TITLE: Abuse and Misuse Potential of Drugs for Attention Deficit/Hyperactivity Disorder: A Review of the Clinical Evidence

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CONTEXT AND POLICY ISSUES

Attention Deficit Hyperactivity Disorder (ADHD) is the neurobehavioral disorder occurring in 5% to 12% of school-aged children in Canada.[1] Males (8% to 10%) have higher risk than females (3% to 4%) to have ADHD under the age of 18 years.[1] About 80% of children with ADHD continue to have ADHD in adolescence and over 60% will maintain some core symptoms of ADHD into adulthood.[1] The prevalence of ADHD in adults ranged from 3.5% to 4.5%.[2] The medications for ADHD include stimulants (amphetamine and methylphenidate) and non-stimulants (atomoxetine).[3] The stimulant drugs come in long- and short-acting forms, and both have been shown to be clinically effective in treatment of ADHD symptoms depending on the method of use.[3] Likewise, evidence has shown that 70% of children with ADHD given atomoxetine had significant improvement in their symptoms.[3]

Recent literature has indicated that stimulant ADHD medications have potential abuse liability.[4] As the prescriptions of ADHD stimulants increased, the misuse of a stimulant medication has also been growing over the past two decades.[2] There are concerns that greater access to prescription stimulant medication could lead to potential misuse in the general population.[5] Undergraduate university student populations have been the prime focus of many studies since these young adults believe that stimulant ADHD medications can help to improve their study skills and to help them cope with stressful factors in their educational environment.[2] However, little is known about the potential misuse or abuse of ADHD medications, both stimulant and non-stimulant forms, among children, adolescents or adults.

The aim of this report is to review the evidence for abuse and misuse potential of drugs for ADHD among children, adolescents or adults.

RESEARCH QUESTIONS

1. What is the clinical evidence for the potential misuse or abuse of atomoxetine?
2. What is the clinical evidence for the potential misuse or abuse of methylphenidate?
3. What is the clinical evidence for the potential misuse or abuse of amphetamine-based ADHD drugs?

KEY FINDINGS

No conclusions can be drawn regarding the abuse potential of atomoxetine due to the limited data available. Misuse of methylphenidate and amphetamine-based ADHD drugs was found in adolescent and young adult population, particularly among undergraduate university students. Misuse of ADHD stimulants also occurred in non-institutionalized adults. The prevalence of stimulant misuse among studies ranged from 5% to 35% in adults and from 5% to 12% in adolescents.

There was evidence for potential diversion of stimulant ADHD medication from individuals with prescriptions to individuals without prescriptions.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2013, Issue 7), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2003 and July 23, 2013.

Selection Criteria and Methods

One reviewer screened citations to identify publications that met the inclusion criteria. Potentially relevant articles were retrieved based on the review of titles and abstracts. Full-text articles were considered for inclusion based on the selection criteria listed in Table 1.

Table 1: Selection Criteria

Population	Any (Children, teens or adults)
Intervention	ADHD drugs, any formulation (e.g. extended release, controlled release, immediate release): • Atomoxetine (Strattera) • Amphetamine-based drugs (Lisdexamfetaminedimesylate [Vyvanse], amphetamine mixed salts [Adderall], Dextroamphetamine sulfate [Dexedrine]) • Methylphenidate (Ritalin, Biphenitin, Concerta)

Comparator	• Atomoxetine (Strattera) • Amphetamine-based drugs (Lisdexamfetaminedimesylate [Vyvanse], amphetamine mixed salts [Adderall], Dextroamphetamine sulfate [Dexedrine]) • Methylphenidate (Ritalin, Biphenitin, Concerta) • No comparator
Outcomes	Drug abuse, illicit use, misuse, non-medical use (e.g. study aid), drug diversion, addiction potential
Study Designs	Health technology assessments/ systematic reviews/ meta-analysis, randomized controlled trials, non-randomized studies (including case studies, case series)

Exclusion Criteria

Articles were excluded if they did not satisfy the selection criteria, or were full text articles published prior to January 2003. Individual studies were excluded if they were described in a systematic review or meta-analysis included in this report.

Critical Appraisal of Individual Studies

Key methodological aspects relevant to each study design were appraised and summarized narratively. The SIGN checklists were used to critically appraise systematic reviews[6] and controlled trials.[7] The other included studies were critically appraised using the checklist designed by the Center for Evidence-based Management.[8]

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 290 citations. Upon screening titles and abstracts, 270 citations were excluded and 20 potentially relevant articles were retrieved for full-text review. Of the 20 potentially relevant reports, six were excluded. Of the excluded studies, two were reviews and four were found in the included systematic review. One systematic review, one randomized controlled trial (RCT) and 12 observational studies met the inclusion criteria. The process of study selection is outlined in the PRISMA flowchart (Appendix 1).

Summary of Study Characteristics

One systematic review, one RCT and 12 observational studies met the inclusion criteria (Appendix 2).

The systematic review[9] included 21 studies having a total 113,145 participants. The studies were self-reported surveys (76%), chart reviews (5%), direct structured interviews (5%), and both survey and direct structured interviews (15%). The studies included children, adolescents and university students with an age ranging from 10 to 24 years. The systematic review evaluated the use, misuse, and diversion of ADHD stimulants (amphetamine and methylphenidate) in individuals with and without ADHD.

The RCT[10] assessed the abuse potential of atomoxetine in 40 male and female (32 to 53 years old) drug abusers compared to methylphenidate and phentermine as positive controls and

desipramine and placebo as negative controls. The study was a randomized, double-blind, double-dummy, crossover inpatient laboratory study. Each medication was given as a single dose in random order separated by at least 48 hours. The drugs and doses tested were placebo, atomoxetine 45, 90 and 180 mg, desipramine 100 and 200 mg, phentermine 60 mg, and methylphenidate 90 mg. Subjective and physiological effects were collected for 24 hours following each drug treatment. The sample size was chosen to produce 90% power to detect an effect size of 0.8.

Of the 12 included observational studies, there was one case study,[11] one interview,[12] four retrospective database or file reviews,[13-16] and six web-based surveys.[17-22] The study populations included undergraduate students from US universities in five web-based survey studies[17-20,22] and in one interview-based survey.[12] Retrospective database reviews involved adolescents aged 13 to 19 years from the American Association of Poison Control Centers[13] and from the Texas Poison Center Network.[14,15] One Canadian study retrospectively reviewed the files of 450 adolescents seen at the Addiction Center in Calgary, Alberta.[16] Nine studies[11-18,22] assessed misuse-related outcomes for ADHD stimulant medications including methylphenidate and/or amphetamine-based drugs, two studies did not specify the type of ADHD medication,[19,20] and one study evaluated both ADHD simulants and non-stimulants.[21] The reported outcomes included misuse (nonmedical use),[12,17-22] abuse,[11-16] and diversion[18,20-22] of ADHD medications.

Summary of Critical Appraisal

Study strengths and limitations are presented in Appendix 3.

The reporting of the methodology used to conduct the systematic review[9] was poor, thus it was difficult to assess the overall quality of the review. Although the review clearly stated the study inclusion criteria and partially provided the characteristics of the included studies, there was no information on whether there was a protocol, or pre-determined published research objectives. Methods of study selection and data extraction, literature search strategies, list of excluded studies, and quality assessment of the included studies were not provided.

