ADHD and Substance Use Disorders in Adults

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AUTHORS

Author roles, affiliations, and contributions (using the CRediT taxonomy) are listed below.

Author	Role and Affiliation	Report Contribution
Katherine Rieke, PhD, MPH	Research Associate, Providence Evidence Synthesis Program (ESP) Center	Conceptualization, Methodology, Investigation, Data curation, Visualization, Writing – original draft, Writing – review & editing, Project administration
Yuliia Sereda, MPH	Co-Investigator, Providence ESP Center Providence, RI	Conceptualization, Methodology, Investigation, Data curation, Investigation, Writing – review & editing
Htun Ja Mai, MBBS, MPH	Co-Investigator, Providence ESP Center Providence, RI	Conceptualization, Methodology, Investigation, Data curation, Investigation, Writing – review & editing
Madeline B Benz, PhD	Co-Investigator, Providence ESP Center Assistant Professor of Psychiatry and Human Behavior, Brown University Warren Alpert Medical School Clinical Psychologist, Care New England Medical Group Providence, RI	Conceptualization, Methodology, Investigation, Data curation, Investigation, Writing – review & editing
James Rudolph, MD	Co-Director, Providence ESP Center Director, Long Term Services and Supports (LTSS) Center of Innovation (COIN) Professor of Medicine, Brown University School of Public Health Providence, RI	Conceptualization, Methodology, Investigation, Data curation, Visualization, Writing – original draft, Writing – review & editing
Rachel Dew, MD	Subject Matter Expert, Providence ESP Center Providence, RI Assistant Professor of Psychiatry and Behavioral Sciences, Duke University School of Medicine Durham, NC	Conceptualization, Methodology, Investigation, Data curation, Writing – review & editing
Jennifer M. Primack, PhD	Psychologist, Providence VAMC Assistant Professor of Psychiatry and Human Behavior, Brown University Providence, RI	Conceptualization, Methodology, Investigation, Data curation, Writing – review & editing
John E. McGeary, PhD	Clinical Psychologist, Providence VAMC Professor of Psychiatry and Human Behavior, Brown University Providence, RI	Conceptualization, Methodology, Investigation, Data curation, Writing – review & editing
Taylor Rickard, MS	Project Manager, Providence ESP Center	Project administration, Visualization, Investigation, Data curation

Author	Role and Affiliation	Report Contribution
	Providence, RI	
Thomas A. Trikalinos, MD, PhD	Co-Investigator, Providence ESP Center Professor, Brown University School of Public Health Providence, RI	Conceptualization, Methodology, Investigation, Writing – review & editing
Eric Jutkowitz, PhD	Director, Providence ESP Center Associate Professor, Brown University School of Public Health Providence, RI	Conceptualization, Methodology, Investigation, Funding acquisition, Writing – review & editing, Visualization, Writing – original draft, Writing – review & editing

PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to conduct timely, rigorous, and independent systematic reviews to support VA clinicians, program leadership, and policymakers to improve the health of Veterans. ESP reviews have been used to develop evidence-informed clinical policies, practice guidelines, and performance measures; to guide implementation of programs and services that improve Veterans' health and wellbeing; and to set the direction of research to close important evidence gaps. Four ESP Centers are located across the US. Centers are led by recognized experts in evidence synthesis, often with roles as practicing VA clinicians. The Coordinating Center, located in Portland, Oregon, manages program operations, ensures methodological consistency and quality of products, engages with stakeholders, and addresses urgent evidence synthesis needs.

Nominations of review topics are solicited several times each year and submitted via the ESP website. Topics are selected based on the availability of relevant evidence and the likelihood that a review on the topic would be feasible and have broad utility across the VA system. If selected, topics are refined with input from Operational Partners (below), ESP staff, and additional subject matter experts. Draft ESP reviews undergo external peer review to ensure they are methodologically sound, unbiased, and include all important evidence on the topic. Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. In seeking broad expertise and perspectives during review development, conflicting viewpoints are common and often result in productive scientific discourse that improves the relevance and rigor of the review. The ESP works to balance divergent views and to manage or mitigate potential conflicts of interest.

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Operational Partners

Operational partners are system-level stakeholders who help ensure relevance of the review topic to the VA, contribute to the development of and approve final project scope and timeframe for completion, provide feedback on the draft report, and provide consultation on strategies for dissemination of the report to the field and relevant groups.

Eric Hermes, MD
National Director, Psychopharmacology and Somatic Treatments
VA Office of Mental Health

Daina Wells, PharmD, MBA, BCPS, BCPP
Assistant Chief Consultant
PBM Academic Detailing Service, VA

Matthew J. Barry, DO
Co-Chief of Psychiatry
VA Finger Lakes Healthcare System

Matthew Schreiber, MD, PhD
Psychiatrist
Seattle VA Medical Center

Robert Shura, PsyD, ABPP-CN
Neuropsychologist
W.G. (Bill) Hefner VA Medical Center

Jonathan S. Emens M.D., F.A.B.S.M.
Chief of Psychiatry
VAPORHCS

Technical Expert Panel

To ensure robust, scientifically relevant work, the technical expert panel (TEP) guides topic refinement; provides input on key questions and eligibility criteria, advising on substantive issues or possibly overlooked areas of research; assures VA relevance; and provides feedback on work in progress. TEP members included:

Elisa Gumm, DO
Physician
Tucson VA Medical Center

Mark Sandberg, PhD, ABPP, ABN
Neuropsychologist
Northport VA Medical Center

Andrew Saxon, MD
Director
Center of Excellence in Substance Abuse Treatment and Education (CESATE), VA Puget Sound Health Care System
Professor
Department of Psychiatry and Behavioral Sciences, UW Medicine

Cynthia Smith-Seidel, PhD
Psychologist
Martinsburg VA Medical Center

Disclosures

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The findings and conclusions in this document are those of the author(s) who are responsible for its contents and do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. The final research questions, methodology, and/or conclusions may not necessarily represent the views of contributing operational and content experts. No investigators have affiliations or financial involvement (*eg*, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

Main Report

Evidence Synthesis Program

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ABBREVIATIONS TABLE

Abbreviation	Definition
AARS	Adult ADHD Rating Scale
ADHD	Attention-deficit/hyperactivity disorder
aHR	Adjusted hazard ratio
AISRS	Adult ADHD Investigator Symptom Rating Scale
AUD	Alcohol use disorder
CAARS	Conners Adult ADHD Rating Scales
CBT	Cognitive behavioral therapy
CGI	Clinical Global Improvement Scale
DSM	Diagnostic and Statistical Manual of Mental Disorders
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ICD	International classification of disease
KQ	Key question
M	Mean
MD	Mean difference
MeSH	Medical subject headings
N	Number
NRCS	Non-randomized comparative studies
OMHSP	Office of Mental Health and Suicide Prevention
OR	Odds ratio
RCT	Randomized controlled trial
SD	Standard deviation
SRDR+	Systematic Review Data Repository
SUD	Substance use disorders
TAADDS	Targeted Adult Attention Deficit Disorder Scale
TEP	Technical expert panel
THC	Tetrahydrocannabinol
VA	US Department of Veterans Affairs
VHA	Veterans Health Administration

BACKGROUND

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental condition that has been recorded in the medical literature for the last 2 centuries under various names.[1, 2] While diagnostic criteria for ADHD have evolved over time, symptoms of ADHD generally include inattention, hyperactivity, and/or impulsivity.[3, 4] Typically, ADHD symptoms initially appear in childhood, and nearly 50% of diagnosed children will continue to experience some symptoms into adulthood.[5-7] Most research on ADHD has focused on children, but over the past decade there has been an increase in the documented prevalence and incidence of ADHD among adults.[8-10] Moreover, despite the United States military having enrollment restrictions for people with ADHD,[11] the prevalence and incidence of diagnoses of ADHD among Veterans has also increased.[12-14] One retrospective study conducted in the Department of Veterans Affairs (VA) found the annual prevalence of ADHD diagnoses among Veterans increased 258% (from 0.23% to 0.84%) and annual incidence increased 240% (from 0.14% to 0.48%) between 2009 and 2016.[12]

The mechanism of ADHD is likely multimodal.[15, 16] People with ADHD may have structural or functional differences of the brain. These include reduced volume in areas of the brain, including the prefrontal cortex and reductions in the basal ganglia, which can impact factors such as impulsivity and cognition.[17, 18] Pharmaceutical treatments for ADHD, including prescription psychostimulants, are thought to target regulation of these neurotransmitters.[19]

Adults with ADHD can experience negative occupational consequences,[20-22] financial burden,[23] social problems,[24] increased risk for other mental health diagnoses and higher mortality.[25, 26] ADHD has also been associated with high health care use and costs.[2, 27] Potential consequences of untreated ADHD in adults include an increased risk of substance use, criminality, psychiatric disorders, suicide ideation or attempts, and fractures.[28-30] However, treating ADHD in adults also presents challenges given the population may have, or be at risk for, comorbid psychological disorders. Longitudinal studies have found a higher incidence of mental health disorders, including mood, anxiety, and personality disorders among military service members treated for ADHD.[14, 31] ADHD and substance use disorder (SUD) are frequently co-occurring. Previous research has found that up to 40% of ADHD people in the general population may have co-occurring SUD,[31] and that over 20% of people with SUD have co-occurring ADHD.[6] Dysregulation of dopamine, which can impact impulse control and inattention, is thought to be involved in both ADHD and SUD.[32, 33] However, concerns remain over whether certain treatments for ADHD can impact brain development in ways that may increase SUD risk.[34]

Prescription psychostimulants, such as methylphenidate and amphetamine-based products (*eg*, lisdexamfetamine), are first-line pharmacologic treatments for ADHD in adults.[35] This is also true in the military, where 1 study found that approximately 60% of service members with ADHD were prescribed ADHD medications, and more than 79% of these were prescribed psychostimulants.[14] Misuse and diversion of psychostimulants have been reported in previous literature, and there is concern these medications may increase the risk of developing a SUD.[34, 36] However, these studies have often explored misuse in people who were not prescribed ADHD medications, or have included older medications with higher misuse potential (typically immediate-release formulations, in contrast to extended-release or prodrug formulations that are now commonly prescribed).[36] In addition, the age of participants in previous studies (adolescents and young adults in college) places them in an environment where diversion is both easier and in higher demand and this may not be consistent with the "adult" experience of ADHD.[37] Still, because of the potential for misuse, caution has been urged when considering the use of stimulant medications for ADHD in people with SUD.[38, 39] Non-

pharmacologic treatments may be alternatives to psychostimulants,[40] but there is uncertainty in their effectiveness, especially in populations with co-occurring SUD.[41] This is of particular concern within the VA, where, in 2021, nearly 16% of the population had an SUD in the previous year.[42]

Despite the growing number of adults with an ADHD diagnosis, and several guidelines outside of the US,[43, 44] to date there has never been a consensus clinical practice guideline for the treatment of adults with ADHD. Though existing systematic reviews have examined the use of stimulant medications in ADHD, or have examined the relationship between ADHD and SUD, none have focused on stimulant use and SUD in adults in non-inpatient populations.[45-51] To inform guidance on the management of ADHD in Veterans, the Veterans Health Administration (VHA) Office of Mental Health (OMH) requested the following systematic review on the incidence of SUD in adults with ADHD who are prescribed psychostimulant medications as well as the benefits and harms of psychostimulant treatment of ADHD in adults with comorbid SUD.

