ADHD and Substance Use Disorders in Adults

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Health Systems Research

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Appendix

APPENDIX A. SEARCH STRATEGIES

Search		Search Statement	Results
PubMed	1	"Attention Deficit Disorder with Hyperactivity"[Mesh] OR "attention deficit hyperactivity disorder"[tiab] OR "ADHD"[tiab] OR "attention deficit disorder"[tiab] OR "ADDH" [tiab] OR "attention disorder" [tiab] OR "hyperactive disorder" [tiab]	49,561
	2	"Attention Deficit Disorder with Hyperactivity/drug therapy"[Majr] OR "Central Nervous System Stimulants"[MeSH] OR "Methylphenidate"[MeSH] OR Dexmethylphenidate[MeSH] OR "Dextroamphetamine"[MeSH] OR "Adderall"[Supplementary Concept] OR "lisdexamfetamine dimesylate"[Supplementary Concept] OR "Amphetamine"[MeSH] OR "Central Nervous System Stimulants" [Pharmacological Action] OR "Central Nervous System Stimulants"[tiab] OR "psychostimulant"[tiab] OR "Methylphenidate"[tiab] OR "Methylphenidate Hydrochloride"[tiab] OR "Aptensio"[tiab] OR "Concerta"[tiab] OR "Ritalin"[tiab] OR "Ritalin LA"[tiab] OR "Medikinet"[tiab] OR "Equasym"[tiab] OR "Quillivant"[tiab] OR "Metadate"[tiab] OR "Daytrana"[tiab] OR Dexmethylphenidate OR "Dexmethylphenidate Hydrochloride"[tiab] OR "Focalin"[tiab] OR "Dextroamphetamine"[tiab] OR "Dexedrine"[tiab] OR Dextrostat OR "ProCentra"[tiab] OR "Zenzedi"[tiab] OR "mixed amphetamine salts"[tiab] OR "Adderall" [tiab] OR "lisdexamfetamine"[tiab] OR "lisdexamfetamine dimesylate"[tiab] OR "Vyvanse"[tiab] OR "Venvanse"[tiab] OR "Elvanse"[tiab] OR "Tyvense"[tiab] OR "Dyanavel"[tiab] OR "Evekeo"[tiab] OR "ADHD medications"[tiab] OR "Adzenys"[tiab] OR "Amfetamine"[tiab] OR "Amphetamine"[tiab] OR "amphetamine aspartate"[tiab] OR "Amphetamines"[tiab] OR "Aptensio"[tiab] OR "Biphentin"[tiab] OR "Central Nervous System Stimulants"[tiab] OR "Concerta"[tiab] OR "dexamfetamine"[tiab] OR "dexamphetamine"[tiab] OR "Dexedrine"[tiab] OR "Dexmethylphenidate"[tiab] OR "dextroamfetamine"[tiab] OR "Dextroamphetamine"[tiab] OR "Dyanavel"[tiab] OR "Equasym"[tiab] OR "Evekeo"[tiab] OR "Focalin"[tiab] OR "lisdexamfetamine"[tiab] OR "lisdexamphetamine"[tiab] OR "Medikinet"[tiab] OR "Metadate"[tiab] OR "Methamphetamine"[tiab] OR "methylfenidate"[tiab] OR "Methylin"[tiab] OR "methylphenidate"[tiab] OR "ProCentra"[tiab] OR "QuilliChew"[tiab] OR "Quillivant"[tiab] OR "Ritalin"[tiab] OR "Stimulant"[tiab] OR "Vyvanse"[tiab] OR "Zenzedi"[tiab]	139,188
	3	"Substance-Related Disorders"[Mesh] OR "Drug abuse" OR "drug misuse" OR "drug dependence" OR "drug addiction" OR "substance use disorder" OR "substance abuse" OR "substance misuse" OR "substance dependence" OR "substance addiction" OR "prescription abuse" OR "Alcoholism"[Mesh] OR "cannabis use disorder" OR "alcohol use disorder" OR "stimulant use disorder" OR "hallucinogen use disorder" OR "opioid use disorder" OR "inhalant use disorder" OR "diversion"[tiab] OR "illicit drug use"[tiab] OR "illegal drug use"[tiab] OR "problem substance use"[tiab] OR "problematic substance use"[tiab] OR "risky substance use"[tiab] OR "substance use consequences"[tiab] or ((Alcohol OR "Alcoholic Beverages"[Mesh] OR cannabis OR Marijuana OR "Cannabis"[Mesh] OR "Marijuana Abuse"[Mesh] OR "Marijuana Smoking"[Mesh] OR opioids OR "Narcotics"[Mesh] OR "Analgesics, Opioid"[Mesh] OR kratom OR hallucinogens OR "Psychotropic Drugs"[Mesh] OR inhalants OR toluene OR stimulants OR "Central Nervous System Stimulants"[Mesh] OR "Amphetamines"[Mesh] OR Sedatives OR "Hypnotics and Sedatives"[Mesh] OR Benzodiazepines OR "Benzodiazepines"[Mesh] OR Anthramycin OR Bromazepam OR Clonazepam OR Devazepide OR Diazepam OR Flumazenil OR Flunitrazepam OR Flurazepam OR Fentanyl OR Alprazolam OR Clonidine OR Hashish Clonidine OR Lorazepam OR Nitrazepam OR	778,690

	Oxazepam OR Pirenzepine OR Prazepam OR Temazepam OR Chlordiazepoxide OR Clorazepate Dipotassium OR Estazolam OR Medazepam OR Midazolam OR Triazolam OR opioid* OR opiate* OR Heroin OR opium OR "Morphine Derivatives"[Mesh] OR Codeine OR Hydrocodone OR Oxycodone OR Dihydromorphine OR Ethylmorphine OR Heroin OR Hydromorphone OR Morphine OR Oxymorphone OR Thebaine OR Cocaine OR "Cocaine"[Mesh] OR Methamphetamine* OR "Methamphetamine"[Mesh] OR Benzphetamine OR anabolic steroids OR "Testosterone Congeners"[Mesh] OR antihistamines OR nitrous oxide OR betel nut OR kava OR Ecstasy OR phenylalkylamines OR mescaline OR 2,5-dimethoxy-4-methylamphetamine OR MDMA OR 3,4-methylenedioxymethamphetamine OR indoleamine* OR psilocybin OR psilocin OR dimethyltryptamine OR ergoline* OR lysergic acid diethylamide OR "morning glory seeds" OR "Salvia divinorum" OR jimsonweed OR anxiolytic OR benzodiazepine* OR zolpidem OR zaleplon OR carbamate* OR glutethimide OR meprobamate OR barbiturate* OR secobarbital OR barbiturate* OR glutethimide OR methaqualone OR amphetamine OR dextroamphetamine OR methamphetamine OR gabapentin OR baclofen OR diacetylmorphine OR kratom OR polydrug OR "poly-drug" OR polysubstance OR "poly-substance" OR "injection drug") AND (addict* OR abus* OR misus* OR disorder* OR mis-use OR dependen*))	
4	((#1) AND (#2)) AND (#3)	9,423
5	(#4) AND (1994:2024[pdat])	8,573
6	(#5) NOT (child[MH] NOT adult[MH])	4,877
7	(#6) NOT ("address"[pt] OR "autobiography"[pt] OR "bibliography"[pt] OR "biography"[pt] OR "case reports"[pt] OR "comment"[pt] OR "congress"[pt] OR "dictionary"[pt] OR "directory"[pt] OR "festschrift"[pt] OR "government publication"[pt] OR "historical article"[pt] OR "interview"[pt] OR "lecture"[pt] OR "legal case"[pt] OR "legislation"[pt] OR "news"[pt] OR "newspaper article"[pt] OR "patient education handout"[pt] OR "periodical index"[pt] OR "comment"[ti] OR "Editorial"[Publication Type] OR "ephemera"[pt] OR "in vitro techniques"[mh] OR "introductory journal article"[pt] OR ("Animals"[Mesh] NOT "Humans"[Mesh]) OR rats[tw] OR rat[tw] OR cow[tw] OR cows[tw] OR chicken*[tw] OR horse[tw] OR horses[tw] OR mice[tw] OR mouse[tw] OR bovine[tw] OR sheep[tw] OR ovine[tw] OR murinae[tw] OR cats[tw] OR cat[tw] OR dog[tw] OR dogs[tw] OR rodent[tw])	3,255
8	(#6) NOT ("address"[pt] OR "autobiography"[pt] OR "bibliography"[pt] OR "biography"[pt] OR "case reports"[pt] OR "comment"[pt] OR "congress"[pt] OR "dictionary"[pt] OR "directory"[pt] OR "festschrift"[pt] OR "government publication"[pt] OR "historical article"[pt] OR "interview"[pt] OR "lecture"[pt] OR "legal case"[pt] OR "legislation"[pt] OR "news"[pt] OR "newspaper article"[pt] OR "patient education handout"[pt] OR "periodical index"[pt] OR "comment"[ti] OR "Editorial"[Publication Type] OR "ephemera"[pt] OR "in vitro techniques"[mh] OR "introductory journal article"[pt] OR ("Animals"[Mesh] NOT "Humans"[Mesh]) OR rats[tw] OR rat[tw] OR cow[tw] OR cows[tw] OR chicken*[tw] OR horse[tw] OR horses[tw] OR mice[tw] OR mouse[tw] OR bovine[tw] OR sheep[tw] OR ovine[tw] OR murinae[tw] OR cats[tw] OR cat[tw] OR dog[tw] OR dogs[tw] OR rodent[tw]) Limits: Humans	2,813
9	(#6) NOT ("address"[pt] OR "autobiography"[pt] OR "bibliography"[pt] OR "biography"[pt] OR "case reports"[pt] OR "comment"[pt] OR "congress"[pt] OR "dictionary"[pt] OR "directory"[pt] OR "festschrift"[pt] OR "government publication"[pt] OR "historical article"[pt] OR "interview"[pt] OR "lecture"[pt] OR "legal case"[pt] OR "legislation"[pt] OR "news"[pt] OR "newspaper article"[pt] OR "patient education	2,656

		handout"[pt] OR "periodical index"[pt] OR "comment"[ti] OR "Editorial"[Publication Type] OR "ephemera"[pt] OR "in vitro techniques"[mh] OR "introductory journal article"[pt] OR ("Animals"[Mesh] NOT "Humans"[Mesh]) OR rats[tw] OR rat[tw] OR cow[tw] OR cows[tw] OR chicken*[tw] OR horse[tw] OR horses[tw] OR mice[tw] OR mouse[tw] OR bovine[tw] OR sheep[tw] OR ovine[tw] OR murinae[tw] OR cats[tw] OR cat[tw] OR dog[tw] OR dogs[tw] OR rodent[tw]) Limits: Humans, English	
EMBASE	1	("Attention Deficit Disorder with Hyperactivity" or "attention deficit hyperactivity disorder" or "ADHD" or "attention deficit disorder" or "ADDH" or "attention disorder" or "hyperactive disorder").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	86674
	2	("Attention Deficit Disorder with Hyperactivity/drug therapy" or "Central Nervous System Stimulants" or "Methylphenidate" or "Dexmethylphenidate" or "Dextroamphetamine" or "Adderall" or "lisdexamfetamine dimesylate" or "Amphetamine" or "psychostimulant" or "Methylphenidate" or "Methylphenidate Hydrochloride" or "Aptensio" or "Concerta" or "Ritalin" or "Ritalin LA" or "Medikinet" or "Equasym" or "Quillivant" or "Metadate" or "Daytrana" or "Focalin" or "Dexedrine" or "Dextrostat" or "ProCentra" or "Zenzedi" or "mixed amphetamine salts" or "lisdexamfetamine" or "Vyvanse" or "Venvanse" or "Elvanse" or "Tyvense" or "Dyanavel" or "Evekeo" or "ADHD medications" or "Adzenys" or "Amfetamine" or "amfetamine aspartate" or "amphetamine aspartate" or "Amphetamines" or "Apo-methylphenidate" or "Apo-MPH" or "Attenta" or "Biphentin" or "dexamfetamine" or "dexamphetamine" or "Dexmethylphenidate" or "dextroamfetamine" or "lisdexamphetamine" or "Methamphetamine" or "methylfenidate" or "Methylin" or "QuilliChew" or "Stimulant").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	125585
	3	("Substance-Related Disorders" or "Drug abuse" or "drug misuse" or "drug dependence" or "drug addiction" or "substance use disorder" or "substance abuse" or "substance misuse" or "substance dependence" or "substance addiction" or "prescription abuse" or "Alcoholism" or "cannabis use disorder" or "alcohol use disorder" or "stimulant use disorder" or "hallucinogen use disorder" or "opioid use disorder" or "inhalant use disorder" or "diversion" or "illicit drug use" or "illegal drug use" or "problem substance use" or "problematic substance use" or "risky substance use" or "substance use consequences" or ((Alcohol or "Alcoholic Beverages" or cannabis or Marijuana or "Cannabis" or "Marijuana Abuse" or "Marijuana Smoking" or opioids or "Narcotics" or "Analgesics, Opioid" or kratom or hallucinogens or "Psychotropic Drugs" or inhalants or toluene or stimulants or "Central Nervous System Stimulants" or "Amphetamines" or Sedatives or "Hypnotics and Sedatives" or Benzodiazepines or "Benzodiazepines" or Anthramycin or Bromazepam or Clonazepam or Devazepide or Diazepam or Flumazenil or Flunitrazepam or Flurazepam or Fentanyl or Alprazolam or Clonidine or Hashish Clonidine or Lorazepam or Nitrazepam or Oxazepam or Pirenzepine or Prazepam or Temazepam or Chlordiazepoxide or Clorazepate Dipotassium or Estazolam or Medazepam or Midazolam or Triazolam or opioid* or opiate* or Heroin or opium or "Morphine Derivatives" or Codeine or Hydrocodone or Oxycodone or Dihydromorphine or Ethylmorphine or Heroin or Hydromorphone or Morphine or Oxymorphone or Thebaine or Cocaine or "Cocaine" or Methamphetamine* or "Methamphetamine" or Benzphetamine or anabolic steroids or "Testosterone Congeners" or antihistamines or nitrous oxide or betel nut or kava or Ecstasy or	758206

		phenylalkylamines or mescaline or 2,5-dimethoxy-4-methylamphetamine or MDMA or 3,4-methylenedioxymethamphetamine or indoleamine* or psilocybin or psilocin or dimethyltryptamine or ergoline* or lysergic acid diethylamide or "morning glory seeds" or "Salvia divinorum" or jimsonweed or anxiolytic or benzodiazepine* or zolpidem or zaleplon or carbamate* or glutethimide or meprobamate or barbiturate* or secobarbital or barbiturate* or glutethimide or methaqualone or amphetamine or dextroamphetamine or methamphetamine or gabapentin or baclofen or diacetylmorphine or kratom or polydrug or "poly-drug" or polysubstance or "poly-substance" or "injection drug") and (addict* or abus* or misus* or disorder* or mis-use or dependen*))).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	
	4	1 and 2 and 3	9371
	5	child/	2135811
	6	adult/	9406839
	7	5 not 6	1451340
	8	4 not 7	7228
	9	limit 8 to (human and yr="1994 -Current" and (article or article in press) and "humans only (removes records about animals)")	2850
	10	limit 9 to english language	2729
	11	limit 10 to english language	2729
PsycINFO	1	MA ("Attention Deficit Disorder with Hyperactivity" or "attention deficit hyperactivity disorder" or "ADHD" or "attention deficit disorder" or "ADDH" or "attention disorder" or "hyperactive disorder") OR TI ("Attention Deficit Disorder with Hyperactivity" or "attention deficit hyperactivity disorder" or "ADHD" or "attention deficit disorder" or "ADDH" or "attention disorder" or "hyperactive disorder") OR AB ("Attention Deficit Disorder with Hyperactivity" or "attention deficit hyperactivity disorder" or "ADHD" or "attention deficit disorder" or "ADDH" or "attention disorder" or "hyperactive disorder")	41656
	2	MA ("Attention Deficit Disorder with Hyperactivity/drug therapy" or "Central Nervous System Stimulants" or "Methylphenidate" or "Dexmethylphenidate" or "Dextroamphetamine" or "Adderall" or "lisdexamfetamine dimesylate" or "Amphetamine" or "psychostimulant" or "Methylphenidate" or "Methylphenidate Hydrochloride" or "Aptensio" or "Concerta" or "Ritalin" or "Ritalin LA" or "Medikinet" or "Equasym" or "Quillivant" or "Metadate" or "Daytrana" or "Focalin" or "Dexedrine" or "Dextrostat" or "ProCentra" or "Zenzedi" or "mixed amphetamine salts" or "lisdexamfetamine" or "Vyvanse" or "Venvanse" or "Elvanse" or "Tyvense" or "Dyanavel" or "Evekeo" or "ADHD medications" or "Adzenys" or "Amfetamine" or "amfetamine aspartate" or "amphetamine aspartate" or "Amphetamines" or "Apo-methylphenidate" or "Apo-MPH" or "Attenta" or "Biphentin" or "dexamfetamine" or "dexamphetamine" or "Dexmethylphenidate" or "dextroamfetamine" or "lisdexamphetamine" or "Methamphetamine" or "methylfenidate" or "Methylin" or "QuilliChew" or "Stimulant") OR TI ("Attention Deficit Disorder with Hyperactivity/drug therapy" or "Central Nervous System Stimulants" or "Methylphenidate" or "Dexmethylphenidate" or "Dextroamphetamine" or "Adderall" or "lisdexamfetamine dimesylate" or "Amphetamine" or "psychostimulant" or "Methylphenidate" or "Methylphenidate Hydrochloride" or "Aptensio" or "Concerta" or "Ritalin" or "Ritalin LA" or "Medikinet" or "Equasym" or "Quillivant" or "Metadate" or "Daytrana" or "Focalin" or "Dexedrine" or "Dextrostat" or "ProCentra"	34708