The RCT[10] was a single site, randomized, double blind and crossover trial. There was no indication of concomitant treatment and the only difference between groups was the treatment under investigation. All relevant outcomes were measured in a standard, valid and reliable way. However, it is unclear if the study addressed an appropriate and clearly focused question. The concealment method was not reported. Since there were 13% of participants who dropped out, it was unclear if the intention-to-treat analysis was applied. The trial was funded by industry.

All the included observational studies,[12-22] with the exception of the case report,[11] addressed a clearly focused question and assessed statistical significance. Five studies[14,15,19,21,22] provided confidence intervals for the main results. The method of selection of the subjects was clearly described in nine studies.[12-18,21,22] The measurements in four studies[13,15,18,21] were likely to be valid and reliable. The findings of most studies lacked generalizability and there was only one study[21] whose sample of subjects might be representative to the population to which the findings were referred. There was no pre-determined sample size and it was unclear if the response rate was satisfactory achieved in all included studies. Three studies[11,16,17] did not report the source of funding, eight studies[12-15,18-20,22] received public funding and one study[21] was sponsored by industry.

Summary of Findings

Details of the results of the systematic review, RCT and the observational studies are available in Appendix 4. The reported outcomes were classified and defined as follows:[9] The term "*misuse*" was defined as using ADHD medications not prescribed to the individual or using ADHD medications differently than they were prescribed, often referred as nonmedical use or illicit use of ADHD stimulants. The term "*abuse*" referred to overuse leading to clinically significant impairment or distress. The term "*diversion*" was defined as transfer (selling, trading or giving away) of ADHD medications from an individual who does have a prescription to another individual who does not have a prescription. In addition, the context of stimulant misuse, abuse and diversion was examined in relation to demographic features (sex, race, socioeconomic status), psychiatric and substance abuse disorder, medication preference, route of administration, co-administration with other illicit drugs, and from whom the drugs are obtained.

Misuse

In the systematic review,[9] past year prevalence of stimulant misuse ranged from 5% to 9% for grade school and high school students. Canadian students in grades 7 to 12 used non-prescribed methylphenidate (6.6%) and amphetamine (8.7%), and US students in grades 6 to 11 (5%) reported lifetime ADHD stimulant misuse.

From the systematic review and the observational studies included in this report, misuse of ADHD stimulants among university students ranged from 5%[9,19,22] to 35%.[9,17] The prevalence of misuse of ADHD stimulants among university students who had prescriptions for ADHD medication ranged from 31% to 49%.[12,18,20] Commonly prescribed medications were Adderall and Concerta.[18]

A self-administered internet survey of 4,297 civilian, non-institutionalized US adults aged 18 to 49 years old revealed that 7.1% reported nonmedical use of any ADHD medication at least once in their lifetime.[12] In this study, 4.3% of adults aged 18 to 25 and 1.3% of adults aged 26 to 49 were among those who used ADHD medication nonmedically. Misuse of long acting (5.4%) products was more prevalent than short acting (2.1%) products.

A retrospective file review[16] of substance-abusing adolescents (12 to 18 years) seen at the Addiction Centre between 1993 to 1999 in Calgary found that 23% (105/450) reported nonmedical use of methylphenidate or dextroamphetamine. Of those who had a prescription for ADHD medication, 44% (38/87) reported nonmedical use.

Abuse

In the RCT,[10] the results from DRUG Rating Questionnaire-Subject showed that there were no statistically significant differences in terms of "liking" the drug, between any atomoxetine dose and placebo. Methylphenidate and phentermine were "liked" significantly ($P<0.05$) more than placebo, atomoxetine or desipramine. The Addition Research Center Inventory showed that methylphenidate significantly ($P<0.05$) increased the measured euphoria score compared to atomoxetine, desipramine or placebo. From the Drug Identification Questionnaire, 64% and 44% of subjects identified methylphenidate and phentermine as a stimulant, respectively, while 10% to 20% of subjects identified each dose of atomoxetine, desipramine and placebo as a stimulant. From the Street Value Assessment Questionnaire, methylphenidate, phentermine and desipramine had significantly ($P<0.05$) higher street value than atomoxetine or placebo. The

authors of the study concluded that "*Atomoxetine has significantly less abuse liability than methylphenidate or phentermine and no greater abuse liability than desipramine.*"

Between 1998 and 2005 at the American Association of Poison Control Centers,[13] cases related to adolescent abuse of ADHD medication rose 76% over 8-year period while ADHD medications rose 80%. Specifically, amphetamine/dextroamphetamine-related calls to the Poison Control Center increased 476% per year while prescriptions of those medications increased 133% per year. Methylphenidate related calls decreased 30% per year, while prescriptions increased 52% per year.

Data from six poison control centers of Texas during 1994 to 2004 showed that 8.5%[15] and 12%[14] of the calls involved abuse of methylphenidate and amphetamine (Adderall) among adolescents, respectively.

A retrospective file review of 450 adolescents seen at the Addiction Centre in Calgary between 1993 and 1999 found that 6% were diagnosed as abusers of methylphenidate or dextroamphetamine.[16]

One case report[11] described a 23-year-old Caucasian female with comorbid ADHD and poly substance abuse who admitted to ingesting six times the prescribed dose (54 mg) of Concerta (methylphenidate) in order to "get high". The patient also admitted that, with a dose of 18 mg of Concerta, she experienced cravings and positive stimulant effects.

Diversion

There was evidence that individuals with ADHD prescriptions were approached to give, sell, or trade their medications. Studies in the systematic review[9] showed that 16% of grade school and high school students and 23% of university students with diagnosed ADHD were asked to give, sell or trade their medications. Of the high school students having ADHD prescriptions, 15% gave them away, 7% sold them, and 4% had their medications stolen. Among university students with ADHD and prescriptions, 29% had sold their medications.[9]

Web-based surveys of university students who had a prescription for ADHD medication showed that 54%[22] to 56%[20] reported being approached by a peer to give or sell their medication, and 26%[20] reported giving or selling their medication. Students who had misused ADHD medication were more likely to divert their medication than those who had not (59% vs. 22%).[20] The source of medication for those who did not have prescriptions were friends, peers or family members.[21,22]

Context

The systematic review[9] reported that there were sex differences in stimulant misuse. Men reported more misuse than women. There was higher incidence of misuse among whites and Hispanics than African Americans and Asian Americans. Individuals with ADHD symptoms were at higher risk of misuse of stimulants. There was higher risk of misuse of stimulants in junior and senior high school students if other students in the classroom had been prescribed ADHD stimulants. Preferred misused stimulants included methylphenidate, amphetamine, d-amphetamine and mixed amphetamine. Most misuse of stimulants was by oral administration, although 38% to 40% was intranasal administration. Individuals with psychiatric disorders or substance abuse issues often misused or diverted stimulants.

