-analyses, systematic reviews, and individual studies identified in the literature review was rated using standardized assessment scales. Appraisals were conducted by two independent members of the research team using the AMSTAR-2 tool for systematic reviews and meta-analyses,[14] the revised Cochrane Risk of Bias (RoB 2) tool for randomized trials,[15] and the Cochrane Risk of Bias In Non-randomized Studies – of Interventions (ROBINS-I) tool for nonrandomized trials.[16] A third senior member of the research team reconciled any disagreements in the appraisals. Evidence identified in the supplemental literature searches conducted during the recommendation development process at the request of the CGC were not individually appraised due to time constraints. Research results were summarized in a narrative literature review.

Existing guidelines on relevant topics were listed in the corresponding EtD table. Recommendations made in some non-systematic reviews identified in the literature search but excluded based on publication type were extracted at the request of the CGC when other existing recommendations could not be found.

Guideline Development

Ideally, a CPG is based on scientific evidence that is translated into practical recommendations for use by clinicians, policymakers, and the public. Recommendations are meant to inform decision-makers of evidence-based practices and standards of care. **The GRADE approach includes four elements to consider when translating evidence into recommendations**:

1. the balance of benefits and harms of the intervention in question,
2. the certainty of evidence about the benefits and harms,
3. the values and preferences of the populations affected by the guideline, and
4. the acceptability and feasibility of implementing the recommendation.[12]

Other criteria can also be considered, such as the cost and/or burden of the intervention and the impact of the recommendation on health equity.

The results of the literature review inform estimates of the size of benefits and harms and the certainty of the evidence of effects. A survey distributed to the patient panel and the clinical experience of the CGC informed judgments about patient preferences for different intervention outcomes. The feasibility of interventions was determined primarily by the clinical experience of the CGC, as acceptability and feasibility were not targets of the literature review.

Evaluations of these criteria are reflected in the strength of a recommendation and phrasing that may make the recommendation conditional (eg, depending on patient values, resource availability, or setting), discretionary (eg, based on the opinion of the patient or practitioner), or qualified (eg, by an explanation regarding the issues that would lead to different decisions).

Strong recommendations support actions in which benefits clearly outweigh harms, or vice versa, and for which patients have expressed clear and consistent values or preferences. They generally apply to most patients in most circumstances. Strong recommendations are typically based on high- or moderate-certainty evidence. A strong recommendation may be based on low-certainty evidence, for example, when the evidence indicates a substantial net benefit in a life-threatening situation or when there is limited evidence for a practice that is considered standard of care.

Moderate or conditional recommendations are often based on lower-certainty evidence that shows benefits more closely balanced with harms or variability in patient preferences. They may apply to many but not most patients. Implementation is often determined by variation in individual clinical situations—including disease factors, patient preferences and characteristics, and resource use—and usually involves a shared decision-making process.

Recommendations may be made even when there is low-certainty or insufficient evidence. The evidence base is still accumulating in many areas of addiction treatment, but the urgency and severity of SUD-related issues demand that clinicians act, even in the face of imperfect empirical evidence. Recommendations based solely on clinical consensus are clearly indicated and their rationale explained.

Rating Outcomes

Healthcare decision-making involves balancing multiple potential benefits and harms. When comparing treatment options that produce different sets of outcomes, it is helpful to first establish each outcome's relative importance before evaluating and comparing options. The literature review generated a list of outcomes measured in clinical research on StUD-related interventions. The CGC and patient panel independently rated outcomes to prioritize in terms of their importance to clinical decision-making or patient values, respectively, via an online survey (with patient panel participation limitations noted in Overview of Approach). Importance was indicated on a 1-to-9 scale, with an average below 4 indicating limited importance, 4 to 6 as important but not critical, and greater than 6 as critically important for decision-making. More important outcomes carried more weight when comparing interventions with different outcomes.

Rating Quality of Evidence

Evidence from the literature review was organized by intervention and outcome in a Summary of Findings table for each recommendation. The certainty of the body of evidence (ie, compiled across evidence types) for each intervention and outcome pair was rated by one member of the research team as high, moderate, low, or very low based on the following indicators:

- the quality or risk of bias in the included evidence assessed as part of the literature review,
- the consistency of findings across the evidence,
- the precision of estimated treatment effects,
- the directness or generalizability of the evidence to the guideline population, and
- the possibility of publication bias.

In situations where no direct or relevant experimental evidence was found related to a given recommendation, the certainty of evidence was labeled clinical consensus.

Developing Evidence to Decision Tables

Following the GRADE framework, the CGC used EtD tables to document the evidence and decisions made while drafting, deliberating, and finalizing the recommendations. EtD tables ensure transparency around judgments that result from interpretation of the evidence, considerations made for different subpopulations, and decisions about how judgments on different recommendation criteria influence the proposed recommendation. Where evidence was lacking, the EtD tables identify how the decision to rely on clinical expertise was made and the clinical perspective and assumptions used to inform judgments in those areas. EtD tables were formulated around the clinical questions presented in Appendix E.

One committee member initially rated the size of the positive and negative effects of an intervention, certainty of evidence, patient values and preferences, implementation feasibility, and other considered elements. Judgments were reviewed and discussed in subcommittee meetings and revised as appropriate based on the consensus of the subcommittee and/or CGC. Narrative summaries for each of these judgments were written by subcommittee members and the research team.

Summaries of findings and EtD tables are available for download as an online supplement.

Developing Recommendation Statements

The recommendation statements were informed by the literature review, EtD tables, and clinical expertise of the CGC members. This was an iterative process where CGC subcommittees drafted recommendations, and a review and discussion of the evidence profile and clinical considerations might have led the CGC to revise the recommendation. In the absence of relevant evidence, several recommendations were developed based on clinical consensus.

The CGC addressed evidence deemed negative or inadequate to accurately assess the net benefit of an intervention overall or in certain patient or intervention subgroups in Appendix F.

Approving the Recommendations

The CGC voted to approve each recommendation proposed by the subcommittees in a single round of asynchronous voting. At least 75% agreement among eligible voters was required to approve a recommendation. If the threshold was not met, the CGC discussed the recommendation in a virtual meeting with the full committee. The recommendation could then be approved by voice vote, revised and approved by voice vote, returned to the

subcommittee for further amendment (often to revise the supporting EtD table), or dropped.

Rating the Strength of Recommendations

The CGC voted on the strength of each accepted recommendation as strong, conditional, or weak based on the overall balance of benefits and harms, the certainty or quality of the evidence on treatment effects, and patient preferences and values. Strength was indicated on a 1-to-3 scale; the average was used as the overall strength measure, with less than 1.66 indicating weak, 1.66 to 2.33 indicating conditional, and greater than 2.33 indicating strong.

Developing the Guideline Document

The Guideline document includes the recommendations approved by the CGC, each with its recommendation strength rating and evidence quality assessment. Each recommendation statement is followed by its certainty of evidence rating (high, moderate, low, or very low certainty) and strength rating (strong, conditional, or weak). Each recommendation is also accompanied by narrative that describes its rationale and highlights its evidence and clinical considerations. Additionally, the narrative may describe the CGC's deliberations to further inform readers about factors that led to specific recommendation statements.

The narrative also discusses how the Guideline and its recommendations for StUD fit into the general management of SUD. Rather than duplicate recommendations made in existing high-quality general SUD guidelines, the CGC attempted to keep the scope of this Guideline narrowly focused on StUD and how clinical practices differ for this population compared to other SUDs. However, the CGC did not want the Guideline to be so limited in scope that it could function only as a supplement. Therefore, good general practices for SUD are discussed, but any declarative statements made in the narrative are not considered recommendations within this Guideline. Individuals seeking specific guidance on these topics should access additional resources; a list of related guidelines and other resources can be found in Appendix G.

Engaging Stakeholders

The draft Guideline was sent out for public comment in May 2023. ASAM and AAAP invited their respective Boards, major stakeholders and stakeholder organizations, relevant committees, and the patient panel to comment. The opportunity to comment was also sent to all ASAM and AAAP members and made public through ASAM and AAAP websites, newsletters, and social media.

ASAM and AAAP staff collated the public comments, and the CGC analyzed the feedback and made necessary revisions prior to finalization and publication. Major revisions, including additional recommendation statements, were subject to a vote by the CGC.

Treatment of Stimulant Use Disorder

Patients with StUD often have co-occurring mental health and biomedical needs. Effective management may involve interdisciplinary treatment teams that include physicians across multiple specialties (eg, psychiatry, addiction medicine, medical toxicology), nurses, behavioral health professionals, nutritionists, and peer support specialists, among others. Care should be coordinated with appropriate patient consent. Principles of interdisciplinary care and coordination across the full continuum of care are described in *The ASAM Criteria*.[17]

Assessment

StUD is primarily diagnosed based on the history provided by the patient and a comprehensive assessment that may include collection of information from collateral sources, such as family or friends, when available and with patient consent. Subsequent workup (eg, ordering indicated clinical testing and/or imaging) should be based on the history and clinical exam findings.

The extent of the clinical exam and medical workup for stimulant intoxication and withdrawal can be based on presenting signs and symptoms and severity of intoxication or withdrawal and is discussed in the Stimulant Intoxication and Withdrawal section of this Guideline.

Initial Assessment

When assessing patients for StUD, the first clinical priority should be to identify any urgent or emergent biomedical or psychiatric signs or symptoms that may be present and make appropriate referrals. Identifying urgent or emergent biomedical or psychiatric concerns is necessary to preserve the health and safety of patients who present for StUD treatment; acute issues, including signs of acute intoxication or overdose, need to be addressed immediately.

Initial Assessment Recommendations

1. When assessing patients for StUD, the first clinical priority should be to identify any urgent or emergent biomedical or psychiatric signs or symptoms, including acute intoxication or overdose, and provide appropriate treatment or referrals (*Clinical consensus, Strong Recommendation)*.

Comprehensive Assessment

After first addressing any urgent or emergent biomedical or psychiatric signs and symptoms, patients should receive, or be referred to an addiction treatment provider for, a comprehensive assessment that includes diagnostic investigation, StUD-focused history and physical examination, mental status examination, and full biopsychosocial assessment. Assessment for StUD should be based on accepted criteria, such as that outlined in the current version of the American Psychiatric Association's (APA) *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*)—which is the Fifth Edition, Text Revision (*DSM-5-TR*) at the time of publication of this Guideline.[18] The *DSM* classifies substance use disorders (including StUD) as mild, moderate, or severe based on how many of 11 criteria are met: mild StUD meets 2 to 3 criteria, moderate StUD meets 4 to 5 criteria, and severe StUD meets 6 or more criteria. Many factors influence the progression of StUD, including the potency and pharmacokinetics of the stimulants used, frequency of use, route of administration, and age of first use, among others.[19,20]

A StUD-focused history and physical examination includes a detailed history of the patient's past and current substance use and SUDs and an assessment of non-acute signs and symptoms of stimulant use, including complications. A mental status exam should identify concerns such as psychosis, cognitive impairment, and risk of harm to self or others.

A full biopsychosocial assessment of patients with StUD (or a provisional diagnosis of StUD) is critical to identify the broad range of biomedical, psychiatric, and psychosocial challenges that may need to be addressed as part of effective, comprehensive care. Patients' use of unprescribed stimulants may relate to co-occurring conditions such as eating disorders, cognitive impairment, or attention-deficit/hyperactivity disorder (ADHD).[21–24] If such issues are identified, the patient should be assessed—or referred for assessment—by an appropriately qualified clinician (see Co-occurring Disorders).

The biopsychosocial assessment should include age of onset of substance use, family history of SUD-related issues, ongoing risks related to substance use and SUD-related behaviors, treatment history and outcomes, psychosocial functioning, and factors in the patient's recovery environment that may impact their treatment and recovery support needs. As with all SUDs, the comprehensive assessment should incorporate social

determinants of health (SDOH)—conditions within a person's home, family, school, and community that can impact their ability to recover, such as access to safe housing, economic well-being, exposure to stigma and discrimination, and transportation challenges, among others.[25–29] A summary of the biopsychosocial assessment can be found in Appendix H.

While comprehensive assessment is vital for each patient's treatment planning for StUD, completion of all assessments should not delay or preclude initiation of treatment, particularly for critical needs (eg, toxicity, psychosis, suicidality, withdrawal). A comprehensive assessment may be completed over a period of time and may involve multiple clinicians (eg, social workers, counselors, psychologists, nurses, physicians).

As part of a comprehensive assessment for StUD, clinicians should conduct routine baseline laboratory testing (see Laboratory Testing). While no research was identified on ordering routine or as-needed laboratory testing in patients presenting for StUD treatment, the higher prevalence of HIV, viral hepatitis, and sexually transmitted infections (STIs) in patients with StUD justifies baseline testing in this population.‡ Clinicians should consider all sites of sexual exposure—including urogenital, pharyngeal, and rectal—when testing for chlamydia and gonorrhea. As with all patients with SUDs, clinicians should assess each patient's risks related to sexual practices and consider the need for preexposure prophylaxis (PrEP) and/or safer sexual practice counseling.

Despite the lack of direct evidence, non-infectious disease screening labs (eg, complete blood count [CBC], comprehensive metabolic panel [CMP]) can help identify comorbidities as part of a comprehensive assessment. In addition to baseline labs and in alignment with recommendations from the Centers for Disease Control and Prevention (CDC), the CGC recommended that vaccines for hepatitis A virus (HAV) and hepatitis B virus (HBV) be offered to all patients who are not already immune.[31,32] See Appendix I for more information about routine baseline laboratory testing.

As with any SUD-focused assessment, toxicology and drug testing may be provided as part of the comprehensive assessment for StUD. The CGC noted the inherent limitations of drug testing but agreed that testing could be utilized when the outcome would impact clinical decision-making or be important for medication monitoring or psychiatric follow-up. Clinicians should consider the technical limitations of the selected matrix and drug panel. Clinicians should also be aware of which substances are present in the local market and consider that in testing; for example, testing for fentanyl due to frequent presence in the stimulant drug supply. If stimulant use is suspected but presumptive testing is negative, clinicians should consider either confirmatory testing for a strongly suspected substance or

‡ See recommendations compiled by the CDC for infectious disease screening.[30]

the possibility of novel or designer psychoactive stimulants. The CGC noted that tests for novel or designer stimulants are often expensive with limited availability. Consultation with laboratory personnel may be helpful when selecting the panel or interpreting results.

For additional considerations, see ASAM's *Appropriate Use of Drug Testing in Clinical Addiction Medicine* consensus statement (major principles of this document are outlined in Appendix J) and ASAM's public policy statement on *Ethical Use of Drug Testing in the Practice of Addiction Medicine*.[33,34]

The CGC agreed that clinicians should have an elevated degree of suspicion for cardiovascular disease when evaluating patients with long-term or heavy stimulant use. Clinicians should have a lower threshold for conducting cardiac evaluation based on patient history and physical exam results. At this time, the CGC does not recommend that all patients with long-term or heavy stimulant use receive an electrocardiogram (ECG). Clinical management of long-term or heavy stimulant use as it relates to cardiac injury remains individualized, with strong clinical suspicion of cardiac injury guiding screening, diagnostics, and treatment.

There is insufficient evidence to recommend routine screening for rhabdomyolysis or renal disease among patients who use stimulants. However, clinicians should have an elevated degree of suspicion for these conditions when evaluating patients with long-term or heavy stimulant use. Consider ordering relevant tests—such as creatine kinase [CK] for rhabdomyolysis, blood urea nitrogen [BUN]/creatinine ratio [BCR], urine albumin (ie, proteinuria) for renal disease—at a lower threshold of suspicion based on patient history and physical exam findings.

If concerns are identified during the assessment, clinicians should either treat or refer the patient to an appropriate biomedical or psychiatric provider or setting for care. If signs or symptoms of infection are identified, clinicians should provide treatment or referrals as appropriate (eg, STI clinic, HIV clinic). Education on and referrals for harm reduction services (eg, syringe service programs [SSPs]) should also be considered. Clinicians should work with the patient to develop strategies to address barriers to accessing care that were identified during the assessment (eg, childcare or transportation support, telehealth).

Comprehensive Assessment Recommendations

2. After first addressing any urgent biomedical or psychiatric signs or symptoms, patients should undergo a comprehensive assessment that includes:
    a. assessment for StUD based on diagnostic criteria (eg, current *DSM*; *Clinical consensus, Strong Recommendation)*;

   b. a StUD-focused history and physical examination (*Clinical consensus, Strong Recommendation)*;
   c. a mental status exam to identify co-occurring psychiatric conditions, such as signs and symptoms of psychoses, ADHD, mood disorders, cognitive impairment, and risk of harm to self or others (*Clinical consensus, Strong Recommendation)*; and
   d. a full biopsychosocial assessment (*Clinical consensus, Strong Recommendation)*.

3. Clinicians treating StUD should conduct routine baseline laboratory testing (*Clinical consensus*, *Strong Recommendation)*.
   a. Clinicians should conduct other clinical tests as necessary based on each patient's clinical assessment findings (*Clinical consensus, Conditional Recommendation)*.

4. When evaluating patients with long-term or heavy stimulant use, clinicians should exercise:
   a. an elevated degree of suspicion for cardiac disorders (*Clinical consensus, Conditional Recommendation)*,
   b. a lower threshold for considering ECG testing based on findings of the history and physical exam (*Clinical consensus, Conditional Recommendation)*,
   c. a lower threshold for considering CK testing for rhabdomyolysis based on findings of the history and physical exam (*Clinical consensus, Strong Recommendation)*, and
   d. an elevated degree of suspicion for renal disorders (*Clinical consensus, Conditional Recommendation)*.

Behavioral Treatment

Contingency Management

Contingency management (CM) is an evidence-based psychosocial intervention in which patients are given tangible rewards to reinforce positive behaviors related to treatment participation or outcomes; vouchers, prizes, and access to employment have been used successfully as incentives.[35–37] Decades of research support the effectiveness of CM at reinforcing behaviors—such as abstinence from substances, treatment attendance, and medication adherence—across different SUDs, including opioid, stimulant, tobacco, and alcohol use disorder.[38–41] CM can also be combined with other psychosocial interventions, such as community reinforcement and cognitive behavioral therapy (CBT).[42]

Contingency management (CM) has demonstrated the best effectiveness in the treatment of stimulant use disorders (StUDs) compared to any other intervention studied and represents the current standard of care.

There is strong evidence that CM is an effective intervention for increasing treatment engagement and reducing stimulant use. A systematic review that evaluated reviews covering various psychosocial and pharmacological interventions for StUD found that CM was the only efficacious intervention.[43] Multiple systematic reviews have shown positive effects of CM on methamphetamine use,[44,45] and one showed effectiveness in reducing cocaine use in adults.[46] CM has demonstrated the best effectiveness in the treatment of StUDs compared to any other intervention studied and represents the current standard of care.

Implementation Considerations

Despite its effectiveness, CM is not widely implemented; less than 10% of addiction treatment programs utilize CM.[47] Barriers to implementing CM include regulatory obstacles, financial costs, stakeholder buy-in, and program resources. These barriers, along with implementation and dissemination strategies, are well described elsewhere; the following serves as a general overview alongside CGC comments.[48–51] The CGC noted that while available research suggests CM alone is effective at promoting desired behaviors, patients with greater or more complex therapeutic needs are likely to benefit from additional behavioral interventions.

Regulatory Barriers

Treatment providers must be mindful of the federal Anti-Kickback Statute, which prohibits remuneration of patient referrals or generation of business involving medical services billed to the federal government.[52] Concern regarding interpretation of this statute has been a significant policy barrier to the use of CM. In December 2020, the Office of the Inspector General (OIG) published clarification—known as the "OIG Final Rule"—that CM interventions, while not a "safe harbor" (ie, practices not considered kickbacks), are not inherently in violation of the Anti-Kickback Statute and can be analyzed on a case-by-case basis.[53] However, implementation of CM in compliance with the OIG Final Rule is not well defined; programs can seek guidance from the OIG but are not required to do so. A recent report by the Motivational Incentives Policy Group—a stakeholder coalition of CM experts in policy, research, and legal analysis—outlines "guardrails" that serve as unofficial guidelines for the use of CM incentives in alignment with the OIG Final Rule.[48]

Financial Costs

A commonly reported barrier to implementing CM is financial cost. A consistent funding source—typically government funding or payer reimbursement—is needed to support implementation. Fortunately, this is beginning to occur; Montana, Washington, and California have all begun state-funded pilot programs that implement CM.[48] Additionally, some payers have begun reimbursing select CM programs.[51]

Stakeholder Buy-in

Anecdotally, the CGC noted that resistance to the use of CM for the treatment of SUDs has been rapidly declining as information about its effectiveness is more broadly disseminated; however, resistance remains among some stakeholders. The CGC agreed that they would expect key stakeholders to accept CM, especially when presented with evidence of its effectiveness.

Clinicians and other staff may initially resist adopting CM due to misconceptions that CM is rewarding people for substance use and, thus, inappropriate.[48,54] However, these attitudes can be changed through training and exposure.[55–57]

CM is also gaining support at the federal level. On April 1, 2021, the federal government issued a statement on drug policy priorities, including goals to "identify and address policy barriers related to contingency management interventions (motivational incentives) for stimulant use disorder" and "explore reimbursement for motivational incentives and digital treatment for addiction, especially stimulant use disorder."[58] Addressing these priorities would reduce regulatory and financial barriers and facilitate adoption of CM.

Program Resources

CM interventions require programs to develop protocols around its use and dedicate resources, including staff training and time, toward its implementation. Some published protocols exist for voucher- and prize-based interventions,[59,60] as well as some introductory trainings.§ Effective CM interventions are attentive to the schedule, magnitude, timing, and type of reinforcement; this can be cumbersome in busy treatment settings, but technology may ease the burden (see Technology-Based Interventions).

Effective implementation of CM requires availability of several components, including funding, training, capacity for drug testing, and—typically—at least twice weekly clinical engagement. The CGC emphasized that clinically effective monetary value as contingency rewards are necessary, though this may be limited by regulations and/or payer policies. **Using an incentive value that is too low does not represent evidence-based practices and is unlikely to be effective**; such implementations may lead decision-makers to erroneously conclude that CM is not effective.[51]

Another consideration when implementing CM is the sensitivity of the immunoassay drug test. It is possible for a drug test to produce a false positive. Clinicians may need to send for confirmatory laboratory testing, and such a delay could decrease the effectiveness of the incentives. If other medications prevent the use of CM to promote abstinence from substances, CM could instead be used to reinforce treatment attendance or other behaviors related to successful treatment; however, this is less effective.[61]

Community Reinforcement Approach

Community reinforcement approach (CRA) is a comprehensive behavioral therapy based on operant conditioning theory.[62] Clinicians work closely with patients to adjust aspects of their lives that interfere with a healthy lifestyle, seeking to build a new way of living without substances that is more rewarding than their life with substance use.[62,63]

Moderate evidence exists that suggests CRA is effective for achieving and sustaining abstinence in patients with cocaine use disorders. Compared to other behavioral treatments, CRA achieves somewhat better outcomes of abstinence duration, abstinence rates, and treatment retention among patients with cocaine use disorder, particularly with longer duration of treatment.[42,64]

§ For example, through the Addiction Technology Transfer Center Network (ATTC) at https://attcnetwork.org/centers/northwest-attc/cm.

For cocaine use disorder, the certainty of the evidence was judged to be modest given that CRA did not outperform other treatments in all studies.[42,64] However, the quality of the evidence favoring CRA is high, coming from well-conducted randomized controlled trials (RCTs).

All the reviewed evidence for CRA was based on participants with cocaine use disorder. The CGC emphasized that no evidence was found for using CRA alone in patients who use amphetamine-type stimulants (ATS) or methamphetamine. However, the CGC agreed that there is reason to believe that CRA would be similarly effective with patients who use ATS as it is with those who use cocaine. CRA by definition needs to be tailored to contextual factors in the patient's environment, so any differences in behavioral or environmental concomitants of the substance being used should be addressed by the intervention.[65]

CRA combined with CM appears to be effective for reduced stimulant use and treatment retention. A meta-analysis that analyzed 50 clinical studies on 12 different psychosocial interventions found that CM combined with CRA was the most efficacious treatment for StUD, especially cocaine use disorder.[42] The CGC concluded that CRA is associated with apparent benefits and no known undesirable effects.

While CRA appears to be one of the more promising behavioral interventions for StUD, especially when combined with CM, it has not been widely implemented outside of research settings.[66] Substantial barriers have limited implementation of CRA; it requires a great deal of resources and patient commitment relative to other behavioral interventions.[66] Few settings have workforces that are appropriately trained to deliver CRA, and few experts are available to train clinicians in its delivery.[66] CRA is costly and labor intensive; funding and staff levels would have to be increased for adequate implementation.[66]

Cognitive Behavioral Therapy

CBT is a type of psychotherapy—delivered by clinicians trained in its use—in which negative patterns of thought about the self and the world are challenged and skills to cope with high-risk situations are developed to alter unwanted behavior patterns and treat SUDs and psychiatric disorders.[67–69] Some evidence supports CBT as superior to usual treatment options, such as individual and group counseling, on stimulant use and abstinence outcomes during treatment and at follow-up, as well as for treatment retention.[42,64] However, CBT has not been found to be superior to usual treatment options for longest duration of continuous stimulant abstinence or stimulant use at study endpoint.[42,70]

CBT is a widely utilized and accepted treatment modality. CBT does require resources—namely, the availability of highly trained clinicians for proper delivery. On the other hand,

CBT can be delivered in group sessions, which makes it more feasible for many programs compared to other behavioral interventions.

Clinicians should be trained in CBT delivery to promote fidelity. The CGC suggested using an evidence-based CBT manual, such as Project MATCH's *Cognitive-Behavioral Coping Skills Therapy Manual*; the National Institute on Drug Abuse's (NIDA) Therapy Manual for Drug Addiction, *A Cognitive-Behavioral Approach: Treating Cocaine Addiction*; or the US Department of Veterans Affairs' (VA) *CBT-SUD Among Veterans: Therapist Manual*.[68,69,71]

Matrix Model

The Matrix Model of addiction treatment is a structured, multicomponent behavioral therapy that delivers individual counseling; CBT, family education, and social support groups; and encouragement for mutual support group participation over 16 weeks.[72] Moderate evidence supports use of the Matrix Model for treatment of StUD. Studies have demonstrated that the Matrix Model produced greater reductions in methamphetamine use compared to standard treatment or a wait-list control group.[73–75] The Matrix Model also reduced craving and risky behavior compared to a wait-list control.[45]

With respect to implementation, the Matrix Model is compatible with the structure and staffing at many SUD treatment programs and has been widely adopted, demonstrating feasibility. Programs should assess staffing needs and their network of providers prior to implementation. As with any new intervention, staff training is an important consideration.

The CGC underscored the superiority of CM as a primary component of treatment for StUD. Where CM is not available, several other behavioral interventions—notably, CRA, CBT, and the Matrix Model—should be considered as other effective treatment options.

Behavioral Treatment Recommendations

5. Contingency Management (CM) should be a primary component of the treatment plan in conjunction with other psychosocial treatments for StUD (*High certainty, Strong Recommendation)*.
6. The following three interventions have the most supportive evidence and are preferred alongside CM:
    a. Community Reinforcement Approach (CRA) (*Low certainty, Conditional Recommendation)*,
    b. Cognitive Behavioral Therapy (CBT) (*Moderate certainty, Strong Recommendation)*, and

c. The Matrix Model (*Moderate certainty, Conditional Recommendation)*.

Please see the supplementary EtD document for the following related summaries of evidence, relevant citations, and CGC judgments:

- Table 1. Contingency Management
- Table 2. Community Reinforcement Approach
- Table 3. Cognitive Behavioral Therapy
- Table 4. Matrix Model

Technology-Based Interventions

Technology-based interventions—such as computer, web, or mobile applications—can be used to implement evidence-based interventions (EBIs) for SUD, such as CBT and CM.[76,77] These applications allow for standardized implementation, reduced staff burden, and increased access to care.[76,77]

A number of CBT-focused web applications have been developed to deliver SUD treatment, such as Snow Control for cocaine use disorder, Breaking the Ice for ATS use disorder, and Computer Based Training for CBT (CBT4CBT) for SUD.[76,78–81] The Therapeutic Education System (TES), an interactive web-based program based on CRA, also contains a CBT component.[82]

CBT4CBT can be combined with weekly monitoring check-ins[80,81]; studies have found significant reductions in substance use and improved retention in treatment using CBT4CBT relative to in-person CBT.[81,83] In addition to supporting outpatient programs, evidence suggests that patients in residential treatment programs can also benefit from web-based CBT interventions.[84] A few individual studies across technology-based interventions reported reduced substance use, particularly in patients who use cocaine.[81,82,85–87] The literature revealed less evidence of efficacy for ATS and methamphetamine use.

CBT4CBT and TES appear to improve stimulant use outcomes when added to other behavioral interventions; however, these effects are not always durable.[82,83] Some evidence suggested that these interventions may be similarly effective to clinician delivered treatment, including CBT. One study suggested the positive effect of TES was greater in those with a drug positive urine test at baseline.[82] While evidence is strongest for cocaine use, the CGC has no reason to believe the effectiveness would be significantly different for ATS use.

CM interventions have used webcams and mobile applications to promote cessation of nicotine/tobacco, alcohol, and illicit drug use.[51,88] One model to digitally implement CM is

through smartphone–smartcard platforms, where a smartphone application allows for remote salivary and breathalyzer drug testing at individualized random schedules. The application tracks the individual's history of drug tests and treatment attendance and provides appointment reminders. Incentives are delivered via an anonymous credit card that cannot be used to withdraw cash and has additional purchasing protections. Studies show preliminary effectiveness of this model in patients with OUD, including one with patients who have concurrent StUD.[89–91]

The CGC reviewed available evidence for a number of technology-based and alternative interventions but found it to be insufficient to include in the recommendation statements at this time. These items can be found in Appendix F: Topics with Insufficient or Negative Evidence.

Implementation Considerations

The CGC expressed concern over the use of standalone technology-delivered interventions. CBT4CBT has been shown to be effective as a standalone treatment in a few studies, but this is insufficient evidence to recommend it as a standalone treatment.[81,83,92] While some patients may opt for this approach because they favor the convenience, many will require more intensive treatment. Additionally, the lack of clinician interactions could make it more difficult to identify signs of decompensation, such as suicidal ideation or behavior. Patients who do not have ready access to a computer and the internet and/or who have low computer literacy could find these interventions difficult to access, disproportionately impacting patients with lower socioeconomic status.[93] Clinicians should be aware that the Affordable Care Act covers access to phone and internet services for those in need, as well as training and assistance with computer and phone literacy. Finally, the CGC noted that text messaging interventions for StUD are promising as add-on interventions; however, there is insufficient evidence to recommend them at this time.