METHODS

TOPIC DEVELOPMENT

We worked with representatives from the OMHSP and our technical expert panel (TEP) to refine the scope and develop key questions (KQ). We focused on studies that reported incident outcomes of SUD (including alcohol use disorder or alcohol abuse) or medication misuse or diversions (KQ 1), and those that examined the effect of stimulant use in people with both ADHD and SUD (KQ 2). We excluded studies that did not report outcomes in adulthood (≥18 years of age) and studies that only evaluated tobacco or caffeine use as an SUD.

KEY QUESTIONS AND PROTOCOL REGISTRATION

The following key questions were the focus of this review:

Key Question 1	Among adults diagnosed with ADHD and prescribed psychostimulant medications, what is the incidence of misuse of the prescribed medications, the incidence of diversion of the prescribed medications, and the incidence of SUD in this population?
Key Question 2	Among adults diagnosed with ADHD with a co-occurring SUD, what are the benefits and harms of non-stimulant ADHD pharmacological and/or nonpharmacological treatment of ADHD compared to ADHD psychostimulant medications?

A preregistered protocol for this review can be found on the PROSPERO international prospective register of systematic reviews (CRD42024517093).

SEARCHING AND STUDY SELECTION

We conducted a preliminary search in Medline (via PubMed) that was focused on medical subject headings (MeSH) and free text terms for *ADHD*, *SUD*, *misuse*, *diversion*, and *psychostimulant medications*. We adapted search strategies from several related systematic reviews [36,46,52-60] and worked with subject matter experts and the topic nominator to identify terms related to psychostimulant medications for ADHD.

For our final searches, we searched Medline (via PubMed), Embase, and PsycINFO from inception to December 14, 2023, in the Cochrane library from inception to January 30, 2024, and ClinicalTrials.gov from inception to February 23, 2024 (see Appendix A for complete search strategies). Citations for relevant systematic reviews were identified from hand-searching reference lists. A draft version of this report was reviewed by external peer reviewers; their comments and author responses are located in Appendix K.

Citations were entered into EndNote, where duplicates were removed. We screened citation in Systematic Review Data Repository (SRDR+) which has machine learning algorithms to prioritize relevant citations. Based on empirical evidence, we stopped screening when all remaining unscreened abstracts had a prediction value of <0.40 (on a 0–1 scale), and subsequently 400 abstracts in a row were rejected. To ensure common understanding of the eligibility criteria among the research team, we ran 5 pilot rounds of 100 citations, where all team members screened the title and abstract of the same citations, and conflicts were resolved as a group. After the pilot rounds, citations were screened in duplicate with conflicts resolved by group discussion or by the lead researcher. Accepted abstracts underwent full-text review using an evidence mapping process by 1 researcher with confirmation of

excluded articles by a second researcher. When necessary, the reviewers consulted a third senior researcher. Appendix B lists studies excluded at the full-text review phase, along with the reason for their exclusion.

Study eligibility criteria are listed in Table 1. For both KQs, eligible studies were required to enroll people diagnosed with ADHD using Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV through DSM 5-TR criteria or comparable criteria. Because of this, we excluded studies published before 1994 based on the publication date of the DSM-IV. To manage resources needed to address the topic, citations were excluded during abstract screening if the title or abstract did not state that the population included people with ADHD, did not explicitly mention the use of prescription stimulant medications, or did not include any explicit mention of substance use, medication misuse, or diversion. For both KQs, if the study sample included people with various psychological disorders, at least 80% of the baseline sample needed to be diagnosed with ADHD.

For KQ 1, our focus was on reporting incident SUD diagnosis, or misuse or diversion of prescribed psychostimulants in adulthood. To ensure studies reported incident SUD diagnoses, we excluded cross-sectional studies and studies where the sample had SUD at baseline. We also excluded studies that only evaluated self-reported substance use and not SUD diagnoses. For KQ 1, outcomes of interest needed to be assessed in adulthood (≥18 years of age). For studies with outcomes reported in both adolescents and adults, at least 80% of the outcomes needed to be reported in people ≥18 years of age. Studies that only reported mean age at baseline and total follow-up were excluded if the estimated mean age was <18 years. We included RCTs, nonrandomized comparative studies (NRCS), and single-group studies. To evaluate the overall incidence of SUD, we analyzed the stimulant arms from comparative studies and single-group studies. We used comparative studies to determine whether taking stimulant medication for ADHD increases the risk of SUD diagnosis in people without a SUD at baseline. Outcomes of misuse were operationalized as using medications not as directed (*eg,* dose, frequency, route of administration, or purpose, including poisoning or overdose) and diversion was operationalized as the sale, purchase, theft, or giving away of ADHD medication.

For KQ 2, eligible studies compared stimulant treatment alone to other ADHD treatments, placebo, or no treatment in people with both ADHD and SUD. All subjects had to be ≥18 years of age at baseline. We excluded studies that did not include people with both ADHD and SUD at baseline. For studies that included ADHD people with and without SUD at baseline, at least 80% of the baseline population had to have a diagnosis of SUD to be included. For KQ 2, we only included RCTs and NRCS.

Table 1. Eligibility Criteria

	Inclusion Criteria	Exclusion Criteria
Population	KQ 1: People diagnosed with ADHD using DSM-IV, IV-TR, 5, 5-TR or comparable criteria (*eg,* ICD codes, validated instruments) who have been prescribed psychostimulant medications for ADHD and are without a history or current diagnosis of ADHD medication misuse or diversion, or SUD KQ 2: Adults ≥18 diagnosed with ADHD using DSM-IV, IV-TR, 5, 5-TR or comparable criteria (*eg*, ICD codes, validated instruments) with a history or current diagnosis of a SUD	KQs 1 & 2: Those without ADHD diagnosis (*ie,* just symptoms or self-diagnosed) KQ 1: History or current diagnosis of ADHD medication misuse or diversion, or SUD at the time of ADHD prescription KQ 2: • Adolescent/children/pediatric populations • People without SUD • People that only have SUDs relating to tobacco/nicotine or caffeine.

	Inclusion Criteria	Exclusion Criteria
Exposure	KQ 1: Prescribed psychostimulant medications KQ2 2: Prescribed psychostimulant medications for ADHD alone, including short- and long-acting types	
Comparator	KQ 1: None/any KQ 2: • Non-psychostimulant pharmacological ADHD medication. • Psychotherapeutic interventions intended to improve ADHD management skills and/or symptoms (*eg,* behavior management interventions like cognitive behavioral therapy) • Treatment as usual (including those that compare an experimental to standard dose of stimulants) or no treatment	KQ 2: • Studies where the comparator includes the use of alternative medicine interventions (*eg,* yoga) • Nonpharmacologic interventions which do not focus on ADHD skills • Nonpharmacologic interventions which are not conducted by trained clinicians • Studies that only compare different stimulant types
Outcomes	KQ 1: • ADHD medication misuse or diversion in adulthood (including poisoning/overdose) • Incident SUD/dependence/substance-related psychosis/abuse diagnosis in adulthood KQ 2: • Change in ADHD symptoms/severity • Change in functional ability or impairment • SUD relapse/misuse/ diversion • Treatment adherence (SUD and ADHD) • Side effects • Mortality • Quality of life and satisfaction • Other mental health diagnoses, including change in severity or symptoms	KQs 1& 2: • Only report tobacco/nicotine or caffeine outcomes • Outcomes not reported in adulthood
Timing	KQs 1 & 2: Studies conducted in/after 1994	
Setting	KQ 1: Community setting KQ 2: Outpatient, residential, or community settings	KQ 1 & 2: Incarcerated populations KQ 2: Inpatient populations
Study Design	KQs 1 & 2: • RCT • NRCS KQ 1: Single-group studies	KQs 1 & 2: • Studies with fewer than 11 people meeting our inclusion criteria • Cross-sectional studies • Case report/case series, protocols, studies that do not report patient-level data KQ 1: Studies with less than 3 months of follow-up KQ 2: Non-comparative studies

Abbreviations. ADHD=attention-deficit/hyperactivity disorder; DSM=Diagnostic and Statistical Manual of Mental Disorders; ICD=International Classification of Diseases; KQ=key question; NRCS=non-randomized comparative study; SUD=substance use disorder; TR=text revision.

DATA ABSTRACTION AND RISK OF BIAS ASSESSMENT

We created a data extraction form in SRDR+. For all KQs, we extracted the following data from eligible studies: study design, setting, sample size, population characteristics, methods for diagnosing ADHD, treatment details (*eg*, total stimulant dose), duration of follow-up, and outcomes of interest. All data extraction was first completed by 1 reviewer and then confirmed by a second reviewer, with consultation from other team members as needed.

Risk of bias was independently assessed by 1 reviewer using questions derived from the Cochrane Risk of Bias tool for RCTs and ROBINS-I (Risk of Bias In Non-randomized Studies – of Intervention tool for other study design) tools (Appendix C) and confirmed by a second. For NRCS, we evaluated what strategies were used to deal with potential confounders (low risk of bias if they used propensity scores, moderate risk of bias if they used multivariable regression, and high risk of bias if there were concerns about the adjusted analysis). We also evaluated whether the article was free of discrepancies and adequately defined patient eligibility criteria, interventions, and outcomes assessed. Studies were rated as low overall risk of bias if they were determined to be low risk of bias in all domains or unclear risk of bias for 1 domain. Studies were rated as moderate overall risk of bias if there was unclear risk of bias for ≥2 domains, or either high risk of bias for 1 domain but low risk of bias for all others, or high risk of bias for 1 domain and unclear risk of bias for ≥2 domains. Studies were rated as high overall risk of bias if they were rated as high risk of bias in ≥2 domains.

SYNTHESIS AND STRENGTH OF EVIDENCE

For KQ 1, we examined the incidence of SUD among people diagnosed with ADHD who were prescribed stimulant medications. Additionally, we compared the incidence of SUD between those who were and were not prescribed stimulant medications. In this report, we categorize substance use disorder outcomes into 3 groups. Outcomes not focused on a specific substance (*eg*, cocaine) were classified as SUD. Outcomes specific to alcohol use were categorized as alcohol use disorder (AUD). Outcomes focused on specific drug use disorders or those examining drugs separately from alcohol were categorized as non-alcohol substance use or stimulant use disorders. The categorization of substance use outcomes in each study is described in Appendix G.

For KQ 2, we extracted outcomes from studies in people with co-occurring ADHD and SUD who were taking prescription stimulant medications versus a comparison group. We compared results in study groups using odds ratios (OR) and hazard ratios (HR) for dichotomous outcomes. When a study had 0 events in one group, we added 0.5 to all cells before calculating an OR. We compared continuous data using mean differences (MD) between interventions. When necessary, we estimated MDs and their standard deviations from reported data, including from reported medians and ranges. Adjusted analyses were preferentially extracted over unadjusted (crude) comparisons. Where there were at least 3 studies reporting results from sufficiently similar analyses (based on population, interventions, comparators, and outcomes), we conducted random-effects meta-analyses using the meta package for R version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria).[61] Statistical heterogeneity is reported with the I^2 statistic, which estimates the proportion of all variation in effects that is due to true differences in effects between studies.

