Evidence-based Practice Center Systematic Review Protocol

Project Title: Interventions for Substance Use Disorders in Adolescents: A Systematic Review

I. Background and Objectives for the Systematic Review

In 2015, in the United States, an estimated 1.3 million adolescents, aged 12 to 17, and 5.4 million young adults, aged 18 to 25, met diagnostic criteria for having a substance use disorder (SUD); the vast majority were untreated.[1] Adolescents with SUD are at risk of experiencing a cascade of far-reaching adverse outcomes that often persist into adulthood, including sexually transmitted infections[2], unintended pregnancy[3], criminal involvement[4], school truancy[5], psychiatric disorders[6], and physical health problems.[7] Adolescent substance use is associated with the leading causes of death in this age cohort: suicide, unintentional injury, and violence.[8, 9]

Prescription and over-the-counter medications are the most commonly misused substances, after alcohol, marijuana, and tobacco, among twelfth graders[10]; with 1 percent of youth between the ages of 12 and 17 reporting current opioid misuse.[11] Youth who use opioids are more likely to use other substances.[10] Among youth under 21 who initiate heroin use, 80 percent misused prescription and/or over-the-counter medication before the age of 18.[12] National concerns about opioid misuse, encompassing nonmedical use of prescription opioid-based medications (e.g., morphine, fentanyl) and the use of illegal opiates (e.g., heroin), have brought heightened attention to the significant risk of drug overdose death in adolescents.[13]

The pervasive negative consequences associated with untreated or ineffectively treated adolescent substance use (SU), and the high lethality of opioid misuse in particular, underscore the importance of treating substance use in adolescents.

In 2005, the American Academy of Child and Adolescent Psychiatrists (AACAP) created a Practice Parameter (PP) for the Assessment and Treatment of Children and Adolescents with SUDs. The 2005 Practice Parameters made eight recommendations pertaining to treatment. For behavioral treatments, AACAP concluded that family therapy models "have the most supporting evidence" and "individual approaches such as cognitive-behavioral therapy, both alone and with motivational enhancement therapy, have been shown to be efficacious." AACAP recommended that "medication can be used when indicated," noting that this recommendation was "not based on empirical research in adolescents but rather on research and experience with adults."[14] The AACAP also recommended that psychiatrists consider co-occurring mental health disorders, since the majority of adolescents with substance use problems present with a co-occurring mental health diagnosis. Recommendations made in the 2005 PP were limited by a relative lack of rigorous trials at the time.

Since the publication of the initial PP, there has been a proliferation of adolescent substance use treatment trials, many of which have employed more rigorous designs, larger samples, random assignment, direct comparisons of two or more active treatments, improved measures of substance use and other variables, manual-guided interventions, and longer-term outcome assessments. Reviews of the adolescent substance use literature have typically focused

only on behavioral treatments,[15-17] pharmacologic treatment of a specific SUD,[18] or on a specific treatment model (e.g., motivational interviewing[19] and screening, brief interventions, and referral to treatment).[20] In 2014, a guide developed by the National Institute of Drug Abuse (NIDA), identified multiple approaches to treating adolescent SUDs, which were divided into behavioral approaches, family-based approaches, addiction medicine, and recovery support services, but this report did not synthesize evidence on comparative effectiveness.[21] The American Academy of Pediatrics (AAP) Committee on Substance Use and Prevention recommended consideration of pharmacotherapy for adolescent and young adult patients with severe opioid use disorders or co-occurring alcohol use disorders.[22] Thus, there is a significant need for a rigorous and comprehensive synthesis of the adolescent substance use treatment literature that addresses both pharmacological and psychological treatments.

The planned systematic review (SR) will inform a Clinical Update and Clinical Practice Guideline to update the 2005 AACAP PP for the Assessment and Treatment of Children and Adolescents with SUDs. Given the high co-occurrence of substance use and other mental illnesses, and the increased focus on integrated treatment, there is significant need and opportunity to engage and educate psychiatrists as well as primary care physicians.[23]

The overarching goal of the review is to evaluate the available evidence for the treatment effects (and comparative effects) of available behavioral and pharmacologic interventions. In addition, the review will evaluate treatment effects across population subgroups and identify evidence (or gaps in evidence) regarding the key ingredients of successful interventions for problematic substance use in adolescents.