Another point of caution is that little regulatory oversight currently exists for many of these technology-based tools. Most digital technologies have little to no evidence of effectiveness; existing evidence may be low quality or those conducting the studies may have conflicts of interest. Clinicians should independently evaluate digital technologies for quality before integrating them into patient care. The APA's App Advisor can be used to assess mobile applications; the tool provides reviews by APA members using the App Advisor assessment framework.[94]

Telemedicine

Current evidence for the use of telemedicine in the treatment of StUD primarily involves telephone-based (ie, audio only) interventions, which are often provided after some amount of in-person care.[95–97] The evidence for telephone-based follow-up care of

individuals with cocaine use disorder is mixed.[96–100] One RCT of a mixed population of patients with cocaine and methamphetamine use disorders found positive effects on reduced substance use, suggesting that telemedicine may be effective in the treatment of methamphetamine use disorder.[95] The research base regarding telemedicine is expected to expand rapidly as a result of increased use during and following the COVID-19 pandemic. Available resources for utilizing telemedicine include those developed by the Substance Abuse and Mental Health Services Administration (SAMHSA) and the National Council for Mental Wellbeing.[101,102]

While video-based telemedicine has not been studied in this population, the CGC noted that it is reasonable to think that it would perform similarly to audio-only telemedicine. There may be acceptability issues due to patients being uncomfortable appearing on camera. However, with the patient on camera, the clinician may be better able to detect signs of substance use and/or distress. Telemedicine is also an important tool for expanding access to care, particularly in rural and underserved areas where SUD treatment services are limited.

Technology-Based Interventions Recommendations

7. Clinicians can consider offering evidence-based behavioral interventions delivered via digital therapeutics or web-based platforms as add-on components to treatment for StUD, but they should not be used as standalone treatment (*Low certainty, Strong Recommendation)*.
8. Clinicians should consider using telemedicine to deliver behavioral treatment for StUD to patients who may face challenges accessing in-person care (*Moderate certainty, Strong Recommendation)*.

Please see the supplementary EtD document for the following related summaries of evidence, relevant citations, and CGC judgments:

- Table 5. Computer-Delivered Treatment
- Table 6. Telehealth

Continuing Care

Research has demonstrated that patients with StUD who have not achieved their treatment goals during the initial phase of treatment may benefit from extended treatment with EBIs to facilitate long-term recovery.[95,99,103,104] CM should be provided to support continuing care for patients with StUD as they transition through the phases of treatment. Patients with StUD who are not progressing as hoped toward achieving their goals in an initial phase of treatment may benefit from extended treatment with EBIs to facilitate long-term

recovery.[95,99,103,104] Addiction is a chronic illness best addressed with a chronic care model of disease management. As described in *The ASAM Criteria*, patients should remain engaged in the continuum of care; patients who achieve sustained remission (as defined in the current edition of the *DSM*) should receive ongoing recovery management checkups to support rapid reengagement in care in the event of recurrence.[17] Clinicians can consider the use of telemedicine to deliver continuing care.

Pharmacotherapy

No pharmacotherapies have been approved by the US Food and Drug Administration (FDA) for the treatment of StUD. The following sections discuss considerations for when pharmacotherapies may be prescribed off-label. The CGC recognized that some clinicians may be reluctant to prescribe medications off-label. The CGC acknowledged that the existing evidence for treating StUD with medications is relatively low quality. Despite the limitations of the evidence, the CGC agreed that medications may be helpful for some patients with StUD, particularly in the context of certain co-occurring disorders (see Co-occurring Disorders). The CGC reviewed available evidence related to several medications that are not included in the recommendations in this section due to negative or insufficient evidence. These items can be found in Appendix F: Topics with Insufficient or Negative Evidence.

The pharmacotherapy recommendations in this Guideline discuss both non-psychostimulant and psychostimulant medications. The CGC emphasized the importance of careful and ongoing risk–benefit assessments and close monitoring when prescribing medications for StUD. Clinicians should monitor patient symptoms and functional status regularly in response to all pharmacotherapies, with increased monitoring when using medications with higher risk profiles, such as psychostimulants. Clinicians should monitor medication adherence and nonmedical use through strategies such as frequent clinical contact, drug testing, pill counts, and prescription drug monitoring program (PDMP) checks.

The recommendations for non-psychostimulant and psychostimulant medications have been categorized by substance type (ie, cocaine use disorder and ATS use disorder) due to their different pharmacological mechanisms of action, which may impact the effectiveness of pharmacotherapies. Cocaine and ATS both increase dopamine signaling in the brain[105]; cocaine blocks the reuptake of dopamine, whereas methamphetamine both increases dopamine release and blocks its reuptake, resulting in much higher concentrations.[105] In addition, methamphetamine's half-life of 10 to 12 hours is significantly longer than cocaine's 1-hour half-life, leading to more prolonged effects.[105]

Non-Psychostimulant Medications

Cocaine Use Disorder

Bupropion

Bupropion is a dual dopamine and norepinephrine reuptake inhibitor that is FDA-approved for the treatment of major depressive disorder (MDD), seasonal affective disorder, and smoking cessation.[106] A small amount of evidence exists for bupropion facilitating abstinence from cocaine use. While bupropion was not found to be superior to placebo on cocaine abstinence at the end of treatment or on treatment retention, it was superior to placebo on sustained (ie, 3 or more weeks) abstinence in two RCTs.[107,108]

Though both desirable and undesirable effects are small, the CGC concluded that the potential benefits of bupropion outweigh the potential risks. Especially in the context of the lack of strongly supported medication alternatives, the CGC agreed that bupropion may be considered as a pharmacotherapeutic option for cocaine use disorder.

Bupropion has been shown to reduce nicotine/tobacco use in patients who smoke cigarettes or use other nicotine/tobacco products.[109] Therefore, the CGC agreed that bupropion could be given additional consideration for patients with co-occurring tobacco use disorder (TUD). Given bupropion's efficacy in treating MDD, the CGC also agreed that this medication could be given additional consideration for patients with co-occurring depressive disorders.[110]

The generic formulation of bupropion is commonly available on medication formularies, and it is relatively easy to titrate dosing. Bupropion is contraindicated in individuals with history of seizure or anorexia or bulimia nervosa and should be used with caution in individuals with elevated seizure risk.[111]

Cocaine Use Disorder: Bupropion Recommendations

9. For patients with cocaine use disorder, clinicians can consider prescribing bupropion to promote cocaine abstinence (*Low certainty, Conditional Recommendation)*.
    a. Clinicians can give bupropion additional consideration for patients with co-occurring TUD, as this medication can also reduce nicotine/tobacco use (*Low certainty, Conditional Recommendation)*.
    b. Clinicians can give bupropion additional consideration for patients with co-occurring depressive disorders, as this medication can also treat depression (*Low certainty, Conditional Recommendation)*.

Please see the supplementary EtD document for the following related summaries of evidence, relevant citations, and CGC judgments:

- Table 7. Bupropion for Cocaine Use Disorder

Topiramate

Topiramate is an anticonvulsant medication that is FDA-approved for the treatment of epilepsy and migraine. It is known to have several molecular actions, including blocking voltage-dependent sodium channels, increasing gamma-aminobutyric acid A (GABA-A) receptor activity, antagonizing some glutamate receptor subtypes, and inhibiting carbonic anhydrase.[112,113] The evidence for topiramate in cocaine use disorder outcomes is mixed; a meta-analysis demonstrated a higher rate of continuous stimulant abstinence over three weeks with topiramate versus placebo.[114] While the CGC judged that the evidence only somewhat favors topiramate, they concluded that topiramate might be considered for patients with cocaine use disorder, especially those who are highly motivated to achieve abstinence.

The desirable effects of topiramate are somewhat offset by known side effects (eg, cognitive effects, paresthesia) and variable tolerability, which can be improved by slow titration.[115] In addition, topiramate can cause appetite suppression, which is an important consideration when treating patients who are underweight or at risk of being underweight.[115]

Topiramate has been shown to reduce alcohol use and is utilized off-label for treatment of alcohol use disorder (AUD).[116] Therefore, the CGC agreed that topiramate could be given additional consideration for patients with co-occurring cocaine use disorder and AUD.

Cocaine Use Disorder: Topiramate Recommendations

10. For patients with cocaine use disorder, clinicians can consider prescribing topiramate to reduce cocaine use (*Low certainty, Conditional Recommendation)*.
    a. Clinicians can give topiramate additional consideration for patients with co-occurring AUD, as this medication can also reduce alcohol consumption (*Low certainty, Conditional Recommendation)*.

Please see the supplementary EtD document for the following related summaries of evidence, relevant citations, and CGC judgments:

- Table 8. Topiramate for Cocaine Use Disorder

Amphetamine-Type Stimulant Use Disorder

Bupropion

Data from systematic reviews and meta-analyses suggest that bupropion alone is not as effective for individuals with ATS use disorder with respect to stimulant use and abstinence outcomes compared to the findings in cocaine use disorder.[117–119] However, the evidence is suggestive of an effect for patients with less than daily ATS use. A subgroup analysis within a high-quality systematic review showed that bupropion was associated with higher abstinence rates in patients who used ATS less than 18 days per month and in patients who were adherent to the medication as confirmed by objective measures.[119] No difference in adverse events between bupropion and placebo was noted in any of the studies.

Though both desirable and undesirable effects are small, the CGC concluded that the potential benefits of bupropion outweigh the potential risks. Especially in the context of the lack of strongly supported medication alternatives, the CGC supported consideration of bupropion for ATS use disorder, specifically in patients with low- to moderate-frequency (ie, less than 18 days per month) stimulant use.

Bupropion has been shown to reduce nicotine/tobacco use in patients who smoke cigarettes or use other nicotine/tobacco products.[109] Therefore, the CGC agreed that bupropion could be given additional consideration for patients with co-occurring TUD. Given bupropion's efficacy in treating MDD, the CGC also agreed that this medication could be given additional consideration for patients with co-occurring depressive disorders.[110]

Bupropion dosing is relatively easy to titrate, and the generic formulation is commonly available on medication formularies. Bupropion is contraindicated in individuals with history of seizure or anorexia or bulimia nervosa and should be used with caution in individuals with elevated seizure risk.[111]

Amphetamine-Type Stimulant Use Disorder: Bupropion Recommendations

11. For patients with ATS use disorder with low- to moderate-frequency (ie, less than 18 days per month) stimulant use, clinicians can consider prescribing bupropion to promote reduced use of ATS (*Low certainty, Conditional Recommendation)*.
    a. Clinicians can give bupropion additional consideration for patients with co-occurring TUD, as this medication can also reduce nicotine/tobacco use (*Low certainty, Conditional Recommendation)*.
    b. Clinicians can give bupropion additional consideration for patients with co-occurring depressive disorders, as this medication can also treat depression (*Low certainty, Conditional Recommendation)*.

Please see the supplementary EtD document for the following related summaries of evidence, relevant citations, and CGC judgments:

- Table 9. Bupropion for Amphetamine-Type Stimulant Use Disorder

Bupropion and Naltrexone

While the evidence for bupropion alone is somewhat weak in patients with ATS use disorder, two recent studies using combination bupropion and naltrexone have shown more promise in terms of stimulant use outcomes.[120,121] Naltrexone is a mu opioid receptor antagonist that is FDA-approved for the treatment of AUD and OUD; its extended-release formulation is also approved for the prevention of OUD recurrence.[122] Both studies—one open label and one RCT—included patients with moderate to severe methamphetamine use disorder. The CGC considered it appropriate to extend the evidence to other ATS use disorder populations because the pharmacotherapeutic mechanisms of effect are expected to be similar.

Because naltrexone is an FDA-approved treatment for AUD, the CGC agreed that bupropion–naltrexone combination treatment could be given additional consideration for patients with co-occurring ATS use disorder and AUD. Similarly, this combination could be given additional consideration for patients with ATS use disorder and co-occurring nicotine/tobacco use or depressive disorders, because bupropion is FDA-approved for the treatment of TUD and MDD.

The recommendations in this Guideline do not address the use of bupropion in combination with naltrexone for patients with OUD. However, clinicians may consider this combination for patients with co-occurring OUD who are already prescribed naltrexone for OUD or are in OUD remission and not currently prescribed opioid agonist medication. No studies were available that evaluated the impact of this medication combination for co-occurring methamphetamine use disorder and OUD.

With the increasing concurrent use of stimulants and opioids and concerns surrounding contamination of the stimulant supply with high potency synthetic opioids such as fentanyl, as well as intentional co-use of stimulants and opioids, an important unanswered research question is if treatment with naltrexone could be protective against opioid overdose in this population.

While the evidence for combination bupropion and naltrexone is promising, the CGC noted a few implementation considerations. The available research used relatively high doses of bupropion (ie, 450 mg of an extended-release formulation). The standard dosing of injectable naltrexone is every four weeks for the treatment of AUD and prevention of OUD recurrence.[120,121] In the open label trial, naltrexone was administered every four weeks, whereas in the RCT it was administered every three weeks to reduce potential blood level

fluctuations.[120,121] While bupropion and naltrexone are generally well tolerated, both studies reported a moderate number of adverse events. The combination of these medications would most likely be prescribed by an addiction specialist, potentially limiting access and increasing health inequities. Confirmation of the patient's opioid free status is required prior to initiating naltrexone.

The trials above evaluated injectable—but not oral—naltrexone in combination with bupropion for treatment of StUD. While clinical trials have evaluated both oral and injectable formulations of naltrexone for ATS use disorder, oral naltrexone has not been studied in combination with bupropion.[120,121] At the time of this publication, bupropion and oral naltrexone are available in generic formulations. The CGC noted that there is no reason to believe that oral naltrexone would be less effective in this population if the patient is adherent to treatment, although injectable medications can facilitate adherence. Given the potential challenges with access to injectable naltrexone, consideration of combination bupropion and oral naltrexone would be reasonable, particularly for patients who are highly motivated.

Despite these potential barriers, the CGC concluded that in certain patients, this treatment option may be useful in reducing ATS use and other co-occurring symptoms.

Bupropion is contraindicated in individuals with history of seizure or anorexia or bulimia nervosa and should be used with caution in individuals with elevated seizure risk.[111]

Amphetamine-Type Stimulant Use Disorder: Bupropion and Naltrexone Recommendations

12. For patients with ATS use disorder, clinicians can consider prescribing bupropion in combination with naltrexone to promote reduced use of ATS (*Moderate certainty, Conditional Recommendation)*.
    a. Clinicians can give this combination additional consideration for patients with co-occurring AUD, as naltrexone can also reduce alcohol consumption (*Moderate certainty, Conditional Recommendation)*.
    b. Clinicians can give this combination additional consideration for patients with co-occurring TUD, as bupropion can also reduce nicotine/tobacco use (*Moderate certainty, Conditional Recommendation)*.
    c. Clinicians can give this combination additional consideration for patients with co-occurring depressive disorders, as bupropion can also treat depression (*Moderate certainty, Conditional Recommendation)*.

Please see the supplementary EtD document for the following related summaries of evidence, relevant citations, and CGC judgments:

- Table 10. Bupropion + Naltrexone for Amphetamine-Type Stimulant Use Disorder

Topiramate

The evidence for topiramate in ATS use disorder outcomes is mixed. Evidence from two RCTs demonstrated reduction in methamphetamine use via urine drug testing with topiramate compared to placebo.[118,119] Reductions in SUD severity were also found, suggesting improvements in SUD-related consequences and functioning. Another multisite RCT found that while topiramate did not increase abstinence for the overall treatment group, it significantly reduced amount of methamphetamine use and recurrence of use in the subgroup of individuals who were abstinent at the start of treatment.[123]

The desirable effects of topiramate are somewhat offset by known side effects (eg, cognitive effects, paresthesia) and variable tolerability, which can be improved by slow titration.[115] Topiramate can cause appetite suppression; this is an important consideration when treating patients who are underweight or at risk of being underweight.[115]

Topiramate has been shown to reduce alcohol use and is utilized off-label for treatment of AUD.[116] While potential effects are small, the CGC agreed that topiramate could be given additional consideration for patients with co-occurring ATS use disorder and AUD to reduce use of ATS and alcohol consumption.

Amphetamine-Type Stimulant Use Disorder: Topiramate Recommendations

13. For patients with ATS use disorder, clinicians can consider prescribing topiramate to reduce use of ATS (*Low certainty, Conditional Recommendation)*.
    a. Clinicians can give topiramate additional consideration for patients with co-occurring AUD, as this medication can also reduce alcohol consumption (*Low certainty, Conditional Recommendation)*.

Please see the supplementary EtD document for the following related summaries of evidence, relevant citations, and CGC judgments:

- Table 11. Topiramate for Amphetamine-Type Stimulant Use Disorder

Mirtazapine

Mirtazapine is an FDA-approved medication for the treatment of MDD that acts at multiple sites, including adrenergic, serotonergic, and histaminergic receptors.[124,125] While meta-analyses and systematic reviews largely reported mixed or no evidence for mirtazapine, two randomized placebo-controlled trials showed a small reduction in ATS use.[126,127] Both studies also reported a significant reduction in sexual risk behaviors in patients treated with mirtazapine compared to placebo. Mirtazapine also had a positive effect on sleep. While both studies were conducted specifically with men who have sex with men (MSM),

the CGC felt it appropriate to extend these results to the general population of patients with ATS use disorder.

Mirtazapine is widely available and straightforward to prescribe. It is FDA-approved to treat depression, may also help treat anxiety and improve sleep quality, and has no known potential for misuse.[128] These benefits may be tempered by side effects such as weight gain, drowsiness, and metabolic issues (eg, poor glucose control) for some patients.

While the evidence is relatively weak, the CGC determined that, because there are few medication options available, mirtazapine may be preferable to no treatment at all, particularly for MSM.

Amphetamine-Type Stimulant Use Disorder: Mirtazapine Recommendations

14. For patients with ATS use disorder, clinicians can consider prescribing mirtazapine to promote reduced use of ATS (*Low certainty, Conditional Recommendation)*.
    a. Clinicians can give mirtazapine additional consideration for patients with co-occurring depressive disorders, as this medication can also treat depression (*Low certainty, Conditional Recommendation)*.

Please see the supplementary EtD document for the following related summaries of evidence, relevant citations, and CGC judgments:

- Table 12. Mirtazapine for Amphetamine-Type Stimulant Use Disorder

Psychostimulant Medications

A number of psychostimulant medications have been evaluated for the treatment of StUD (see Appendix K). The CGC recognized that the evidence is relatively limited for the use of these medications, and evidence demonstrating positive outcomes came from controlled trials characterized by close physician oversight and frequent monitoring. The medications discussed in this section have risks that may outweigh their benefits, and many clinicians may be reluctant to prescribe medications with psychostimulant properties to patients with StUD. Clinicians should generally avoid use of psychostimulant medications to treat StUD in patients with histories of stimulant-induced mood disorders.

Given the limitations of current evidence and the inherent risks for prescribing psychostimulants for StUD, the CGC recommended that only physician specialists board certified in addiction medicine or addiction psychiatry—or physicians with commensurate training, competencies, and capacity for close patient monitoring—should prescribe these medications for this purpose. This level of expertise is needed to conduct the thorough risk–benefit analysis needed for this complex patient population. ASAM and AAAP will

continue to monitor the evolving evidence on this topic and update the recommendations as appropriate.

When a careful decision is made to prescribe controlled medications, including psychostimulant medications, clinicians should closely monitor patients and regularly reassess the risk–benefit profile for each patient to inform potential dose adjustments and/or tapering when clinically indicated. Clinicians should implement strategies for monitoring medication adherence and nonmedical use, such as pill counts, PDMP checks, and drug testing. Extended-release and prodrug formulations are available for several of the medications listed in this section and should be considered.

While current federal law[**] generally prohibits clinicians from prescribing a Schedule II narcotic drug[††]—which 21 USC §802 has defined to include opioid and cocaine analogs—for the treatment of substance withdrawal or SUD without a specific registration. The medications outlined in this section do not fall under this definition. However, clinicians should be aware of state laws where they practice that may restrict prescribing of psychostimulant medications for StUD.

General Psychostimulant Medication Recommendations

15. Recommendations related to the prescription of psychostimulant medications to treat StUD are only applicable to:
    a. physician specialists who are board certified in addiction medicine or addiction psychiatry; and
    b. physicians with commensurate training, competencies, and capacity for close patient monitoring *(Clinical consensus, Strong Recommendation)*.

[**] Prescriptions. 21 CFR §1306 (1971).

[††] The term "narcotic drug" means any of the following, whether produced directly or indirectly by extraction from substances of vegetable origin, independently by means of chemical synthesis, or by a combination of extraction and chemical synthesis: (A) Opium, opiates, derivatives of opium and opiates, including their isomers, esters, ethers, salts, and salts of isomers, esters, and ethers, whenever the existence of such isomers, esters, ethers, and salts is possible within the specific chemical designation. Such term does not include the isoquinoline alkaloids of opium. (B) Poppy straw and concentrate of poppy straw. (C) Coca leaves, except coca leaves and extracts of coca leaves from which cocaine, ecgonine, and derivatives of ecgonine or their salts have been removed. (D) Cocaine, its salts, optical and geometric isomers, and salts of isomers. (E) Ecgonine, its derivatives, their salts, isomers, and salts of isomers. (F) Any compound, mixture, or preparation which contains any quantity of any of the substances referred to in subparagraphs (A) through (E).

16. When prescribing psychostimulant medications for StUD, clinicians should maintain a level of monitoring commensurate with the risk profile for the given medication and patient. Monitoring may include pill counts, drug testing, more frequent clinical contact, and more frequent PDMP checks *(Clinical consensus, Strong Recommendation)*.

Cocaine Use Disorder

Modafinil

Modafinil is a wakefulness-promoting medication used in the treatment of narcolepsy, obstructive sleep apnea, and shift work-related sleep disorder.[129] The exact mechanism of action of modafinil is unclear, though in vitro studies have shown that it modulates multiple neurotransmitter systems, including dopamine, serotonin, and norepinephrine reuptake, as well as histamine and hypocretin signaling. Modafinil also activates glutamatergic circuits while inhibiting GABA.[130,131]

The evidence is mixed regarding the effectiveness of modafinil in reducing cocaine use in patients with cocaine use disorder. Two meta-analyses found no effect on sustained cocaine abstinence but a positive effect on cocaine abstinence rates at the end of the treatment trial in patients treated with modafinil.[132,133] Notably, many of the studies included in the meta-analyses reported low medication adherence rates. Modafinil has shown more promising efficacy in certain subpopulations, including those without co-occurring AUD and those with high adherence to treatment. The CGC agreed that modafinil may be considered, particularly for patients with higher frequency of cocaine use at the start of treatment.[133]

Modafinil is generally well tolerated, and the two meta-analyses reported no significant differences in the rate of serious or other adverse events. The CGC noted that modafinil inhibits metabolism of hormonal contraceptives and can reduce the effectiveness of this type of birth control; patients with childbearing potential should be counseled to use an alternative birth control method. Clinicians should generally avoid use of modafinil or psychostimulant medications to treat StUD in patients with histories of psychoses, whether substance-induced or preexisting.[134]

Cocaine Use Disorder: Modafinil Recommendations

17. For patients with cocaine use disorder and without co-occurring AUD, clinicians can consider prescribing modafinil to reduce cocaine use and improve treatment retention (*Low certainty, Conditional Recommendation)*.

Please see the supplementary EtD document for the following related summaries of evidence, relevant citations, and CGC judgments:

- Table 13. Modafinil for Cocaine Use Disorder

Topiramate and Extended-Release Mixed Amphetamine Salts

Extended-release mixed amphetamine salts (MAS-ER)—such as Adderall and Mydayis—are composed of dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate, and/or amphetamine sulfate. These medications increase the release of dopamine and norepinephrine and inhibit the reuptake of these neurotransmitters.[135] While evidence is mixed for topiramate alone, a meta-analysis found that MAS-ER and topiramate in combination had positive effects for achieving a period of cocaine abstinence during treatment compared to placebo.[136] Additionally, one RCT from that meta-analysis showed that cocaine craving decreased more rapidly in the treatment group compared to placebo.[137] The CGC noted that these effects may be more pronounced in patients with more frequent cocaine use.

Because topiramate has been shown to reduce alcohol use and is utilized off-label for treatment of AUD, the CGC agreed that combination topiramate and MAS-ER treatment could be given additional consideration for patients with co-occurring cocaine use disorder and AUD.[138,139] Similarly, this combination could be given additional consideration for patients with co-occurring cocaine use disorder and ADHD as MAS-ER is an effective treatment for ADHD.[140]

While the evidence for combination topiramate and MAS-ER is promising, the CGC noted a few implementation considerations. While both medications are available in generic formulations, the combination would more likely be prescribed by an addiction specialist, potentially limiting access and increasing health inequities. Despite these potential barriers, the CGC concluded that in certain patients, this treatment option may be useful in reducing cocaine use and other co-occurring symptoms.

Cocaine Use Disorder: Topiramate and Extended-Release Mixed Amphetamine Salts Recommendations

18. For patients with cocaine use disorder, clinicians can consider prescribing a combination of topiramate and MAS-ER to reduce cocaine use and cocaine craving (*Moderate certainty, Conditional Recommendation)*.
    a. Clinicians can give this combination additional consideration for patients with co-occurring AUD, as topiramate can also reduce alcohol consumption (*Moderate certainty, Conditional Recommendation)*.
    b. Clinicians can give this combination additional consideration for patients with co-occurring ADHD, as MAS-ER can also reduce ADHD symptoms (*Moderate certainty, Conditional Recommendation)*.

Please see the supplementary EtD document for the following related summaries of evidence, relevant citations, and CGC judgments:

- Table 14. Topiramate + Extended-Release Mixed Amphetamine Salts for Cocaine Use Disorder

Amphetamine Formulations

Prescription amphetamine formulations are FDA-approved for the treatment of ADHD and narcolepsy. These medications increase dopamine and norepinephrine signaling by increasing the release and inhibiting the reuptake of these neurotransmitters.[141] A high-quality meta-analysis demonstrated that prescription psychostimulant medications—including modafinil, methylphenidate, MAS-ER, lisdexamfetamine, and dextroamphetamine—were associated with better cocaine-related outcomes, including reported sustained abstinence and cocaine-negative urine drug results.[136] No difference was noted on treatment retention. Another meta-analysis reported similar results but included a broader array of medications, including non-psychostimulant medications (eg, bupropion).[132]

The CGC emphasized the importance of adequate dosing. Higher doses of prescription psychostimulants were associated with the best outcomes for cocaine use disorder.[136] The CGC recognized that clinicians may be hesitant to prescribe higher-than-typical doses of these medications, particularly given the small sample sizes in the available studies. As discussed at the beginning of the Psychostimulant Medications section, careful monitoring and management of risk of misuse and diversion is important when prescribing these medications.

When prescribing amphetamine formulations, thorough cardiovascular screening (eg, ECG, stress test) at baseline—including baseline assessment of cardiovascular function—should be considered, particularly if the patient has underlying risk factors. Clinicians should monitor for signs and symptoms of cardiovascular dysfunction during the early phase of treatment. Known effects of psychostimulant medications on blood pressure can be managed by close monitoring and dose adjustments.

In addition to reduction of cocaine use, there is evidence that psychostimulant medications can reduce ADHD symptoms in adults with co-occurring ADHD. While a systematic review showed mixed results,[142] these may have been impacted by insufficient dosing (see Concurrent Management of StUD and ADHD).

Cocaine Use Disorder: Amphetamine Formulation Recommendations

19. For patients with cocaine use disorder, clinicians can consider prescribing a long-acting amphetamine formulation psychostimulant to promote cocaine abstinence (*Low certainty, Conditional Recommendation)*.
    a. Clinicians can give long-acting amphetamine formulation psychostimulants additional consideration for patients with co-occurring ADHD, as these medications can also reduce ADHD symptoms (*Low certainty, Conditional Recommendation)*.
    b. When prescribing a long-acting amphetamine formulation psychostimulant, clinicians can consider dosing at or above the maximum dose approved by the FDA for the treatment of ADHD to effectively reduce cocaine use (*Low certainty, Conditional Recommendation)*.

Please see the supplementary EtD document for the following related summaries of evidence, relevant citations, and CGC judgments:

- Table 15. Psychostimulant Amphetamines for Cocaine Use Disorder

Amphetamine-Type Stimulant Use Disorder

Methylphenidate Formulations

Methylphenidate (MPH) inhibits the reuptake of norepinephrine and dopamine and is FDA-approved for the treatment of ADHD and narcolepsy.[143,144] A high-quality meta-analysis did not show a significant effect of MPH on amphetamine abstinence overall; however, subgroup analysis demonstrated that higher doses were associated with short-term abstinence.[136] No difference was noted on treatment retention. Two other systematic reviews suggested that MPH was associated with reduced use of and craving for methamphetamine.[118,119] Clinical trials suggest that methylphenidate for ATS use disorder may be more effective with patients who have a moderate or higher frequency of ATS use at treatment start, which the trials defined as greater than 10 days per month.[118,119]

In addition to reduction of ATS use, there is evidence that MPH formulations can reduce ADHD symptoms in adults with ATS use disorder and co-occurring ADHD.[140] The CGC agreed that clinicians could give MPH formulations additional consideration for patients with co-occurring ATS use disorder and ADHD due to the effects of MPH on ADHD symptoms.

Clinicians should note the importance of thorough cardiovascular screening at baseline, including baseline assessment of cardiovascular function. Clinicians should monitor for signs and symptoms of cardiovascular dysfunction during the early phase of treatment.

Known effects of psychostimulant medications on blood pressure can be managed by close monitoring and dose adjustments.

The CGC recognized that clinicians may be hesitant to prescribe higher-than-typical doses of these medications but also emphasized that risk of misuse or diversion can be managed. As discussed at the beginning of the Psychostimulant Medications section, careful monitoring and management of risk of misuse and diversion is important when prescribing these medications.

Amphetamine-Type Stimulant Use Disorder: Methylphenidate Formulations Recommendations

20. For patients with ATS use disorder, clinicians can consider prescribing a long-acting MPH formulation to promote reduced use of ATS (*Low certainty, Conditional Recommendation)*.
    a. Clinicians can give long-acting MPH formulations additional consideration for patients with moderate or higher frequency of ATS use at treatment start (ie, 10 or more days per month; *Low certainty, Conditional Recommendation)*.
    b. Clinicians can give long-acting MPH formulations additional consideration for patients with co-occurring ADHD, as these medications can also reduce ADHD symptoms (*Low certainty, Conditional Recommendation)*.
    c. When prescribing a long-acting MPH formulation, clinicians can consider dosing at or above the maximum dose approved by the FDA for the treatment of ADHD to effectively reduce ATS use (*Low certainty, Weak Recommendation)*.