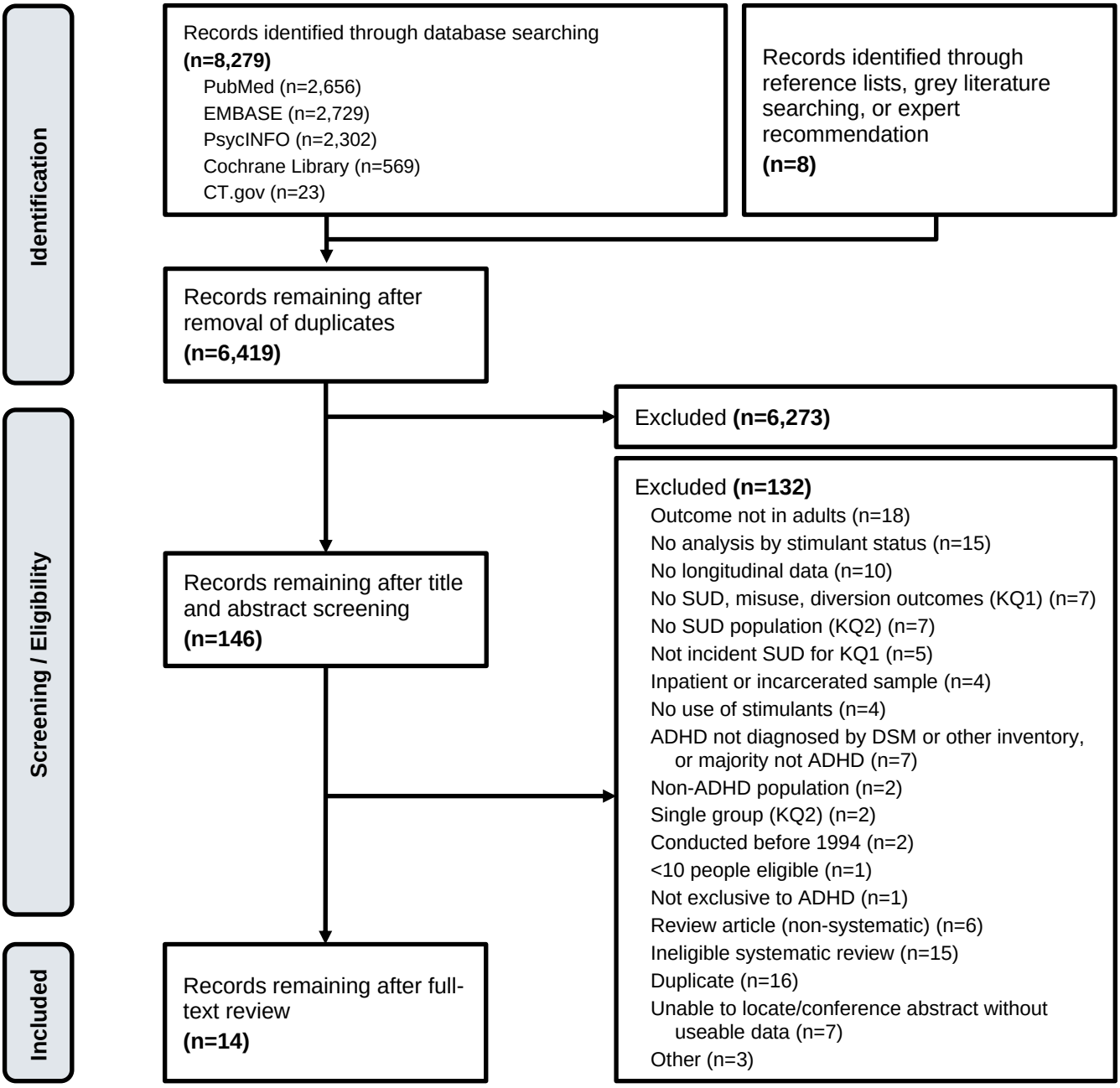
We assessed certainty of evidence using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology.[62] We compiled key study findings in evidence profiles, which provide the basis for determination of certainty of evidence and summarize conclusions for outcomes. Within each outcome, we considered the study design, the number of studies and

participants, methodological limitations, directness of the evidence, precision of the findings, consistency across studies, and other issues. We did not GRADE outcomes only informed from noncomparative studies. In addition, we did not GRADE studies reporting the incidence of outcomes among persons prescribed stimulants for ADHD. However, for these studies we assessed the various GRADE domains to communicate information about the characteristics of the studies, but we did not provide an overall rating for how the incidence estimates compare with a reference incidence (*eg*, the corresponding incidence in the general population). For KQ 2 (comparison of outcomes in persons prescribed stimulants versus not), we provide overall assessments for the strength of the evidence. Outcomes with inconclusive results were rated as insufficient evidence.

RESULTS

LITERATURE FLOW DIAGRAM

The literature flow diagram summarizes the results of the study selection process. A full list of excluded studies is provided in Appendix B.



Notes. We reviewed references from 15 applicable systematic reviews and/or meta-analyses; no meta-analysis included results that were fully applicable to this review.

Abbreviations. ADHD=attention-deficit/hyperactivity disorder; DSM=Diagnostic and Statistical Manual of Mental Disorders; KQ=key question; SUD=substance use disorder.

OVERVIEW OF INCLUDED STUDIES

Of 6,419 unique records screened, 146 underwent full-text review. Upon reviewing these, 7 studies were eligible for KQ 1[63-69] and 7 were eligible for KQ 2.[70-76] The most common reasons for exclusion included outcomes not being reported in adult or majority adult samples (*N* = 18), studies not reporting outcomes by stimulant use status (*N* = 15), and studies not including longitudinal data (*N* = 10).

Table 2 shows the summary characteristics of the eligible studies. Appendix D presents design details and Appendix E presents baseline characteristics. Two studies used a similar set of data, specifically 1 study examined outcomes in an original cohort, and the second examined outcomes in these same probands along with qualifying siblings.[63, 69] Similarly, in a different set of publications, 1 examined outcomes from a RCT, and another examined outcomes in a subgroup of people within this study.[74, 75] Reporting the co-publications as separate studies, there were 6 RCTs, 4 NRCS, and 4 single-group studies. All 6 RCTs compared psychostimulant medications to placebo with cognitive behavioral therapy (CBT) or individual skills training targeted at substance use, and 1 of these studies also included a non-stimulant ADHD medication treatment arm. Most of the studies were conducted in the US (*N* = 9), followed by Denmark (*N* = 2), Sweden (*N* = 2), and Norway (*N* = 1). ADHD was defined using the DSM-IV-TR (*N* = 6), DSM III-R (later reassessed using the DSM-IV) (*N* = 2), ICD-10 codes (*N* = 2), Conners' Adult ADHD self and observer rating scales (*N* = 1), by a regional expert committee (*N* = 1), or some combination of these (*N* = 2).

The studies evaluated a variety of interventions (Appendix F). Across both KQs, 10 studies explicitly mentioned methylphenidate as part of the stimulant treatment (either alone or in combination with other treatments, 2 studies included only mixed amphetamine salts,[74, 75] and 2 studies did not specify the medications included as part of the stimulant group.[69, 70]

Table 2. Summary Characteristics of Eligible Studies

Characteristics	KQ1 (*N* = 7)[a]	KQ2 (*N* = 7)[a]
Design		
RCT (*N* = *6*)	0	6
NRCS (*N* = *4*)	3	1
Single group (*N* = *4*)	4	0
Risk of Bias		
Low (*N* = 5)	3	2
Moderate (*N* = 8)	4	4
High (*N* = 1)	0	1
Countries		
United States (*N* = 9)	3	6
Denmark (*N* = 2)	2	0
Norway (*N* = 1)	1	0
Sweden (*N* = 2)	1	1
Stimulant Treatment (Number of Studies That Included the Following)		
Stimulants (any/multiple/not specified) (*N* = 5)	4	1
Methylphenidate only (*N* = 7)	3	4
Mixed amphetamine salts (*N* = 2)	0	2

Characteristics	**KQ1 (*N* = 7)[a]**	**KQ2 (*N* = 7)[a]**
Stimulant plus another active pharmaceutical for ADHD (*N* = 1)	1	0
Non-stimulant pharmaceutical comparison, no treatment, or placebo (*N* = 10)	3	7[b,c]
Outcomes (Number of Studies That Included the Following)[d]		
Incident SUD (KQ1) (*N* = 7)	7	-
Diversion or Misuse Outcomes (*N* = 2)	1	1
ADHD Treatment Adherence (*N* = 4)	0	4
SUD Treatment Adherence (*N* = 2)	0	2
ADHD Symptom Change (*N* = 5)	0	5
SUD Symptom Change (*N* = 2)	0	2
Abstinence (KQ2) (*N* = 5)	-	5
Substance Use (KQ2) (*N* = 5)	-	5
Other Symptom Change (*N* = 1)	0	1
Adverse Events (*N* = 4)	0	4

Notes.[a]In 2 co-publications, 1 study examined outcomes in an original cohort, and the second examined outcomes in these same probands along with qualifying siblings; [b]Six of these included either CBT or individual skills training for SUD in all groups; [c]Some studies included multiple comparison groups, but each study was only counted once in this table; [d]Studies may have reported multiple results for a given outcome category, but each study was only counted once per outcome category in this table.

Abbreviations. ADHD=attention-deficit/hyperactivity disorder; KQ=key question; N=number; NRCS=non-randomized comparative study; SUD=substance use disorder.

EFFECT OF STIMULANTS ON THE INCIDENCE OF SUD, MISUSE, AND DIVERSION IN PEOPLE WITH ADHD WITHOUT SUD AT BASELINE

Seven studies (3 NRCS and 4 single group) enrolling participants between 1970 and 2010 (3 studies did not report dates of enrollment) included 58,077 people.[63-69] Wilens et al 2006 added data of siblings to the participants included in Biederman et al 2008 (treated as 2 separate publications).[63, 69] Three studies were conducted in the US, 2 in Denmark, 1 in Norway, and 1 in Sweden. Three studies included a comparator group of people either untreated for ADHD, treated with non-stimulant ADHD medications, or some combination of these groups.[63,64,67] Methylphenidate was the most commonly used stimulant (*N* = 6), followed by dexamphetamine (*N* = 2), amphetamine products (*N* = 2), and pemoline (*N* = 1). One study did not specify the type of stimulant used.[69] Only 2 studies reported stimulant dosage (mean 41.7 mg methylphenidate;[66] mean maximum dose of 58.7 mg methylphenidate[68]). Stimulant treatment duration ranged from approximately 2 years to up to 6 years in 4 studies that reported this information.[63, 66-68] In 5 of these studies, length of follow-up ranged from 3 to 19 years, with 4 of these having 10 or more years of follow-up. Two studies did not report length of follow-up. Two studies reported loss to follow-up (15% and 20%),[63, 66] and 5 studies did not report any information on attrition.

In all 7 studies, people were without SUD at baseline. At baseline, the age of people was between 6 and 46 years old. For 4 studies that included people diagnosed with ADHD in childhood, 2 studies reported a mean age at baseline of 10.5 and 15.2 years[63, 67] and 2 reported the age at baseline ranged from 6 to 17.[66, 69] In the single study that enrolled only adults, the mean age was 28.4.[68] In the 1 study that included adults and children at baseline, approximately 75% were age 8–25, 13.3% were aged 26–35, and 11.4% were 36–46 years old.[64] Only 2 studies reported mean age at treatment initiation (both 8 years of age).[63, 66] Three studies reported that samples were majority White (100% in all),[63,66,69] and the remaining studies did not report information about race/ethnicity. All studies included mostly males (range = 65.4%–100%).