From the systematic review and many web-based surveys of university students, the common reasons for ADHD stimulant misuse were academic reasons, i.e., to improve study skill, (33% to 89%)[9,12,17,18,20] and non-academic reasons including to "get high" (9% to 22%)[9,12,18,20] or use with

alcohol or illicit drugs (17% to 30%).[9,18,20] High substance use and attention problems were predictors of ADHD medication misuse.[9,18,19] Compared to non-misusers, misusers were more likely to consume alcohol (97% vs. 77%) and marijuana (53% vs. 27%).[20] Although oral administration was the main route of stimulant misuse among university students (75.5%), nasal inhalation also occurred in this population (13.8%). Of the three most prevalent types of prescription, inhalation was most frequent with methylphenidate (17.3%), followed by amphetamine/dextroamphetamine (13.1%), and methylphenidate XR (3.8%).[12]

The motivation for nonmedical use among civilian non-institutionalized adults included productivity (40%), staying awake (23%), to "get high" (13%), for tension relief (10%), for fun (5%), and to facilitate alcohol use (1%).[21] In this population, 68% of ADHD nonmedical misusers were more likely to use illicit drugs including cocaine (20%), marijuana (26%) and alcohol (53%).[21] Most nonmedical users never had a prescription and common sources of ADHD medications were from friends and family members.[21]

Data from six poison control centers of Texas revealed that the incidence of abuse-related calls of amphetamine[14] and methylphenidate[15] was high in males (57% and 62%, respectively) and adolescents (69% and 55%, respectively). Frequent exposure sites for amphetamine and methylphenidate were own residence (68% and 77%, respectively) and school (22% and 15%, respectively). The route of administration for methylphenidate was mostly by ingestion (92.5%), followed by inhalation (6.8%) and parenteral (2.5%) routes.[15] Calls related to ADHD medication abuse had more serious medical outcomes than non-abuse calls. A retrospective file review of 450 adolescents seen at the Addiction Center in Calgary found that abusers were more likely to be out of school or have eating disorders than non-abusers.[16] Methylphenidate and dextroamphetamine were the seventh most commonly used substances.[16]

Limitations

The results of the systematic review[9] must be interpreted in light of the fact that there was limited information presented on the characteristics of the individual studies and poor reporting of methods to conduct the review. Most studies were of survey design, which may have potential risks of bias. Due to substantial heterogeneity of the study population, the systematic review narratively described the results of each individual study without providing overall point estimates for the rates of diversion, misuse and abuse. The systematic review was further limited by the publication date of the included studies. It included studies from 1995 to 2006, and mainly focused in adolescents and young adults who misused and diverted ADHD stimulant medications including amphetamine and methylphenidate. There was no information regarding the ADHD non-stimulant drug, atomoxetine.

The RCT[10] had several limitations. The sample size was relatively small (N=40) although it was indicated that the sample size was chosen to produce 90% power to detect an effect size of 0.8, based on previous studies of methylphenidate and phentermine. With respect to comparators, methylphenidate and phentermine were used as positive controls for atomoxetine, rather than amphetamine which is the most commonly misused ADHD medication among students. In addition, the study only examined single doses of active drugs. It is unclear if atomoxetine might result in greater "liking" and abuse if it was used repeatedly. The study was conducted in stimulant abusers whose findings might not be informative to predict misuse and abuse of medication in ADHD patients prescribed therapeutically.

The findings of many of the web-based surveys and direct interviews of university students might lack generalizability as these samples were convenience samples, not random samples,[12,17,19,20] and were from one or two universities in the US.[12,17-20,22] The numbers of

respondents were much smaller than the numbers initially invited.[17,19,20] It is therefore unclear if the participants represent the true population of students with prescribed ADHD medication. Similarly, the low number of respondents relative to the number of e-mail invitations raises concerns about selection bias in the self-administered internet survey of civilian, non-institutionalized adults.[21] Because of the self-reported design, recall and non-response bias might occur and students who reported misuse of ADHD medication might also be more likely to report the use of illicit drugs. The use of marketing names, rather than street names, of ADHD medication in the study surveys might have potential of underreport of ADHD medication use.

The data accuracy and completeness of abuse cases from retrospective database review cannot be verified.[13-15] The findings therefore cannot be generalized to the adolescent population. The sample in the retrospective file review of adolescents seen in the Addiction Center in Calgary might not represent substance-abusing adolescents in general since 95% of the individuals had comorbid psychiatric disorders.[16]

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The potential misuse and abuse of ADHD medications was evaluated in one systematic review, one RCT and 12 observational studies which met the inclusion criteria.

The prevalence of misuse or abuse of methylphenidate or amphetamine among junior school and high school students ranged from 5% to 12%, and among undergraduate university students or other adults ranged from 5% to 35%. Both individuals with and without ADHD misused ADHD medications.

Individuals with ADHD prescriptions were approached to sell or give away their medications. Sources of ADHD medications for those who did not have prescriptions were friends, peers or family members. The motivation for nonmedical use included both academic and nonacademic reasons.

Information on the abuse potential of atomoxetine was limited to one laboratory based clinical study of acute drug exposures. Atomoxetine was found to have less abuse liability than methylphenidate in this short term study.

The results of the included studies should be interpreted with caution as many studies had several limitations regarding the study design and sample selection, which may bias the results and impact the generalizability of the findings. No conclusions can be drawn regarding the abuse potential of atomoxetine due to the limited data available.

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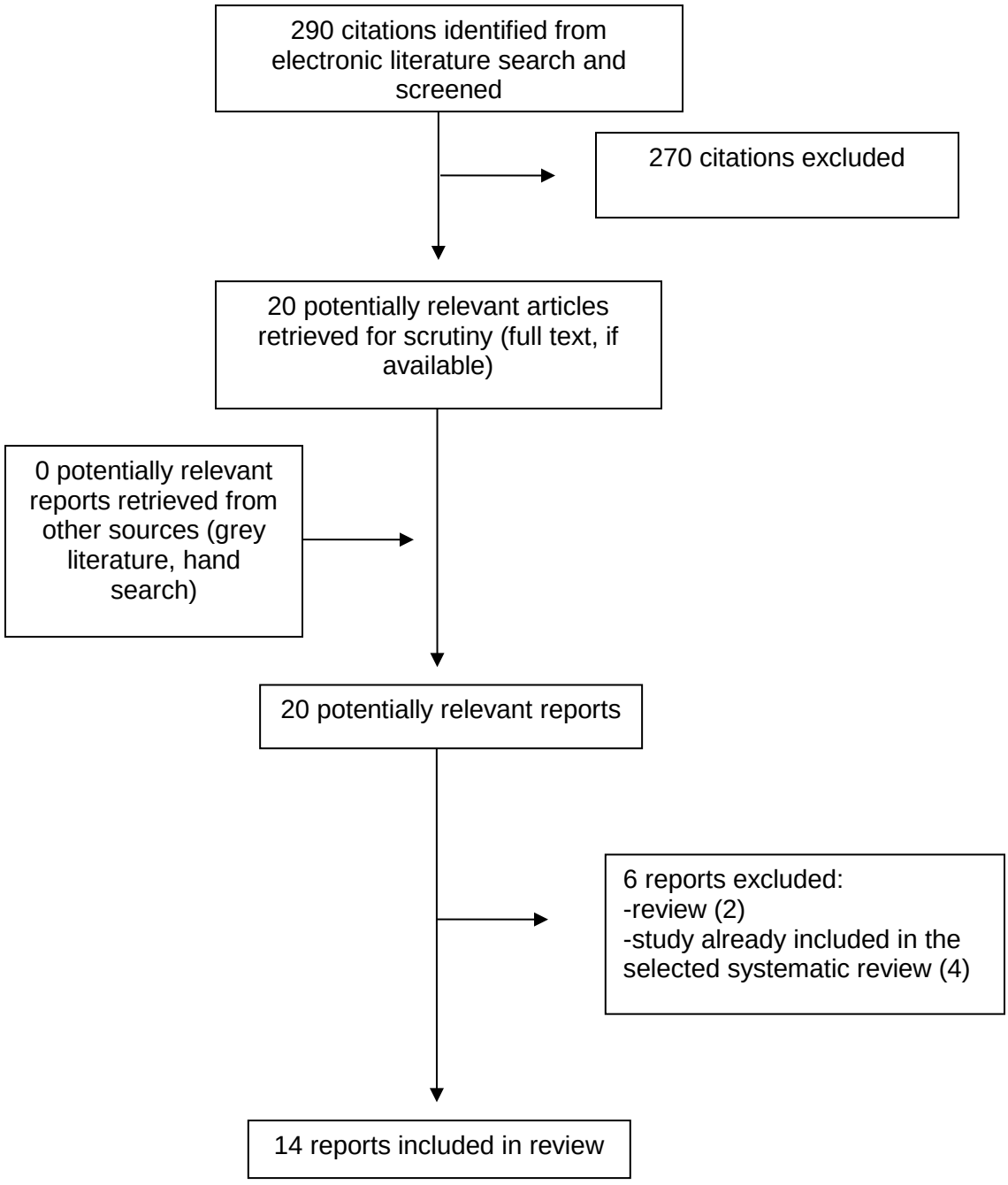
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Clinical Studies