II. The Key Questions

The following are the Key Questions (KQs) to be addressed by this systematic review:

KQ 1: What are the effects of behavioral, pharmacologic, and combined interventions compared with placebo or no active treatment for substance use disorders and problematic substance use[1] in adolescents to achieve abstinence, reduce quantity and frequency of use, improve functional outcomes, and reduce substance-related harms?

a. How do benefits and adverse outcomes of interventions vary by subpopulations?[2]
b. How do benefits and adverse outcomes of interventions vary by intervention characteristics?[3]

KQ 2 What are the comparative effects of active interventions for substance use disorders and problematic substance use[1] in adolescents to achieve abstinence, reduce quantity and frequency of use, improve functional outcomes, and reduce harms?

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[1] Substances considered: alcohol, cannabis, opioids, sedatives/hypnotics/anxiolytics, stimulants, inhalants and hallucinogens. Tobacco is excluded.

[2] Subpopulations considered: **psychiatric co-morbidities**, **age** (early, middle and late adolescence), **sex and gender**, **race/ethnicity**, socioeconomic status and related characteristics (e.g., homelessness, poverty), pregnant, postpartum, and parenting adolescents, demographic/family characteristics. Factors in **bold** will be prioritized if necessary.

[3] Intervention characteristics: **target** (e.g. teen, family or group of teens), duration and setting.

a. How do comparative benefits and adverse outcomes of interventions vary by subpopulations? [2]
b. How do comparative benefits and adverse outcomes of interventions vary by intervention characteristics? [3]

III. Study Eligibility Criteria

Population (all KQs)

- Age: Adolescents (12 – 20 years inclusive)
  - *Exclude* if > 20 percent of study sample (or identifiable subgroup) is <12 or >20 years, combined
- SUD or problematic use of:
  - Alcohol
    - *Exclude* primary studies of treatment of alcohol use disorder/problematic alcohol use in the college setting (we will include existing systematic reviews)
  - Cannabis
  - Opioids
    - Nonmedical prescription drug use (codeine, hydrocodone, oxycodone)
    - Illicit (e.g., heroin, illicit synthetics)
  - Sedatives, hypnotics, or anxiolytics (e.g., benzodiazepines, carbamates, barbiturates, methaqualone)
  - Stimulants
    - Nonmedical prescription drug use (e.g., methylphenidate)
    - Illicit (e.g., cocaine, methamphetamine)
  - Inhalants
  - Hallucinogens (e.g., phencyclidine, ketamine, MDMA, LSD)
  - Unspecified or polysubstance use
    - *Exclude* if predominately tobacco/nicotine use
  - *Exclude* tobacco/nicotine use disorder or problematic tobacco/nicotine use
  - *Exclude* limited (or experimental) substance use that has not been deemed to be at least "problematic"
- Subpopulations of interest (not necessary for eligibility)
  - **Psychiatric comorbidities**
    - Attention deficit hyperactivity disorder (ADHD), depression, other internalizing and externalizing disorders.
  - ***Age***
    - Early adolescence (12 – 14 years)
    - Middle adolescence (15 – 17 years)
    - Late adolescence (18 – 20 years)
  - ***Sex and gender***
    - Male vs. female
    - Gender identity (cis vs. transgender)
    - Sexual orientation
  - ***Racial/ethnic minority***

- Socioeconomic status and related characteristics (e.g., homelessness, poverty)
- Pregnant, postpartum, and parenting adolescents
- Demographic/family characteristics
  - Demographics
  - Family and community dynamics (i.e. substance using family member)
  - Involvement with child protection services.

Interventions

- Behavioral health treatments (major intervention models are indicated by arrowhead bullets, in bold)
  - **Family Therapies**
    - Family behavioral therapy (FBT)
    - Family systems therapy (FST)
      - Brief strategic family therapy (BSFT)
    - Functional family therapy (FFT)
    - Ecological family therapy
    - Multidimensional family therapy (MDFT)
    - Ecologically based family therapy (EBFT)
    - Family systems network (FSN)
    - Educational family therapy
    - Multi-systemic therapy (MST)
  - **Cognitive behavioral therapy (CBT)**
    - Adolescent community reinforcement approach (ACRA)
    - Dialectical behavior therapy
    - Cognitive therapy
  - **Contingency management**
  - **Motivational interviewing/ Motivation enhancement therapy**
  - **Multi-component interventions** consisting of two or more models (e.g., MST + CBT; FFT + CBT)
  - **Psychoeducation**
  - **Treatment as usual** (does not meet criteria for any of the above categories)
  - **Integrated interventions** for substance use and a co-occurring disorder
  - **Other**
    - Culturally sensitive interventions
  - **Recovery support**
    - 12-step programs
    - Peer-based and/or peer supports
    - Assertive continuing care (ACC)

  Exclude primary (universal) and secondary preventive interventions.