	or "Zenzedi" or "mixed amphetamine salts" or "lisdexamfetamine" or "Vyvanse" or "Venvanse" or "Elvanse" or "Tyvense" or "Dyanavel" or "Evekeo" or "ADHD medications" or "Adzenys" or "Amfetamine" or "amfetamine aspartate" or "amphetamine aspartate" or "Amphetamines" or "Apo-methylphenidate" or "Apo-MPH" or "Attenta" or "Biphentin" or "dexamfetamine" or "dexamphetamine" or "Dexmethylphenidate" or "dextroamfetamine" or "lisdexamphetamine" or "Methamphetamine" or "methylfenidate" or "Methylin" or "QuilliChew" or "Stimulant") OR AB ("Attention Deficit Disorder with Hyperactivity/drug therapy" or "Central Nervous System Stimulants" or "Methylphenidate" or "Dexmethylphenidate" or "Dextroamphetamine" or "Adderall" or "lisdexamfetamine dimesylate" or "Amphetamine" or "psychostimulant" or "Methylphenidate" or "Methylphenidate Hydrochloride" or "Aptensio" or "Concerta" or "Ritalin" or "Ritalin LA" or "Medikinet" or "Equasym" or "Quillivant" or "Metadate" or "Daytrana" or "Focalin" or "Dexedrine" or "Dextrostat" or "ProCentra" or "Zenzedi" or "mixed amphetamine salts" or "lisdexamfetamine" or "Vyvanse" or "Venvanse" or "Elvanse" or "Tyvense" or "Dyanavel" or "Evekeo" or "ADHD medications" or "Adzenys" or "Amfetamine" or "amfetamine aspartate" or "amphetamine aspartate" or "Amphetamines" or "Apo-methylphenidate" or "Apo-MPH" or "Attenta" or "Biphentin" or "dexamfetamine" or "dexamphetamine" or "Dexmethylphenidate" or "dextroamfetamine" or "lisdexamphetamine" or "Methamphetamine" or "methylfenidate" or "Methylin" or "QuilliChew" or "Stimulant")	
3	MA ("Substance-Related Disorders" or "Drug abuse" or "drug misuse" or "drug dependence" or "drug addiction" or "substance use disorder" or "substance abuse" or "substance misuse" or "substance dependence" or "substance addiction" or "prescription abuse" or "Alcoholism" or "cannabis use disorder" or "alcohol use disorder" or "stimulant use disorder" or "hallucinogen use disorder" or "opioid use disorder" or "inhalant use disorder" or "diversion" or "illicit drug use" or "illegal drug use" or "problem substance use" or "problematic substance use" or "risky substance use" or "substance use consequences" or ((Alcohol or "Alcoholic Beverages" or cannabis or Marijuana or "Cannabis" or "Marijuana Abuse" or "Marijuana Smoking" or opioids or "Narcotics" or "Analgesics, Opioid" or kratom or hallucinogens or "Psychotropic Drugs" or inhalants or toluene or stimulants or "Central Nervous System Stimulants" or "Amphetamines" or Sedatives or "Hypnotics and Sedatives" or Benzodiazepines or "Benzodiazepines" or Anthramycin or Bromazepam or Clonazepam or Devazepide or Diazepam or Flumazenil or Flunitrazepam or Flurazepam or Fentanyl or Alprazolam or Clonidine or Hashish Clonidine or Lorazepam or Nitrazepam or Oxazepam or Pirenzepine or Prazepam or Temazepam or Chlordiazepoxide or Clorazepate Dipotassium or Estazolam or Medazepam or Midazolam or Triazolam or opioid* or opiate* or Heroin or opium or "Morphine Derivatives" or Codeine or Hydrocodone or Oxycodone or Dihydromorphine or Ethylmorphine or Heroin or Hydromorphone or Morphine or Oxymorphone or Thebaine or Cocaine or "Cocaine" or Methamphetamine* or "Methamphetamine" or Benzphetamine or anabolic steroids or "Testosterone Congeners" or antihistamines or nitrous oxide or betel nut or kava or Ecstasy or phenylalkylamines or mescaline or 2,5-dimethoxy-4-methylamphetamine or MDMA or 3,4-methylenedioxymethamphetamine or indoleamine* or psilocybin or psilocin or dimethyltryptamine or ergoline* or lysergic acid diethylamide or "morning glory seeds" or "Salvia divinorum" or jimsonweed or anxiolytic or benzodiazepine* or zolpidem or zaleplon or carbamate* or glutethimide or meprobamate or barbiturate* or secobarbital or barbiturate* or glutethimide or methaqualone or amphetamine or dextroamphetamine or methamphetamine or gabapentin or baclofen or diacetylmorphine or kratom or polydrug or	226471

"poly-drug" or polysubstance or "poly-substance" or "injection drug") and (addict* or abus* or misus* or disorder* or mis-use or dependen*))) OR TI ("Substance-Related Disorders" or "Drug abuse" or "drug misuse" or "drug dependence" or "drug addiction" or "substance use disorder" or "substance abuse" or "substance misuse" or "substance dependence" or "substance addiction" or "prescription abuse" or "Alcoholism" or "cannabis use disorder" or "alcohol use disorder" or "stimulant use disorder" or "hallucinogen use disorder" or "opioid use disorder" or "inhalant use disorder" or "diversion" or "illicit drug use" or "illegal drug use" or "problem substance use" or "problematic substance use" or "risky substance use" or "substance use consequences" or ((Alcohol or "Alcoholic Beverages" or cannabis or Marijuana or "Cannabis" or "Marijuana Abuse" or "Marijuana Smoking" or opioids or "Narcotics" or "Analgesics, Opioid" or kratom or hallucinogens or "Psychotropic Drugs" or inhalants or toluene or stimulants or "Central Nervous System Stimulants" or "Amphetamines" or Sedatives or "Hypnotics and Sedatives" or Benzodiazepines or "Benzodiazepines" or Anthramycin or Bromazepam or Clonazepam or Devazepide or Diazepam or Flumazenil or Flunitrazepam or Flurazepam or Fentanyl or Alprazolam or Clonidine or Hashish Clonidine or Lorazepam or Nitrazepam or Oxazepam or Pirenzepine or Prazepam or Temazepam or Chlordiazepoxide or Clorazepate Dipotassium or Estazolam or Medazepam or Midazolam or Triazolam or opioid* or opiate* or Heroin or opium or "Morphine Derivatives" or Codeine or Hydrocodone or Oxycodone or Dihydromorphine or Ethylmorphine or Heroin or Hydromorphone or Morphine or Oxymorphone or Thebaine or Cocaine or "Cocaine" or Methamphetamine* or "Methamphetamine" or Benzphetamine or anabolic steroids or "Testosterone Congeners" or antihistamines or nitrous oxide or betel nut or kava or Ecstasy or phenylalkylamines or mescaline or 2,5-dimethoxy-4-methylamphetamine or MDMA or 3,4-methylenedioxymethamphetamine or indoleamine* or psilocybin or psilocin or dimethyltryptamine or ergoline* or lysergic acid diethylamide or "morning glory seeds" or "Salvia divinorum" or jimsonweed or anxiolytic or benzodiazepine* or zolpidem or zaleplon or carbamate* or glutethimide or meprobamate or barbiturate* or secobarbital or barbiturate* or glutethimide or methaqualone or amphetamine or dextroamphetamine or methamphetamine or gabapentin or baclofen or diacetylmorphine or kratom or polydrug or "poly-drug" or polysubstance or "poly-substance" or "injection drug") and (addict* or abus* or misus* or disorder* or mis-use or dependen*))) OR AB ("Substance-Related Disorders" or "Drug abuse" or "drug misuse" or "drug dependence" or "drug addiction" or "substance use disorder" or "substance abuse" or "substance misuse" or "substance dependence" or "substance addiction" or "prescription abuse" or "Alcoholism" or "cannabis use disorder" or "alcohol use disorder" or "stimulant use disorder" or "hallucinogen use disorder" or "opioid use disorder" or "inhalant use disorder" or "diversion" or "illicit drug use" or "illegal drug use" or "problem substance use" or "problematic substance use" or "risky substance use" or "substance use consequences" or ((Alcohol or "Alcoholic Beverages" or cannabis or Marijuana or "Cannabis" or "Marijuana Abuse" or "Marijuana Smoking" or opioids or "Narcotics" or "Analgesics, Opioid" or kratom or hallucinogens or "Psychotropic Drugs" or inhalants or toluene or stimulants or "Central Nervous System Stimulants" or "Amphetamines" or Sedatives or "Hypnotics and Sedatives" or Benzodiazepines or "Benzodiazepines" or Anthramycin or Bromazepam or Clonazepam or Devazepide or Diazepam or Flumazenil or Flunitrazepam or Flurazepam or Fentanyl or Alprazolam or Clonidine or Hashish Clonidine or Lorazepam or Nitrazepam or Oxazepam or Pirenzepine or Prazepam or Temazepam or Chlordiazepoxide or Clorazepate Dipotassium or Estazolam or

		Medazepam or Midazolam or Triazolam or opioid* or opiate* or Heroin or opium or "Morphine Derivatives" or Codeine or Hydrocodone or Oxycodone or Dihydromorphine or Ethylmorphine or Heroin or Hydromorphone or Morphine or Oxymorphone or Thebaine or Cocaine or "Cocaine" or Methamphetamine* or "Methamphetamine" or Benzphetamine or anabolic steroids or "Testosterone Congeners" or antihistamines or nitrous oxide or betel nut or kava or Ecstasy or phenylalkylamines or mescaline or 2,5-dimethoxy-4-methylamphetamine or MDMA or 3,4-methylenedioxymethamphetamine or indoleamine* or psilocybin or psilocin or dimethyltryptamine or ergoline* or lysergic acid diethylamide or "morning glory seeds" or "Salvia divinorum" or jimsonweed or anxiolytic or benzodiazepine* or zolpidem or zaleplon or carbamate* or glutethimide or meprobamate or barbiturate* or secobarbital or barbiturate* or glutethimide or methaqualone or amphetamine or dextroamphetamine or methamphetamine or gabapentin or baclofen or diacetylmorphine or kratom or polydrug or "poly-drug" or polysubstance or "poly-substance" or "injection drug") and (addict* or abus* or misus* or disorder* or mis-use or dependen*)))	
	4	s1 AND s2 AND s3	4608
	5	s4 NOT (childhood[AG] NOT adulthood[AG])	4608
	6	s5 (Limiters - Methodology: BRAIN IMAGING, CLINICAL TRIAL, EMPIRICAL STUDY, -Experimental Replication, -Followup Study, -Longitudinal Study, ---Prospective Study, ---Retrospective Study, FIELD STUDY, -Systematic Review, META ANALYSIS, METASYNTHESIS, QUANTITATIVE STUDY, TREATMENT OUTCOME, TWIN STUDY)	3062
	7	s6 (Limiters - Publication Year: 1994-2024; Peer Reviewed; Publication Type: Peer Reviewed Journal; Population Group: Human; Document Type: Journal Article)	2353
	8	s7 (Limiters - English language)	2302
Cochrane Library	1	Attention Deficit Disorder with Hyperactivity or "attention deficit hyperactivity disorder" or "ADHD" or "attention deficit disorder" or "ADDH" or "attention disorder" or "hyperactive disorder"	7648
	2	Attention Deficit Disorder with Hyperactivity drug therapy or "Central Nervous System Stimulants" or "Methylphenidate" or "Dexmethylphenidate" or "Dextroamphetamine" or "Adderall" or "lisdexamfetamine dimesylate" or "Amphetamine" or "psychostimulant" or "Methylphenidate" or "Methylphenidate Hydrochloride" or "Aptensio" or "Concerta" or "Ritalin" or "Ritalin LA" or "Medikinet" or "Equasym" or "Quillivant" or "Metadate" or "Daytrana" or "Focalin" or "Dexedrine" or "Dextrostat" or "ProCentra" or "Zenzedi" or "mixed amphetamine salts" or "lisdexamfetamine" or "Vyvanse" or "Venvanse" or "Elvanse" or "Tyvense" or "Dyanavel" or "Evekeo" or "ADHD medications" or "Adzenys" or "Amfetamine" or "amfetamine aspartate" or "amphetamine aspartate" or "Amphetamines" or "Apo-methylphenidate" or "Apo-MPH" or "Attenta" or "Biphentin" or "dexamfetamine" or "dexamphetamine" or "Dexmethylphenidate" or "dextroamfetamine" or "lisdexamphetamine" or "Methamphetamine" or "methylfenidate" or "Methylin" or "QuilliChew" or "Stimulant"	10547
	3	Substance-Related Disorders or "Drug abuse" or "drug misuse" or "drug dependence" or "drug addiction" or "substance use disorder" or "substance abuse" or "substance misuse" or	128415

		"substance dependence" or "substance addiction" or "prescription abuse" or "Alcoholism" or "cannabis use disorder" or "alcohol use disorder" or "stimulant use disorder" or "hallucinogen use disorder" or "opioid use disorder" or "inhalant use disorder" or "diversion" or "illicit drug use" or "illegal drug use" or "problem substance use" or "problematic substance use" or "risky substance use" or "substance use consequences" or addict* or abus* or misus* or mis-use or dependen*	
	4	#1 AND #2 AND #3	569
CT.gov	1	(Attention Deficit Disorder with Hyperactivity OR "attention deficit hyperactivity disorder" OR "ADHD" OR "attention deficit disorder" OR "ADDH" OR "attention disorder" OR "hyperactive disorder") AND ("Central Nervous System Stimulants" OR "Methylphenidate" OR "Dexmethylphenidate" OR "Dextroamphetamine" OR "Adderall" OR "lisdexamfetamine dimesylate" OR "Amphetamine" OR "psychostimulant" OR "Methylphenidate" OR "Methylphenidate Hydrochloride" OR "Aptensio" OR "Concerta" OR "Ritalin" OR "Ritalin LA" OR "Medikinet" OR "Equasym" OR "Quillivant" OR "Metadate" OR "Daytrana" OR "Focalin" OR "Dexedrine" OR "Dextrostat" OR "ProCentra" OR "Zenzedi" OR "mixed amphetamine salts" OR "lisdexamfetamine" OR "Vyvanse" OR "Venvanse" OR "Elvanse" OR "Tyvense" OR "Dyanavel" OR "Evekeo" OR "ADHD medications" OR "Adzenys" OR "Amfetamine" OR "amfetamine aspartate" OR "amphetamine aspartate" OR "Amphetamines" OR "Apo-methylphenidate" OR "Apo-MPH" OR "Attenta" OR "Biphentin" OR "dexamfetamine" OR "dexamphetamine" OR "Dexmethylphenidate" OR "dextroamfetamine" OR "lisdexamphetamine" OR "Methamphetamine" OR "methylfenidate" OR "Methylin" OR "QuilliChew" OR "Stimulant") AND (Substance-Related Disorders OR "Drug abuse" OR "drug misuse" OR "drug dependence" OR "drug addiction" OR "substance use disorder" OR "substance abuse" OR "substance misuse" OR "substance dependence" OR "substance addiction" OR "prescription abuse" OR "Alcoholism" OR "cannabis use disorder" OR "alcohol use disorder" OR "stimulant use disorder" OR "hallucinogen use disorder" OR "opioid use disorder" OR "inhalant use disorder" OR "diversion" OR "illicit drug use" OR "illegal drug use" OR "problem substance use" OR "problematic substance use" OR "risky substance use" OR "substance use consequences" OR addict* OR abus* OR misus* OR mis-use OR dependen*)	23
		Total	8,280
		Total after deduplication	6419

APPENDIX B. STUDIES EXCLUDED DURING FULL-TEXT SCREENING

Citation and *Reason for Exclusion*
Abel KF, Bramness JG, Martinsen EW. Stimulant medication for ADHD in opioid maintenance treatment. *Journal of Dual Diagnosis*. 2014;10(1):32-38. doi:10.1080/15504263.2013.867657. *Single group (KQ2).*
Adler LA, Lynch LR, Shaw DM, et al. Medication adherence and symptom reduction in adults treated with mixed amphetamine salts in a randomized crossover study. *Postgraduate Medicine.* September 2011;123(5):71-79. *No SUD population (KQ2).*
Aharonovich E, Garawi F, Bisaga A, et al. Concurrent cannabis use during treatment for comorbid ADHD and cocaine dependence: Effects on outcome. *The American Journal of Drug and Alcohol Abuse*. 2006;32(4):629-635. doi:10.1080/00952990600919005. *No analysis by stimulant medication status.*
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Barkley RA, Fischer M, Smallish L, Fletcher K. Does the treatment of attention-deficit/hyperactivity disorder with stimulants contribute to drug use/abuse? A 13-year prospective study. *Pediatrics.* 01 Jan 2003;111(1):97-109. *ADHD not diagnosed by DSM or some other inventory, or majority not ADHD.*
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Blevins D, Choi CJ, Pavlicova M, et al. Impulsiveness as a moderator of amphetamine treatment response for cocaine use disorder among ADHD patients. *Drug and Alcohol Dependence.* 2020;213doi:10.1016/j.drugalcdep.2020.108082. *No analysis by stimulant medication status.*
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labeling? *Drugs - Real World Outcomes*. 01 Mar 2018;5(1):69-79. *Not incident SUD for KQ1 (had SUD at baseline).*
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Citation and *Reason for Exclusion*
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Citation and *Reason for Exclusion*
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Notes. 16 records were excluded as duplicates during title and abstract cleaning, however 6 of those were found to be duplicates within.