Table 1: Summary of Systematic Review

Author, year, study design, funding source	Key inclusion criteria, N studies	Interventions	Outcomes
Wilens et al., 2008[9] Public funding	English-language articles assessing use, misuse, abuse, and/or diversion of ADHD stimulant medications methylphenidate or amphetamine in children, adolescents, or adults. Not included studies had cocaine or methamphetamine N=21 (113,145 participants)	ADHD stimulants (methylphenidate or amphetamine)	• Use • Misuse • Abuse • Diversion
ADHD=attention-deficit/hyperactivity disorder			

Table 2: Summary of included studies

Author, year, type of study, country, funding source	Inclusion and exclusion criteria	Interventions	Key Outcomes
Randomized Controlled Trials			
Jasinski et al., 2008[10] Randomized, double-blind, double-dummy, crossover USA Funded by manufacturer	• Adults (32 to 52 years), current abusers of psychomotor stimulants including cocaine and/or amphetamine Exclusion criteria • Cytochrome P_{450}2D6 (CYP2D6) poor metabolizers of atomoxetine • Psychiatric disorders • Dependence on benzodiazepines, opiates, or alcohol	Placebo, atomoxetine (45, 90, and 180 mg), desipramine (100 and 200 mg), phentermine 60 mg, and methylphenidate 90 mg. In patient laboratory consisting of 8 sessions separated by at least 48 hours.	• Subjective effects (questionnaires for drug rating, drug identification, specific drug effects, addiction, street value assessment) • Physiological effects (blood pressure, pulse rate before and after dosing)
Observational studies			
Peterkin et al., 2011[17] Web-based survey USA No report on source of funding	• Students (18 to 30 years) of George Mason University, North Virginia during January 2009. 190 surveys	ADHD medications (Ritalin, Concerta, Adderall)	Link between ADHD medication misuse and a positive screen for adult ADHD symptoms
Rizkallah et al., 2011[11] Case report Canada Not applicable	• Not applicable	Concerta (methylphenidate)	Report on incidence of abuse of Concerta

Author, year, type of study, country, funding source	Inclusion and exclusion criteria	Interventions	Key Outcomes
Sepulveda et al., 2011[18] Web-based survey USA Public funding	• Undergraduate university students • Random sample (n=1,738)	Prescribed stimulant medication for ADHD (Ritalin, Dexedrine, Adderall, Concerta, methylphenidate)	• Misuse • Diversion • Use with alcohol or other drugs
Rabiner et al., 2010[19] Web-based survey USA Public funding	• Undergraduate students (n=843) from one private and one public university	ADHD medication (not specified)	• Nonmedical ADHD medication use
Rabiner et al., 2009[20] Web Survey USA Public funding	• Undergraduate students (n=115) from one private and one public university	Prescribed ADHD medication (not specified)	• Misuse • Diversion
Setlik et al., 2009[13] Retrospective (database) USA Public funding	• American Association of Poison Control Center's National Poison Data system for the years 1998-2005 for all cases involved people aged 13 to 19 years	Prescribed stimulant ADHD medication (amphetamine/dextroamphetamine or methylphenidate/d-methylphenidate)	• Exposure • Prescriptions • Abuse

Author, year, type of study, country, funding source	Inclusion and exclusion criteria	Interventions	Key Outcomes
Arria et al., 2008[12] Interview USA Public funding	• First year university students (17 to 20 years), n=1,253	Prescription stimulants for ADHD (amphetamine/dextroamphetamine, or methylphenidate)	• Nonmedical ADHD medication use • Overuse • Association with illicit drug use
Forrester 2007[14] Retrospective (database) USA Public funding	• Data from the six poison control centers of the Texas Poison Center Network (Toxicall software and Toxic Exposure Surveillance System database)	Adderall (amphetamine)	• Abuse
Novak et al., 2007[21] Web-based survey USA Funded by manufacturer	• Non-institutionalized civilian adults aged 18 to 49 (n=4,297) living in the United States	Prescribed ADHD medication (stimulants and non-stimulants)	• Non-medical use • Diversion • Non-medical use in combination with selected drugs
Forrester, 2006[15] Retrospective (database) USA Public funding	• Data from the six poison control centers of the Texas Poison Center Network (Toxicall software and Toxic Exposure Surveillance System database)	Methylphenidate	• Abuse

Author, year, type of study, country, funding source	Inclusion and exclusion criteria	Interventions	Key Outcomes
McCabe et al., 2006[22] Web-based survey USA Public funding	• Undergraduate university students of a large public Midwestern university in 2003 • Random sample of 9,161 undergraduate students	Prescription stimulants for ADHD (Ritalin, Dexedrine, Adderall, Concerta)	• Medical use • Illicit (non-medical) use • Diversion
Williams et al., 2004[16] Retrospective file review Canada No report on source of funding	• Substance-abusing adolescents (n=450) with comorbid mental health problems from the Addiction Centre in Calgary	Methylphenidate, dextroamphetamine	• Abuse
ADHD=attention-deficit/hyperactivity disorder			