  Exclude interventions used in population that do not aim to reduce substance use (e.g., needle exchange).
- **Pharmacologic interventions**
  - *Exclude* medications being used to treat overdose (e.g., naloxone)
  - *Exclude* pharmacologic management of acute withdrawal symptoms
  - Medications to reduce and/or eliminate substance use and to prevent relapse (See Appendix B for details of FDA approvals)

        - Alcohol
            - Gabapentin
            - Naltrexone
            - Acamprosate
            - Disulfiram
            - Topiramate
            - Ondansetron
        - Cannabis
            - N-acetylcysteine (NAC)
        - Opioids
            - Methadone
            - Buprenorphine
            - Buprenorphine/Naloxone
            - Naltrexone
    - Medications to treat co-occurring psychiatric disorders in patients in patients with concurrent problematic substance use or SUD.

Comparators

KQ 1

- No active treatment
    - Wait list
    - Placebo (for medications)
- Usual care (if not a clearly defined behavioral intervention)

KQ 2

- Active interventions (we will evaluate other comparisons if the evidence allows)
    - Pharmacologic plus behavioral vs. behavioral or pharmacologic alone
    - Between major behavioral intervention models (e.g. family therapy, cognitive behavioral therapy)
    - Multicomponent interventions vs. single behavioral intervention model

Outcomes

- **Abstinence**
    - Urine drug test results (from substance identified on admission to treatment, abstinence from all substances, duration of abstinence)
- **Quantity, frequency, or severity of use** (of primary substance identified on entry to treatment and other substances)
    - Days of use/abstinence over specified time period
    - Quantity of use over specified time period
    - Substance-related problems/symptom count scales
- **Functional outcomes**
    - School performance and educational attainment
        - Attendance
        - Grades / academic performance
        - Graduation rates
        - Entering higher education (including trade schools)
    - Social relationships

        - Family functioning
        - Peer relationships
- **Harmful consequences associated with SUD**
    - Mental health outcomes
        - Suicidal ideation and behavior
    - Physical health outcomes
        - Mortality
            - All-cause
            - Drug-related, including fatal overdose
        - Morbidity
            - Injuries (non-fatal)
        - Infections
            - HIV
            - Hepatitis C
            - Other sexually transmitted infections
    - Legal outcomes
        - Arrests
        - Drunk or impaired driving
        - Contact with juvenile justice system
- **Adverse effects of intervention(s)**
    - Side effects of pharmacologic interventions
    - Loss of privacy/confidentiality
    - Stigmatization/discrimination
    - Iatrogenic effects of group therapy due to peer deviance
    - Other reported adverse effects ascribed to interventions

Study Designs and Information Sources

- Published, peer reviewed articles and data from clinicaltrials.gov
    - Randomized controlled trials (including cross-over trials)
        - N ≥10 participants per study group
    - Large nonrandomized comparative studies with longitudinal follow-up
        - N ≥ 100 participants per study group
        - Must report multiple regression, other adjustment, matching, propensity scoring, or other method to account for confounding.
    - Single arm pharmacologic studies with at least 200 participants and longitudinal follow-up (to identify side-effects of medications)
    - We will summarize information from existing systematic reviews specific to treatment of alcohol SUD on college campuses
        - SR eligible if inclusion criteria for individual studies consistent with our PICODT criteria for individual studies.

Exclusions

- Case-control studies
- Cross-sectional studies
- Single-arm studies of behavioral interventions
- Conference abstracts letters, and other non-peer reviewed reports

