The ASAM/AAAP Clinical Practice Guideline on the Management of Stimulant Use Disorder

DRAFT for Public Comment

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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 prevention and treatment of stimulant use disorders (StUD), stimulant intoxication, and stimulant withdrawal. 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 been rising precipitously over the past decade.[1] Between 2012 and 2021, the rate of overdose deaths involving cocaine more than tripled from 1.4 (per 100k) in 2012 to 7.3 in 2021; increasing on average by 21% per year.[1] Over the same time period deaths involving methamphetamine, amphetamine and prescription stimulants increased from 0.8 (per 100k) in 2012 to 10.0 in 2021.[1]

While rates of cocaine use have been relatively flat, rates of cocaine use disorders, methamphetamine use, and methamphetamine use disorder are rising.[2–5] In addition there has been a large increase in the risk from use due to the increasing potency of illicit stimulants and increasing use in combination with opioids, which can increase toxicity.[6] An increasing number of people with opioid use disorder (OUD) are using stimulants intentionally.[7] Others may be unaware that the stimulants they use are contaminated with fentanyl.[8]

In 2021, 50 percent of all overdose deaths in the US involved stimulants*; 23 percent involved cocaine and 30 percent involved psychostimulants (primarily methamphetamine). Beyond the mortality risk, StUD can also lead to long term health problems including cardiac, pulmonary, psychiatric, dental, nutritional, skin, and cognitive issues.[9] Further, injection stimulant use puts people at risk for infectious diseases including HIV and viral hepatitis.[9]

The DEA's most recent National Drug Threat Assessment reports stable or rising availability and potency, and low prices for cocaine and methamphetamine which are expected to exacerbate these trends.[6] To address this urgent issue, ASAM and AAAP

* Stimulants ICD-10 codes (T40.5 & T43.6) in CDC WONDER

convened a committee of experts to jointly develop a clinical practice guideline (CPG) for the prevention and treatment of StUD.

Scope of Guideline

The 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 for screening for risky stimulant use and secondary prevention of StUD. With a few exceptions, recommendations that address general practice for all substance use disorders (SUDs) are not included.

Intended Audience

The intended audience of this guideline includes clinicians, including behavioral health professionals, physicians, nurse practitioners, physician assistants, nurses, and pharmacists who provide treatment for stimulant intoxication, withdrawal, or StUD in specialty addiction treatment settings as well as non-specialty settings including primary care offices and hospitals. 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 involve consideration of 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 Section) 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, as outlined, are followed. 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 an active party to shared decision making whenever feasible. ASAM and AAAP recognize that there are challenges to implementation of these guidelines

in certain settings, particularly in relation to the availability of contingency management and community reinforcement approaches in various communities and settings. However, this guideline aims to set the standard for best clinical practice, 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, improvement in quality of care should be the goal. 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). The CGC 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. Members were selected to represent a diverse spectrum of clinical practitioners who manage StUD patients. One member resigned prior to completion of the consensus process, leaving 13 total members of the CGC.

Nine subcommittees were formed on topics determined by the QIC: Intoxication & Withdrawal, Behavioral Treatment, Pharmacotherapy, Co-Occurring Conditions, Adolescents and Young Adults, Pregnant and Postpartum Patients, Secondary and Tertiary Prevention, Technology-Based Interventions, and Health Disparities. 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 GRADE evidence profiles, recommendation development, and drafting of the Guideline document.

A patient panel of seven was convened with help from Faces and Voices of Recovery and Young People in Recovery 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.

All QIC, Board, and CGC members, and external reviewers of the document are required to disclose all current relevant relationships with industry and other entities which may represent an actual, potential, or perceived conflict of interest.

GRADE Methodology

The Guideline was developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Evidence to Decision (EtD) framework for producing recommendations in health care.[10] GRADE provides a systematic, transparent approach to developing recommendations based on scientific evidence and the clinical judgment of experts. The GRADE process encompasses a systematic review of clinical evidence and its quality, review of existing guidelines, expert committee consensus, stakeholder comment and reconciliation, and document development.

Literature Review

A systematic literature review was conducted to support the development of **GRADE Evidence Profiles** used as part of the guideline 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 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 also primary research published since the writing of high-quality systematic reviews. The third stage of the literature review used targeted literature searches to identify research on key questions identified by the QIC. These searches were limited to a ten-year period.

Titles and abstracts, as well as 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 the 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 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 PsychInfo literature databases on June 1, 2021. All text fields were searched, and the search was limited to articles published about humans in the prior 10

years 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 search for original research on topics for which high quality reviews were not available and to capture literature released after the publication of high-quality systematic reviews was conducted in PubMed and PsychInfo on August 11, 2021. Primary literature searches used a title, abstract, and keyword field search. For each combination of search terms where a high-quality systematic review was found, the date was limited to one year prior to the review's publication date up to the date of the search. All clinical study designs with random and nonrandom assignment were included, but case studies were excluded. If an article reflected a secondary analysis of data from a relevant study, the original report was also included in the literature review.

Gray Literature Search

An internet search for gray literature was conducted during June 2021, targeting published and unpublished clinical guidelines related to management of StUD. The search followed the suggested Institute of Medicine process for searching gray literature.[11] The search was not limited by publication date, however where the recommending bodies had published updates of a guideline, only the most recent version was included.

Literature Extraction

Meta-analysis, systematic review, and individual study methods were extracted by one member of the research team. The quality of the systematic reviews, meta-analyses, 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,[12] the revised RoB 2 Cochrane tool for randomized trials,[13] and the ROBINS-I Cochrane tool for non-randomized trials.[14] 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 GDC was not individually appraised due to time constraints. Research results were summarized in a narrative literature review.

Recommendations made in existing guidelines were extracted in **Existing Recommendation** tables. Recommendations made in some non-systematic reviews

identified in the literature search but excluded on publication type were also extracted when other existing recommendations could not be found and at the request of the CGC.

Guideline Development

Ideally, a clinical practice guideline is based on scientific evidence which is translated into practical recommendations that can be used 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**: the balance of benefits and harms of the intervention in question, the certainty of evidence about the benefits and harms, the values and preferences of the populations affected by the guideline, and the acceptability and feasibility of implementing the recommendation.[10] Other criteria can also be considered such as the costs 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 also 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 which may make the recommendation conditional (depending on patient values, resource availability, or setting), discretionary (based on opinion of patient or practitioner), or qualified (by an explanation regarding the issues which would lead to different decisions).

Strong recommendations support actions in which benefits clearly outweigh harms, or vice versa, and for which patients have clear and consistent values or preferences. They generally apply to most patients in most circumstances. Strong recommendations are generally 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.

Moderate or conditional recommendations are often based on evidence that is of lower certainty, shows benefits more closely balanced with harms, or shows variability in patient preferences. They may apply to many but not most patients. Their 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. There are many areas of addiction treatment in which the evidence base is still accumulating, but the urgency and severity of addiction-related issues demand that clinicians act even in the face of imperfect empirical evidence. Recommendations based solely on clinical judgement and clinical experience are clearly indicated and their rationale explained.

Rating Outcomes

Health care 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 the options. The literature review generated a list of outcomes measured in clinical research on StUD-related interventions. The CGC and the patient panel independently rated outcomes to prioritize in terms of their importance to clinical decision making or patient values via an online survey. Importance was indicated on a 1-9 scale, with an average below 4 indicating limited importance, 4-6 as important but not critical, and >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 quality—or strength—of the body of evidence (i.e., compiled across evidence types) for each intervention and outcome pair was rated by one member of the research team as high, moderate, or low based on consideration of several 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 possibility of publication bias.

Developing Evidence to Decision Tables

Following the GRADE framework, the CGC used **Evidence-to-Decision (EtD)** tables to document the evidence and decisions made while drafting, deliberating, and finalizing the recommendations. EtD tables ensure transparency around judgements that result from interpretation of the evidence, considerations made for different subpopulations, and decisions about how judgments on different recommendation criteria actually bear on the proposed recommendation. Where there was a lack of evidence, they also identify how the

decision to rely on clinical expertise was made and the clinical perspective and assumptions used to inform judgements in those areas.

One subcommittee 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 elements considered. Judgments were reviewed and discussed in subcommittee meetings and edited 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 research staff.

Summary of findings tables and EtD tables are available for download at the following link: https://bit.ly/41MqrwV.

Developing Recommendation Statements

The recommendation statements were informed by the literature review, EtD tables, and the clinical experience of the CGC members. This was an iterative process where recommendations were drafted by CGC subcommittees, and a review and discussion of the Evidence Profile and clinical considerations might lead the CGC to revise the recommendation.

When evidence was deemed inadequate to accurately assess the net benefit of an intervention overall or in particular patient or intervention subgroups, the CGC addressed this in a section of the guideline dedicated to inconclusive areas of evidence (See Appendix F). Topics addressed include patients with multiple comorbid conditions, differences by sex or race, patients at higher or lower risk for the condition, variation in patient preferences, or treatment burden. In a few cases, the CGC identified key research priorities to address important uncertainties in relation to the recommendations.

Consensus Process

The CGC voted to approve or not 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 recommendation was discussed in a CGC full committee virtual meeting. The recommendation could then be approved by voice vote; revised and approved by voice vote; returned to the subcommittee for additional work (often to revise the supporting EtD table); or dropped.

Rating Strength of Recommendations

The CGC voted on the strength of each accepted recommendation as strong, moderate, or low on the basis of 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 1-3 scale, and the average was used as the overall strength measure, with <1.66 indicating weak, 1.66-2.33 indicating moderate or conditional, and >2.33 indicating strong.

Developing Guideline Document

The guideline document includes the recommendations approved by the CGC committee, each with its recommendation strength rating and evidence quality assessment. Each recommendation will also be accompanied by a narrative describing the rationale for the recommendation, highlighting evidence and clinical considerations. It may also describe the deliberations of the CGC to further inform readers about factors that led to specific recommendation statements.

The narrative also discusses how the Guideline and its recommendations for StUD fits into the management of SUD in general. Rather than duplicate recommendations made in already existing high-quality general SUD guidelines, the CGC attempted to keep the scope of the Guideline narrowly focused on StUD and how clinical practice differs 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 practice for SUD" are discussed in the narrative, but any declarative statements made in the course of this discussion are not considered recommendations within this document. Individuals seeking specific guidance on these topics should seek out additional resources. A list of related guidelines and other resources referenced in this Guideline are listed in Appendix H.

Stakeholder Review

The Guideline draft will be sent out for public comment. ASAM and AAAP invite major stakeholder organizations, relevant committees, the patient panel, and their respective Boards to provide comments. An opportunity to provide comments will also be sent to all ASAM and AAAP members, and will be made public on ASAM and AAAP's websites.

ASAM and AAAP staff will collate all of the recommendations and the CGC will be convened to analyze the feedback and identify issues that need to be addressed before finalization and publication. Major edits will be subject to a vote by the CGC.

Recommendations for the Treatment of Stimulant Use Disorder

Assessment

StUD is primarily diagnosed based on the history provided by the patient and a comprehensive assessment which may include collection of information from collateral sources such as family or friends (when available and with patient consent).

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. Subsequent workup (ordering indicated clinical testing and/or imaging) should be based on the history and exam findings.

Initial Assessment

When assessing patients for StUD, the first clinical priority should be to identify and make appropriate referrals for any urgent or emergent medical or psychiatric issues that may be present. Identifying urgent or emergent medical or psychiatric problems is needed to preserve the health and safety of patients who present for StUD treatment. If the patient is exhibiting signs of acute intoxication or overdose, those issues need to be immediately addressed.

Initial Assessment Recommendations

1. When assessing patients for StUD, the first clinical priority should be to identify and make appropriate referral for any urgent or emergent medical or psychiatric problem(s), including acute intoxication or overdose. (Approve 100%, Strong 63%)

Please see the following evidence to decision table(s) on pages 6-7 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- Initial Assessment

Comprehensive Assessment

After first addressing any urgent medical or psychiatric problems, patients should receive a comprehensive assessment, including diagnostic assessment, StUD focused history and physical examination, a mental status examination, and a full biopsychosocial assessment.

Assessment for StUD should be based on accepted criteria such as the current Diagnostic and Statistical Manual of Mental Disorders (DSM-5-TR). A StUD focused history and physical examination should include a detailed history of past and current substance use and SUDs, and an assessment of non-acute issues and complications of stimulant use. A mental status exam should identify complications such as psychosis, cognitive impairments, and risk of harm to self or others. The committee emphasized that patients who are using stimulants for the purposes of weight loss (except when prescribed for this purpose) should be assessed, or referred for an assessment, for the presence of an eating disorder. Finally, a full biopsychosocial assessment of patients with StUD (or a provisional diagnosis of StUD) is critical for identifying the broad range of biomedical, psychiatric, and psychosocial challenges that may need to be addressed as part of providing effective, comprehensive care.

While comprehensive assessment of the patient is critical for treatment planning, completion of all assessments should not delay or preclude initiating treatment for critical needs (e.g., toxicity, psychosis, suicidality). A comprehensive assessment may be completed over a period of time and may involve multiple clinicians (e.g., social workers/counselors) as well as physicians.

As part of a comprehensive assessment for StUD, clinicians should conduct routine baseline lab work. While no research was identified on ordering routine or as-needed laboratory testing in patients presenting for StUD treatment, the higher prevalence of human immunodeficiency virus (HIV), viral hepatitis, and sexually transmitted infections (STIs) in patients with StUD justifies obtaining baseline testing in patients who receive StUD treatment. While there is no direct evidence regarding non-infectious disease screening labs (e.g., CBC, CMP), these labs can help identify comorbidities as part of a comprehensive assessment. In addition to baseline labs, the committee recommends that the Hepatitis A vaccine be offered for patients at increased risk for infection (e.g., patients who inject drugs) and who are not already immune, and that the Hepatitis B vaccine be offered to all patients who are not already immune.

As with any SUD-focused assessment, toxicology testing could be considered in the comprehensive assessment for StUD. The committee noted limitations inherent in toxicology testing, but agreed testing could be utilized when the outcome would impact clinical decision making or when it is important for medication monitoring or psychiatric follow up. Clinicians should consider the technical limitations of the matrix and drug panel that is selected. If stimulant use is suspected but presumptive testing is negative, clinicians should consider either confirmatory testing for a strongly suspected substance or the possibility of novel or designer psychoactive stimulants. The committee noted that tests for these novel stimulants are often expensive and have limited availability. For additional information on toxicology testing, see ASAM's *Appropriate Use of Drug Testing in Clinical Addiction Medicine*[15] guidance document.

The committee agreed that clinicians should have an elevated degree of suspicion for cardiac disease when evaluating patients with long-term and/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 committee 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 and/or heavy stimulant use. Consider ordering relevant tests (e.g., creatine kinase (CK) for rhabdomyolysis; blood urea nitrogen (BUN)/creatinine ratio (BCR), urine albumin for renal disease) at a lower threshold of suspicion, based on patient history and physical exam findings. When testing is indicated, if the patient is stable, shows no signs or symptoms of dehydration, is able to take fluids, and shows no other signs of acute renal failure, testing can be delayed until the acute effects of stimulant intoxication or withdrawal have resolved. Further research should examine if routine testing leads to benefits for this population.

If problems are identified during the assessment, clinicians should treat OR refer the patient to an appropriate medical or psychiatric provider or setting for treatment. If signs and symptoms of infection are identified, clinicians should provide treatment or referrals as appropriate (e.g., STI clinic, HIV clinic, etc.). Referrals for harm reduction services (e.g., syringe services programs) should also be considered, Clinicians should work with patients to develop strategies to address barriers to accessing care identified during the assessment (e.g., childcare or transportation support, telehealth, etc.).

Comprehensive Assessment Recommendations

1. After first addressing any urgent medical or psychiatric problem(s), patients should be comprehensively assessed, including:
    a. Assessment for StUD based on diagnostic criteria (e.g., current Diagnostic Statistical Manual) (Approve 100%, Strong 44%)
    b. A StUD focused history and physical examination (Approve 100%, Strong 67%)
    c. A mental status exam to identify psychiatric co-morbidities and complications, such as: psychosis, attention deficit hyperactivity disorder (ADHD), mood disorders, cognitive deficits, risk of harm to self or others. (Approve 100%, Strong 56%)
    d. A full biopsychosocial assessment. (Approve 100%, Strong 44%)

2. Clinicians should conduct routine baseline lab work (see Appendix C). (Approve 100%, Strong 45%)
    a. Clinicians should conduct other clinical tests as necessary based on clinical assessment findings. (Approve 100%, Conditional 57%)
3. When evaluating patients with long-term or heavy stimulant use, clinicians should have:
    a. An elevated degree of suspicion for cardiac disorders. (Approve 100%, Conditional 44%)
    b. A lower threshold for considering ECG testing based on findings of the history and physical exam. (Approve 100%, Conditional 33%)
    c. A lower threshold for considering creatine kinase (CK) testing for rhabdomyolysis based on findings of the history and physical exam. (Approve 100%, Strong 44%)
    d. An elevated degree of suspicion for renal disorders. (Approve 100%, Conditional 56%)

Please see the following evidence to decision table(s) on pages 8-23 on the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- Comprehensive Assessment
- Baseline Labs
- Cardiac Evaluation
- Renal Evaluation

Behavioral Treatment

Contingency Management (CM)

Contingency management (CM) is an evidence-based psychosocial intervention in which patients are given tangible rewards to reinforce positive behaviors such as treatment participation or abstinence. There is strong evidence that CM is an effective intervention for increasing treatment engagement and reducing stimulant use. The CGC understands that there are barriers to implementing contingency management including the financial costs, regulatory barriers, and ambivalence regarding the underlying strategy. However, CM has the best effectiveness in the treatment of StUDs compared to any other intervention studied and represents the current standard of care. While CM alone seems to perform as well as CM combined with other behavioral treatment, patients with higher or more complex therapeutic needs are likely to benefit from additional behavioral intervention.