APPENDIX 3: Critical Appraisal of Clinical Studies

Author, year, type of study	Strengths	Limitations
Systematic reviews		
Wilens et al., 2008[9] Public funding	• Study inclusion and exclusion criteria were clearly stated • Characteristics of included studies were provided	• Unclear if a protocol or research objectives were developed a priori • Methods for literature search, selection, extraction and quality assessment not reported • No assessment of publication bias was provided
RCTs		
Jasinski et al., 2008[10] Funded by manufacturer	• Randomization was used to determine treatment order • Double blind design • A period of 48 hours in between treatments was adequate for washout • All relevant outcomes were measured in a standard, valid and reliable way	• Unclear if the study address appropriate and clearly focused question • 13% of participants dropped out before completing study. • Unclear if intention to treat analysis was applied • Single center study with limited sample size (N=46) • Based on single dose exposure to drugs
Observational studies		
Peterkin et al., 2011[17] Web-based survey No report on source of funding	• The study addressed a clearly focused question • The method of selection of the subjects is clearly described • Statistical significance was assessed	• Unclear if the research method was appropriate for answering the research question • The way the sample obtained could introduce bias • The sample of subjects might not be representative of all college students • No pre-determined sample size • Unclear if the response rate was satisfactory achieved • Unclear if the questionnaires were likely to be valid and reliable • Confidence intervals for the main results were not given • No account for potential confounding factors • Unclear if the results can be applied to other university settings

Author, year, type of study	Strengths	Limitations
Rizkallah et al., 2011[11] Case study	•	• Single case report
Sepulveda et al., 2011[18] Web-based survey Public funding	• The study addressed a clearly focused question • The research method was appropriate for answering the research question • The method of selection of the subjects was clearly described • The measurements were likely to be valid and reliable • Statistical significance was assessed	• The way the sample obtained could introduce bias • The sample of subjects might not be representative of all college students • No pre-determined sample size • Unclear if the response rate was satisfactory achieved • Confidence intervals for the main results were not given • No account for potential confounding factors • Unclear if the results can be applied to other university settings
Rabiner et al., 2010[19] Web-based survey USA Public funding	• The study addressed a clearly focused question • Statistical significance was assessed • Confidence intervals for the main results were given	• Unclear if the research method was appropriate for answering the research question • The method of selection of the subjects was not clearly described • The way the sample obtained could introduce bias • The sample of subjects might not be representative of all college students • No pre-determined sample size • Unclear if the response rate was satisfactory achieved • The measurements were not likely to be valid and reliable • No account for potential confounding factors • Unclear if the results can be applied to other university settings

Author, year, type of study	Strengths	Limitations
Rabiner et al., 2009[20] Web Survey USA Public funding	• The study addressed a clearly focused question • Statistical significance was assessed	• Unclear if the research method was appropriate for answering the research question • The method of selection of the subjects was not clearly described • The way the sample obtained could introduce bias • The sample of subjects might not be representative of all college students • No pre-determined sample size • Unclear if the response rate was satisfactory achieved • The measurements were not likely to be valid and reliable • Confidence intervals for the main results were not given • No account for potential confounding factors • Unclear if the results can be applied to other university settings
Setlik et al., 2009[13] Retrospective (database) USA Public funding	• The study addressed a clearly focused question • The method of selection of the subjects was clearly described • The measurements were likely to be valid and reliable • Statistical significance was assessed	• Unclear if the research method was appropriate for answering the research question • The way the sample obtained could introduce bias • The sample of subjects might not be representative to the population to which the findings were referred • No pre-determined sample size • Confidence intervals for the main results were not given • No account for potential confounding factors • Unclear if the results can be applied to the adolescent population

Author, year, type of study	Strengths	Limitations
Arria et al., 2008[12] Interview USA Public funding	• The study addressed a clearly focused question • The research method was appropriate for answering the research question • The method of selection of the subjects was not clearly described • Statistical significance was assessed	• The way the sample obtained could introduce bias • The sample of subjects might not be representative to the population to which the findings were referred • No pre-determined sample size • Unclear if the response rate was satisfactory achieved • Unclear if the measurements were likely to be valid and reliable • Confidence intervals for the main results were not given • No account for potential confounding factors • Unclear if the results can be applied to the other university settings
Forrester 2007[14] Retrospective (database) USA Public funding	• The study addressed a clearly focused question • The method of selection of the subjects was clearly described • The measurements were likely to be valid and reliable • Statistical significance was assessed • Confidence intervals for the main results were given	• Unclear if the research method was appropriate for answering the research question • The way the sample obtained could introduce bias • The sample of subjects might not be representative to the population to which the findings were referred • No pre-determined sample size • No account for potential confounding factors • Unclear if the results can be applied to the adolescent population

Author, year, type of study	Strengths	Limitations
Novak et al., 2007[21] Web-based survey USA Funded by manufacturer	• The study addressed a clearly focused question • The research method was appropriate for answering the research question • The method of selection of the subjects was clearly described • The way the sample obtained could minimize bias • The sample of subjects might be representative to the population to which the findings were referred • The measurements were likely to be valid and reliable • Statistical significance was assessed • Confidence intervals for the main results were given	• No pre-determined sample size • Unclear if the response rate was satisfactory achieved • No account for potential confounding factors • Unclear if the results can be applied to the general population
Forrester, 2006[15] Retrospective (database) USA Public funding	• The study addressed a clearly focused question • The method of selection of the subjects was clearly described • The measurements were likely to be valid and reliable • Statistical significance was assessed • Confidence intervals for the main results were given	• Unclear if the research method was appropriate for answering the research question • The way the sample obtained could introduce bias • The sample of subjects might not be representative to the population to which the findings were referred • No pre-determined sample size • No account for potential confounding factors • Unclear if the results can be applied to the adolescent population

Author, year, type of study	Strengths	Limitations
McCabe et al., 2006[22] Web-based survey USA Public funding	• The study addressed a clearly focused question • The method of selection of the subjects is clearly described • Statistical significance was assessed • Confidence intervals for the main results were given	• Unclear if the research method was appropriate for answering the research question • The way the sample obtained could introduce bias • The sample of subjects might not be representative of all college students • No pre-determined sample size • Unclear if the response rate was satisfactory achieved • Unclear if the questionnaires were likely to be valid and reliable • No account for potential confounding factors • Unclear if the results can be applied to other university settings
Williams et al., 2004[16] Retrospective file review Canada No report on source of funding	• The study addressed a clearly focused question • The method of selection of the subjects was clearly described • Statistical significance was assessed	• Unclear if the research method was appropriate for answering the research question • The way the sample obtained could introduce bias • The sample of subjects might not be representative of substance-abuse adolescents • No pre-determined sample size • Unclear if the response rate was satisfactory achieved • Confidence intervals for the main results were not given • No account for potential confounding factors • Unclear if the results can be applied to all adolescents

APPENDIX 4: Summary of Results of Clinical Studies

Author, year, type of study, country, funding source	Results	Comments
Systematic Review		
Wilens et al., 2008[9] USA Public funding	<u>Stimulant Misuse:</u> • Prevalence: 5% to 9% for grade and high school children; 5% to 35% in university students. • Canadian students in grade 7 to 12 had used non-prescribed methylphenidate (6.6%) and amphetamine (8.7%). • US students in grade 6 to 11 (5%) reported lifetime stimulant misuse. • Case reports from a poison center revealed a three-fold increase in methylphenidate–related adverse experiences in adolescents between 1993 and 1999. • 5% of undergraduate university students had stimulant misuse and abused other substances concomitantly. • White males, students in fraternities/sororities, and students with lower grade point averages often had lifetime use history (6.9%) and past-month use history (2.1%) of prescription stimulants. • 17% of university students reported ever having misused methylphenidate. • 35% undergraduates in a psychology class reported stimulant misuse (methylphenidate or amphetamine) without a prescription within the past year. • Of those university students misusing non-prescribed methylphenidate, 70% used recreationally and 30% used for studying (lifetime use). • From the National Survey on Drug Use and Health, 0.9% of the 12- to 17-year-old group and 1.3% of the 18- to 25-year-old group had misused ADHD stimulants non-medically within the past year. • Females were as likely as males to report stimulant misuse, whites had greater misuse rates than African Americans, and metropolitan	Narrative review without meta-analysis Type of studies: mostly surveys Age group: adolescents and young adults <u>Limitations</u>: Did not provide overall rates of diversion, misuse and illicit use, as well as quantifiable predictors and correlates.