APPENDIX C. RISK OF BIAS ASSESSMENTS

Author, Year, PMID, Design	Detection Bias (Blinding of Outcome Accessors)	Attrition Bias	Clear Reporting	Eligibility Criteria Clear	Intervention Adequately Described	Outcomes Fully Defined	RCT					NRCS & Single groups	NRCS		Other Bias	Overall RoB
							Blinding of Participants and Personnel	Random Sequence Generation	Allocation Concealment	Selective reporting	ITT	Cohort representativeness	Comparator representativeness	Confounder Adjustment		
Key Question 1																
Biederman, 2008, 18316421, NRCS	Unclear	No (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	N/A	N/A	N/A	N/A	N/A	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	No (Low concern)	Low RoB (NRCS)
Wilens 2006 16601645, Single group	Unclear	Yes (High concern)[a]	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	N/A	N/A	N/A	N/A	N/A	Yes (Low concern)	N/A	N/A	No (Low concern)	Moderate RoB (Single group)
Chang, 2014, 25158998, NRCS	Unclear	No (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	N/A	N/A	N/A	N/A	N/A	Yes (Low concern)	Unclear	Yes (Low concern)	No (Low concern)	Moderate RoB (NRCS)
Dalsgaard, 2014, 24090624, Single group	Unclear	No (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	N/A	N/A	N/A	N/A	N/A	No (High concern)[b]	N/A	N/A	No (Low concern)	Moderate RoB (Single group)
Mannuzza, 2008, 18381904, Single group	Yes (Low concern)	No (Low concern)	No (High concern)[c]	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	N/A	N/A	N/A	N/A	N/A	Yes (Low concern)	N/A	N/A	No (Low concern)	Moderate RoB (Single Group)
Steinhausen 2014 24314850, NRCS	Unclear	No (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	N/A	N/A	N/A	N/A	N/A	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	No (Low concern)	Low RoB (NRCS)
Torgersen 2013 23104523, Single group	Unclear	No (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	N/A	N/A	N/A	N/A	N/A	Yes (Low concern)	N/A	N/A	No (Low concern)	Low RoB (Single group)
Key Question 2																
Levin 2006 16102908, RCT	Unclear	Yes (High concern)[d]	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Unclear	Unclear	No (Low concern)	Yes (Low concern)	N/A	NA	N/A	No (Low concern)	Moderate RoB (RCT)
Levin 2007 16930863, RCT	Unclear	Yes (High concern)[e]	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Unclear	Unclear	No (Low concern)	Yes (Low concern)	N/A	N/A	N/A	No (Low concern)	Moderate RoB (RCT)

Author, Year, PMID, Design	Detection Bias (Blinding of Outcome Accessors)	Attrition Bias	Clear Reporting	Eligibility Criteria Clear	Intervention Adequately Described	Outcomes Fully Defined	RCT					NRCS & Single groups	NRCS		Other Bias	Overall RoB
							Blinding of Participants and Personnel	Random Sequence Generation	Allocation Concealment	Selective reporting	ITT	Cohort representativeness	Comparator representativeness	Confounder Adjustment		
Levin 2015 25887096, RCT	Yes (Low concern)	Yes (High concern)[f]	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	No (Low concern)	Yes (Low concern)	N/A	N/A	N/A	No (Low concern)	Moderate RoB (RCT)
Notzon 2016 28051838, RCT	Yes (Low concern)	Yes (High concern)[g]	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	No (Low concern)	Yes (Low concern)	N/A	N/A	N/A	No (Low concern)	Moderate RoB (RCT)
Konstenius 2010 20015599, RCT	Unclear	No (Low concern)	Unclear (NR)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	No (Low concern)	Yes (Low concern)	N/A	N/A	N/A	No (Low concern)	Low RoB (RCT)
Kast 2021 33988929, NRCS	Unclear	No (Low concern)	No (High Concern[h]	No (High concern)[i]	Yes (Low concern)	No (High concern[j]	N/A	N/A	N/A	N/A	N/A	Yes (Low concern)	Yes (Low concern)	No (High concern)[k]	No (Low concern)	High RoB (RCT)
Schubiner 2002 12233989, RCT	Yes (Low concern)	No (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	N/A	N/A	N/A	No (Low concern)	Low RoB (RCT)

Notes. Co-publications are Biederman-2008 and Wilens-2006, Levin-2015 and Notzon-2016.

[a]Low retention at 10 years of follow-up (55 out of 140); [b]Cases with high severity of ADHD; [c] Poorly reported overall methods and results; [d]Only 25/33, 21/32, and 23/33 patients completed the 12 weeks of the trial for the placebo, MPH, and BPR groups; [e]Only 44% of patients completed the entire 14-week trial; [f]Thirty-three participants (26.2%) dropped out prior to maintenance phase completion (end of week 13); [g]The dropout rate in the placebo group was 30% compared to a dropout rate of 24.3% in the active arm; [h]Outcome and comparison groups were not clear; [i]It was not clear which diagnoses of ADHD were used when/in what way; [j]There was no clear definition of "retention"; [k]Crude analysis.

Abbreviations. N/A=not applicable; NRCs=non-randomized comparative study; ROB=risk of bias.

APPENDIX D. DESIGN DETAILS

Author Year PMID Protocol/Trial	Country Setting Funding	Study Design	Enrollment Dates	Inclusion Criteria	Exclusion Criteria	ADHD Definition	SUD Definition (KQ 2)
Key Question 1							
Biederman 2008 **18316421**	USA Outpatient NR	NRCS (P)	NR	Individuals derived from longitudinal case-control study of ADHD.	Adopted; nuclear family was not available; major sensorimotor disabilities (paralysis, deafness, blindness); psychosis; autism, inadequate English language; IQ<80.	DSM-III-R	–
Wilens 2006 **16601645**	USA Outpatient Non-Industry	Single Group (P)	NR	Aged 6-17 years	Adoption; nuclear family is not available; sensorimotor handicaps; psychosis, autism, inadequate command of the English language; Full Scale IQ < 80	DSM-III-R	–
Chang 2014 **25158998**	Sweden Outpatient Non-Industry	NRCS (R)	2006-2009	Born during 1960-1998 in Sweden; ≥1 outpatient ADHD diagnosis during 2001-2009 in the National Patient Register.	NR	ICD-10 code: F90	–
Dalsgaard 2014 **24090624**	Denmark Outpatient Non-Industry	Single Group (P)	NR	Treated with methylphenidate or dexamphetamine in childhood.	NR	DSM-IV, ICD-10	–
Mannuzza 2008 **18381904**	USA Outpatient Non-Industry	NRCS (P)	1970-1977	Referral to a psychiatric clinic for behavioral problems; elevated ratings on standard scales of hyperactivity by teachers and parents; behavior problems in settings other than school; a diagnosis of DSM-II hyperkinetic reaction by a child psychiatrist; IQ score >85,	Prior treatment with stimulants; psychosis or neurological disorder; referrals that involved aggressive or other serious antisocial behaviors.	DSM-IV	–

Author Year PMID Protocol/Trial	Country Setting Funding	Study Design	Enrollment Dates	Inclusion Criteria	Exclusion Criteria	ADHD Definition	SUD Definition (KQ 2)
				English speaking parents; home phone.			
Steinhausen 2014 24314850	Denmark Community NR	NRCS (R)	1994-2010	Diagnosed with ADHD between 1994 and 2010 in the Danish psychiatric central register (DPCR)	NR	ICD-8 or 10	–
Torgersen 2013 23104523	Norway Outpatient NR	Single Group (R)	1997-2005	Adult ADHD diagnosis (≥18 years); initiated central stimulant treatment.	NR	ADHD confirmed by a regional expert committee for hyperkinetic disorders according to national guidelines	–
Key Question 2							
Kast 2021 33988929	USA Outpatient Non-Industry	NRCS (R)	2014-2020	ADHD Diagnosis; referred or presenting newly to an addiction psychiatry clinic.	NR	DSM 5 ICD-10 code F90	DSM 5
Konstenius 2010 20015599 ISRCTN81602628	Sweden Community Industry	RCT	NR	Treated at outpatient addiction units in the Stockholm metropolitan region; amphetamine dependence during the last 12 months.	Current or past diagnosis of any other substance dependence except nicotine; history of major psychiatric disorder or any current psychiatric condition requiring medication; use of opioid medication or illicit opiates in the last month; current use of benzodiazepines; traces of illicit substance in the urine; serious somatic disease; pregnant or lactating; known hypersensitivity for methylphenidate; IQ < 70.	Conners' adult ADHD self and observer rating scales (CAARS:SV and CAARS:O)	DSM IV (amphetamine dependence)
Levin 2006 16102908	USA Outpatient Non-Industry	RCT	NR	DSM-IV criteria for opiate dependence and adult ADHD; aged 18-60; the	Met DSM-IV criteria for current psychiatric disorders (other than	DSM-IV	DSM-IV (opiate dependence)

Author Year PMID Protocol/Trial	Country Setting Funding	Study Design	Enrollment Dates	Inclusion Criteria	Exclusion Criteria	ADHD Definition	SUD Definition (KQ 2)
				same dose of methadone for at least 3 weeks.	ADHD/SUD); history of eating disorder; physiologically dependent on sedatives or alcohol; suicidal or homicidal behavior within the past 2 years; prescribed psychotropic medications other than methadone; unstable medical condition (i.e., uncontrolled diabetes); sensitivity to MPH or BPR; nursing and/or pregnant; unable to give informed consent		
Levin 2007 16930863	USA Outpatient Non-Industry	RCT	1998-2004	Aged 18–60 years; cocaine dependence and seeking treatment for cocaine use; persistent adult ADHD.	Psychiatric disorders (other than ADHD or SUD) requiring psychiatric intervention; physiologically dependent on opioids, sedatives, or alcohol; suicidal or homicidal behavior within the past 2 years; current psychotropic medication; unstable medical condition (i.e. uncontrolled diabetes); known sensitivity to MPH; nursing and/or pregnant; unable to give consent.	DSM-IV	DSM-IV
Levin 2015 25887096 NCT00553319	USA Community Non-Industry	RCT	2007-2013	Current treatment for cocaine use disorder; aged 18-60 years, medically and psychiatrically stable, diagnosis of cocaine dependence and adult ADHD.	Past mania, schizophrenia, or any psychotic disorder other than transient psychosis due to drug abuse; uncontrolled hypertension or coronary vascular disease; cardiac symptoms, fainting, open-heart surgery, and/or arrhythmia; legally	DSM-IV-TR	DSM-IV-TR

Author Year PMID Protocol/Trial	Country Setting Funding	Study Design	Enrollment Dates	Inclusion Criteria	Exclusion Criteria	ADHD Definition	SUD Definition (KQ 2)
					mandated to substance abuse treatment.		
Notzon 2016 28051838	USA Outpatient NR	RCT	2007-2013	Aged 18–60; adult ADHD and current cocaine dependence; marijuana use in the 30 days prior to study enrollment.	History of mania, schizophrenia, or any psychosis beyond transient symptoms related to drug use; abnormal cardiac function; any unstable medical or psychiatric conditions	DSM IV	Conners Adult ADHD Diagnostic Interview for DSM-IV and the SCID for DSM-IV
Schubiner 2002 12233989	USA Outpatient NR	RCT	2002-NR	Aged 18-55 years; current cocaine dependence; provided urine specimen with a positive urine toxicology result for cocaine metabolite; ADHD in childhood and adulthood; willing to enter an intensive outpatient treatment program.	IQ < 75 on the Shipley Institute of Living scale	DSM IV	DSM–IV (cocaine dependence)

Abbreviations. ADHD=attention-deficit/hyperactivity disorder; DSM=Diagnostic and Statistical Manual of Mental Disorders; ICD=International Classification of Diseases; IQ=intelligence quotient score; KQ=key question; NR=not reported; NRCS=non-randomized comparative study; (P)=prospective; PMID=PubMed ID; (R)=retrospective; SCID=Structured Clinical Interview for DSM Disorders; SUD=substance use disorder.

APPENDIX E. BASELINE CHARACTERISTICS

Author Year PMID, Study Design	N at Baseline	Race /Ethnicity, %	Age at Baseline (Years), Mean (SD)	Age at Treatment Initiation (Years), Mean (SD)	Male, %	Comorbidities, %/Mean (SD)	Socioeconomic Status Details, %/Mean (SD)
Key Question 1							
Biederman, 2008, 18316421, NRCS (P)	131	White 100	10.5 (2.9)[a,b]	8.8 (3.5)[b]	100	Conduct disorder, 45.8[b,c]	Hollingshead Scale, 1.86 (1.0)[b]
Wilens, 2006, 16601645, Single group (P)	55 [d,e]	White 100	Range: 6-17	NR	82	NR	Hollingshead scale: 2 (1)
Chang. 2014, 25158998, NRCS (R)	38,753	NR	8-15= 44.5% 16-25= 30.7% 25-35= 13.3% 36-46= 11.4%	NR	68	Nonsubstance psychiatric diagnosis, 60.7	Employed, 24 Living in a metropolitan area, 14
Dalsgaard, 2014, 24090624, Single group (P)	208	NR	NR	NR	88	NR	NR
Mannuzza, 2008, 18381904, Single group (P)	176	White 100	6-12	8.7 (1.6) Range: 6-12	100	NR	Hollingshead and Redlich index, 3.3 (1.0)[b]
Steinhausen, 2014, 24314850, NRCS (R)	18,702[f]	NR	15.20 (10.08)[g]	NR	75.4[g]	NR	NR
Torgersen, 2013, 23104523, Single group (R)	52[h]	NR	28.4 (8.2)	NR	65.4	Comorbid antisocial personality disorder, 1.9 Comorbid borderline personality disorder, 13.5	NR

Key Question 2							
Kast, 2021, 33988929, NRCS (R)	203	White 89.6	38.0 (11.0)[b]	NR	57.6	Cocaine use disorder, 30.5	NR
Konstenius, 2010, 20015599, RCT	24	NR	37.4 (9.9)[b]	NR	75	NR	Means of livelihood: Employed, 20.8 Social welfare, 70.8 Unspecified, 8.3
Levin, 2006, 16102908, RCT	98	White 39.8 Hispanic 39.8 Black 20.4	39.0 (7.4)[b]	NR	57	Current substance use disorders Alcohol, 17.3 Marijuana, 18.4 Cocaine, 53.1 Opiate, 53.1 Psychiatric disorders *Current:* Affective, 17.3 Anxiety, 17.3 *Lifetime:* Affective, 26.5 Anxiety, 12.2	Education (years), 12 (3) [b] Currently employed, 57.1 Average income, $20,574 ($14525)[b]
Levin, 2007, 16930863, RCT	106	White 60.4 Hispanic 14.2 African American 19.8 Others 5.7	37 (23-52)[b] Mean (range)	NR	83	Current substance use disorders: Alcohol, 40.6 Marijuana, 40 Opiate, 0.9 Psychiatric disorders: Lifetime anxiety/affective, 19.8 Current anxiety/affective, 45.3	Employment: Full-time, 56.6 Part-time, 18.9 Unemployed, 16 Income: <25k, 34 25–50k, 37.7 >50k, 16
Levin, 2015, 25887096, RCT	126	White 57.1 Hispanic 20.6 Black 17.5 Asian 7.9	40.4 (8.1)[b]	NR	84.1	Alcohol dependence: Current, 22.2 Lifetime, 51.6 Cannabis dependence: Current, 10.3 Lifetime, 30.2	Current employment: Full-time, 32.5 Part-time, 10.3 Unemployed, 54.8

Notzon, 2016, 28051838, RCT	57[i]	White 64.9 Hispanic 10.5 Black 17.5 Asian 1.8	38.3 (8.0)[b]	NR	78.9	NR	Education (years), 14.1 (2.20)
Schubiner, 2002, 12233989, RCT	48	White 62.5	37.1 (6.7)[b]	NR	89.6	BDI scores, 22.5 (9.0)[b] Addiction Severity Index (psychiatric status), 0.3 (0.2)[b] Any Axis I comorbidity[j] 56.3	NR

Notes. Co-publications are Biederman-2008 and Wilens-2006, Levin-2015 and Notzon-2016.

[a]Samples restricted to subjects who were assessed at the 10-year follow-up (no stimulant treatment history, *N* = 30 and stimulant therapy subjects, *N* = 82); [b]Calculated by the research team; [c] Patients with lifetime history of conduct disorder (status at baseline); [d]Data represents ADHD group; [e]64% of subjects in this study were probands from the Biederman, 2008; [f]Data include all individuals in the methylphenidate, mixed medication, and no treatment groups less those with SUD prior to onset of medication; [g]Data represents estimates from full population included in the study (*N* = 20,742); [h]No comorbid substance use disorder group only; [i]Only included those with marijuana outcomes analyses from the Levin 2015 study; [j]Axis I comorbidity data represents Affective, Anxiety and Other Axis I disorders.

Abbreviations. BDI=Beck Depression Inventory, NR=not reported, NRCS=non-randomized comparative studies, P=prospective, R=retrospective.