Please see the supplementary EtD document for the following related summaries of evidence, relevant citations, and CGC judgments:

- Table 16. Psychostimulant Methylphenidate for Amphetamine-Type Stimulant Use Disorder

Co-occurring Disorders

This section addresses the most common and/or problematic co-occurring psychiatric disorders known to be caused by and/or exacerbated by StUDs, including psychosis, depression, and anxiety. General treatment principles of co-occurring disorders are not addressed here; rather, this section targets specific factors that would alter clinical management of either condition. ADHD is addressed in more detail due to the clinical complexity of utilizing psychostimulant medications in individuals with co-occurring StUD and ADHD.

The CGC noted that people with StUDs and co-occurring psychiatric disorders experience additional barriers to accessing and remaining in SUD treatment. Clinicians should facilitate referrals and access to appropriate care whenever possible. Care should be coordinated when patients are receiving concurrent care for a co-occurring condition.

General Guidance

The CGC agreed that clinicians should treat StUD and any co-occurring psychiatric disorders concurrently. The CGC recommended that clinicians use an integrated behavioral treatment approach whenever possible. Integrated care can range from concurrent care with coordination between providers to treatment by a provider or program that provides skilled interventions for both conditions and addresses the interactions between them.

Studies on integrated behavioral treatment approaches are limited and heterogeneous in design, target population, and outcomes of evaluation. Included studies are not specific to StUD and include approaches that target mixed SUDs and co-occurring depression, anxiety disorders, or post-traumatic stress disorder (PTSD); findings are mixed, but some benefits in reduction of substance use or psychiatric symptoms likely apply to populations with StUD.[145–149] Integrated treatment of StUD and co-occurring mental health conditions is expected to be more convenient and cost-effective for patients than parallel or sequential treatment models, with benefits likely to largely outweigh risks or harms.

The CGC recommended that symptoms of psychosis related to or co-occurring with StUD be treated with indicated pharmacotherapy. Almost all evidence for treating symptoms of psychosis from systematic reviews and meta-analyses is based on stimulant-induced or unspecified causes of psychosis.[114,117,119,150–155] These studies generally noted a large beneficial effect of pharmacotherapy for both preexisting and stimulant-induced psychosis, as well as preexisting and stimulant-induced mania. Undesirable side effects would be similar to those experienced from the use of these medications in any context. The CGC noted that clinicians should be aware of differences in side effect profiles, particularly between typical and atypical antipsychotic medications. Clinicians should generally avoid use of modafinil or psychostimulant medications to treat StUD in patients with histories of psychoses, whether substance-induced or preexisting.[134] Similarly, clinicians should generally avoid use of psychostimulant medications to treat StUD in patients with histories of stimulant-induced mood disorders.

If stimulant-induced psychosis or mania is suspected, the CGC suggested that clinicians consider a gradual taper off antipsychotic medications after a period of symptom remission. No evidence was found regarding discontinuation of antipsychotic medications in this context; however, the CGC considered the desirable effects from protection against unnecessary exposure to and development of known adverse effects of chronic antipsychotic or mood stabilizing medications (eg, lithium, valproate). The only undesirable effect noted was the risk of recurrence of psychotic symptoms; no reliable evidence was found to predict the risk of symptom recurrence after tapering using factors such as history of psychosis or symptom severity. Thus, the CGC concluded that the benefits of tapering outweigh potential risks, particularly for patients with stimulant-induced psychosis or mania.

Symptoms of depression, anxiety, insomnia, and/or attentional problems are commonly observed during periods of ongoing stimulant use and withdrawal. While these symptoms often resolve with effective management of withdrawal, the CGC recommended considering initiation of pharmacotherapy if warranted based on symptom severity and chronicity, even if symptoms are judged to be stimulant induced.

When initiating treatment for StUD in patients with preexisting co-occurring psychiatric disorders, the CGC recommended continuing current medications when appropriate and with consideration for their safety in the context of potential continued use of stimulants or other substances. Despite the lack of direct evidence, continuing a patient's medications for co-occurring psychiatric disorders while reviewing their treatment history and plan and integrating treatment for StUD is likely to yield improved outcomes in psychiatric disorder management compared to discontinuation of treatment in the majority of cases, particularly when psychiatric symptoms are severe or persistent.[156,157]

Clinicians should be aware that adherence to and effectiveness of medications for psychiatric conditions is likely to be reduced in the context of ongoing stimulant use. Additionally, unknown potential adverse interactions between medications and stimulants could occur. The CGC noted that clinician expertise in both StUD and psychiatric disorders is helpful when treating patients with co-occurring conditions.

General Guidance Recommendations

21. Clinicians should treat both StUD and co-occurring disorder(s) concurrently (*Very low certainty, Strong Recommendation)*.
22. Clinicians should use an integrated behavioral treatment approach that addresses both conditions when available (*Very low certainty, Strong Recommendation)*. Otherwise, clinicians should tailor recommended behavioral therapy for StUD (eg, CM, CBT, CRA) to address possible interactions between a patient's StUD and co-occurring disorder(s) (*Very low certainty, Strong Recommendation)*.
23. Symptoms of psychosis or mania should be treated with indicated pharmacotherapy (*Moderate certainty, Strong Recommendation)*.
    a. If stimulant-induced psychosis or mania is suspected, clinicians should consider a gradual taper off antipsychotic medication after a period of remission of psychotic symptoms (*Moderate certainty, Strong Recommendation)*.

24. When developing a treatment plan for symptoms of depression, anxiety, insomnia, and/or attentional problems observed during periods of stimulant use or withdrawal, clinicians should:
    a. consider pharmacotherapy based on symptom severity and duration, even if symptoms are stimulant induced (*Very low certainty, Strong Recommendation)*; and
    b. consider whether the patient's clinical presentation follows the expected time course of stimulant-induced symptoms given the phase of use (ie, active use, waning intoxication, acute withdrawal, post-acute withdrawal, post-withdrawal abstinence) or are present at other times (*Very low certainty, Strong Recommendation)*.
25. Clinicians initiating treatment for StUD in a patient with a preexisting co-occurring diagnosis should:
    a. review the patient's existing treatment plan, ideally in coordination with the patient's existing treatment provider(s) (*Clinical consensus, Strong Recommendation)*; and
    b. continue current medications as appropriate (*Clinical consensus, Strong Recommendation)*, with consideration for safety in the context of the patient's potential continued use of stimulants and other substances (*Clinical consensus, Strong Recommendation)*.

Please see the supplementary EtD document for the following summaries of evidence, relevant citations, and CGC judgments:

- Table 17. Integrated Care
- Table 18. Psychosis
- Table 19. Psychosis Taper
- Table 20. Other Symptoms

Concurrent Management of StUD and ADHD

Management of ADHD in patients with ongoing use of nonprescribed stimulants may be challenging. Clinicians should be aware that nonmedical use of prescription stimulants does not preclude the presence of ADHD; studies have shown high levels of co-occurring psychiatric disorders, especially ADHD, in the context of chronic use of stimulants.[156,158] A biopsychosocial assessment for StUD should include screening for ADHD, and assessment and treatment should be offered—directly or through referral—if indicated.[159]

Evidence supports the use of multimodal interventions, including psychostimulant medications, to treat ADHD in individuals with co-occurring StUD.[142] Some—but not all—

studies have demonstrated significant reduction in ADHD symptoms associated with psychostimulant prescription in individuals with StUD without an increase in stimulant misuse.[142,160] Non-stimulant medications for the treatment of ADHD—such as atomoxetine, off-label clonidine, and off-label bupropion—may be considered in individuals with StUD, although these medications are not judged to be as effective as long-acting stimulant medications. As with other co-occurring conditions, behavioral interventions should be considered in conjunction with medication. The CGC noted that individuals with StUD who have acquired tolerance for the effects of stimulants may require higher doses of prescribed psychostimulant medications to reach clinical benefit.

The use of prescription stimulant medications, which are controlled substances, remains controversial due to the perceived risk of medication misuse and/or development of tolerance and StUD.[161] No research was found on the effectiveness of strategies to prevent nonmedical use and diversion of stimulant medications among patients with co-occurring StUD and ADHD. Evaluations of risk mitigation strategies are found in studies of patients with ADHD, but these focus on the prevalence of practices to prevent stimulant medication diversion and misuse rather than their efficacy.[142,162] Despite the lack of research in this area, the CGC emphasized the importance of establishing risk mitigation measures. Clinicians should review the PDMP prior to prescribing stimulants to any patient with SUD, especially StUD. Use of extended-release[‡‡] or prodrug formulations can mitigate risks related to misuse and the addictive potential of prescription stimulants by producing less rapid onset of effect, maintaining more steady serum levels of medication, and/or preventing or reducing effects when alternative routes of administration are used. However, health insurance coverage may vary. Other strategies that clinicians can consider to mitigate risks in accordance with standard precautions for prescribing controlled substances include monitoring via drug testing, conducting pill counts, and increasing frequency of visits to facilitate adequate clinical monitoring.

Similarly, no research was found on the effectiveness of strategies to prevent nonmedical use and diversion of stimulant medications among adolescent or young adult patients with co-occurring StUD and ADHD. Arranging for a parent, guardian, or other trusted adult to directly observe adolescent patients' medication administration is recommended to reduce the likelihood of nonmedical use. Further, conducting pill counts and counseling families on safe storage of controlled medications is in accordance with standard precautions for prescribing controlled substances. See Adolescents and Young Adults for more information on managing StUD in this patient population.

[‡‡] Including osmotic-controlled release oral delivery system (OROS) and spheroidal oral drug absorption system (SODAS) medications.

When prescribing stimulant medications, clinicians should monitor for adverse effects, including secondary hypertension and other cardiac outcomes. Preexisting hypertension, cardiovascular disease, or psychosis should prompt greater caution in using psychostimulants to treat ADHD in StUD.

Concurrent Management of StUD and ADHD Recommendations

26. For patients with co-occurring StUD and ADHD, clinicians should address ADHD symptoms as part of the treatment of StUD (*Low certainty, Strong Recommendation)*. Clinicians should consider:
    a. prescribing psychostimulant medications to manage ADHD when the benefits of the medication outweigh the risks (*Low certainty, Strong Recommendation)*,
    b. prescribing non-stimulant medications to manage ADHD when the benefits of psychostimulant medications do not outweigh the risks (*Low certainty, Strong Recommendation)*, and
    c. behavioral approaches (*Low certainty, Strong Recommendation)*.
27. When prescribing psychostimulant medications to a patient with co-occurring StUD and ADHD, clinicians should consider:
    a. using extended-release formulations (*Clinical consensus, Strong Recommendation)*; and
    b. maintaining a level of monitoring commensurate with the risk profile for the given medication and patient—monitoring may include pill counts, drug testing, more frequent clinical contact, and more frequent PDMP checks (*Clinical consensus, Conditional Recommendation)*.
28. For adolescent and young adult patients with co-occurring StUD and ADHD, clinicians should additionally consider:
    a. arranging for a parent, health professional (eg, trained school nurse), or other trusted adult to directly observe administration of the medication, especially if using a short-acting formulation (*Clinical consensus, Strong Recommendation)*; and
    b. counseling families on the importance of safely storing and restricting access to controlled medications (*Clinical consensus, Conditional Recommendation)*.

Please see the supplementary EtD document for the following related summaries of evidence, relevant citations, and CGC judgments:

- Table 21. ADHD

Population-Specific Considerations

Adolescents and Young Adults

The 2021 National Survey on Drug Use and Health (NSDUH) reported that among adolescents (ie, ages 12 to 17), 1.2% reported nonmedical use of prescription stimulants, 0.2% reported use of cocaine, and 0.1% reported use of methamphetamine in the past year.[163] Stimulant use rates are higher among young adults (ie, ages 18 to 25): 3.7% reported nonmedical use of prescription stimulants, 3.5% reported use of cocaine, and 0.5% reported use of methamphetamine in the past year.[163] In the US, the peak age for initiating nonmedical use of prescription stimulants is 16 to 19 years, and the median age of initiation of cocaine and methamphetamine use is approximately 20 years.[164,165] Adolescents and young adults often cite cognitive enhancement as a reason for prescription stimulant misuse.[166]

StUD is rare among adolescents, with 0.1% meeting criteria for methamphetamine use disorder, 0.0% for cocaine use disorder, and 0.9% for prescription stimulant use disorder in 2021. Among young adults, 3.5% met criteria for a prescription stimulant use disorder, 0.6% for methamphetamine use disorder, and 0.6% for cocaine use disorder. Adolescents with ADHD are at increased risk for SUD compared to the general population.[167] However, research has shown that pharmacological treatment of ADHD in this population, including with psychostimulant medications, reduces the risk for development of SUD.[168]

Clinicians should provide adolescents and young adults who use stimulants with the same treatment, harm reduction, and recovery support services (RSS) as adults in a developmentally responsive manner. Similarly, standard multimodal interventions, including pharmacotherapy, should be used to treat ADHD in adolescent and young adult patients with this co-occurring disorder.[169] Clinicians should be aware that patients may not always take their psychostimulant medication daily and may accumulate a surplus of medications which can be a source of misuse and diversion.[170] See the American Academy of Child and Adolescent Psychiatry's (AACAP) guide on *Medication: Preventing Misuse and Diversion* for additional discussion.[171]

Clinicians should evaluate the "set and setting" to understand the context for adolescent and young adult substance use as part of their clinical assessment. Set and setting refer to the patient's mindset and the social and physical environment(s) where they use substances. The context of use should inform the assessment of substance use-related risks and risky SUD-related behaviors. When treating adolescents and young adults, clinicians should always evaluate for co-occurring mental health conditions and integrate treatment for co-occurring conditions and other psychosocial needs into the treatment plan for StUD.

When treating adolescents and young adults, the CGC noted that it is especially important to seek additional sources of collateral information beyond family members—such as teachers, guidance counselors, coaches, and roommates—with patient permission. This is also important when establishing a late diagnosis of ADHD in patients with StUD, which requires symptoms to present prior to age 12, even if the diagnosis is made later. However, collateral sources who are able to account for symptoms that started before the StUD may not always be available, which can present significant challenges for the clinician.

Adolescent and Young Adult Assessment and Treatment Planning

The assessment and treatment planning recommendations defined earlier in this Guideline apply to all patients, including adolescents and young adults. This section presents unique considerations related to the adolescent and young adult population.

The CGC noted that building trust with adolescent and young adult patients and conducting careful clinical interviews are the preferred approaches to determine whether adolescents and young adults are misusing stimulants. While building and maintaining trust are important in all clinical encounters, it is especially critical when engaging adolescents and young adults in the SUD assessment and treatment process. Evidence has shown that when clinicians provide assurance of confidentiality, adolescents and young adults are more likely to disclose substance use and other sensitive information.[172]

Data are limited on the potential benefits and harms of drug testing for adolescents and young adults with StUD. While drug testing can be a helpful adjunct to clinical assessment for StUD—especially when symptomatology is unclear or collateral information is unavailable—it should be accompanied by careful clinical interview and physical examination. However, the CGC recommended against the routine use of drug tests to screen or monitor for stimulant use in primary care and other general medical settings because it can degrade trust, particularly when such testing is performed without patient permission.[173] Further, the CGC recognized that drug testing may result in false negatives and positives and should only be performed by clinicians with expertise pertaining to its correct use. When considering drug testing in patients under the age of 18, clinicians should ask the patient for permission to test, even if parental/guardian consent was given.

For additional considerations, see ASAM's *Appropriate Use of Drug Testing in Clinical Addiction Medicine* consensus statement (major principles of this document are outlined in Appendix J) and ASAM's public policy statement on *Ethical Use of Drug Testing in the Practice of Addiction Medicine*.[33,34]

While adolescent and young adult patients with StUD can present with a range of co-occurring mental health conditions (eg, depression, anxiety), clinicians should pay particular attention to signs or symptoms of ADHD and eating disorders, as these are

particularly common comorbidities in these populations.[21–24] In some cases, adolescents and young adults who misuse stimulants do so to address underlying symptoms of ADHD or, in other cases, to lose weight as part of an eating disorder. Although no clinical trials have been conducted that examine StUD treatment outcomes when underlying ADHD or eating disorders are treated, a general principle in the care of adolescents and young adults with SUD is to address underlying mental health conditions with an integrated approach.

Similar to adults, adolescents and young adults who use stimulants present with a wide range of other assorted issues, including risky sexual behaviors. A meta-analysis showed a relationship between general substance use and risky sexual behaviors, such as unprotected sex and multiple partners among adolescents.[174] Psychosocial screening for adolescents who use stimulants should include screening for risky sexual behaviors. If the screen is positive, clinicians should follow the recommendations for the general population outlined in Secondary and Tertiary Prevention.

Ideally, adolescent and young adult patients would be referred to age-specific treatment and other support programs to address identified biopsychosocial needs, including programs to address food or housing insecurity or transportation needs. However, the CGC noted that few such programs exist, depending on the region, and emphasized that the lack of available specialized programs should not delay or preclude initiation of treatment.

Adolescent and Young Adult Assessment and Treatment Planning Recommendations

29. Clinicians should avoid routine drug testing to screen adolescents and young adults for StUD (*Clinical consensus, Strong Recommendation)*.
    a. When considering drug testing in patients under the age of 18, clinicians should ask patients for permission to test, even if parental/guardian consent was given, unless obtaining assent is not possible (eg, loss of consciousness; *Clinical consensus, Strong Recommendation)*.
30. Clinicians should pay particular attention to signs or symptoms of ADHD and eating disorders in adolescent and young adult patients (*Clinical consensus, Strong Recommendation)*.
31. If available, clinicians should refer adolescent and young adult patients to age-specific treatment and support programs to address identified biopsychosocial needs (*Clinical consensus, Strong Recommendation)*.

Adolescent and Young Adult Treatment

Despite the relative lack of evidence on adolescent- and young adult-specific treatment for StUD, the CGC concurred on a number of interventions and other strategies that are reasonable based on their effectiveness in adolescents and young adults with SUDs in general and/or their effectiveness for adults with StUD.

Specifically, the CGC agreed that clinicians should consider delivering behavioral interventions that have been demonstrated to be effective in the treatment of other SUDs in adolescents (eg, CM, CBT, CRA, family therapy) and in the treatment of StUDs in adults (eg, CM, CBT, CRA).

While data are available regarding the efficacy of CM and family therapy for adolescents and young adults with SUD, data evaluating other therapy modalities (eg, CBT, CRA) are lacking.[175,176] The recommendations related to these other modalities are based on studies evaluating these therapies in adolescents and young adults with other SUDs, adults with StUD, and clinical experience. Various therapy modalities can be offered; some adolescents and young adults may find one or a combination of therapies most beneficial for StUD. Treatment plans should be adjusted based on the individual's response to treatment.

While there are no data on adolescent- and young adult-specific or developmentally responsive treatment specific to StUD, the standard of care for adolescent- and young adult SUD treatment is to use interventions that are specifically tailored or designed for their unique developmental stage.[177,178,179] Adolescent- and young adult-specific models or tailored treatment for StUD are expected to be moderately more effective than nonspecific treatment and less likely to expose patients to peers who use other substances. Given limited evidence, these recommendations are based on the experiences of clinicians with subject matter expertise in treating adolescents and young adults with StUD.

Adolescent and young adult patients should be referred to the level of care appropriate for providing safe and effective treatment while maintaining the least restrictive environment. Clinicians should tailor a referral that is adolescent- and young adult-specific, accessible, and encourages ongoing contact and support. Peer-based services may provide adolescents and young adults with an additional level of support.

Contingency Management

CM in combination with other behavioral health interventions has been shown to have a small effect on reducing adolescent and young adult cannabis use and increasing treatment retention compared to behavioral health interventions without CM.[180,181] Additionally, in adults with StUD, CM represents the current standard of care: CM has been consistently associated with longer durations of continuous abstinence and lower rates of stimulant use

than noncontingent reinforcement (ie, rewards that are not contingent on the desired behavior) and treatment as usual.[42] These effects were strongest during treatment and appeared to decrease gradually over post-treatment follow-ups.

The CGC recommended a few modifications so that CM is delivered in the most developmentally appropriate manner possible. For example, CM generally uses drug test results to identify desired behaviors. Adolescent patients may be understandably hesitant to participate in CM as part of StUD treatment because they do not want their parents/guardians to be informed of positive results. However, while state laws vary regarding confidentiality and parental/guardian notification of treatment progress, clinicians can work with parents/guardians so that positive drug test results are not met with punitive outcomes. Another possible modification would be for parents/guardians to supplement CM as part of StUD treatment by offering additional or alternative developmentally appropriate incentives. For some adolescent and young adult patients, engaging in prosocial behaviors—such as receiving permission to attend events or spend time with friends—may be more incentivizing than cash or voucher rewards.

Family Therapy

Current data suggest that family therapy can be more effective than other therapeutic modalities in reducing substance use in adolescents and young adults with SUDs, but this research is not specific for StUD.[182] However, given the success in reducing other substance use, the CGC inferred that family therapy could also be effective and appropriate to recommend for adolescents and young adults with StUD who consent to family therapy. It is important to recognize that family therapy may uncover other dynamics—including co-occurring disorders in other family members, challenges in communication between family members, or more serious issues such as physical or sexual abuse—that may reveal additional treatment needs and/or impact adolescent and young adult patients' engagement in continuing family therapy.

Family therapy is often helpful in establishing goals and communication strategies around substance use and can also allow clinicians to begin to understand how the dynamic of the family may contribute to ongoing substance use, such as structure, boundaries, and/or consequences at home. The CGC noted that clinicians should take a broad view on how family is defined and attempt to identify the persons of significance who can help individual patients in their treatment and recovery.

For a more detailed discussion, see SAMHSA's Treatment Improvement Protocol (TIP) 39: *Substance Use Disorder Treatment and Family Therapy*.[183]

Group Counseling and Therapy

For behavioral treatment in group formats, the CGC recommended using peer-age groups when possible and avoiding incorporating adolescents and young adults into group behavioral treatment with older adults. Clinical experience and best practice approaches suggest a potential negative influence from combining age groups. Being exposed to older individuals—who tend to have used substances for longer and, therefore, tend to have developed more severe SUDs—can reduce the effectiveness of behavioral interventions for adolescents and young adults and increase their experiences of negative pressure from other participants.[184] Additionally, survey evidence suggests that adolescents and young adults prefer to be in groups comprised of peers of their own age.[185,186]

Pharmacotherapy

Clinicians can consider treating adolescents and young adults with StUD with the off-label pharmacotherapies detailed in the Pharmacotherapy section when the developmentally contextualized benefits outweigh the harms. Though available clinical trials did not typically include participants under 18 years of age, it is likely that many of the benefits observed in adults over 18 years of age would be expected in older adolescents (ie, 16- and 17-year-olds). Given the potentially life-threatening consequences of StUD, the CGC felt that clinicians might consider pharmacotherapy on a case-by-case basis, balancing potential benefits and harms. The recommendation to offer pharmacotherapy to adolescents is based on expert opinion; the recommendation to offer pharmacotherapy to young adults is based on small amounts of clinical trial data.

Family Involvement

The CGC's clinical experience suggested that the involvement of family members is often beneficial in the treatment of adolescents and young adults with SUDs, and trusted adults should be incorporated when appropriate.[187] Though no evidence is available for the role that family involvement may play in adolescents and young adults with StUD, the CGC recognized that family involvement can enhance both engagement and efficacy of treatment in adult populations and would be a worthwhile endeavor to explore with adolescent and young adult patients. However, clinicians should take into account the adolescent or young adult patient's relationship and interest in engaging with their family to ensure that family members or other trusted adults share a mutual understanding of the patient's treatment goals and are equipped with effective methods to provide support.

Clinicians should counsel parents/guardians not to conduct drug tests at home to assess stimulant use in adolescents and young adults without the oversight of a trained clinician. The CGC acknowledged the lack of studies on home urine drug testing, but—based on expert opinion and current recommendations from the American Academy of Pediatrics

(AAP) that urine drug testing only be used in conjunction with a careful, confidential history and physical examination[188]—the CGC recommended against home drug testing without the oversight of an appropriately trained clinician to interpret results. Clinicians should counsel parents/guardians to not conduct drug tests at home to assess stimulant use in adolescents and young adults without this oversight.

Consent for Treatment

There are unique considerations regarding privacy and confidentiality for adolescent patients with StUD and common co-occurring health conditions that may differ across states and jurisdictions. A full discussion of these issues is beyond the scope of this Guideline and are discussed elsewhere.[189–191]

For minors under age 18, clinicians should be familiar with state laws on adolescents' ability to consent to treatment.[192,193] All states have laws that describe what minors may and may not consent to without parental/guardian approval, but there is tremendous variability between states.[192,193] For example, some state laws address alcohol and substance use, while some specify only one or the other.[192,193] Some states prohibit disclosure to parents/guardians, some leave this to the clinician's discretion, and others require disclosure under certain circumstances.[192,193] States may also have different rules (eg, age thresholds) for an adolescent consenting to treatment for SUD versus screening and/or treatment for comorbidities such as HIV and STIs.[189,192,193]

In some states, minors can initiate SUD treatment without involvement of a parent or legal guardian; in other states, parental/guardian consent may be required before proceeding with some or all aspects of treatment.[186,187]

The CGC underscored that it is essential for clinicians to understand the laws regarding care for adolescents in the state(s) where they are licensed to practice. The CGC also recognized that although all states require parental/guardian consent for most medical care provided to minors, there are several exceptions. One is provision of health care to emancipated minors, generally understood to refer to minors who are living apart from their parents or legal guardians and are financially independent. Minors may be considered emancipated if they are married, parents, or in the military.[194] In general, emancipated minors can independently consent to all healthcare interventions, including SUD treatment.[189]

Parental/guardian consent is not required for treatment of young adults; however, clinicians should initiate a conversation with young adult patients about whether their treatment plan might be enhanced by involving a parent/guardian or other trusted older adult.

Adolescent and Young Adult Treatment Recommendations

32. When treating adolescents and young adults for StUD, clinicians should:

a. consider delivering behavioral interventions that have been demonstrated to be effective in the treatment of other SUDs in adolescents and young adults (eg, CM, CBT, CRA, family therapy) and in the treatment of StUDs in adults (eg, CM, CBT, CRA; *Low certainty*, *Strong Recommendation)*;

b. use an adolescent- and young adult-specific treatment model (eg, adolescent CRA [A-CRA]) or tailor existing treatments to be developmentally responsive (*Moderate certainty, Strong Recommendation)*;

c. use peer-age groups for behavioral treatment in group formats when possible and avoid incorporating adolescents and young adults into group behavioral treatment with older adults (*Very low certainty, Strong Recommendation)*;

d. consider treating adolescents and young adults with StUD with the off-label pharmacotherapies detailed in the Pharmacotherapy section when the developmentally contextualized benefits outweigh the harms (*Very low certainty, Weak Recommendation)*;

e. counsel parents/guardians to not conduct home drug tests to assess stimulant use in adolescents and young adults without the oversight of a trained clinician (*Clinical consensus, Strong Recommendation)*;

f. recognize that involvement of family members is often beneficial in the treatment of adolescents and young adults with SUDs and involve family members and/or trusted adults when appropriate (*Clinical consensus, Strong Recommendation)*;

g. be familiar with state laws on adolescents' ability to consent to treatment when treating minors under age 18; in some states, minors can proceed with treatment without involvement of a parent or legal guardian in their care, whereas in other states, parental/guardian consent may be required before proceeding with some or all aspects of treatment (*Clinical consensus, Strong Recommendation)*; and

h. understand that while parental/guardian consent is not required for treatment of young adults, clinicians should initiate a conversation with the young adult patient about whether their treatment plan might be enhanced by involving a trusted adult (*Clinical consensus, Strong Recommendation)*.

Please see the supplementary EtD document for the following related summaries of evidence, relevant citations, and CGC judgments:

- Table 22. Contingency Management
- Table 23. Other Psychotherapy
- Table 24. Family Therapy
- Table 25. Specific Treatment
- Table 26. Group Treatment
- Table 27. Pharmacotherapy

Pregnant and Postpartum Patients

Pregnant and Postpartum Patients Assessment

Treatment of StUD in patients who are pregnant presents unique clinical challenges. Patients who are pregnant should be referred to a prenatal care provider if one has not already been established; however, treatment of StUD should not be delayed or withheld in the absence of prenatal care. While no direct evidence was found regarding referrals to obstetric care providers, given the known benefits of prenatal care, such referrals are expected to be beneficial. Existing guidelines stress using multidisciplinary teams, providing comprehensive prenatal care, and screening for complications of pregnancy and fetal health.[195–197] Patients presenting with high-risk pregnancies, including fetal health complications, may warrant management by a maternal-fetal medicine specialist, when accessible. Coordination of prenatal care and treatment for StUD is encouraged.

Clinicians should review eligibility criteria for locally available programs that specifically address biopsychosocial needs related to pregnancy and parenting (eg, childcare; Special Supplemental Nutrition Program for Women, Infants, and Children [WIC]).

Clinicians should pay particular attention to factors that impact pregnancy and fetal development when screening for acute signs and symptoms, complications, and sequalae associated with stimulant use. Existing guidelines strongly support screening for blood-borne pathogens, STIs, depression, and nutritional deficiencies in those using stimulants.[195–197] Management of stimulant intoxication and withdrawal in pregnant patients is discussed in Stimulant Intoxication and Withdrawal.

While drug testing can be conducted to clarify treatment needs with similar potential utility in both patients who are pregnant and the general population with StUD or other SUDs (see Toxicology Testing), the ramifications of a positive test result for patients who are pregnant may be more severe. Laws that penalize pregnant patients for substance use serve to prevent them from obtaining prenatal care and SUD treatment, which may worsen outcomes for both parent and child.[198] Drug testing may result in false positive results that

are misleading and potentially devastating for the patient. The CGC also noted that overuse of drug testing is more common in minoritized populations with SUD.[199,200]

Before conducting drug testing in patients who are pregnant, the CGC recommended that clinicians be familiar with their state's requirements on mandatory reporting and ramifications of reporting. The potential benefits and risks of utilizing drug testing in patients with StUD who are pregnant should be weighed carefully in a shared decision-making process. Because drug testing is known to introduce potential bias against minoritized populations, the CGC recommended the use of consistent standards for indications to conduct drug testing. Informed consent should be obtained unless there is immediate clinical need and obtaining consent is not possible (eg, loss of consciousness).