The 7 studies reported various measures of SUD outcomes. Two studies reported SUD, and 3 studies reported AUD separately from other substances or SUD. Finally, 2 studies reported the use of drugs separately from AUD or SUD (*ie*, non-alcohol substance use or stimulant use disorders). When studies reported SUD, AUD, or non-alcohol substance use disorders, it was not always clear whether these were mutually exclusive. As noted above, Appendix G reports the categorization of substance use outcomes in each study.

Three studies (1 NRCS and 2 single group) were rated moderate risk of bias because they did not clearly report whether outcome assessors were masked and had an additional concern (high attrition, inclusion of only people with high ADHD severity that may not be representative of the average ADHD population, and unclear reporting of comparator representativeness) (Appendix C).[64,65,69] One single group study was rated as moderate risk of bis for having unclear reporting.[66] Three studies (2 NRCS and 1 single group) had no concerns (*ie*, low risk of bias).[63,67,68]

In summary (Table 3), 1 in 7 (14%) people prescribed stimulants for ADHD is newly diagnosed with SUD, though estimates varied drastically across studies. There were insufficient data to pool estimates for the incidence of AUD or non-alcohol substance use or stimulant use disorders in those with ADHD prescribed stimulant medications. One small single-group study assessed diversion (11% of people) or misuse (10% to 31% depending on definition) among people prescribed stimulants for ADHD. There was no evidence of a difference for SUD for people with ADHD prescribed stimulant medications

compared to those who were not prescribed stimulant medications (low confidence). Studies provide insufficient evidence (no conclusion) for AUD and non-alcohol substance use or stimulant use disorders for people with ADHD prescribed stimulant medications compared to those who did not. Comparative studies did not assess diversion or misuse.

Table 3. Summary of Findings for Incidence of SUD

Outcome	Studies (People); Design	Methodological Limitations	Indirectness	Imprecision	Inconsistency	Other Issues	Summary	Overall Confidence
Incidence of Stimulants on SUD and Diversion/Misuse[a]								
SUD	5 (12823); 1 NRCS and 4 Single group	Moderate[b]	Direct	Imprecise[c]	Inconsistent[d]	None	Pooled proportion = 0.14, 95% CI (0.02, 0.35)	(Not graded)[e]
AUD	2 (384); 2 Single group	Moderate[f]	Direct	Imprecise[c]	Inconsistent[d]	None	No conclusion • AUD = 0.05 (0.03, 0.09) and 0.28 (0.21, 0.35)	(Not graded)[e]
Non-alcohol substance use or stimulant use disorder	1 (176); 1 Single group	Moderate[g]	Direct	N/A[a]	N/A[a]	Single study	No conclusion • Non-alcohol disorders = 0.37(0.30, 0.45); • Stimulant disorders = 0.24 (0.18, 0.31)	(Not graded)[e]
Diversion or misuse	1 (55); Single group	Moderate[h]	Direct	N/A[a]	N/A[a]	Single study	No conclusion • 11% reported diversion, 22% reported misusing medications and 31% reported using ADHD medication with drugs or alcohol.	(Not graded)[e]
Effect of Stimulants on Incidence of SUD and Diversion/Misuse[i]								
SUD	2 (57,455); NRCS	Moderate[j]	Direct	Precise	Inconsistent[k]	None	No evidence of a difference stimulant use • 2 studies found no significant difference in SUD. • 1 found significantly more incident SUD in a mixed medicine group.	Low
AUD	1 (131); NRCS	Low	Direct	N/A[a]	N/A[a]	Single study	No conclusion	Insufficient evidence

Outcome	Studies (People); Design	Methodological Limitations	Indirectness	Imprecision	Inconsistency	Other Issues	Summary	Overall Confidence
Non-alcohol substance use or stimulant use disorder	1 (131); NRCS	Low	Direct	N/A[a]	N/A[a]	Single study	No conclusion	Insufficient evidence
Diversion or misuse		NA	NA	NA	NA	NA	NA	No evidence

Notes. [a]Informed by single group data; [b]Three studies had moderate risk (concerns about cohort representativeness, lack of clear reporting, high attrition and unclear blinding of outcome assessor); [c]Wide confidence interval for pooled estimate; [d]Wide variation in estimates; [e]See Methods: we assessed the various GRADE domains to communicate information about the characteristics of the studies but did not provide an overall rating for how the incidence estimates compare with a reference incidence (*eg,* the corresponding incidence in the general population); [f]Two had moderate risk of bias (concerns about cohort representativeness, lack of clear reporting, and unclear blinding of outcome assessor); [g]One had moderate risk of bias (unclear reporting); [h]Moderate risk of bias due to high attrition and unclear blinding of outcome assessor; [i]Informed by comparative data; [j]One study had moderate risk of bias (unclear blinding of outcome assessor and unclear comparator representativeness), and 1 had no concerns (low risk); [k]Variation in estimate direction.

Abbreviations. N/A=not applicable; NRCS=non-randomized comparative study; SUD=substance use disorder.

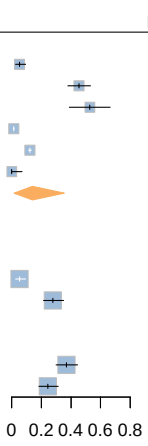
Incident SUD

Five studies found that the proportion of people with a new SUD diagnosis in people prescribed stimulants for ADHD ranged between 0.00 to 0.53 (pooled proportion = 0.14, 95% CI [0.02, 0.35]; Figure 1).[65-69] There was high heterogeneity across the studies with differences in baseline age and follow-up duration. The baseline age was between 6 and 17 years in 2 studies reporting ≥45% of people developed a SUD diagnosis following a prescription of stimulant medications. In 4 studies reporting ≤12% of people with SUD among those prescribed stimulants, mean baseline age was 15 years in 2 studies, 28 in 1 study, and was not reported in the fourth study. One study reported 0 cases of new SUD diagnoses among those prescribed stimulants. Two studies found the proportion of people with a new AUD after being prescribed psychostimulants for ADHD was 0.05 and 0.28 (Figure 1). [65,66] Two studies did not report length of follow-up and 1 study did not report age at baseline.

One study found that among those prescribed stimulants for ADHD (mean age at follow-up 25 years), 37% of people had a non-alcohol disorder and 24% had a stimulant use disorder.[66]

Figure 1. Incidence of SUD Among People With ADHD Treated With Stimulant Medications

Study	Substance	Outcome	Age at baseline	Follow-up	Intervention	n	N	Prop	95% CI
Alcohol & Drugs									
Dalsgaard 2014	Any	Disorder	NR	At mean age of 31	Stimulants	11	208	0.05	[0.03; 0.09]
Mannuzza 2008	Any	Disorder	Range 6-12	At mean age of 25	MPH	80	176	0.45	[0.38; 0.53]
Wilens 2006	Any	Disorder	Range 6-17	10 y	ADHD med (96% stim)	29	55	0.53	[0.39; 0.66]
Steinhausen 2014[a]	Any	Disorder	Mean 15 (SD 10)	15 y	MPH	102	7211	0.01	[0.01; 0.02]
Steinhausen 2014[a]	Any	Disorder	Mean 15 (SD 10)	15 y	Mixed med (84% MPH)	627	5121	0.12	[0.11; 0.13]
Torgersen 2013	Any	Disorder	Mean 28 (SD 8)	43 mo	MPH	0	52	0.00	[0.00; 0.07]
Overall Estimate								**0.14**	**[0.02; 0.35]**
Heterogeneity: I^2 = 99%									
Alcohol[b]									
Dalsgaard 2014	Alcohol	Abuse/Depend	NR	At mean age of 31	Stimulants	11	208	0.05	[0.03; 0.09]
Mannuzza 2008	Alcohol	Disorder	Range 6-12	At mean age of 25	MPH	49	176	0.28	[0.21; 0.35]
Drugs[c]									
Mannuzza 2008	Non-Alcohol	Disorder	Range 6-12	At mean age of 25	MPH	65	176	0.37	[0.30; 0.45]
Mannuzza 2008	Stimulant	Disorder	Range 6-12	At mean age of 25	MPH	43	176	0.24	[0.18; 0.31]



Notes. [a]Two groups from the Steinhausen 2014 study were included, numbers include data for people without SUD at the time of medication onset (across all study groups, 97 people had an SUD diagnosis before the beginning of the prescription register, so their medication status was unknown); [b]Estimates were not pooled since data were only from 2 studies; [c]Estimates were not pooled since data were only from 1 study.

Abbreviations. depend=dependence; mo=month; med=medication; MPH=methylphenidate; n/N=number; NR=not reported; prop=proportion; SD=standard deviation; stim=stimulants; y=years.

Diversion/Misuse

One study reported on prescription stimulant diversion or misuse over 10 years of follow-up among adults with ADHD diagnoses and no history of SUD at baseline.[69] Importantly, this was a small study (N = 55), it included adolescents and college-age adults, and also likely included older stimulant medications. In this study, 11% of the people reported they sold their medication, 22% took too much of their prescribed medication or misused it in some way, and 10% got high on their medication. The study also reported that 16% of people reported skipping their medication to use alcohol or drugs, 31% used their medications with alcohol, and 5% experienced a reaction when using their ADHD medication and alcohol or drugs.

Effect of Stimulants on Incident SUD

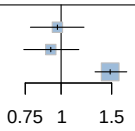
Three NRCS reported new SUD diagnoses among adults with ADHD who had been prescribed stimulant medications during their lives compared to those were never prescribed stimulants (Appendix H).[63,64,67] Because of differences in substances assessed (*eg*, general substance use, general drug, alcohol), and effect measures, we did not pool these data. Figure 2 provides a non-pooled visualization of the outcomes from the comparative studies for SUD.

SUD

Two NRCS found no significant difference in incident SUD diagnoses between people with ADHD prescribed stimulant medications compared to those with ADHD who were not prescribed stimulants (Figure 2).[64, 67] One NRCS found no significant difference in new SUD diagnoses over 3 years between people with ADHD prescribed stimulants versus those with ADHD not prescribed stimulants (aHR = 0.97, 95% CI [0.78, 1.20]).[64] Another NRCS followed people (~15 years) with ADHD prescribed various medications (*eg*, methylphenidate only, antidepressants only, antipsychotics only) and people with ADHD who had not received medications.[67] This study found no significant difference in incident SUD between the methylphenidate-only group compared to those who had not received medications (aHR = 0.92, 95% CI [0.74, 1.15]). The same NRCS found significantly more incident SUD diagnoses for people prescribed mixed medications (where the majority included stimulants plus some other ADHD medication) compared to those who had not received medications (aHR = 1.48, 95% CI [1.31, 1.69]).[67]

Figure 2. Incident SUD Diagnoses Among People With ADHD Prescribed Stimulant Medications versus People With ADHD Not Prescribed Stimulants

Study	Definition	Follow-up	Intervention	n/N (%)	Comparator	n/N (%)	aHR	95% CI
Chang 2014	ICD-10	3 y	Stimulants	NR/NR (NR)	No stimulant med	NR/NR (NR)	0.97	[0.78; 1.20][a]
Steinhausen 2014[b]	ICD-8, ICD-10	15 y	MPH	102/7211 (1.4)	No medication	72/6370 (1.1)	0.92	[0.74; 1.15][c]
Steinhausen 2014[b]	ICD-8, ICD-10	15 y	Mixed med (84% MPH)	627/5121 (12.2)	No medication	72/6370 (1.1)	1.48	[1.31; 1.69][c]



Notes. [a]Adjusted for sex, age, civil status, employment, living in metropolitan area, income psychiatric diagnosis, and criminal convictions; [b]Two groups from the Steinhausen 2014 study were included, numbers include data for people without SUD at the time of medication onset (across all study groups, 97 people had an SUD diagnosis before the beginning of the prescription register, so their medication status was unknown); [c]Adjusted for mood disorder, anxiety disorder, personality disorder, conduct disorder, hyperkinetic disorder unspecified, autism spectrum disorder, disturbance of activity and attention, and age at diagnosis.