APPENDIX F. STUDY INTERVENTIONS

Study, Year, PMID, Study Design, Trial Registration Number	Arms	Description of Arms	Length of Treatment, Mean (SD)	Length of Follow-Up	Attrition Rate
Key Question 1					
Biederman, 2008[a], 18316421, NRCS (P)	Lifetime stimulant therapy	Subjects reported a lifetime history of treatment with any stimulant (amphetamine products, methylphenidate products, and pemoline)[b] and did not meet criteria for the substance use outcome before the onset of treatment.	6 (4.7) years	10 years	20% (N=28) lost to follow-up
	No stimulant therapy	Untreated subjects and subjects who began stimulant treatment after the onset of the substance use.	NR		
Wilens, 2006[a,c], 16601645 Single Group (P)	ADHD medication	Stimulants (96%)[d]	NR	10 years	NR
Chang, 2014, 25158998, NRCS (R)	Stimulant ADHD medication	Use of Methylphenidate (N06BA04), amphetamine (N06BA01), dexamphetamine (N06BA02) on January 1, 2006.	NR	3 years	NR
	No stimulant ADHD medication	Non-stimulant ADHD medication or unmedicated on January 1, 2006.	NR		
Dalsgaard, 2014, 24090624, Single Group (P)	Stimulant medication	Methylphenidate or dexamphetamine in childhood	NR	NR	NR
Mannuzza, 2008, 18381904, Single group (P)	ADHD group	Methylphenidate; 41.7mg (SD=12.4) daily	23.2 (18.6) months	Estimated 13-19 years[e]	15% loss (85% retention at adult assessment)
Steinhausen, 2014, 24314850, NRCS (R)	Methylphenidate	Methylphenidate (NA06BA04 and NA06BA11)	2.69 (3.04)[f] years	Estimated 14 years	NR
	Mixed Medication	Methylphenidate (83.51%), antidepressants (62.69%), antipsychotics (59.45%), other ADHD-specific drugs (32.74%), and amphetamines (3.40%)	5.19 (6.36)[f] years	Estimated 14 years	NR
	No medication	N/A	N/A	Estimated 14 years	NR

Study, Year, PMID, Study Design, Trial Registration Number	Arms	Description of Arms	Length of Treatment, Mean (SD)	Length of Follow-Up	Attrition Rate
Torgersen, 2013, 23104523, Single Group (R)	ADHD with No comorbid SUD	Methylphenidate; maximum dose 58.7 (23.3), maintenance dose 60 (22.8)	41.4 (30.4) months	Minimum of 43 months	NR
Key Question 2					
Kast, 2021, 33988929, NRCS (R)	Stimulant group	Those receiving stimulants within 90 days of admission[g]	Estimated 2 years[h]	5.5-years	NR
	Non-Stimulant	Those receiving non-stimulants within 90 days of admission.	Estimated 2 years[h]	5.5-years	NR
	No medication	No Treatment	NR	5.5-years	NR
Konstenius, 2010, 20015599, RCT, ISRCTN 81602628	Methylphenidate	Extended-release methylphenidate; starting dose (18 mg) of methylphenidate which was titrated over period of 10 days to the maximum dose of 72 mg. All subjects participated once weekly in an individual skills training program which targeted risk for relapse in drug use and ADHD symptoms.	12 weeks[i]	12 weeks[i]	NR
	Placebo	Placebo. All subjects participated once weekly in an individual skills training program which targeted risk for relapse in drug use and ADHD symptoms.	12 weeks[i]	12 weeks[i]	NR
Levin, 2006, 16102908, RCT	Methylphenidate	Sustained-release methylphenidate (two capsules and two tablets twice per day); Started at 10 mg/day and increased by 10 mg/day, up to 40 mg/day. The standard formula then replaced the Sustained-release formulation and dose was increased to maximal dose of 80 mg/day. Patients who could not tolerate at least 40 mg/day of methylphenidate were discontinued. All participants attended weekly individual CBT.	10 weeks[j]	10 weeks[j]	None (ITT analysis); 11 (34.4%) did not completed the treatment period
	Bupropion	Sustained release bupropion (two capsules and two tablets twice per day); Started at 100 mg/day and increased by 100 mg by the end of the first week and increased to a maximum dose of 400 mg/day in the second week. Patients who could not tolerate a dose of at least 200 mg/day of bupropion were discontinued. All participants attended weekly individual CBT.	10 weeks[j]	10 weeks[j]	None (ITT analysis); 10 (30.3%) did not completed the treatment period
	Placebo	Placebo (2 capsules and 2 tablets twice per day); 1 mg tablet of folic acid Also, after 49 randomized patients, 100 mg/day of	10 weeks[j]	10 weeks[j]	None (ITT analysis); 8 (24.2%) did not

Study, Year, PMID, Study Design, Trial Registration Number	Arms	Description of Arms	Length of Treatment, Mean (SD)	Length of Follow-Up	Attrition Rate
		riboflavin was added to all capsules to track compliance. All participants attended weekly individual CBT.			completed the treatment period
Levin, 2007, 16930863, RCT	Methylphenidate	Methylphenidate 2 times/day (2 capsules twice a day) and CBT 1/week; dosing initiated at 10 mg/day of standard formulation methylphenidate and increased up to 20 mg two times a day (40 mg/day). If tolerated, sustained-released formulation replaced the standard formula and used at either 20 mg 2 times a day or 60mg/day (20mg 1/day and 40mg 1/day). Patients who could not tolerate a dose of at least 40 mg/day of methylphenidate were discontinued off the medication but were continued in the trial.	13 Weeks[k]	13 Weeks[k]	None (ITT analysis); 30 (56.6%) did not completed the treatment period
	Placebo	Placebo 2 times/day (2 capsules twice a day) and CBT 1/week; Folic acid in the form of a 1 mg tablet and 25 mg of riboflavin was added to each of the four prescribed capsules (approximately 100 mg/day) to track compliance.	13 Weeks[k]	13 Weeks[k]	None (ITT analysis); 29 (54.7%) did not completed the treatment period
Levin, 2015[l], 25887096, RCT, NCT00553319	60mg mixed amphetamine salts	60-mg/day extended-release mixed amphetamine salts in 100 mg of riboflavin tablet; plus CBT 1/week. Participants unable to tolerate the maximum doses had their doses reduced based on clinical assessment.	13 weeks[m]	13 weeks[m]	None (ITT analysis); 10 (25%) did not completed the treatment period
	Placebo	Placebo in 100 mg of riboflavin tablet; plus CBT 1/week	13 weeks[m]	13 weeks[m]	None (ITT analysis); 14 (32.6%) did not completed the treatment period
Notzon, 2016[l], 28051838, RCT	Extended-release mixed amphetamine salt	Extended-release mixed amphetamine salts; 60 or 80 mg daily. Weekly CBT addressing cocaine use.	13 weeks[m]	NR	NR

Study, Year, PMID, Study Design, Trial Registration Number	Arms	Description of Arms	Length of Treatment, Mean (SD)	Length of Follow-Up	Attrition Rate
	Placebo	Weekly CBT addressing cocaine use.	13 weeks[m]	NR	NR
Schubiner, 2002, 12233989, RCT	Methylphenidate	The doses were titrated from an initial dosage for the first 2 or 3 days (10 mg three times a day) to a second-level dosage (20 mg three times a day) for the next 4 to 5 days and finally to the target dosage of 30 mg three times a day by Day 8. All participants received twice-weekly CBT for cocaine dependence and weekly CBT for ADHD.	12 weeks[n]	12 weeks[n]	55% did not complete the study
	Placebo	All participants received twice-weekly CBT for cocaine dependence and weekly CBT for ADHD.	12 weeks[n]	12 weeks[n]	42% did not complete the study

Notes. [a]Copublication; [b]Amphetamine products included mixed amphetamine salts, D-amphetamine; methylphenidate products included immediate-release methylphenidate, osmotic-release oral system methylphenidate, transdermal methylphenidate, d-methylphenidate, extended-release methylphenidate; [c]64% of subjects in this study were probands from Biederman, 2008 who were taking medications; [d]Other medications included selective serotonin reuptake inhibitors (31%), tricyclic antidepressants (21%), a-adrenergic agents (15%), neuroleptics (6%), and benzodiazepines (4%); [e]Based on age at baseline and average follow-up time for adult assessment; [f]Based on full study sample; [g]67% were extended release or prodrug formulations; [h]Based on figure provided; [i] Trial duration was 13 weeks, which included baseline measurements and 12 weeks of treatment; [j]Trial was 12 weeks and included a 2-week placebo lead-in phase, a 2-week dose titration period, followed by 8 weeks at a stable dose; [k]1-week placebo lead-in phase, a 2-week dose titration phase followed by 11 weeks at a stable dose; [l]Copublication; [m]A placebo lead-in period [week 1] preceded randomization followed by a 13-week trial with dose titrated in the first week and tapered down in the last week; [n]Included 1 week of baseline testing and 12 weeks of treatment.

Abbreviations. ADHD=attention-deficit/hyperactivity disorder; CBT=cognitive behavioral therapy; ITT=intention to treat; mg=milligram; N/A=not applicable; N=number; NR=not reported; NRCS=non-randomized comparative study; P=prospective; PMID=PubMedID; R=retrospective; SD=standard deviation.

APPENDIX G. SUBSTANCE USE DISORDER OUTCOMES CATEGORIZATION

Author, Year, PMID	Study Outcome Definition	Categorization for Report
Chang, 2014, 25158998	Substance Abuse [Hospital visits or deaths with ICD-10 codes: F11–F16, F19; deaths, and convictions for a substance-related crime]	SUD
Steinhausen, 2014, 24314850	Substance Use Disorder [ICD-8: 303, 304; ICD-10: F1]	SUD
Dalsgaard, 2014, 24090624	Substance Use Disorder [Psychiatric admissions in adulthood due to substance use disorder (ICD-8 or ICD-10: 304 or F 11.x–19.x)]	SUD
Mannuzza, 2008, 18381904	Substance Use Disorder [DSM-III-R substance use disorder diagnosed in late adolescence or young adulthood]	SUD
Torgersen, 2013, 23104523	Substance Use Disorder [DSM-IV; alcohol, amphetamines, cannabis and opiates]	SUD
Wilens, 2006, 16601645	Substance Use Disorder [DSM-IV]	SUD
Biederman, 2008, 18316421	Alcohol Abuse Disorder [DSM-IV]	AUD
	Alcohol Dependence Disorder [DSM-IV]	AUD
Dalsgaard, 2014, 24090624	Alcohol Abuse Disorder / Alcohol Dependence [Psychiatric admissions in adulthood due to alcohol use disorder or alcohol dependence (ICD-8 or ICD-10: 291, 303 or F 10.x)]	AUD
Mannuzza, 2008, 18381904	Alcohol Use Disorder [DSM-III-R]	AUD
Biederman, 2008, 18316421	Drug Abuse Disorder [DSM-IV]	Non-alcohol substance use disorders or stimulant use disorders
	Drug Dependence Disorder [DSM-IV]	
Mannuzza, 2008, 18381904	Non-Alcohol Substance Use Disorder [DSM-III-R]	Non-alcohol substance use disorders or stimulant use disorders
	Stimulant Use Disorder [DSM-III-R]	Non-alcohol substance use disorders or stimulant use disorders

APPENDIX H. CATEGORICAL OUTCOMES

Table H1. SUD Outcomes (KQ1) - Comparative

Author, Year, PMID	Outcome	Outcome Details	Population	Follow-up	Group/Comparators	n/N (%)	Effect Size (95% CI), p-Value
Biederman 2008 18316421	Substance Use Disorder	Alcohol Abuse Disorder [DSM-IV]	All	10 y	Lifetime stimulant therapy	NR/92 (NR)	aHR 1.1 (0.6, 2.1) p = 0.66
					No stimulant therapy	NR/39 (NR)	
	Substance Dependence	Alcohol Dependence Disorder [DSM-IV]	All	10 y	Lifetime stimulant therapy	NR/92 (NR)	aHR 1.0 (0.5, 2.4) p = 0.93
					No stimulant therapy	NR/39 (NR)	
	Substance Use Disorder	Drug Abuse Disorder [DSM-IV]	All	10 y	Lifetime stimulant therapy	NR/92 (NR)	aHR 1.6 (0.8, 3.2) p = 0.23
					No stimulant therapy	NR/39 (NR)	
	Substance Dependence	Drug Dependence Disorder [DSM-IV]	All	10 y	Lifetime stimulant therapy	NR/92 (NR)	aHR 1.0 (0.4, 2.6) p = 0.96
					No stimulant therapy	NR/39 (NR)	
Chang 2014 25158998	Substance Use Disorder	Substance Abuse [Hospital visits or deaths with ICD-10 codes: F11–F16, F19; deaths, and convictions for a substance-related crime]	≥20 y at baseline	3 y	Stimulant therapy	NR/NR (NR)	aHR 0.97 (0.78, 1.20) p: NR
					No stimulant therapy	NR/NR(NR)	
Steinhausen 2014 24314850	Substance Use Disorder	Substance Use Disorder [ICD-8: 303, 304; ICD-10: F1]	All	15 y	Methylphenidate	102/7314 (1.4%)	aHR 0.92 (0.74, 1.15) p: NR
					No medication	72/6370 (1.1%)	
	Substance Use Disorder	Substance Use Disorder [ICD-8: 303, 304; ICD-10: F1]	All	15 y	Mixed medication	627/5494 (11.4%)	aHR 1.48 (1.31, 1.69) p: NR
					No medication	72/6370 (1.1%)	

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

Table H2. SUD Outcomes (KQ1) - Single Group

Author, Year, PMID	Outcome	Outcome Details	Population	Follow-Up	Group/Comparators	n/N (%)
Dalsgaard 2014 24090624	Substance Use Disorder	Substance Use Disorder [Psychiatric admissions in adulthood due to substance use disorder (ICD-8 or ICD-10: 304 or F 11.x–19.x)]	All	At mean age of 31 (SD 6.6)	Methylphenidate or dexamphetamine in childhood	11/208 (5.3%)
	Substance Use Disorder	Alcohol Abuse Disorder / Alcohol Dependence [Psychiatric admissions in adulthood due to alcohol use disorder or alcohol dependence (ICD-8 or ICD-10: 291, 303 or F 10.x)]	All	At mean age of 31 (SD 6.6)	Methylphenidate or dexamphetamine in childhood	11/208 (5.3%)

Author, Year, PMID	Outcome	Outcome Details	Population	Follow-Up	Group/Comparators	n/N (%)
Mannuzza 2008 18381904	Substance Use Disorder	Substance Use Disorder [DSM-III-R substance use disorder diagnosed in late adolescence or young adulthood]	ADHD group	At mean age of 25.3 (SD 1.3)	Methylphenidate	80/176 (45.4%)
	Substance Use Disorder	Alcohol Use Disorder [DSM-III-R]	ADHD group	At mean age of 25.3 (SD 1.3)	Methylphenidate	49/176 (27.8%)
	Substance Use Disorder	Non-Alcohol Substance Use Disorder [DSM-III-R]	ADHD group	At mean age of 25.3 (SD 1.3)	Methylphenidate	65/176 (36.9%)
	Substance Use Disorder	Stimulant Use Disorder [DSM-III-R]	ADHD group	At mean age of 25.3 (SD 1.3)	Methylphenidate	43/176 (24.4%)
Torgersen 2013 23104523	Substance Use Disorder	Substance Use Disorder [DSM-IV; alcohol, amphetamines, cannabis and opiates]	ADHD with no comorbid SUD	43 m	Methylphenidate	0/52 (0%)
Wilens 2006 16601645	Substance Use Disorder	Substance Use Disorder [DSM-IV]	All	10 y	Stimulants (96%)	29/55 (53%)

Abbreviations. DSM=Diagnostic and Statistical Manual Of Mental Disorders; ICD=International Classification of Disease; m=months; n/N=number; SD=standard deviation; y=year

Table H3. Diversion or Misuse Outcomes (KQ1) - All Single Group

Author, Year, PMID	Outcome	Outcome Details	Population	Follow-Up	Group/Comparators	n/N (%)
Wilens 2006 16601645	ADHD Medication Diversion	Sold ADHD medication within the past 4 years	All	10 y	Stimulants (96%)	6/55 (11%)
	ADHD Medication Misuse	Used too much of ADHD medication within the past 4 years	All	10 y	Stimulants (96%)	12/55 (22%)
	ADHD Medication Misuse	Got high on ADHD medication within the past 4 years	All	10 y	Stimulants (96%)	5/55 (10%)
	ADHD Medication Misuse	Misused ADHD medication within the past 4 years	All	10 y	Stimulants (96%)	12/55 (22%)
	ADHD Medication Misuse	Skipped ADHD medication to use alcohol or drugs within the past 4 years	All	10 y	Stimulants (96%)	9/55 (16%)
	ADHD Medication Misuse	Used ADHD medication with alcohol or drugs within the past 4 years	All	10 y	Stimulants (96%)	17/55 (31%)
	ADHD Medication Misuse	Experienced a reaction with ADHD medication and alcohol or drugs within the past 4 years	All	10 y	Stimulants (96%)	3/55 (5%)

Abbreviations. ADHD=attention-deficit/hyperactivity disorder; n/N=number; y=year.

Table H4. ADHD Treatment Adherence (KQ2)

Author, Year, PMID	Outcome	Outcome Details	Population	Follow-Up	Group/Comparators	n/N (%)	Effect Size (95% CI), p-Value
Konstenius 2010 20015599	ADHD Treatment Adherence	Treatment retention	Treatment Completers	13 w	Methylphenidate	5[a]/12 (41%)	OR 3.65 (0.53, 25.01)[a] p = 0.188[a]
					Placebo	2[a]/12 (16%)	
Levin 2006 16102908	ADHD Treatment Adherence	Treatment compliance by Riboflavin fluorescence testing	All	12 w	Methylphenidate	NR/NR (77%)	ES: NR p: NR
					Placebo	NRNR (83%)	
	ADHD Treatment Adherence	Treatment compliance by Riboflavin fluorescence testing	All	12 w	Methylphenidate	NR/NR (77%)	ES: NR p: NR
					Bupropion	NR/NR (91%)	

Notes. [a]Calculated by the research group.