The committee noted that resistance to the use of CM for the treatment of SUD has been rapidly declining as information about its effectiveness is more broadly disseminated;

However, resistance remains among some stakeholders. There is anecdotal evidence that acceptance of CM in the treatment field is lower than expected, although available research does not address this issue directly. The committee agreed that they would expect CM to be acceptable to key stakeholders, especially when presented with evidence of its effectiveness.

With respect to implementation, effective operation of CM requires several components to be available, including funding, training, capacity to obtain point of care toxicology testing, and typically at least twice weekly clinical engagement. The committee emphasized that clinically effective monetary value for the contingency rewards are necessary, although this may be limited by regulations and/or payer policies.

Community Reinforcement Approach (CRA):

Community Reinforcement Approach (CRA) is a comprehensive behavioral therapy that is based on operant conditioning theory. 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.[16]

Moderate evidence exists that 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. CRA combined with CM appears to be effective for stimulant abstinence and treatment completion. The committee concluded that there are apparent benefits associated with CRA, and no known undesirable effects.

For cocaine use disorder the certainty of the evidence is modest given that CRA did not outperform other treatments in all studies. The quality of the evidence favoring CRA is high given that it comes from well conducted, randomized, clinical trials.

The committee emphasized that no evidence was found for using CRA in patients who use amphetamine type stimulants (ATS) or methamphetamine. While all the evidence reviewed was based on participants with cocaine use disorder, the committee agreed that there is no reason to believe that CRA would not be as effective with patients who use ATS as it is with patients who use cocaine.

While CRA seems to be one of the more promising behavioral interventions for StUD, there are substantial barriers to the implementation of CRA. CRA has not been widely implemented outside of research settings. It requires a great deal of resources and patient commitment relative to other behavioral interventions. Few settings have the workforce appropriately trained to deliver CRA, and few experts are available to train clinicians in the delivery of CRA. CRA is also costly and labor intensive; funding and staff levels would have to be increased to implement it adequately.

Cognitive Behavioral Therapy (CBT):

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 in order to alter unwanted behavior patterns or treat SUD and mental health disorders.[17] Some evidence supports that CBT is 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. However, CBT has not been found to be superior to usual treatment options for longest duration of continuous stimulant abstinence or stimulant use at the study endpoint.

CBT is a widely utilized and accepted treatment modality. CBT does require resources, given that the availability of highly trained clinicians is needed for CBT to be properly delivered. On the other hand, the fact that CBT can be delivered in group sessions makes it more feasible for many programs compared to other behavioral interventions.

The CGC suggests using an evidence-based CBT manual such as, Project MATCH, NIDA CBT (Carroll), or VA CBT-SUD Manual. Additionally, clinicians should be trained in CBT delivery to ensure fidelity.

Matrix Model:

The Matrix Model is a structured, multi-component behavioral therapy delivered over 16 weeks that incorporates individual counseling, CBT groups, family education groups, social support groups, and encouragement for mutual support group participation.[18] Moderate evidence supports the use of the Matrix Model for treatment of StUD. Studies have demonstrated that the Matrix Model produced greater reductions in methamphetamine use compared to TAU or a wait list control group.[19–21] The Matrix model also reduced craving and risky behavior compared to a waitlist control.[22]

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 implementing. As with any new intervention, staff training is an important consideration.

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

Behavioral Treatment Recommendations

1. Contingency management (CM) should be a primary component of the treatment plan in conjunction with other psychosocial treatments for StUD. (Approve 100%, Strong 55%)
2. The following three interventions have the most supportive evidence and are preferred alongside contingency management:
    a. Community Reinforcement Approach (CRA) (Approve 100%, Conditional 56%)
    b. Cognitive Behavioral Therapy (CBT) (Approve 100%, Strong 44%)
    c. Matrix Model CBT (Approve 100%, Conditional 56%)

Please see the following evidence to decision table(s) on pages 24-155 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- Contingency Management
- Community Reinforcement Approach
- Cognitive Behavioral Therapy
- Matrix Model

Technology-Based Interventions

A number of computer-based interventions have been developed to treat StUD. A small meta-analysis found no effect across 4 computer-based interventions on stimulant use including three web-based CBT applications (Snow Control developed to treat CUD, Breakingtheice developed to treat ATS use disorder, and CBT4CBT developed to treat SUD) and the therapeutic education system (TES) an interactive web-based program based on CRA. TES, rebranded ReSET®, is an FDA approved prescription digital therapeutic for the treatment of SUD that is available via smartphone application (through prescription only),

A few individual studies of particular technology-based interventions reported reduced substance use, particularly in patients who use cocaine. The literature revealed less evidence of efficacy for amphetamine and methamphetamine use.

CBT4CBT and TES appear to improve stimulant use outcomes during treatment or at the end of treatment when added to other behavioral interventions. However, these effects are no longer evident at post-treatment follow-ups. These interventions may be similarly effective to clinician delivered CBT/treatment, however there is less evidence for this. One study suggested the positive effect of TES was greater in those with a drug positive urine test at baseline. While evidence is strongest for cocaine use, the committee has no reason to believe it would be significantly different for ATS use.

The CGC expressed concern over the use of technology delivered interventions as standalone interventions. While one study was found, which found positive effects for CBT4CBT as a standalone treatment, this is insufficient evidence to recommend it as a standalone treatment. 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 thoughts or behavior. These interventions will also be difficult to access for patients who do not have access to a computer and internet access, and/or who have low computer literacy, disproportionately impacting patients with lower socioeconomic status. Finally, the CGC noted that text messaging interventions for StUD are promising as add-on interventions, but there is insufficient evidence to recommend them at this time.

The current evidence for the use of telemedicine in the treatment of StUD primarily involves telephone-based (audio only) interventions, often provided after some amount of in person care. The evidence for telephone-based follow up care of individuals with cocaine use disorder is mixed, with some positive and some negative studies. There was one RCT of a mixed population of patients with cocaine and methamphetamine use disorder that found positive effects on reduced drug use, suggesting telemedicine is also effective for methamphetamine use disorder. The research base regarding telemedicine is expected to expand rapidly as a result of increased use during and following the COVID-19 pandemic.

While video-based telemedicine has not been studied in this population, the CGC noted there is no reason to think that it would not perform similarly to audio only telemedicine. There may be acceptability issues due to patients being uncomfortable appearing on camera. On the other hand, with the patient on camera, the clinician would be better able to detect signs of substance use and/or distress.

Technology-Based Interventions Recommendations

1. Clinicians can offer 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. (Approve 100%, Strong 50%)
2. Clinicians should consider using telehealth to deliver behavioral treatment for StUD to patients who may have challenges accessing in-person care. (Approve 100%, Strong 54%)

Please see the following evidence to decision table(s) on pages 156-179 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- Computer-Delivered Treatment
- Telehealth

Continuing Care

Patients with StUD who have not achieved their treatment goals during the initial phase of treatment may benefit from extended treatment with an evidence-based intervention to facilitate long-term recovery. CM should be provided to support continuing care for patients with StUD as they transition through the phases of treatment. Patients with StUD who have not made good progress in achieving the goals of an initial phase of treatment may benefit from extended treatment with evidence-based interventions to facilitate long-term recovery. Clinicians can consider the use of telehealth to deliver continuing care.

Pharmacotherapy

There are no FDA approved pharmacotherapies for the treatment of StUD. The sections below discuss considerations for when pharmacotherapies may be prescribed off-label. The committee recognized the reluctance of some clinicians to prescribe medications off label, but agreed that certain medications may be helpful for some patients with StUD, particularly in the context of certain co-occurring disorders.

Unlike other sections, the Pharmacotherapy recommendations are separated by substance type (e.g., Cocaine Use Disorder and Amphetamine-Type StUD). Cocaine and ATS have different mechanisms of action as well as different cultural, psychological, and behavioral concomitants. Cocaine and ATS both increase dopamine signaling in the brain.[23] Cocaine blocks the reuptake of dopamine while methamphetamine both increases dopamine release and blocks its reuptake, resulting in much higher concentrations.[23] In addition, methamphetamine has a significantly longer half-life than cocaine (12 hours vs 1 hour), leading to a more prolonged effects.[23]

The recommendations below discuss both psychostimulant and non-stimulant medications. The CGC emphasized the importance of careful and ongoing risk/benefit assessment and close monitoring when prescribing medications for StUD. Clinicians should regularly monitor patient symptoms and functional status in response to all medication treatments with increased medication monitoring when using medications with higher risk profiles, such as psychostimulants. Clinicians should monitor medication adherence and non-medical use, through use of the PDMP, drug testing, pill counts, and/or other available strategies.

In patients with a history of psychosis (substance-induced or pre-existing), clinicians should not treat StUD with modafinil or psychostimulant medications. When prescribing controlled medication, clinicians should regularly monitor patients for medication adherence and non-medical use, through use of the Prescription Drug Monitoring Program (PDMP), drug testing, etc.

Cocaine Use Disorder

Bupropion

Bupropion is a dual dopamine and norepinephrine reuptake inhibitor that is FDA approved for the treatment of major depressive disorder, seasonal affective disorder, and smoking cessation.[24] 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 found to be superior to placebo on sustained (3+ week) abstinence in two RCTs.[25,26]

Although both desirable and undesirable effects are small, the committee concluded that the potential benefits of bupropion outweigh the potential risks. Especially in the context of the lack of strongly supported medication alternatives, the committee agreed that bupropion for cocaine use disorder treatment.

Bupropion has been shown to reduce tobacco use in patients who smoke cigarettes or use other tobacco products. Therefore, the committee agreed that bupropion could be given additional consideration for patients with co-occurring tobacco use.

A generic formulation is available and is commonly available on medication formularies, and it is relatively easy to titrate dosing. Bupropion should be avoided in individuals with history of seizure or eating disorders and used with caution in individuals with elevated seizure risk.

Bupropion Recommendations

1. For patients with cocaine use disorder, clinicians may consider prescribing bupropion to promote cocaine abstinence. (Approve 82%, Weak 56%/Conditional 22%)
    a. Clinicians can give bupropion additional consideration for patients with a co-occurring tobacco use disorder as it can also reduce tobacco use. (Approve 100%, Conditional 44%)
    b. Clinicians can give bupropion additional consideration for patients with co-occurring depression as this medication can also treat depression.

Please see the following evidence to decision table(s) on pages 180-185 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- Bupropion for Cocaine Use Disorder

Modafinil[27]

Modafinil is a wakefulness-promoting medication used in the treatment of narcolepsy, obstructive sleep apnea, and shift work sleep disorder. The exact mechanism of action of Modafinil is unclear, although 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 gamma-aminobutyric acid (GABA).

There is mixed evidence for 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.[28,29] Notably, many of the studies included in the meta-analyses reported low medication adherence rates. Modafinil has shown particular efficacy in certain subpopulations, including those without comorbid alcohol use disorder and those with high adherence to treatment. The committee also agreed that modafinil may be particularly beneficial for patients with higher frequency of cocaine use at the start of treatment.

Modafinil is generally well tolerated. There were no significant differences in the rate of serious or other adverse events in 2 meta-analyses. The committee noted that modafinil inhibits metabolism of hormonal contraceptives and can reduce the effectiveness of this type of birth control. Women with childbearing potential should be counseled to use an alternative birth control method.

Modafinil Recommendations

1. For patients with cocaine use disorder and without a co-occurring alcohol use disorder, clinicians can consider prescribing modafinil to reduce cocaine use and improve treatment retention. (Approve 82%, Conditional 44%)

Please see the following evidence to decision table(s) on pages 186-197 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- Modafinil for Cocaine Use Disorder

Topiramate

Topiramate is an anticonvulsant medication, FDA approved for the treatment of epilepsy and migraine. It is known to have several molecular actions including blocking voltage-dependent sodium channels, increasing GABA-A activity antagonizing some glutamate receptor subtypes, and inhibiting carbonic anhydrase.[30,31] The evidence for topiramate on cocaine use disorder

outcomes is mixed. A meta-analysis demonstrated a higher rate of continuous stimulant abstinence over three weeks with topiramate versus placebo.[32] While the committee judged that the evidence only somewhat favors topiramate, the committee concluded that this medication might be considered for patients with cocaine use disorder, especially those who are motivated to achieve abstinence.

The desirable effects of topiramate are somewhat offset by known side effects (cognitive effects and paresthesia), and variable tolerability of the medication. Tolerability can be improved by slow titration. In addition, topiramate can cause appetite suppression; this is an important consideration when treating patients who are at risk of malnourishment or underweight.

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

While potential effects are small, the committee did agree that topiramate could be considered to reduce use of cocaine, as well as alcohol consumption.

Topiramate Recommendations

1. For patients with cocaine use disorder, clinicians can consider prescribing topiramate to reduce cocaine use. (Approve 100%, Conditional 44%)
    a. Clinicians can give topiramate additional consideration for patients with co-occurring alcohol use disorder as it can also reduce alcohol consumption. (Approve 100%, Strong 56%)

Please see the following evidence to decision table(s) on pages 198-205 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- Topiramate for Cocaine Use Disorder

Topiramate + Extended-release Mixed Amphetamine Salts (MAS-ER)

MAS-ER (e.g., Adderall, Mydayis), are comprised of dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate, amphetamine sulfate. These medications increase the release of dopamine and norepinephrine and inhibit the reuptake of these neurotransmitters.[33] While there is mixed evidence for topiramate alone, a meta-analysis found that MAS-ER + topiramate treatment had positive effects for achieving a period of cocaine abstinence during treatment compared to placebo.[34] Additionally, one RCT from that meta-analysis showed cocaine craving decreased more rapidly in the treatment compared to the placebo group.[35] The committee

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 committee agreed that this combination treatment could be given additional consideration for patients with co-occurring cocaine and alcohol use disorders. Similarly, this combination could be given additional consideration for patients with co-occurring cocaine use disorder and ADHD, due to the effects of MAS-ER on ADHD symptoms.

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

Topiramate + Extended-release Mixed Amphetamine Salts (MAS-ER) Recommendations

1. For patients with cocaine use disorder, clinicians can consider prescribing a combination of topiramate and extended-release mixed amphetamine salts to reduce cocaine use and cocaine craving. (Approve 91%, Conditional 44%)
    a. Clinicians can give this combination additional consideration for patients with co-occurring alcohol use disorder as it also reduces alcohol use. (Approve 82%, Conditional 33%)
    b. Clinicians can give this combination additional consideration for patients with co-occurring ADHD as it can also reduce ADHD symptoms. (Approve 91%, Conditional 33%)

Please see the following evidence to decision table(s) on pages 206-214 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- 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.[36] A high-quality meta-analysis demonstrated that prescription psychostimulant medications

(including modafinil, methylphenidate, mixed amphetamine salts, lisdexamphetamine, and dextroamphetamine) were associated with better cocaine-related outcomes including reported sustained abstinence and cocaine-negative urine drug results.[34] No difference was noted on treatment retention. Another meta-analysis reported similar results, but included a broader array of psychostimulant medications including bupropion .[28]

The committee emphasized the importance of adequate dosing. Higher doses of prescription psychostimulants were associated with the best outcomes for cocaine use disorder.[34] The committee 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. They emphasized the importance of careful monitoring when using these medications off-label. The committee also highlighted the importance of managing risk of misuse and diversion (see also co-managing StUD and ADHD section).

Clinicians should note that thorough cardiovascular screening at baseline is important, including a 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 patient monitoring and dose adjustment.

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,[37] these results may have been impacted by insufficient dosing.

Amphetamine Formulation Recommendations

1. For patients with cocaine use disorder, clinicians can consider prescribing a long-acting amphetamine formulation psychostimulant to promote cocaine abstinence. (Approve 91%, Conditional 56%)
    a. Clinicians should give long-acting amphetamine formulation psychostimulants additional consideration for patients with co-occurring ADHD as these medications can also reduce ADHD symptoms. (Approve 100%, Strong 56%)
    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. (Approve 89%, Conditional 43%)

Please see the following evidence to decision table(s) on pages 215-230 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- Psychostimulant Amphetamines for Cocaine Use Disorder

Amphetamine-type StUD

Bupropion

Data from systematic reviews and meta-analyses suggest that bupropion is not as effective for individuals with ATS use disorder with respect to stimulant use and abstinence outcomes, relative to findings in cocaine use disorder. 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. No difference in adverse events between bupropion and placebo was noted in any of the studies.

Although both desirable and undesirable effects are small, the committee concluded that the potential benefits of bupropion outweigh the potential risks. Especially in the context of the lack of strongly supported medication alternatives, the use of bupropion for ATS use disorder was supported by the committee, specifically in patients with low to moderate frequency of stimulant use.

Bupropion has been shown to reduce tobacco use in patients who smoke cigarettes or use other tobacco products. Therefore, the committee agreed that bupropion could be given additional consideration for patients with co-occurring tobacco use.

Bupropion dosing is relatively easy to titrate. A generic formulation is available, and is commonly available on medication formularies. Bupropion should be avoided in individuals with history of seizure or eating disorders and used with caution in individuals with elevated seizure risk.