Author, year, type of study, country, funding source	Results	Comments
	areas more so than rural areas. Diversion: • 16% of grade and high school students were asked to give, sell, or trade their medications. 4% had their medications stolen. • 23% of university students with diagnosed ADHD were approached to give, sell, or trade their medications. • Of the high school students having ADHD prescriptions, 15% gave them away, 7% sold them, and 4% had medications stolen. • Of the students prescribed methylphenidate, 24% had given, 19% had sold their medication, and 6% had medication coerced or stolen. • Among adults with ADHD, 11% had sold their medications during the past 4 years. • Adults with ADHD who misused (escalating dose) or skipped their stimulants to use other drugs or alcohol were more likely to divert (sell) their medications. • Among university students with ADHD and prescriptions, 29% had sold their medications in their lifetime. Context: • There were sex differences in stimulant misuse. Men reported more misuse than women. Female stimulant misusers were more likely to develop dependence than male users. Rates of stimulant misuse patterns were similar in males and females. • Higher incidence of misuse among whites and Hispanics than African Americans and Asian Americans. • Individuals with higher baseline ADHD symptoms (independent of a former diagnosis) were at higher risk for misuse of stimulants. • Motivations for misusing of stimulants among university students included to concentrate, to improve alertness, to “get high”, and to experiment.	

Author, year, type of study, country, funding source	Results	Comments
	• There was a higher risk for misuse of stimulants in junior and senior high school students if other students in the classroom were prescribed stimulants. • Preferred misused stimulants included methylphenidate, amphetamine, d-amphetamine and mixed amphetamine. • Most misuse of stimulants was by oral administration, although 38% to 40% reported intranasal administration. • Individuals who misuse or divert stimulants may have other psychiatric disorders such as conduct disorder and/or substance abuse.	
Authors' conclusions: "*the available literature suggests that consistent misuse and diversion of stimulants is occurring in adolescent and young adult samples often in the context of academic performance and substance abuse and is often linked with academic performance or their euphoric properties.*"		
Randomized Controlled Trial		
Jasinski et al., 2008[10] Randomized, double-blind, double-dummy, crossover study USA Funded by manufacturer	Drug Rating Questionnaire-Subject: • Methylphenidate and phentermine were "liked" significantly ($p<0.05$) more than placebo, atomoxetine, or desipramine (judged by drug "liking" scores). • No statistically significant treatment differences between any atomoxetine dose and placebo. • "Liking" scores for atomoxetine were similar or lower than desipramine. Addition Research Center Inventory: • Methylphenidate and phentermine significantly ($p<0.05$) increased MBG score (measure of euphoria) compared to atomoxetine, desipramine and placebo. Drug Identification Questionnaire: • 64% and 44% of subjects identified methylphenidate and phentermine as stimulant, respectively. • 10% to 20% of subjects identified each dose of atomoxetine, desipramine and placebo as stimulant. Street Value Assessment Questionnaire: • Methylphenidate, phentermine and desipramine	Population consisted of 46 male (76%) and female (24%), age from 32 to 53 years, current drug abusers including cocaine and amphetamines. 40 completed the study Limitations: Small sample size; use methylphenidate and phentermine as positive controls, rather than D-amphetamine; the study examined only acute doses of active drugs (if use repeatedly, atomoxetine might

Author, year, type of study, country, funding source	Results	Comments
	had significantly ($p<0.05$) higher street value than placebo. • No atomoxetine dose was valued significantly differently than placebo. <u>Specific Drug Questionnaire-Subject</u>: • Placebo: feeling relaxed (28%) • Desipramine: feeling relaxed (31% to 46%) and sleepy (37% to 38%) • Methylphenidate: feeling relaxed (57%), full of energy (45%), surrounding seemed different or unreal (48%). • Atomoxetine: feeling relaxed (40% to 54%), sleepy (28% to 34%) <u>Physiological effects</u>: • Methylphenidate and atomoxetine 180 mg had significantly increased heart rate compared to placebo. • All active medication doses had significantly higher blood pressure (systolic and diastolic) compared to placebo	result in greater liking and abuse); study was conducted in stimulant abusers whose findings might not be informative to predict misuse of medication in patients prescribed therapeutically.
Authors' conclusions: "*Atomoxetine has significantly less abuse liability than methylphenidate or phentermine and no greater abuse liability than desipramine.*"		
Observational Studies		
Peterkin et al., 2011[17] Web-based survey USA No report on source of funding	<u>Misuse</u>: • 45 (24%) of students surveyed misused ADHD medications; 29 (64%) males and 16 (36%) females. <u>Misuse related to ADHD symptoms</u>: • 32 (70%) of 46 students screened positive for ADHD symptoms misused ADHD medications. • 13 (9.7%) of 134 screened negative for ADHD misused ADHD medications. • Misusers who had ADHD (71%); non-misusers who had ADHD (10%). <u>Context</u>: • Of the 45 total misusers, the common reasons for ADHD medication misuse included "to improve study skill" (89%), "to stay awake" (40%), academic reasons (87%), non-academic reasons (4%). • 34 (76%) of 45 indicated that their grades improved, 10 (22%) indicated that their grade	190 university students (18 to 30 years); 184 used for analysis Male (52%), female (48%) <u>Limitations</u>: Sample was not simple random (convenience sample); prevalence was at high end and may not reflect the national prevalence of ADHD medication misuse.

Author, year, type of study, country, funding source	Results	Comments
	did not change, and 1 (2%) indicated that his or her grades lowered.	
Authors' conclusions: "*ADHD stimulant misuse in college students is found to be stronger linked to having symptoms of adult ADHD. The desire for cognitive performance enhancement in college students may be a form of self-treatment for undiagnosed ADHD."*		
Rizkallah et al., 2011[11] Case report Canada Source of funding not specified	Patient was admitted to an inpatient detoxification facility in Montreal for rehabilitation and psychiatric stabilization. Patient was then diagnosed to have ADHD and was treated with methylphenidate (Concerta 18 mg and then 54 mg) and was transferred to another facility. Two weeks later, patient had signs of intoxication (nausea, severe lateral headache, agitation, blurred and double vision). <u>Abuse</u>: • Patient admitted to ingest six times the prescribed dose (54 mg) of Concerta in order to "get high." • Patient admitted that, with a dose of 18 mg of Concerta, she experienced cravings and positive stimulant effects.	23-year-old Caucasian female with poly substance abuse (alcohol, amphetamine, cocaine, cannabis) <u>Limitations</u>: Only one case
Authors' conclusions: "*Concerta misused was detected in an adult patient with comorbid ADHD and substance use disorder… This case report reveals possible misuse of long-acting stimulant preparations and suggests that cravings and subjective positive stimulant effects can be felt even at a low dosage of a long-acting stimulant preparation.*"		
Sepulveda et al., 2011[18] Web-based survey USA Public funding	<u>Misuse</u>: • 22 (49%) of 55 students reported misuse of prescribed ADHD stimulants. • Commonly prescribed medications were Adderall and Concerta. <u>Diversion</u>: • 18 (33%) of 55 reported diversion. • Misusers (12 of 22; 55%) were more likely to divert their prescribed stimulants than non-misusers (6 of 33; 18%), p<0.01. • Adderall and Adderall XR were most often diverted (n=12). <u>Context</u>: • Reasons of misuse: to get high (9%), intentional use with alcohol or other drugs (19%)	55 past-year prescribed stimulant users were identified from a random sample (n=1,738) at a large Midwestern research university; males (60%) females (40%) <u>Limitations</u>: Small sample (n=55) of past-year prescribed stimulant users may impact the generalizability of the findings;