For additional considerations, see ASAM's *Appropriate Use of Drug Testing in Clinical Addiction Medicine* consensus statement (major principles of this document are outlined in Appendix J) and ASAM's public policy statement on *Ethical Use of Drug Testing in the Practice of Addiction Medicine*.[33,34]

Pregnant and Postpartum Patients Assessment Recommendations

33. Clinicians should incorporate additional elements into the comprehensive assessment of StUD for patients who are pregnant, including:
    a. providing referrals to prenatal care providers if not already established (*Low certainty, Strong Recommendation)*, and
    b. reviewing eligibility criteria for locally available programs that specifically address biopsychosocial needs related to pregnancy and parenting (eg, childcare, WIC programs; *Low certainty, Strong Recommendation)*.
34. Coordination of prenatal care and treatment of StUD is encouraged (*Low certainty, Strong Recommendation)*.
35. When screening for acute issues, complications, and sequalae associated with stimulant use in patients who are pregnant, clinicians should pay particular attention to factors that impact pregnancy and fetal development (*Low certainty, Strong Recommendation)*.

36. Since the ramifications of a positive drug test result for patients who are pregnant may be more severe than the general populations, before conducting drug testing in patients who are pregnant, clinicians should:
    a. know their state's requirements on mandatory reporting and ramifications of reporting (*Clinical consensus, Strong Recommendation)*;
    b. weigh the potential benefits with the risks of utilizing drug testing in this population (*Clinical consensus, Strong Recommendation)*; and
    c. obtain informed consent, unless there is immediate clinical need and obtaining consent is not possible (eg, loss of consciousness; *Clinical consensus, Strong Recommendation)*.

Please see the supplementary EtD document for the following related summaries of evidence, relevant citations, and CGC judgments:

- Table 28. Prenatal Care Referral
- Table 29. Screen Social Services – Pregnancy & Postpartum
- Table 30. Screen Factors Pregnancy

Treatment of Pregnant and Postpartum Patients

No direct evidence was found on the efficacy and safety of medications for treatment of StUD in patients who are pregnant. Risk versus benefit for both the patient and fetus or infant should be considered when medications are used to manage StUD, stimulant intoxication, or stimulant withdrawal in this cohort. The CGC agreed that concern for fetal well-being should not be prioritized over the health of the pregnant patient. Risk level often varies depending upon trimester, and the CGC emphasized that this should be considered.

Treatment of stimulant-induced intoxication and withdrawal in pregnant patients is addressed in Stimulant Intoxication and Withdrawal.

Wherever possible, clinicians should incorporate psychosocial treatments targeted toward meeting the additional needs of patients who are pregnant, including parent-focused (eg, parenting skills training) and family-based treatment modalities. While no direct evidence addresses the efficacy of additional psychosocial services, clinical judgment supports provision of these services as very likely to be beneficial. Need for parenting and family support are expected to be greater in those with StUDs, who often face greater disintegration of usual social supports and family structure.

Clinicians should consider CM to incentivize attendance at prenatal appointments, if feasible, in addition to usual targets (eg, stimulant abstinence). Evidence is mixed regarding the effect of CM on prenatal care participation; studies have found either increased rates of

attendance or no significant effect, with two low-quality studies showing a slight increase in attendance.[201] Nonetheless, prenatal care has been shown to reduce negative effects of substance use during pregnancy; thus, desirable effects of increasing prenatal care attendance are likely large.

Clinicians should consider providing additional treatment support around the time of birth; the postpartum period is typically a time of increased stress, which may lead to increased risk of return to stimulant use and heightened potential for overdose. Some low-quality evidence suggests that patients may be at increased risk of return to use during the postpartum period; small studies in cocaine use disorder showed 27% and 41% of participants returned to use after 3 months and 2 years, respectively.[202] The risk of developing postpartum depression in this population is nearly 20% and corresponds with higher rates of return to use.[203–205] Access to both antenatal and postpartum care continues to be problematic and subject to significant health inequities in diagnosing and appropriately managing postpartum depression in minoritized populations.

Pregnant and Postpartum Patients Treatment Recommendations

37. Risk versus benefit to the fetus or infant should be considered when medications are used to manage StUD, stimulant intoxication, or stimulant withdrawal (*Very low certainty, Strong Recommendation)*.
38. Wherever possible, clinicians should incorporate psychosocial treatments targeted toward meeting the additional needs of patients who are pregnant (*Clinical consensus, Strong Recommendation)*, including:
    a. Parent-focused treatment modalities (eg, parenting skills training; *Clinical consensus, Strong Recommendation)*, and
    b. family-based treatment modalities (*Clinical consensus, Strong Recommendation)*.
39. Clinicians should consider CM to incentivize attendance at prenatal appointments, if feasible, in addition to usual targets (eg, stimulant abstinence; *Low certainty, Strong Recommendation)*.
40. Clinicians should consider providing additional treatment support around the time of birth, as the postpartum period may be a time of increased stress and risk of return to stimulant use (*Very low certainty, Conditional Recommendation)*.

Please see the supplementary EtD document for the following related summaries of evidence, relevant citations, and CGC judgments:

- Table 31. Pharmacotherapy – Pregnancy & Postpartum
- Table 32. Prenatal Care Incentives
- Table 33. Postpartum Care

Breastfeeding

Breastfeeding has numerous benefits to the patient and infant; however, breastmilk may contain high levels of stimulants, which has the potential to harm infants. Although no known data exist for outcomes in neonates, the CGC recommended against breastfeeding by patients who are actively using stimulants. Clinicians should provide pregnant and postpartum patients with proper education and counseling regarding the risk of stimulants in breastmilk. Support and education should also be provided to patients who have achieved sustained abstinence from stimulants and desire to breastfeed.

The CGC noted that none of the medications that have been studied for treatment of StUD are contraindicated during breastfeeding.

Breastfeeding Recommendations

41. Clinicians should educate patients who use stimulants on the risks of use while breastfeeding and counsel patients not to breastfeed if they are actively using stimulants (except as prescribed; *Very low certainty, Strong Recommendation)*.

Please see the supplementary EtD document for the following related summaries of evidence, relevant citations, and CGC judgments:

- Table 34. Breastfeeding

Additional Population-Specific Considerations

While studies were found that examined the effectiveness of treatment interventions within particular populations, the literature review did not identify any studies on interventions with the specific aim of reducing health disparities in treatment outcomes across various subpopulations of individuals who use stimulants.

As with most areas of health care, evidence suggests that treatment outcomes for StUD are impacted by racial-, ethnic-, and gender-related disparities.[206–210] These findings may be due, in part, to the increased prevalence and severity of underlying risk factors that negatively impact treatment outcomes, such as history of exposure to violence and trauma, prevalence of co-occurring psychiatric disorders and biomedical conditions, and poverty. Disparities in the prevalence of StUD among minoritized populations are exacerbated by longstanding inequities in structural and social determinants of health that pervade society. These determinants often reflect stigmatizing and discriminatory ideologies—such as racism, sexism, homophobia, transphobia, and ableism—and actualize as inequitable resource distribution that limits access to preventive services and quality treatment, which further drive health disparities. Progress toward achieving health equity can be best

addressed through structural changes that include but are not limited to the healthcare system.

Of note, sex- and gender-related disparities and the intersection between sex and gender, substance use, and victimization should be considered in the context of StUD.[211–213] Sex trafficking and substance use coercion disproportionately impact females. Further, both cis- and transgender women are significantly more likely to participate in sex work, which increases risk for victimization.

The legacy of the United States criminal and carceral systems' punitive approach to stimulant use—which disproportionately impacts racial and ethnic minoritized individuals—has been widely documented.[214] The CGC did not find evidence of clinical interventions that demonstrated differences in effectiveness among racial and ethnic minoritized patients with StUD, though clinicians should consider myriad structural and program-level changes. Clinicians can advocate for or adopt program-level changes aimed at reducing disparities in treatment delivery, such as making decisions about practice settings, focusing on particular patient populations, and implementing workforce preparations to provide patients with culturally humble and responsive care. Guidelines aimed at reducing health disparities generally recommend that clinicians receive training to work effectively with the populations they directly serve.[214]

Racism and other forms of discrimination are traumatizing.[215] In addition, racial and ethnic minority patients experience more adverse childhood events (ACEs), including greater exposure to criminal and legal system trauma.[216–218] Providing trauma-sensitive care is especially important when working with patients from populations who are disproportionately impacted by structural threats to their health and wellness and experience health inequities. The high co-occurrence of trauma and SUD led the CGC to recommend that all patients with stimulant intoxication, withdrawal, or use disorder be screened for trauma (see Assessment). Central to trauma-sensitive care is maintaining an awareness of trauma; conducting strengths-based, trauma-informed and -responsive screening that prioritizes patient safety and autonomy; and responding to the impact of trauma in the patient's treatment plan. Clinicians should use validated screening instruments and trauma-sensitive approaches when collecting the clinical histories of all patients who have or are suspected to have StUD.[§§]

[§§] For more information on trauma-informed care, see SAMHSA's TIP 57: *Trauma-Informed Care in Behavioral Health Services*.[219]

Sexual Orientation and Gender Identity

Sexual and gender minoritized (SGM) individuals include those who identify as lesbian, gay, bisexual, queer, questioning, asexual, transgender, and/or gender diverse. A meta-analysis of 13 studies of behavioral interventions that co-targeted mental health, alcohol and/or drug use, and sexual risk behavior among gay and bisexual men found a small positive effect on reducing substance use and sexual risk behavior.[220] Of 23 studies in a systematic review of behavioral interventions that address substance use and sexual risk among gay, bisexual, and other MSM who use methamphetamine, 18 reported a statistically significant effect in one or more sexual health-related outcomes. The CGC noted that these effects may be due to increased treatment engagement, which can help reduce substance use, though this outcome was not specifically examined in the reviews identified. The available evidence has not evaluated the impact of SGM-affirming programs on substance-specific treatment outcomes for patients with StUD who identify as SGM. Therefore, the clinical focus of the CGC's recommendations was on supporting SGM patients' overall access to StUD treatment rather than recommending that all SGM patients obtain SGM-tailored treatment.

The CGC also noted that not all SGM patients require tailored programming; insistence on requiring it could lead to decreased access to general programming if misapplied and, in the worst case, could be used to discriminate against certain populations. However, some patients may benefit from SGM-focused programs. Clinicians should consider each individual patient's needs when making treatment recommendations; for example:

- Is the patient experiencing distress related to their sexual orientation and/or gender identity?
- Are they comfortable discussing issues related to their sexual orientation and/or gender identity in a general population setting?
- Does the patient prefer a tailored treatment setting?

The intent of the CGC's recommendation was to make tailored treatment both more responsive and more equitably accessible for SGM patients.

Clinicians should be comfortable taking a sexual practice history and capable of determining when a referral to an SGM-affirming program should be made based on the patient's history and/or behavior. Clinicians may want to wait to assess sexual practice history until sufficient rapport has been established.[221]

Sexual Orientation and Gender Identity Recommendations

42. Clinicians should consider referring SGM patients with StUD to SGM-affirming programs when their history and/or behavior suggest they may not be comfortable fully participating in a general population setting (eg, distress related to their identities, difficulties discussing drug-related sexual activities, inner conflicts, trauma histories) (*Low certainty, Strong Recommendation)*.

Please see the supplementary EtD document for the following related summaries of evidence, relevant citations, and CGC judgments:

- Table 35. Sexual and Gender Minoritized Individuals

Patients with Cognitive and/or Physical Disabilities

Clinicians should recognize that people with physical and cognitive disabilities have higher rates of StUD and lower rates of treatment engagement than those without these disabilities.[222,223] In addition, StUD is associated with moderate cognitive deficits.[224] Patients with severe chronic health concerns tend to have a slower response to treatment with fewer days abstinent compared to patients without them.[225]

The literature review did not identify any studies of interventions designed to reduce barriers to treatment access or completion among people with StUD and physical disabilities. However, people with physical and cognitive disabilities have complex clinical needs. When treating patients with physical or cognitive disabilities, the CGC agreed that clinicians should follow the best practices outlined in SAMHSA's 2019 *Advisory: Mental and Substance Use Disorder Treatment for People With Physical and Cognitive Disabilities* to increase accessibility of treatment.[222]Clinicians should remove or mitigate barriers to accessibility of StUD treatment for people with physical or cognitive disabilities to the extent possible.[226]

Patients Involved in the Criminal and/or Legal Systems

Evidence suggests that treatment should be initiated as soon as feasible for individuals in the criminal and/or legal systems, including within jails and prisons.[187,227] Research also shows that incorporating telephone monitoring and counseling in follow-up care—in addition to usual care—for patients with cocaine use disorder who have criminal and/or legal system involvement can reduce recidivism.[228] The CGC noted that there is no reason to expect this practice to be differentially effective for patients with ATS use disorder.

Individuals with SUD are at a significantly greater risk of overdose upon reentry; therefore, continuity of care is critical during this vulnerable period.[229] Clinicians should connect

patients with criminal and/or legal system involvement to appropriate support services (eg, reentry programs, vocational rehabilitation, transportation, housing assistance) on reentry.[187]

Patients Involved in the Criminal and/or Legal Systems Recommendations

43. Initiation of treatment for StUD is recommended for individuals in the criminal and/or legal systems, including within jails and prisons (*Clinical consensus, Strong Recommendation)*.

Patients Experiencing Homelessness or Unstable Housing

Stimulant use is highly prevalent among individuals who are homeless; a recent systematic review found that roughly 30% endorsed past year cocaine use.[230] Among homeless and unstably housed women in San Francisco, 47% reported use of cocaine or methamphetamine in the past 6 months, and 14% of those who did not use stimulants at baseline initiated stimulant use within 6 months.[231]

Physical and sexual victimization are common among people who experience homelessness and use methamphetamine.[232] People experiencing homelessness or unstable housing may use stimulants for functional reasons, such as to increase alertness and safety while on the street.[233]

People experiencing homelessness or unstable housing often have highly complex biopsychosocial needs due to comorbidities or other factors—such as injecting substances,[234] using multiple substances, engaging in transactional survival sex, and experiencing serious mental illness and other mental health conditions and trauma—that exacerbate or make it more challenging to manage stimulant use. They also have high rates of chronic health conditions and infectious diseases such as HIV and hepatitis C virus (HCV).[187] Attending to this patient population's SDOH would be expected to support overall health and wellness but not necessarily reduce substance use. Addressing homelessness can help prevent substance use initiation and progression to SUD.[235] This may include linkages to available benefits to improve stability of housing and care coordination. These strategies

> *"**Housing First** is an effective approach to reducing homelessness in the United States. The philosophy of Housing First is to connect individuals and families experiencing homelessness quickly and successfully to stable housing without preconditions and barriers to entry, such as sobriety, treatment for mental health and/or substance use disorders, or service participation requirements. Supportive services are offered, and it is up to the individual to decide whether to accept them."[231]*
>
> *—SAMHSA*

help make treatment more accessible to patients experiencing homelessness, housing insecurity, food insecurity, and/or poverty.

Homelessness and housing insecurity create significant barriers to both treatment and recovery. In 2021, the US Department of Housing and Urban Development (HUD) launched *House America: An All-Hands-on-Deck Effort to Address the Nation's Homelessness Crisis*, a federal initiative to coordinate efforts to address homelessness by providing significant new resources for housing and promoting a Housing First approach.[236] As part of this initiative, SAMHSA released new guidance on *Expanding Access to and Use of Behavioral Health Services for People Experiencing Homelessness.*[237]

Patients Experiencing Homelessness or Unstable Housing Recommendations

44. For patients experiencing homelessness, housing insecurity, food insecurity, and/or poverty, clinicians might consider:
    a. providing case management services or a referral to a case manager or other appropriate service provider(s) who can help the patient navigate health and social safety net resources (*Clinical consensus, Strong Recommendation)*; and
    b. providing a referral to a recovery residence based on the patient's needs (*Clinical consensus, Strong Recommendation)*.

Veterans

While this Guideline does not include any recommendation statements specific to veterans, the CGC emphasized that veterans should receive the same clinical care as other adults. Clinicians should be mindful of additional issues faced by veterans, especially psychological trauma. The CGC viewed health disparities faced by veterans to be driven primarily by increased exposure to other risk factors for health disparities (see Additional Population-Specific Considerations) rather than merely their membership in this population. Clinical considerations for addressing risk factors are covered in other sections (eg, trauma, disability, homelessness, co-occurring psychiatric issues).

Stimulant Intoxication and Withdrawal

In developing this Guideline, the CGC sought to include recommendations that were specific to StUD or of increased importance in the treatment of this illness. This section of the Guideline is focused on the clinical management of signs and symptoms resulting from stimulant use when it differs from general clinical management. This approach is intended to give this Guideline more clinical utility and reduce redundancy with other guidelines.

However, it is important for clinicians to deliver the full standard of care that should be provided to any patient with SUD.

Acute intoxication from novel synthetic stimulants such as cathinones (eg, mephedrone) may present with severe symptoms, including agitation and psychosis. Available drug screening panels may not include regionally prevalent substances. As such, clinical presentation may not align with toxicologic findings. However, the principles of intoxication management outlined below apply similarly.

The recommendations in this section apply to adolescent, young adult, and adult patients.

Where the evidence allowed the GRADE approach to be used, the full evidence profiles can be downloaded as an online supplement.

Assessment and Diagnosis

The *DSM-5-TR* criteria are the clinical standard for diagnosis of stimulant intoxication or withdrawal in the United States.[18] Stimulant intoxication and withdrawal, as well as complications and comorbidities associated with StUD, are primarily diagnosed based on history, physical examination, and findings from any laboratory and/or toxicology testing. Common conditions to consider in the differential diagnosis of a patient who presents with stimulant intoxication are outlined in Appendix C, and recommendations for laboratory and toxicology testing are discussed in this section.[238]

Initial and Comprehensive Assessment

Assessment and Diagnostic Tools

No studies were identified that evaluated diagnostic tools for stimulant intoxication or withdrawal or tools for assessing the severity of stimulant intoxication. While several studies were found that evaluated tools to assess stimulant withdrawal symptom severity—including the Obsessive Compulsive Cocaine Scale (OCCS), the Cocaine Selective Severity Assessment (CSSA), and the Stimulant Selective Severity Assessment (SSSA)—the CGC determined that these studies mainly provided evidence for their use as research measures rather than as clinical tools.[239–241] No tools were identified for diagnosing or assessing stimulant intoxication or withdrawal in a clinical context. The CGC discussed the use of the Poisoning Severity Score (PSS)—a standardized scale for grading the severity of acute poisoning based on observed signs and symptoms—for intoxication assessment; however, given the lack of specific evidence, the CGC deemed it more appropriate to use standard categorizations of sign and symptom severity.[242]

Patient Evaluation

No studies were identified that evaluated strategies for diagnosing or assessing stimulant intoxication or withdrawal. A number of gray literature sources discussed clinical assessment standards, including US guidelines from SAMHSA and the VA and over a dozen international guidelines from the UK, Canada, Australia, Germany, and the World Health Organization (WHO; see Appendix G).[116,187,243–245] The recommendations in this Guideline are based on a review of these guidelines and the clinical expertise of the CGC.

Stimulant intoxication and withdrawal can result in acute issues and complications that require urgent medical management (see Appendix L). In non-acute care settings, clinicians should conduct an initial assessment to identify any acute issues and complications of stimulant intoxication or withdrawal. A basic assessment of vital signs and focused mental status evaluation can determine the need for urgent or emergent treatment or referral for further medical evaluation.

When a patient presents in an acute care setting with a toxicologic emergency, standard management involves responding to urgent and emergent signs and symptoms (eg, airway and circulation management).[246] Interventions may be refined as additional information is obtained. While laboratory and toxicology testing may provide helpful information, completion of tests should not preclude or delay initiating supportive treatment for suspected acute stimulant intoxication or withdrawal.

After addressing any urgent medical or psychiatric concerns, patients should be given or referred for a comprehensive assessment that includes a stimulant-focused history and physical examination (including gathering relevant collateral information, if available) and an assessment of non-acute complications and sequalae of stimulant use (see Appendix M). The extent of the clinical exam and medical workup for stimulant intoxication and withdrawal should be based on the patient's presenting signs and symptoms and severity of intoxication. Clinical testing (ie, laboratory testing and/or diagnostic imaging) should be based on the history and physical exam findings. A safety assessment of the patient's risk of harm to self and others should also be conducted.

Safety Assessment

People who use stimulants have an elevated risk of suicide and self-harm. Acute methamphetamine psychosis is associated with particularly high risk for harm.[247] A review of 300 cases from Australian data (2009–2015) found that suicide comprised 18.2% of all methamphetamine-related deaths.[248] The CGC recommended evaluation of suicidality as part of the routine assessment of patients with a diagnosis of stimulant intoxication or withdrawal. It is important to use a validated instrument—such as the Columbia–Suicide Severity Rating Scale (C-SSRS)—when assessing suicidality.[249] In the CGC's clinical

experience, suicide risk may resolve more rapidly in stimulant withdrawal compared to other substance withdrawal syndromes. If patients screen positive for suicide risk, they should be managed according to best practices, including assessment by a qualified mental health professional and safety assessment, with consideration for the need for involuntary psychiatric hospitalization.

Psychological Trauma

There is a high co-occurrence of psychological trauma and StUD. Among patients with lifetime ATS use disorder, 29.3% reported four or more ACEs, 28.7% reported two to three ACEs, 21.6% reported one ACE, and 20.4% reported no ACEs.[250]

No studies were identified on implementing routine screening for trauma-related concerns in patients with stimulant intoxication or withdrawal. Given the strong correlation between psychological trauma and StUD, the CGC recommended that all patients with stimulant intoxication or withdrawal be screened for trauma. When intoxication or withdrawal management is delivered in an acute care setting, the clinician providing follow-up StUD care can conduct screening following stabilization of the patient's urgent or emergent signs and symptoms. Clinicians should use a validated screening instrument and a trauma-sensitive approach to asking screening questions.[***]

When implementing screening for psychological trauma, it is important for treatment providers to consider how to:

- ensure that staff have adequate training in trauma-informed and -responsive care;
- attend to patient readiness to participate in screening for trauma, which may include considering delaying screening until the acute effects of stimulant intoxication or withdrawal have resolved;
- establish psychological safety before raising topics that could be destabilizing;
- use nonjudgmental language; and
- implement EBIs.

Body Stuffing or Packing

Body stuffing or packing is the practice of hiding drugs in the body for the purpose of concealment. Body stuffing generally refers to smaller amounts of hastily—and often poorly—wrapped drugs to evade law enforcement detection, while body packing refers to preplanned and often well-wrapped larger amounts seen in drug smuggling. Body stuffing

[***] For more information on trauma-informed care, see SAMHSA's TIP 57: *Trauma-Informed Care in Behavioral Health Services*.[219]

or packing can result in more severe and prolonged symptoms of intoxication and should be managed in acute care settings.

While there are studies comparing imaging techniques to detect body stuffing or packing and monitoring asymptomatic individuals, limited information was identified on the appropriate medical workup for a patient who becomes intoxicated from a ruptured package of body-concealed stimulants.[251–255] Given the relative rarity of this event and that care should be provided in emergency settings by physicians with critical care experience (eg, medical toxicologists, emergency medicine and critical care physicians), the CGC did not provide recommendations for managing this population.

Laboratory Testing

Laboratory testing can detect some of the acute issues and complications of stimulant intoxication and withdrawal. No research was identified on ordering routine or as-needed laboratory testing in patients presenting with stimulant intoxication or withdrawal. The CGC agreed that some tests may be considered based on symptomatology and presence of risk factors. Clinicians should consider a CBC, a CMP; liver function tests (LFTs); and markers for muscle breakdown (eg, CK, lactate), cardiac injury (eg, troponin), and renal injury (eg, BCR, urine albumin).

When ordering a CBC, clinicians should be alert to neutrophil levels in patients with cocaine intoxication or withdrawal.[256] Levamisole is a common adulterant in the cocaine supply and can cause immunosuppression—in particular, neutropenia—and small vessel vasculitis. The amount of levamisole contaminating the drug supply and the resulting degree of clinical concern varies by region and over time.

While there is no direct evidence regarding infectious disease screening as part of the comprehensive assessment for stimulant intoxication and withdrawal, these tests help identify common comorbid conditions that can then be treated. The higher prevalence of HIV, hepatitis, and STIs in patients who use stimulants justifies testing.††† As noted in the general Assessment section, clinicians should consider all sites of sexual exposure, which may include urogenital, pharyngeal, and/or rectal, when testing for chlamydia and gonorrhea.

For some patients, the impact of routine laboratory testing (see Appendix I) could be substantial given the benefit of early detection and treatment for some conditions (eg, HIV, hepatitis). For some diagnoses, the effect of early detection and treatment is less substantial (eg, liver function). Implementing these recommendations should be highly

††† See recommendations compiled by the CDC for infectious disease screening.[30]

feasible in hospital and community settings where intoxication or withdrawal management would occur. However, these settings should have processes in place to facilitate appropriate follow-up. Health insurance coverage for routine lower value tests (eg, LFTs, renal function) may vary.

Toxicology Testing

No studies were identified that evaluated the use of toxicology testing as routine diagnostics for patients with suspected stimulant intoxication or withdrawal. There are limitations to the utility of toxicology testing for the management of stimulant intoxication or withdrawal, particularly in emergency settings when samples need to be sent to external laboratories. Toxicology testing may answer specific questions regarding a patient's recent substance use but is limited by the specific test, as some stimulants are not included on typical screening panels. When performing toxicology testing for stimulant intoxication in acute care settings, clinicians should be aware of the limitations of the tests used. A tradeoff exists between the time delay to process a test versus the accuracy and specificity of the information obtained. Screening (ie, presumptive testing) results are often available but less accurate than confirmatory tests and have limited utility in acute intoxication or withdrawal management. Observation of clinical effects and patient self-report are often more informative and more immediate than toxicology testing.

Despite these limitations, toxicology testing in acute care settings has some potential utility by providing valuable information to clinicians delivering follow-up StUD care. It can help inform clinical thinking regarding the differential diagnosis of a patient who presents with unspecified agitation, confusion, delirium, psychosis, chest pain, seizure, or autonomic hyperactivity. Toxicology testing can also help identify substances (both prescribed and nonprescribed) that could potentially produce drug–drug interactions when considering pharmacotherapy to manage stimulant intoxication or withdrawal. As well, toxicology testing in acute clinical settings remains important for public health surveillance and forensics.

Panels used in acute care settings should ideally test for regionally or demographically prevalent stimulants rather than screening for every testable stimulant. **It is critical to keep in mind that a negative test result only confirms that the particular target of the test was not detected in the sample.** Immunoassays for the cocaine metabolite, benzoylecgonine, have high sensitivity and specificity, whereas available immunoassays for amphetamines have lower specificity and often require confirmatory testing.

As discussed in ASAM's *Appropriate Use of Drug Testing in Clinical Addiction Medicine* consensus statement, there are known limitations to urine immunoassays for amphetamines, and providers should be cautious when interpreting their results. A recent review found that amphetamine immunoassays are subject to a roughly 4% to 10% false

positive rate.[257] Confirmatory testing for amphetamines can rule out false positive from other drugs (eg, bupropion, MPH, pseudoephedrine).[258] Clinicians should refer to the test manufacturer and/or consult with their laboratory to determine the capabilities and cross-reactivity of specific assays.

If stimulant intoxication is suspected but presumptive testing is negative, clinicians should consider the possibility of novel psychoactive stimulants. The growing influence of synthetic drugs and drug adulteration and contamination means that clinicians may be making treatment decisions in the absence of toxicological confirmation with increasing frequency. Regional surveillance reporting is often available on the prevalence of novel psychoactive substances, including stimulants and their frequency of detection with other substances.

Toxicology testing that is comprehensive, accurate, and interpreted correctly may be useful for educating patients and providers and, occasionally, as a diagnostic tool. The informational value of testing depends on the clinical importance of the outcome. For this reason, testing is unnecessary if the result would not alter the treatment plan (eg, to confirm stated methamphetamine use in obvious methamphetamine toxidrome) and becomes more necessary as the outcome becomes more clinically important (eg, to assess potential pediatric exposure, to differentiate psychiatric decompensation from methamphetamine-associated psychosis).

It is also important for clinicians to remember that a positive toxicologic test does not exclude a concurrent medical emergency, which may be the primary cause of the patient's clinical presentation. These tests indicate exposure, which may have occurred 72 or more hours prior. A positive test result may produce an anchoring bias; For example, a patient presenting with an aortic dissection or epidural abscess may be agitated, tachycardic, and hypertensive unrelated to any stimulants still detectable in their urine; a positive drug test may increase the risk that these types of diagnoses are not pursued.

A detailed discussion of considerations regarding patient consent for drug testing is beyond the scope of this Guideline. Providers should thoroughly explain all rules regarding confidentiality, consent, and sharing test results with outside entities to patients. For additional considerations, see ASAM's *Appropriate Use of Drug Testing in Clinical Addiction Medicine* consensus statement (major principles of this document are outlined in Appendix J) and ASAM's public policy statement on *Ethical Use of Drug Testing in the Practice of Addiction Medicine*.[33,34]

Implementation Considerations

When implementing toxicology testing, clinicians should consider the technical limitations of the selected matrix and drug panel. Clinicians should understand it is impossible to

detect all adulterants or contaminants with toxicology testing and should be careful to avoid overinterpretation of findings. Patient consent should generally be obtained prior to testing unless there is an immediate clinical need and obtaining consent is not possible (eg, loss of consciousness). Clinicians should stay abreast of which stimulants are prevalent within certain demographics in their region; testing laboratories often track this information.

Indications for useful toxicology testing, including screening and confirmatory testing, include but are not limited to when:

- the etiology of signs and symptoms is unclear,
- the clinical findings are not fully consistent with stimulant intoxication alone (ie, suggestive of other substance exposure), and
- the information is clinically important (eg, to assess potential pediatric exposure, to differentiate psychiatric decompensation from methamphetamine-associated psychosis).

Confirmatory testing should be considered when:

- the findings from a presumptive test are inconsistent with findings in the history or physical exam, and
- presumptive testing is not available for a substance that is important to evaluate (eg, fentanyl when co-intoxication with opioids is suspected in a region where fentanyl commonly contaminates the stimulant supply).

Assessment and Diagnosis Recommendations

Initial Assessment Recommendations

45. The clinical examination should first identify any acute concerns and complications of stimulant intoxication or withdrawal that would indicate the patient requires a higher level of care (*Clinical consensus, Strong Recommendation)*. This includes an assessment of hyperadrenergic symptoms, including tachycardia, hypertension, hyperthermia, and agitation (*Clinical consensus, Strong Recommendation)*.
46. The initial clinical examination when evaluating for suspected stimulant intoxication or withdrawal should include (*Clinical consensus, Strong Recommendation)*:
    a. a clinical interview (as feasible),
    b. physical examination,
    c. observation of signs and patient-reported symptoms,
    d. review of any available collateral information, and
    e. a safety assessment of the patient's risk of harm to self and others.