Bupropion Recommendations

1. For patients with amphetamine-type StUD with low to moderate frequency of stimulant use (e.g., <18 days/month), clinicians can consider prescribing bupropion to promote reduced use of amphetamine-type stimulants. (Approve 100%, Conditional 22%)
2. For patients with co-occurring amphetamine-type StUD and tobacco use disorder, clinicians can consider prescribing bupropion to promote stimulant abstinence and as a smoking cessation aid. (Approve 100%, Strong 56%)

Please see the following evidence to decision table(s) on pages 231-237 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- 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.[38,39] Naltrexone is a μ opioid receptor antagonist FDA approved for the treatment of AUD; its extended release formulation is also approved for the prevention of OUD recurrence.[40] Both studies, one open label and one RCT, included patients with moderate to severe methamphetamine use disorder. The CGC viewed it as 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 a treatment for AUD, the committee agreed that this combination treatment could be given additional consideration for patients with co-occurring ATS and alcohol use disorders. Similarly, this combination could be given additional consideration for patients with co-occurring ATS use disorder and tobacco use, because bupropion is FDA approved for the treatment of tobacco use disorder.

The recommendations do not address the use of bupropion in combination with naltrexone in patients with OUD. However, clinicians may consider this combination in patients with cooccurring OUD who are already prescribed naltrexone for OUD or are in OUD remission and not currently prescribed opioid agonist medication. No studies were available studying the impact of this medication combination for co-occurring methamphetamine and OUD. While the evidence for combination bupropion and naltrexone is promising, the committee noted a few implementation considerations. The available research used higher doses of bupropion (i.e., 450 mg of an extended-release formulation). In both studies injectable naltrexone was administered every three weeks, as opposed to every 4 weeks indicated for the treatment of AUD and the prevention of OUD recurrence. 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.

While bupropion and naltrexone are available in generic formulations the clinical trials evaluated injectable naltrexone which may be less feasible and/or acceptable as it requires confirmation of opioid free status of the patient† and health plans may not cover this formulation. Oral naltrexone has not been studied in combination with bupropion, as such there is no evidence for or against its use. The CGC noted that there is no reason to believe oral naltrexone would be less effective in this patient population; given the potential challenges with access to injectable naltrexone it is not unreasonable to consider the combination of bupropion and oral naltrexone.

† See the ASAM *National Practice Guideline for the Treatment of Opioid Use Disorder* for guidance on initiation of naltrexone in patients with OUD.

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

Bupropion should be avoided in individuals with history of seizure or eating disorders and used with caution in individuals with elevated seizure risk.

Bupropion and Naltrexone Recommendations

1. For patients with amphetamine-type StUD, clinicians can consider prescribing bupropion in combination with naltrexone to promote reduced use of amphetamine-type stimulants. (Approve 91%, Conditional 44%)
    a. Clinicians should give this combination additional consideration for patients with a co-occurring alcohol use disorder as it can also reduce alcohol consumption. (Approve 100%, Strong 67%)
    b. Clinicians should give this combination additional consideration for patients with a co-occurring tobacco use disorder as it can also reduce tobacco use. (Approve 100%, Strong 56%)

Please see the following evidence to decision table(s) on pages 238-245 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- Bupropion + Naltrexone for Amphetamine-Type Stimulant Use Disorder

Topiramate

The evidence for topiramate on ATS use disorder outcomes is mixed. Evidence from two RCTs has demonstrated reduction in methamphetamine use via urine drug testing associated with topiramate compared to placebo. Reductions in addiction severity were also found, suggesting improvements in addiction-related consequences and functioning.

The desirable effects of topiramate are somewhat offset by known side effects (cognitive effects and paresthesia), and variable tolerability of the medication. Tolerability can be improved by slow titration. As mentioned earlier, topiramate can cause appetite suppression; this is an important consideration when treating patients who are at risk of malnourishment or underweight.

Topiramate has been shown to reduce alcohol use and is utilized off-label for treatment of AUD. Therefore, the committee agreed that topiramate could be given additional consideration for patients with co-occurring ATS and alcohol use disorders.

While potential effects are small, the committee agreed that topiramate could be considered to reduce use of ATS, as well as alcohol consumption.

Topiramate Recommendations

1. For patients with amphetamine-type StUD, clinicians can consider prescribing topiramate to reduce use of ATS. (Approve 100%, Conditional 44%)
    a. Clinicians should give topiramate additional consideration for patients with co-occurring alcohol use disorder as it can also reduce alcohol consumption. (Approve 100%, Strong 56%)

Please see the following evidence to decision table(s) on pages 246-250 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- Topiramate for Amphetamine-Type Stimulant Use Disorder

Mirtazapine

Mirtazapine is an FDA approved medication for the treatment of major depressive disorder with multiple sites of action including adrenergic, serotonergic, and histaminergic receptors.[41,42] While meta-analyses and systematic reviews reported largely mixed or no evidence for mirtazapine, two randomized, placebo-controlled trials showed a small reduction in ATS use.[43,44] 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 for the treatment of depression, may also help treat anxiety and improve sleep quality, and has no known potential for misuse. These benefits may be tempered by side effects such as weight gain and drowsiness for some patients.

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

Mirtazapine Recommendations

1. For patients with amphetamine-type StUD, clinicians can consider prescribing mirtazapine to promote reduced use of amphetamine-type stimulants. (Approve 100%, Conditional 50%)
    a. Clinicians can give mirtazapine additional consideration for patients with co-occurring depression as this medication can also reduce depression symptoms.

Please see the following evidence to decision table(s) on pages 251-264 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- Mirtazapine for Amphetamine-Type Stimulant Use Disorder

Methylphenidate Formulations (MPH)

Methylphenidate inhibits the reuptake of norepinephrine and dopamine and is FDA approved for the treatment of ADHD and narcolepsy.[45,46] A high-quality meta-analysis was suggestive that MPH were associated with ATS abstinence and reduced ATS use.[34] No difference was noted on treatment retention. Another meta-analysis reported similar results, but included a broader array of psychostimulant medications including bupropion and modafinil.[28]

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

Clinicians should note that thorough cardiovascular screening at baseline is important, including a 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 patient monitoring and dose adjustment.

The committee recognized that clinicians may be hesitant to prescribe higher than typical doses of these medications, the committee also emphasized that risk of misuse or diversion can be managed (see also co-managing StUD and ADHD section).

Psychostimulant Methylphenidate Formulations (MPH) Recommendations

1. For patients with amphetamine-type StUD, clinicians can consider prescribing a long-acting methylphenidate formulation to promote reduced use of amphetamine-type stimulants. (Approve 100%, Conditional 44%)
    a. Clinicians can give long-acting methylphenidate formulations additional consideration for patients with moderate or higher frequency of ATS use at treatment start (e.g., 10+ days/month). (Approve 73%, Strong 38%/Conditional 38%)
    b. Clinicians should give long-acting methylphenidate formulations additional consideration for patients with co-occurring ADHD as they can also reduce ADHD symptoms. (Approve 100%, Strong 44%)
    c. When prescribing a long-acting methylphenidate formulation, clinicians can consider dosing at or above the maximum dose approved by the FDA for the

treatment of ADHD to effectively reduce amphetamine-type stimulant use. (Approve 90%, Conditional 38%/Weak 38%)

Please see the following evidence to decision table(s) on pages 265-274 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- 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 principles of treatment 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 clinical misunderstanding around utilizing medications in individuals with co-occurring StUD and ADHD.

People with StUD 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.

General Guidance

The committee agreed that clinicians should treat StUD and any co-occurring psychiatric disorders simultaneously. Whenever possible, the committee recommended that clinicians use an integrated behavioral treatment approach. Studies on integrated behavioral treatment approaches are limited and heterogeneous in design, target population, and outcomes of evaluation. Studies are not specific to StUD and include approaches that target mixed SUDs and co-occurring depression, anxiety disorders, or PTSD; findings are mixed, but some benefits in reduction of substance use or psychiatric symptoms likely apply to StUD populations. Integrating treatment of SUD and co-occurring mental health disorders is likely more convenient and cost-effective for patients than parallel or sequential treatment models, with benefits likely to largely outweigh risks or harms.

The committee recommends that symptoms of psychosis related to or co-occurring with StUD be treated with an indicated pharmacotherapy. Almost all systematic and meta-analysis evidence for treating symptoms of psychosis is from stimulant-induced or unspecified causes of psychosis. These studies generally noted a large beneficial effect for both pre-existing and stimulant-induced psychosis, as well as pre-existing and stimulant-

induced mania. Undesirable side effects would be similar to the use of these medications in any context. The committee noted that clinicians should be aware of the differences in side effect profiles, particularly differences between typical and atypical antipsychotic medications. As mentioned in the Pharmacotherapy Section, in patients with a history of psychosis (substance-induced or pre-existing), clinicians should not treat StUD with modafinil or psychostimulant medications. Similarly, clinicians should not use psychostimulant medications to treat StUD in patients with a history of stimulant induced mood disorder.

If stimulant-induced psychosis or mania is suspected, the committee suggests that clinicians consider a gradual taper off antipsychotic medication after a period of symptom remission. No research evidence was found regarding discontinuation of antipsychotic medications in this context; however, the committee considered the desirable effects from protecting against unnecessary exposure and development of known adverse effects of chronic antipsychotic or mood stabilizing (e.g., lithium, valproate) medications. The only undesirable effect noted was the potential risk of recurrence of psychotic symptoms. No reliable evidence was found to predict the risk of recurring symptoms after tapering using factors such as history of psychosis or symptom severity. The committee 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 as well as during withdrawal. While these symptoms often resolve with effective management of withdrawal, the committee recommended considering initiation of pharmacotherapy if warranted based on symptom severity and chronicity, even if the symptoms are judged to be stimulant induced.

When initiating treatment for StUD in patients with a pre-existing co-occurring psychiatric disorder, the committee recommended continuing current medications when appropriate and with consideration for their safety in the context of potential continued stimulant or other substance use. While there was no direct evidence found, continuing medications for co-occurring psychiatric disorders, while reviewing the 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. Clinicians should be aware that adherence to, as well as effectiveness of, medications for psychiatric conditions is likely to be reduced in the context of ongoing stimulant use. Additionally, there may be unknown potential adverse interactions between medications and stimulants. The committee noted that clinician expertise in both SUD and psychiatric disorders would be preferred.

General Guidance Recommendations

1. Clinicians should treat both StUD and co-occurring disorder(s) simultaneously. (Approve 100%, Strong 69%)
2. Clinicians should use an integrated behavioral treatment approach that addresses both conditions when available. (Approve 100%, Strong 69%) Otherwise, clinicians should tailor a recommended behavioral therapy for StUD (e.g., CM, CBT, CRA) to address possible interactions between a patient's StUD and co-occurring disorder(s). (Approve 100%, Strong 58%)
3. Symptoms of psychosis or mania should be treated with indicated pharmacotherapy. (Approve 100%, Strong 69%)
    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. (Approve 100%, Strong 54%)
4. For symptoms of depression, anxiety, insomnia, and/or attentional problems observed during periods of stimulant use or withdrawal:
    a. Even if symptoms are stimulant induced, pharmacotherapy should still be considered based on symptom severity and duration. (Approve 85%, Strong 67%)
    b. Consider whether the patient's symptoms follow the expected time-course of stimulant-induced symptoms given the phase of use (active use, waning intoxication, acute withdrawal, post-acute withdrawal, post-withdrawal abstinence) or are present at other times. (Approve 85%, Strong 67%)
5. Clinicians initiating treatment for StUD in a patient with a pre-existing co-occurring diagnosis should:
    a. Review the patient's existing treatment plan, ideally in coordination with the patient's existing treatment provider (Approve 92%, Strong 67%)
    b. Continue current medications if appropriate (Approve 100%, Strong 58%), with consideration for their safety in the context of potential continued stimulant and other substance use by the patient. (Approve 92%, Strong 83%)

Please see the following evidence to decision table(s) on pages 275-354 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- Integrated
- Psychosis
- Psychosis Taper
- Other Symptoms
- Pre-existing Diagnosis

Co-managing StUD and ADHD

Management of ADHD in patients with ongoing use of stimulants (other than as prescribed) may be challenging. Clinicians should be aware that non-medical use of prescription stimulants does not preclude the presence of ADHD. In fact, studies have shown high levels of co-occurring psychiatric disorders, especially ADHD in the context of chronic use of stimulants. A biopsychosocial assessment for StUDs should include assessment for ADHD, and treatment should be offered (directly or through referral) if indicated.

Evidence generally supports the use of psychostimulants to treat ADHD in individuals with co-occurring StUD. Some, but not all studies have demonstrated significant reduction in ADHD symptoms associated with psychostimulant prescription in individuals with StUD. The majority of studies have demonstrated no significant difference in stimulant use or abstinence between individuals treated with prescription stimulants vs. placebo. The committee agreed that clinicians should give additional consideration for behavioral interventions and/or non-stimulant pharmacotherapy (e.g., atomoxetine, clonidine, off-label bupropion) approaches in patients with StUD and ADHD. Non-stimulant medications for the treatment of ADHD may be considered in individuals with StUD, such as atomoxetine, clonidine, and off-label bupropion. The committee also agreed that stimulant medications can be considered when the benefits of the medication outweigh the risks. The committee noted that individuals with StUD who have acquired tolerance for the effects of stimulants may require higher doses of prescribed psychostimulant medication to reach clinical benefit.

Prescription stimulants are controlled substances, and the use of these medications remains controversial due to risk of medication misuse and/or development of tolerance and use disorders. No meta-analyses, systematic reviews, or individual studies on the effectiveness of strategies to prevent non-medical use and diversion of stimulant medications among patients with co-occurring StUD and ADHD were found. Studies of risk mitigation strategies are found in studies of ADHD patients, but even these focus on the prevalence of practices to prevent ADHD stimulant diversion and misuse, rather than their efficacy. Despite this, the committee emphasized the importance of having risk mitigation measures in place. Use of extended-release formulations mitigates risk related to misuse and addictive potential of prescription stimulants by producing less rapid onset of effect and more steady serum levels of medication. Conducting pill counts is in accordance with standard precautions for prescribing controlled substances. Clinicians should utilize the PDMP prior to prescribing prescription stimulants to any patients with SUD, especially StUD. Increasing frequency of visits would facilitate adequate monitoring.

Similarly, no meta-analyses, systematic reviews, or individual studies on the effectiveness of strategies to prevent non-medical use and diversion of stimulant medications among adolescent or young adult patients with co-occurring StUD and ADHD were found. Arranging for a parent or other trusted adult to directly observe administration of

medications in adolescent patients will reduce the likelihood of non-medical use. Conducting pill counts and counseling families on safe storage of controlled medications is in accordance with standard precaution for prescribing controlled substances.

When prescribing a stimulant medication, clinicians should monitor for adverse effects including blood pressure and other cardiac outcomes. Pre-existing hypertension, cardiovascular disease, or psychosis may prompt greater caution in using psychostimulants to treat ADHD in StUD.

Co-managing StUD and ADHD Recommendations

1. For patients with co-occurring StUD and ADHD, clinicians should address ADHD symptoms as part of the treatment of StUD. (Approve 100%, Strong 58%)
    a. Clinicians should give additional consideration to behavioral (Approve 100%, Strong 58%) and/or non-stimulant pharmacotherapeutic approaches for ADHD. (Approve 100%, Strong 50%)
    b. Stimulant medications can be considered when the benefits of the medication outweigh the risks. (Approve 100%, Strong 50%)
2. When prescribing stimulant medications to a patient with co-occurring StUD and ADHD, clinicians should consider:
    a. Using extended-release formulations (Approve 100%, Strong 69%)
    b. Conducting pill counts (Approve 100%, Conditional 23%)
3. For adolescent or young adult patients with co-occurring StUD and ADHD, clinicians should additionally consider:
    a. Arranging for a parent, health professional (e.g., trained school nurse), or other trusted adult to directly observe administration of the medication, especially if using a short-acting formulation. (Approve 100%, Strong 54%)
    b. Counseling families on the importance of safely storing and restricting access to medications. (Approve 100%, Conditional 38%)

Please see the following evidence to decision table(s) on pages 355-381 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- ADHD
- Prevent Prescription Stimulant Misuse
- Prevent Prescription Stimulant Misuse in Adolescents

Special Populations

Adolescents and Young Adults

Clinicians should provide adolescents and young adults who use stimulants with the same treatment, harm reduction, and recovery support services as adults, in a developmentally responsive manner.

Clinicians should evaluate the "set and setting" to understand the context for adolescent 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 youth, clinicians should always evaluate patients for co-occurring mental health conditions and integrate treatment for co-occurring conditions and other psychosocial needs into the treatment plan for StUD.

If a risky sexual behavior screen is positive, clinicians should follow the positive screening recommendations for the general population outlined in the Secondary and Tertiary Prevention section.

The CGC noted that it is especially important to seek additional sources of collateral information in addition to family members (e.g., teachers, guidance counselors, coaches, roommates) with patient permission.

Assessment and Treatment Planning

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

The CGC noted that building trust with an adolescent or young adult and conducting a careful clinical interview is the preferred approach to determine whether an adolescent is misusing stimulants. While drug testing can be a helpful adjunct to a clinical assessment for StUD, it should be accompanied by a careful clinical interview and physical examination. When considering toxicology testing in patients under the age of 18, clinicians should ask the patient for permission to test even if parent/guardian consent was given.