Abbreviations. ADHD=attention-deficit/hyperactivity disorder; ES=effect size; n/N=number; NR=not reported; OR=odds ratio; w=weeks.

Table H5. SUD Treatment Adherence (KQ2)

Author, Year, PMID	Outcome	Outcome Details	Population	Follow-Up	Group/Comparators	n/N (%)	Effect Size (95% CI), p-Value
Kast 2021 33988929	SUD Treatment Adherence	Treatment attrition	All	90 days	Stimulants within 90 days of admission	8[a]/171 (5%)	aHR: 0.59 (0.40, 0.87) p = 0.008
					No stimulants within 90 days of admission	11[a]/32 (35%)	

Note. [a]Calculated by the research group.

Abbreviations. aHR=adjusted hazard ratio; SUD=substance use disorder.

Table H6. SUD Symptom Change (KQ2)

Author, Year, PMID	Outcome	Outcome Details	Population	Follow-Up	Group/Comparators	n/N (%)	Effect Size (95% CI), p-Value
Levin 2007 16930863	SUD Symptom Change	Improved on the CGI [Clinical Global Improvement, score of <3 for cocaine use]	All	14 w	Methylphenidate	32/53 (60%)	OR 1.58 (0.73, 3.42)[a] p = 0.24
					Placebo	26/53 (49%)	

Notes. [a]Calculated by the research group.

Abbreviations. CGI=clinical global improvement scale; n/N=number; OR=odds ratio; SUD=substance use disorder; w=weeks.

Table H7. ADHD Symptom Change (KQ2)

Author, Year, PMID	Outcome	Outcome Details	Population	Follow-Up	Group/Comparators	n/N (%)	Effect Size (95% CI), p-Value
Levin 2006 16102908	ADHD Symptom Change	CGI [Clinical Global Improvement] score of <3 at the end of the study	All	12 w	Methylphenidate	6/32 (19%)	OR 0.36 (0.11, 1.10)[a] p=0.072[a]
					Placebo	13/33 (39%)	
	ADHD Symptom Change	CGI [Clinical Global Improvement] score of <3 at the end of the study	All	12 w	Methylphenidate	6/32 (19%)	OR 0.53 (0.17, 1.69)[a] p=0.283[a]
					Bupropion	10/33 (30%)	
	ADHD Symptom Change	≥30% reduction in AARS [Adult ADHD Rating Scale]	All	12 w	Methylphenidate	11/32 (34%)	OR 0.63 (0.23, 1.71)[a] p=0.363[a]
					Placebo	15/33 (46%)	
	ADHD Symptom Change	≥30% reduction in AARS [Adult ADHD Rating Scale]	All	12 w	Methylphenidate	11/32 (34%)	OR 0.56 (0.2, 1.51)[a] p=0.25[a]
					Bupropion	16/33 (49%)	
	ADHD Symptom Change	≥30% reduction in AARS & improved on CGI [Adult ADHD Rating Scale; Clinical Global Improvement scale; score of <3]	All	12 w	Methylphenidate	3/32 (9%)	OR 0.38 (0.09, 1.64) p=0.197
					Placebo	7/33 (21%)	
	ADHD Symptom Change	≥30% reduction in AARS & improved on CGI [Adult ADHD Rating Scale; Clinical Global Improvement scale; score of <3]	All	12 w	Methylphenidate	3/32 (9%)	OR 0.58 (0.13, 2.66)[a] p=0.482[a]
					Bupropion	5/33 (15%)	
Levin 2007 16930863	ADHD Symptom Change	Much or very much improved on the GCI [Clinical Global Improvement scale for ADHD]	All	14 w	Methylphenidate	18/53 (34%)	OR 1.19 (0.53, 2.69)[a] p=0.68
					Placebo	16/53 (30%)	
	ADHD Symptom Change	≥30% reduction in AARS [Adult ADHD Rating Scale]	All	14 w	Methylphenidate	25/53 (47%)	OR 0.74 (0.34, 1.59)[a] p=0.44
					Placebo	29/53 (55%)	
	ADHD Symptom Change	≥30% reduction in AARS & improved on CGI [Adult ADHD Rating Scale; Clinical Global Improvement scale; score of <3]	All	14 w	Methylphenidate	16/53 (30%)	OR 1.10 (0.47, 2.53)[a] p=0.83
					Placebo	15/53 (28%)	
	ADHD Symptom Change	≥30% reduction on the TAADDS [Targeted Adult Attention Deficit Disorder Scale]	All	14 w	Methylphenidate	21/53 (40%)	OR 1.66 (0.74, 3.75)[a] p=0.22
					Placebo	15/53 (28%)	
Levin 2015 25887096	ADHD Symptom Change	CGI [Clinical Global Impression score of <3	All	14 w	Mixed amphetamine salts	31/83 (37%)	OR 4.53 (1.61, 12.73)[a] p=0.004[a]
					Placebo	5/43 (12%)	
	ADHD Symptom Change	≥30% reduction in AISRS [Adult ADHD Investigator Symptom Rating Scale]	All	14 w	Mixed amphetamine salts	55/83 (66%)	OR 3.00 (1.40, 6.44)[a] p=0.005[a]
					Placebo	17/43 (40%)	
Schubiner 2002 12233989	ADHD Symptom Change	Moderate improvement by physician ratings (1 or 2 on 7-point scale	All	12 w	Methylphenidate	18.48/24 (77%)	OR 12.59 (3.21, 49.41)[a] p<0.001[a]
					Placebo	5.04/24 (21%)	
			All	12 w	Methylphenidate	17.52/24 (73%)	

Author, Year, PMID	Outcome	Outcome Details	Population	Follow-Up	Group/Comparators	n/N (%)	Effect Size (95% CI), p-Value
	ADHD Symptom Change	Moderate improvement by patient ratings (1 or 2 on 7-point scale)			Placebo	10.08/24 (42%)	OR 3.73 (1.11, 12.55)[a] p=0.033[a]

Notes. [a]Calculated by the research group.

Abbreviations. AARS=Adult ADHD Rating Scale; ADHD=attention-deficit/hyperactivity disorder; AISRS=Adult ADHD Investigator Symptom Rating Scale; CGI=clinical global improvement; n/N=number; OR=odds ratio; TAADS=Targeted Adult Attention Deficit Disorder Scale; w=weeks.

Table H8. Abstinence (KQ2)

Author, Year, PMID	Outcome	Outcome Details	Population	Follow-Up	Group/Comparators	n/N (%)	Effect Size (95% CI), p-Value
Levin 2006 16102908	Abstinence	≥2 consecutive weeks of abstinence	All	12 w	Methylphenidate	3/32 (9%)	OR 0.58 (0.13, 2.66)[a] p=0.482[a]
					Placebo	5/33 (15%)	
	Abstinence	≥2 consecutive weeks of abstinence	All	12 w	Methylphenidate	3/32 (9%)	OR 1.60 (0.25, 10.29)[a] p=0.619[a]
					Bupropion	2/33 (6%)	
	Abstinence	≥2 consecutive weeks of abstinence	Current cocaine abusing/ dependent individuals	12 w	Methylphenidate	2/13 (15%)	OR 1.09 (0.16, 7.59)[a] p = 0.95
					Placebo	3/21 (14%)	
	Abstinence	≥2 consecutive weeks of abstinence	Current cocaine abusing/ dependent individuals	12 w	Methylphenidate	2/13 (15%)	OR 1.45 (0.18, 11.94)[a] p=0.727[a]
					Bupropion	2/18 (11%)	
Levin 2007 16930863	Abstinence	≥2 consecutive weeks of abstinence	All	14 w	Methylphenidate	8/53 (15%)	OR 0.87 (0.31, 2.46)[a] p=0.69
					Placebo	9/53 (17%)	
Levin 2015 25887096	Abstinence	≥3 consecutive weeks of abstinence [by urine screens and self-report]	All	14 w	Mixed amphetamine salts	20/83 (24.1%)	aOR 8.74 (1.78, 42.97) p=0.008
					Placebo	3/43 (7%)	

Notes. [a]Calculated by the research group.

Abbreviations. aOR=adjusted odds ratio; n/N=number; OR=odds ratio; w=weeks.

Table H9. Substance Use (KQ2)

Author, Year, PMID	Outcome	Outcome Details	Population	Follow-Up	Group/Comparators	n/N (%)	Effect Size (95% CI), p-Value
Levin 2006 16102908	Substance use	Proportion of weeks positive for opiates	Patients x 12 weeks	12 w	Methylphenidate	130/384 (34%)	OR 0.74 (0.55, 0.99)[a] p=0.044[a]
					Placebo	162/396 (41%)	
	Substance use	Proportion of weeks positive for opiates	Patients x 12 weeks	12 w	Methylphenidate	130/384 (34%)	OR 0.84 (0.63, 1.13)[a] p=0.245[a]
					Bupropion	150/396 (38%)	
Levin 2007 16930863	Substance Use	Probability of THC positive urine sample (>100 ng/ml)	All	14 w	Methylphenidate	NR/53 (NR)	OR 2.56 (1.85, 3.57) p: NR[b]
					Placebo	NR/53 (NR)	
	Substance Use	Illicit amphetamine use	All	14 w	Methylphenidate	0/53 (0%)	OR 0.24 (0.01, 5.52)[a,c] p=0.374[a]
					Placebo	2/53 (4%)	
	Substance Use	Illicit opiate use	All	14 w	Methylphenidate	1/53 (2%)	OR 1.00 (0.06, 16.42)[a] p=1[a]
					Placebo	1/53 (2%)	
Notzon 2016 28051838	Substance Use	Cannabis smoking	All	14 w	Mixed amphetamine salts	18.13/37 (~49%)[d]	OR 0.20 (0.05, 0.75)[a] p=0.017[a]
					Placebo	16.60/20 (~83%)[d]	

Notes. [a]Calculated by the research group; [b]The study reported OR for Placebo vs Methylphenidate. The reported estimate was inverted to make the Placebo group a reference category; [c]0.5 correction for zero-cells; [d]Percentages were extracted from the figure.

Abbreviations. NR=not reported; OR=odds ratio; THC=tetrahydrocannabinol; w=weeks.

Table H10. Medication Misuse or Diversion (KQ2)

Author, Year, PMID	Outcome	Outcome Details	Population	Follow-Up	Group/Comparators	n/N (%)	Effect Size (95% CI), p-Value
Levin 2006 16102908	ADHD Medication Diversion	ADHD Medication Diversion [any reports from counsellors, clinical staff or patients]	All	12 w	Methylphenidate	0/32 (0%)	Not applicable
					Placebo	0/33 (0%)	
	ADHD Medication Diversion	ADHD Medication Diversion [any reports from counsellors, clinical staff or patients]	All	12 w	Methylphenidate	0/32 (0%)	Not applicable
					Bupropion	0/33 (0%)	
	ADHD Medication Misuse	ADHD medication made them high or euphoric [any reports from counsellors, clinical staff or patients]	All	12 w	Methylphenidate	0/32 (0%)	Not applicable
					Placebo	0/33 (0%)	
	ADHD Medication Misuse	ADHD medication made them high or euphoric [any reports from counsellors, clinical staff or patients]	All	12 w	Methylphenidate	0/32 (0%)	Not applicable
					Bupropion	0/33 (0%)	

Abbreviations. ADHD=attention-deficit/hyperactivity disorder; n/N=number; w=weeks.

APPENDIX I. CONTINUOUS OUTCOMES

Table I1. ADHD Treatment Adherence (KQ2, Continuous)

Author, Year, PMID	Outcome	Outcome Details	Population	Follow-Up	Group/Comparators	N	Mean (SD) or Median [25th , 75th percentiles]	Effect Size (ES), p-Value
Levin 2007 16930863	ADHD Treatment Adherence	Proportion of samples with positive fluorescence	All	14 w	Methylphenidate	43	0.84 (0.16)	MD 0.02 (-0.05, 0.09)[a] p=0.566[a]
					Placebo	48	0.82 (0.17)	
Levin 2015 25887096	ADHD Treatment Adherence	Proportion of samples with positive fluorescence	All	14 w	Mixed amphetamine salts (80mg)	41	1 [0.897, 1]	ES: NR p=0.57
					Mixed amphetamine salts (60mg)_	38	1 [0.954, 1]	
					Placebo	41	1 [0.929, 1]	

Notes. [a]Calculated by the research group.

Abbreviations. ADHD=attention-deficit/hyperactivity disorder; ES=effect size; MD=mean difference; N=number; SD=standard deviation; w=weeks.

Table I2. SUD Treatment Adherence (KQ2, Continuous)

Author, Year, PMID	Outcome	Outcome Details	Population	Follow-Up	Group/Comparators	N	Mean (SD) or Median [25th , 75th percentiles]	Effect Size (ES), p-Value
Levin 2015 25887096	SUD Treatment Adherence	Count of attended CBT sessions, out of 12 sessions	All	14 w	Mixed amphetamine salts	79	9.29 (3.88)[a]	MD 1.19 (-0.36, 2.74)[a] p=0.131[a]
					Placebo	41	8.1 (4.4)	

Notes. [a]Calculated by the research group.

Abbreviations. CBT=cognitive behavioral therapy; ES=effect size; MD=mean difference; N=number; SD=standard deviation; SUD=substance use disorder; w=weeks.

Table I3. SUD Symptom Change (KQ2, Continuous)

Author, Year, PMID	Outcome	Outcome Details	Population	Follow-Up	Group/Comparators	N	Mean (SD) or Median [25th , 75th percentiles]	Effect Size (ES), p-Value
Konstenius 2010 20015599	Other Symptom Change	Change in craving [7-point visual analog craving scale adapted from the Tiffany craving scale]	All	13 w	Methylphenidate	12	2.3 (1.3)	MD -0.5 (-1.83, 0.83)[a] p=0.670
					Placebo	12	2.8 (1.8)	

Notes. [a]Calculated by the research group.

Abbreviations. ES=effect size; MD=mean difference; N=number; SD=standard deviation; W=weeks.

Table I4. ADHD Symptom Change (KQ2, Continuous)

Author, Year, PMID	Outcome	Outcome Details	Population	Follow-Up	Group/Comparators	N	Mean (SD) or Median [25th , 75th percentiles]	Effect Size (ES), p-Value
Konstenius 2010 20015599	ADHD Symptom Change	Change in CAARS (S) [Conners Adult ADHD Rating Scale; self-rated scale]	All	13 w	Methylphenidate	12	19.1[a] (13.2)	MD 10.6 (-3.65, 24.85)[b] p=0.137
					Placebo	12	8.5[a] (19.8)	
	ADHD Symptom Change	Change in CAARS (O) [Conners Adult ADHD Rating Scale; observer-rated scale]	All	13 w	Methylphenidate	12	3.9[a] (11.9)	MD -0.10 (-11.01, 10.81) p=0.686
					Placebo	12	4.0[a] (13.8)	
Levin 2015 25887096	ADHD Symptom Change	Change in the AISRS [Adult ADHD Investigator Symptom Rating Scale], Calculated as the value at week 0 minus the value at the last week	All	14 w	Mixed amphetamine salts	79	18.0 (12.2)[b]	MD 9.41 (4.75, 14.07)[b] p<0.001
					Placebo	41	8.59 (12.24)	
	ADHD Symptom Change	Change in CGI psychopathology subscale for ADHD [Clinical Global Improvement], Calculated as the value at week 0 minus the value at the last week	All	14 w	Mixed amphetamine salts	79	1.44 (1.15)[b]	MD 0.64 (0.19, 1.09)[b] p=0.001
					Placebo	41	0.80 (1.23)	
	ADHD Symptom Change	Change in CAARS (Total score) [Conners Adult ADHD Rating Scales], Calculated as the value at week 0 minus the value at the last week	All	14 w	Mixed amphetamine salts	76	16.1 (15.3)[b]	MD 11.09 (5.48, 16.70)[b] p<0.001
					Placebo	40	5.01 (12.84)	
	ADHD Symptom Change	Change in CAARS (Hyperactive) [Conners Adult ADHD Rating Scales], Calculated as the value at week 0 minus the value at the last week	All	14 w	Mixed amphetamine salts	77	14.30 (13.9)[b]	MD 8.88 (3.33, 14.43)[b] p=0.002
					Placebo	39	5.42 (14.92)	
	ADHD Symptom Change	Change in CAARS (Inattentive) [Conners Adult ADHD Rating Scales], Calculated as the value at week 0 minus the value at the last week	All	14 w	Mixed amphetamine salts	77	14.9 (15.3)[b]	MD 10.87 (5.34, 16.40)[b] p<0.001
					Placebo	39	4.03 (11.66)	
Schubiner 2002 12233989	ADHD Symptom Change	No. inattentive symptoms	All	12 w	Methylphenidate	24	2.13 (2.85)	MD -0.70 (-2.39, 0.99)[b] p=0.408[b]
					Placebo	24	2.83 (2.96)	
	ADHD Symptom Change	No. hyperactive symptoms	All	12 w	Methylphenidate	24	3.42 (2.67)	MD -1.36 (-3.07, 0.35)[b] p=0.115[b]
					Placebo	24	4.78 (3.18)	

Notes. [a]The reported change score was a follow-up minus baseline score. To make it consistent with Levin's 2015 study, we recalculated it as a baseline minus the follow-up score; [b]Calculated by the research group.

Abbreviations. ADHD=attention-deficit/hyperactivity disorder; AISRS=Adult ADHD Investigator Symptom Rating Scale; CAARS(S)=Conners Adult ADHD Rating Scale; self-rated scale; CAARS(O)=Conners Adult ADHD Rating Scale- observer-rated scale; CGI=Clinical Global Improvement; ES=effect size; MD=mean difference; N=number; SD=standard deviation; w=weeks.