Comprehensive Assessment Recommendations

47. Stimulant intoxication and withdrawal are primarily diagnosed based on the patient history and physical examination, as well as findings from any clinical, diagnostic, and/or toxicology testing (*Clinical consensus, Strong Recommendation)*.
48. If some elements of the medical workup are not available in given a setting, the results from a basic assessment of vital signs and focused mental status evaluation should be used to determine the urgency of further medical evaluation or referral for more comprehensive medical evaluation (*Clinical consensus, Strong Recommendation)*.
49. Clinical testing should be based on presenting signs and symptoms and should include a CBC, a CMP, LFTs, markers for muscle breakdown (eg, CK, lactate [in cases of muscle breakdown and acidosis]) or cardiac injury (eg, CK, troponin; *Clinical consensus, Strong Recommendation)*.
50. When analyzing CBC results for patients with cocaine intoxication or withdrawal, clinicians should be alert to neutrophil levels, as levamisole is a common adulterant in the cocaine supply and can cause immunosuppression—in particular, neutropenia—and small vessel vasculitis (*Clinical consensus, Conditional Recommendation)*.

Toxicology Testing Recommendations

51. In patients presenting with stimulant intoxication or withdrawal, clinicians can use toxicology testing to:
    a. inform clinical thinking regarding the differential diagnosis, along with other clinical information (*Clinical consensus, Strong Recommendation)*; and
    b. identify substance use that could produce drug–drug interactions when considering pharmacotherapy to manage signs and symptoms of stimulant intoxication or withdrawal (*Clinical consensus, Conditional Recommendation)*.
52. Clinicians should consider the possibility of novel psychoactive stimulants if stimulant intoxication is suspected but presumptive testing is negative (*Clinical consensus, Conditional Recommendation)*.

Setting Determination

No studies were identified that addressed level of care determination when managing the risks associated with stimulant intoxication and withdrawal. The recommendations in this Guideline are based on a review of existing guidelines and the clinical expertise of the CGC.[184,244]

Patients with stimulant intoxication and withdrawal should be managed in a setting that provides the intensity of care necessary to address the anticipated severity of their intoxication or withdrawal syndrome. Treatment needs are determined by a number of dynamic factors, meaning they will change throughout the course of intoxication or withdrawal. The CGC recommended the use of a multidimensional assessment—such as that described in *The ASAM Criteria*—to determine the appropriate clinical setting for the management of a given patient's stimulant intoxication or withdrawal.[17]

Individuals presenting with stimulant intoxication or withdrawal may be treated in lower acuity clinical settings if emergency interventions are not indicated. Clinical features that typically indicate the need for emergency medical treatment include high fever, seizure, chest pain, psychosis, and suicidality.

Some patients should be managed in higher acuity settings because they require close monitoring in a setting that has the capacity to manage evolving clinical presentations. Serious co-occurring medical or psychiatric health concerns can be exacerbated by stimulant intoxication or withdrawal. Co-intoxication with opioids, alcohol, or other sedatives can alter both the time course and severity of intoxication and acute effects in unexpected ways. Individuals who have concealed stimulants by consuming or inserting packages in a body cavity (ie, body stuffing or packing) should be observed in an acute care setting with ready access to emergency treatment, as it is difficult to know the actual amount of substance consumed, quality of the packaging, and risk of exposure.

An appropriate treatment setting allows for assessment of acute issues and complications, screening for acute intoxication potential, monitoring of the intoxication syndrome, and administration of appropriate clinical interventions. If any of these are not possible in the current setting due to patient agitation or limitations in staff capability or resources, the patient should be transferred to a more intensive level of care with the appropriate capabilities. However, transfers involve some risk, as patients may choose to leave treatment rather than initiate and engage in treatment elsewhere. The use of health information technologies and patient navigators may help facilitate effective transfers by bridging care between settings.

Setting Determination Recommendations

53. Patients with severe clinical concerns or complications related to stimulant intoxication should be managed in acute care settings (*Clinical consensus, Conditional Recommendation)*.
54. Some patients with acute stimulant intoxication can be safely managed in lower acuity clinical settings if (*Clinical consensus, Conditional Recommendation)*:
    a. the patient is cooperative with care;

b. the patient is responsive to interventions (eg, verbal and nonverbal de-escalation strategies, medications) that can be managed in the clinical setting;
c. the patient is not experiencing more than mild hyperadrenergic symptoms or is responsive to medications that can be managed in the clinical setting; and
d. clinicians are able to:
    i. assess for acute issues and complications of stimulant intoxication,
    ii. monitor vital signs,
    iii. assess and monitor suicidality,
    iv. monitor for worsening signs and symptoms of intoxication and emergent complications related to stimulant intoxication,
    v. provide adequate hydration,
    vi. provide a low-stimulation environment,
    vii. manage the risk of return to stimulant use, and
    viii. coordinate clinical testing as indicated.

Managing Stimulant Intoxication and Withdrawal

Stimulant Intoxication

Mild stimulant intoxication can typically be managed with behavioral and environmental interventions meant to help the patient feel calm and safe. More severe behavioral concerns include severe agitation, psychosis, and risk of harm to self or others, which can be managed by a combination of pharmacotherapies and behavioral and environmental interventions.

Clinicians can consult with the Poison Center for 24/7 advice through their toll-free number (800-222-1222), or with their institution's clinical toxicology service, which may reduce the duration of hospital stay.[259] Expert consultation may be particularly helpful when medication shortages impact the availability of recommended medications.

Environmental Interventions

Environmental interventions involve isolation in a non-stimulating environment that is quiet with low lighting. No studies were found on the effectiveness of environmental interventions for managing stimulant intoxication and withdrawal. The gray literature search identified multiple clinical guidelines that discuss behavioral and environmental strategies to help keep patients calm, including guidance from SAHMSA, the American

Association of Family Physicians (AAFP), the United Nations Office on Drugs and Crime (UNODC), and other international guidelines.[187,243,244] The CGC agreed that treatment settings should provide a quiet environment to rest, avoid stimulant exposure, and assist with social support.

Supportive Care

No studies were found on the types of supportive care that should be provided to patients experiencing stimulant intoxication and withdrawal. Supportive care should be provided according to best practices for general substance toxicity, including:

- providing vitamins, fluids, and nutritional support, including thiamine and dextrose;
- correcting electrolyte and fluid imbalances; and
- talking to the patient, including:
    - orienting to time and place,
    - providing reassurance, and
    - communicating what they can expect from treatment.

Behavioral and Psychiatric Symptoms of Stimulant Intoxication

The CGC suggested that clinicians follow an established clinical protocol for managing general agitation when treating stimulant-induced agitation during intoxication or withdrawal, such as the American College of Emergency Physicians' (ACEP) Best Practices in the Evaluation and Treatment of Agitation (Project BETA).[260]

Nonpharmacological Management Strategies for Behavioral and Psychiatric Symptoms

The process of engaging the patient as an active partner in their assessment, treatment, and recovery is important to alleviating distress and reducing risk. The management of agitation and psychosis related to stimulant intoxication should start with behavioral management strategies. The CGC agreed that not all patients with stimulant intoxication require pharmacological interventions; intoxication management is an evolving process where the clinician should continuously evaluate a patient's response to an intervention.

The CGC emphasized that the use of restraints should be avoided unless absolutely necessary to protect the safety of patients and/or staff. While restraints can temporarily prevent violent behavior, their application increases the risk of injury to patients and staff and can be psychologically traumatic for patients. Clinicians should administer medications to reduce agitation whenever a patient is placed into physical restraints and closely monitor for hyperthermia and dehydration. See ACEP's Project BETA guidelines, the American Medical Association's (AMA) Code of Ethics Opinion 1.2.7: *Use of Restraints*, and ACEP's policy statement on *Use of Patient Restraints* for further discussion.[260–262]

> *"All patients have the right to be free from physical or mental abuse, and corporal punishment. All patients have the right to be free from restraint or seclusion, of any form, imposed as a means of coercion, discipline, convenience, or retaliation by staff. Restraint or seclusion may only be imposed to ensure the immediate physical safety of the patient, a staff member, or others and must be discontinued at the earliest possible time."*[261]
>
> *—Centers for Medicare & Medicaid Services (CMS)*

Pharmacological Management of Behavioral and Psychiatric Symptoms

Richards et al (2015) reviewed six high-quality studies supporting the use of antipsychotics and benzodiazepines to manage agitation and psychosis.[152] In a comprehensive systematic review, Connors et al (2019) concluded that antipsychotics administered in the context of acute stimulant intoxication did not pose significant risk for harm (eg, neuroleptic malignant syndrome [NMS]) to the extent previously thought.[263] The gray literature search identified multiple clinical guidelines that address pharmacological options for management of agitation and psychosis, including guidance from SAHMSA, AAFP, UNODC, and other international guidelines (see Appendix G).[187,243,244]

Pharmacological Management of Agitation

Benzodiazepines are generally considered first-line treatment for the management of stimulant-induced agitation (see Appendix N for additional agents to consider). Significant

agitation should typically be managed in acute care settings given the need for a higher level of monitoring and clinical resources (eg, intravenous [IV] medications, telemetry, cooling) than are typically available outside of controlled settings. Clinicians should monitor for medication side effects with usual care.

In situations of severe stimulant-induced agitation refractory to benzodiazepines and antipsychotics where rapid control of agitation is necessary for patient and/or staff safety (most commonly related to methamphetamine intoxication), clinicians can consider IV or intramuscular (IM) ketamine. Onset of IM ketamine is very rapid, which makes it particularly useful when a patient is experiencing severe agitation such that placing an IV would be challenging and delay effective care.

Pharmacological Management of Psychosis

ATS use is associated with greater risk for psychosis compared to cocaine use.[264] Recent research suggested that olanzapine or quetiapine may be preferred for the management of methamphetamine-induced psychosis; however, the evidence is considered low quality due to the studies' high risk of bias.[150] When managing psychosis prior to confirming the etiology of stimulant intoxication or withdrawal, clinicians should conduct an evaluation with a focus on identifying potential causes of the patient's psychosis other than stimulant intoxication. Clinicians should focus treatment of psychosis on management of the underlying causes of the patient's psychotic symptoms and monitor for medication side effects with usual care.

Behavioral and Psychiatric Symptoms of Stimulant Intoxication Recommendations

55. Clinicians should evaluate the patient to identify causal factors for agitation and/or psychosis other than stimulant intoxication; treatment should address all underlying causes (*Clinical consensus, Strong Recommendation)*.
56. Clinicians should use verbal and nonverbal de-escalation strategies to calm patients who are agitated, delirious, and/or psychotic to support their cooperation with care (*Clinical consensus, Strong Recommendation)*.
57. Clinicians can consider treating stimulant-induced agitation or confusion with medication (*High certainty, Conditional Recommendation)*.
    a. Benzodiazepines can be considered a first-line treatment for managing stimulant-induced agitation and/or confusion (*High certainty, Conditional Recommendation)*.
58. De-escalation strategies should not delay the use of medication to manage patients who are agitated, delirious, and/or psychotic and at imminent risk for severe complications (*High certainty, Strong Recommendation)*.

59. Clinicians should treat stimulant-induced psychotic symptoms with an antipsychotic medication (*High certainty, Strong Recommendation)*.
    a. The urgency, formulation, and duration of antipsychotic pharmacotherapy should be based on etiology and symptomatology (*High certainty, Strong Recommendation)*.
    b. Clinicians should avoid the use of chlorpromazine and clozapine for stimulant-induced psychosis as these medications may place patients at increased risk for seizures (*High certainty, Strong Recommendation)*.
60. For agitation and/or psychosis that is moderate to severe or escalating, clinicians should:
    a. conduct a medical evaluation focused on identifying life-threatening medical signs and symptoms that require referral for emergent hospital workup and management (*Clinical consensus, Strong Recommendation)*, and
    b. conduct a mental status evaluation focused on evaluating the patient's danger to self and others that would require immediate referral for full psychiatric assessment and/or involuntary containment and evaluation (*Clinical consensus, Strong Recommendation)*.
61. If agitation and/or psychosis does not respond to the setting's available de-escalation and/or medication management interventions, clinicians should coordinate transition to a more intensive level of care (*Clinical consensus, Strong Recommendation)*.
    a. When possible, interventions that address agitation, confusion, delirium and/or psychosis should be initiated while arranging for transport (*Clinical consensus, Strong Recommendation)*.
62. Clinicians should monitor for progression of psychiatric symptoms, breakthrough psychosis, suicidality, and emergence of trauma-related symptoms; in particular, suicidality may increase during waning intoxication and acute withdrawal (*Clinical consensus, Conditional Recommendation)*.

Please see the supplementary EtD document for the following related summaries of evidence, relevant citations, and CGC judgments:

- Table 36. Agitation Medication
- Table 37. Psychosis Medication

Hyperadrenergic Symptoms of Stimulant Intoxication

The literature review identified several studies on the management of hyperadrenergic signs and symptoms in patients with stimulant intoxication.[114,117,118,151–154,263,265] In a systematic review focused on cocaine-related cardiovascular toxicity, Richards et al (2016)

concluded that calcium channel blockers may decrease hypertension and vasospasm but not necessarily tachycardia, whereas benzodiazepines appear safe for non-cardiovascular related symptoms.[153]

When assessing stimulant intoxication, clinicians should assess hyperadrenergic signs and symptoms, including tachycardia, hypertension, hyperthermia, and agitation. Ongoing monitoring and management of vital signs—especially heart rate and blood pressure—is critical to prevent complications that may result from untreated sympathomimetic toxicity. GABAergic agents are the primary treatment for stimulant-related hyperadrenergic symptoms. Significant hyperadrenergic symptoms should typically be managed in an acute care setting.

Beta blockers are generally contraindicated in patients with cocaine intoxication and cardiovascular disease[246]; this is an area of ongoing controversy in the field. Many experts recommend alternative medications such as calcium channel blockers, alpha-1 adrenergic antagonists, alpha-2 adrenergic agonists, and nitric oxide-mediated vasodilators, as symptoms indicate, to achieve similar effects in patients with stimulant intoxication. It is important to consider that these pharmaceutical classes may be most beneficial in treating hypertension and vasospasm but may result in poor control of reflex tachycardia. Limited data indicate that alpha-2 adrenergic agonists (eg, dexmedetomidine for more severe symptoms, clonidine for mild to moderate symptoms) are beneficial in treating stimulant-induced agitation and can also be useful in the treatment of hypertension and tachycardia and, thus, should be considered in the management of the hyperadrenergic state of stimulant intoxication.[152,153] Clinicians should monitor for medication side effects with usual care.

If considering pharmacotherapy with a beta blocker, one with concomitant alpha-1 antagonism (eg, labetalol) is preferred due to low risk of unopposed alpha stimulation. Clinicians should consider consulting with a specialist (eg, cardiologist, medical toxicologist) in these instances.

Hypertensive Emergency

Two systematic reviews were identified that examined treatment for stimulant-associated hypertensive emergency.[152,153] All evidence came from case reports and case series; cocaine-associated hypertensive emergencies were successfully treated with dexmedetomidine, and ATS-associated hypertensive emergencies were successfully treated with propranolol, sodium nitroprusside, nifedipine, labetalol, and phentolamine.

The CGC determined that hypertensive emergency can be managed with short-acting agents such as sodium nitroprusside, phentolamine, or dihydropyridine calcium channel blockers. Long-acting antihypertensives should be avoided because of the risk of abrupt

hemodynamic collapse. Additionally, the CGC recommended the use of nitroglycerin if signs or symptoms of cardiac ischemia are present.

Hyperadrenergic Symptoms of Stimulant Intoxication Recommendations

63. When patients present with hyperadrenergic symptoms, clinicians should provide ongoing monitoring and management of vital signs—especially heart rate and blood pressure—to prevent complications that may result from untreated sympathomimetic toxicity (*Clinical consensus, Strong Recommendation)*.
64. Clinicians should treat patients in a stimulant-induced hyperadrenergic state with GABAergic agents (eg, benzodiazepines, phenobarbital, propofol); benzodiazepines can be considered first-line treatment for this purpose (*Low certainty, Strong Recommendation)*.
65. If the hyperadrenergic state persists despite appropriate improvement in agitation and neuromuscular hyperactivity following treatment with benzodiazepines or other GABAergic agent, clinicians can consider adjunctive treatment with the following medications:
    a. A beta blocker with concomitant alpha-1 antagonism (eg, carvedilol, labetalol; *Moderate certainty, Conditional Recommendation)*.
    b. An alpha-2 adrenergic agonist (eg, dexmedetomidine for severe symptoms, clonidine for mild to moderate symptoms; *Moderate certainty, Conditional Recommendation)*.
    c. Where beta blockers are contraindicated, clinicians can consider other pharmacological options such as calcium channel blockers, alpha-1 adrenergic antagonists, alpha-2 adrenergic agonists, and nitric oxide-mediated vasodilators, with consideration of other clinically relevant signs and symptoms (*Moderate certainty, Conditional Recommendation)*.
    d. While calcium channel blockers, alpha-1 adrenergic antagonists, alpha-2 adrenergic agonists, and nitric oxide-mediated vasodilators may be most beneficial in treating hypertension and vasospasm, clinicians should be alert to potential side effects, including poor control over tachycardia or reflex tachycardia (*Moderate certainty, Strong Recommendation)*.
66. If a patient with stimulant intoxication is experiencing a hypertensive emergency, clinicians should:
    a. use short-acting agents such as sodium nitroprusside, phentolamine, or dihydropyridine calcium channel blockers (*Very low certainty, Strong Recommendation)*;

b. avoid long-acting antihypertensives to avoid abrupt hemodynamic collapse (*Very low certainty, Strong Recommendation)*; and

c. use nitroglycerin if the patient exhibits signs or symptoms of cardiac ischemia (*Very low certainty, Strong Recommendation)*.

Please see the supplementary EtD document for the following related summaries of evidence, relevant citations, and CGC judgments:

- Table 38. Hyperadrenergic Medications
- Table 39. Hyperadrenergic Adjunct
- Table 40. Hypertensive Emergency

Acute Issues and Complications

Acidosis

Acidosis from stimulant intoxication is typically due to a combination of excessive movement or muscle activity and drug-specific effects (eg, temperature elevation). Seizures may also contribute to acidosis. In this context, control of agitation, seizures, and neuromuscular hyperactivity is critical. No studies were identified on managing acidosis specific to stimulant intoxication or withdrawal. The CGC did not propose any clinical recommendations for treating acidosis specific to stimulant intoxication or withdrawal; in general, treating agitation will help address acidosis.

Significant acidosis—that is, acidosis associated with persistent chemistry abnormalities, persistent neuromuscular agitation, temperature elevation, and/or long duration of intoxication—should be managed in acute care settings according to best practices. GABAergic medications are first-line agents for this purpose. IV fluids and cooling can also help improve acidosis after attenuation of neuromuscular excitation. Temperature should be closely monitored. In cases of severe acidosis—that is, where acidosis is associated with other complications (eg, cardiac, hemodynamic)—more acute measures (eg, cardiac and electrolyte monitoring, administration of sodium bicarbonate) may be indicated.

Chest Pain

Cardiac complications of stimulant use include chest pain with elevated risks for acute coronary syndrome (ACS) and cardiac-related mortality. Hyperadrenergic states secondary to stimulant use can lead to hypertension and tachycardia.

Chest pain in patients with stimulant intoxication should be treated with GABAergic medications, such as benzodiazepines, phenobarbital, or propofol (depending on symptom severity and level of care). If chest pain does not improve as the signs and symptoms of

stimulant intoxication improve, clinicians should evaluate and treat ACS following current standards of care. If chest pain is not responding or not resolving, clinicians can consider concomitant treatment with one of the adjunct medications recommended for persistent hyperadrenergic symptoms.

Historically, beta blockers have been avoided when treating cocaine intoxication due to case reports theorizing risks associated with unopposed alpha stimulation. Unopposed alpha stimulation can result in an acute increase in blood pressure and/or coronary artery vasoconstriction following beta blocker administration. Evidence suggests that this risk is lower than hypothesized.[266–268] Shin et al (2019) conducted a systematic review and meta-analysis on the use of beta blockers to treat cocaine intoxication and cocaine-associated chest pain, finding that beta blockers were not associated with adverse events—including myocardial infarction (MI), myocardial necrosis, or death—during hospitalization and long-term follow-up.[269] However, this issue remains an area of controversy in the field. For complex cases, consult with cardiology and/or medical toxicology.

Chest Pain Recommendations

67. For patients experiencing chest pain during stimulant intoxication, clinicians should initiate treatment for the underlying intoxication with GABAergic agents (eg, benzodiazepines, phenobarbital, propofol) as long as there are no clinical contraindications (*Moderate certainty, Conditional Recommendation)*.
68. Alternative agents (eg, calcium channel blockers, vasodilators) are generally preferred for management of cardiac ischemia in patients experiencing stimulant intoxication. However, if beta blockers are used in patients with stimulant intoxication, clinicians should consider using a medication with concomitant alpha-1 antagonism (eg, carvedilol, labetalol). If an unopposed beta blocker was used in a patient who is or was recently stimulant intoxicated, clinicians should also consider providing a coronary vasodilator (eg, nitroglycerin, calcium channel blocker). For complex cases, consult with cardiology and/or medical toxicology (*Low certainty, Conditional Recommendation)*.
69. While treating underlying stimulant intoxication in patients experiencing chest pain, clinicians should concomitantly evaluate for ACS and other causes of acute chest pain in stimulant intoxication (eg, pulmonary, musculoskeletal [MSK]). Chest pain that does not fully resolve as signs and symptoms of stimulant intoxication improve should be evaluated and treated following current standards of care (*Moderate certainty, Strong Recommendation)*.

Please see the supplementary EtD document for the following related summaries of evidence, relevant citations, and CGC judgments:

- Table 41. Chest Pain Medication
- Table 42. Chest Pain Management of Cardiac Ischemia

- Table 43. Chest Pain Evaluation

Dehydration and Electrolyte and Fluid Imbalances

Dehydration is a common consequence of stimulant intoxication that can result in electrolyte and fluid imbalances. No studies were identified on managing dehydration or electrolyte and fluid imbalances specific to stimulant intoxication or withdrawal. The CGC did not propose any clinical recommendations related to these concerns; dehydration and electrolyte and fluid imbalance should be managed according to standard best practices.

Hyponatremia in the context of stimulant use is typically seen in patients who present with confusion, reduced consciousness, or seizures caused by water intoxication from excessive hydration during 3,4-methylenedioxymethamphetamine (MDMA) intoxication.[270] In alignment with existing guidelines, the CGC agreed that stimulant-related hyponatremia should be managed according to best practices by replacing sodium.[270] Patient follow-up should include routine and ongoing screening for electrolyte levels and renal function.

Hyperthermia

Hyperthermia caused by autonomic hyperactivity during acute stimulant intoxication can complicate management of intoxication and may require cooling interventions.[271] No studies were found on managing hyperthermia in patients with stimulant intoxication. The CGC did not propose any clinical recommendations specific to hyperthermia in stimulant intoxication or withdrawal; hyperthermia should be managed according to best practices. For severe hyperthermia (ie, generally greater than 40.5°C/105°F), immersion in a cooling water bath is typically indicated as it is rapidly effective and may be combined with pharmacological treatment (eg, sedatives, neuromuscular blocking agents) to accelerate cooling; for less severe hyperthermia, evaporative methods (eg, mist, fan) are appropriate.[272,273]

Neutropenia

Neutropenia, while generally rare and transient, can be life-threatening. No studies were found on managing neutropenia in patients who use stimulants. The CGC did not propose any clinical recommendations specific to neutropenia in the context of stimulant intoxication or withdrawal and determined that neutropenia should be managed according to best practices. While neutropenia typically improves quickly in most patients after cessation of exposure to levamisole, if neutropenia is not improving and there is concern for neutropenic fever or infection, clinicians should consider consulting hematology.

QRS Widening

Cocaine has local anesthetic effects and can cause QRS widening and impaired cardiac contractility. QRS widening is a particular complication that occurs when large amounts of cocaine are consumed rapidly, such as in body stuffing or packing, and should be treated in an acute care setting. If QRS widening or impaired cardiac contractility are identified, 2 ampoules of sodium bicarbonate should be administered in a bolus to improve the conduction block and contractility, as well as acidosis if present. If sodium bicarbonate is unavailable, 3% hypertonic saline can be used (200 mL = 2 ampoules of sodium bicarbonate) for the conduction block.

If QRS widening is not responsive to use of sodium bicarbonate or 3% hypertonic saline or the patient is in cardiac arrest and not responding to standard advanced cardiac life support (ACLS) protocol, a 20% lipid emulsion concentration (ie, Intralipid in a 1 mL/kg bolus [100 mL in an adult]) can be considered for patients with cocaine intoxication or overdose. Note that this should only be administered in acute care settings.

In animal models and studies of cocaine toxicity, sodium bicarbonate improved blood pressure and myocardial function.[274,275] Literature reviews on the use of sodium bicarbonate in humans have identified cocaine as one of the causal factors for QRS widening.[276] While improvement in cardiac function is the main goal with sodium bicarbonate treatment, correction of metabolic acidosis will also occur. However, this treatment can exacerbate the risk for QT prolongation, if present, by lowering serum potassium concentrations. In the event of sodium bicarbonate shortages, 3% hypertonic saline has been used as a sodium replacement, but it does not correct metabolic acidosis.

QRS Widening Recommendations

70. Cocaine has local anesthetic-like effects at sodium channels and can cause QRS widening with impairment in cardiac contractility during severe cocaine intoxication. If these issues are identified, in addition to treating intoxication, clinicians should administer sodium bicarbonate to improve the conduction block and contractility; this will also improve metabolic acidosis if present (*High certainty, Strong Recommendation)*.

Please see the supplementary EtD document for the following related summaries of evidence, relevant citations, and CGC judgments:

- Table 44. QRS Widening

Rhabdomyolysis

In patients with stimulant intoxication, rhabdomyolysis most commonly occurs following episodes of severe agitation and hyperthermia. No studies were identified on managing rhabdomyolysis specific to stimulant intoxication or withdrawal. The CGC did not propose any clinical recommendations specific to rhabdomyolysis in the context of stimulant intoxication or withdrawal and determined that rhabdomyolysis should be managed according to best practices, including:

- replacing fluids to ensure a urine output of >2 mL/kg/h;
- avoiding urinary alkalinization as it inhibits amphetamine elimination and instead focusing primary management strategies on fluid replacement and management of agitation and hyperthermia;
- following up with routine and ongoing screening of renal function in patients with movement disorders or seizures; and
- checking serum creatine phosphokinase (CPK) when rhabdomyolysis occurs in relation to agitation or hyperthermia.

Seizure

No studies were identified that evaluated strategies for assessment and diagnosis of stimulant-related seizures. Consensus in existing clinical guidelines is to evaluate seizures according to best practices.[187,270,277]

While the recommendations below reflect standard treatment for any toxicity- or withdrawal-related seizures, the CGC included it in this Guideline because of its importance in this patient population. In animal models of stimulant-induced seizures, GABAergic agents have shown greater efficacy in reducing seizure recurrence compared to standard anticonvulsant agents or sodium channel blockers.[278] Benzodiazepines are generally preferred as first-line treatment because of their relatively wide availability and ease of use rather than superior effectiveness. Phenobarbital and propofol are second-line agents for management of stimulant-induced seizures, though propofol is preferred if seizures are severe or refractory. Acute care settings should have order sets for withdrawal seizures, with considerations for medication shortages.

In cases where a seizure is associated with a complication of stimulant use (eg, hyponatremia, trauma) rather than stimulant toxicity, standard treatments should be provided, including standard seizure medications when indicated. If a seizure is hyponatremia-related, the underlying hyponatremia should be treated by replacing sodium (see Dehydration and Electrolyte and Fluid Imbalances).

Monitoring can proceed according to standard practices for seizure management. The risks associated with undersedation (ie, not controlling the seizure) are greater than those

associated with oversedation (ie, side effects from medications); side effects can be anticipated and are tolerable when compared to the harm of recurrent seizures. The risk of over- and undersedation can be reduced through clinician education on appropriate dosing and titration.[279]

If seizures are not controlled by GABAergic medications during severe stimulant intoxication, clinicians may consider emergently inducing paralysis with monitoring (ie, EEG). If a patient is at the level of end-organ dysfunction, cooling should be achieved via medications to inhibit muscle activity (eg, with benzodiazepines) and, potentially, other strategies (eg, IV fluids, lavage, evaporative cooling, ice baths if life-threatening).

Seizure Workup

Seizures are one of the most severe complications of stimulant toxicity. Over 6% of new onset seizures are substance-related; in adults, 9% of status epilepticus is substance-induced.[277] Seizures can occur in association with methamphetamine use, with epileptic seizures being a frequent complication of methamphetamine intoxication.[270,280] While cocaine use is also frequently cited as a cause of seizure, there is some disagreement regarding the methodological rigor of positive findings outside of those associated with bag ruptures following body stuffing or packing.[281] Some medications, such as bupropion, raise the risk for seizures. Seizure may be related to hyponatremia when stimulants are used and is also more likely with polysubstance rather than single substance use.

Established guidelines are available for neurological evaluation of the first episode of unprovoked seizure in both adolescents and adults.[282,283] However, given stimulants' proconvulsive activity, there is debate over whether all components of this evaluation—which involves neurology consultation and evaluation, including electroencephalogram (EEG) follow-up testing—are necessary when the seizure is likely to be stimulant-induced. Waiving a full workup saves time and resources, including avoiding an overnight hospital stay and follow-up appointments. However, missed identification of nontoxicologic causes of seizure is possible.

No studies were identified that evaluated strategies for assessment and diagnosis of stimulant-related seizures. Consensus in clinical guidelines is that determination for comprehensive evaluation following a seizure can be made according to best practices based on symptomatology and presence of risk factors.[187,270,277] Common indications for waiving a comprehensive neurological evaluation following a seizure include:

- known preexisting seizure disorder,
- history of traumatic brain injury (TBI),
- strong family history of epilepsy,
- hyponatremia detected by laboratory testing, and
- the seizure is well-explained by substance use or withdrawal.

The consensus of the CGC was that a seizure is well-explained by substance use or withdrawal when, for example, the patient is known to use medications that lower seizure threshold (eg, tramadol, bupropion) or has a history of stimulant- or other substance use-related seizure. In these instances, there is no evidence that a full neurological workup, which requires significant healthcare resources, is of benefit.

When the etiology of seizure is not well-explained by substance use, the workup and management should proceed according to usual best practices in an acute care setting.

Even if full neurological workup is waived, clinicians might still order diagnostic testing (eg, computed tomography [CT] scan of the head) to rule out other etiologies based on clinical exam findings (eg, neurological findings suggestive of stroke). Additional evaluation is indicated if seizures recur despite adequate management of stimulant intoxication.