Author, year, type of study, country, funding source	Results	Comments
	• 13 (59%) of 22 past-year misusers had active symptoms of ADHD. • Cigarette smoking, alcohol use (binge drinking), cocaine use, and illicit drug use were more common in misusers than non-misusers.	potential of survey nonresponse bias as there were students did not respond to the survey; recall bias might occur; students who reported misuse of ADHD medication might be also more likely to report the use of illicit drugs.
Authors' conclusions: "*There is a strong relationship between misuse of prescribed stimulants for ADHD and substance use behaviors, as well as other deleterious behaviors such as diversion. These findings suggest the need for close screening, assessment, and therapeutic monitoring of medication use in the college population*."		
Rabiner et al., 2010[19] Web-based survey USA Public funding	Misuse (nonmedical use): • 45 (5.3%) of students surveyed reported in the second survey that they had misused ADHD medication since beginning college (onset non-prescriber users). Context: • High substance use and attention problems were predictors of non-medical ADHD use.	843 undergraduates of a private and public university in southeastern US. Males (39%), females (61%), Caucasian (70%) Two surveys: 1st time during 1st semester freshman and a 2nd time during the 2nd semester of sophomore year Non-medical use = use without prescription, misuse Limitations: Lack of generalizability as sample was from two universities; the number of students who initiated nonmedical use is

Author, year, type of study, country, funding source	Results	Comments
		small; potential underreported due to lack of inclusion of street manes of ADHD medication.
Authors' conclusions: "*Attention difficulties contribute to the onset of nonmedical ADHD medication use in a significant minority of nonmedical users. These students may begin using ADHD medication to address attention problems they experience as undermining their academic success.*"		
Rabiner et al., 2009[20] Web Survey USA Public funding	Misuse: • 36 (31%) of 115 students prescribed ADHD medications reported having their medication at a higher dose or more often than prescribed, or using someone else's medication since beginning college. Diversion: • 64 (56%) of 115 reported being approached by a peer to give or sell their medication. • 30 (26%) of 115 reported giving or selling their medication • Students who had misused ADHD medication were more likely to divert their medication than those who had not (59% vs. 22%). Context: • 9 (7.8%) of 115 reported using through nasal administration. • Common reasons of misusing medication included to concentrate (63%), to study longer (63%), to feel less restless while studying (48%), to concentrate better in class (33%), to feel less restless in class (26%), and to feel better (22%). • Most common adverse effects from misusing ADHD medication were appetite reduction (74%), sleep difficulties (63%) and irritability/headache (50%). • 34 (30%) of 115 used ADHD medication in conjunction with alcohol and 19 (17%) of 115 used in conjunction with marijuana. • Compared to non-misusers, misusers often had higher rates of hyperactive impulsive symptoms (3.49 vs. 3.13, p<0.06), but did not report	115 university students had prescription for ADHD medication Males (31%), females (69%) Misuse = use larger or more frequent doses, or use someone else's medication Limitations: Sample from two universities (generalizability unknown); unclear if the participants represent true population of students with prescribed ADHD medication; unclear if students had ADHD though self-reported diagnosis.

Author, year, type of study, country, funding source	Results	Comments
	higher levels of attention difficulties (3.98 vs. 3.75, p=0.24). • Compared to non-misusers, misusers were more likely to have consumed alcohol (97% vs. 77%, p<0.01) and marijuana (53% vs. 27%, p<0.01); rates of cocaine use and cigarette use were similar.	
Authors' conclusions: "*Although most students used their medication as prescribed, misuse and diversion is not uncommon. Because enhancing academic performance was the primary motive for misuse, the results raise questions about whether undergraduates with ADHD perceive their treatment as adequate and the extent to which physicians and students communicate about issues related to medication adjustments.*"		
Setlik et al., 2009[13] Retrospective (database) USA Public funding	Abuse: • Cases related to adolescent abuse of prescription ADHD medication rose 76% from 330 to 581 over 8-year period. • Over same time period, sales data show that ADHD prescriptions for 3- to 19-year-olds rose 80%. • Amphetamine/dextroamphetamine-related calls increased 476% from 71 to 409 per year, while prescriptions for those medications increased 133% per year. • Methylphenidate-related calls decreased 30% from 246 to 172 per year, while prescriptions increased 52% per year. • More boys (1 death, 49 major effects) had severe ingestion effects than girls (3 deaths, 9 major effects).	Cases related to teenagers exposed to prescription ADHD medication between 1998 and 2005 at the American Association of Poison control Center Limitations: Cases might be underreported; data accuracy and completeness cannot be verified; findings cannot be generalized to the teenaged population; no incidence data or the absolute value was provided, but instead, only trends that are thought to be occurring in this age group.
Authors' conclusions: "*The sharp increase, out of proportion to other poison center calls, suggests a rising problem with teen ADHD stimulant medication abuse. Case severity increased over time. Sales data of ADHD medications suggest that the use and call-volume increase reflects availability, but the increase disproportionately involves amphetamine.*"		
Arria et al., 2008[12]	Misuse (nonmedical use): • Of the 1253 students surveyed, 45 had	1253 university students completed

Author, year, type of study, country, funding source	Results	Comments
Interview USA Public funding	prescribed ADHD medication and 1208 had no ADHD prescription. • 15 (33%) of 45 students with prescribed ADHD medication used prescription stimulants non-medically. • 218 (18%) of 1208 students without prescribed ADHD medication used prescription stimulants non-medically. • Commonly misused drugs were amphetamine/dextroamphetamine (89.3%), methylphenidate (25.8%), methylphenidate XR (13.8%). [correlated with the rates of prescriptions] Context: • Reasons for nonmedical use were to concentrate studying (73.3%), curiosity (17.8%), to get high (6.7%), to enhance wakefulness while partying (8.9%), and peer pressure (4.9%). • Administration through nasal inhalation: methylphenidate (17.3%), amphetamine/dextroamphetamine (13.1%), methylphenidate XR (3.8%). • Nonmedical use of prescription stimulants was associated with alcohol (OR 1.8; 95% CI 1.2 to 2.8) and marijuana (OR 4.0; 95% CI 2.3 to 7.0) dependence.	2 h interview during an eight-month period of their 1st academic year. Males (49%), females (51%), white (72%). Misuse = Nonmedical use, over use, or use someone else's medication Limitations: Sample from single university; students might underreport drug use behaviors during interview; students in the non ADHD group might have ADHD if they received clinical assessment.
Authors' conclusions: "*Physicians should be vigilant for possible overuse and/or diversion of prescription stimulants among ADHD+ patients attending college, as well as the co-occurrence of illicit drug use with nonmedical use of prescription stimulants (NPS). Initiation of comprehensive drug prevention activities that involve parents as well as colleges to raise awareness of NPS and its association with illicit drug use.*"		
Forrester 2007[14] Retrospective (database) USA Public funding	Abuse: • Of the 3152 human exposures of Adderall, 391 (12%) calls involved abuse. Context: • Drug abuse calls were high in males (57%) and adolescents (69%). • Frequent exposure sites included own residence (68%) and school (22%). • Compared with nonabuse exposures, drug	Data from six poison control centers of Texas All abuse calls involving Adderall (amphetamine) during 1998-2004 Limitations:

Author, year, type of study, country, funding source	Results	Comments
	abuse calls were more likely to involve exposures at another residence (6% vs. 3%), school (22% vs. 5%) and public areas (2% vs. 0.4%). At own residence, the rates was 90.5% and 67.7% for nonabuse exposures and abuse exposures, respectively. • Adverse events were neurological, cardiovascular and gastrointestinal. Adderall abusers had more serious medical outcomes than non-abusers.	Lack of generalizability due to missing or incomplete data; potential bias from a retrospective database review.
Authors' conclusions: "*Adderall abusers are more likely to be adolescents. Adderall abuse as compared to other exposures is more likely to occur outside of the person's home and involve more serious medical outcomes.*"		
Novak et al., 2007[21] Web-based survey USA Funded by manufacturer	<u>Misuse (nonmedical use)</u>: • 7.1% US adults (18 to 49 years) used nonmedically any ADHD medication at least once in their lifetime. • Misuse was reported among 4.3% of adults aged 18 to 25 versus 1.3% of adults aged 26 to 49. • Misuse of long acting products (5.4%) was more prevalent than short-acting (2.1%) agents. <u>Diversion</u>: • For those did not have prescriptions, common sources of ADHD medications were friend and family members (66%), stolen medication from friends, family or other sources (34%). • Other sources included fraudulent prescriptions from doctors (20%), internet (5%) <u>Context</u>: • 68% of nonmedical abusers were more likely to abuse illicit drugs including cocaine (20%), marijuana (26%) and alcohol (53%). • Higher rates of nonmedical use were observed in those who had prescriptions for ADHD medications, although most nonmedical users never had a prescription. • Common sources of ADHD medications were friends and family members. • Motivations of nonmedical use included	Self-administered internet survey of civilian, non-institutionalized adults (N=4,297) aged 18 to 49 in US. Nonmedical use of prescription ADHD medications. <u>Limitations</u>: Validity of self-reported drug use over internet is questioned; concerns about selection bias from low number of respondents relative to number of e-mail invitations; lack of generalizability as many nonmedical abusers may be more unlikely to report.

Author, year, type of study, country, funding source	Results	Comments
	productivity (40%), staying awake (23%), to "get high" (13%), for tension relief (10%), for fun (5%), or to facilitate alcohol use (1%).	
Authors' conclusions: "*Because most prescriptions ADHD medications currently are highly regulated, policy options for supply-side reduction of nonmedical use may include identifying those medications with lower abuse liability for inclusion on insurance formularies. Patient and physician education programs also may be useful tools to heighten awareness on intentional and unintentional diversion of ADHD medications for nonmedical purposes.*"		
Forrester, 2006[15] Retrospective (database) USA Public funding	Abuse: • Of the 3789 human exposures of methylphenidate, 322 (8.5%) calls involved abuse. Context: • Drug abuse calls were high in males (62%) and adolescents (55%). • Frequent exposure sites included own residence (77%) and school (15%). • Compared with nonabuse exposures, drug abuse calls were more likely to involve exposures at another residence (4.3% vs. 2.7%), school (15% vs. 6%) and public areas (2.6% vs. 0.4%). • Administration routes: ingestion (92.5%), inhalation (6.8%), parenteral (2.5%). • Abuse calls had more serious medical outcomes than nonabuse calls (5.8% vs. 2.0%).	Data from six poison control centers of Texas All abuse calls involving methylphenidate during 1998-2004. Limitations: Lack of generalizability due to missing or incomplete data; potential bias from a retrospective database review.
Authors' conclusions: "*Methylphenidate abusers are more likely to be adolescents. Methylphenidate abuse as compared to other exposures is more likely to occur outside of the person's home and to involve more serious medical outcomes.*"		
McCabe et al., 2006[22] Web-based survey USA Public funding	Misuse: • 744 (8.1%) of 9,161 students surveyed had misused prescription stimulants in their lifetime, and 5.0% in the past year (n=458). Diversion: • Of the students who had prescribed ADHD medication, 54% had been approached to sell, trade or give away their medication. • Sources of diversion were friends, peers, family members.	Random sample of 9,161 undergraduate students in a public Midwestern university Males (44%), females (56%) Limitations: Limited in generalizability (one university having

Author, year, type of study, country, funding source	Results	Comments
	Context: • Characteristics associated with misuse ADHD stimulants included undergraduate men and White students, students living in fraternity/sorority houses, off-campus houses/apartments, students with lower GPA, students who had prescribed medication for ADHD. • Compared to nonusers, misusers of prescription ADHD stimulants were more likely to be associated with binge drinking (88% vs. 49%), marijuana use (93% vs. 34%), cocaine use (33% vs. 2%), ecstasy use (27% vs. 2%), and use of hallucinogens (34% vs. 3%).	predominantly White and relatively affluent students); nonresponse bias; recall bias from self-report
Authors' conclusions: "*the present findings suggested a strong relationship between certain prescription patterns of stimulant medication for ADHD and the likelihood for subsequent illicit use of prescription stimulants and other substance use.*"		
Williams et al., 2004[16] Retrospective file review Canada No report on source of funding	Misuse (nonmedical use): • 105 (23%) of 450 substance abusing adolescents reported nonmedical use of methylphenidate or dextroamphetamine. • 38 (44%) of 87 who had a prescription reported nonmedical use of ADHD medications. Abuse: • 26 (6%) of 450 were diagnosed as abusers of methylphenidate or dextroamphetamine. • Common method of administration was through inhalation. Context: • Abusers were more likely to be out of school and have an eating disorder than non-abusers. • Methylphenidate and dextroamphetamine were the seventh most commonly used substances.	450 adolescents (12 to 18 years) seen at the Addition Centre between 1993 and 1999. Limitations: Sample may not represent substance-abusing adolescent in general as 95% of individuals had psychiatric disorders as co-morbid; potential recall bias from self-report
Authors' conclusions: "*The present study found that 23% of adolescents referred for a substance-abuse assessment at an outpatient clinic reported nonmedical use of methylphenidate or dextroamphetamine at some point in their lives*."		
ADHD=attention-deficit/hyperactivity disorder; **CI**=confidence interval; **OR**=odds ratio; **XR**=extended release		