Timing

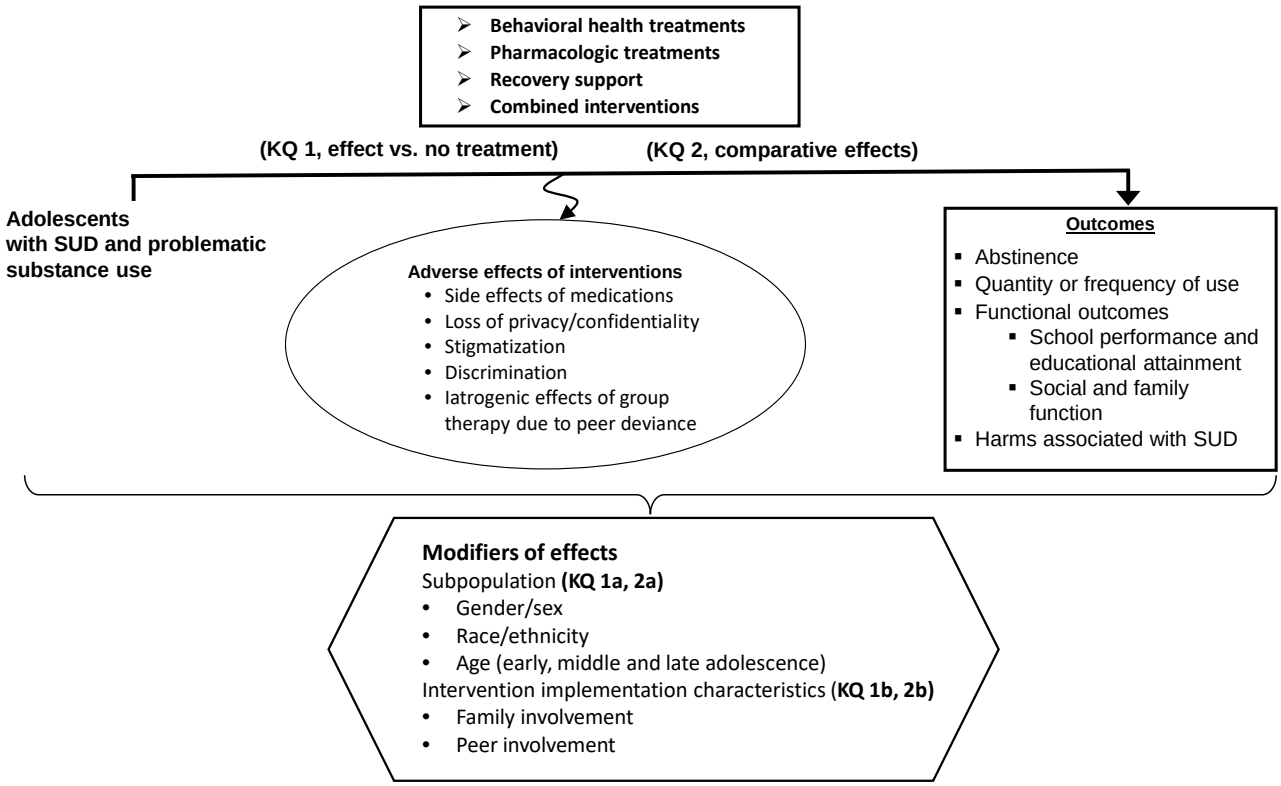
- Any duration of treatment
- Duration of follow-up of at least a month (but must be longitudinal with separation in time between intervention and outcomes)

Setting

- Any setting, including (but not limited to) primary care, school, outpatient, emergency department, in-patient, intensive outpatient, partial hospitalization, intensive inpatient/residential, juvenile justice

  Exclude: laboratory-based assessments.

IV. Analytic Framework for the Key Questions



V. Methods

Criteria for Inclusion/Exclusion of Studies in the Review

Please refer to Section II, The Key Questions, where the Eligibility Criteria are listed.

Searching for the Evidence

Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions

We will conduct literature searches in MEDLINE, the Cochrane CENTRAL Trials Registry, EMBASE, CINAHL, and PsycINFO databases (from inception) to identify primary studies meeting our criteria. A separate search for SRs of interventions for alcohol are disorders/problematic alcohol use in the college setting will be conducted in MEDLINE, Cochrane Database of Systematic Reviews, and Epistemonikos. We anticipate using the search strategy in Appendix A, which is designed for the PubMed interface of MEDLINE, adapted as needed for each database. The search strategy will be peer reviewed by an independent, experienced information specialist/librarian. We will ask the Technical Expert Panel (TEP) to provide citations of potentially relevant articles. Additionally, we will peruse the reference lists of published clinical practice guidelines, and relevant systematic reviews (as identified in MEDLINE, the *Cochrane Database of Systematic Reviews*, and Epistemonikos) for eligible studies. For evaluation of the treatment of alcohol use disorders/problematic alcohol use in the college setting, we will summarize existing systematic reviews only, as this literature is vast and has been extensively reviewed. We will search ClinicalTrials.gov to identify unpublished studies and studies that are ongoing. We will also search the FDA websites for pharmacologic trials.

Peer and public review will provide an additional opportunity for the TEP and other experts in the field to ensure that no key publications have been missed. We will update the search upon submission of the draft report for peer and public review.

Finally, a Supplemental Evidence and Data for Systematic review (SEADS) portal and Federal Register Notice will be posted for this review.