Seizure Recommendations

71. When a patient presents to the ED with seizures following stimulant use, full neurological workup is not necessary if the seizures are well explained by substance use or withdrawal (*Clinical consensus, Conditional Recommendation)*.
    a. When the etiology of the seizures is not well explained by stimulant use, the workup and management of seizures should proceed according to usual best practices (*Clinical consensus, Strong Recommendation)*.
72. For stimulant intoxication-related seizures or concomitant alcohol- or sedative-related seizures, clinicians should treat with benzodiazepines (*High certainty, Strong Recommendation)*.
    a. If seizures are refractory to benzodiazepines, clinicians can consider treating with either phenobarbital or propofol (*High certainty, Strong Recommendation)*.

Please see the supplementary EtD document for the following related summaries of evidence, relevant citations, and CGC judgments:

- Table 45. Seizure Medication

Follow-up

Following management of acute intoxication or withdrawal, clinicians should address non-acute issues identified in the assessment and conduct additional screening or assessment as appropriate. Some patients may require monitoring for emergence of renal and cardiac concerns.

A nationally representative 2007 survey of Australian adults estimated that 50.4% of individuals who use stimulants nonmedically would develop a StUD within 14 years of onset of use.[284] Preexisting psychiatric disorders were significantly associated with increased risk. Screening for StUD presents an opportunity for clinicians to engage patients in brief interventions using motivational interviewing (MI) or motivational enhancement therapy (MET) to facilitate referrals for assessment for StUD, if indicated. While existing evidence suggests that referral to treatment alone does not result in effective engagement in ongoing care, the benefit of treating those in need of treatment is substantial. Evidence suggests that patients find referrals to be acceptable.[285,286]

Follow-up Recommendations

73. Clinicians should screen patients for StUD and engage them in brief interventions using MI or MET to facilitate referral for assessment for StUD, if indicated (*Very low certainty, Conditional Recommendation)*.

Please see the supplementary EtD document for the following related summaries of evidence, relevant citations, and CGC judgments:

- Table 46. Screening, Brief Intervention, & Referral to Treatment (SBIRT)

Stimulant Withdrawal

Abrupt discontinuation or reduction in stimulant use can cause stimulant withdrawal syndrome. Many patients will experience 12 to 24 hours of somnolence and irritability—likely due to catecholamine depletion and sleep deprivation.

During periods of abrupt stimulant reduction or discontinuation, clinicians should be attentive to the patient's physical and mental health signs and symptoms. The current standard of care for managing stimulant withdrawal focuses on ameliorating presenting signs and symptoms and minimizing risks. Behavioral and environmental interventions should be used to foster a calming environment (see Setting Determination).

A few pharmacotherapies have been investigated for the treatment of stimulant withdrawal; however, most of the studies are small and of low quality. A 2009 Cochrane review on treatment of amphetamine withdrawal that included four RCTs involving 125 participants did not find any pharmacotherapies to be effective for treating general stimulant withdrawal.[265] While some preliminary findings have shown potential promise, outcomes need to be replicated in larger cohorts before adoption in clinical practice.

Medications may help reduce signs and symptoms associated with stimulant withdrawal. Signs and symptoms that may require pharmacotherapeutic management include agitation,

psychosis, depression, and insomnia, among others. Mental health symptoms that are acute or not resolving as expected as withdrawal symptoms improve can be managed with antidepressants and antipsychotics, as indicated, in addition to psychosocial interventions. See Co-occurring Disorders for additional information on determining whether signs and symptoms are preexisting or induced by stimulant withdrawal, which will influence treatment planning.

It is important to differentiate between short-term symptoms of stimulant withdrawal and underlying psychiatric disorders to determine appropriate treatment. When considering pharmacotherapies, clinicians should always consider the risks (eg, NMS, serotonin syndrome) and benefits in the context of each patient's full clinical presentation.

Treating symptoms such as insomnia and muscle aches with over-the-counter (OTC) or prescription medications may help support ongoing treatment engagement. Nutritional interventions may also be indicated.

Post-Acute Symptoms of Withdrawal

Many patients with StUD also experience persistent challenges with post-acute symptoms of withdrawal—including depression, anxiety, insomnia, and paranoia, among others—that can last for weeks to months. It is important to assess for and treat these symptoms to reduce the risk for decompensation and return to stimulant use.

Patients may experience increased sleep during the initial withdrawal period, followed by sleep disturbances that can be persistent. In some patients, this may be managed with behavioral interventions, including promotion of good sleep hygiene. For more serious or persistent insomnia, pharmacotherapy may be needed. Existing guidelines provide guidance on the pharmacological management of insomnia, including the use of prescription medications such as sedating antidepressants, antipsychotics, antihistamines, the antihypertensive clonidine, or OTC medications such as melatonin.[287]

Clinicians should exercise caution when prescribing sedative–hypnotic medications to manage insomnia secondary to post-acute stimulant withdrawal given the risks associated with their regular use. When prescribed, the risks and benefits of the medication should be regularly reassessed.

Monitoring

No studies were found on strategies for monitoring psychiatric or hyperadrenergic symptoms in patients with stimulant intoxication or withdrawal. The CGC agreed that clinicians should consider clinically monitoring patients until their mental status and other

signs and symptoms of acute intoxication or withdrawal have stabilized to minimize and prevent adverse events such as risks for falls, altercations, and motor vehicle crashes. Clinicians should monitor for progression of psychiatric symptoms such as breakthrough psychosis, suicidality, and emergence of trauma-related symptoms. In particular, suicidality may increase as intoxication wanes and acute withdrawal begins and should be addressed. When patients present with hyperadrenergic signs and symptoms, clinicians should provide ongoing monitoring and management of vital signs—especially heart rate and blood pressure—to prevent complications that may result from untreated sympathomimetic toxicity.

Suicidality

No studies were identified on managing suicidality within the context of stimulant intoxication or withdrawal. Existing guidelines emphasize the importance of monitoring for and managing suicide risk.[288] The CGC determined that suicidality should be managed according to best practices, including psychiatric consultation, safety assessment, and involuntary psychiatric hospitalization if necessary. Effective stimulant intoxication and withdrawal management can reduce the risk for suicide.[289]

Managing Stimulant Intoxication and Withdrawal in Pregnant Patients

In general, acute stimulant intoxication and withdrawal in patients who are pregnant should be managed according to standard practices, including assessment of fetal well-being, regardless of pregnancy status. As with all patients, clinicians should conduct risk–benefit assessments to determine the appropriate course of treatment; the risk–benefit assessment should consider both the patient and the fetus. Concern for fetal well-being should not be prioritized over the health of the pregnant patient. While some medications used to treat intoxication or acute withdrawal may pose risks to the fetus, greater risks may occur as a result of untreated stimulant intoxication or withdrawal. Untreated withdrawal also increases the risk for return to stimulant use, which poses direct risks to the fetus.

It is often extremely difficult, if not impossible, to differentiate methamphetamine-induced hypertension from gestational hypertension. Hypertension in pregnancy and postpartum should be managed according to best practices, which currently include[290]:

- labetalol or nifedipine to manage hypertension, and
- magnesium for seizure prophylaxis.

Secondary and Tertiary Prevention

This section addresses secondary and tertiary prevention for patients with or at high risk for StUD. Primary prevention of StUD is beyond the scope of this Guideline.

- Secondary prevention constitutes clinical practices to:
    - identify patients who use stimulants in nonmedical ways but do not meet diagnostic criteria for StUD, and
    - intervene to prevent escalation to StUD.
- Tertiary prevention constitutes clinical recommendations to reduce the harm associated with nonmedical stimulant use, regardless of the presence of a diagnosis of StUD.

Screening

For patients in general medical settings, screening for substance use, including stimulants, is an essential first step to identifying potential misuse (ie, nonmedical or nonprescribed use of substances) and conducting further assessment for risky stimulant use, StUD, and other conditions that may increase the risk of StUD (eg, ADHD, eating disorders). **Screening involves asking questions about an individual's substance use and related risks using validated screening instruments; screening does not involve drug testing.** The US Preventive Services Task Force (USPSTF) recommends screening for substance use, including stimulants, in primary care settings.[2]

There is limited evidence on the appropriate frequency of substance use screening in the general population. Evidence does exist that taking psychostimulants as prescribed does not increase the risk of developing StUD and that early and intense treatment of ADHD with psychostimulant medications may even have protective effects against development of StUD.[291,292] A positive screen can indicate the need for counseling or other interventions to prevent misuse of psychostimulant medications. Therefore, the CGC agreed that clinicians should consider more frequent screening for stimulant misuse in patients who take prescribed psychostimulant medications.

Finally, clinicians should check their state's PDMP prior to prescribing psychostimulant medications. While the evidence is weak, clinical experience suggests that the information gained by checking the PDMP can lead to large benefits in patient safety and indicate the need for patient education and/or treatment interventions.[293] The CGC cautioned that clinicians could misinterpret the PDMP and use it punitively, though the likelihood of this

can be reduced through education. The CGC noted the risk of misusing PDMP information would not preclude the benefit of initiating a conversation about a patient's prescriptions.

Screening Recommendations

74. When general healthcare providers screen adolescents or adults for risky substance use per USPSTF guidelines,[2] they should include screening for stimulant misuse (ie, nonmedical or nonprescribed use; *Very low certainty, Strong Recommendation)*.
75. Clinicians should consider more frequent screening for stimulant misuse in patients who take prescribed psychostimulant medications (*Very low certainty, Strong Recommendation)*.
76. Clinicians should check their state's PDMP prior to prescribing psychostimulant medications (*Moderate certainty, Strong Recommendation)*.

Please see the supplementary EtD document for the following related summaries of evidence, relevant citations, and CGC judgments:

- Table 47. Screening for Stimulants
- Table 48. Screening for Prescription Psychostimulants
- Table 49. Check Prescription Drug Monitoring Program

Assessment

Although the context is different, the medical workup of patients who misuse stimulants but do not meet the diagnostic criteria for StUD is similar to that for StUD. For patients who screen positive for stimulant misuse, clinicians should conduct a focused history and clinical exam to evaluate for complications of use related to route of administration and type of preparation used and provide treatment or referrals as appropriate.

Evidence suggests that certain patterns of use lead to more negative consequences.[294] In order to properly determine psychosocial and harm reduction service needs, clinicians should gather information about patterns of stimulant use, including frequency and amount of use, whether stimulants are used alone or with others, and whether other substances are used concurrently with stimulants. History of stimulant-related ED visits and hospitalizations, as well as history of overdose, should also be gathered. Finally, clinicians should inquire about routes of administration, particularly injection drug use. A variety of screening tools are available to screen for injection drug use.[295]

As evidence suggests that risky sexual behaviors are more prevalent in individuals who use stimulants, clinicians should gather information from the patient about their sexual

behaviors to properly determine psychosocial and harm reduction service needs.[174] These include:

- using drugs to enhance sexual experiences (ie, chemsex),[296]
- not using condoms or lubricants consistently,[297]
- having a history of bacterial STIs (ie, chlamydia, syphilis, gonorrhea) within the past six months,[298]
- being diagnosed with an STI within the past year,[297]
- belonging to a population that has a high STI prevalence,[299]
- having a partner(s) at high risk for STIs,[297]
- having a recent unintended pregnancy or a sexual partner having a recent unintended pregnancy,[298]
- having multiple sexual partners,[297]
- being the receptive penetrative partner (anal or vaginal) without protection,[174] and
- having a recent history of being a victim of sexual assault.[300]

The CGC emphasized that gathering detailed information to tailor harm reduction interventions (eg, PrEP, education) could have a large potential benefit. The CGC noted that screening for risky sexual behaviors interacts with factors such as interpersonal and intimate partner violence (IPV), trauma, race, sexual orientation, and gender. Subgroup population differences may influence the preferred intervention (eg, transgender, IPV or trauma history, patients and/or their partners who are HIV positive). While the possibility exists for patients to experience feelings of stigma or bias, this may depend on clinician expertise in interviewing. The possibility of confidentiality violations through medical record documentation exists, but the CGC deemed the likelihood of this happening low. The CGC concluded that the benefits of identifying individuals who would be helped by targeted harm reduction interventions outweighed the risks. A variety of validated screening tools are available to screen for risky sexual behaviors.

Clinicians should consider asking patients about the context of their stimulant use (eg, chemsex, weight loss, academic or work performance, staying awake), as well as history of trauma and IPV. While no direct evidence was found supporting this recommendation, contextualizing the reasons for patients' stimulant use can facilitate conversations around harm reduction. While implementation of this practice is straightforward, clinicians may require training on trauma-sensitive and culturally humble approaches to ask about the context of substance use in a nonjudgmental and destigmatizing manner.

Clinical experience suggests that patients who engage in nonmedical use of prescription stimulants are more likely to exhibit symptoms of ADHD and should be evaluated for ADHD. While it is unclear whether the underlying rate of undiagnosed ADHD is higher in people who misuse prescription stimulants in general, the CGC noted that this rate is higher in college students who use stimulants nonmedically.[301] The CGC emphasized that there is

currently debate within the field as to the utility of universal screening for ADHD; however, patients who exhibit symptoms of ADHD not accounted for by stimulant use should be further assessed by a qualified clinician.

Assessment Recommendations

77. For patients who screen positive for stimulant misuse:

a. Clinicians should conduct a focused history and clinical exam to evaluate complications of use related to route of administration and type of preparation used and provide treatment or referrals as appropriate (*Very low certainty, Strong Recommendation)*.

b. Clinicians should assess the following to determine harm reduction service and counseling needs:

   i. risky patterns of stimulant use, including:

      1. frequency and amount of use, including binge use (*High certainty, Strong Recommendation)*;
      2. use of stimulants with no one else present (*High certainty, Strong Recommendation)*;
      3. concurrent use of prescribed and nonprescribed medications and other substances, particularly opioids, alcohol, and other central nervous system depressants (*High certainty, Strong Recommendation)*;
      4. history of overdose (*High certainty*, Strong Recommendation); and
      5. history of stimulant-related ED visits and hospitalizations (*High certainty, Strong Recommendation)*;

   ii. routes of administration, particularly injection drug use (*Very low certainty, Strong Recommendation)*; and

   iii. risky sexual behaviors (*High certainty, Strong Recommendation)*.

c. Clinicians should consider asking patients about:

   i. the context of their stimulant use (eg, chemsex, weight loss, academic or work performance, staying awake; *Clinical consensus, Strong Recommendation)*,

   ii. trauma (*Clinical consensus, Strong Recommendation)*, and

   iii. IPV (*Clinical consensus, Strong Recommendation)*.

d. Clinicians should conduct baseline laboratory testing based on clinical assessment of risk factors (see Assessment; *Clinical consensus, Strong Recommendation)*.

78. Patients who engage in nonmedical use of prescription stimulants should be evaluated for ADHD, which may also require treatment (*Clinical consensus, Strong Recommendation)*.

Please see the supplementary EtD document for the following related summaries of evidence, relevant citations, and CGC judgments:

- Table 50. Assess Route Complications – Prevention
- Table 51. Assess Risky Patterns – Prevention
- Table 52. Assess Risky Sex – Prevention

Early Intervention for Risky Stimulant Use

Interventions to Reduce Risky Stimulant Use

Clinicians should consider providing brief interventions using MI techniques to patients with any risky stimulant use to encourage them to make changes that will reduce their risk of harm, including progressing to StUD. While no direct evidence exists to suggest that brief interventions are effective for stimulant use outcomes, it is a necessary first step to providing harm reduction education and treatment for stimulant use, which can reduce harms stemming from use and increase readiness to change and motivation for treatment. Clinicians should be aware of some of the unique motivators for stimulant use (eg, chemsex, weight loss, academic or work performance, staying awake) and be prepared to discuss and suggest safer alternatives and use practices—such as using clean snorting or injecting equipment, not sharing equipment, not using alone, and keeping opioid reversal medication (eg, naloxone) on hand—as part of brief interventions for stimulant use. The benefits of engaging patients in meaningful harm reduction practices are significant (see Harm Reduction).

Interventions to Reduce Risky Stimulant Use Recommendations

79. Clinicians should consider providing brief interventions to patients with any risky stimulant use using MI techniques to encourage patients to reduce or stop their use (*Very low certainty, Strong Recommendation)*.

80. Clinicians should be aware of some of the unique motivators of stimulant use and be prepared to discuss and suggest safer alternatives as part of brief interventions for stimulant use (eg, chemsex, weight loss, academic or work performance, staying awake; *Clinical consensus, Strong Recommendation)*.

Please see the supplementary EtD document for the following related summaries of evidence, relevant citations, and CGC judgments:

- Table 53. Early Intervention SBI

Referral to Treatment for Stimulant Use Disorder

While direct evidence for referral to treatment is relatively weak, the CGC judged the clinical benefits of facilitating treatment for those who need it to be substantial. Therefore, the CGC recommended that for patients who screen positive for risky stimulant use, clinicians should conduct or offer a referral for comprehensive assessment for potential StUD. When making referrals, linkage support—including warm handoffs—should be provided. For patients who are ambivalent about referrals for StUD assessment or treatment, clinicians should consider using interventions to enhance motivation for treatment (eg, MI, MET).

Peer navigators are increasingly being used to help patients access StUD assessment and treatment. While evidence for this intervention is limited, the CGC noted that the benefits of effective engagement in treatment are likely substantial and there is no evidence of harm.[302]

Referral to Treatment for Stimulant Use Disorder Recommendations

81. For patients who screen positive for risky stimulant use, clinicians should conduct or offer referrals for comprehensive assessment and treatment for potential StUD with linkage support, including warm handoffs (*Very low certainty, Strong Recommendation)*.
82. For patients who are ambivalent about referrals for StUD assessment or treatment, clinicians should consider using interventions to enhance motivation for treatment (eg, MI, MET; *Very low certainty, Strong Recommendation)*.
83. Clinicians should consider the use of peer navigators to link patients to StUD assessment and treatment (*Low certainty, Weak Recommendation)*.

Please see the supplementary EtD document for the following related summaries of evidence, relevant citations, and CGC judgments:

- Table 54. Early Intervention Refer to Treatment
- Table 55. Early Intervention Peer Navigation

Harm Reduction

According to the principles of harm reduction, clinicians can engage patients who use stimulants in treatment and prevention services, accounting for patients' desires and levels of interest, motivation, and engagement.

Harm Reduction Education

When education is paired with other harm reduction practices, evidence is strong for a variety of outcomes. The CGC emphasized that education is an important component of change and relatively easy to implement; the importance of patient education is readily supported across a range of other medical conditions. Therefore, clinicians should provide education to patients who use stimulants nonmedically, particularly with respect to safer stimulant use, injection practices, sexual practices, and overdose prevention.

Harm Reduction Education Recommendations

84. For patients who engage in risky stimulant use, clinicians should:

a. offer basic harm reduction education about safer stimulant use (*Low certainty, Strong Recommendation)*,

b. tailor harm reduction education to the patient's patterns of substance use (eg, context of use, route of administration, type of preparation; *Low certainty, Strong Recommendation)*,

c. refer to relevant local harm reduction services as indicated based on the patient's clinical assessment (*Low certainty, Strong Recommendation)*,

d. offer harm reduction education on overdose prevention and reversal (*High certainty, Strong Recommendation)*, and

e. offer harm reduction education regarding safer sexual practices (*High certainty, Strong Recommendation)*.

Please see the supplementary EtD document for the following related summaries of evidence, relevant citations, and CGC judgments:

- Table 56. Education Stimulants
- Table 57. Prevention Refer to Harm Reduction
- Table 58. Education Overdose
- Table 59. Education Sex

Overdose Prevention and Reversal

The US is currently experiencing an historic rise in drug overdoses and overdose deaths due to high-potency synthetic opioids.[303] These synthetic drugs, particularly fentanyl and its analogs, are increasingly used with stimulants.[10] Overdose reversal medications such as naloxone are well known to prevent opioid overdose deaths. To the extent that patients intentionally or unintentionally use opioids with stimulants, the CGC agreed that education on and access to overdose reversal medications are likely to be beneficial with relatively little risk. Therefore, for patients who use stimulants from nonmedical sources or engage socially with others who do, clinicians should prescribe or distribute overdose reversal medications (eg, naloxone) or refer patients to locations where they can obtain these medications in the community (eg, pharmacies). In March 2023, the FDA approved the first OTC naloxone nasal spray.[304]

Drug checking is becoming a standard harm reduction practice. Some evidence was found that people who use substances would use less if fentanyl was detected before use.[305,306] At least one study found that access to comprehensive drug checking services was associated with reduced overdose rates.[305,306] These findings varied by population studied (eg, festivals, people who inject drugs), and studies focused on opioid use, though people who use stimulants were not explicitly excluded.

When using drug checking kits, it is important that patients follow package instructions to avoid false negatives.[307] Patients should also understand that these tests have limitations; similar to point-of-care drug tests used in healthcare settings, these drug checking tests may not detect all potentially dangerous contaminants in the drug supply. For example, fentanyl test strips may not detect other highly potent synthetic opioids, including carfentanil.[308] Similar to presumptive drug testing, these test strips may also produce false positives that may limit patient reliance on the results.

Some harm reduction programs may provide more comprehensive drug checking services, including Fourier-transform infrared spectroscopy (FTIR), which can assess contaminants and verify the main component of the sample. While FTIR has high specificity, it has been shown to have lower sensitivity for detecting fentanyl compared to fentanyl test strips.[309] Fentanyl test strips and other drug checking supplies are prohibited in some states; clinicians should be aware of local laws when advising their use.[310]

While rare in the US, supervised consumption sites (SCS) are effective at reducing the incidence of drug use-related morbidity and mortality.[311] The impact of SCS varies depending on the their frequency of use. While SCS are associated with a small reduction in infections, they are associated with a moderate reduction in risky injection behaviors and a moderate to large increase in SUD treatment initiation.[311] Therefore, the CGC agreed that clinicians should consider referring individuals who use stimulants nonmedically to local

SCS when available. It is important to note that SCS are currently illegal under federal law.[312]

Overdose Prevention and Reversal Recommendations

85. For patients who use stimulants from nonmedical sources or are socially engaged with others who do, clinicians should prescribe or distribute overdose reversal medications (eg, naloxone) or refer patients to locations where they can obtain these medications in the community (*High certainty, Strong Recommendation)*.
86. Clinicians should recommend that patients perform comprehensive drug checking, including using fentanyl test strips, every time they obtain a new batch of stimulants from nonmedical sources and review the technique for using fentanyl test strips when permitted by state law (*Moderate certainty, Conditional Recommendation)*.
87. Clinicians should consider referring individuals to local SCS when available (*Moderate certainty, Strong Recommendation)*.

Please see the supplementary EtD document for the following related summaries of evidence, relevant citations, and CGC judgments:

- Table 60. Prevention Naloxone
- Table 61. Prevention Drug Checking
- Table 62. Prevention Supervised Consumption

Safer Sexual Practices and Contraception

While no specific evidence was found on referring or providing STI testing to people who use stimulants, it is known that risky sexual behaviors are more prevalent in this population, and earlier identification of STIs is beneficial and reduces transmission.[174] Therefore, the CGC recommended that clinicians offer or refer for STI testing at least every three to six months as per CDC and USPSTF guidelines. More frequent testing may be indicated depending on the individual patient's risk.

Clinicians can support harm reduction by educating patients about safer sexual practices (eg, using condoms and lubricant) or offering referrals to local programs that provide psychosocial sex education and harm reduction interventions. Clinicians should also inquire about contraceptive practices and related needs to help patients avoid unintended pregnancies. Further, if patients are engaging in compulsive sexual behaviors that cause them distress, they may benefit from referral to qualified treatment professionals.

Safer Sexual Practices and Contraception Recommendations

88. For patients who engage in risky sexual behaviors, clinicians should:

a. offer or refer for STI testing at least every 3 to 6 months or more frequently depending on the individual patient's risk (*Moderate certainty, Strong Recommendation)*;

i. consider providing information about local STI testing services where patients can obtain free or low-cost testing (*Moderate certainty, Strong Recommendation)*;

b. consider offering a referral to a local psychosocial sex education program or harm reduction program that addresses risky sexual behavior for additional or continuing harm reduction intervention (*Low certainty, Strong Recommendation)*; and

c. offer condoms and lubrication or advice about where to obtain them (*Clinical consensus, Strong Recommendation)*.

Please see the supplementary EtD document for the following related summaries of evidence, relevant citations, and CGC judgments:

- Table 57. Prevention Refer to Harm Reduction
- Table 63. Prevention Routine STI Testing

Injection Drug Use

SSPs are associated with safer injection technique; fewer wounds; and reductions in HIV, HCV, other blood-borne infections, and complicated infections.[313–317] Combining the provision of safe injection supplies with other interventions—such as linkage to treatment and addiction medications (eg, for co-occurring OUD)—can increase the magnitude of desirable effects. The CGC acknowledged that lack of community acceptance can be a barrier to implementing programs focused on safer injection practices; however, concern that provision of safer injection supplies increases injection drug use is refuted by evidence.[318] Therefore, the CGC recommended that clinicians provide or refer for harm reduction education on safer injection practices and safe injection supplies.

Harm reduction education related to injection drug use may include safer practices for preparing an injection, including using new supplies and clean surfaces, limiting overuse of acidifiers, and preventing injection site infections and vein damage—for example, see the Lancaster Harm Reduction Project's guide on *Safer Crack Injection*.[319,320]

Injection Drug Use Recommendations

89. For patients who inject stimulants, clinicians should:
    a. provide or refer for harm reduction education on safer injection practices and include information specific to the patient's stimulant(s) and preparation(s) of choice (eg, safer acid pairings for crack cocaine injection; *Low certainty, Strong Recommendation)*, and
    b. provide or refer for safe injection supplies and harm reduction services (*Moderate certainty, Strong Recommendation)*.

Please see the supplementary EtD document for the following related summaries of evidence, relevant citations, and CGC judgments:

- Table 64. Education Injection Drug Use
- Table 65. Prevention Injection Drug Use Kits

HIV Preexposure Prophylaxis

Strong evidence exists that PrEP is effective at preventing HIV overall, as well as consistently across subgroups with the highest risk for HIV.[321,322] While this is indirect evidence (ie, not explicitly tested in people who use stimulants), substantial benefits are expected. PrEP has not been shown to increase risky sexual or injection behaviors.[323] While PrEP is associated with some undesirable side effects, prevention of HIV is a critically important outcome. Therefore, in alignment with CDC and USPSTF guidelines, the CGC recommended that clinicians offer HIV PrEP to patients who use stimulants and are at increased risk for HIV due to risky sexual behaviors or injection drug use.[298,324]

HIV Preexposure Prophylaxis Recommendations

90. Clinicians should offer HIV PrEP to patients who use stimulants and are at increased risk for HIV, including those who:
    a. engage in risky sexual behaviors (*High certainty, Strong Recommendation)*,
    b. access postexposure prophylaxis (PEP) regularly (*High certainty, Strong Recommendation)*, and/or
    c. inject drugs (*High certainty, Strong Recommendation)*.

Please see the supplementary EtD document for the following related summary of evidence:

- Table 66. Prevention PrEP

Oral Health

People who use stimulants are well known to be at high risk of dental complications—such as poor dentition, dental caries, and abscesses—and poor oral health is associated with subsequent malnutrition.[325] Therefore, the CGC recommended that clinicians encourage patients who use stimulants to maintain good oral hygiene and receive regular dental care and offer referrals to dental care providers if needed. While this recommendation is straightforward, the CGC recognized challenges with regard to implementation; many insurance plans do not adequately cover dental care, and clinicians need to be aware of local resources to make referrals.

Oral Health Recommendations

91. People who use stimulants are at high risk of dental complications, such as poor dentition, dental caries, abscesses, and subsequent malnutrition. Clinicians should:
    a. encourage patients who use stimulants to maintain good oral hygiene and receive regular dental care (*High certainty, Strong Recommendation)*, and
    b. offer referrals to dental care providers if needed (*High certainty, Strong Recommendation)*.

Please see the supplementary EtD document for the following related summaries of evidence, relevant citations, and CGC judgments:

- Table 67. Prevention Oral Health

Nutrition

People who use stimulants often experience appetite suppression and go for long periods without appropriate nutrition, placing them at high risk for nutritional deficits such as malnutrition, cachexia, and sequalae of specific vitamin deficiencies.[326] Based on clinical expertise, the CGC recommended that clinicians inquire about diet, nutrition, and food security and encourage patients who use stimulants to eat nutritious food.

Nutrition Recommendations

92. People who use stimulants may experience appetite suppression and go for long periods without appropriate nutrition, placing them at high risk for nutritional deficits such as malnutrition, cachexia, and sequalae involving specific vitamin deficiencies. Clinicians should:

a. inquire about diet, nutrition, and food security (*Clinical consensus, Strong Recommendation)*; and

b. encourage patients who use stimulants to eat nutritious food (*Clinical consensus, Conditional Recommendation)*.