While targeted use of drug testing can provide clinically important information, the CGC recommends against the routine use of urine drug tests to screen for stimulant use in otherwise healthy adolescents and young adults because it can degrade trust, particularly when such testing is performed without patient permission. Data are limited on the potential benefits and harms of drug testing for adolescents with StUD. The CGC recognized that drug tests may result in false negatives and false positives that can make their interpretation difficult, and thus they should only be performed by a clinician with

expertise pertaining to their correct use (See ASAM's *Appropriate Use of Drug Testing in Clinical Addiction Medicine* [15] Consensus Document).

While adolescent and young adult patients with StUD can present with a range of comorbid mental health disorders (e.g., 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. 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 there are no clinical trials that examine StUD treatment outcomes when underlying ADHD or an eating disorder is treated, a general principle in the care of young people with SUD is to address underlying mental health conditions in an integrated fashion.

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. The CGC noted that few such programs exist, depending on the region.

Assessment and Treatment Planning Recommendations

1. Clinicians should avoid routinely using toxicology testing to screen adolescents and young adults for StUD. (Approve 92%, Strong 50%)
    a. When considering toxicology testing in patients under the age of 18, clinicians should ask the patient for permission to test even if parent/guardian consent was given, unless obtaining permission is not possible (e.g., loss of consciousness). (Approve 92%, Strong 67%)
2. Clinicians should pay particular attention to signs or symptoms of ADHD and eating disorders in adolescent and young adult patients. (Approve 100%, Strong 50%)
3. If available, refer patients to adolescent and young-adult specific support programs to address identified biopsychosocial needs. (Approve 100%, Strong 58%)

Please see the following evidence to decision table(s) on pages 382-401 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- Toxicology
- Screen Other
- Specific Support

Adolescent and Young Adult Treatment

Despite the relative lack of evidence on adolescent-specific treatment for StUDs specifically, the CGC concurred on a number of interventions and other strategies that are reasonable,

based on their effectiveness in adolescents 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 (e.g., CM, CBT, CRA, Family Therapy) and in the treatment of StUDs in adults (e.g., CM, CBT, CRA).

While data are available regarding the efficacy of CM and family therapy for adolescents and young adults with StUD, data evaluating other therapy modalities (e.g., CBT, CRA) is lacking. The recommendations related to these other modalities are based on studies evaluating these therapies in adolescents and young adults with other SUDs and clinical experience. There are various therapy modalities that can be offered; some adolescents 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.

The standard of care for SUDs is to use adolescent-specific treatment. While there are no data on adolescent-specific or developmentally responsive treatment for StUD the CGC recommends extending this standard to StUD. Adolescent-specific models or tailored treatment for StUD are expected to be moderately more effective than non-specific treatment and less likely to expose them to peers who use other substances. Given limited evidence, these recommendations are based on the experiences of clinicians with subject matter expertise in treating youth with StUD.

Adolescent patients should be referred to the most appropriate level of care while maintaining the least restrictive environment. Clinicians should tailor a referral that is adolescent-specific, accessible, and encourages ongoing contact and support. Peer-based services may provide youth 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 cannabis use and increasing treatment retention compared to behavioral health interventions without CM. Additionally, in adults with StUD, CM is consistently associated with longer durations of continuous abstinence and lower rates of stimulant use than non-contingent reinforcement (placebo) and treatment as usual. These effects were strongest during treatment and appeared to decrease gradually over post-treatment follow-ups.

The CGC recommended that a few modifications could be made so that CM is delivered in the most developmentally appropriate manner possible. For example, CM generally uses toxicology test results to identify desired behaviors. An adolescent patient may be understandably hesitant to participate in CM as part of StUD treatment because they do not want parents to be informed of positive result. However, while state laws vary regarding

confidentiality and parental notification of treatment progress, clinicians can work with parents so that positive results are not met with punitive outcomes, in accordance with the principle of CM to preferentially reinforce desired behaviors rather than punish undesired behaviors. Another possible modification would be for parents to supplement CM as part of StUD treatment by offering additional or different developmentally appropriate incentives. For some patients, engaging in prosocial behaviors such as permission to attend events or spend time with friends may be more incentivizing than cash or voucher rewards.

Family Therapy

Current data suggest that utilizing family therapy can be more effective than other therapy modalities in reducing substance use in youth with SUDs, but this research is not specific for StUDs. However, given the success in reducing other substances use, the CGC infers that family therapy could also be effective and appropriate to recommend for adolescents 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 or challenges in communication between family members that may impact the adolescents' engagement in continuing family therapy.

Family therapy is often helpful in establishing goals and communication strategies around substance use, but we can also begin to understand how the dynamic of the family may contribute to ongoing substance use (including setting up structure, boundaries, and/or consequences at home). The CGC noted that clinicians should think broadly on how family is defined and attempt to identify the persons of significance in helping the individual patient in treatment and recovery.

Group Counseling and Therapy

For group-format behavioral treatment, the CGC recommends using peer-age groups when possible, avoiding incorporating youth into group behavioral treatment with older adults. Clinical experience and best practice approaches suggest that there could be a 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 experience of negative pressure from other participants. Additionally, survey evidence suggests that adolescents and young adults prefer to be in groups comprised of their own age group.[47,48]

Pharmacotherapy

Clinicians can consider treating youth with StUD with the off-label pharmacotherapies detailed in the Pharmacotherapy section when the developmentally contextualized benefits

outweigh the harms. Although available clinical trials did not typically include adolescents (under 18 years of age), it is likely that many of the same benefits observed by adults ≥18 would be expected in older adolescents (e.g., 16- and 17-year-olds). The CGC cannot routinely recommend use of pharmacotherapy in adolescents <18 given the lack of evidence for this age group. Nonetheless, the CGC felt that given the potentially life-threatening consequences of StUD, 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 amount of clinical trial data.

Family Involvement

The CGC's clinical experience suggests that the involvement of family members is often beneficial in the treatment of youth SUDs and trusted adults should be incorporated when appropriate. Although there is no evidence for the role family involvement may play in adolescents with SUD, the CGC recognizes that family involvement can enhance both engagement and efficacy of treatment in adult populations and would be a worthwhile endeavor to explore with adolescents. Clinicians should take into account, however, the relationship an adolescent has with their family and interest in engaging their family members to ensure the family members or other trusted adults and the patient have a mutual understanding of treatment goals and ways 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)[49] that urine drug testing only be used in conjunction with a careful, confidential history and physical examination, the CGC recommended against home stimulant testing occurring without the oversight of a clinician to interpret results.

Consent for Treatment

For minors under age 18, clinicians should be familiar with state laws on adolescents' ability to consent to treatment. In some states, minors can proceed with SUD treatment without a parent or legal guardian involved in their care; in other states, parental/guardian consent may be required before proceeding with some or all aspects of treatment. All states have laws which describe what minors may or may not consent to without parental or guardian approval, but there is tremendous variability among state laws. For example, some state laws cover alcohol and substance use, some specify only one or the other. Some states prohibit disclosure to parents, some leave this to the physician's discretion, and others require disclosure under certain circumstances. States may also have different rules

(e.g., age thresholds) for an adolescent consenting to treatment for SUD versus screening and/or treatment for comorbidities such as HIV and STI.[50]

CGC underscores that it is essential for treating clinicians to understand their state laws to provide appropriate care to adolescents. CGC also recognizes that although all states require parental consent for most medical care provided to minors, there are several exceptions. One is provision of health care to the "emancipated minor," generally understood to refer to the minor who is living apart from the parent and is financially independent. A minor may be considered emancipated if he or she is married, a parent, or in the military. In general, an emancipated minor can consent to all health care interventions, including StUD treatment, independently.[50]

Parental/guardian consent is not required for treatment of young adults (18 – 25 years old); however, clinicians should initiate a conversation with the patient about whether their treatment plan might be enhanced by involving a parent or other trusted older adult.

Adolescent and Young Adult Treatment Recommendations

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

1. Consider delivering behavioral interventions that have been demonstrated to be effective in the treatment of other SUDs in adolescents (e.g., CM, CBT, CRA, Family Therapy) and in the treatment of StUDs in adults (e.g., CM, CBT, CRA). (Approve 100%, Strong 50%)
2. Use an adolescent-specific treatment model (e.g., A-CRA) or tailor existing treatments to be developmentally responsive. (Approve 92%, Strong 58%)
3. For group-format behavioral treatment, use peer-age groups when possible; avoid incorporating youth into group behavioral treatment with older adults. (Approve 100%, Strong 50%)
4. Clinicians can consider treating youth with StUD with the off-label pharmacotherapies detailed in the Pharmacotherapy section when the developmentally contextualized benefits outweigh the harms. (Approve 77%, Weak 58%)
5. 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. (Approve 100%, Strong 42%)
6. Clinicians should recognize that the involvement of family members is often beneficial in the treatment of youth SUDs and should incorporate trusted adults when appropriate. (Approve 100%, Strong 75%)
7. For minors under age 18, clinicians should be familiar with state laws on adolescents' ability to consent to treatment. In some states, minors can proceed with treatment without a parent or legal guardian involved in their care; in other states, parental/guardian consent may be required before

proceeding with some or all aspects of treatment. (Approve 100%, Strong 73%)

8. Parental/guardian consent is not required for treatment of young adults (18 – 25 years old); however, clinicians should initiate a conversation with the patient about whether their treatment plan might be enhanced by involving a trusted adult. (Approve 100%, Strong 73%)

Please see the following evidence to decision table(s) on pages 402-453 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- Contingency Management
- Other Psychotherapy
- Family Therapy
- Specific Treatment
- Group Treatment
- Pharmacotherapy
- Home Drug Testing
- Family Involvement
- Minor Consent

Pregnant and Postpartum Patients

Assessment

Patients with StUD who are pregnant present unique clinical challenges. Pregnant patients should be referred to a prenatal care provider, if one has not already been established. While no direct evidence was found regarding providing a referral to obstetric care, given the known benefits of prenatal care, providing a referral is expected to be beneficial. Existing guidelines stress using multidisciplinary teams, providing comprehensive prenatal care, and screening for fetal health and complications of pregnancy. Known fetal health complications of patients using stimulants may warrant higher levels of specialization provided through management by a maternal-fetal medicine specialist.

Clinicians should also review eligibility criteria for special programs and extra support available locally to address biopsychosocial needs related to pregnancy and parenting (e.g., childcare, Special Supplemental Nutrition Program for Women, Infants, and Children [WIC program]). Coordination of prenatal care and treatment of SUD is encouraged.

When screening for acute issues, complications, and sequalae associated with stimulant use, clinicians should pay particular attention to factors impacting pregnancy and fetal development. Existing guidelines suggest strong support of screening for blood borne pathogens, STIs, depression, and nutritional deficiencies in those using stimulants.

While toxicology testing has similar potential utility in clarifying treatment need compared to the general population with StUD or other SUDs (see Toxicology Testing section), the ramifications of a positive test result for a pregnant patient may be more severe. Before toxicology testing in pregnant patients, the committee recommended that clinicians be familiar with their state's requirements on reporting and ramifications of reporting. Additionally, the committee noted that overuse of drug testing is more common for minoritized populations with SUD. The potential benefits and risks of utilizing toxicology testing in patients with StUD who are pregnant should be carefully weighed in a shared decision-making process with the patient. Because toxicology testing is known to introduce potential bias, the committee recommended the use of consistent standards for indications for toxicology testing. Informed consent should be obtained unless there is an immediate clinical need and obtaining consent is not possible (e.g., loss of consciousness).

Assessment Recommendations

1. Clinicians should add the following to the comprehensive assessment of StUD for pregnant patients:
    a. Referral to a prenatal care provider if not already established. (Approve 100%, Strong 69%)
    b. Review eligibility criteria for special programs and extra support available locally to address biopsychosocial needs related to pregnancy and parenting (e.g., childcare, WIC programs). (Approve 100%, Strong 67%)
2. Coordination of prenatal care and treatment of SUD is encouraged. (Approve 100%, Strong 69%)
3. When screening for acute issues, complications, and sequalae associated with stimulant use, clinicians should pay particular attention to factors impacting pregnancy and fetal development. (Approve 100%, Strong 77%)
4. While toxicology testing has similar potential utility compared to the general population with StUD or other SUDs (see Toxicology Testing section), the ramifications of a positive test result for a pregnant patient may be more severe. (Approve 85%, Strong 62%) Before toxicology testing in pregnant patients, clinicians should:
    a. Know their state's requirements on reporting and ramifications of reporting. (Approve 100%, Strong 77%)
    b. Weigh the potential benefits with the risks of utilizing toxicology testing in this population. (Approve 100%, Strong 78%)
    c. Obtain informed consent unless there is an immediate clinical need and obtaining consent is not possible (e.g., loss of consciousness). (Approve 100%, Strong 80%)

Please see the following evidence to decision table(s) on pages 454-492 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- Prenatal Care Referral
- Screen Social Services – Pregnancy & Postpartum
- Screen Factors Pregnancy
- Toxicology – Pregnancy & Postpartum

Treatment

No direct evidence was found for the efficacy or safety of medications for treatment of StUD in pregnant patients. Risk versus benefit to the fetus or infant should be considered when medications are used to manage stimulant intoxication, withdrawal, or use disorder in patients who are pregnant. The committee emphasized that risk level often varies depending upon trimester, and this should be considered.

Most medications that address stimulant-induced intoxication are largely contraindicated in pregnancy. However, the committee agreed these medications might be used in instances where the risk of harm (e.g., due to psychosis) is greater than the potential risk to the pregnancy.

Wherever possible, clinicians should incorporate psychosocial treatment targeted towards meeting the additional needs of pregnant patients, including parent-focused treatment modalities (e.g., parenting skills training and other interventions) and family-based treatment. While no direct evidence addresses efficacy of additional psychosocial services, clinical judgement 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 face greater disintegration of usual social supports and family structure.

Clinicians should consider contingency management (CM), if feasible, to incentivize attendance at prenatal appointments in addition to the usual targets of CM (e.g., stimulant abstinence). Evidence for the effect of CM on prenatal care participation is mixed. Studies have found either increased rates of attendance or no significant effect. Two low quality studies showed a slight increase in attendance. However, prenatal care has been shown to reduce negative effects of substance use during pregnancy, and so desirable effects of increasing prenatal care attendance are likely large.

Clinicians should consider providing additional treatment support around the time of birth as the post-partum period may be a time of increased stress and risk of return to stimulant use. There is some low-quality evidence 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% return to use after 3 months and 2 years respectively. The risk of developing post-partum depression in this population is nearly 20 percent with a resulting higher rates of

return to use. Access to care both antenatally and post-partum continues to be problematic and subject to significant health inequities in diagnosing and appropriately managing post-partum depression in marginalized populations.

Treatment Recommendations

1. Risk versus benefit to the fetus or infant should be considered when medications are used to manage stimulant intoxication, withdrawal, or use disorder. (Approve 85%, Strong 77%)
2. Wherever possible clinicians should incorporate psychosocial treatment targeted towards meeting the additional needs of pregnant patients, including: (Approve 85%, Strong 54%)
    a. Parent-focused treatment modalities (e.g., parenting skills training and other interventions) (Approve 85%, Strong 54%)
    b. Family based treatment (Approve 85%, Strong 54%)
3. Clinicians should consider contingency management (CM), if feasible, to incentivize attendance at prenatal appointments in addition to the usual targets of CM (e.g., stimulant abstinence). (Approve 85%, Strong 46%)
4. Clinicians should consider providing additional treatment support around the time of birth as the post-partum period may be a time of increased stress and risk of return to stimulant use. (Approve 100%, Conditional 54%)

Please see the following evidence to decision table(s) on pages 493-521 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- Pharmacotherapy – Pregnancy & Postpartum
- Psychosocial Additions – Pregnancy & Postpartum
- Prenatal Care Incentives
- Postpartum Care

Breastfeeding

Breastfeeding has been found to have numerous benefits to mom and baby, however levels of stimulants in breastmilk have been found to be high with the potential to harm the baby. Although there are no known data for outcomes in newborns, the CGC recommends against breastfeeding in women who are actively using stimulants. Proper education and counseling should be completed regarding risks of stimulants in breastmilk. Support and education should be provided for women who have achieved sustained abstinence from stimulant use who desire breastfeeding.

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

Breastfeeding Recommendations

1. Clinicians should educate patients who use stimulants on the risks of stimulant use while breastfeeding and counsel patients not to breastfeed if they are actively using stimulants (except as prescribed). (Approve 100%, Strong 54%)

Please see the following evidence to decision table(s) on pages 521-531 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- Breastfeeding

Additional Special Populations

While studies examining the effectiveness of treatment interventions within particular special populations were found, the review did not identify any studies on interventions with the specific aim of reducing health disparities in treatment outcome across populations of stimulant users.

As with most areas of health care, evidence suggests that there are race-, ethnicity-, and gender-related disparities in treatment outcomes for StUD.[51–53] These findings may be partly due to the prevalence and severity of underlying risk factors that negatively impact treatment outcome (e.g., history of violence/trauma, co-occurring psychiatric disorders, underlying medical conditions, etc.). They may also be due to inequities in resource availability and investment in prevention and treatment capacity. The CGC believes disparities in StUD treatment outcomes stemming from differences in underlying risk factors and investment are best addressed by structural changes to the healthcare system.