Screening Studies for Eligibility

For citation screening, we will initially conduct a series of pilot training sessions to achieve a satisfactory level of agreement among researchers regarding the nuances of the eligibility criteria for title and abstract screening. Because abstracts sometimes do not mention all outcomes that are reported in the full-text, we will not exclude titles and abstracts based on outcomes. We will conduct all abstract screening using the open-source, online software Abstrackr (http://abstrackr.cebm.brown.edu/). We will use the predictive algorithm capabilities of Abstrackr to assist with screening. We will begin with double, independent screening of abstracts. Conflicts will be resolved during full-group meetings. Using the labels (accept, reject) given to screened abstracts, Abstrackr will determine a prediction value for all remaining unscreened citations and sort these such that the most-likely-to-be-accepted abstracts are screened first. Based on empirical research on Abstrackr (that is soon to be submitted for publication), when all remaining unscreened abstracts have a prediction value <0.40 (on a scale of 0 to 1), we will switch to single screening of remaining abstracts. The empirical research suggests that at this threshold, all remaining abstracts will be rejected. Typically, this threshold is reached when about half the abstracts have been screened.

We will obtain the full-texts of all citations that are screened in during abstract screening. The reference lists from systematic reviews will be reviewed for the presence of additional primary studies. will be We will evaluate these articles using an Evidence Map structure in which we will gather basic data on each article (e.g., study design, sample size, confirmation of SUD/problematic use, age data, intervention(s), confirmation of outcomes of interest). Articles

derived from the same studies (multiple publications, secondary analyses) will be grouped. This evidence map process will help to determine final eligibility status for each study.

Data Extraction

Each study with multiple publications or secondary analyses will be extracted together (as one study). One methodologist will extract data for each study. The extraction will be verified by at least one other experienced methodologist and discrepancies will be discussed between them, as needed.

Data will be extracted into customized forms in the Systematic Review Data Repository (SRDR) online system (http://srdr.ahrq.gov) and Excel spreadsheets designed to capture all elements relevant to the KQs. Upon completion of the review, the Excel spreadsheets will be uploaded into SRDR and the SRDR database will be published (made accessible to the public, with capacity to read, download, and comment on data).

The basic elements and design of these forms will be the similar to those we have used for other comparative effectiveness reviews and will include elements that address population characteristics; descriptions of the interventions and comparators; outcome definitions; effect modifiers; enrolled and analyzed sample sizes; study design features; funding source; results; and risk of bias.

We do not plan to contact study authors for additional data.

Assessment of Risk of Bias

We will assess the risk of bias (methodological quality) of each study based on predefined criteria. For RCTs, we will use the Cochrane risk of bias tool[24] assessing randomization method and adequacy, allocation concealment method and adequacy, use of intention-to-treat analysis, and masking (blinding). For observational studies, we will use relevant questions from the Newcastle Ottawa Scale.[25] For SRs of interventions for alcohol use disorder or problematic alcohol use in the college setting, we will assess risk of bias using the AMSTAR 2 tool.[26] Any quality issues pertinent to specific outcomes within a study will be noted and applied to those outcomes. Any quality issues pertinent to specific outcomes within a study will be noted and considered when determining the overall strength of evidence for conclusions related to those outcomes.

Data Synthesis

Synthesis

We will summarize all included studies in narrative form and in summary tables containing the important features of the study populations, design, interventions, outcomes, and results. Tables will include descriptions of the study design, sample size, intervention(s), followup duration, outcomes, and study quality.

We will analyze different study designs separately and, if appropriate, together. We will compare and contrast populations, exposures, and results across study designs. We will examine any differences in findings between randomized and nonrandomized studies. We will evaluate the risk of bias factors as possible explanations for any heterogeneity.

We may conduct random effects model meta-analyses of comparative studies if at least three studies are sufficiently similar in population, interventions, outcomes, and study design. Specific methods and metrics (summary measures) to be meta-analyzed will depend on available,

reported study data, but we expect to summarize odds ratios of categorical outcomes and, if pertinent, standardized mean differences of net change of continuous outcomes (e.g., quality of life scores). Statistical heterogeneity will be explored qualitatively and, if appropriate data are available, we may also conduct meta-regression analyses to evaluate study, patient, and intervention features, (as listed in the KQs) and to evaluate dose-response. We will explore subgroup differences within (and possibly across) studies based on the list of comparisons described in the KQs. We will explore the possibility of conducting a network meta-analysis of clinical outcomes to compare treatment alternatives across studies. We will also explore the use of hierarchical (random intercept/random slope) meta-regression analyses to tease out the additive effect of each intervention attribute. Sensitivity analyses will examine robustness of results to alternative prior distributions; attribute definitions, and non-additivity of intervention components. As needed, we will use methods for the multivariate pairwise and multiple-treatment meta-analysis of correlated outcomes.