Abbreviations. aHR=adjusted hazard ratio; DSM=Diagnostic and Statistical Manual of Mental Disorders; ICD=International Classification of Disease; med=medication; MPH=methylphenidate; n/N=number; NR=not reported; y=year.

Alcohol Use Disorders

One NRCS found no significant difference in alcohol abuse and alcohol dependence diagnoses over 10 years between those prescribed stimulants at some time in their lives compared to those who never took a stimulant (alcohol abuse aHR = 1.1, 95% CI [0.6, 2.1] and alcohol dependence (aHR = 1.0, 95% CI [0.5, 2.4]).[63] In this study, it was unclear whether the same people were counted in the measure of abuse and dependence.

Non-Alcohol Substance Use or Stimulant Use Disorder

One NRCS reported no significant differences in drug abuse (aHR= 1.6, 95% CI [0.8, 3.2]) or drug dependence (aHR= 1.0, 95% CI [0.4, 2.6]) diagnoses over 10 years between people who were ever prescribed stimulants in their lifetime compared to those never prescribed stimulants.[63] It was unclear whether the same participants were included in both outcomes.

Diversion/Misuse

No comparative study reported data on diversion or misuse.

EFFECT OF STIMULANTS ON ADHD AND SUD SYMPTOM AND TREATMENT OUTCOMES IN PEOPLE WITH CO-OCCURRING ADHD AND SUD

Seven studies (6 RCTS and 1 NRCS) enrolling participants between 1998 and 2020 (2 studies did not report dates) analyzed 662 people. Notzon 2016 was a subset of the Levin 2015 study population that had used marijuana within the 30 days prior to enrollment (treated as 2 separate publications).[74, 75] Study inclusion and exclusion criteria varied. The studies included people with a comorbid cocaine or amphetamine use disorder (*N* = 5) and people receiving methadone treatment for opioid use disorder (*N* = 1) or SUD (*N* = 1). Six studies were conducted in the US[70, 72-76] and 1 in Sweden.[71] Four RCTs compared methylphenidate (dose range = 40–90 mg/day) to placebo,[71,72,74,76] and 1 study also included a third comparison group of bupropion (maximum dose of 400 mg/day).[73] Two RCTs compared extended-release mixed amphetamine salts (60 and/or 80 mg daily) to placebo.[74, 75] Importantly, in the 6 RCTs all groups also received either cognitive behavioral therapy (CBT) or individual skills training targeted at substance use during the study. One NRCS compared any stimulant (dose not reported) to non-stimulant treatment or those receiving no treatment.[70] Treatment duration in the RCTs ranged from 12–14 weeks[71-76] and treatment duration in the NRCS was estimated to be approximately 2 years.[70] In the RCTs, the length of follow-up ranged from 12–14 weeks[71-76] and loss to follow-up ranged from 25%–56.6% in the stimulant treatment groups and 24.2%–54.7%in the comparison groups.[72-74, 76] Loss to follow-up was not reported in the NRCS.[70]

Overall, mean age of people at baseline ranged from 37–40.4 years. Most participants (57%–89.6%) were male. Six studies reported race/ethnicity information of samples with the proportion of people who were White ranged from 39.8–89.6%.

Four RCTs did not blind outcome assessors and had incomplete outcome data with high dropout rates (*ie*, medium risk of bias). The remaining 2 RCTs had no methodological concerns (*ie*, low risk of bias). The 1 NRCS reported results from a crude analysis with no clear reporting of eligibility between comparison groups, unclear reporting for some outcomes, and concerns of incomplete outcome data (*ie*, high risk of bias).

In summary (Table 4), there was no evidence of differences in ADHD treatment adherence, substance use, SUD symptom change, or abstinence from SUD in people with co-occurring ADHD and SUD prescribed stimulants versus their counterparts not prescribed stimulants (low confidence for all). Studies provide insufficient evidence (no conclusion) for ADHD symptom change, SUD treatment adherence, medication misuse/diversion, and measures of depression and anxiety. There was no evidence of a difference in various measures of adverse events (strength of evidence not assessed).

Table 4. Summary of Findings for Stimulants in People With Co-Occurring ADHD and SUD

Outcome	Studies (People); Design	Methodological Limitations	Indirectness	Imprecision	Inconsistency	Other Issues	Summary	Overall Confidence
ADHD symptom change	5 (402); RCT	Moderate[a]	Direct	Imprecise[b]	Inconsistent[c]	None	No conclusion[d] • Three studies reported no significant difference, 1 study reported a significant improvement in the stimulant group and 1 study reported mixed findings.	Insufficient evidence
ADHD treatment adherence	4 (354); RCT	Moderate[e]	Direct	Imprecise[f]	Consistent	None	No evidence of a difference in ADHD treatment adherence for stimulants compared to placebo • 3 of 4 studies found no significant difference in a measure of treatment adherence.	Low
Substance use	5 (333); RCT	Moderate[a]	Direct	Precise	Inconsistent[c]	None	No evidence of a difference in substance use for stimulants compared to placebo • Mixed results for opiate, alcohol and cannabis use. • No difference in illicit amphetamine, cocaine, “other” or “any” drug use and time to relapse.	Low
SUD symptom change	2 (130); RCT	Moderate[g]	Direct	Precise	Inconsistent[h]	None	No evidence of a difference in SUD symptom change.	Low
SUD treatment adherence	2 (329); NCRS, RCT	High[i]	Direct	Precise	Inconsistent[c]		No conclusion • One study reported significantly longer SUD treatment retention in the stimulant group. • One study reported no significant differences in number of completed CBT sessions.	Insufficient evidence

Outcome	Studies (People); Design	Methodological Limitations	Indirectness	Imprecision	Inconsistency	Other Issues	Summary	Overall Confidence
Abstinence	5 (402); RCT	Moderate[a]	Direct	Precise	Inconsistent[j]	None	No evidence of a difference in abstinence outcomes • Four of 5 studies found no significant differences in abstinence outcomes.	Low
Medication misuse/ diversion	1 (98); RCT	Moderate[k]	Direct	N/A[l]	N/A[l]	Small single study	No conclusion • One study found no reports of misuse or diversion in any patients.	Insufficient evidence
Other	1 (24); RCT	Low	Indirect[m]	N/A[l]	N/A[l]	Small single study	No conclusion • One study found no significant differences in Beck Depression Inventory, Beck Anxiety Inventory, or Stroop Test scores between stimulant and comparison groups	Insufficient evidence

Notes. [a]Three studies had moderate risk of bias (high attrition, unclear blinding of outcome assessor, unclear allocation concealment, and/or unclear random sequence generation) and 2 studies had low risk; [b]Wide confidence intervals in 2 studies; [c]Studies used a variety of measures, and direction of results varied across studies; [d]One study also included a bupropion arm, but overall evidence was assessed for stimulants compared to any other treatments; [e]Three studies had moderate risk of bias (high attrition, unclear blinding of outcome assessor, unclear allocation concealment, and/or unclear random sequence generation) and 1 study had low risk; [f]One study had a wide confidence interval and another did not report any measures of variability; [g]One study had moderate risk of bias (high attrition, unclear blinding of outcome assessor, allocation concealment, and random sequence generation) and 1 study had low risk; [h]Different assessments used; [i]One study had high risk of bias (an NRCS with unclear reporting, unclear eligibility criteria, outcomes not fully defined, and no adjustment for confounding) and 1 study had moderate risk of bias (high attrition); [j]Directions of results varied across studies; [k]Study had moderate risk of bias (high attrition, unclear blinding of outcome assessor, allocation concealment, and random sequence generation); [l]Single study; [m]Assessments did not directly align with key question.

Abbreviations. ADHD=attention-deficit/hyperactivity disorder; CBT=cognitive behavioral therapy; NRCS=non-randomized comparative study; SUD=substance use disorder.

ADHD Symptom Change

Categorical Measures of Symptom Change

Four RCTs reported 6 different categorical measures of ADHD symptom change (Appendix H and Appendix I).[72-74, 76] Three of these RCTs were published by the same authorship group, which accounted for 86% of the ADHD symptom change outcomes.[72-74]

Three RCTs from the same author group reported no significant difference in the proportion of people who had improvement on the Clinical Global Improvement (CGI) scale from baseline to follow-up (12 or 14 weeks) between people who received either methylphenidate or mixed amphetamine salts with CBT compared to placebo with CBT (pooled OR = 1.27, 95% CI [0.32, 5.09]; Figure 3).[72-74] One of these RCTs also found no significant difference in change on the CGI from baseline to follow-up between people who received either methylphenidate with CBT compared to bupropion with CBT (OR = 0.53, 95% CI [0.17, 1.69]).[73]

Two RCTs found no significant difference in symptom change (≥30% reduction in Adult ADHD Rating Scale [AARS]) between those in the methylphenidate with CBT group compared to those taking a placebo with CBT during the 12 and 14 week trials (OR = 0.63, 95% CI [0.23, 1.71] and 0.74 [0.34, 1.59]).[72, 73] These 2 RCTs also found no significant difference in people who had a combined improvement of ≥30% reduction in AARS and CGI rating of <3 for people who received methylphenidate with CBT compared to placebo with CBT (OR = 0.38, 95% CI [0.09, 1.64] and 1.10 [0.47, 2.53]).[72, 73] In addition, 1 of these RCTs also compared people taking methylphenidate with CBT to those assigned to receive bupropion. This RCT found no significant differences in people with >30% reduction in AARS (OR = 0.56, 95% CI [0.2, 1.51]) or those with a combined CGI <3 and ≥30% reduction in AARS (OR = 0.58, 95% CI [0.13, 2.66]) between the methylphenidate with CBT and bupropion with CBT groups.[73]

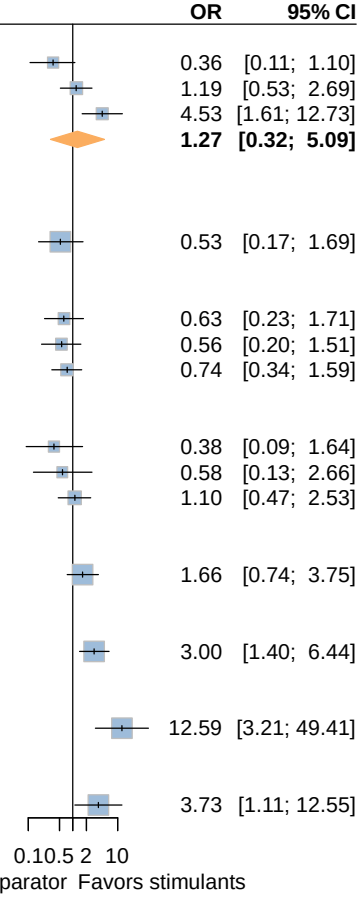
One RCT reported no significant difference in symptom change (≥30% reduction in the Targeted Adult Attention-Deficit/Hyperactivity Disorder [TAADDS]) between people who received methylphenidate with CBT compared to placebo with CBT over 14 weeks (OR = 1.66, 95% CI [0.74, 3.75]).[72]