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Appendix A. Glossary of Terms

addiction: A treatable chronic medical disease involving complex interactions among brain circuits, genetics, the environment, and an individual's life experiences. People with addiction use substances or engage in behaviors that become compulsive and often continue despite harmful consequences. Prevention efforts and treatment approaches for addiction are generally as successful as those for other chronic diseases.

addiction medicine: A medical subspecialty concerned with the prevention, evaluation, diagnosis, treatment, and recovery of people with the disease of addiction and substance-related health conditions, as well as people who use substances—including nicotine, alcohol, prescription medications, and other licit and illicit drugs—in an unhealthy manner (see **addiction**, **substance use disorder**). Addiction medicine is recognized as a distinct medical subspecialty within preventive medicine by the American Board of Medical Specialties (ABMS; see **addiction specialist physician**).

addiction medication: Medications that are specifically indicated for and prescribed to treat substance use disorders (SUDs) as an initial lifesaving measure, motivational engagement strategy (ie, withdrawal management), and as part of a long-term treatment plan similar to medications used to treat other chronic diseases such as bipolar disorder or diabetes (see **substance use disorder**).

addiction psychiatry: A psychiatric subspecialty concerned with the evaluation and treatment of individuals with alcohol, drug, or other substance-related disorders and of individuals with co-occurring substance-related and other psychiatric disorders (see **addiction**, **substance use disorder**). Addiction psychiatry is recognized as a distinct medical subspecialty within psychiatry by the American Board of Medical Specialties (ABMS; see **addiction specialist physician**).[327]

addiction specialist physician: A licensed physician who has specialty board certification in addiction medicine or addiction psychiatry (see **addiction medicine**, **addiction psychiatry**).

adolescent: A person who is 12 to 17 years of age.

cultural humility: A process of entering a relationship with another person with the intention of honoring their beliefs, customs, and values. It entails an ongoing self-exploration and self-critique combined with a willingness to learn from others.[328] One component of trauma-sensitive practices (TSP; see **trauma-sensitive practices**).

drug testing: The process of analyzing a biological specimen to check for the presence of chemicals that indicate exposure to selected substances.

patient: An individual receiving substance use disorder treatment. Interchangeable with client, which is used more commonly in nonmedical settings.

psychosocial services (as treatment)**:** Interventions that seek to enhance a patient's social and mental functioning, including psychotherapy, counseling, contingency management (CM), psychoeducation, and mental health services.[329]

recovery: A process of change through which individuals improve their health and wellness, live a self-directed life, and strive to reach their full potential.[330]

recovery support services (RSS): The collection of services that provide emotional and practical support for continuing recovery, as well as daily structure and rewarding alternatives to substance use (see **recovery**).[331]

recurrence: A return of substance use disorder (SUD) symptoms, including substance use, after a period of remission from SUD (see **recovery**, **substance use disorder**).[329]

social determinants of health (SDOH): The conditions in the environments where people are born, live, learn, work, play, worship, and age that affect a wide range of health, functioning, and quality-of-life outcomes and risks.[332]

substance use disorder (SUD): A medical illness consisting of a cluster of cognitive, behavioral, and physiological symptoms caused by repeated misuse of a substance or substances. Characterized by clinically significant impairments in health, social function, and impaired control over substance use (see **addiction**).[331]

substance-induced disorders: Illnesses or conditions that are directly caused by substance use. Distinct from independently co-occurring mental disorders in that all or most of the psychiatric signs and symptoms are the direct result of substance use (see **substance use disorder**).[18]

telehealth: The use of electronic information and telecommunications technologies to support delivery of health care, health-related education, and other health-related services and functions, including but not limited to electronic health records, mobile applications, telemedicine, and web-based tools (see **telemedicine**).[333]

telemedicine: Services that utilize telecommunication platforms to perform direct (ie, synchronous) patient services when healthcare providers are located at a distance from patients (see **telehealth**).

toxicology testing: Also called toxicology screening, this term refers to the process of testing for the presence of toxins or poisons (see **drug testing**).

trauma-informed care (TIC): The process of engaging in trauma-based educational training, including gathering information on the various types of traumas, the physiological and emotional impact of surviving trauma, and healing modalities to prevent disruptive aftereffects.

trauma-responsive care (TRC): An ongoing process that furthers trauma-based education through information embodiment by asking treatment providers to understand and comprehend information through self-exploration, self-awareness, and reflective practices to develop a concrete understanding of their own emotional literacy and how this impacts the care that they provide. One component of trauma-sensitive practices (TSP; see **trauma-sensitive practices**).

trauma-sensitive practices (TSP): A system of care that facilitates opportunities that advance clinician knowledge, expand clinician attitudes, and offer therapeutic practices designed around each patient's unique culture, life experiences, and present circumstances. Comprised of trauma-informed care (TIC), trauma-specific care (TSC), trauma-responsive care (TRC), and cultural humility (see **cultural humility**, **trauma-informed care**, **trauma-responsive care**, **trauma-specific care**)

trauma-specific care (TSC): An ongoing process where treatment providers engage with trauma knowledge and information to impact, refine, and improve the ways in which healthcare services are provided to support better patient outcomes. One component of trauma-sensitive practices (TSP; see **trauma-sensitive practices**).

warm handoff: A care transition in which the referring clinician facilitates a direct (ie, face-to-face) introduction of the patient to the receiving clinician at their next level of care.

young adult: A person who is 18 to 25 years of age.

Appendix B. Abbreviations and Acronyms

AAAP	American Academy of Addiction Psychiatry
AACAP	American Academy of Child and Adolescent Psychiatry
AAFP	American Association of Family Physicians
AAP	American Academy of Pediatrics
ABMS	American Board of Medical Specialties
ACE	adverse childhood event
ACEP	American College of Emergency Physicians
ACLS	advanced cardiac life support
A-CRA	adolescent community reinforcement approach
ACS	acute coronary syndrome
ADHD	attention-deficit/hyperactivity disorder
AMA	American Medical Association
APA	American Psychiatric Association
ASAM	American Society of Addiction Medicine
ATS	amphetamine-type stimulant
ATTC	Addiction Technology Transfer Center Network
AUD	alcohol use disorder
BCR	blood urea nitrogen/creatinine ratio
BMI	body mass index
BUN	blood urea nitrogen
BZD	benzodiazepine
CBC	complete blood count
CBT	cognitive behavioral therapy
CBT4CBT	Computer Based Training for Cognitive Behavioral Therapy
CDC	US Centers for Disease Control and Prevention
CDC WONDER	US Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiological Research
CFR	US Code of Federal Regulations
CGC	Clinical Guideline Committee
CK	creatine kinase

CLIA	Clinical Laboratory Improvement Amendments of 1988
CM	contingency management
CMP	comprehensive metabolic panel
CMS	Centers for Medicare & Medicaid Services
COVID-19	coronavirus disease 2019
CPG	clinical practice guideline
CPK	creatine phosphokinase
CRA	community reinforcement approach
CSSA	Cocaine Selective Severity Assessment
C-SSRS	Columbia–Suicide Severity Rating Scale
CT	computed tomography
d-AMP	dextroamphetamine
DEA	US Drug Enforcement Administration
DSM	*Diagnostic and Statistical Manual of Mental Disorders*
DSM-5-TR	*Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition, Text Revision
EBI	evidence-based intervention
ECG	electrocardiogram
ED	emergency department
EEG	electroencephalogram
EtD	Evidence to Decision
FAVOR	Faces & Voices of Recovery
FDA	US Food and Drug Administration
FTIR	Fourier-transform infrared spectroscopy
GABA	gamma-aminobutyric acid
GABA-A	gamma-aminobutyric acid A
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HUD	US Department of Housing and Urban Development
ICD-10	*International Classification of Diseases*, 10th Revision

IM	intramuscular
IPV	intimate partner violence
IRETA	Institute for Research, Education and Training in Addictions
IV	intravenous
LDX	lisdexamfetamine
LFT	liver function test
MAS-ER	extended-release mixed amphetamine salts
MATCH	Matching Alcoholism Treatments to Client Heterogeneity
MDD	major depressive disorder
MDMA	3,4-methylenedioxymethamphetamine
MET	motivational enhancement therapy
MI	motivational interviewing
MI	myocardial infarction
MPH	methylphenidate
MSK	musculoskeletal
MSM	men who have sex with men
NAM	National Academy of Medicine
NIDA	National Institute on Drug Abuse
NMDA	N-methyl-D-aspartate
NMS	neuroleptic malignant syndrome
NSDUH	National Survey on Drug Use and Health
OCCS	Obsessive Compulsive Cocaine Scale
OIG	Office of the Inspector General
OROS	osmotic-controlled release oral delivery system
OTC	over-the-counter
OUD	opioid use disorder
PBO	phenobarbital
PDMP	prescription drug monitoring program
PEP	postexposure prophylaxis
PrEP	preexposure prophylaxis
Project BETA	Best Practices in the Evaluation and Treatment of Agitation
PSS	Poisoning Severity Score

PTSD	post-traumatic stress disorder
QIC	ASAM's Quality Improvement Council
RCT	randomized controlled trial
RoB 2	revised Cochrane Risk of Bias tool
ROBINS-I	Cochrane Risk of Bias in Non-randomized Studies – of Interventions tool
RSS	recovery support services
SAMHSA	Substance Abuse and Mental Health Services Administration
SBIRT	screening, brief intervention, and referral to treatment
SCS	supervised consumption sites
SDOH	social determinants of health
SGM	sexual and gender minorities
SSP	syringe service program
SSSA	Stimulant Selective Severity Assessment
STI	sexually transmitted infection
StUD	stimulant use disorder
SUD	substance use disorder
TB	tuberculosis
TBI	traumatic brain injury
TES	Therapeutic Education System
TIP	Treatment Improvement Protocol
TUD	tobacco use disorder
UNODC	United Nations Office on Drugs and Crime
USC	Code of Laws of the United States of America
USPSTF	US Preventive Services Task Force
VA	US Department of Veterans Affairs
WHO	World Health Organization
WIC	Special Supplemental Nutrition Program for Women, Infants, and Children
YPR	Young People in Recovery

Appendix C. Differential Diagnosis for Agitation and Psychosis

The differential diagnosis for agitation and psychosis is very broad. Comprehensive discussion of this topic is addressed well elsewhere. The following highlights common conditions to consider in the differential diagnosis of agitation or psychosis in patients with stimulant intoxication and is not meant to be an exhaustive list. ACEP's Project BETA provides a helpful and comprehensive resource.

Indications to perform head CT include:

- altered mental status;
- neurologic symptoms;
- signs of physical trauma (eg, TBI);
- found unconscious or comatose, which can be the result of trauma or stroke, including stimulant-induced stroke; and
- anoxic injury.

Indications to perform lumbar puncture and blood tests for encephalitis include:

- unexplained fever, and
- meningeal signs and symptoms (eg, stiff neck, photophobia, back pain).

Indications for EEG include:

- seizure not well explained,
- neurologic signs and symptoms not well explained, and
- persistent encephalopathy.

Additional causes of agitation and psychosis include (but are not limited to):

- nutritional deficiencies (eg, Wernicke encephalopathy),
- neurologic disorders (eg, Parkinson's disease, dementia),
- brain tumors,
- infections,
- endocrine dysfunction,
- thyroid toxicity (eg, thyrotoxicosis),
- hormonal abnormalities (eg, steroid-induced psychosis),
- autoimmune diseases,
- N-methyl-D-aspartate (NMDA) receptor encephalitis, and
- medication reactions that cause neuropsychiatric symptoms.

Appendix D. Disclosures of Interest

Clinical Guideline Committee Members

Clinical Guideline Committee Member	Employment	Consulting	Research	Investments and Proprietary Interests	Healthcare-Related Organizations	Advocacy/ Lobbying
Steven L. Baki, MD	Department of Veteran Affairs (Attending Physician); University of California San Francisco (Professor)	None	None	None	None	None
Dan Ciccarone, MD, MPH	University of California San Francisco (Professor)	Celero Systems (Scientific Advisory Board Member)**; Expert Witness**	None	None	Remedy Alliance (Medical Director)	None
Scott E. Hadland, MD, MPH, FASAM	Massachusetts General Hospital (Chief); Harvard Medical School (Associate Professor)	None	None	None	American Academy of Pediatrics (Education)*	None
Brian Hurley, MBA, FAPA, DFASAM	County of Los Angeles (Medical Director); Friends Research Institute (Senior Research Scientist); Cedar Sinai Health System (Contracted Psychiatrist); Private Practice	Centers for Care Innovation for the American Psychiatric Association (Consulting)	None	None	None	None
Kimberly Kabernagel, DO, FASAM	Geisinger Marworth (Medical Director)	None	None	None	None	None
Frances R. Levin, MD	New York State Psychiatric Institute (Psychiatrist)	Major League Baseball (Consultant)*	Indivior; US World Meds; SAMHSA; NCATS; NIDA	None	None	None
James McKay, PhD	University of Pennsylvania (Professor)	None	None	None	None	None

Clinical Guideline Committee Member	Employment	Consulting	Research	Investments and Proprietary Interests	Healthcare-Related Organizations	Advocacy/ Lobbying
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Siddarth Puri, MD	Los Angeles County Department of Public Health (Associate Medical Director)	Expert Witness**	None	None	None	None
Andrew J. Saxon, MD, FASAM	VA Puget Sound Health Care System (Director)	Expert Witness**	None	None	UpToDate Inc** (Section Editor)	None
Kevin A. Sevarino, MD, PhD, FASAM	Rushford-Hartford Hospital (Psychiatrist)	None	None	GlaxoSmithKline (Stockholder)*	UpToDate* (Section Author)	None
Kevin Simon, MD	Boston Children's Hospital (Pediatric Addiction Medicine Psychiatrist)	None	None	None	None	None
Timothy J. Wiegand, MD, FACMT, FAACT, DFASAM	University of Rochester Medical Center (Director, Program Director)	None	None	None	None	None

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ASAM Quality Improvement Council Members

Quality Improvement Council Member	Salary	Consulting	Research	Investments and Proprietary Interests	Healthcare-Related Organizations	Advocacy/ Lobbying
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Kenneth I. Freedman, MD, MS, MBA, FACP, AGAF, DFASAM	Aetna/CVS Health (Medical Director); The Recovery Research Network (Medical Director)	None	None	None	None	None
Michael P. Frost, MD, FACP, DFASAM	Wayspring (Chief Medical Officer); Frost Medical Group LLC (Owner)	None	None	Pocket Naloxone Corp (Shareholder)**	Accord Healthcare UK* (Training Fees)	None
R. Jeffrey Goldsmith, MD, DLFAPA, DFASAM	None	None	None	Merck and Co (Stockholder)*; Pfizer Inc (Stockholder)*; Amgen Inc (Stockholder)*; Gilead Sciences Inc (Stockholder)*	None	None
Margaret A. E. Jarvis, MD, DFASAM	Geisinger (Chief, Addiction Medicine Division)	Expert Witness**	None	None	American Board of Preventive Medicine (Exam Committee Member)	None
Navdeep Kang, PsyD, HSP	Acadia Healthcare (Chief Quality Officer)	Everest Health (Advisor)	None	Brightview Health/Shore Capital Partners (Equity Shareholder)**	Talbert House (Board Member)	None
Tiffany Y. Lu, MD, MS, FASAM	Montefiore Medical Center (Staff Physician); ModMed EHR System (Spouse/Medical Director)	None	None	None	None	None
Tami Mark, PhD, MBA	RTI International (Distinguished Fellow and Director of Behavioral Health Financing and Quality Measurement)	None	None	None	None	None

Quality Improvement Council Member	Salary	Consulting	Research	Investments and Proprietary Interests	Healthcare-Related Organizations	Advocacy/ Lobbying
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ASAM Board Members

ASAM Board Member	Salary	Consulting	Research	Investments and Proprietary Interests	Healthcare-Related Organizations	Advocacy/ Lobbying
Brian Hurley, MD, MBA, FAPA, DFASAM	County of Los Angeles (Medical Director); Friends Research Institute (Senior Research Scientist); Cedar Sinai Health System (Contracted Psychiatrist); Private Practice	Centers for Care Innovation for the American Psychiatric Association (Consulting)	None	None	None	None
Stephen M. Taylor, MD, MPH, DFAPA, DFASAM	Pathway Healthcare, LLC (Chief Medical Officer); National Basketball Association/National Basketball Players Association (Medical Director); Private Practice	Expert Witness	None	None	Medical Review Officer Certification Council (Board Member); Addiction Prevention Coalition (Board Member)	None
Aleksandra E. Zgierska, MD, PhD, DFASAM	Pennsylvania State University (Associate Director)	Pennsylvania Medicaid (Single-Time Advisor)*	National Institutes of Health/ National Institute on Drug Abuse*	None	American Academy of Pain Medicine* (Substance Use Disorder Shared Interest Group Co-Chair)	None
Anika Alvanzo, MD, MS, FACP, DFASAM	Uzima Consulting Group, LLC (Managing Partner); Pyramid Healthcare, Inc (Regional Medical Director)	Triple Track Treatment (Potential Consultant); Behavioral Administration, Maryland Department of Health (Consultant)*	None	None	None	None
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William F. Haning, III, MD, DLFAPA, DFASAM	None (retired)	None	None	None	None	None
Kelly S. Ramsey, MD, MPH, MA, FACP, DFASAM	Office of Addiction Services and Supports (OASAS)	None	None	None	New York Society of Addiction Medicine (Board Member)	None
Itai Danovitch, MD, MBA, DFAPA, DFASAM	Cedars-Sinai Medical Center	Expert Witness**	None	Workit Health (Shareholder)*; Science 37 (Shareholder)**; Bexson Biomedical (Receives Equity Options)*	Bexson Biomedical* (Board Member); California Mental Health Services (Commissioner)	None

ASAM Board Member	Salary	Consulting	Research	Investments and Proprietary Interests	Healthcare-Related Organizations	Advocacy/ Lobbying
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Megan Buresh, MD, DFASAM	Johns Hopkins School of Medicine (Assistant Professor); Behavioral Health Leadership Institute (Lead Physician)	None	National Institutes on Drug Abuse*	None	Association of Medical Education and Research in Substance Abuse (2023-2024 Conference Planning Co-Chair); American Journal of Medicine Open* (Associate Editor)	None
Emily Brunner, MD, DFASAM	Hazelden Betty Ford Foundation, Gateway Recovery Center	None	None	None	None	None
Christina E. Jones, MD, FASAM	Teleleaf, LLC (Provider)	None	None	None	None	None
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ASAM Board Member	Salary	Consulting	Research	Investments and Proprietary Interests	Healthcare-Related Organizations	Advocacy/ Lobbying
Surita Rao, MD, FASAM	University of Connecticut Medical School (Associate Professor)	None	None	None	None	None
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Kenneth I. Freedman, MD, MS, MBA, FACP, AGAF, DFASAM	Aetna/CVS Health (Medical Director); The Recovery Research Network (Medical Director)	None	None	None	None	None
Margaret A. E. Jarvis, MD, DFASAM	Geisinger (Chief of Addiction Medicine Division)	Expert Witness**	None	None	American Board of Preventive Medicine (Exam Committee Member)	None
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AAAP Executive Committee

AAAP Executive Committee	Salary	Consulting	Research	Investments and Proprietary Interests	Healthcare-Related Organizations	Advocacy/ Lobbying
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John Mariani, MD	Columbia University, New York State Psychiatric Institute (Directors of STARS)	None	None	None	None	None
Larissa Mooney, MD	University of California Los Angeles (Professor of Clinical Psychiatry)	Expert Witness	Aelis Farma	None	American Academy of Addiction Psychiatry (President)	None
Rebecca Payne, MD	University of South Carolina (Assistant professor of Neuropsychiatry and Behavioral Science)	None	None	None	None	None
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Carol Weiss, MD	Weill Cornel Medical College (Clinical Associate Professor of Psychiatry)	None	None	None	None	None

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Appendix E. Clinical Questions

This appendix presents the clinical questions posed for each topic as outlined in the supplementary EtD document. If a clinical question resulted in a recommendation based only on clinical consensus, there is no corresponding table in the EtD document.

Treatment of Stimulant Use Disorder

Assessment

1. Initial assessment:
    a. What components should be included in the initial assessment for patients presenting with StUD?
2. Comprehensive assessment:
    a. What components should be included in the comprehensive assessment for patients with StUD?
3. Baseline laboratory testing:
    a. Should baseline laboratory testing be conducted for all patients with StUD or based on clinical assessment of risk factors?
    b. What is the effect of conducting baseline laboratory testing when assessing patients with StUD?
    c. What contextual factors and implementation strategies may influence the effects of baseline laboratory testing?
    d. What are the most impactful and appropriate baseline laboratory tests to conduct when assessing patients who misuse use stimulants?
4. Cardiac evaluation:
    a. Should clinicians routinely request or refer patients for a cardiac evaluation or ECG?
        i. Patients with stimulant intoxication or withdrawal
        ii. Patients with StUD
    b. What is the effect of routine screening for cardiac disorders in patients with StUD?

   c. What contextual factors and implementation strategies may influence the effects of screening for cardiac disorders?
   d. Is there a subpopulation that would particularly benefit from routine ECG?
5. Renal evaluation:
   a. For patients diagnosed with stimulant intoxication or withdrawal, should clinicians routinely request or refer patients for an evaluation of renal function?
   b. For patients diagnosed with StUD, should clinicians routinely request or refer patients for an evaluation of renal function?
   c. Is there a subpopulation who would benefit from an evaluation of renal function?

Behavioral Treatment

1. Contingency Management (Table 1):
   a. Is CM an effective and appropriate treatment for StUD?
   b. Does the addition of another treatment to CM improve outcomes for StUD?
   c. What contextual factors and implementation strategies may influence the effects of CM?
2. Community Reinforcement Approach (Table 2):
   a. Is CRA (with or without background treatment) an effective and appropriate treatment for StUD?
   b. Is CRA more effective than other behavioral treatments for StUD?
   c. Does adding CM to CRA improve outcomes for StUD?
   d. What additional considerations and implementation strategies may influence the effects of CRA?
3. Cognitive Behavioral Therapy (Table 3):
   a. Is CBT (with or without background treatment) effective at reducing stimulant use and increasing treatment retention in patients in treatment for StUD?
   b. Is CBT more effective than other behavioral treatments for StUD?
   c. Does adding CM to CBT improve outcomes for StUD?
   d. What additional considerations and implementation strategies may influence the effects of CBT?

4. Matrix Model (Table 4):
    a. Is the Matrix Model an effective and appropriate treatment for StUD?
    b. Is the Matrix Model more effective than other behavioral treatments for StUD?
    c. Does adding CM to the Matrix Model improve outcomes for StUD?
    d. What additional considerations and implementation strategies may influence the effects of the Matrix Model?

Technology-Based Interventions

1. Computer-Delivered Treatment (Table 5):
    a. What is the effect of computer-delivered treatment for StUD?
    b. What contextual factors and implementation strategies may influence the effects of computer-delivered treatment?
2. Telehealth (Table 6):
    a. What is the effect of telehealth-delivered treatment for StUD?
    b. What contextual factors and implementation strategies may influence the effects of telehealth-delivered treatment?

Pharmacotherapy

1. Bupropion for Cocaine Use Disorder (Table 7):
    a. Is bupropion safe and effective at reducing stimulant use and increasing treatment retention in patients with cocaine use disorder?
2. Topiramate for Cocaine Use Disorder (Table 8):
    a. Is topiramate safe and effective at reducing stimulant use and increasing treatment retention in patients with cocaine use disorder?
3. Bupropion for Amphetamine-Type Stimulant Use Disorder (Table 9):
    a. Is bupropion safe and effective at reducing stimulant use and increasing treatment retention in patients with ATS use disorder?
4. Bupropion + Naltrexone for Amphetamine-Type Stimulant Use Disorder (Table 10):
    a. Is the combination pharmacotherapy of bupropion and naltrexone safe and effective at reducing stimulant use and increasing treatment retention in patients with ATS use disorder?

   b. What contextual factors and implementation strategies may influence the effects of bupropion + naltrexone?

5. Topiramate for Amphetamine-Type Stimulant Use Disorder (Table 11):
   a. Is topiramate safe and effective at reducing stimulant use and increasing treatment retention in patients with ATS use disorder?
6. Mirtazapine for Amphetamine-Type Stimulant Use Disorder (Table 12):
   a. Is mirtazapine a safe and effective treatment for ATS use disorder?
7. Modafinil for Cocaine Use Disorder (Table 13):
   a. Is modafinil a safe and effective treatment for patients with cocaine use disorder?
8. Topiramate + Extended-Release Mixed Amphetamine Salts for Cocaine Use Disorder (Table 14):
   a. Is the combination pharmacotherapy of topiramate and MAS-ER safe and effective treatment for patients with cocaine use disorder?
   b. What contextual factors and implementation strategies may influence the effects of topiramate + MAS-ER?
9. Psychostimulant Amphetamines for Cocaine Use Disorder (Table 15):
   a. Are long-acting amphetamine formulations of prescription psychostimulants safe and effective at reducing stimulant use and increasing treatment retention in patients with cocaine use disorder?
10. Psychostimulant Methylphenidate for Amphetamine-Type Stimulant Use Disorder (Table 16):
   a. Are long-acting MPH formulations or prescription psychostimulants safe and effective at reducing stimulant use and increasing treatment retention in patients with ATS use disorder?

Co-occurring Disorders

1. Integrated Care (Table 17):
   a. What are the most effective and appropriate behavioral interventions for the treatment of StUD in patients with co-occurring psychiatric disorders?
   b. What contextual factors and implementation strategies may influence the effects of behavioral interventions?

2. Psychosis (Table 18):
    a. Should clinicians use pharmacotherapy to treat psychosis or mania if it is unclear whether the condition is preexisting or stimulant-induced?
    b. What contextual factors and implementation strategies may influence the decision to use pharmacotherapy?
    c. What are the most effective and appropriate interventions for treating psychosis in patients with StUD?
3. Psychosis taper (Table 19):
    a. What is the optimal duration of antipsychotic treatment for persons who are presumed to be experiencing stimulant-induced psychosis or mania?
    b. What is the clinical effectiveness of different antipsychotic tapering strategies?
4. Other Symptoms (Table 20):
    a. Should clinicians use pharmacotherapy to treat depression, anxiety, insomnia, and/or attentional problems in patients with StUD if it is unclear whether the condition is preexisting or stimulant-induced?
    b. What contextual factors and implementation strategies may influence the decision to use pharmacotherapy?
    c. What are the most effective and appropriate pharmacotherapies for treating depression, anxiety, insomnia, and/or attentional problems in patients with StUD?
5. Preexisting diagnosis:
    a. Should patients change or discontinue treatment for a co-occurring disorder when initiating treatment for StUD?
    b. What contextual factors and implementation strategies may influence the decision to modify the existing treatment plan?
6. Attention-Deficit/Hyperactivity Disorder (Table 21):
    a. What are the most effective and appropriate interventions to treat ADHD in patients with StUD?
    b. Are stimulant medications safe and effective to treat ADHD in patients with StUD?
    c. What contextual factors and implementation strategies may influence the safety and effectiveness of ADHD treatment?

7. Prevention of prescription stimulant misuse:
    a. When prescribing stimulant medications to a patient with co-occurring StUD and ADHD, what implementation strategies may influence the effect and appropriateness of treatment?
8. Prevention of prescription stimulant misuse in adolescents and young adults:
    a. When prescribing stimulant medications to an adolescent or young adult patient with co-occurring StUD and ADHD, what implementation strategies may influence the effect and appropriateness of treatment?

Adolescents and Young Adults

1. Toxicology:
    a. What is the most effective and appropriate use of toxicology testing for the treatment of StUD, stimulant intoxication, and stimulant withdrawal in adolescent and young adult patients?
    b. What contextual factors and implementation strategies may influence the effects of toxicology testing?
2. Screening – other:
    a. What is the effect of screening for other co-occurring conditions when assessing adolescent and young adult patients for StUD?
        i. StUD outcomes
        ii. Other outcomes
    b. What contextual factors and implementation strategies may influence the effects of screening for other co-occurring conditions?
3. Specific support:
    a. Should adolescent patients be referred to adolescent-specific support services or are adult services effective and appropriate?
    b. Do young adult-specific social supports services exist?
    c. What contextual factors and implementation strategies may influence the effectiveness of a support service referral?
4. Contingency Management (Table 22):
    a. Is CM for patients with StUD as effective and appropriate for adolescents and young adults as it is for adults?

   b. What contextual factors and implementation strategies may influence the effects of CM for adolescents and young adults?
   c. What modifications should be made so that CM is delivered in a developmentally appropriate manner?

5. Other Psychotherapy (Table 23):
   a. What are the most effective and appropriate psychotherapy interventions for the treatment of StUD in adolescent and young adult patients?
   b. What contextual factors and implementation strategies may influence the effects of psychotherapy interventions?

6. Family Therapy (Table 24):
   a. Is family therapy effective in treating adolescents and young adults with StUD?
   b. What contextual factors and implementation strategies may influence the effects of family therapy?

7. Specific Treatment (Table 25):
   a. Are adolescent-specific behavioral treatment models (eg, A-CRA) effective and appropriate treatment for StUD in adolescents and young adults?
   b. Should adolescents be referred to adolescent-specific behavioral treatment models (eg, A-CRA) or are adult treatment models effective and appropriate?
   c. What modifications should be made so that behavioral treatment is delivered in a developmentally appropriate manner?

8. Group Treatment (Table 26):
   a. Are there modifications that should be made to behavioral treatment so that it is delivered in a developmentally appropriate manner to adolescent and young adult patients?
   b. Should adolescents and young adults who use stimulants be referred to adolescent- and young adult-specific group-based treatment or is adult group-based treatment as effective and appropriate?

9. Pharmacotherapy (Table 27):
   a. What are the most effective and appropriate pharmacotherapies for the treatment of StUD in adolescent and young adult patients?
   b. What contextual factors and implementation strategies may influence the effects of pharmacotherapy?

10. Home drug testing:
   a. What are the potential benefits and harms of home drug testing?

11. Family involvement:
    a. Are there modifications that should be made to behavioral treatment so that it is delivered in a developmentally appropriate manner to adolescent and young adult patients?
    b. Is family involvement in the treatment of StUD in adolescent and young adult patients effective and appropriate?
12. Minor consent:
    a. What considerations should be included regarding consent for treatment for minor patients?

Pregnant and Postpartum Patients

1. Prenatal Care Referral (Table 28):
    a. What additional considerations should clinicians have when evaluating StUD in persons who are pregnant?
    b. What additional considerations should be included when establishing a treatment plan for StUD in persons who are pregnant?
2. Screen Social Services – Pregnancy and Postpartum (Table 29):
    a. Are there additional social service needs that should be addressed when assessing persons who are pregnant or is the standard assessment for StUD appropriate and effective?
3. Screen Factors Pregnancy (Table 30):
    a. Are there additional health conditions that should be evaluated in persons who are pregnant or is the standard assessment for StUD appropriate and effective?
4. Toxicology – pregnancy and postpartum:
    a. Are there additional considerations when conducting toxicology testing in persons who are pregnant or are standard considerations for StUD appropriate and effective?
5. Pharmacotherapy – Pregnancy and Postpartum (Table 31):
    a. What additional considerations should be included when considering pharmacotherapy for StUD, stimulant intoxication, or stimulant withdrawal in persons who are pregnant or breastfeeding?
6. Psychosocial additions – pregnancy and postpartum:
    a. Are there additional treatment needs that should be addressed with pregnant patients or is standard treatment for StUD appropriate and effective?

7. Prenatal Care Incentives (Table 32):
    a. What are the most effective and appropriate interventions for increasing prenatal care access and attendance in patients being treated for StUD?
8. Postpartum Care (Table 33):
    a. Are there additional treatment needs for patients with StUD in the postpartum period? For patients with any level of stimulant use?
9. Breastfeeding (Table 34):
    a. Should patients with StUD breastfeed?
    b. When can a patient who uses stimulants safely breastfeed?
    c. Can clinicians increase the rate of safe breastfeeding in patients with a StUD? With any stimulant use?