Grading the Strength of Evidence for Major Comparisons and Outcomes

We will grade the strength of the body of evidence as per the AHRQ methods guide on assessing the strength of evidence.[27, 28]

We expect that we will have at least some data for a multitude of comparisons. However, it is impractical to provide strength of evidence assessments for all possible combinations of interventions and outcomes. We will assess the strength of evidence for comparisons of major interventions (i.e., behavioral intervention methods, pharmacologic interventions, and combinations) to no treatment and to each other that have at least three comparative studies or at least 1000 participants in total. Comparisons with only one or two smaller studies (in total N<1000) will likely have insufficient or very low strength of evidence because of imprecision; for such comparisons we *do not plan* to formally evaluate and present the strength of evidence. While this *a priori* threshold is arbitrary, it is consistent with the concept that for imprecise evidence "any estimate of effect is very uncertain," the definition of Very Low quality evidence per GRADE.[29] Based on further evaluation of the evidence base, we may lower the minimum sample size from 1000 for when there are fewer than three similar studies, especially if there are large effects (i.e., standardized mean difference ≥0.8; see next paragraph), particularly for patient-centered outcomes.

To our knowledge, there is no information on the minimal clinically importance differences for the outcomes we consider. We therefore define *a priori* cutoffs in the magnitude of the intervention effect to categorize effect magnitudes. For continuous outcomes we will consider *small, modest,* and *large* effects to correspond to standardized mean differences smaller than 0.2, between 0.2 and 0.8, and at least 0.8, respectively, in either direction. By this definition, small effects correspond to a change in the mean of the outcome that is more extreme than the measurements in 16% of the population in the controls. Moderate effects correspond to mean changes that are more extreme than the measurements in 16% to 58% of the controls, and large effects to changes that are more extreme than the measurements in 58% of the controls. For non-rare categorical outcomes (operationally defined as having prevalence >5%), we will consider small odds ratios that are between 1 and 1.2 (or between 1 and 0.83, in the other direction), moderate odds ratios that are between 1.2 and 2.0 (or between 0.83 and 0.5), and large odds ratios >2 (or <0.5). For rare categorical outcomes (with observed prevalence <5%) we will not make such judgments, unless the outcomes are critical (namely, overall mortality, cause-specific mortality, or suicide attempts).

These effect size magnitudes will be used as a proxy of whether a difference between two treatments is likely to be clinically important: For statistically significant difference with point estimates that are modest or large in magnitude, we will deem that, in terms of clinical importance, the favored intervention is favored "moderately" or "strongly", respectively. When the intervention effect is small in magnitude and/or statistically nonsignificant, we will consider a difference as "clinically not important".

Conversely, we will judge the evidence on "clinical equivalence" between two interventions based on the 95 percent confidence intervals of the intervention effects. We operationally define that there is strong evidence of clinical equivalence if the bounds of the confidence interval exclude effects of at least moderate magnitude equivalence; and moderate evidence of clinical equivalence when the 95 percent confidence intervals exclude large effects, but not moderate effects, in either direction.

For each evaluated comparison, we will assess the number of studies, their study designs, the study limitations (i.e., risk of bias and overall methodological quality), the directness of the evidence to the KQs, the consistency of study results, the likelihood of reporting bias, in addition to the precision and magnitude of the effect estimate across studies. Based on these assessments, we will assign a strength of evidence rating as being either high, moderate, low, or insufficient evidence to estimate an effect. The data sources, basic study characteristics, and each strength-of-evidence dimensional rating will be summarized in a "Summary of Evidence Reviewed" table detailing our reasoning for arriving at the overall strength of evidence rating.

Assessing Applicability

We will assess the applicability within and across studies with reference to adolescents in the populations of interest (i.e. type and severity of abuse, early vs. middle vs. late adolescent age group and setting), and whether interventions and comparators are used in current practice.

VI. References

1. Lipari RN, Park-Lee E, Van Horn S. America's Need for and Receipt of Substance Use Treatment in 2015. The CBHSQ Report. Rockville (MD); 2016:1-7.
2. Dembo R, Belenko S, Childs K, et al. Drug use and sexually transmitted diseases among female and male arrested youths. J Behav Med. 2009 Apr;32(2):129-41. doi: 10.1007/s10865-008-9183-2. PMID: 18979194.
3. Chapman SL, Wu LT. Substance Use among Adolescent Mothers: A Review. Child Youth Serv Rev. 2013 May 01;35(5):806-15. doi: 10.1016/j.childyouth.2013.02.004. PMID: 23641120.
4. Racz SJ, Saha S, Trent M, et al. Polysubstance Use among Minority Adolescent Males Incarcerated for Serious Offenses. Child Youth Care Forum. 2015 Apr 16;45(2):205-20. doi: 10.1007/s10566-015-9334-x. PMID: 26997851.
5. Crosnoe R. The Connection Between Academic Failure and Adolescent Drinking in Secondary School. Sociol Educ. 2006;79(1):44-60. PMID: 20216913.
6. Volkow N. Comorbidity: Addiction and Other Mental Illnesses, . National Institute on Drug Abuse. https://d14rmgtrwzf5a.cloudfront.net/sites/default/files/rrcomorbidity.pdf. Accessed on 21 January, 2018.
7. The National Center on Addiction and Substance Abuse (CASA). Adolescent Substance Use: America's #1 Public Health Problem. http://centeronaddiction.org/addiction-research/reports/adolescent-substance-use. Accessed on 22 January, 2018.