Clinicians can advocate for or adopt program level changes aimed at reducing disparities in treatment delivery. Guidelines aimed at reducing health disparities generally support training interventions designed for clinicians. Clinicians should ensure that the staff working with patients with StUD are trained to work with the populations served by the clinic.[54]

Racism and other forms of discrimination are traumatizing.[55] In addition, racial and ethnic minority patients experience greater exposure to adverse childhood events (ACEs).[56–58] Providing trauma-informed care is especially important when working with clients from populations who experience health inequity. 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 sections). An aspect of trauma-informed

care is trauma-informed screening. Clinicians should use a validated screening instrument and trauma-informed approach to asking the questions. For more information on trauma-informed care, see the Substance Abuse and Mental Health Services Administration's (SAMHSA)[59] treatment improvement protocol on trauma-informed care in behavioral health services.

Sexual Orientation and Gender Identity

Sexual and gender minority (SGM) individuals include lesbian, gay, bisexual, questioning, and asexual patients (LGBQ+) as well as transgender and gender diverse individuals, A meta-analysis of 13 studies of behavioral interventions co-targeting mental health, alcohol, and/or drug use, as well as sexual risk behavior among gay and bisexual men had a small positive effect on reducing substance use and sexual risk behavior. [60] In a systematic review of behavioral interventions that address substance use and sexual risk among gay, bisexual, and other men who have sex with men who use methamphetamine, 18 out of the 23 studies reviewed reported a statistically significant effect on 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, although this outcome was not looked at specifically in the reviews identified.

The CGC also noted that not all SGM patients require tailored programing; insisting on requiring it could lead to decreased access to general programming if misapplied, and in worst case, could be used to discriminate against people. However, some patients may benefit from SGM-focused programs and clinicians should consider the individual patient's needs when making treatment recommendations. For example, is the patient experiencing distress related to their sexual orientation or gender identity? Are they comfortable discussing issues related to their sexual orientation or gender identity in a general population setting? Does the patient prefer a tailored treatment setting? The recommendation below is intended to make tailored treatment 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 or behavior. Clinicians may want to wait to assess sexual practice history until sufficient rapport has been established.[54]

Sexual and Gender Minorities Recommendations

1. Clinicians should consider referring SGM patients with StUD to SGM affirming programs when their history or behavior suggest that they may not be comfortable fully participating in a general population setting (e.g., distress related to their

identities, difficulty discussing drug related sexual activities, inner conflicts, trauma history, etc.). (Approve 100%, Strong 55%)

Please see the following evidence to decision table(s) on pages 532-551 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- Sexual and Gender Minorities

Patients with Cognitive and/or Physical Disabilities

Clinicians should recognize that people with StUD have a higher prevalence of physical and cognitive disabilities and lower rates of treatment engagement.[61] Patients with severe chronic health problems tend to have a slower response to treatment, with fewer days abstinent, compared to patients without them.[62]

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 a physical or cognitive disability, 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.[61]

Clinicians should remove or mitigate barriers of accessibility to StUD treatment for people with physical or cognitive disabilities to the extent possible.

Patients with Cognitive and/or Physical Disabilities Recommendations

1. When treating patients with a physical or cognitive disability, 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*.[61] (Approve 100%, Conditional 27%)

Please see the following evidence to decision table(s) on pages 552-562 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- Disability

Patients Involved in the Criminal/Legal System

Evidence suggests that treatment should be initiated as soon as feasible for individuals in the criminal/legal system, including within jails and prisons. Research suggests that incorporating telephone monitoring and counseling in follow up care for patients with cocaine use disorder that have criminal/legal system involvement, in addition to usual care, can reduce recidivism.[63]. There is no reason to expect it to be differentially effective for patients with an ATS use disorder. Clinicians should connect patients with criminal/legal system involvement to appropriate support services (e.g., reentry programs, vocational rehabilitation, transportation, and housing assistance) on re-entry.[64]

Patients Involved in the Criminal/Legal System Recommendations

1. Initiation of treatment for StUD is recommended for individuals in the criminal/legal system, including within jails and prisons. (Approve 100%, Strong 80%)

Please see the following evidence to decision table(s) on pages 563-572 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- Criminal/Legal System

Homelessness/Unstable Housing

People experiencing homelessness and unstable housing have higher rates of comorbidities for other factors which exacerbate or make it more challenging to manage stimulant use, including injection drug use,[65] polysubstance use, engaging in transactional survival sex, serious mental illness and other mental health disorders, and a history of trauma. They also have higher rates of chronic health conditions and infectious diseases such as HIV and HCV.[64]

Physical and sexual victimization are highly prevalent among persons who experience homelessness and use methamphetamine.[66] People experiencing homelessness and unstable housing may also use stimulants for functional reasons. People who were recently evicted reported using methamphetamine to increase alertness and safety while on the street.[67]

Attending to the social determinants of health is expected to support overall health and wellness, not necessarily reduce substance use. This helps make treatment more accessible to patients experiencing homelessness, housing insecurity, food insecurity, and/or poverty.

Homelessness/Unstable Housing Recommendations

1. For patients experiencing homelessness, housing insecurity, food insecurity, and/or poverty clinicians might consider:
    a. Providing or referring to a case manager or other appropriate staff who can help the patient navigate health and social safety net resources. (Approve 100%, Strong 60%)
    b. Referral to a recovery residence based on individual needs. (Approve 100%, Strong 71%)

Please see the following evidence to decision table(s) on pages 573-585 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- Homelessness/Unstable Housing

Veterans

While no recommendation statements specific to veterans are included in this guideline, the CGC emphasized that veterans should receive the same clinical care as other adults, and clinicians should be mindful of additional issues they face, especially psychological trauma. Veterans with StUD face additional challenges accessing and completing treatment compared to the general population. The committee views health disparities faced by veterans to be driven primarily by increased exposure to other risk factors for health disparities, rather than merely their membership in this population. Clinical considerations for addressing risk factors are covered in other sections (e.g., 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. The CGC wished to identify where the clinical management of stimulant-related signs and symptoms would differ from the clinical management of those signs and symptoms in general. Following this approach is intended to give the Guideline more clinical utility and reduce redundancy with other guidelines. However, it is important for clinicians to provide the full standard of care that should be provided to any patient with SUD.

Where the evidence allowed the GRADE approach to be used, the full evidence profiles can be downloaded at the following link: https://bit.ly/41MqrwV.

Assessment & Diagnosis

The DSM-5-TR criteria are the clinical standard for diagnosis of stimulant intoxication or withdrawal in the US.[69] Stimulant intoxication and withdrawal, as well as complications or comorbidities associated with StUD, are primarily diagnosed based on history and physical examination as well as findings from any laboratory and/or toxicology testing.

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 seven studies were found evaluating tools to assess stimulant withdrawal symptom severity (including the Obsessive-Compulsive Cocaine Scale, the Cocaine Selective Severity Assessment, and the Stimulant Selective Severity Assessment, the CGC determined that they mainly provided evidence for their use as research measures, rather than clinical tools.[70–72] No tools diagnosing or assessing stimulant intoxication or withdrawal in a clinical context were identified. The CGC discussed the use of the Poisoning Severity Score for intoxication assessment, but given the lack of specific evidence, the use of more general categorization of symptom severity was deemed appropriate.[73]

Patient Evaluation

A number of gray literature sources discuss clinical assessment standards, including guidelines from SAMHSA, the Veterans Administration (VA), and over a dozen international guidelines from the UK, Canada, Australia, Germany, and the World Health Organization

(WHO). The following recommendations are based on a review of these guidelines and the clinical expertise of the CGC.

While comprehensive assessment of the patient is critical for treatment planning, for patients with suspected acute stimulant intoxication or withdrawal, completion of all assessments should not delay or preclude initiating treatment of critical needs (See Appendix A). Clinicians should conduct an initial clinical assessment to **first** identify any acute issues and complications of stimulant intoxication and withdrawal. A basic assessment of vital signs and a focused mental status evaluation can determine the need for urgent or emergent treatment or referral for further medical evaluation.

After addressing any urgent medical or psychiatric problem(s), patients should be given a comprehensive assessment focused on non-acute complications and sequalae of stimulant use and other factors which impact treatment planning (See Appendix D). The assessment should include 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. The extent of the clinical exam and medical workup for stimulant intoxication and withdrawal should be based on presenting signs and symptoms and severity of intoxication. Clinical testing (lab and/or imaging) should be based on the findings from history and exam. A safety assessment of the patient's risk of harm to self and others should also be conducted. No studies were identified that evaluated strategies for **diagnosing or assessing** stimulant intoxication or withdrawal. The gray literature search identified several clinical guidelines that address these issues. There is agreement that the American Psychiatric Association's Diagnostic and Statistical Manual (DSM) criteria are the standard for diagnosis of stimulant intoxication or withdrawal in the US. Considerations for differential diagnosis are outlined in Appendix B and recommendations for laboratory and toxicology testing are discussed below.

Safety Assessment

There is an elevated risk of suicide and self-harm in people who use stimulants. A review of 300 cases of methamphetamine-related suicides from Australian data (2009-2015) found that suicide comprised 18.2% of all methamphetamine-related deaths.[74] The CGC recommends evaluation of suicidality as a part of 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.[75] In the CGC's experience, suicide risk may resolve more rapidly in stimulant withdrawal compared to other substance withdrawal syndromes. If the patient screens positive for suicide risk, they should be managed according to best practices including psychiatric consultation 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 ≥4 adverse childhood experiences (ACEs), 28.7% reported 2-3 ACEs, 21.6% reported 1 ACE, and 20.4% reported no ACEs.[76]

No studies were identified on implementing routine screening for trauma-related problems in patients with stimulant intoxication or withdrawal. Given the strong correlation between trauma and StUD, the CGC recommends that all patients with stimulant intoxication or withdrawal should be screened for trauma. Clinicians should use a validated screening instrument and a trauma-informed approach to asking screening questions. For more information on trauma-informed care, see the Substance Abuse and Mental Health Services Administration's treatment improvement protocol (TIP) 57: Trauma-Informed Care in Behavioral Health Services.[59]

Implementation Considerations

- Ensure adequate staff training in trauma-informed care
- Attend to patient readiness to participate in the screening
- Consider delaying screening until the acute effects of stimulant intoxication or acute withdrawal have resolved
- Establish psychological safety before raising topics that could be destabilizing
- Use neutral language
- Use evidence-based tools

Assessment and Diagnosis Recommendations

Initial Assessment Recommendations

1. The clinical examination should first identify any acute issues and complications of stimulant intoxication and withdrawal that would indicate that the patient requires a higher level of care. (Approve 100%, Strong 71%) This includes an assessment of hyperadrenergic symptoms including tachycardia, hypertension, hyperthermia, and agitation. (Approve 100%, Strong 71%)
2. The initial clinical examination when evaluating for suspected stimulant intoxication or withdrawal should include: (Approve 98%, Strong 68%)
    a. A clinical interview (as feasible)
    b. Physical examination
    c. Observation of signs and patient-reported symptoms
    d. Review of any available collateral information
    e. A safety assessment of the patient's risk of harm to self and others

Comprehensive Assessment Recommendations

1. Stimulant intoxication and withdrawal are primarily diagnosed based on the history and physical examination as well as findings from any clinical and/or toxicology testing. (Approve 77%, Strong 88%)
2. If some elements of medical workup are not available at a setting, the results from a basic assessment of vital signs and a focused mental status evaluation should be used to determine the urgency of further medical evaluation or referral for a more comprehensive medical evaluation. (Approve 91%, Strong 50%)
3. Clinical testing should be based on presenting signs and symptoms and should include complete blood count (CBC), comprehensive metabolic panel (CMP), liver function tests (LFTs), markers for muscle breakdown (e.g., CK, lactate [in cases of muscle breakdown and acidosis]) or cardiac injury (e.g., CK and troponin). (Approve 100%, Strong 50%)
4. In 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 both immunosuppression (in particular, neutropenia) and small vessel vasculitis. (Approve 91%, Conditional 20%)

Please see the following evidence to decision table(s) on pages 586-600 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- Initial Assessment – Intoxication & Withdrawal
- Comprehensive Assessment – Intoxication & Withdrawal
- Baseline Labs – Intoxication & Withdrawal

Body Stuffing/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 (often poorly) wrapped drugs to evade police detection, while body packing refers to pre-planned, often well-wrapped larger amounts seen in drug smuggling. Body stuffing/packing can result in more severe and prolonged symptoms of intoxication and thus should be managed in an acute care setting.

While there are studies comparing imaging techniques to detect body stuffing/packing and on monitoring asymptomatic individuals, no studies were identified on the appropriate medical workup for a patient who becomes intoxicated from a ruptured package of body concealed stimulants.[77] Given the relative rarity of this event and that care should be provided in emergency settings by knowledgeable critical care physicians, the CGC did not provide recommendations for managing this population.

Laboratory testing

Laboratory testing can be used to 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. While there is no direct evidence regarding non-infectious disease screening labs (e.g., CBC, CMP), as part of a comprehensive assessment these labs help identify common comorbid conditions that can then be treated. The higher prevalence of HIV, hepatitis, and STIs in patients who use stimulants justifies the need for obtaining baseline testing in patients who receive stimulant intoxication or withdrawal treatment.

The CGC agreed that some tests may be considered based on symptomatology and presence of risk factors. Clinicians should consider complete blood count (CBC), comprehensive metabolic panel (CMP); liver function tests (LFTs); markers for muscle breakdown (e.g., CK, lactate), cardiac injury (e.g., troponin), or renal injury (e.g., BCR, urine albumin). Clinicians should be alert to neutrophil levels in patients with cocaine intoxication or withdrawal. Levamisole is a common adulterant in the cocaine supply and can cause both immunosuppression (in particular, neutropenia) and small vessel vasculitis. How much levamisole is currently contaminating the drug supply, and therefore how concerned clinicians should be about it, varies by region and over time.

For some patients the impact of routine testing (see Appendix C) could be substantial given the benefit of early detection and treatment for some conditions (e.g., HIV, hepatitis). For some diagnoses the effect of early detection and treatment is less substantial (e.g., liver function). Implementing these recommendations should be highly feasible in hospital settings and community settings where intoxication or withdrawal management would occur. However, settings need to have linkage between testing and treatment service to realize the potential benefits of testing, and health insurance coverage for routine lower values tests may vary (e.g., liver, kidney).

Toxicology Testing

No studies were identified that evaluated the use of toxicology testing as a routine part of 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 an emergency setting. Observation of clinical effects and patient self-report are often more informative and are more immediate compared to toxicology testing. Utility for acute management is limited when samples need to be sent out to laboratories, or when the stimulants that were used are not included on a typical screening panel. Toxicology testing has the ability to answer specific questions regarding a patient's recent substances use but has limitations determined by the technology used by the specific test. There is a tradeoff between the time delay vs accuracy/specificity of the

information. Screening (presumptive tests) results are often available rapidly, increasing their utility for acute management, but are less accurate than confirmatory tests.

Toxicology testing in the emergency department (ED) is useful diagnostically as a component of differential diagnosis when patients present with unspecified agitation, confusion, delirium, psychosis, chest pain, seizure, or autonomic hyperactivity. Toxicology testing in acute clinical settings may also remain important for public health surveillance or forensic utility. Toxicology testing can also be used to identify potential medication interactions (both prescribed and non-prescribed) when considering medication to manage stimulant intoxication or withdrawal symptoms.

Rather than testing for every stimulant for which a test is available, it is appropriate to first use a panel test for regionally or demographically prevalent stimulants. It is critical to keep in mind that a negative test result does **not** confirm that a stimulant was not used, just that the particular target of the test was not detected in the sample. Immunoassays for the cocaine metabolite, benzoylecgonine, has high sensitivity and specificity, available immunoassays for amphetamines have lower specificity and often require confirmatory testing.

While false positives for amphetamine on immunoassay tests have been reported this is rare with most currently available immunoassays for amphetamine.[78] Confirmatory testing for amphetamines can rule out false positive from other drugs (e.g., bupropion, methylphenidate, pseudoephedrine, ephedrine).[78] Clinicians should refer to the test manufacturer and/or consult with their laboratory to determine the capabilities and cross-reactivity of specific assays.

Consider the possibility of novel psychoactive stimulants if stimulant intoxication is suspected but presumptive testing is negative. The growing influence of synthetic drugs and drug adulteration/contamination combinations 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.

If testing is comprehensive, accurate, and interpreted correctly, it is 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 not necessary if the result would not alter the treatment plan (e.g., to confirm stated methamphetamine use in obvious methamphetamine toxidrome) and becomes more necessary as the outcome becomes more clinically important (e.g., in potential pediatric exposure or differentiating psychiatric decompensation from methamphetamine-associated psychosis).

For additional considerations see ASAM's Appropriate Use of Drug Testing in Clinical Addiction Medicine[15] Consensus Document and ASAM's public policy statement on Ethical Use of Drug Testing in the Practice of Addiction Medicine.[79]

Implementation Considerations

When implementing drug testing, clinicians should keep in mind the technical limitations of the matrix and drug panel that is selected. Patient consent should generally be obtained before testing unless there is an immediate clinical need. Clinicians should also keep up to date on what stimulants are prevalent within certain demographics in their region. Testing laboratories often track this information.

Indications for toxicology testing information include but are not limited to:

- The etiology of signs and symptoms is unclear
- The clinical findings are not fully consistent with stimulant intoxication alone (i.e., suggestive of possible adulterant/contaminant or other substance use)
- When the information is clinically important (e.g., in possible pediatric exposure or differentiating psychiatric decompensation from methamphetamine-associated psychosis).