Table I5. Substance Use (KQ2, Continuous)

Author, Year, PMID	Outcome	Outcome Details	Population	Follow-Up	Group/Comparators	N	Mean (SD) or Median [25th , 75th percentiles]	Effect Size (ES), p-Value
Konstenius 2010 20015599	Substance Use	Amphetamine use, days [positive urine toxicology]	All	13 w	Methylphenidate	12	10.6 (8.8)	MD 2.00 (-5.04, 9.04)[a] p=0.472
					Placebo	12	8.6 (7.8)	
	Substance Use	Other illicit drug use, days [positive urine toxicology]	All	13 w	Methylphenidate	12	4.1 (3.6)	MD 0.60 (-2.49, 3.69)[a] p=0.501
					Placebo	12	3.5 (3.7)	
	Substance Use	Amphetamine use, days [self-reported]	All	13 w	Methylphenidate	12	4.6 (7.9)	MD 0.5 (-5.07, 6.07)[a] p=0.698
					Placebo	12	4.1 (4.9)	
	Substance Use	Other illicit drug use, days [self-reported]	All	13 w	Methylphenidate	12	0.5 (1.0)	MD -4.10 (-8.33, 0.13)[a] p=0.160
					Placebo	12	4.6 (7.0)	
	Substance Use	Alcohol use <60 g/day, days	All	13 w	Methylphenidate	12	1.3 (2.0)	MD -11.00 (-20.89, -1.11)[a] p=0.038
					Placebo	12	12.3 (16.4)	
	Substance Use	Alcohol use >60 g/day, days	All	13 w	Methylphenidate	12	4.2 (10.0)	MD -3.80 (-12.18, 4.58)[a] p=0.184
					Placebo	12	8.0 (9.8)	
	Substance Use	Time to relapse, days (by urine sample)	All	13 w	Methylphenidate	12	3.33, CI= 2.2–5.4	ES: NR p: NS
					Placebo	12	3.80, CI= 1.8–4.9	
Levin 2006 16102908	Substance Use	Proportion of positive weeks for any drug	All	12 w	Methylphenidate	32	0.94 (0.08)	MD 0.03 (-0.01, 0.07))[a] p=0.161)[a]
					Placebo	33	0.91 (0.09)	
	Substance Use	Proportion of positive weeks for any drug	All	12 w	Methylphenidate	32	0.94 (0.08)	MD 0.01 (-0.03, 0.05)[a] p=0.616[a]
					Bupropion	33	0.93 (0.08)	
	Substance Use	Proportion of positive weeks for Cocaine	Current cocaine abusing/ dependent individuals	12 w	Methylphenidate	13	0.86 (0.25)	MD 0.00 (-0.19, 0.19)[a] p=1[a]
					Placebo	21	0.86 (0.28)	
	Substance Use	Proportion of positive weeks for Cocaine	Current cocaine Abusing /dependent individuals	12 w	Methylphenidate	13	0.86 (0.25)	MD -0.05 (-0.23, 0.13)[a] p=0.569[a]
					Bupropion	18	0.91 (0.23)	
Levin 2007 16930863	Substance Use	Proportion of weeks that were cocaine positive	All	14 w	Methylphenidate	43	0.73 (0.29)	MD 0.03 (-0.05, 0.15)[a] p=0.623[a]
					Placebo	48	0.70 (0.29)	
	Substance Use	Mean level of THC in urine samples, ng/ml	Patients x 14 weeks x 3 samples per week	14 w	Methylphenidate	1806[b]	413 (482)	MD 239.00 (216.54, 261.46)[a] p<0.001[a]
					Placebo	2016[b]	174 (170)	

Author, Year, PMID	Outcome	Outcome Details	Population	Follow-Up	Group/Comparators	N	Mean (SD) or Median [25th , 75th percentiles]	Effect Size (ES), p-Value
Schubiner 2002 12233989	Substance Use	Proportion of urine samples tested negative for cocaine	All	12 w	Methylphenidate	24	0.50 (0.50)	MD 0.08 (-0.16, 0.32)[a] p=0.512[a]
					Placebo	24	0.42 (0.32)	

Notes. [a]Calculated by the research team; [b]Estimated as a product of arm sample size, total follow-up length in weeks, and a count of samples per week (N=3).
Abbreviations. ES=effect size; MD=mean difference; N=number; NS=not significant; SD=standard deviation; SUD=substance use disorder; THC=tetrahydrocannabinol; w=weeks.

Table I6. Abstinence (KQ2, Continuous)

Author, Year, PMID	Outcome	Outcome Details	Population	Follow-Up	Group/Comparators	N	Mean (SD) or Median [25th , 75th percentiles]	Effect size (ES), p-Value
Konstenius 2010 20015599	Abstinence	Longest period of abstinence, days	All	13 w	Methylphenidate	12	4.6 (3.4)	MD 0.70 (-2.01, 3.41)[a] p=0.614
					Placebo	12	3.9 (3.0)	
Schubiner 2002 12233989	Abstinence	Longest continuous abstinence, days	All	12 w	Methylphenidate	24	5.17 (6.22)	MD 0.00 (-3.42, 3.42)[a] p=1[a]
					Placebo	24	5.17 (5.53)	

Notes. [a]Calculated by the research team.
Abbreviations. ES=effect size; MD=mean difference; N=number; SD=standard deviation; w=weeks.

Table I7. Other Symptom Change (KQ2, Continuous)

Author, Year, PMID	Outcome	Outcome Details	Population	Follow-Up	Group/Comparators	N	Mean (SD) or Median [25th , 75th percentiles]	Effect size (ES), p-Value
Konstenius 2010 20015599	Other Symptom Change	Change in Beck's Depression Inventory	All	13 w	Methylphenidate	12	−6.9 (9.8)	MD -7.30 (-14.18, -0.42)[a] p=0.138
					Placebo	12	0.4 (6.0)	
	Other Symptom Change	Change in Beck's Anxiety Inventory	All	13 w	Methylphenidate	12	−0.5 (6.4)	MD -3.9 (-8.45, 0.65)[a] p=0.098
					Placebo	12	3.4 (4.1)	
	Other Symptom Change	Change in Stroop-test [reaction time and directed attention]	All	13 w	Methylphenidate	12	−2.6 (22.0)	MD 4.40 (-9.92, 18.72)[a] p=0.193
					Placebo	12	−7.0 (9.4)	

Notes. [a]Calculated by the research team.
Abbreviations. ES=effect size; MD=mean difference; N=number; SD=standard deviation; w=weeks.

APPENDIX J. ADVERSE EVENTS OUTCOMES

Author, Year, PMID	Outcome	Outcome Details	Population	Follow-Up	Group/Comparators	n/N (%)	Effect Size (95% CI), p-Value
Levin 2006	Adverse Events	Fatigue	All	12 w	Methylphenidate	0/32 (0)	OR 0.13 (0.01, 2.70)[a] p=0.190[a]
					Placebo	3[1]/33 (9)	
	Adverse Events	Increased sweating	All	12 w	Methylphenidate	2[1]/32 (6)	OR 0.67 (0.10, 4.28)[a] p=0.669[a]
					Bupropion	3[1]/33 (9)	
	Adverse Events	Ended trial due to side effects	All	12 w	Methylphenidate	1/32 (3)	OR 0.50 (0.04, 5.80)[a] p=0.579[a]
					Placebo	2/33 (6)	
	Adverse Events	Had dosage lowered during study	All	12 w	Methylphenidate	3/32 (9)	OR 3.31 (0.33, 33.63)[a] p=0.312[a]
					Bupropion	1/33 (3)	
Levin 2015 25887096	Adverse Events	Tolerated the assigned dose	Completed induction	14 w	Mixed amphetamine salts	53/81 (65%)	OR 0.27 (0.09, 0.77)[a] p=0.014[a]
					Placebo	35/40 (88%)	
	Adverse Events	Medication discontinuation due to intolerable adverse effects or to blood pressure or heart rate above strict study parameters	All	14 w	Mixed amphetamine salts	12/83 (14%)	OR 1.65 (0.50, 5.46)[a] p=0.413[a]
					Placebo	4/43 (10%)	
	Adverse Events	Anxiety	All	14 w	Mixed amphetamine salts	13/83 (16%)	OR 2.48 (0.67, 9.22)[a] p=0.176[a]
					Placebo	3/43 (7%)	
	Adverse Events	Insomnia	All	14 w	Mixed amphetamine salts	12/83 (14%)	OR 7.1 (0.89, 56.56)[a] p=0.064[a]
					Placebo	1/43 (2.3%)	
	Adverse Events	Dry Mouth	All	14 w	Mixed amphetamine salts	12/83 (14%)	OR 14.86 (0.86, 257.43)[a] p=0.064[a]
					Placebo	0/43 (0%)	
	Adverse Events	Decreased appetite	All	14 w	Mixed amphetamine salts	9/83 (11%)	OR 5.11 (0.63, 41.73)[a] p=0.128[a]
					Placebo	1/43 (2.3%)	
	Adverse Events	Fidgety / Jittery	All	14 w	Mixed amphetamine salts	5/83 (6%)	OR 2.69 (0.3, 23.81)[a] p=0.373[a]
					Placebo	1/43 (2.3%)	
	Adverse Events	Headache	All	14 w	Mixed amphetamine salts	2/83 (2%)	OR 0.33 (0.05, 2.05)[a] p=0.234[a]
					Placebo	3/43 (7.0%)	
	Adverse Events	Racing Heart	All	14 w	Mixed amphetamine salts	4/83 (5%)	OR 2.13 (0.23, 19.64)[a] p=0.506[a]
					Placebo	1/43 (2.3%)	
	Adverse Events	Fatigue	All	14 w	Mixed amphetamine salts	4/83 (5%)	OR 4.81 (0.25, 91.5)[a] p=0.296[a]
					Placebo	0/43 (0%)	
	Adverse Events	Nausea	All	14 w	Mixed amphetamine salts	1/83 (1%)	

Author, Year, PMID	Outcome	Outcome Details	Population	Follow-Up	Group/Comparators	n/N (%)	Effect Size (95% CI), p-Value
					Placebo	1/43 (2%)	OR 0.51 (0.03, 8.39)[a] p=0.639[a]
	Adverse Events	Breathing Difficulty	All	14 w	Mixed amphetamine salts	2/83 (2%)	OR 2.61 (0.12, 55.55)[a] p=0.539[a]
					Placebo	0/43 (0%)	
	Adverse Events	Chest Palpitations	All	14 w	Mixed amphetamine salts	1/83 (1%)	OR 0.51 (0.03, 8.39)[a] p=0.639[a]
					Placebo	1/43 (2%)	
	Adverse Events	Chest Pain	All	14 w	Mixed amphetamine salts	1/83 (1%)	OR 0.51 (0.03, 8.39)[a] p=0.639[a]
					Placebo	1/43 (2%)	
	Adverse Events	Rash	All	14 w	Mixed amphetamine salts	2/83 (2%)	OR 2.61 (0.12, 55.55)[a] p=0.539[a]
					Placebo	0/43 (0%)	
	Adverse Events	Itchiness	All	14 w	Mixed amphetamine salts	1/83 (1%)	OR 0.51 (0.03, 8.39)[a] p=0.639[a]
					Placebo	1/43 (2%)	
	Adverse Events	Vomiting	All	14 w	Mixed amphetamine salts	1/83 (1%)	OR 1.55 (0.06, 38.75)[a] p=0.791[a]
					Placebo	0/43 (0%)	
	Adverse Events	Depression	All	14 w	Mixed amphetamine salts	0/83 (0%)	OR 0.25 (0.01, 7.74)[a] p=0.432[a]
					Placebo	1/43 (2%)	
	Adverse Events	Dizziness	All	14 w	Mixed amphetamine salts	1/83 (1%)	OR 1.55 (0.06, 38.75)[a] p=0.791[a]
					Placebo	0/43 (0%)	
	Adverse Events	Diarrhea	All	14 w	Mixed amphetamine salts	1/83 (1%)	OR 1.55 (0.06, 38.75)[a] p=0.791[a]
					Placebo	0/43 (0%)	
	Adverse Events	Agitation	All	14 w	Mixed amphetamine salts	1/83 (1%)	OR 1.55 (0.06, 38.75)[a] p=0.791[a]
					Placebo	0/43 (0%)	
	Adverse Events	Obsessive thoughts	All	14 w	Mixed amphetamine salts	1/83 (1%)	OR 1.55 (0.06, 38.75)[a] p=0.791[a]
					Placebo	0/43 (0%)	
	Adverse Events	Increased libido	All	14 w	Mixed amphetamine salts	1/83 (1%)	OR 1.55 (0.06, 38.75)[a] p=0.791[a]
					Placebo	0/43 (0%)	
	Adverse Events	Sinus infection	All	14 w	Mixed amphetamine salts	1/83 (1%)	OR 1.55 (0.06, 38.75)[a]p=0.791[a]
					Placebo	0/43 (0%)	
	Adverse Events	Staph infection	All	14 w	Mixed amphetamine salts	1/83 (1%)	OR 1.55 (0.06, 38.75)[a] p=0.791[a]
					Placebo	0/43 (0%)	
	Adverse Events	Shoulder pain	All	14 w	Mixed amphetamine salts	1/83 (1%)	OR 1.55 (0.06, 38.75)[a] p=0.791[a]
					Placebo	0/43 (0%)	
	Adverse Events	Prickly sensation	All	14 w	Mixed amphetamine salts	0/83 (0%)	

Author, Year, PMID	Outcome	Outcome Details	Population	Follow-Up	Group/Comparators	n/N (%)	Effect Size (95% CI), p-Value
					Placebo	1/43 (2%)	OR 0.25 (0.01, 7.74)[a] p=0.432[a]
	Adverse Events	Back pain	All	14 w	Mixed amphetamine salts	1/83 (1%)	OR 1.55 (0.06, 38.75)[a] p=0.791[a]
					Placebo	0/43 (0%)	
	Adverse Events	Stomach pain	All	14 w	Mixed amphetamine salts	1/83 (1%)	OR 1.55 (0.06, 38.75)[a] p=0.791[a]
					Placebo	0/43 (0%)	
	Adverse Events	Possible seizure	All	14 w	Mixed amphetamine salts	1/83 (1%)	OR 1.55 (0.06, 38.75)[a] p=0.791[a]
					Placebo	0/43 (0%)	
	Adverse Events	Abscess	All	14 w	Mixed amphetamine salts	1/83 (1%)	OR 1.55 (0.06, 38.75)[a] p=0.791[a]
					Placebo	0/43 (0%)	
Levin 2007 16930863	Adverse Events	Headache (moderate/severe)	All	14 w	Methylphenidate	4.24/53 (8%)	OR 4.26 (0.49, 37.09)[a] p=0.189[a]
					Placebo	1.06/53 (2%)	
	Adverse Events	Gastrointestinal upset (moderate/severe)	All	14 w	Methylphenidate	4.24/53 (8%)	OR 2.09 (0.38, 11.36)[a] p=0.395[a]
					Placebo	2.12/53 (4%)	
	Adverse Events	Diarrhea (moderate/severe)	All	14 w	Methylphenidate	1.06/53 (2%)	OR 0.21 (0.02, 1.76)[a] p=0.148[a]
					Placebo	4.77/53 (9%)	
	Adverse Events	Insomnia (moderate/severe)	All	14 w	Methylphenidate	4.77/53 (9%)	OR 4.85 (0.57, 41.22)[a] p=0.148[a]
					Placebo	1.06/53 (2%)	
	Adverse Events	Stopped medication due to adverse events	All	14 w	Methylphenidate	1/53 (2%)	OR 1 (0.06, 16.42)[a] p=1[a]
					Placebo	1/53 (2%)	
	Adverse Events	Medication dose lowered due to adverse events	All	14 w	Methylphenidate	4/53 (8%)	OR 4.24 (0.46, 39.31)[a] p=0.203[a]
					Placebo	1/53 (2%)	
Schubiner 2002 12233989	Adverse Events	Chest pain	All	12 w	Methylphenidate	0/24 (0%)	OR 0.24 (0.01, 5.8)[a] p=0.383[a]
					Placebo	1.92/24 (8%)	
	Adverse Events	Palpitations	All	12 w	Methylphenidate	0/24 (0%)	OR 0.51 (0.02, 16.35)[a] p=0.704[a]
					Placebo	0.96/24 (4%)	
	Adverse Events	Dizzy	All	12 w	Methylphenidate	1.92/24 (8%)	OR 2.09 (0.17, 25.9)[a] p=0.567
					Placebo	0.96/24 (4%)	
	Adverse Events	Stomachaches	All	12 w	Methylphenidate	3.12/24 (13%)	OR 1 (0.19, 5.38)[a] p=1[a]
					Placebo	3.12/24 (13%)	
	Adverse Events	Nightmares	All	12 w	Methylphenidate	5.04/24 (21%)	OR 1.78 (0.38, 8.32)[a] p=0.464[a]
					Placebo	3.12/24 (13%)	
	Adverse Events	Headaches	All	12 w	Methylphenidate	6/24 (25%)	OR 1 (0.27, 3.69)[a]

Author, Year, PMID	Outcome	Outcome Details	Population	Follow-Up	Group/Comparators	n/N (%)	Effect Size (95% CI), p-Value
					Placebo	6/24 (25%)	p=1[a]
	Adverse Events	Nausea or upset stomach	All	12 w	Methylphenidate	7.92/24 (33%)	OR 1.85 (0.51, 6.8)[a]p=0.352[a]
					Placebo	5.04/24 (21%)	
	Adverse Events	Euphoric, unusually happy	All	12 w	Methylphenidate	10.08/24 (42%)	OR 1.77 (0.54, 5.87)[a] p=0.349[a]
					Placebo	6.96/24 (29%)	
	Adverse Events	Drowsiness	All	12 w	Methylphenidate	6/24 (25%)	OR 0.46 (0.13, 1.57)[a] p=0.216[a]
					Placebo	10.08/24 (42%)	
	Adverse Events	Tics or nervous movements	All	12 w	Methylphenidate	4.08/24 (17%)	OR 0.77 (0.18, 3.28)[a] p=0.724[a]
					Placebo	5.04/24 (21%)	
	Adverse Events	Decreased appetite	All	12 w	Methylphenidate	12/24 (50%)	OR 3.00 (0.88, 10.18)[a] p=0.078[a]
					Placebo	6/24 (25%)	
	Adverse Events	Insomnia or trouble sleeping	All	12 w	Methylphenidate	15.12/24 (63%)	OR 3.46 (1.05, 11.34)[a] p=0.041[a]
					Placebo	7.92/24 (33%)	
	Adverse Events	Irritability	All	12 w	Methylphenidate	13.92/24 (58%)	OR 1.18 (0.38, 3.68)[a] p=0.78[a]
					Placebo	12.96/24 (54%)	
	Adverse Events	Sadness	All	12 w	Methylphenidate	15.12/24 (63%)	OR 2.78 (0.86, 8.94)[a] p=0.087[a]
					Placebo	9.12/24 (38%)	
	Adverse Events	Talk less with others	All	12 w	Methylphenidate	11.04/24 (46%)	OR 0.85 (0.27, 2.65)[a] p=0.782
					Placebo	12/24 (50%)	
	Adverse Events	Stare a lot or daydreaming	All	12 w	Methylphenidate	12/24 (50%)	OR 0.41 (0.12, 1.34)[a] p=0.14[a]
					Placebo	17.04/24 (71%)	
	Adverse Events	Anxious	All	12 w	Methylphenidate	18.96/24 (79%)	OR 2.21 (0.61, 7.99)[a] p=0.227[a]
					Placebo	15.12/24 (63%)	
	Adverse Events	Medication dose lowered due to adverse events	All	12 w	Methylphenidate	6/24 (25%)	OR 3.83 (0.67, 21.84)[a] p=0.13[a]
					Placebo	1.92/24 (8%)	

Notes. [a]Calculated by the research group, with 0.5 correction added to all cells when there were 0 events in 1 group.