8. Keyes KM, Brady JE, Li G. Effects of minimum legal drinking age on alcohol and marijuana use: evidence from toxicological testing data for fatally injured drivers aged 16 to 25 years. Inj Epidemiol. 2015 Jan;2. doi: 10.1186/s40621-014-0032-1. PMID: 26301177.
9. Wong SS, Zhou B, Goebert D, et al. The risk of adolescent suicide across patterns of drug use: a nationally representative study of high school students in the United States from 1999 to 2009. Soc Psychiatry Psychiatr Epidemiol. 2013 Oct;48(10):1611-20. doi: 10.1007/s00127-013-0721-z. PMID: 23744443.
10. Johnston LD, O'Malley PM, Miech RA, et al. Monitoring the Future national survey results on drug use, 1975-2015: Overview, key findings on adolescent drug use. Ann Arbor: Institute for Social Research, The University of Michigan; 2016. http://www.monitoringthefuture.org/pubs/monographs/mtf-overview2015.pdf. Accessed on October 2, 2018.
11. Center for Behavioral Health Statistics and Quality (2016). Key substance use and mental health indicators in the United States: Results from the 2015 National Survey on Drug Use and Health (HHS Publication No. SMA 16-4984, NSDUH Series H-51). https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2015/NSDUH-FFR1-2015/NSDUH-FFR1-2015.htm
12. Cerda M, Santaella J, Marshall BD, et al. Nonmedical Prescription Opioid Use in Childhood and Early Adolescence Predicts Transitions to Heroin Use in Young Adulthood: A National Study. J Pediatr. 2015 Sep;167(3):605-12 e1-2. doi: 10.1016/j.jpeds.2015.04.071. PMID: 26054942.
13. Curtin SC, Tejada-Vera B, Warner M. Drug Overdose Deaths among Adolescents Aged 15-19 in the United States: 1999-2015. NCHS Data Brief. Number 282. National Center for Health Statistics. 2017.
14. Bukstein OG, Bernet W, Arnold V, et al. Practice parameter for the assessment and treatment of children and adolescents with substance use disorders. J. Am. Acad. Child Adolesc. Psychiatry. 2005 2005/6;44(6):609-21. doi: 10.1097/01.chi.0000159135.33706.37.
15. Hogue A, Henderson CE, Becker SJ, et al. Evidence base on outpatient behavioral treatments for adolescent substance use: Updates and recommendations 2014 – 2017. . Journal of Clinical Child and Adolescent Psychology. in press.
16. Hogue A, Henderson CE, Ozechowski TJ, et al. Evidence base on outpatient behavioral treatments for adolescent substance use: updates and recommendations 2007-2013. J. Clin. Child Adolesc. Psychol. 2014 2014/6/13;43(5):695-720. doi: 10.1080/15374416.2014.915550.
17. Tanner-Smith EE, Wilson SJ, Lipsey MW. The comparative effectiveness of outpatient treatment for adolescent substance abuse: a meta-analysis. J Subst Abuse Treat. 2013 Feb;44(2):145-58. doi: 10.1016/j.jsat.2012.05.006. PMID: 22763198.
18. Minozzi S, Amato L, Bellisario C, et al. Maintenance treatments for opiate -dependent adolescents. Cochrane Database Syst Rev. 2014 Jun 24(6):CD007210. doi: 10.1002/14651858.CD007210.pub3. PMID: 24957634.
19. Barnett E, Sussman S, Smith C, et al. Motivational Interviewing for adolescent substance use: a review of the literature. Addict Behav. 2012 Dec;37(12):1325-34. doi: 10.1016/j.addbeh.2012.07.001. PMID: 22958865.
20. Mitchell SG, Gryczynski J, O'Grady KE, et al. SBIRT for adolescent drug and alcohol use: current status and future directions. J Subst Abuse Treat. 2013 May-Jun;44(5):463-72. doi: 10.1016/j.jsat.2012.11.005. PMID: 23352110.