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

Toxicology Testing Recommendations

1. In patients presenting with stimulant intoxication or withdrawal, clinicians can use toxicology testing to inform differential diagnosis (along with other clinical information) (Agree 100%, Strong 56%) and to identify possible interactions when considering medication to manage stimulant intoxication or withdrawal symptoms. (Approve 91%, Conditional 50%)
2. When performing diagnostic testing for stimulant intoxication in acute care settings, it should include toxicology testing for regionally or demographically prevalent stimulants. (Approve 100%, Conditional 17%)
3. Consider the possibility of novel psychoactive stimulants if stimulant intoxication is suspected but presumptive testing is negative. (Approve 100%, Conditional 33%)

Please see the following evidence to decision table(s) on pages 601-607 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- Intoxication Toxicology

Seizure Workup

Seizures are one of the most severe complications of stimulant toxicity. Over 6% of new onset seizures are drug-related with 9% of adults with status epilepticus having substance-induced seizures.[80] Seizures can occur in association with methamphetamine use, with epileptic seizures being a frequent complication of methamphetamine intoxication.[81,82] 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 in body-packers.[83] Some medications, such as bupropion, raise the risk for seizures. A seizure may also be related to hyponatremia when stimulants such as MDMA are used. Seizure is also more likely with polysubstance than single substance use.

Established guidelines are available for neurological evaluation of first episode, non-provoked seizure in both adolescents and adults. However, given stimulants' physiology of proconvulsive activity, there is debate over whether all components of this evaluation (including neurology consultation and evaluation including EEG follow-up testing) are necessary when the seizure is confirmed 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 non-toxicologic cause of seizure is possible. No studies were identified that evaluated strategies for assessment and diagnosis of stimulant-related seizure. Consensus in clinical guidelines is that the determination for obtaining a comprehensive evaluation following a seizure can be made according to best practice, based on symptomatology and presence of risk factors.[64,80,82] The CGC noted that indications for waiving a comprehensive neurological evaluation following a seizure include:

- Known pre-existing seizure disorder
- History of traumatic brain injury
- Strong family history of epilepsy
- Hyponatremia detected by laboratory testing
- The seizure is well explained by substance use or withdrawal

The consensus of the CGC is that a seizure is well explained by substance use or withdrawal when, for example, there is known use of seizure-threshold lowering medications such as tramadol or bupropion, or the patient has a history of stimulant- or other substance use-related seizure and no history of non-stimulant related seizure. In these instances, there is no evidence of benefit of a full neurological work up, and significant healthcare resources are required.

When the etiology of the seizure(s) is not well explained by substance use, the workup and management of seizures should proceed according to usual best practice**.**

Even if a full neurological work-up is waived, clinicians might still order testing (e.g., head CT) to rule out other causes, especially if the clinical exam is suggestive of other causes

(e.g., neurological findings suggestive of stroke). Additional evaluation is indicated if seizures recur despite control of stimulant intoxication.

Setting Determination

No studies were identified that addressed level of care determination when managing the risks associated with stimulant intoxication and withdrawal. The following recommendations are based on a review of existing guidelines and the clinical expertise of the CGC.

Patients with stimulant intoxication and withdrawal should be managed in a setting which provides the intensity of care necessary to address the anticipated severity of the intoxication or withdrawal syndrome. Treatment needs are determined by a number of dynamic factors, meaning they will change throughout the course of intoxication and withdrawal. The CGC recommends the use of a multidimensional assessment such as is described in *The ASAM Criteria* to determine the appropriate clinical setting for management of stimulant intoxication or withdrawal.[84]

Individuals presenting with stimulant intoxication or withdrawal may be treated in a lower acuity clinical setting if emergency interventions are not indicated. Clinical features which would typically indicate the need for emergency medical treatment such as high fever, seizure, chest pain, psychosis, or suicidality, should be treated in an emergency medical care setting.

Some patients should be managed in higher acuity settings because they need close monitoring and a setting with alertness to evolving presentation. Serious co-occurring medical or psychiatric health issues 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 should be observed in a setting with ready access to emergency treatment, as it is hard to know the actual amount consumed, the quality of the packaging, and risk of exposure.

This means the setting must allow for assessment of acute issues and complications, screening for acute intoxication potential, monitoring the intoxication syndrome, and administering appropriate clinical interventions. If any of the above are not possible in the current setting due to staff or resource capability or patient agitation, the patient should be transferred to a more intensive level of care with the appropriate capabilities. However, there is risk involved in transfer, as patients may choose to leave treatment rather than initiate treatment elsewhere. The use of health information technology and patient navigators to bridge care between settings may help reduce facilitate an effective transfer.

Setting Determination Recommendations

1. Patients with severe clinical problems or complications related to stimulant intoxication should be managed in acute care settings. (Approve 100%, Conditional 50%)
2. Some patients with acute stimulant intoxication can be safely managed in lower acuity clinical settings, if: (Approve 95%, Conditional 37%)
    a. The patient is cooperative with care;
    b. The patient is responsive to interventions (e.g., 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 by 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.
        viii. Coordinate clinical testing if indicated.

Please see the following evidence to decision table(s) on pages 608-613 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- Intoxication Setting

Managing Stimulant Intoxication and Withdrawal

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 to self or others which can be managed by a combination of pharmacotherapies and behavioral/environmental interventions.

Clinicians can consult with the Poison Control Center (PCC) through their toll-free number (800-222-1222) for advice 24/7, or with their institution's clinical toxicology service, which may reduce the duration of hospital stay.[85] 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 which discuss behavioral and environmental strategies to help keep the patient calm, including guidance from SAHMSA, the American Association of Family Physicians (AAFP), the United Nations Office of Drug Control, and other international guidelines.[64,86,87] 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 what supportive care should be provided to patients with stimulant intoxication and withdrawal. Supportive care should be provided according to best practices for general substance toxicity, including:

- Providing vitamins, fluids, and nutrition, including thiamine and dextrose
- Correcting electrolyte and fluid imbalance
- Talking to the patient
    - Orienting to time and place
    - Providing reassurance
    - Communicating on what to expect from treatment

Monitoring

No studies were found on strategies for **monitoring** psychiatric or hyperadrenergic symptoms in patients with stimulant intoxication or withdrawal. The committee agreed that clinicians should consider clinically monitoring patients until their mental status and other signs and symptoms of acute intoxication have been normalized to prevent risks for falls, altercations, motor vehicle crashes, and other adverse events. Clinicians should monitor for progression of psychiatric symptoms, breakthrough psychosis, suicidality, and the emergence of trauma-related symptoms. Suicidality in particular may increase during the waning intoxication/acute withdrawal phase and should be addressed. 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 hyperadrenergic symptoms.

Behavioral and Psychiatric Symptoms of Stimulant Intoxication

The CGC suggests that clinicians follow an established clinical protocol for managing general agitation when managing agitation caused by stimulant intoxication or withdrawal, such as the American Association of Emergency Psychiatry's Best Practices in the Evaluation and Treatment of Agitation (Project BETA).[88]

Non-pharmacological Management Strategies for Behavioral and Psychiatric Symptoms

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

The committee emphasized that the use of restraints should be avoided unless absolutely necessary to protect the safety of patients and staff. While restraints can temporarily prevent violent behavior, the application of restraints 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.

Pharmacological Management of Behavioral and Psychiatric Symptoms

Richards et al reviewed six high quality studies supporting the use of antipsychotics and benzodiazepines for agitation and psychosis and nine high quality studies supporting the use of beta blockers for control of hypertension and tachycardia associated with stimulant toxicity, including amphetamines, related derivatives, and analogues. Finally, in a recent comprehensive systematic review, Connors et al concluded that antipsychotics did not show a clear benefit over benzodiazepines for the management of toxicity, however neither did they show significant harm to the extent previously thought.[90] The gray literature search identified multiple clinical guidelines that address **pharmacological** options for management of agitation and psychosis, including guidance from SAHMSA,[64] the American Association of Family Physicians (AAFP),[86] the United Nations Office of Drug Control,[87] and other international guidelines.

Pharmacological Management of Agitation

Benzodiazepines are generally considered first-line treatment for the management of stimulant-induced agitation. Significant agitation should typically be managed in acute care settings given the risks associated with the use of sedative-hypnotic medications for patients with clinical instability when treating 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 control of agitation is necessary to protect patient and/or staff safety (most commonly related to methamphetamine intoxication), clinicians can consider IV ketamine. Intramuscular ketamine may be used if IV ketamine is not feasible.

Pharmacological Management of Psychosis

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

Suicidality

No studies were identified on managing suicidality specific to stimulant intoxication or withdrawal. Existing guidelines emphasize the importance of monitoring for and managing suicide risk. The CGC determined that suicidality should be managed according to best practice, including a psychiatric consultation, safety assessment, and involuntary psychiatric hospitalization if necessary.

Behavioral and Psychiatric Symptoms of Stimulant Intoxication Recommendations

1. Clinicians should evaluate the patient to identify other causal factors for agitation/psychosis in addition to stimulant intoxication. Treatment should address all underlying causes. (Approve 100%, Strong 71%)

2. Clinicians should use verbal and nonverbal de-escalation strategies to calm agitated/delirious/psychotic patients to support their cooperation with care. (Approve 100%, Strong 75%)
3. When verbal and nonverbal de-escalation strategies are insufficient to manage agitation/confusion, clinicians can consider treating symptoms with a medication. (Approve 100%, Conditional 29%) Benzodiazepines can be considered first line treatment. See Appendix G for additional agents to consider. (Approve 100%, Conditional 29%)
4. Clinicians should treat stimulant induced psychotic symptoms with an antipsychotic medication. (Approve 100%, Strong 50%)
    a. The urgency, formulation, and duration of antipsychotic medication treatment should be based on etiology and symptomatology. (Approve 100%, Strong 67%)
    b. Clinicians should avoid the use of chlorpromazine and clozapine for stimulant induced psychosis as these medications may place patients at increased risk for seizure. (Approve 100%, Strong 83%)
5. For agitation/psychosis that is moderate to severe or escalating, clinicians should:
    a. Conduct a medical evaluation focused on identifying life-threatening medical issues that require a referral for emergent hospital workup and management. (Approve 100%, Strong 82%)
    b. Conduct a mental status evaluation focused on evaluating the patient's danger to self or others that would require an immediate referral for a full psychiatric assessment and/or involuntary containment and evaluation. (Approve 92%, Strong 75%)
6. If agitation/psychosis does not respond to the available de-escalation and/or medication management interventions, clinicians should coordinate a transition to a higher level of care. (Approve 80%, Strong 67%) When possible, interventions that address agitation, confusion, delirium and/or psychosis should be initiated while arranging for transport. (Approve 80%, Strong 50%)
7. Clinicians should monitor for progression of psychiatric symptoms, breakthrough psychosis, suicidality, and the emergence of trauma-related symptoms. Suicidality in particular may increase during the waning intoxication/acute withdrawal phase. (Approve 90%, Conditional 57%)

Please see the following evidence to decision table(s) on pages 614-663 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- Agitation – Psychosis Differential
- Agitation – Psychosis De-Escalation
- Agitation Medication
- Psychosis Medication

- Agitation – Psychosis Evaluation
- Agitation – Psychosis Transfer
- Psych Monitoring

Hyperadrenergic Symptoms of Stimulant Intoxication

The literature review identified several studies on the management of hyperadrenergic symptoms in patients with stimulant intoxication. In a systematic review focused on cocaine related cardiovascular toxicity, Richards et al concluded that calcium channel blockers may decrease hypertension and vasospasm, but not necessarily tachycardia, whereas benzodiazepines appear safe for non-cardiovascular related symptoms.

When assessing stimulant intoxication, clinicians should be assessing hyperadrenergic symptoms including tachycardia, hypertension, hyperthermia, and agitation. Ongoing monitoring and management of vital signs, especially heart rate and blood pressure, is critical for the prevention of complications that may result from untreated hyperadrenergic symptoms. GABAergic agents are the primary treatment for stimulant related hyperadrenergic symptoms.

Beta-blockers are generally contraindicated in patients with cocaine intoxication and heart disease.[92] If beta blocker are being considered a beta blocker with concomitant alpha-1 antagonism is preferred (labetalol for example) due to a low risk of unopposed alpha-stimulation. Where beta blockers are contraindicated, and as symptoms indicate, other pharmaceutical options such as calcium channel blockers, alpha 1 blockers and alpha 2 agonists, and nitric oxide-mediated vasodilators can be considered.

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 alpha2-adrenergic agonists (e.g., dexmedetomidine for more severe hyperadrenergic symptoms, clonidine for mild to moderate symptoms) are not only beneficial in treating stimulant-induced agitation but can be useful in the treatment of hypertension and tachycardia and should be considered in the management of the hyperadrenergic state of stimulant intoxication. Clinicians should monitor for medication side effects with usual care.

Hyperadrenergic Symptoms of Stimulant Intoxication Recommendations

1. 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 hyperadrenergic symptoms. (Approve 100%, Strong 83%)

2. Clinicians should treat patients in a stimulant-induced hyperadrenergic state with GABAergic agents (e.g., benzodiazepines, phenobarbital, propofol). Benzodiazepines can be considered first line treatment for this purpose. (Approve 100%, Strong 60%)
3. 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 (e.g., carvedilol, labetalol) (Approve 100%, Conditional 50%)
    b. An alpha2-adrenergic agonist (e.g., clonidine for mild to moderate symptoms, dexmedetomidine for severe symptoms) (Approve 100%, Conditional 33%)
    c. Where beta blockers are contraindicated, clinicians can consider other pharmaceutical options such as calcium channel blockers, alpha2 agonists or alpha1 antagonists, and nitric oxide-mediated vasodilators with consideration of other clinically relevant signs and symptoms. (Approve 100%, Conditional 50%)
    d. While calcium channel blockers, alpha2 agonists, alpha1 antagonists, and nitric oxide-mediated vasodilators may be most beneficial in treating hypertension or vasospasm, clinicians should be alert to potential side effects including poor control over, or reflex, tachycardia. (Approve 100%, Strong 50%)
4. If there is a hypertensive emergency in a patient with stimulant intoxication, clinicians should:
    a. Use short-acting agents such as sodium nitroprusside, phentolamine, or dihydropyridine-type calcium channel blockers (Approve 100%, Strong 50%)
    b. Avoid long acting antihypertensives to avoid abrupt hemodynamic collapse (Approve 100%, Strong 50%)
    c. Use nitroglycerin if there are signs of cardiac ischemia. (Approve 100%, Strong 50%)

Please see the following evidence to decision table(s) on pages 664-693 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- Hyperadrenergic Monitoring
- Hyperadrenergic Medications
- Hyperadrenergic Adjunct
- Hypertensive Emergency

Withdrawal Symptoms

Mental health symptoms including depression, anxiety, and psychosis are common during stimulant withdrawal and in StUD (See Co-Occurring Disorders section). The current standard of care for managing stimulant withdrawal is focused on ameliorating symptoms and minimizing risks. Mental health comorbidities can be managed with psychosocial interventions as well as antidepressants and antipsychotics, as indicated.

Behavioral and environmental interventions should be used to create a calming environment. Symptoms that may require pharmacotherapeutic management include agitation, psychosis, depression, and insomnia, among others. It is important to differentiate between short term symptoms and an underlying mental health disorder to determine appropriate treatment.

Many patients with StUD have persistent challenges with insomnia. Patients may experience increased sleep during the initial crash 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 pharmacological management, including with sedating antidepressants or antipsychotics.

A few pharmacotherapies have been investigated for the treatment of stimulant withdrawal. However, most of the studies are small and of low quality. A Cochrane review on treatment of amphetamine withdrawal was reviewed that included four RCTs involving 125 participants. No pharmacotherapies were found to be effective for treating general stimulant withdrawal. There have been some potentially promising preliminary findings; however, these findings need to be replicated in larger cohorts before leading to changes in clinical practice.

Medications may be helpful to reduce symptoms associated with stimulant withdrawal. For example, treating insomnia, muscle aches, and other symptoms of withdrawal with over the counter or prescription medications may help support ongoing treatment engagement. In addition, for patients who experience acute or persistent depressive symptoms that are not resolving as expected as withdrawal symptoms improve, antidepressants (e.g., mirtazapine, bupropion) may be appropriate. See the Co-occurring section for additional information on determining whether symptoms are pre-existing, or withdrawal induced, which will influence the treatment plan.

Acute Issues and Complications

Acidosis

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

Significant acidosis (i.e., acidosis associated with persistent chemistry abnormalities, persistent neuromuscular agitations, temperature elevation, and/or a long duration of intoxication) should be managed in acute care settings according to best practice. 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 more acute measures (e.g., cardiac and electrolyte monitoring, administration of sodium bicarbonate, etc.) may be indicated.

Chest Pain

The 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 medications that activate the GABA type A chloride channel, such as benzodiazepines, phenobarbital, propofol. 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," but evidence suggests that the risk is much lower than hypothesized.[93–95] Shin et al[96] conducted a systematic review and meta-analysis of the use of beta blockers to treat cocaine intoxication and cocaine-associated chest pain. Beta blockers were not associated with adverse events,

> Unopposed alpha-stimulation can result in an acute increase in blood pressure and/or coronary artery vasoconstriction following beta-blocker administration.

including MI/myocardial necrosis or death during hospitalization and long-term follow up.[97] For complex situations, consult with cardiology or toxicology.