APPENDIX K. PEER REVIEW COMMENTS AND RESPONSES

Comment Number	Reviewer Number	Comment	Author Response
Are the objectives, scope, and methods for this review clearly described?			
1	1	Yes	Thank you.
2	2	No - The way the to KQ's are written in the intro to the executive summary does not match how they are described in the key finding, which makes the key finding and the executive summary VERY hard to read. Clarify definitions Substance use disorder categories used in the Executive Summary and Key findings sections: "general SUD", "alcohol use disorder", "other drug dependencies", "other drug use disorder" the terms are confusing and make the bulleted findings in the Key findings section very hard to understand.	We edited the Executive Summary and key findings for consistency and clarity. We appreciate the thoughtful comments provided on the PDF version of the report. At times, the literature used confusing language to describe substance use. The methods section (Executive Summary and Main Report) now describes how we operationalized the different descriptions of substance use in the literature. In addition, the revised report includes Appendix G, which describes how substance use is defined in the studies.
3	3	Yes	Thank you.
4	4	Yes	Thank you.
5	5	Yes	Thank you.
6	6	Yes	Thank you.
7	7	Yes	Thank you.
8	11	No - See comments below.	Thank you. We provide responses to the individual comments below.
Is there any indication of bias in our synthesis of the evidence?			
9	1	No	Thank you.
10	2	No	Thank you.
11	3	No	Thank you.

Comment Number	Reviewer Number	Comment	Author Response
12	4	No	Thank you.
13	5	No	Thank you.
14	6	No	Thank you.
15	7	No	Thank you.
16	11	No	Thank you.
Are you aware of any <u>published</u> or <u>unpublished</u> studies that we may have overlooked?			
17	1	No	Thank you.
18	2	No	Thank you.
19	3	No	Thank you.
20	4	No	Thank you.
21	5	No	Thank you.
22	6	No	Thank you.
23	7	No	Thank you.
24	11	No	Thank you.
Additional suggestions or comments can be provided below. If applicable, please indicate the page and line numbers from the draft report.			
25	1	Page vii, line 30: Make “stimulants” singular.	We have fixed the typo.
26	1	Page vii, line 44: OMHSP no long exists. It is now OMH	We have corrected this.
27	1	Page viii, line 8: It should be DSM-5 (Arabic Numeral).	We have corrected this.
28	1	Page viii, line 10: Remove comma.	We have fixed the typo.
29	1	Page viii, line 41: Need to be specific about which medication dosing refers to, presumably methylphenidate.	Thank you. We revised the sentence for clarity. *“(1 study reported a mean dose 41.7 mg of methylphenidate and another study a mean maximum dose of 58.7 mg).”*
30	1	Page viii, line 48: Change “report” to “reporting.”	We have fixed the typo.

Comment Number	Reviewer Number	Comment	Author Response
31	1	Page viii, line 55: It I unclear what the definition of "general SUD" is.	At times, the literature used confusing language to describe substance use. The methods section of the main report now describes how we operationalized the different descriptions of substance use in the literature. In addition, the revised report includes Appendix G, which describes how substance use is defined in the studies. We have also provided the following text in the executive summary to help clarify: *Studies reported various substance use disorder outcomes for KQ1. Two studies reported SUD (ie, any substance), and 3 studies reported alcohol use disorder (AUD) diagnosis separately from SUDs. Finally, 2 studies reported non-alcohol substance use disorders or stimulant use disorders. When studies reported SUD, AUD or other non-alcohol substance use disorders it was not always clear whether these were mutually exclusive.*
32	1	Page x, line 28: Change "dually-diagnosed individuals" to "individuals with co-occurring SUD and ADHD."	Thank you. We have revised the text accordingly.
33	1	Page x, line 36: Change "opiate" to "opioid." ("Opiate" refers to compounds occurring naturally in the poppy plant. "Opioid" includes the opiates and all other compounds that bind to opioid receptors.)	Thank you. We have revised the text accordingly.
34	1	Page xi, line 30: Not clear why the terminology, "other drug dependencies" is introduced here or what it specifically means. Wouldn't it be better to stick simply with "SUD?"	The methods section of the main report now describes how we operationalized the different descriptions of substance use in the

Comment Number	Reviewer Number	Comment	Author Response
			literature. In addition, the revised report includes Appendix G, which describes how substance use is defined in the studies. We have also provided the following text in the executive summary to help clarify: *Studies reported various substance use disorder outcomes for KQ1. Two studies reported SUD (ie, any substance), and 3 studies reported alcohol use disorder (AUD) diagnosis separately from SUDs. Finally, 2 studies reported non-alcohol substance use disorders or stimulant use disorders. When studies reported SUD, AUD or other non-alcohol substance use disorders it was not always clear whether these were mutually exclusive.*
35	1	Page 4, line 46: Change “SUD patients” to “patients with SUD” (less stigmatizing language).	We have corrected this.
36	1	Page 4, line 57: Remove “for.”	We have fixed the typo.
37	1	Page 6, line 8: It should be DSM-5 (Arabic Numeral).	We have corrected this.
38	1	Table 1: It should be DSM-5 (Arabic Numeral).	We have corrected this.
39	1	Table 1: Not clear why psychosis is included in outcomes. It is not mentioned in the text, and incidence of psychosis is a separate issue from incidence of SUD (though there could be overlap obviously).	Thank you for this comment. We have updated the table to clarify that this outcome is “*substance-related psychosis.*” Substance-related psychosis was identified by the technical expert panel as an important outcome to evaluate.
40	1	Page 7, line 57: Remove “for.”	We have fixed the typo.

Comment Number	Reviewer Number	Comment	Author Response
41	1	Page 12, lines 15-17: Unless the medications are specified, dosage amounts are meaningless. Also, the dosages as reported don't even make sense. How can the mean maintenance dose be higher than the mean maximum dose?	Thank you for this comment. We have revised the text for clarity. *Only 2 studies reported stimulant dosage (mean 41.7 mg methylphenidate;[70] mean maximum dose of 58.7 mg methylphenidate[72]).*
42	1	Page 12, line 35: Please rewrite this confusing sentence.	This text has been removed due to other edits.
43	1	Page 12, lines 45-53: Typically SUD would include alcohol use disorder. Throughout the manuscript confusion remains about overlap or non-overlap between what is being call SUD vs. AUD alone. It is unclear what "general SUD" means. It is not clear what "other drug disorders" is referring to.	Thank you for this comment. The methods section now describes how we addressed the different substance use measures described in the literature. We have also added Appendix G, which provides the study definition and our categorization of these outcomes.
44	1	Page 17, lines 44-46: Please rewrite this sentence.	Thank you. This sentence now says: *It was unclear whether the same participants were included in both outcomes.*
45	1	Page 18, line 16: Change "methadone-maintained patients" to "patients receiving methadone treatment for opioid use disorder."	Thank you. We revised the text accordingly.
46	1	Page 18, line 44: Change "were" to "was."	We have fixed the typo.
47	1	Page 21, lines 29-31: This sentence is hard to understand.	Thank you. This sentence now says: *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.*
48	1	Page 21, line 33: Change "RCTs" to "RCT."	We have fixed the typo.

Comment Number	Reviewer Number	Comment	Author Response
49	1	Page 23, line 26: Change “opiate” to “opioid.”	Thank you. We have revised the text accordingly.
50	1	Page 23, line 42: Change “methadone-maintained patients” to “patients receiving methadone treatment for opioid use disorder.”	Thank you. We have revised the text accordingly.
51	1	Page 23, lines 43-46: It is confusing when higher levels of use are reported, but then odds ratios less than 1 are reported.	Thank you. We have revised the sentence for clarity.
52	1	Page 23, lines 46-48: Not clear why, if the participants had amphetamine dependence, opiate outcomes would be reported. (In the past when urine drug testing was done, it detected only morphine and codeine, natural constituents of the opioid poppy; thus, “opiate” may be correct in this context.)	Thank you. This study included individuals with cocaine dependence and reported use of other substances and “opiates”. Based on an earlier comment, we revised the description of the trial: *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]).
53	1	Page 24, lines 24-28: What this sentence is trying to say is unclear. How can there be fewer days of alcohol use with no difference in mean days. Also not clear what the <60 gm vs. >60 gm is referring to unless it is heavy drinking days	Thank you; we revised the sentence for clarity: *One RCT of people with comorbid ADHD and amphetamine dependence reported significantly fewer days of alcohol use of <60g/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 >60g/day between groups (MD = -3.80 days, 95% CI [-12.18, 4.58].*

Comment Number	Reviewer Number	Comment	Author Response
54	1	Page 24, line 35: Change "methadone-maintained patients" to "patients receiving methadone treatment for opioid use disorder."	We revised the text accordingly.
55	1	Page 24, line 58: Change "methadone-maintained patients" to "patients receiving methadone treatment for opioid use disorder."	We revised the text accordingly.
56	1	Page 25, line 7: Change "methadone-maintained patients" to "patients receiving methadone treatment for opioid use disorder."	We revised the text accordingly.
57	1	Page 26, line 40: Add "a" before "large."	We have fixed the typo.
58	1	Page 26, line 44: Statistically is misspelled.	We have fixed the typo.
59	1	Page 27, lines 6-7: Change "ADHD patients" to "patients with ADHD."	We revised the text accordingly.
60	1	Page 28, line 34: Change "verses" to "versus."	We have fixed the typo.
61	1	Page 28, line 54: Change "ADHD patients" to "patients with ADHD."	We have corrected this.
62	1	Page 29, line 27: Change "education" to "educating."	We have fixed the typo.
63	1	Page 30, line 42: Remove "a" before "standardized."	We have fixed the typo.
64	1	Page 30, line 50: Change "ADHD patients" to "patients with ADHD."	We have corrected this.
65	1	Page 31, lines 6-8: Change "dually-diagnosed individuals" to "individuals with co-occurring SUD and ADHD."	We have corrected this.
66	1	Page 31, line 34: Change "opiate" to "opioid."	We have corrected this.
67	1	Page 31, line 54: Again, not entirely clear what is intended by "other drug dependencies."	The methods section now describes how we addressed the different substance use measures described in the literature. In addition, the revised report includes Appendix G, which describes how substance use is defined in the studies.
68	2	1. Key findings, "the effect of stimulants in people with co-occurring ADHD and SUD" section. The two bulleted statements of finding in this section are VERY difficult to understand and to differentiate. For this work to be impactful, these statements should be clarified. The difference appears to be the level of evidence (No Vs. Insufficient) and the outcomes evaluated. But as it is written this is VERY hard to untangle. Statement 1: "There is no evidence of a difference in ADHD treatment adherence, substance use, SUD symptom change, or abstinence from	Thank you. Your interpretation of these statements is correct, and we have edited the text for clarity.

Comment Number	Reviewer Number	Comment	Author Response
		substances in people with co-occurring ADHD and SUD who are vs are not prescribed stimulants (all with low confidence).” My interpretation of this statement: Among clinical trials enrolling People with co-occurring ADHD and SUD who are either prescribed Vs. NOT prescribed stimulants, there is no evidence of a difference in key health outcomes (ADHD Treatment Adherence, substance use, SUD symptom change, abstinence). Statement 2: There is insufficient evidence for ADHD symptom change, SUD treatment adherence, misuse or diversion, and depression / anxiety outcomes in patients with co-occurring ADHD and SUD who are vs are not prescribed stimulants medications (all no conclusion). My interpretation of this statement: Among clinical trials enrolling People with co-occurring ADHD and SUD who are either prescribed Vs. NOT prescribed stimulants, There is insufficient evidence for ADHD symptom change, SUD treatment adherence, misuse or diversion, and depression / anxiety outcomes	
69	2	2. One of our key clinical questions derived from provider in put is the risk of stimulant misuse and diversion among adults with ADHD who are prescribed stimulants. It appears there one study that evaluated these outcomes: “diversion (11%) or misuse (10% to 31% depending on definition of misuse)” but this study was not graded for evidence. Why? Given this clinical importance of this question to VA providers, why not highlight this in the key findings? Could highlight: (1) there was only one study, (2) this is why it was not graded, but (3) this is what the outcomes where.	The methods section (full report) describes our approach for grading studies. For outcomes only informed by single group studies we assessed the various GRADE domains to communicate information about the characteristics of the studies but did not provide an overall rating for outcomes. We updated the key findings to highlight the findings from this study and we note the finding is from a small single group study.
70	2	3. Two sections of the results in the executive summary: these two section titles need to be written in a way the reader can clearly and easily differentiate them. In the first heading you have an outcome list (SUD, Misuse, Diversion) and in the second heading you have the group comparison but now outcomes.	Thank you for this helpful suggestion. We have revised the section headings accordingly.

Comment Number	Reviewer Number	Comment	Author Response
			The effect of stimulants on the incidence of substance use disorders (SUD), misuse and diversion in people with attention-deficit/hyperactivity disorder (ADHD) without SUD at baseline And *The effect of stimulants on ADHD and SUD symptom and treatment outcomes in people with co-occurring ADHD and SUD.*
71	2	4. First paragraph of the discussion is VERY confusing. I have made several comments directly on the PDF.	Thank you for your suggested comments on the PDF of the report. We edited the Discussion for clarity.
72	2	5. Implication for VA policies section: We tend not to develop "policies" on prescribing so as not to interfere with provider-patient decision making. We do develop "guidance" and "guidelines" and provide education on best practices. That is the point of this evidence synthesis.	Thank you for this important comment. We revised the Discussion (Executive Summary and Main Report) to indicate a need for *"guidance and education"* to clinicians treating ADHD, rather than a need for policy development. "*Given the increasing rates of ADHD diagnoses in the Veteran population, the VA needs to provide guidance and education is necessary for clinicians treating ADHD.*"
73	3	The review is very thorough and detailed and addresses areas of clinical practice that yearn for clarification. The report indicates that varying definitions of ADHD and SUD were included, from various DSM versions, the ICD, and other diagnostic frameworks, noting that these criteria vary in the requirements needed for diagnosis. This variability can lead to differences in patient populations across studies, particularly concerning symptom presentation. The evolving nature of DSM	Thank you and we appreciate your concise summary of some of the limitations of this body of research.