21. National Institute on Drug Abuse. Principles of Adolescent Substance Use Disorder Treatment: A Research-Based Guide. January 2014. https://d14rmgtrwzf5a.cloudfront.net/sites/default/files/podata_1_17_14.pdf
22. Committee On Substance USE, Prevention. Medication-Assisted Treatment of Adolescents With Opioid Use Disorders. Pediatrics. 2016 2016/9;138(3). doi: 10.1542/peds.2016-1893.
23. MacIntyre J, Pruitt D, Houston M, et al. Back to Project Future: plan for the coming decade. Washington, DC: American Academy of Child and Adolescent Psychiatry. 2014.
24. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011 Oct 18;343:d5928. doi: 10.1136/bmj.d5928. PMID: 22008217.
25. Wells GA, Shea B, O'Connell B, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
26. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008. doi: 10.1136/bmj.j4008. PMID: 28935701.
27. Berkman ND, Lohr KN, Ansari M, et al. AHRQ Methods for Effective Health Care Grading the Strength of a Body of Evidence When Assessing Health Care Interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: An Update. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008.
28. Berkman ND, Lohr KN, Ansari MT, et al. Grading the strength of a body of evidence when assessing health care interventions: an EPC update. J Clin Epidemiol. 2015 Nov;68(11):1312-24. doi: 10.1016/j.jclinepi.2014.11.023. PMID: 25721570.
29. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Bmj. 2008 Apr 26;336(7650):924-6. doi: 10.1136/bmj.39489.470347.AD. PMID: 18436948.
30. Leichsenring F, Abbass A, Driessen E, et al. Equivalence and non-inferiority testing in psychotherapy research. Psychol Med. 2018 Aug;48(11):1917-9. doi: 10.1017/S0033291718001289. PMID: 29747714.

VII. Definition of Terms

Cognitive behavioral therapy: a therapy approach that aims to modify cognitive processes, beliefs, individual behaviors, or environmental reinforcers associated with the adolescent's substance use. Variants of this approach include cognitive therapy, dialectical behavior therapy, and the adolescent community reinforcement approach.

Contingency management / motivational incentives: a treatment approach that provides the adolescent with tangible rewards for reaching pre-specified treatment goals (e.g., abstinence, attendance, reduced use).

Ecological family therapy: a family-focused therapy approach that expands the boundaries of treatment beyond the family and utilizes individualized strategies to target adolescent substance use in the context of multiple interrelated, nested systems. Example models include

multisystemic therapy, multidimensional family therapy, family support network, and ecological based family therapy.

Family behavioral therapy: a family-focused therapy approach that applies principles of operant and social learning within the family context to promote prosocial behaviors and reduce substance use.

Family education: a family-focused treatment approach that focuses on providing education about the signs and harms of substance use to the family of the adolescent substance user.

Family systems therapy: a family-focused therapy approach that attempts to restructure problematic family interaction patterns associated with the adolescent's substance use

Functional family therapy: a family-focused therapy approach that integrates principles of both systems and behavioral approaches.

Integrated treatment: a treatment approach that combines an intervention for substance use and an intervention for a co-occurring mental health disorder.

Motivational interviewing / motivational enhancement therapy: a therapy approach that focuses on building the adolescent's motivation to reduce his/her substance use.

Multi-component treatment: a treatment approach that combines two or more distinct intervention models. Example multi-component approaches include (but are not limited to) motivational enhancement therapy / cognitive behavioral therapy and functional family therapy + cognitive behavioral therapy.

Problematic (substance) use: Use of a substance with a negative impact.

Psychoeducation: a treatment approach that aims to provide education about the signs and harms of adolescent substance use

Substance use disorder (SUD): Maladaptive use of a controlled, illicit, or other substance. Per the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), An SUD diagnosis is made if an individual exhibits at least two of 11 maladaptive behaviors and symptoms across four domains (social problems, loss of control, risk behaviors, and physiological changes) within a 12-month period. Severity may be mild, moderate, or severe.

VIII. Summary of Protocol Amendments

No protocol amendments to date.

IX. Review of Key Questions

The Agency for Healthcare Research and Quality (AHRQ) is posting the KQs and protocol on the AHRQ Effective Health Care Website for public comment. The Evidence-based Practice Center (EPC) will refine and finalize the KQs after review of the public comments, and

additional input from Key Informants. The protocol will be further refined based on input from the Technical Expert Panel (TEP). This input is intended to ensure that the KQs are specific and relevant.

X. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The AHRQ Task Order Officer (TOO) and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and suggest approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The AHRQ TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XII. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published three months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $5,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XIII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than $1,000 will usually disqualify EPC core team investigators.

XIV. Role of the Funder

This project was funded under Contract No. HHSA 290-2015-00002-I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The AHRQ Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

XV. Registration

This protocol will be registered in the international prospective register of systematic reviews (PROSPERO).