Additional Population-Specific Considerations

1. Sexual and Gender Minoritized individuals (Table 35):
    a. What are the most effective and appropriate interventions for the treatment of StUD in SGM patients?
    b. Should SGM patients with StUD be referred to SGM-focused programs?
    c. What additional consideration should clinicians have when evaluating and treating StUD in SGM patients?
2. Disability:
    a. What are the most effective and appropriate interventions for the treatment of StUD in patients with disabilities?
    b. What additional considerations should clinicians have when evaluating and treating StUD in persons with disabilities?
3. Criminal/legal system:
    a. What are the most effective and appropriate interventions for the treatment of StUD in patients with criminal/legal system involvement?
    b. What additional considerations should clinicians have when evaluating and treating StUD in patients with criminal/legal system involvement?
4. Homelessness/unstable housing:
    a. What are the most effective and appropriate interventions for the treatment of StUD in patients with unstable housing or who are experiencing homelessness?

b. Should patients with unstable housing or who are experiencing homelessness be referred specialized StUD programs or is general StUD treatment effective and appropriate?

c. What additional considerations should clinicians have when evaluating and treating StUD in persons with unstable housing or who are experiencing homelessness?

Stimulant Intoxication and Withdrawal

Assessment and Diagnosis

1. Initial assessment – intoxication and withdrawal:
    a. For patients with suspected stimulant intoxication or withdrawal, should an initial assessment for acute issues and complications related to stimulant intoxication and withdrawal be part of routine assessment or only as needed?
    b. What is the appropriate medical workup when evaluating a patient with suspected stimulant intoxication or withdrawal?
2. Comprehensive assessment – intoxication and withdrawal:
    a. For patients with a diagnosis of stimulant intoxication or withdrawal, should comprehensive assessment for acute issues and complications related to stimulant intoxication and withdrawal be part of routine assessment or only as needed?
    b. What is the appropriate medical workup when evaluating a patient with stimulant intoxication or withdrawal?
    c. Should laboratory testing be ordered (or a referral for testing be provided) routinely or as needed according to clinical judgment and based on symptomatology and presence of risk factors?
3. Baseline laboratory testing – intoxication and withdrawal:
    a. Should laboratory testing be ordered (or a referral for testing be provided) for all patients with stimulant intoxication or withdrawal or based on clinical assessment of risk factors?
    b. What is the effect of conducting baseline laboratory testing when assessing patients?
    c. What contextual factors and implementation strategies may influence the effects of baseline laboratory testing?

   d. What are the most appropriate baseline laboratory tests to conduct when assessing patients who use stimulants?

4. Intoxication toxicology:
   a. For patients with suspected stimulant intoxication or withdrawal, should toxicology testing for stimulants be a routine part of diagnostics?
      i. Does this depend on the setting?
   b. If toxicology testing is done as needed, what are the indications?
5. Intoxication setting:
   a. In what setting should patients with stimulant intoxication and withdrawal be managed?
   b. Can suspected stimulant intoxication be managed safely in lower acuity clinical settings?
   c. Which patients with stimulant intoxication be managed safely in lower acuity clinical settings?

Managing Stimulant Intoxication and Withdrawal

1. Agitation–psychosis differential diagnosis:
2. What are indications of different or additional causes of agitation and psychosis?
3. Agitation–psychosis de-escalation:
4. What is the effectiveness of de-escalation techniques for managing stimulant-induced aggression, agitation, or toxic psychosis?
5. Agitation Medication (Table 36):
   a. What are the most effective and appropriate interventions for the treatment of agitation in patients experiencing stimulant intoxication?
   b. What contextual factors and implementation strategies may influence the effects of the intervention for agitation?
6. Psychosis Medication (Table 37):
   a. What are the most effective and appropriate interventions for the treatment of psychosis in patients experiencing stimulant intoxication?
   b. Should clinicians treat stimulant-induced psychotic symptoms with antipsychotics?
7. Agitation–psychosis evaluation:

   a. What are the indications for an immediate need for acute care management in a hospital or ED?

8. Agitation–psychosis transfer:
   a. What factors should be considered when determining whether to transfer a patient presenting with agitation or psychosis to a more intensive level of care?
9. Psychiatric monitoring:
   a. What are the most effective and appropriate strategies to monitor psychiatric symptoms when treating patients experiencing stimulant intoxication or withdrawal?
   b. For patients diagnosed with stimulant intoxication or withdrawal, should clinicians routinely assess for trauma-related problems or only as needed?
   c. What should the frequency of reassessment be during monitoring?
10. Hyperadrenergic monitoring: No clinical questions in the EtD document.
   a. What are the most effective and appropriate strategies to monitor hyperadrenergic signs and symptoms when treating patients experiencing stimulant intoxication or withdrawal?
   b. What should the frequency of reassessment be during monitoring?
11. Hyperadrenergic Medications (Table 38):
   a. What are the most effective and appropriate interventions for the treatment of hyperadrenergic symptoms that typically accompany stimulant intoxication?
12. Hyperadrenergic Adjunct (Table 39):
   a. What adjunctive treatments can be considered for managing hyperadrenergic symptoms that typically accompany stimulant intoxication?
13. Hypertensive Emergency (Table 40):
   a. What are effective interventions for hypertensive emergency accompanying stimulant intoxication?
14. Chest Pain Medication (Table 41):
   a. What are the most effective and appropriate interventions for the treatment of chest pain in patients experiencing stimulant intoxication?
15. Chest Pain Beta Blockers (Table 42):
   a. What is the effectiveness of beta blockers for managing the cardiac consequences of stimulant intoxication?
   b. Can beta blockers be used safely to treat chest pain in patients experiencing stimulant intoxication?

16. Chest Pain Evaluation (Table 43):
    a. Should the presence of stimulant intoxication impact the standard evaluation of chest pain?
17. QRS Widening (Table 44):
    a. What are the most effective and appropriate interventions for the treatment of QRS widening following cocaine use?
18. Seizure workup:
    a. Should a full neurological workup be ordered for all patients presenting to the ED with a seizure following stimulant use?
19. Seizure Medication (Table 45):
    a. What are the most effective and appropriate interventions for the treatment of seizure following stimulant use?
20. Screening, Brief Intervention, and Referral to Treatment (SBIRT; Table 46):
    a. How accurate are drug use screening instruments for risky stimulant use?
    b. Does screening for stimulant use reduce stimulant use or improve other risky behaviors?
    c. What are the harms of screening for risky stimulant use?
    d. Do brief counseling interventions to reduce stimulant use, with or without referral, reduce stimulant use or improve other risky behaviors in patients with a positive screen?
    e. What are the harms of brief interventions to reduce stimulant use in patients with a positive screen?

Secondary and Tertiary Prevention

Screening

1. Screening for Stimulants (Table 47):
    a. How accurate are drug use screening instruments for risky stimulant use?
    b. Does screening for stimulant use reduce stimulant use or improve other risky behaviors?
    c. What are the harms of screening for risky stimulant use?

2. Screening for Prescription Psychostimulants (Table 48):
    a. What additional considerations should be applied when screening for prescription psychostimulant misuse?
3. Check Prescription Drug Monitoring Program (Table 49):
    a. What are the benefits and harms of checking PDMPs for patients with StUD?

Assessment

1. Assessing Route Complications – Prevention (Table 50):
    a. What are effective strategies for assessing route of administration and related history of complications?
2. Assessing Risky Patterns – Prevention (Table 51):
    a. What are effective strategies for assessing risky patterns of stimulant use?
3. Assessing Risky Sex – Prevention (Table 52):
    a. What are effective strategies for assessing risky sexual behaviors in patients with SUD/StUD?
4. Assessing context of stimulant use – prevention:
    a. What are effective strategies for assessing the context of a patient's stimulant use?
5. Assessing trauma – prevention:
    a. What are effective strategies for assessing trauma in patients with SUD/StUD?
6. Assessing baseline laboratory testing – prevention:
    a. What are the most effective and appropriate baseline laboratory tests to conduct when assessing patients who misuse or use stimulants?
    b. What is the effect of conducting baseline laboratory testing when assessing patients who misuse stimulants?
        i. For StUD outcomes
        ii. For other outcomes
    c. Should baseline laboratory testing be conducted for all patients who misuse or use stimulants or based on clinical assessment of risk factors?
    d. What contextual factors and implementation strategies may influence the effects of baseline laboratory testing?

7. Assessing ADHD – prevention:
    a. Should all patients who misuse or use stimulants be assessed for ADHD?
    b. What factors should be considered when determining which patients to assess for ADHD?

Early Intervention for Risky Stimulant Use

1. Early Intervention – Screening and Brief Intervention (Table 53):
    a. Do brief counseling interventions to reduce stimulant use, with or without referral, reduce stimulant use or improve other risky behaviors in patients with a positive screen?
    b. What are the harms of brief interventions to reduce stimulant use in patients with a positive screen?
2. Early Intervention Refer to Treatment (Table 54):
    a. Does referral to treatment reduce stimulant use or improve risky behaviors in patients with a positive screen?
    b. What are effective strategies for referral to treatment for StUD?
3. Early Intervention Peer Navigation (Table 55):
    a. Does peer navigation improve referral for treatment in patients with a positive screen?

Harm Reduction

1. Education Stimulants (Table 56):
    a. What are effective educational strategies for reducing harms related to stimulant use or StUD-related behaviors?
2. Prevention – Refer to Harm Reduction (Table 57):
    a. Does referral for harm reduction services reduce harms related to stimulant use or StUD-related behaviors?
3. Education – Overdose (Table 58):
    a. What are effective strategies for preventing overdose in patients with StUD?
4. Education – Sex (Table 59):
    a. What are effective strategies for preventing risky sex-related harms in patients with StUD?

5. Prevention – Condoms:
    a. What are effective strategies for increasing condom use in patients with StUD?
6. Prevention – Routine Sexually Transmitted Infection Testing:
    a. How often should STI testing be conducted in patients with StUD and other StUD-related risk factors?
7. Prevention – Naloxone (Table 60):
    a. What are effective strategies for distributing naloxone to patients with StUD?
8. Prevention – Drug Checking (Table 61):
    a. Is drug checking an effective strategy for reducing harms related to StUD?
9. Prevention – Supervised Consumption (Table 62):
    a. Is referral to SCS effective for reducing harms related to StUD?
10. Prevention – Routine Sexually Transmitted Infection Testing (Table 63):
    a. How often should STI testing be conducted in patients with StUD and other StUD-related risk factors?
11. Education – Injection Drug Use (Table 64):
    a. What educational interventions are effective for reducing harms related to injection drug use?
12. Prevention – Injection Drug Use Kits (Table 65):
    a. Are injection drug use kits effective for reducing harms related to injection drug use?
13. Prevention – HIV Preexposure Prophylaxis (PrEP) (Table 66):
    a. What factors should be considered when determining the appropriateness of HIV PrEP for patients with StUD?
14. Prevention – Oral Health (Table 67):
    a. What interventions are effective for preventing oral health-related harms in patients with StUD?
15. Prevention – Nutrition:
    a. What interventions are effective for preventing nutrition-related harms in patients with StUD?

Appendix F. Topics with Insufficient or Negative Evidence

The following table presents interventions for which the evidence considered by the CGC was determined to be insufficient or not supportive.

Intervention Type	Intervention
Technology-based interventions	Text messaging interventions for StUD
Technology-based interventions	Noninvasive brain stimulation for StUD
Alternative interventions	Exercise as standalone or add-on treatment for StUD
Alternative interventions	Auricular acupuncture for ATS use disorder
Pharmacotherapy	Topiramate and mixed amphetamine salts for ATS use disorder
Pharmacotherapy	Bupropion and naltrexone for cocaine use disorder
Pharmacotherapy	Modafinil for ATS use disorder
Pharmacotherapy	Mirtazapine for cocaine use disorder
Pharmacotherapy	Disulfiram
Pharmacotherapy	Naltrexone
Pharmacotherapy	Naltrexone and N-acetylcysteine

ATS, amphetamine-type stimulants; StUD, stimulant use disorder

Appendix G. Additional Resources

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Appendix H. Substance Use Disorder Biopsychosocial Assessment

In developing this Guideline, the CGC sought to include recommendations that were specific to StUD or of increased importance in the treatment of this illness. However, it is important for clinicians to deliver the full standard of care that should be provided to any patient with SUD, including a full biopsychosocial assessment that evaluates:

- substance use-related risks (eg, risks associated with current patterns of substance use);
- social and environmental factors, including SDOH, that may impact access to or efficacy of care, such as housing, transportation, and childcare needs, among others;
- trauma-related concerns using trauma-sensitive screening practices;
- biomedical comorbidities;
- post-acute symptoms of withdrawal;
- psychiatric comorbidities and psychiatric disorder history;
- risk factors for infectious diseases, such as HIV and viral hepatitis (eg, HAV, HBV, HCV), including:
    - sexual practice history to screen for risky sexual behaviors in accordance with current guidance,
        - When taking a sexual history and addressing risk factors for STI, clinicians should pay particular attention to patient comfort, seek to maximize rapport, and be responsive to the patient's readiness to discuss their sexual practices.
    - injection drug use, and
    - sharing drug preparation supplies;
- co-occurring behavioral addictions and/or compulsions (eg, gambling disorder, internet use, gaming, sex);
- family and/or household substance use, SUDs, and psychiatric histories; and
- contraceptive practices and related needs.

Appendix I. Baseline Laboratory Testing

In developing this Guideline, the CGC sought to include recommendations that were specific to StUD or of increased importance in the treatment of this illness. However, it is important for clinicians to deliver the full standard of care that should be provided to any patient with SUD, including routinely ordering baseline laboratory testing for patients with a newly diagnosed SUD or psychiatric disorder.

In non-acute care settings, clinicians should order the following clinical tests for most patients:

- CBC,
- CMP (eg, renal panel, LFTs),
- screening for infectious diseases in accordance with current guidance,
- HIV and HCV for all patients,
- HBV for patients at increased risk for infection,
- screening for STIs (eg, gonorrhea, chlamydia, syphilis), and
- pregnancy testing for all patients with childbearing potential.

Clinicians can also consider ordering the following clinical tests:

- tuberculosis (TB) for patients at increased risk for infection;
- HAV for patients at increased risk for infection; and
- other clinical tests as necessary based on clinical assessment, such as CK if signs of rhabdomyolysis are present (eg, increased muscle tone/rigidity, elevated temperature).

Appendix J. Principles of Drug Testing During Withdrawal Management

This appendix outlines the major principles in ASAM's *Appropriate Use of Drug Testing in Clinical Addiction Medicine* consensus statement. For additional guidance, please refer to the full statement.

1. Drug testing can be used to help inform clinical decision-making for patients with SUD or at risk for substance withdrawal.
2. Drug testing can neither diagnose nor rule out SUD.
3. Drug test results should be used in combination with patient history, physical exam, and psychosocial assessment to determine the patient's care plan.
4. Drug testing can be an important supplement to patient self-report because patients may not be aware of the composition of the substances they have used.
5. Drug test selection should be individualized based on specific patients and clinical scenarios. Before choosing the type of test and matrix, the clinician should determine the questions they are seeking to answer and consider the benefits and limitations of each test and matrix (eg, urine, blood, saliva, hair). The methods used will impact interpretation of the results:
    a. Each matrix has advantages and disadvantages (eg, ease of collection, window of detection, susceptibility to tampering).
    b. Tests are designed to measure if specific substances have been used within particular windows of time.
    c. Selection of a drug testing panel should be based on the patient's self-reported use, prescribed medications, and substances commonly used in the geographic area and by the patient's peer group.
        i. Note that many drug test panels do not detect fentanyl and fentanyl analogs.
    d. It is important to understand the difference between presumptive drug tests, which are routinely used for point-of-care testing, versus definitive tests, which are used to confirm the results of presumptive tests and rule out false positives.
        i. Definitive testing is done by CLIA-certified laboratories.
6. Definitive testing should be used when the results inform clinical decisions with major clinical or nonclinical implications for the patient (eg, changes in medications or legal status).

7. Drug test results should be interpreted by a clinician whose scope of practice includes ordering drug tests and interpreting drug test results and who will consider the limitations of the specific test used.
8. Discrepancies between patient self-report and drug tests should be discussed with the patient.
9. Clinicians should keep drug test results confidential to the extent permitted by law.
10. Providers should be aware of the adverse legal and social consequences of detecting substance use via drug testing in pregnant patients. The patient should be made aware of local and state reporting requirements before drug tests are conducted.

Appendix K. Medication Dosing in Clinical Trials

This appendix presents a summary of dosing strategies used in the clinical trials reviewed, but is not intended as a dosing guide.

Table 1. Medication Dosing: Psychostimulant

Study	Drug	Dose	SUD
Modafinil			
Anderson et al, 2009[334]	Modafinil	200 mg or 400 mg/day	Cocaine
Anderson et al, 2012[335]	Modafinil	200 mg or 400 mg/day	Cocaine, ATS
Dackis et al, 2005[336]	Modafinil	400 mg/day	Cocaine
Dackis et al, 2012[337]	Modafinil	200 mg or 400 mg/day	Cocaine
Heinzerling, 2010[338]	Modafinil	400 mg/day	Cocaine, ATS
Kampman et al, 2015[339]	Modafinil	300 mg/day	Cocaine
Kampman, 2018[340]	Modafinil	300 mg/day	Cocaine
Kampman, 2020[341]	Modafinil	400 mg/day	Cocaine
Karila et al, 2016[342]	Modafinil	200–400 mg/day	Cocaine
Morgan et al, 2010[343]	Modafinil	200–400 mg/day	Cocaine
Morgan et al, 2016[344]	Modafinil	100–400 mg/day	Cocaine
Schmitz et al, 2012[345]	Modafinil	400 mg/day	Cocaine
Schmitz et al, 2014[346]	Modafinil	200 mg BID	Cocaine
Shearer et al, 2009[347]	Modafinil	Max 200 mg/day	ATS
Topiramate			

Study	Drug	Dose	SUD
Levin et al, 2020[137]	Topiramate + MAS-ER	Topiramate max 100 mg BID + MAS-ER max 60 mg/day	Cocaine
Mariani et al, 2012[348]	Topiramate + MAS-ER	Topiramate max 150 mg BID + MAS-ER max 60 mg/day	Cocaine
MAS-ER			
Levin et al, 2015[349]	MAS-ER	60 or 80 mg/day	Cocaine
Dextroamphetamine/Lisdexamfetamine			
Charnaud and Griffiths, 1998[350]	Dextroamphetamine (d-AMP)	Individualized	ATS
Galloway et al, 2011[351]	Dextroamphetamine (d-AMP-SR)	30 mg BID	ATS
Grabowski et al, 2001[352]	Dextroamphetamine (d-AMP-SR)	Max 60 mg/day	Cocaine
Grabowski et al, 2004[353]	Dextroamphetamine (d-AMP-SR)	Max 60 mg/day	Cocaine
Longo et al, 2010[354]	Dextroamphetamine (d-AMP-SR)	Max 110 mg/day	ATS
Merrill et al, 2005[355]	Dextroamphetamine (d-AMP)	Max 100 mg/day	ATS
Mooney et al, 2015[356]	Lisdexamfetamine (LDX)	70 mg/day	Cocaine
Nuijten et al, 2016[357]	Dexamphetamine (d-AMP-SR)	60 mg/day	Cocaine
Schmitz et al, 2012[345]	Dextroamphetamine (d-AMP-SR) + modafinil	d-AMP-SR 15 mg BID + modafinil 200 mg/day	Cocaine
Shearer et al, 2001[358]	Dexamphetamine (d-AMP)	Max 60 mg/day	ATS
Shearer et al, 2003[359]	Dexamphetamine (d-AMP-SR)	Max 60 mg/day	Cocaine
White, 2000[360]	Dexamphetamine (d-AMP)	Max 90 mg/day	ATS
White et al, 2006[361]	Dexamphetamine (d-AMP)	30–60 mg/day	ATS
Selegiline transdermal system patch			
Elkashef et al, 2006[362]	Selegiline transdermal system patch	Continuous release 6 mg/24h	Cocaine

Study	Drug	Dose	SUD
Methylphenidate			
Dürsteler-MacFarland et al, 2013[363]	Methylphenidate	30 mg BID	Cocaine
Grabowski et al, 1994[364]	Methylphenidate	20–25 mg BID	Cocaine
Grabowski et al, 1997[365]	Methylphenidate SR	Max 45 mg/day	Cocaine
Konstenius et al, 2010[366]	Methylphenidate ER	18–72 mg/day	ATS
Konstenius et al, 2014[367]	Methylphenidate ER	Max 180 mg/day	Cocaine, ATS
Levin et al, 2006[368]	Methylphenidate SR	20–40 mg BID	Cocaine
Levin et al, 2007[369]	Methylphenidate SR	20–40 mg BID	Cocaine
Ling et al, 2014[370]	Methylphenidate SR	54 mg/day	ATS
Miles et al, 2013[371]	Methylphenidate ER	54 mg/day	ATS
Minařík et al, 2016[372]	Methylphenidate short acting	Mean 37.6 mg/day	ATS
Rezaei et al, 2015[373]	Methylphenidate SR	54 mg/day	ATS
Schubiner et al, 2002[374]	Methylphenidate	30 mg TID	Cocaine
Solhi et al, 2014[375]	Methylphenidate	Max 10 mg/day	ATS
Tiihonen et al, 2007[376]	Methylphenidate SR	54 mg/day	ATS
Mazindol			
Stine et al, 1995[377]	Mazindol	2 mg/day	Cocaine
Margolin et al, 1995[378]	Mazindol	1 mg/day	Cocaine
Margolin et al, 1997[379]	Mazindol	1 or 8 mg/day	Cocaine
Perry et al, 2005[380]	Mazindol	2 mg TID	Cocaine
Oral methamphetamine			
Mooney et al, 2009[381]	Oral methamphetamine	Immediate release 5 mg six times daily SR 30 mg/day	Cocaine

ATS, amphetamine-type stimulant; BID, two times per day; d-AMP, dextroamphetamine; d-AMP-SR, sustained-release dextroamphetamine; ER, extended release; LDX, lisdexamfetamine; MAS-ER, extended-release mixed amphetamine salts; SR, sustained release; TID, three times per day

Table 2. Medication Dosing: Non-Psychostimulant

Study	Drug	Dose	SUD
Bupropion			
Anderson et al., 2015[382]	Bupropion SR	150 mg bid	Methamphetamine
Das et al., 2010[383]	Bupropion XL	300 mg	Methamphetamine
Elkashef et al., 2008[384]	Bupropion SR	150 mg bid	Methamphetamine
Heinzerling et al., 2014[385]	Bupropion SR	150 mg bid	Methamphetamine
Margolin et al., 1995[386]	Bupropion HCL	100 mg bid or tid	Cocaine/ Opioid
McCann and Li 2012[387]	Bupropion SR	150 mg bid	Methamphetamine
Poling et al., 2006[107]	Bupropion hydrochloride SR	300 mg/d	Cocaine/ Opioid
Shoptaw et al., 2008[108]	Bupropion hydrochloride	150 mg bid	Cocaine
Shoptaw et al., 2008[388]	Bupropion SR	150 mg bid	Methamphetamine
Winhusen et al., 2014[389]	Bupropion hydrochloride XL+ Nicotine inhaler	300 mg/d 6-16 cartridges/d (ad libitum)	Cocaine/ Methamphetamine
Bupropion and Naltrexone			
Mooney et al., 2016[120]	Bupropion (ER) and Naltrexone (ER, injectable)	450 mg/d and 380 mg (Once/month)	Methamphetamine
Trivedi et al., 2021[121]	Bupropion (ER) and Naltrexone (ER, injectable)	450 mg/d and 380 mg (every 3 weeks)	Methamphetamine
Mirtazapine			
Coffin et al., 2020[126]	Mirtazapine	30 mg/d	Methamphetamine
Colfax et al., 2011[127]	Mirtazapine	30 mg/d	Methamphetamine
Cruickshank et al., 2008[390]	Mirtazapine	30 mg/d	Methamphetamine

Kongsakon et al., 2005[391]	Mirtazapine	15-60 mg/d	Amphetamine
McGregor et al., 2008[289]	Mirtazapine	60 mg/d	Methamphetamine
Topiramate			
Baldacara et al., 2016[392]	Topiramate	200 mg/d	Cocaine
Elkashef et al., 2012[123]	Topiramate	200 mg/d	Methamphetamine
Johnson et al., 2013[393]	Topiramate	100-150 mg bid	Cocaine
Kampman et al., 2004[394]	Topiramate	200 mg/d	Cocaine
Kampman et al., 2013[395]	Topiramate	150 mg bid	Cocaine/ Alcohol
Nuijten et al., 2014[396]	Topiramate	200 mg/d	Cocaine
Rezaei et al, 2016[397]	Topiramate	200 mg/d	Methamphetamine
Umbricht et al., 2014[398]	Topiramate	150 mg bid	Cocaine/ Opioid

Bid, twice a day; ER, extended-release; SR, sustained release; tid, three times a day; XL extended-release

Appendix L. Acute Issues and Complications of Stimulant Intoxication and Withdrawal

Acute issues and complications of stimulant intoxication and withdrawal include but are not limited to:

- electrolyte and fluid imbalances (eg, dehydration, acidosis, hyperkalemia, hyponatremia);
- hyperthermia;
- agitation;
- psychosis;
- cardiovascular dysfunction such as cardiac arrhythmias, hypertensive emergency, acute decompensated heart failure, and takotsubo cardiomyopathy;
- acute neurologic complications such as seizures and cerebrovascular accidents;
- serious infections such as infective endocarditis, osteomyelitis, epidural abscesses, septic arthritis, serious skin infections, bacteremia, and sepsis;
- rhabdomyolysis;
- movement disorders;
- gastrointestinal perforation;
- trauma and trauma-related complications; and
- risk for harm to self or others.

Appendix M. Non-acute Issues and Complications of Stimulant Use

Patients with stimulant intoxication should be routinely assessed for complications and sequalae of stimulant use and factors that impact treatment planning. Assess or refer for an assessment of these relevant conditions and issues and treat or refer for treatment in an appropriate medical or psychiatric setting when these conditions and issues are identified. Non-acute issues and complications of stimulant use include but are not limited to:

- general complications, including weight change (eg, body mass index [BMI]) and deficits in hygiene;
- cardiovascular complications, such as hypertension, arrhythmia, ischemia, pulmonary hypertension, and heart failure;
- dental complications, such as poor dentition, dental caries, and abscesses;
- dermatologic complications, such as picking, neurodermatitis, cellulitis, abscesses, and other skin or soft tissue infections;
- hepatic complications, such as drug-induced hepatitis;
- infectious complications, including STIs (eg, HIV, HCV);
- neurologic complications, such as involuntary movement disorders, rigidity, tremor, seizures, stroke, and cognitive impairment (eg, deficits in memory and/or attention);
- nutritional deficits, such as malnutrition, cachexia, and sequalae involving specific vitamin deficiencies;
- oropharyngeal complications, such as teeth grinding and jaw clenching, earache, headache, and facial pain;
- renal complications, such as acute kidney injury and chronic kidney disease;
- rhinologic complications such as rhinitis, mucosal atrophy, rhinorrhea, anosmia, oronasal fistula, and septum perforation; and
- sexual dysfunction (use trauma-sensitive screening practices).

Appendix N. Medications for Managing Intoxication

The information in this table is intended to guide management of stimulant intoxication in a variety of settings. The choice of medication, medication dosing (including initial and redosing), and route of administration should be guided by the patient's signs and symptoms, degree of intoxication, the level of care, and the resources of the setting. This does not represent a comprehensive list but rather provides illustrative examples of medications discussed in the narrative.

Agent/Class	Mechanism	Example dosing	Indications	Other considerations
Sedatives				
Benzodiazepines (BZDs) (first line)	GABAergic	Initial dosing: Lorazepam 1–2 mg IV based on clinical signs and symptoms and duration of effects Diazepam 5–10 mg PO for less severe symptoms based on patient parameters Midazolam 5 mg IM or 0.01-0.05 mg/kg IV for acute agitation in adult patients Redosing frequency and dose should be guided by the degree and duration of the clinical effects of the initial dose	Excitatory symptoms Anxiety/Agitation Neuromuscular excitation Seizures	Parenteral vs. PO administration based on signs and symptom severity and drug availability (eg, parenteral BZD shortages). IM administration allows for administration in agitated patients without IV access. Lorazepam has very slow IM onset (15–30 min) Midazolam has very rapid IV onset, allowing for easy titration, and a relatively fast IM onset If psychosis is primary symptom, antipsychotics should be considered primarily or adjunctively

Agent/Class	Mechanism	Example dosing	Indications	Other considerations
Phenobarbital (PBO)	GABAergic	Incremental 130–260 mg parenteral/IV/PO based on symptoms and patient parameters Loading strategy (eg, 5-10 mg/kg) Titrate based on clinical effects	BZD shortages or contraindications Patient not responding to escalating doses of BZDs Severe sympathomimetic intoxication	High oral bioavailability; PO dosing can be similar to parenteral dosing Onset of effects, while slower than IV, is still fairly quick compared to other PO medications
Propofol	GABAergic + NMDA receptor antagonism	10–50 µg/kg/min based on symptoms and patient parameters	For critically ill patients in the ICU Severe sympathomimetic intoxication not responding to other agents	Patients can be administered BZDs, PBO, and/or propofol concomitantly Intubation is almost always required for propofol administration
Sympatholytics				
Clonidine	Alpha-2 agonism +/- other	0.1–0.2 mg PO every 4 hours as needed	Anxiety	Useful medication adjunct to BZDs Maintain hydration to avoid orthostatic symptoms
Dexmedetomidine	Alpha-2 agonism	Start at 0.2–0.4 µg/kg/hr and titrate every 30 min up to maximum of 1.5 µg/kg/hr	For critically ill patients in the ED or ICU as primary or secondary medication for sedation	Useful medication adjunct to BZDs or other sedation agents Onset of effects generally 30–60 min Sedation without impairments in ventilation
Antipsychotics				
Butyrophenones (2nd gen)	Dopamine antagonism	Haloperidol or droperidol 5 mg IM	Acute agitation with psychosis Agitation not responding to BZDs Toxic psychosis	Consider atypical or newer generation antipsychotics as alternatives Consider risk of QT prolongation

Agent/Class	Mechanism	Example dosing	Indications	Other considerations
Atypical	Dopamine antagonism +/- other	Olanzapine 5 mg PO Quetiapine 50–100 mg PO at night	Anxiety or agitation with psychotic features Stimulant-induced psychosis Stimulant-induced sleep derangements	Consider risk of QT prolongation For olanzapine, degree of symptoms to balance need for PO vs. IM
Other				
Ketamine	NMDA receptor antagonism	1–5 mg/kg IM depending on degree of agitation	For severe agitation as primary or secondary agent	Rapid IM onset of action compared to other agents

BZD, benzodiazepine; ED, emergency department; ICU, intensive care unit; IM, intramuscular; IV, intravenous; NMDA, N-methyl-D-aspartate; PBO, phenobarbital; PO, *per os* (by mouth/oral)