Comment Number	Reviewer Number	Comment	Author Response
		criteria reflects the inherent complexities in diagnosis, where features are influenced by both genetic and environmental factors and often overlap with other disorders. This evolution is crucial because it directly impacts clinicians' diagnostic confidence. Currently, the diagnostic nomenclature does not fully support confident decision-making, often leaving clinicians to navigate uncertainties in defining and differentiating conditions. As diagnostic criteria mature and become more reliable, achieving greater homogeneity, studies can more effectively address the questions central to this project. Improved diagnostic clarity will ultimately enhance clinical decision-making, fostering more confident and accurate prescribing practices. Some considerations, most are merely grammatic	
74	3	Page v111 line 46 47 - report should be reporting	We have fixed the typo.
75	3	Page 4 line 57- Remove the word for	We have fixed the typo.
76	3	Page 7 line 57 - remove the word for	We have fixed the typo.
77	3	Page 8 line 17-20 - The writing was a bit unclear to me. Does this proposed change help and convey the intended message? "For Key Question 1, we examined the incidence of Substance Use Disorder (SUD) among individuals diagnosed with ADHD who were prescribed stimulant medications. Additionally, we compared the incidence of SUD between two groups: individuals with ADHD who were prescribed stimulant medications and those with ADHD who were not prescribed stimulant medications.	Thank you for this suggestion. We revised the text to clarify our meaning. "*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."*
78	3	Page 28 line 27 - Different should be difference	We have fixed the typo.
79	3	Page 28 line 35 the word versus and vs are both used in document	Thank you. We revised the text for consistency.
80	3	Page 28 line 43 remove the word the	We have fixed the typo.
81	3	Page 29 line - 27 education should be educating	We have fixed the typo.
82	3	Page x line 27-29 "Fears that the use of stimulant medications in adults with ADHD can lead to a new SUD diagnosis or precipitate substance-related problems in dually-diagnosed individuals appear not to be broadly supported by the evidence". This sentence suggests that some evidence offers some support - is that the	Thank you. We revised the text for clarity. "*Fears that the use of stimulant medications in adults with ADHD can lead to a new SUD diagnosis or precipitate substance-*

Comment Number	Reviewer Number	Comment	Author Response
		intended message? It may not match a stated conclusion which reads, "There is no evidence that stimulant medication treatment for ADHD increases the risk of some SUD diagnoses.	*related problems in people with co-occurring SUD and ADHD appear not to be supported by the overall evidence*." The conclusion has been updated to say, "However, the overall evidence does not indicate that stimulant medication treatment for ADHD increases the risk of SUD diagnoses."
83	4	I have had the pleasure to review this excellent manuscript by Rieke et al. The team from evidence synthesis program has done an comprehensive job of reviewing extant literature to answer key questions asked by the OMHSP. Authors have done well to categorize different levels of evidence available in the literature and have analyzed the results considering the strength and weakness of various studies looking at ADHD, SUD and medications. The manuscript is well organized into different sections, and it has excellent tables detailing and summarizing the information provided in the text. Authors found that there was limited evidence in the current literature to answer key questions with a sufficient degree of confidence. This manuscript identified significant gaps in literature pertinent to veterans, ADHD treatment with medications in the context of misuse and substance use disorders and agree with heir call for future studies to address the gaps in knowledge for a key clinical area for Veterans and the VA. While the manuscript is overall very impressive it does need to be revised as there are some points that need to be addressed. Please see my itemized comments that need to be addressed by the authors:	Thank you.
84	4	1) Page v Line 1 -Working title of "ADHD among veterans" is misguiding as this review did not specifically address ADHD in veterans. Given the lack of studies looking at veterans with ADHD and SUD this title gives the false impression that the studies reviewed are from adult ADHD in veterans. I would recommend coming up with a more specific title based on the key questions asked answered.	Thank you. The revised title is now "ADHD and Substance Use Disorders in Adults"
85	4	2) Under Key Findings: -Page viii Line 41 in the section	Thank you. We revised the sentence for clarity. *"(mean 41.7mg of*

Comment Number	Reviewer Number	Comment	Author Response
		Effect of Stimulants on Incidence of SUD, Misuse and Diversion Authors state: "2 studies reported information on dosing (mean maximum dose between 58.7mg and 60mg)." - Its not clear which medication dose are the authors referring to. Please clarify which stimulant medication/drug is being referred to here.	*methylphenidate in one study and a mean maximum dose between of 58.7mg)."*
86	4	3) Pages ix-x Under Discussion: Authors state: "Several previous studies on ADHD patients, including adolescents, have reported that exposure to ADHD medications, including stimulant medication, may reduce substance use issues later in life. Partially in support of these observations we found no evidence of a difference for alcohol use disorders or dependence between people with ADHD who were and were not prescribed stimulants." -These statements do not account for the study finding that there was no difference in SUD outcomes including use in those prescribed stimulant medications vs those not prescribed stimulants. Inference of partial support of observation in this instance gives the impression of selective use of evidence to support the claim. I would suggest revision of this statement based on the totality of the evidence gathered.	Thank you, this section has been edited due to other changes in the results. The text now states: "*Given the available data, we concluded that 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 developing an SUD, and evidence was insufficient to assess the effect of stimulant medications on AUD and other non-alcohol substance use disorders."*
87	4	4) Page x Under the header Implications for VA Policy Line 34-35 " Absent more evidence of harm, prescribers should consider stimulant and non-stimulant medications for the treatment of adult ADHD." And Main report Page 31 Line 7-9 "Absent more evidence of harm (ie, incident SUD diagnoses and/or increases in substance-related problems in dually-diagnosed individuals), prescribers should consider stimulant and non-stimulant medications for the treatment of adult ADHD." -While the review showed with a low level of evidence that there was no increased risk of harm, it equally showed (with a similar level of evidence) that there was no difference in response of stimulant medications over placebo	Thank you and we agree. The revised text now states: *"Therefore, prescribers should consider stimulant treatment or other treatments for ADHD after a thorough, individualized risk-benefit discussion with, as well as collaboration with members of the care team."*

Comment Number	Reviewer Number	Comment	Author Response
		over any of the ADHD and SUD outcome measures. Therefore authors' inference and recommendations are based on some low level evidence of no harm and not on the entirety of the evidence gathered for this study and goes beyond the key questions and their findings specifically in the evidence synthesis and refers to literature not included/pertinent to this review to justify prescription of medications. I strongly recommend changing the recommendations to something like " Absent evidence of harm and benefits in the current synthesis, prescriber should consider stimulant and non-stimulant medications for the treatment of adult ADHD after a thorough risk benefit discussion with patients on a case by case basis." I am merely providing an example of a more neutral statement. Authors could revise their statement such that it does not sound as an emphatic call to prescribe more stimulant or non stimulant medications without actually finding evidence for prescribing medications in their own synthesis.	
88	4	5) Main report: Under RESULTS: Page 23 Line 41-49; "One 12 week RCT, which included methadone-maintained patients with both adult ADHD and cocaine dependence/abuse, reported a higher proportion of weeks positive for opiates during the study for those in the methylphenidate group compared to placebo (OR = 0.74, 95% CI [0.55, 0.99]), but not compared to .56 bupropion (OR = 0.84, 95% CI[0.62, 1.13]) Another RCT (14 weeks) in patients with comorbid ADHD and amphetamine dependence reported no significant differences in illicit opiate use between 56 methylphenidate compared to placebo (OR = 1.00, 95% CI [0.06, 16.42])." -2 different studies here have the same reference # 56. Please check references closely.	Thank you. We have corrected the reference.
89	4	6) Under DISCUSSION Page 29 Line 18-37 -A significant amount of this paragraph has been spent on information from the study related to education patients about harms. Education of patients is a very important aspect of harm reduction and should be emphasized. However, this could be done in a more succinct manner. I would recommend authors summarize the findings of the study more succinctly without reducing the point of emphasis while retaining the focus on key questions of the study.	We edited the paragraph with the aim of being concise. "*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*

Comment Number	Reviewer Number	Comment	Author Response
			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."
90	4	7) Page 55 Line 23-26 Authors state: "One RCT reported lower opiate use in patients taking methylphenidate compared to placebo, which may support the theory that individuals with ADHD may use substances to self-medicate or that the change in lifestyle when they are on stimulants may give them a reason to stop using opiates." -This inference by the authors appears to be selective use of evidence synthesized and appears to be conjectural. There were other studies in the evidence synthesis that showed no change in Opiate use among patients on stimulants vs placebo. It would be best if the authors revised this statement based on the entirety of evidence gathered.	Thank you. We have removed the text indicating that this may support the theory of self-medicating.
91	5	[No comments]	Not applicable.
92	6	There are 2 sections that discuss VA implications and "need for policy". These aren't referenced and I believe to be inappropriate for inclusion in this evidence summary. The authors of this evidence summary should do not have authority to suggest that VA develop policy on clinical issues and I am concerned that this report will be published in a public forum without proper review by VHA Executives who oversee policy development. The 2 sections I recommend removing or significantly editing include: line 25-26 on page x and also lines 57-13 on pages 30 and 31.	We revised the section on "Implications for VA Policy" (Executive Summary and Main Report) to note the need for VA to provide guidance and education to clinicians treating ADHD, rather than a need for policy development.
93	7	First, thank you for this great review!	Thank you.
94	7	x, line 25 or 26, I am not in favor a VA policy for this treatment as it might be too prescriptive, but I do think the VA needs to provide education and resources to clinicians treating ADHD and prescribing both stimulant and nonstimulant medications, and leadership needs to support clinicians who determine that stimulant prescribing is not indicated especially when a Veteran wants stimulants.	Thank you and we agree. We revised the section (Executive Summary and Main Report) to note the "*Given the increasing rates of ADHD diagnoses in the Veteran population, the VA needs to provide guidance and education is necessary for clinicians treating ADHD."*

Comment Number	Reviewer Number	Comment	Author Response
95	7	4, line 37 or 28, lisdex is an amphetamine (it just needs GI enzymes to cleave off lysine to make it active dextroamphetamine), so you might want to say "Prescription of psychostimulants, such as methylphenidate and amphetamine-based products, ..	Thank you. We revised the sentence accordingly: *Prescription psychostimulants, such as methylphenidate and amphetamine-based products (eg, lisdexamfetamine),…"*
96	7	4, line 46 nonpharmacologic treatments is often used synonymously with psychotherapeutic interventions, so consider deleting the parenthetical example	Thank you; we have removed the parenthetical example.
97	7	4, line 52, I might word that a little stronger: to date there has never been a consensus clinical practice guideline for the treatment of adults with ADHD.	Thank you. We have updated this sentence to include the suggested language. "*Despite the growing number of adults with an ADHD diagnosis, and several guidelines outside of the US, to date there has never been a consensus clinical practice guideline for the treatment of adults with ADHD.*"
98	11	General comments: There are several different terminologies used re: substances (i.e., other drug dependencies, general SUD, other drug use disorders, substance use) and it makes for an unclear read to not know what these mean. For example, how does "general SUD" differ from "other drug use disorder?"	The methods section (Executive Summary and Main Report) now describes how we operationalized the different descriptions of substance use in the literature. In addition, the revised report includes Appendix G, which describes how substance use is defined in the studies.
99	11	Vii: Key findings don't align well with the KQ and it makes for a confusing read. Bullet point #1: break this up into two. For the statistics provided, consider how to contextualize the finding – e.g., is there a comparator?	We have separated the first bullet and edited the text to clarify when data were obtained from single group or comparative studies. Note that the statistics provided in bullet point #1 are from single group studies.

Comment Number	Reviewer Number	Comment	Author Response
100	11	Bullet points #4 and $5 are difficult to understand the differences and I would suggest revising.	We revised bullet point #4 and #5 for clarity.
101	11	Viii: Method section: how are misuse and diversion being operationalized for this review? I would strongly consider spending time on the definitions in this section and then later on note how these definitions vary and how they were measured in these studies (e.g., self-report, prescriber determination, etc.).	Thank you. We revised the methods section (full report) to describe our operationalization of misuse and diversion. *"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."*
102	11	Line 43: provide M/SD for the 3-19 follow-up years.	Some of studies reported ranges for follow-up or we estimated follow-up duration based on information reported. Therefore, we chose to report the range rather than mean. We have added the following text based on your comment: *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.*
103	11	Line 59: The 10-31% range is large – I would consider breaking this out in more detail. How are these studies defining misuse and what does the % look like when using their definition? This detailed approach will help providers understand what the % means. I say this because providers are concerned about misuse and enhancing detail would be helpful. It may even be useful to consider including a summary table in the executive summary of this – by studying, including their definition of misuse, how it was measured, and %.	Thank you. Of note, only 1 single group study reported on diversion and misuse for KQ1. We have edited the text to provide additional details on how the study reported misuse and diversion. *"Only 1 small study reported on prescription stimulant diversion, with 11% of enrollees self-reporting diversion. The same study found that 22% of people took too much of their prescribed medication or misused it*

Comment Number	Reviewer Number	Comment	Author Response
			in some way, 10% got high on their medication, 16% skipped 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."
104	11	Ix: Line 3: define "general SUD"; Line 7: define "other drug use disorders"	The methods section (Executive Summary and Main Report) now describes how we operationalized the different descriptions of substance use in the literature. In addition, the revised report includes Appendix G, which describes how substance use is defined in the studies.
105	11	Lines 11-39: Consider splitting these results by RCT vs. NRCS and then providing an overall summary.	Thank you for this comment. To keep the Executive Summary succinct, we provide limited details on the study design. Interested readers can find detailed information on findings for specific studies (and their design) in the main report.
106	11	Line 30: Is ADHD treatment adherence referring to medication? I ask since CBT/skills training was mentioned in 6 RCTs above.	We have specified "*medication adherence*" here.
107	11	Line 31: how was SUD symptom change defined? Is this a clinically significant change or merely a change in their score/change score?	Thank you for your question. This was defined by a change in score in the Tiffancy craving scale and change in Clinical Global Improvement score for cocaine use. The Executive Summary provides a high-level summary of the findings. The Main Report and Appendix provides specific details on the names of the measures of SUD symptom change and how these changes were evaluated.

Comment Number	Reviewer Number	Comment	Author Response
108	11	Lines 31-34: Given SUD is broad, what do we know about specific substances (e.g., alcohol, opioids, cannabis)?	Thank you for your comment. While there were limited data on specific substance use disorders (e.g., opioids), the results section of the Main Report, and the accompanying appendix tables, provide details about the specific types of substance use disorders examined in the included studies.
109	11	Lines 34-38: I would expand on this sentence for clarity. I would frame it in the same way as the prior sentence to show how many studies examined each of these aspects.	Thank you. We revised the statement accordingly.
110	11	Line 48: "some substance use" – what does this mean? SUD or using substances?	Thank you. This sentence has been removed due to other edits.
111	11	Line 55: "patient characteristics" – please provide some examples	We revised the text to provide examples of patient characteristics. "*One study (NRCS) reported a higher incidence proportion of SUD in ADHD people treated with mixed medications (combination of stimulants and other medications).*"
112	11	Lines 57-58: I'm unsure we can make this claim, based on the evidence, re: "more severe forms of ADHD" unless the study reported that the additional medication was prescribed specifically the augment the stimulants effects.	Thank you. We have edited this sentence in the Executive Summary and Main Report to say: *"Therefore, it is possible people who received mixed medications may represent those with other comorbidities that may increase the risk of SUD."*
113	11	X: Lines 10-13: Doesn't this just mean that findings were mixed? If you want to report how many were significantly different vs. not significantly different for specificity's sake, you can do that in a parenthetical. How this is currently worded is somewhat confusing.	Thank you; we have updated this sentence to state "mixed findings."
114	11	Line 11: "prioritized outcomes" – define.	The "prioritized outcomes" were those identified by our operational

Comment Number	**Reviewer Number**	**Comment**	**Author Response**
			partners during the development of the review protocol. We have updated this language to "*outcomes of interest*."
115	11	Lines 15-16: But are they using similar types of measures which can provide some insight – e.g., symptom severity measures?	You are correct that these provided insight into change; however, it was challenging to interpret findings across studies since different measures were used to assess symptom change. For instance, some studies used self-reported measures of symptom change, while some studies used observer reported measures. Further some measures were specific to symptom type and measures were further complicating the interpretation across studies.
116	11	Line 19: "substance use" – define.	Thank you for this comment. Outcomes of substance use varied widely across studies. To keep the executive summary succinct, we have not provided details of these definitions here. Interested readers will be able to find the full details of the different substance use outcomes on pages 23-25 of the main report and Tables H9 and I5 of the appendix.
117	11	Line 25: consider suggestion the development of guidelines for providers, not suggesting VA policy. I am unsure if I would advocate for VA-wide policy which would impact a provider's practice in this way.	We agree and have revised the text accordingly. *"Given the increasing rates of ADHD diagnoses in the Veteran population, the VA needs to provide guidance and education is necessary for clinicians treating ADHD."*
118	11	Lines 26-30 (i.e., Fears that the use of stimulant medications in adults with ADHD can lead to a new SUD diagnosis or precipitate substance-related	Thank you for this comment. We have updated the Key findings to

Comment Number	Reviewer Number	Comment	Author Response
		problems in dually-diagnosed individuals appear not to be broadly supported by the evidence. Although no study was explicitly conducted in Veterans or the VA, many of the findings and conclusions likely translate to the VA."): consider putting this piece into your key findings.	include a *Clinical Implications* section that more explicitly states this point.
119	11	Lines 48-49: Given that the follow-ups range from 3-19 years, it actually seems like we're missing the more proximal time period following the stimulant prescription - in the months and year after initiation.	Thank you for this comment. We revised the Discussion to comment on the timing of follow-up. *"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."*
120	11	Lines 54-55: The primary findings surrounding a stimulant use disorder was not made clear earlier in the overview.	Thank you. We revised the text (executive summary, results and discussion) to note that studies addressing KQ 2 predominantly included people with ADHD and co-occurring stimulant use disorder.
121	11	XI: Lines 20-21: This seems to contradict the first sentence.	Thank you. This text has been changed due to other edits.
122	11	Page 4, Line 53: Consider providing citations for the reviews. Can you also provide an overview of what they found specific to SUD, even if it was not the full focus of the review?	The text now references the systematic reviews we referred to the sentence.
123	11	Page 5, Line 10: "alcohol misuse" was included – I thought this was only including SUD?	Thank you. This has been corrected to "abuse."
124	11	Page 9: Why was data excluded pre-1994? I would consider providing a rationale.	We have included the following text in the methods to address note our rationale for excluding studies pre-1994: *"Because of this, we excluded studies published before 1994 based on the publication date of the DSM-IV."*