One RCT found a significant improvement in symptoms, defined as a >30% reduction in Adult ADHD Investigator Symptom Rating Scale (AISRS) score from baseline to 14 week follow-up, in the mixed amphetamine salts with CBT group compared to placebo with CBT group (OR = 3.00, 95% CI [1.40, 6.44]).[74]

Another RCT reported significantly more people had a moderate improvement (defined as 1 or 2 points on 7-point scale) at 12 week follow-up based on either physician (OR = 12.59, 95% CI [3.21, 49.41]) or patient ratings (OR = 3.73, 95% CI [1.11, 12.55]) for those receiving methylphenidate with CBT compared to placebo with CBT.[76]

Figure 3. ADHD Symptom Change (Categorical Measures)

Study	Follow-up	Intervention	n/N (%)	Comparator	n/N (%)	OR	95% CI
CGI < 3 (vs placebo + CBT)							
Levin 2006[a]	12 w	MPH + CBT	6/32 (19)	Placebo + CBT	13/33 (39)	0.36	[0.11; 1.10]
Levin 2007	14 w	MPH + CBT	18/53 (34)	Placebo + CBT	16/53 (30)	1.19	[0.53; 2.69]
Levin 2015	14 w	Mixed amph + CBT	31/83 (37)	Placebo + CBT	5/43 (12)	4.53	[1.61; 12.73]
Overall Estimate						**1.27**	**[0.32; 5.09]**
Heterogeneity: I^2 = 81%							
CGI < 3 (vs bupropion + CBT)							
Levin 2006[a]	12 w	MPH + CBT	6/32 (19)	Bupropion + CBT[b]	10/33 (30)	0.53	[0.17; 1.69]
≥30% reduction in AARS							
Levin 2006[a]	12 w	MPH + CBT	11/32 (34)	Placebo + CBT	15/33 (46)	0.63	[0.23; 1.71]
Levin 2006[a]	12 w	MPH + CBT	11/32 (34)	Bupropion + CBT[b]	16/33 (49)	0.56	[0.20; 1.51]
Levin 2007	14 w	MPH + CBT	25/53 (47)	Placebo + CBT	29/53 (55)	0.74	[0.34; 1.59]
CGI < 3 & ≥30% reduction in AARS							
Levin 2006[a]	12 w	MPH + CBT	3/32 (9)	Placebo + CBT	7/33 (21)	0.38	[0.09; 1.64]
Levin 2006[a]	12 w	MPH + CBT	3/32 (9)	Bupropion + CBT[b]	5/33 (15)	0.58	[0.13; 2.66]
Levin 2007	14 w	MPH + CBT	16/53 (30)	Placebo + CBT	15/53 (28)	1.10	[0.47; 2.53]
≥30% reduction on the TAADDS							
Levin 2007	14 w	MPH + CBT	21/53 (40)	Placebo + CBT	15/53 (28)	1.66	[0.74; 3.75]
≥30% reduction in AISRS							
Levin 2015	14 w	Mixed amph + CBT	55/83 (66)	Placebo + CBT	17/43 (40)	3.00	[1.40; 6.44]
Improved by physician ratings (1 or 2 on 7-point scale)							
Schubiner 2002	12 w	MPH + CBT	18/24 (77)	Placebo + CBT	5/24 (21)	12.59	[3.21; 49.41]
Improved by patient ratings (1 or 2 on 7-point scale)							
Schubiner 2002	12 w	MPH + CBT	18/24 (73)	Placebo + CBT	10/24 (42)	3.73	[1.11; 12.55]



Notes. [a]Study included both a placebo and bupropion comparison group; [b]Data were not pooled due to use of active comparator.

Abbreviations. AARS=Adult ADHD Rating Scale; AISRS=Adult ADHD Investigator Symptom Rating Scale; amph=amphetamine salts; CBT=cognitive behavioral therapy; CGI=Clinical Global Improvement Scale; MPH=methylphenidate; n/N=number; OR=odds ratio; TAADDS=Targeted Adult Attention Deficit Disorder Scale; w=weeks.

Continuous Measures of Symptom Change

Three RCTs reported ADHD symptom change using continuous measures.[71,74,76] One RCT found significant improvements at 14 week follow-up on the CGI as a continuous measure in those taking mixed amphetamine salts with CBT compared to those taking placebo with CBT (MD = 0.64, 95% CI [0.19, 1.09]).[74] The same study also reported significant improvement on the CGI as a categorical measure (described above). The same RCT also reported significant improvements in changes on AISRS scores (MD = 9.41, 95% CI [4.75, 14.07]), Conners Adult ADHD Rating Scales (CAARS) hyperactive scale scores (MD = 8.88, 95% CI [3.33, 14.43]), CAARS inattentive scale scores (MD = 10.87, 95% CI [5.34, 16.40]), and total CAARS scores (MD =11.09, 95% CI [5.48, 16.70]) for people randomized to mixed amphetamine salts with CBT compared to placebo with CBT.[74] Another RCT found no significant differences in the CAARS self-rated scale (MD = -10.6, 95% CI [-3.65, 24.85]) or observer-rated scale (MD = -0.10, 95% CI [-11.01, 10.81]) between those who received methylphenidate with skills training compared to placebo with skills training at 13 weeks follow-up.[71]

One RCT found no significant differences in the number of inattentive (MD = -0.70, 95% CI [-2.39, 0.99]) or hyperactive (MD = -1.36, 95% CI [-3.07, 0.35]) symptoms at 12 week follow-up between people who received methylphenidate with CBT compared to placebo with CBT.[76]

ADHD Treatment Adherence

Three of 4 RCTs found no significant difference in ADHD treatment adherence. One RCT reported lower treatment compliance (based on positive urine fluorescence) over 12 weeks in the methylphenidate with CBT group compared to placebo with CBT and bupropion with CBT groups (77% vs 83% vs 91%, overall $p = 0.40$).[73] One RCT reported no significant difference in the proportion of urine samples with positive fluorescence for ADHD medications in people taking methylphenidate with CBT compared to placebo with CBT over 14 weeks (MD = 0.02 [-0.05, 0.15]).[72] Another RCT reported no significant difference in positive fluorescence between those taking mixed amphetamine salts with CBT compared to placebo with CBT over 14 weeks (effect size not reported, $p = 0.57$).[74] An RCT reported no significant difference in treatment retention over 13 weeks between people randomized to methylphenidate plus skills training or placebo plus skills training (OR = 3.65, 95% CI [0.53, 25.01]).[71]

Substance Use

Categorical Measures of Substance Use

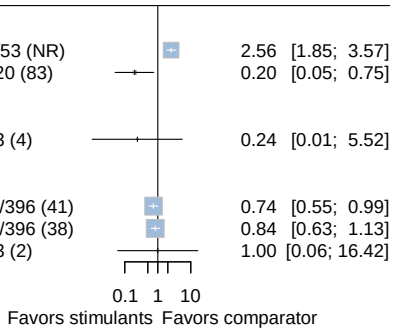
Three RCTs examined either cannabis, amphetamine, or opioid SUD-related outcomes in people with ADHD and SUD at baseline using categorical measures (Figure 4). One RCT, which included people with comorbid ADHD and amphetamine dependence, reported significantly greater odds of having a THC-positive urine sample over 14 weeks among people receiving methylphenidate with CBT compared to placebo with CBT (OR = 2.56, 95% CI [1.85, 3.57]).[72] Conversely, another 14 week RCT limited to people who reported smoking cannabis at baseline reported significantly lower cannabis smoking among people assigned to methylphenidate plus CBT compared to placebo plus CBT (OR = 0.20, 95% CI [0.05, 0.75]).[75]

One RCT of people with comorbid ADHD and amphetamine dependence reported no significant difference in illicit amphetamine use between methylphenidate with CBT and placebo with CBT groups at 14 week follow-up (OR = 0.24, 95% CI [0.01, 5.52]).[72]

Two RCTs reported on opioid use between methylphenidate with CBT and placebo with CBT. One 12-week RCT included people with both adult ADHD and cocaine dependence/abuse and who were also receiving methadone treatment for opioid use disorder. This RCT found a lower proportion of weeks people tested positive for opioids for those who received methylphenidate with CBT compared to placebo with CBT (OR = 0.74, 95% CI [0.55, 0.99]). The same study found a lower (not statistically significant) proportion of weeks people tested positive for opioids between those who received methylphenidate with CBT compared to bupropion (OR = 0.84, 95% CI[0.62, 1.13]).[73] Another RCT (14 weeks) in people with comorbid ADHD and cocaine dependence reported no significant differences in illicit opioid use during the study between methylphenidate with CBT compared to placebo with CBT (OR = 1.00, 95% CI [0.06, 16.42]).[72]

Figure 4. Substance Use (Categorical Measures)

Study	Outcome	Follow-up	Intervention	n/N (%)	Comparator	n/N (%)	OR	95% CI
Cannabis/THC								
Levin 2007	Prob of THC+ urine sample	14 w	MPH + CBT	NR/53 (NR)	Placebo + CBT	NR/53 (NR)	2.56	[1.85; 3.57]
Notzon 2016	Cannabis smoking	14 w	Mixed amph + CBT	18/37 (49)	Placebo + CBT	17/20 (83)	0.20	[0.05; 0.75]
Amphetamine								
Levin 2007	Illicit amphetamine use	14 w	MPH + CBT	0/53 (0)	Placebo + CBT	2/53 (4)	0.24	[0.01; 5.52]
Opiates								
Levin 2006[a]	% wks positive for opiates	12 w	MPH + CBT	130/384 (34)	Placebo + CBT	162/396 (41)	0.74	[0.55; 0.99]
Levin 2006[a]	% wks positive for opiates	12 w	MPH + CBT	130/384 (34)	Bupropion + CBT	150/396 (38)	0.84	[0.63; 1.13]
Levin 2007	Illicit opiate use	14 w	MPH + CBT	1/53 (2)	Placebo + CBT	1/53 (2)	1.00	[0.06; 16.42]



Notes. [a]Study included both a placebo and bupropion comparison group.
Abbreviations. amph=amphetamine salts; CBT=cognitive behavioral therapy; MPH=methylphenidate; n/N=number; NR=not reported; OR=odds ratio; prob=probability; THC=tetrahydrocannabinol; w/wks=weeks.