Chest Pain Recommendations

1. For patients experiencing chest pain during stimulant intoxication, clinicians should initiate treatment for the underlying intoxication with GABAergic agents that activate the GABAA chloride channel (e.g., benzodiazepines, phenobarbital, propofol) as long as there are no clinical contraindications. (Approve 90%, Conditional 50%)
2. If beta-blockers are used in patients with stimulant intoxication experiencing chest pain, clinicians should consider using one with concomitant alpha-1 antagonism such as carvedilol and labetalol. If an unopposed beta-blocker was used in a patient who is or was recently stimulant intoxicated, clinicians should consider also providing a coronary vasodilator (e.g., nitroglycerin, calcium channel blocker). For complex situations, consult with cardiology or toxicology. (Approve 100%, Conditional 50%)
3. While treating underlying stimulant intoxication in patients experiencing chest pain, clinicians should concomitantly evaluate for acute coronary syndromes (ACS) and other causes of acute chest pain in stimulant intoxication (pulmonary, musculoskeletal (MSK), etc.). Chest pain that does not fully resolve with the signs and symptoms of stimulant intoxication should be evaluated and treated following current standards of care. (Approve 100%, Strong 50%)

Please see the following evidence to decision table(s) on pages 694-728 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- Chest Pain Medication
- Chest Pain Beta-Blockers
- Chest Pain Evaluation

Dehydration, Electrolyte and Fluid Imbalance

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

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

water intake during MDMA intoxication.[82] Existing guidelines suggest that treatment proceed as usual.[82] The CGC agreed, determining that stimulant-related hyponatremia should be managed according to best practice by replacing sodium. Patient follow-up should include routine and ongoing screening for electrolyte and kidney problems.

Hypertensive Emergency

The review identified two systematic reviews that examined treatment for stimulant-associated hypertensive emergency. All evidence was from case reports and case series, and found that cocaine-associated hypertensive emergencies were successfully treated by dexmedetomidine and ATS-associated hypertensive emergencies were successfully treated by propranolol, 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-type calcium channel blockers. Long acting antihypertensives should be avoided because of the risk of abrupt hemodynamic collapse. Additionally, they recommended the use of nitroglycerin if there are signs of cardiac ischemia.

Hyperthermia

Hyperthermia caused by autonomic hyperactivity during acute stimulant intoxication can complicate management of intoxication and may require cooling interventions. No studies were found on managing hyperthermia in patients with stimulant intoxication. The CGC did not identify a clinical recommendation specific to stimulant intoxication or withdrawal. Hyperthermia should be managed according to best practice.

Neutropenia

Neutropenia can be life-threatening, although it is generally rare and transient. No studies were found on managing neutropenia in patients who use stimulants. The CGC determined that neutropenia should be managed according to best practice. While neutropenia quickly improves in most patients after cessation of exposure to levamisole, if neutropenia isn't improving, and there is concern for neutropenic fever/infection, clinicians should consider consulting a hematologist.

QRS Widening

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

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

In animal models and studies of cocaine toxicity, sodium bicarbonate improved blood pressure and myocardial function. There are also literature reviews on the use of sodium bicarbonate in humans where cocaine was identified as one of the causal factors for QRS widening. While improvement in cardiac function is the main reason to treat with sodium bicarbonate, correction of metabolic acidosis will also occur. However, this treatment can exacerbate the risk for QT prolongation if present by lowering serum potassium concentrations. There have been sodium bicarbonate shortages at times and 3% hypertonic saline has been used as a sodium replacement, but it doesn't have the effect on acid/base normalization.

QRS Widening Recommendations

1. 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 treat with sodium bicarbonate to improve the conduction block and contractility. This will also improve metabolic acidosis if present. (Approve 89%, Strong 60%)

Please see the following evidence to decision table(s) on pages 729-732 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- QRS Widening

Rhabdomyolysis

No studies were identified on managing rhabdomyolysis specific to stimulant intoxication or withdrawal. The CGC determined that rhabdomyolysis should be managed according to best practices, including:

- Replace fluids to ensure a urine output of > 2 mL/kg/h.
- Avoiding urinary alkalinization, as it inhibits amphetamine elimination.
- Following up with routine and ongoing screening for kidney problems in those with movement disorders or seizures.

Seizure

No studies were identified that evaluated strategies for assessment and diagnosis of stimulant-related seizure. Consensus in clinical guidelines is to evaluate seizure according to best practice.[64,80,82]

While the recommendations below reflect standard treatment for any toxicity or withdrawal-related seizures, the CGC includes it in the Guideline because of its importance. 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.[98] Benzodiazepines are generally preferred as the initial treatment because of their relatively wider availability and ease of use, rather than demonstrating superior effectiveness. Phenobarbital and propofol are second line agents for the management of stimulant induced seizures, although propofol is preferred if seizures are severe or refractory. Acute care setting should have order sets for withdrawal seizures, with consideration for medication shortages.

In cases where seizure is associated with a complication of stimulant use rather than stimulant toxicity (e.g., hyponatremia or trauma), then standard treatments should be provided (including standard seizure medications when indicated). If a seizure is hyponatremia-related, hyponatremia should also be treated by replacing sodium (see Hyponatremia).

Monitoring can proceed according to standard practice for seizure management. While there is a risk of undersedation (not controlling the seizure) vs over-sedation (side effects from medication), side effects can be anticipated and are tolerable given the harm of recurrent seizure. The risk of over and undersedation can be reduced through provider education on appropriate dosing and titration.

During severe stimulant intoxication, if seizures are not controlled by GABAergic medications, clinicians may consider inducing paralysis (emergently) with monitoring (i.e., EEG). If a patient is at the level of end-organ dysfunction cooling should be achieved via

medications to stop muscle activity (e.g., with benzodiazepines), and potentially other strategies (IV fluids, lavage, evaporative, ice bath (if life-threatening)).

Seizure Recommendations

1. When patients present to the emergency department with a seizure following stimulant use, a full neurological work-up is not necessary if the seizure is well explained by substance use or withdrawal. (Approve 90%, Conditional 43%) When the etiology of seizures is not well explained by stimulant use, the workup and management of seizures should proceed according to usual best practices. (Approve 90%, Strong 67%).
2. For stimulant intoxication -related seizure or concomitant alcohol or sedative related seizures, clinicians should treat with a benzodiazepine. (Approve 100%, Strong 50%) If seizures are refractory to benzodiazepines, clinicians can consider treating with either phenobarbital or propofol. (Approve 100%, Strong 50%).

Please see the following evidence to decision table(s) on pages 733-749 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- Seizure Workup
- 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 kidney and cardiac problems.

A nationally representative survey of Australian adults estimated that 50.4% of individuals who use stimulants non-medically would develop a StUD within 14 years of onset of use.[99] Pre-existing mental disorders were significantly associated with increased risk. Screening for StUD presents an opportunity for clinicians to engage patients in a brief intervention using motivational interviewing or enhancement techniques to facilitate referral for an assessment for StUD if indicated. While existing evidence suggests that referral to treatment does not result in effective engagement in ongoing care, the benefit of treating those who need it is substantial. Evidence suggests patients find referrals to be acceptable.

Follow-up Recommendations

1. Clinicians should assess patients for StUD and engage patients in a brief intervention using motivational interviewing or enhancement techniques to facilitate referral for an assessment for StUD if indicated. (Approve 90%, Conditional 50%)

Please see the following evidence to decision table(s) on pages 750-768 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

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

Secondary and Tertiary Prevention

This section addresses secondary and tertiary prevention.

- Secondary Prevention: Clinical practices to identify patients who use stimulants in non-medical ways who do not meet criteria for StUD and to intervene to prevent escalation to StUD
- Tertiary Prevention: Clinical recommendations to reduce the harm associated with non-medical 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 (i.e., non-medical or non-prescribed use of stimulants) and conducting a further assessment for risky stimulant use and StUD. Screening refers to asking questions about substance use and related risks, not toxicology testing. Stimulant misuse can be identified using existing screening instruments. Screening for drug use, including stimulants, in primary care settings is recommended by the US Preventive Services Task Force (USPSTF).[100]

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

Finally, clinicians should check their state's Prescription Drug Monitoring Program (PDMP) prior to prescribing psychostimulant medication. 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. The committee cautioned that clinicians may misinterpret the PDMP and use it punitively, although the likelihood of this can be reduced through education. The committee agreed the risk of misuse of PDMP information would not preclude the benefit of initiating a conversation about a patient's prescriptions.

Screening Recommendations

1. When general healthcare providers screen adolescents or adults for risky substance use (as per USPSTF guidelines[100]), they should include screening for stimulant misuse (i.e., non-medical or non-prescribed use). (Approve 100%, Strong 64%)
2. Clinicians should consider more frequent screening for stimulant misuse in patients who take prescribed psychostimulant medication. (Approve 92%, Strong 42%)
3. Clinicians should check their state's Prescription Drug Monitoring Program (PDMP) prior to prescribing psychostimulant medication. (Approve 92%, Strong 67%)

Please see the following evidence to decision table(s) on pages 769-789 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- Screening for Stimulants
- Screening for Prescription Psychostimulants
- 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 of 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. In order to properly determine psychosocial and harm reduction service needs, clinicians should gather information about patterns of stimulant use. This includes frequency and amount of use, use of stimulants with no one else present, and co-use of other substances. History of stimulant-related emergency department visits and hospitalizations as well as history of overdose also should be gathered. Finally, clinicians should inquire about routes of administration, particularly injection drug use. There are a variety of screening tools available to screen for risky injection drug use. The committee emphasized that gathering detailed information in order to tailor harm reduction interventions would have a large potential benefit.

As evidence suggests that risky sexual behaviors are more prevalent in individuals who use stimulants, clinicians should also gather information about these behaviors to properly determine psychosocial and harm reduction service needs. These include:

- Chemsex (using drugs to enhance sexual experiences)
- Not consistently using condoms or lubricants[101]

- History of bacterial sexually transmitted infections STIs (chlamydia, syphilis, gonorrhea) during the past 6 months[102]
- Being diagnosed with an STI within the past year[101]
- Belonging to a population that has a high STI prevalence
- Having a partner(s) at high risk for STIs[101]
- Recent pregnancy or pregnancy of a sexual partner[102]
- Having multiple sex partners[101]
- Being the receptive penetrative partner (anal or vaginal) without protection
- Recent history of being a victim of sexual assault

The committee emphasized that gathering detailed information in order to tailor harm reduction interventions (e.g., PrEP, education) would have a large potential benefit. The committee noted that screening for risky sexual behaviors interacts with factors such as interpersonal violence (IPV)/trauma, race, sex, and gender identification. Subgroup population differences may influence the intervention given (e.g., Transgender, IPV/trauma history, HIV+ patient/partner). While the possibility exists for patients to experience feelings of stigma or bias, this may depend on clinician expertise in asking questions. While there is the possibility of confidentiality violations through medical record documentation the likelihood of this happening is deemed low. The committee concluded that the benefits of identifying individuals who would benefit from targeted harm reduction interventions outweighed the risk. There are a variety of screening tools available to screen for risky sexual behaviors.

Clinicians should consider asking patients about the context of their stimulant use (e.g., 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 conversation around harm reduction. The committee agreed this is of particular importance for SGM patients. While implementation of this practice is straightforward, there may be a need to train clinicians to ask about the context of substance use in a non-judgmental and non-stigmatizing manner.

Clinical experience suggests that patients who engage in non-medical 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 committee noted the rate is higher in college students who non-medically use stimulants. The committee 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

1. For patients who screen positive for stimulant misuse:
    a. 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. (Approve 100%, Strong 67%)
    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 (Approve 91%, Strong 73%)
            2. Use of stimulants with no one else present
            3. Co-use of other substances, particularly opioids, alcohol, and other central nervous system depressants (Approve 91%, Strong 73%)
            4. History of overdose (Approve 91%, Strong 73%)
            5. History of stimulant-related emergency department visits and hospitalizations (Approve 91%, Strong 64%)
        ii. Routes of administration, particularly injection drug use (Approve 100%, Strong 82%)
        iii. Risky sexual behaviors
    c. Clinicians should consider asking patients about:
        i. The context of their stimulant use (e.g., Chemsex, weight loss, academic or work performance, staying awake) (Approve 91%, Strong 45%)
        ii. Trauma (Approve 83%, Strong 50%)
        iii. Intimate partner violence (Approve 83%, Strong 50%)
    d. Clinicians should conduct baseline lab work based on clinical assessment of risk factors (outlined in the Stimulant Use Disorder Assessment section). (Approve 100%, Strong 45%)
2. Patients who engage in non-medical use of prescription stimulants should be evaluated for ADHD, which may also require treatment. (Approve 100%, Strong 58%)

Please see the following evidence to decision table(s) on pages 790-824 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- Assess Route Complications – Prevention
- Assess Risky Patterns – Prevention
- Assess Risky Sex – Prevention
- Assess Context – Prevention

- Assess Trauma - Prevention
- Assess Baseline Labs – Prevention
- Assess ADHD – Prevention

Early Intervention for Risky Stimulant Use

Interventions to Reduce Risky Stimulant Use

Clinicians should consider providing a brief intervention using motivational interviewing (MI) techniques to patients with any risky stimulant use to encourage patients to reduce or stop their use. While no direct evidence exists to suggest that brief intervention is effective for stimulant use outcomes, brief intervention is a necessary first step to providing harm reduction education and treatment for stimulant use, which can lead to reduced harms stemming from use, increasing readiness to change, and increasing motivation for treatment. Clinicians should be aware of some of the unique motivators for stimulant use and be ready to discuss and suggest safer alternatives as part of a brief intervention for stimulant use (e.g., Chemsex, weight loss, academic and work performance, staying awake). The benefits of engaging the patient in meaningful harm reduction are significant.

Interventions to Reduce Risky Stimulant Use Recommendations

1. Clinicians should consider providing a Brief Intervention to patients with any risky stimulant use using Motivational Interviewing techniques to encourage patients to reduce or stop their use. (Approve 92%, Strong 33%)
2. Clinicians should be aware of some of the unique motivators of stimulant use and be ready to discuss and suggest safer alternatives as part of a Brief Intervention for stimulant use (e.g., Chemsex, weight loss, academic and work performance, staying awake). (Approve 92%, Strong 50%)

Please see the following evidence to decision table(s) on pages 806-809; 825-844 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- Early Intervention SBI
- Assess Context - Prevention

Referral to Treatment for Stimulant Use Disorder

While direct evidence for referral to treatment is relatively weak, the clinical benefits of offering and facilitating treatment for those who need it is substantial. Therefore, the

committee recommends 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 a warm handoff should be provided. For patients who are ambivalent about a referral for StUD assessment or treatment, clinicians should consider using interventions to enhance motivation for treatment (e.g., MI, motivational enhancement therapy [MET]).

Limited evidence exists for the use of peer navigators to link patients to StUD assessment and treatment.

Referral to Treatment for Stimulant Use Disorder Recommendations

1. For patients who screen positive for risky stimulant use, clinicians should conduct or offer a referral for comprehensive assessment and treatment for potential StUD with linkage support, including a warm handoff. (Approve 100%, Strong 67%)
2. For patients who are ambivalent about a referral for StUD assessment or treatment, clinicians should consider using interventions to enhance motivation for treatment (e.g., MI, MET). (Approve 100%, Strong 58%)
3. Clinicians should consider the use of peer navigators to link patients to StUD assessment and treatment. (Approve 83%, Weak 42%)

Please see the following evidence to decision table(s) on pages 845-868 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- Early Intervention Refer to Treatment
- 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.

Stimulant Use Harm Reduction Education

When education is paired with other harm reduction practices, evidence is strong for a variety of outcomes. The committee emphasized that education is the foundation of change and is relatively easy to implement. The importance of patient education is readily supported across a range of other medical conditions. The committee noted that patients with high readiness to change may have the best outcomes. Therefore, clinicians should

provide education to patients with non-medical stimulant use, particularly with respect to safer stimulant use, safer injection practices, safer sexual practices, and overdose prevention.

Stimulant Use Harm Reduction Education Recommendations

1. For patients with risky stimulant use, clinicians should:
    a. Offer basic harm reduction education about safer stimulant use. (Approve 92%, Strong 58%)
    b. Tailor harm reduction education to the patient's patterns of substance use (e.g., context of their use, route of administration, and type of preparation). (Approve 100%, Strong 58%)
    c. Refer to relevant local harm reduction services as indicated based on the clinical assessment.
    d. Offer harm reduction education on overdose prevention and reversal. (Approve 82%, Strong 64%)
    e. Offer harm reduction education regarding risky sexual behaviors. (Approve 100%, Strong 67%)
    f. Offer condoms and lubrication or advice about where to obtain them. (Approve 100%, Strong 50%)
    g. Consider providing information about local STI testing services where patients can obtain free or low-cost testing. (Approve 100%, Strong 58%)

Please see the following evidence to decision table(s) on pages 869-933 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- Education Stimulants
- Prevention Refer to Harm Reduction
- Education Overdose
- Education Sex
- Prevention Condoms
- Prevention Routine STI Testing

Overdose Prevention and Reversal

The US is currently experiencing an historic rise in drug overdose and overdose deaths due to high potency synthetic opioids. These synthetic drugs, particularly fentanyl and its analogs, are increasingly used with stimulants.[8] Naloxone is well known to prevent opioid overdose deaths. To the extent that patients either intentionally or unintentionally use opioids with stimulants, the committee agreed that naloxone education and access are

potentially beneficial with relatively little risk. Therefore, for patients who use stimulants from non-medical sources, or are socially engaged with others who do, clinicians should prescribe or distribute naloxone, or refer patients to where they can obtain naloxone in the community.