Continuous Measures of Substance Use

Four RCTs reported alcohol, cannabis, cocaine, amphetamine, or other SUD outcomes using continuous measures in people with ADHD and SUD at baseline. One RCT of people with comorbid ADHD and amphetamine dependence reported significantly fewer days of alcohol use of <60 g/day for those receiving methylphenidate with skills training compared to placebo with skills training at 13 weeks follow-up (MD = -11.0 days, 95% CI [-20.89, -1.11]). The same trial reported no significant difference in the mean number of days people used alcohol >60 g/day between groups (MD = -3.80 days, 95% CI [-12.18, 4.58].[71]

One RCT reported a higher mean level of THC in urine samples in the methylphenidate with CBT group compared to placebo with CBT group at 14 weeks follow-up (MD = 239.00 ng/ml, 95% CI [216.54, 261.46]).[72]

Three RCTs reported cocaine use between those receiving methylphenidate with CBT compared to placebo with CBT. An RCT of people receiving methadone treatment for opioid use disorder with both adult ADHD and cocaine dependence/abuse reported no significant difference in the proportion of weeks (over 12 weeks) people tested positive for cocaine between methylphenidate with CBT and placebo with CBT (MD = 0.00, 95% CI [-0.19, 0.19]).[73] Another RCT of people with comorbid ADHD and amphetamine dependence also reported no significant difference in the proportion of weeks (over 14 weeks) that were cocaine positive between those receiving methylphenidate with CBT and placebo with CBT (MD = 0.03, 95% CI [-0.05, 0.15]).[72] One RCT found that among those with ADHD seeking treatment for cocaine use disorder, there were no significant differences in the proportion of urine samples that tested positive for cocaine over the 12 week study between methylphenidate with CBT and placebo with CBT groups (MD = 0.08, 95% CI -0.16, 0.32]).[76]

One RCT of people with comorbid ADHD and amphetamine dependence reported no significant difference in days of amphetamine use over 13 weeks between methylphenidate with skills training and placebo with skills training (urine toxicology MD = 2.00 days, 95% CI [-5.04, 9.04] and self-report MD = 0.50 days, 95% CI [-5.07, 6.07]).[71]

Two RCTs reported on other substance use outcomes. One RCT of people with comorbid ADHD and amphetamine dependence reported no significant difference in days of other illicit drug use between

methylphenidate with skills training and placebo with skills training over the 13 week (urine toxicology MD = 0.60 days, 95% CI [-2.49, 3.69] and self-report (MD = -4.10 days, 95% CI [-8.33, 0.13]).[71] This same study reported a similar time to relapse in the methylphenidate with CBT group and placebo with CBT group (mean = 3.33 [2.2–5.4] days vs 3.80 [1.8–4.9] days, *p = NS*). Another RCT that included people receiving methadone treatment for opioid use disorder with both adult ADHD and cocaine dependence/abuse reported no significant difference between groups in the proportion of positive weeks for any drug during the 12 week study (MD = 0.03, 95% CI [-0.01, 0.07]).[73]

One RCT that included people receiving methadone treatment for opioid use disorder with both adult ADHD and cocaine dependence/abuse reported on substance use outcomes between those receiving methylphenidate and those receiving bupropion. This RCT found no significant differences in the mean proportion of positive weeks (based on urine) for cocaine (MD = -0.05 weeks, 95% CI [-0.23, 0.13]) or any drug (MD = 0.01, 95% CI [-0.03, 0.05]) during the 12-week study.[73]

SUD Symptom Change

Two RCTs reported no significant difference in SUD symptom change between methylphenidate with CBT compared to placebo with CBT. One RCT found no significant difference in the proportion of people achieving a CGI cocaine improvement score of <3 in people receiving methylphenidate with CBT compared to placebo with CBT at 14 week follow-up (OR = 1.58, 95% CI [0.73, 3.42]).[72] One RCT reported no significant difference in substance craving based on a 7-point visual analog scale between methylphenidate with skills training and placebo with skills training groups at 13 weeks follow-up (MD = -0.5, 95% CI [-1.83, 0.83]).[71]

SUD Treatment Adherence

One RCT and 1 NRCS reported SUD treatment adherence outcomes. The NRCS reported significantly longer SUD treatment retention for people with comorbid ADHD and SUD who received stimulant medication within 90 days of admission to an outpatient SUD program compared to their counterparts who did not receive stimulants (aHR = 0.59, 95% CI [0.40, 0.87]).[70] One RCT reported no significant difference over 14 weeks in the number of CBT sessions attended between those assigned to receive mixed amphetamine salts with CBT compared to placebo with CBT (MD = 1.19, 95% CI [(-0.36, 2.74]).[74]

Abstinence

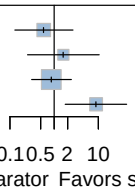
Categorical Measures

Two of 3 RCTs (all from the same author group) reported no significant difference in a categorical measure of abstinence from substance use (Figure 5). One RCT (12 weeks) reported no significant differences in the odds of ≥2 consecutive weeks of abstinence for all participants (OR = 0.58, 95% CI [0.13, 2.66]) or a subgroup of current cocaine abusing/dependent people (OR = 1.09, 95% CI [0.16, 7.59]) for people receiving methylphenidate with CBT compared to placebo with CBT.[73] A 14-week RCT reported no significant difference in the odds of ≥2 consecutive weeks of abstinence between methylphenidate with CBT and placebo with CBT groups (OR = 0.87, 95% CI [0.31, 2.46]).[72] Another 14-week RCT reported significantly more people had ≥3 consecutive weeks of abstinence in the mixed amphetamine salts with CBT group compared placebo with CBT group (aOR = 8.74, 95% CI [1.78, 42.97]).[74] One 12-week RCT reported no significant difference in ≥2 consecutive weeks of abstinence for people randomized to methylphenidate with CBT or bupropion with CBT (OR = 1.60, 95% CI

[0.25, 10.29]). The same RCT found no significant difference in ≥2 consecutive weeks of abstinence in a sub-analysis of current cocaine abusing/dependent people in the methylphenidate with CBT compared to placebo with CBT (OR = 1.45, 95% CI [0.18, 11.94]).[73]

Figure 5. Abstinence (Categorical Measures)

Study	Outcome	Follow-up	Intervention	n/N (%)	Comparator	n/N (%)	OR	95% CI
Levin 2006[a]	≥2 wks abstinence	12 w	MPH + CBT	3/32 (9)	Placebo + CBT	5/33 (15)	0.58	[0.13; 2.66]
Levin 2006[a]	≥2 wks abstinence	12 w	MPH + CBT	3/32 (9)	Bupropion + CBT	2/33 (6)	1.60	[0.25; 10.29]
Levin 2007	≥2 wks abstinence	14 w	MPH + CBT	8/53 (15)	Placebo + CBT	9/53 (17)	0.87	[0.31; 2.46]
Levin 2015	≥2 wks abstinence	14 w	Mixed amph + CBT	20/83 (24)	Placebo + CBT	3/43 (7)	8.74	[1.78; 42.97][b]



Notes. Outcome defined as abstinence from substance use for ≥2 consecutive weeks. [a]Study included both a placebo and bupropion comparison group; [b]Adjusted estimate (covariates not reported).

Abbreviations. amph=amphetamine salts; CBT=cognitive behavioral therapy; MPH=methylphenidate; n/N=number; OR=odds ratio; w/wks=weeks.

Continuous Measures

Two RCTs reported no significant differences in the longest period of abstinence between stimulant and placebo groups over 12 and 13 weeks (MD = 0.00 days, 95% CI [-3.42, 3.42] and 0.70, 95% CI [-2.01, 3.41]).[71, 76]

Medication Misuse or Diversion

One RCT found no instances of ADHD medication diversion or of medications making people subjectively high or euphoric for the methylphenidate with CBT, bupropion with CBT, or placebo with CBT.[73]

Other Symptom Change

One RCT reported no significant differences in change in Beck Anxiety Inventory (MD = -3.9, 95% CI [-8.45, 0.65]) or Stroop test score (MD = 4.40, 95% CI [-9.92, 18.72]) at 13 week follow-up between methylphenidate with skills training and placebo with skills training.[71] This study reported no significant differences in change in the Beck Depression Inventory scores in the article (p = 0.138), though the MD calculated from the data provided in the study indicated a significant reduction in the BDI scores for those taking methylphenidate compared to placebo (MD = -7.30, 95% CI [-14.18, -0.42]).

Side Effects and Adverse Events

Four RCTs reported on side effects or adverse events. Two RCTs reported a large but not statistically significant increase in the proportion of people who needed their medication doses lowered due to side effects between methylphenidate with CBT and placebo with CBT groups (OR = 4.24, 95% CI [0.46, 39.31] and OR = 3.83, 95% CI [0.67, 21.84]).[72, 76] Another RCT reported a large but not statistically significant difference in people who needed their treatment dosages lowered between methylphenidate with CBT and bupropion with CBT arms (OR = 3.31, 95% CI [0.33, 33.63]).[73] Finally, 1 RCT reported significantly fewer people in the mixed amphetamine salts with CBT group tolerated their assigned treatment dose compared to those in the placebo with CBT group (OR = 0.27, 95% CI [0.09, 0.77]).[74]

Three RCTs reported no significant differences in the proportion of people who discontinued their medication or ended the trial due to adverse events between treatment and placebo arms (OR range = 0.50–1.65, all non-significant).[72-74]

One RCT reported more people experienced insomnia or trouble sleeping in those who received methylphenidate with CBT compared to placebo with CBT (OR = 3.46, 95% CI [1.05, 11.34]).[76] However, 2 other RCTs reported no significant difference in insomnia between stimulant and placebo groups (OR = 7.1, 95% CI [0.89, 56.56]; OR = 4.85, 95% CI [0.57, 41.22]).[72, 74]

Four studies reported no significant difference in other side effects including fatigue, anxiety, depression or sadness, headache, irritability or agitation, gastrointestinal or digestive upset (such as vomiting or diarrhea), chest pain, palpitations or racing heart, changes in appetite, or other side effects between treatment arms. A full list of reported side effects can be found in Appendix J.

DISCUSSION

We identified 7 longitudinal studies that reported on incident SUD, and diversion or misuse among people with ADHD prescribed stimulants. Three of these 7 studies also evaluated the risk of incident SUD in people prescribed stimulant medications compared to those not prescribed stimulants. In addition, we identified 7 studies that compared stimulants in people with co-occurring ADHD and SUD. Key findings include the following:

KEY FINDINGS

For the effect of stimulants on the incidence of SUD, misuse, and diversion in people with ADHD without SUD at baseline, key findings are:

- Among people prescribed stimulants for ADHD, 5 studies found that approximately 1 in 7 adults (14%, 95% CI [2%, 35%]) is newly diagnosed with SUD (ie, any substance), though estimates varied drastically across studies (no evidence grading). There was insufficient evidence to pool estimates for the incidence of AUD or non-alcohol substance use disorders or stimulant use disorders among people prescribed stimulants for ADHD.
- Only 1 small single group study assessed diversion or misuse of stimulants among adolescents and college-age adults prescribed stimulants for ADHD. Diversion was reported in 11% of people and misuse in 10% to 31% depending on definition (no evidence grading).
- Among people prescribed stimulants for ADHD compared to people with ADHD who are not prescribed stimulants, there is no evidence of a difference in the risk of a new SUD in adulthood (low confidence).
- Among people prescribed stimulants for ADHD compared to those who are not prescribed stimulants, there is insufficient evidence for a difference in the risk of AUD or non-alcohol substance use or stimulant use disorders (no conclusions).

For the effect of stimulants on ADHD and SUD symptom and treatment outcomes in people with co-occurring ADHD and SUD, key findings are:

- Among people with co-occurring ADHD and SUD who are prescribed versus not prescribed stimulants, there is no evidence of a difference in ADHD treatment adherence, substance use, SUD symptom change, and abstinence (all conclusions with low confidence).
- Among people with co-occurring ADHD and SUD who are prescribed versus not prescribed stimulants, there is insufficient evidence (no conclusion) to assess differences in ADHD symptom change, SUD treatment adherence, misuse or diversion, and depression/anxiety.

The overall clinical implications of these findings are as follows:

- Prescribing stimulants to people with ADHD may have no effect on the risk of subsequent SUD. Available studies did not identify broad evidence of harm associated with the prescription of stimulants for people with ADHD. There are limited data about misuse and diversion of stimulant medications in people with ADHD. Prescribers should consider stimulant medications or other treatments for ADHD after a thorough, individualized risk-benefit discussion.

The incidence proportion of SUD and AUD varied widely in the 7 studies of people with ADHD prescribed stimulants. While not an exact comparison, an estimated 17.3% (prevalence) of the US adult population had an SUD diagnosis in 2022,[77] which is comparable to the pooled 14% SUD incidence proportion reported in the 7 studies identified in this report.

Importantly, 2 comparative studies found no significant difference in incident SUD for people with ADHD between those who were or were not prescribed stimulants. One of these NRCS also reported a higher incidence of SUD in people with ADHD treated with mixed medications, which included combinations of stimulants and other medications, compared to those treated with no medications.[67] However, these data came from an observational study that reported whether medications were prescribed during the entire study period in people with other psychiatric comorbidities; therefore, it is possible that this group of people may represent those with other comorbidities that may have an increased risk of SUD. This same study reported that those who had taken methylphenidate alone had no significant differences in SUD outcomes compared with those who had never received medication.

Although our review found no clear benefits of stimulant treatment on reducing the risk of SUD, most studies found no evidence for increased risk of SUD or AUD when compared to other ADHD treatment groups. Only 1 single-group study reported on longitudinal outcomes of diversion or misuse of ADHD medications in people without SUD at baseline. Diversion was relatively low (11%), and approximately 22% reported misusing their ADHD medications or using too much, and 31% reported using their ADHD medication with other substances, such as alcohol. Importantly, this was a small study of adolescents and college-age adults, so findings may not generalize to adults with ADHD. Diversion and non-medical use of ADHD stimulant medications have been reported amongst younger age groups, including college students.[78] Another study reported that alcohol, illicit drugs, or another medication was present in approximately half of all emergency department visits for ADHD medications in the US in people ages 12 and older.[79] Educating patients about the potential harms of medication misuse, including non-medical use, is important. Although many health providers agree that part of their responsibility is to educate patients about medications, a recent survey of family physicians and college health professionals found that less than 75% felt it was their responsibility to educate patients on the legal risks of misuse or on the effects of misuse on social lives or other relationships.[80]

For people with comorbid ADHD and SUD at baseline, 5 RCTs reported on changes in ADHD symptoms between those treated with stimulants compared to placebo. Two of these studies reported significant improvements in ADHD symptoms for those in the treatment group compared to placebo, and 3 other RCTs found no significant differences between groups in terms of ADHD symptom change. One RCT also reported no significant difference between those treated with a stimulant medication compared to a non-stimulant ADHD medication. Importantly, the evidence base on the effects of stimulants for people ADHD and SUD needs to be interpreted in context. First, the sample sizes for these studies were relatively small, which may have impacted the precision of estimates. It is possible that several of these “non-significant” outcomes may not have reached statistical significance due to the small sample sizes of these studies. Second, virtually all the trials are old and use medications that are now less commonly prescribed, such as immediate release formulations that have largely been superseded by extended-release formulations and/or prodrugs.[81] Newer formulations have both improved efficacy and reduced side effects/misuse potential that make them well suited for treatment of ADHD in people with SUDs due to their lower misuse potential. Third, studies utilized different measures for symptom change assessment. Even when studies used the same measure, such as the CAARS, they used the assessment differently, such as only using specific subscales. Previous

reviews of ADHD symptom assessments have emphasized the need for assessing a broader definition of symptoms, including quality of life and measures of functioning.[82] The variety of assessments used in the included studies may not have captured the full range of potential symptom change that may accompany medication use. Fourth, we concluded that overall, evidence is insufficient for reduction of ADHD symptoms in people with co-occurring ADHD and SUD treated with stimulant medication compared to no stimulants. However, this conclusion does not consider the much larger evidence base showing efficacy of these medications in people with ADHD without SUDs. People with co-occurring ADHD and SUD may be more complex in terms of other factors that may impact ADHD symptoms.

In terms of treatment adherence, 3 studies that included people with comorbid ADHD and SUD reported no significant difference in ADHD treatment adherence based on urine toxicology screens for those assigned to stimulant treatment compared to placebo. Additionally, 1 study reported no significant differences in treatment retention when comparing stimulant to non-stimulant medications among those who completed the treatment course. Relatedly, only 1 study reported lower medication tolerance among those taking stimulant medications compared to those taking placebo. There were no other significant differences in tolerance reported or treatment discontinuation due to side effects. Overall, there appears to be no significant differences in medication adherence in those prescribed stimulants with CBT compared to placebo with CBT.

Overall, there was no evidence of a difference in ADHD treatment adherence, substance use, SUD symptoms, and abstinence from substances for stimulant treatment with CBT in those with comorbid ADHD and SUD when compared to those not receiving these medications and CBT. For SUD treatment adherence, 1 study reported that those in an outpatient treatment program for SUD who received ADHD medication within 90 days had lower attrition in the SUD treatment program. While a different RCT reported no difference in the number of relapse-prevention-focused CBT sessions attended between treatment and control groups, this same study reported greater odds of abstinence in those receiving stimulant treatment compared to placebo.[74] Four other studies reported no difference in abstinence outcomes. Additionally, for substance use, other than potential increased use of cannabis products,[72] no increased risk of substance use was reported. One RCT reported lower opiate use in people taking methylphenidate compared to placebo. Another study reported fewer days of <60 g alcohol consumption for those taking stimulants compared to placebo, but no differences in >60 g consumption. Two other studies examining cannabis/THC use reported mixed outcomes, with one reporting higher use and another reporting lower use in those taking stimulant medications versus placebo. No other significant differences were reported between treatment and placebo groups.

Strengths and Limitations of the Systematic Review Process

There are several limitations to the current review. For KQ 1, we required that outcomes include SUD diagnosis according to the DSM or similar criteria, not just substance use. Similarly, for KQ 2, we required that those included have a diagnosis of both ADHD and SUD using the DSM or similar criteria. By requiring inclusion of people with diagnoses of SUD, the results of this report may not be relevant to people with ADHD with subthreshold substance-related problems or who have not formally received an SUD diagnosis. Requiring a diagnosis of SUD meant that standardized criteria was used across studies to identify substance use. We also included ADHD and SUD definitions from several versions of the DSM, as well as ICD or other similar diagnostic methods, and these definitions are different in terms of criteria needed to fulfill these diagnoses. Therefore, it may be possible that the people included are not homogenous across studies in terms of their symptoms. However, restricting these definitions to only the DSM-5 would have limited the literature base further and may not account

for changes in the understanding of these diagnoses. Relating to diversion and misuse, we only included longitudinal studies and those with outcomes in adult populations, which would have excluded any published cross-sectional studies or those that focused on misuse or diversion in non-adult populations. Additionally, during our abstract screening process, we required that abstracts explicitly state that they included people with ADHD and included information about stimulant use. These screening methods may have missed studies that were relevant to our study but were not explicit about these inclusion criteria in the abstract.

Implications for VA

Given the increasing rates of ADHD diagnoses in the Veteran population, the VA needs to provide guidance and education for clinicians treating ADHD. First and foremost, the evidence base related to these questions for VA policy and practice is remarkably thin (no study was conducted in the VA) and must be supplemented with additional research to increase confidence in these key areas of interest among a Veteran population. That said, fears that the use of stimulant medications in adults with ADHD can lead to a new SUD diagnosis or precipitate substance-related problems in people with co-occurring SUD and ADHD appear not to be supported by the overall evidence. Absent more evidence of harm (*ie,* incident SUD diagnoses and/or increases in substance-related problems in people with co-occurring SUD and ADHD), prescribers should consider stimulant and non-stimulant medications for the treatment of adult ADHD after a thorough, individualized risk-benefit discussion. Considerations about prescription medications should include ADHD symptom severity, comorbidities, as well as social supports and provider consultation. Further, given the advances in these medications, prescribers should also consider newer formulations that may provide symptom benefit and simultaneously offer lower misuse potential.[83] Though evidence was minimal, given the risk for diversion or misuse of these medications, prescriptions should include broad education about the risks of diversion and/or misuse of these medications and may benefit from strategies used in opiate use disorder treatment to reduce these risks (*eg,* ongoing toxicology screens and/or use of bottle recall/pill counts).

FUTURE RESEARCH

This review highlights the limited data on the relationship between psychostimulant treatment for ADHD and SUD outcomes in adulthood. Additional longitudinal studies are needed to examine the long-term outcomes of stimulant exposure as it relates to substance use. Moreover, these studies need to explore not only exposure to stimulants, but timing and dose of stimulant exposure as well. While the scope of the current review did not include specific examination of age at first prescription or duration of stimulant exposure, these may be important factors related to SUD outcomes. For instance, lack of treatment throughout childhood and adolescence may lead to academic and social impairments, and these problem behaviors may be well engrained before ADHD treatment has a chance to improve occupational or social functioning.[84, 85] We also identified only 1 longitudinal study that reported on diversion or misuse outcomes in adulthood. Additional longitudinal studies are needed to understand misuse and diversion outcomes, as well as risk factors for these within patient groups prescribed psychostimulant medications.

To effectively answer the question of whether ADHD stimulant medication use may impact incidence of SUD, predictive modeling studies may be needed to help identify which people may be at increased risk for SUD outcomes. Further, studies included for KQ 2 of this review largely focused on people with cooccurring ADHD and stimulant use disorders, small sample sizes, and old formulations of stimulants. There is a need for sufficiently powered randomized trials of people with ADHD and SUD and modern formulations of stimulants, such as long-acting compounds. In addition, research on

people with other substance use disorders, especially those frequently comorbid with ADHD (*eg*, alcohol, cannabis, benzodiazepine, and opioid use disorders) is needed. More research is needed to prepare VA providers not just for people diagnosed with ADHD as adults, but also for the growing population of people diagnosed in early childhood that have always depended on ADHD treatment as part of their standard health care. Finally, studies generally conducted follow-up over a long period of time (in 4 of 5 studies follow-up was >10 years) and there were limited data on short-term outcomes, such as those that may occur in the immediate months following stimulant initiation.

CONCLUSIONS

Among people prescribed stimulants for ADHD, approximately 1 in 7 is newly diagnosed with SUD. However, the overall evidence does not indicate that stimulant medication treatment for ADHD increases the risk of SUD diagnoses. There are sparse longitudinal data on new onset AUD, or non-alcohol substance use disorders. Little is known about the risk of diversion or misuse among people prescribed stimulants for ADHD.

For people with co-occurring ADHD and SUD, there is no evidence of a difference in ADHD treatment adherence, substance use, SUD symptom change, or abstinence from SUD between those treated with stimulants and those receiving other forms of care. For the same comparison, there is insufficient evidence to assess ADHD symptom change, SUD treatment adherence, and medication misuse or diversion.

Longitudinal data or predictive modeling studies are needed to fill the evidence gap on ADHD medication diversion or misuse among people prescribed stimulants for ADHD. New comparative evidence is needed to assess the effects of stimulants on SUD treatment adherence, and medication misuse or diversion among people with co-occurring ADHD and SUD. Future studies should use a standardized set of measures to evaluate ADHD and SUD-related symptoms.

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