Comprehensive drug checking is becoming a standard harm reduction practice. Some evidence was found that persons who use drugs would use less if fentanyl was detected before use. At least 1 study found that accessing comprehensive drug checking services was associated with reduced overdose rate. These findings varied by population studied (e.g., festivals, people who inject drugs) and studies focused on opioid use, although people who use stimulants were not explicitly excluded.

While not as prevalent in the US, supervised consumption sites (SCS) are effective at reducing the incidence of drug use-related morbidity and mortality. Their impact varies depending on SCS use frequency and site. While SCS is 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. Therefore, the committee agreed that clinicians should consider referring individuals who use stimulants non-medically to local SCS when available. It is important to note that SCS are currently illegal under federal law.

Overdose Prevention and Reversal Recommendations

1. For patients who use stimulants from non-medical sources, or are socially engaged with others who do, clinicians should prescribe or distribute naloxone or refer patients to where they can obtain naloxone in the community. (Approve 90%, Strong 73%)
2. Clinicians should recommend that patients perform comprehensive drug checking, including testing with fentanyl test strips, every time they get a new batch of stimulants from non-medical sources and review the technique for using fentanyl test strips when permitted by state law. (Approve 82%, Strong 40%/Weak 40%)
3. Clinicians should consider referring individuals to local supervised consumption sites if available. (Approve 83%, Strong 83%)

Please see the following evidence to decision table(s) on pages 934-968 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- Prevention Naloxone
- Prevention Drug Checking
- Prevention Supervised Consumption

Safe Sex Practices

While there is no specific evidence on referring or providing STI testing in people who use stimulants, it is known that risky sexual behaviors are more prevalent in this population and that earlier identification of STI is beneficial and reduces transmission. Therefore, the committee recommended that clinicians offer, or refer for, testing for STIs at least every 3 to 6 months. More frequently testing may be indicated depending on the individual patient's risk. Clinicians should also 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.

Safe Sex Practices Recommendations

1. For patients who engage in risky sexual behaviors, clinicians should:
    a. Offer or refer for testing for STIs at least every 3 to 6 months or more frequently depending on the individual patient's risk as per CDC and USPSTF Guidelines.[101,103] (Approve 100%, Strong 64%)
    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. (Approve 100%, Strong 45%)

Please see the following evidence to decision table(s) on pages 882-885; 929-933 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- Prevention Routine STI Testing
- Prevention Refer to Harm Reduction

Injection Drug Use

Syringe services programs are associated with reduced HIV, Hepatitis C (HCV), other blood-borne infections, safer injection technique, fewer wounds and complicated infections. Combining the provision of safe injection supplies with other interventions such as linkage to treatment and addiction medications (e.g., for co-occurring OUD) can increase the magnitude of desirable effects. The committee 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 will increase injection drug use are refuted by evidence. Therefore, the committee recommended that clinicians provide or refer for harm reduction education on safer injection practices and safe injection supplies.

Injection drug use recommendations

1. 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 patients' stimulant(s) and preparation(s) of choice (e.g., safer acid pairings for crack cocaine injection). (Approve 100%, Strong 67%)
b. Provide or refer for safe injection supplies and harm reduction services (Approve 92%, Strong 67%)

Please see the following evidence to decision table(s) on pages 969-1002 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- Education Injection Drug Use
- Prevention Injection Drug Use Kits

HIV Preexposure Prophylaxis (PrEP)

Strong evidence exists that PrEP is effective at preventing HIV overall and consistently across sub-groups with the highest risk for HIV. While this is indirect evidence (not explicitly tested in people who use stimulants), substantial benefits are expected. PrEP has not been shown to increase risky sexual behaviors or risky injection behaviors. While there are some undesirable side-effects, preventing HIV is a critically important outcome. Therefore, the committee recommends that clinicians offer HIV PrEP to patients who use stimulants and are at increased risk for HIV due to risky sexual behavior or injection drug use.

HIV Preexposure Prophylaxis (PrEP) recommendations

1. Clinicians should offer HIV PrEP to patients who use stimulants and are at increased risk for HIV as per CDC and UPSPTF Guidelines, including those who:
    a. Engage in risky sexual behavior (Approve 92%, Strong 75%)
    b. Access postexposure prophylaxis (PEP) regularly (Approve 91%, Strong 70%)
    c. Inject drugs (Approve 91%, Strong 70%)

Please see the following evidence to decision table(s) on pages 1003-1015 of the EtD document:

- Prevention PrEP

Oral Health

It is well known that people who use stimulants are at a high risk of dental complications, such as poor dentition, dental caries, and abscesses. Poor oral health is associated with subsequent malnutrition. Therefore, the committee recommended that clinicians encourage patients who use stimulants to maintain good oral hygiene and receive regular dental care and offer a referral to a dental care provider if they do not already have one. While this recommendation is straightforward, the committee recognized challenges with regard to implementation. Many insurance plans do not cover dental care adequately, and making referrals requires the clinician to be aware of local resources.

Oral Health Recommendations

1. People who use stimulants are at high risk of dental complications, such as poor dentition, dental carries, abscesses, as well as subsequent malnutrition. Clinicians should:
    a. Encourage patients who use stimulants to maintain good oral hygiene and get regular dental care. (Approve 100%, Strong 73%)
    b. Offer a referral to a dental care provider if the patient does not already have one. (Approve 100%, Strong 67%)

Please see the following evidence to decision table(s) on pages 1016-1024 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- Prevention Oral Health

Nutrition

People who use stimulants often experience appetite suppression and go for long periods without appropriate nutrition. These patients are therefore at high risk for nutritional deficits, such as: malnutrition, cachexia, and sequalae of specific vitamin deficiencies. Based on clinical expertise, the committee recommended that clinicians encourage patients who use stimulants to eat nutritious food and inquire about food/nutrition access.

Nutrition recommendations

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

a. Inquire about food/nutrition access. (Approve 78%)
b. Encourage patients who use stimulants to remember to eat nutritious food. (Approve 80%)

Please see the following evidence to decision table(s) on pages 1025-1032 of the EtD document for a summary of evidence, relevant citations, and CGC judgements:

- Prevention Nutrition

Areas for Further Research

Assessment

Additional research is needed regarding:

1. How to routinely screen for end organ damage including but not limited to the following: cardiac remodeling (e.g., structural or functional changes in the heart), dental disease, neurological alterations, dermatological changes, psychiatric disorders, and renal disease as part of an early identification and harm reduction strategy for people who use stimulants. Research should address the components of routine screening and indications for when more than routine screening should be conducted.
2. Assessment of use of potentially adulterated stimulants.
3. Assessment priorities considering the preferred method of use. For example, what tests should be conducted if the main method of use is insufflation or smoking (eg, low dose computer tomography)?
4. Optimal assessment strategies for co-occurring SUDs and/or mental health disorders and how they affect treatment recommendations based on assessment (e.g., how to assess someone with major depressive disorder, suicidality, and methamphetamine use) additional research is required.
5. The appropriateness of modifying the StUD diagnostic criteria in special populations (adolescents, pregnant women, elder population)/special circumstances (progressing rapidly etc.) or in cases where the 12-month diagnostic time criterion is not met yet (following DSM-5 criteria), but the potential consequences are high.

Behavioral Treatment

Additional research is needed regarding:

1. CM in clinical practice
2. CRA implementation barriers
3. CRA in ATS use disorder populations
4. The cultural appropriateness of CRA for minority populations.
5. The combination of CRA with medication treatments such as bupropion or modafinil.

Pharmacotherapy

Additional research is needed regarding:

1. Accelerating development of FDA approved pharmacotherapies for the treatment of StUD.

2. How to optimize outcomes by combining pharmacotherapy and behavioral treatments.
3. Determining the most appropriate treatment of all co-occurring disorders that are present when an individual has a StUD and one or more co-occurring conditions (e.g., ADHD, OUD, major depressive disorder, post-traumatic stress disorder (PTSD), schizophrenia, suicidality, etc.).
    a. Given increasing rates of overdose deaths involving opioids and stimulants, strategies for treating patients with co-occurring OUD and StUD should be prioritized.
4. Further research on off-label use of medication to treat StUD.
5. Development of non-pharmacological interventions for the treatment of StUD such as neuromodulation techniques (Transcranial Magnetic Stimulation- TMS, Transcranial Direct Current Stimulation- tDCS, low intensity focused ultrasound).
6. Pharmacological and non-pharmacological interventions in underrepresented populations, particularly Black, Indigenous, and people of color (BIPOC) and SGM.
7. Treatment of pregnant women.
8. Treatment in correctional settings.

Intoxication

Additional research is needed regarding:

1. Development of a stimulant overdose reversal medication. As, addiction medicine has not established a universal definition for a “stimulant overdose.” Future research should clearly outline the parameters that constitute a stimulant overdose.
2. Management of intoxication and overdose when multiple substances are involved.
3. A universal definition for stimulant induced psychotic disorder, especially in individuals using methamphetamine.
4. Psychopharmacological and psychosocial treatments for stimulant induced psychotic disorder along, including timing of interventions.

Harm Reduction

1. Additional research is recommended on assessment of harm reduction practices including access to and use of safer use equipment and drug checking supplies.

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Appendix A. 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 imbalance: Dehydration, acidosis, hyperkalemia, hyponatremia
- Hyperthermia
- Agitation
- Psychosis
- Cardiovascular dysfunction, such as: cardiac dysrhythmias and hypertensive emergency, acute decompensated heart failure, takotsubo cardiomyopathy.
- Acute neurologic complications such as seizures or cerebrovascular accidents
- Serious infections, such as: infective endocarditis, osteomyelitis, epidural access, septic arthritis, serious skin infections, bacteremia, and sepsis.
- Rhabdomyolysis
- Movement disorders
- Gastrointestinal perforation
- Trauma and trauma-related complications
- Risk for harm to self or others

Appendix B. Differential Diagnosis for Agitation/Psychosis:

- Indications for head CT:
  - Altered mental status
  - Neurologic symptoms
  - Signs of physical trauma (TBI)
  - Found down (comatose) [can be the result of trauma, stroke, stimulant-induced stroke]
  - Anoxic injury
- Indications for lumbar puncture and blood tests for encephalitis:
  - Fever
  - Meningeal signs and symptoms (stiff neck, photophobia, back pain)
  - Indication for EEG
  - Seizure not well explained
  - Neurologic signs and symptoms not well explained
  - Persistent encephalopathy

Additional causes of agitation/psychosis:

- Nutritional deficiencies (e.g., Wernicke's)
- Neurologic disorders (e.g., Parkinson's, dementia)
- Brain tumor
- Infections
- Endocrine problems
- Thyroid toxicity (t3, T4)
- Hormonal abnormalities (e.g., Steroid-induced psychosis)
- Autoimmune problems
- NMDA receptor encephalitis
- Medication reactions that cause neuropsychiatric symptoms

Appendix C. Baseline Laboratory Testing

In developing this Guideline, the CPG Committee 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 provide the full standard of care that should be provided to any patient with SUD, including baseline laboratory testing routinely ordered for new patients with a substance use or psychiatric disorder.

Clinicians should include the following clinical tests for most patients:

- A complete blood count
- Comprehensive Metabolic Panel (CMP; renal panel, liver enzyme tests)
- Screening for infectious diseases in accordance with current guidance
- HIV, Hepatitis C (HCV) for all patients
- Hepatitis B (HBV) for patients at increased risk for infection
- Screening for sexually transmitted infections (gonorrhea, chlamydia, syphilis)
- Pregnancy testing for all patients with childbearing potential

Clinicians can also consider the following clinical tests:

- Tuberculosis for patients at increased risk for infection
- Hepatitis A (HAV) for patients at increased risk for infection
- Other clinical tests as necessary based on clinical assessment (e.g., CK if signs of rhabdomyolysis are present, such as increased muscle tone/rigidity and increased temperature)

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

Patients with stimulant intoxication should be routinely assessed for the following complications and sequalae of stimulant use and factors which impact treatment planning. Assess or refer for an assessment of these relevant conditions and issues and treat or refer to treatment in an appropriate medical or psychiatric setting when these conditions and issues are identified.

- General complications including weight change (e.g., body mass index [BMI]) and deficits in hygiene
- Cardiovascular complications such as: hypertension, arrhythmia, ischemia, pulmonary hypertension, heart failure
- Dental complications, such as: poor dentition, dental caries, abscesses
- Dermatologic complication, such as: picking, neurodermatitis, cellulitis/abscess and other skin/soft tissue infections
- Hepatic complications, such as: drug-induced hepatitis
- Infectious complications, including sexually transmitted infection (HCV, HIV)
- Neurological complications, such as: abnormal involuntary movement disorders, rigidity, tremor; seizures; stroke; cognitive impairment (memory, attention)
- Nutritional deficits, such as: malnutrition, cachexia, and sequalae involving specific vitamin deficiencies
- Oropharyngeal complications, such as: teeth grinding and jaw clenching, earache, headache, facial pain
- Renal complications, such as: acute kidney injury, chronic kidney disease
- Rhinological complications, such as: rhinitis, mucosal atrophy, rhinorrhea, smell, oronasal fistula, septum perforation
- Sexual dysfunction using trauma-informed screening practices.

Appendix E. Substance Use Disorder Biopsychosocial Assessment

In developing this Guideline, the CPG Committee sought to include recommendations that were specific to StUD, or of increased importance in the treatment of this disease. However, it is important for clinicians to provide 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 (e.g., risks associated with current patterns of substance use)
- Social and environmental factors that may impact access to or efficacy of care, such as housing, transportation, and childcare needs, among others.
- Trauma-related concerns using trauma-informed screening practices.
- Biomedical comorbidities
- Psychiatric comorbidities and psychiatric disorder history
- Risk factors for infectious diseases such as HIV and Hepatitis A, B, and C, 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
- Co-morbid behavioral addictions (e.g., problem gambling, internet/gaming addiction, sex addiction)
- Family/household substance use, SUD, and psychiatric history

Appendix F. Topics with Insufficient Evidence

Guideline Section	Intervention
Tech-based/Alternative interventions	Text messaging interventions for StUD
Tech-based/Alternative interventions	Exercise as a standalone or add-on treatment for StUD
Tech-based/Alternative interventions	Auricular acupuncture for ATS use disorder
Tech-based/Alternative interventions	Non-invasive brain stimulation for StUD
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-acetyl cysteine

ATS = Amphetamine-Type Stimulant; StUD=Stimulant Use Disorder

Appendix G. Medications for Managing Intoxication

Agent/Class	Mechanism	Example dosing	Indications	Other considerations
Sedatives				
Benzodiazepines (BZDs) (first line)	GABA-A agonist	Lorazapam 1-2 mg IV based on clinical signs and symptoms and duration of effects Diazapam 5-10 mg orally for less severe symptoms based on patient parameters Midazolam 5 mg IM for acute agitation in adult patients	Excitatory symptoms Anxiety/Agitation Neuromuscular excitation Seizures	Parenteral vs oral administration based on signs and symptom severity and drug availability (e.g., parenteral BZD shortages) Lorazapam has very slow onset IM (15-30 min) If primary symptoms are psychosis, antipsychotics should be considered primarily or adjunctively
Phenobarbital (PBO)	Barbiturate receptor agonist	Incremental 129.6-258.2 mg parenteral/IV/oral based on symptoms and patient parameters Loading strategy (e.g., 5-10 mg/kg)	BZD shortages or contraindications Patient not responding to escalating doses of BZDs Severe sympathomimetic intoxication	Has high oral bioavailability. Oral dosing can be similar to parenteral dosing. Onset of effects, while slower than IV, is still fairly quick compared to other oral medications
Propofol	GABAergic + NMDA receptor antagonism	10-50 mcg/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 for synergy
Sympatholytics				
Clonidine	Alpha2-agonism +/- Other	0.1-0.2 oral q 4 hours PRN	Anxiety	Useful medication adjunctive to BZD Maintain hydration to avoid orthostatic symptoms

Dexmedetomidine		Start at 0.2-0.4 mcg/kg/hr and titrate every 30 minutes up to maximum of 1.5 mcg/kg/hr	For critically ill patients in the ED or ICU as primary or secondary medication for sedation	Useful medication adjunctive to BZD or other sedation agents Onset of effects generally 30-60 minutes 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
Atypical	Dopamine antagonism +/- Other	Olanzapine 5 mg oral Quetiapine 50-100 mg 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 oral/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 onset of action for IM administration compared to other agents

Abbreviations: BZD: Benzodiazepine; ED: Emergency Department; ICU: Intensive Care Unit; IM: Intramuscularly; IV: Intravenously
NMDA: N-methyl-D-aspartate receptor
PBO: Phenobarbital,
PRN: as needed
q: every

Appendix H. Additional Resources

- Intervention from Lotzin's[104] study, *Learning How to Ask*
- SAMHSA's Treatment Improvement Protocol (TIP) 57: Trauma-Informed Care in Behavioral Health Services (https://store.samhsa.gov/product/TIP-57-Trauma-Informed-Care-in-Behavioral-Health-Services/SMA14-4816)
- SAMHSA's Concept of Trauma and Guidance for a Trauma-Informed Approach (https://store.samhsa. gov/product/SMA14-4884): This manual provides a working concept of trauma and key principles of a trauma-informed treatment approach that can be used by behavioral health workers and an array of service systems. It also suggests methods for implementing a trauma-informed approach.
- SAMHSA's Treating Sleep Problems of People in Recovery from Substance Use Disorders
- Substance Abuse and Mental Health Services Administration. Suicide Assessment Five-step Evaluation and Triage (SAFE-T). 2009 [cited 2018 6th June]; Available from: https://www.integration.samhsa.gov/images/res/SAFE_T.pdf.