REVIEW

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# Systematic Review: Nonmedical Use of Prescription Stimulants: Risk Factors, Outcomes, and Risk Reduction Strategies

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**Objective:** To review all literature on the nonmedical use (NMU) and diversion of prescription stimulants to better understand the characteristics, risk factors, and outcomes of NMU and to review risk-reduction strategies.

**Method:** We systematically searched PubMed, PsycINFO, and SCOPUS from inception to May 2018 for studies containing empirical data about NMU and diversion of prescription stimulants. Additional references identified by the authors were also assessed for inclusion.

**Results:** A total of 111 studies met inclusion criteria. NMU and diversion of stimulants are highly prevalent; self-reported rates among population samples range from 2.1% to 58.7% and from 0.7% to 80.0%, respectively. A variety of terms are used to describe NMU, and most studies have examined college students. Although most NMU is oral, non-oral NMU also occurs. The majority of NMU is associated with no, or minor, medical effects; however, adverse medical outcomes, including death, occur in some individuals, particularly when administered by non-oral routes. Although academic and occupational performance enhancement are the most commonly cited motivations, there is little evidence that academic performance is improved by NMU in individuals without attention-deficit/hyperactivity disorder.

**Conclusion:** NMU of stimulants is a significant public health problem, especially in college students, but variations in the terms used to describe NMU and inconsistencies in the available data limit a better understanding of this problem. Further research is needed to develop methods to detect NMU, identify individuals at greatest risk, study routes of administration, and devise educational and other interventions to help reduce occurrence of NMU. Colleges should consider including NMU in academic integrity policies.

**Key words:** attention-deficit/hyperactivity disorder, amphetamine, methylphenidate, misuse, abuse

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In the United States, methylphenidate (MPH) and amphetamine (AMP) prescriptions increased 35.5% from 2008 to 2012,[1] with the greatest rates of increase seen in adolescents and adults. Because they enhance alertness and concentration and induce euphoria, these stimulants are associated with abuse, misuse, and diversion[2] and are classified as Schedule II controlled substances.[3] In 2016, the number of individuals aged ≥12 years in the United States who reported initiating nonmedical use (NMU) of stimulants was 1.4 million, which was greater than the number of persons initiating methamphetamine and cocaine combined.[4]

The American Academy of Pediatrics (AAP) and the American Association for Child and Adolescent Psychiatry (AACAP) recommend that all adolescent patients should be assessed for symptoms of substance abuse,[5,6] and clinicians should monitor symptoms and prescription refill requests for signs of misuse and diversion in patients with attention-deficit/hyperactivity disorder (ADHD).[6] Similarly, the National Institute for Health and Care Excellence (NICE) recommends that providers consider the risks of stimulant misuse and diversion when prescribing medications for ADHD.[7]

The US Food and Drug Administration (FDA) defines *abuse* of prescription drugs as "the intentional, nontherapeutic use of a drug product or substance, even once, to achieve a desirable psychological or physiological effect." *Misuse* is defined as "the intentional therapeutic use of a drug product in an inappropriate way and specifically excludes the definition of abuse."[8] *Diversion* is when medication prescribed for one individual is sold, given to, or taken by another individual.[9] *Malingering* is when an individual fakes or exaggerates symptoms to gain some form of reward, for example a prescription.[10] *Nonmedical use* is

the use of a prescription stimulant without a prescription, or in a way other than prescribed. NMU encompasses both abuse and misuse.[11]

This review provides a systematic overview of the NMU of prescribed stimulants across the lifespan. The intent is to consolidate what is known from previous research and reviews, augment with new information, and prioritize issues of importance for clinical practice and future research. We highlight risk factors and motivations for NMU and diversion, as these can aid in the identification of high-risk patients, and the development of more sophisticated approaches to management. We also review what is known regarding approaches to patient and/or parent education, as these can be crucial for the prevention and treatment of NMU and diversion. Finally, we offer suggestions for reducing the NMU and diversion of stimulant medications that can be implemented in clinical practice.

## METHOD

We conducted a systematic literature review following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[12] Our PRISMA checklist and details are provided in Tables S1 and S2, available online.

### Search Strategy

We searched PubMed, PsycINFO, and SCOPUS using these search criteria:

- (ADHD OR "attention deficit" OR "attention-deficit/hyperactivity disorder" OR "attention deficit hyperactivity disorder") AND
- (crushing OR snorting OR insufflation OR inhalation OR injection OR abuse OR misuse OR diversion OR "illicit use" OR "nonmedical use" OR "non-medical use" OR "cognitive enhancement" OR "feigned ADHD" OR "faking ADHD" OR malingering OR neuroenhancement OR neuro-enhancement OR "cosmetic neuropharmacology" OR "cosmetic neuro-pharmacology" OR "weight loss") AND
- (stimulant OR amphetamine OR methylphenidate)

We limited searches to human studies in English. The search was conducted on May 9, 2018; no lower date limit was set. Additional relevant references were assessed for inclusion if identified during the review process.

### Study Selection

Studies regarding the NMU of MPH or AMP and/or diversion, shopping behavior, or malingering of ADHD were included. We excluded studies regarding substance use disorders, mechanism of action, pharmacokinetics, pharmacodynamics, or instrument validation. Case studies, reviews, editorials, comments, letters, guidelines, and results with no abstract available were excluded. Reference titles were reviewed against the inclusion and exclusion criteria by two Masters-level reviewers. Abstracts were reviewed if the title was ambiguous or met the inclusion criteria. Full-text references were reviewed if the abstract met the inclusion criteria. We extracted the following: country; study design; study population; sample size; stimulant types; prevalence of stimulant NMU; diversion; terminology used to define stimulant NMU; source/frequency/route of administration; demographics and characteristics of misusers; risk factors; motivations; outcomes associated with NMU; risk reduction methods; and findings of interest.

## RESULTS

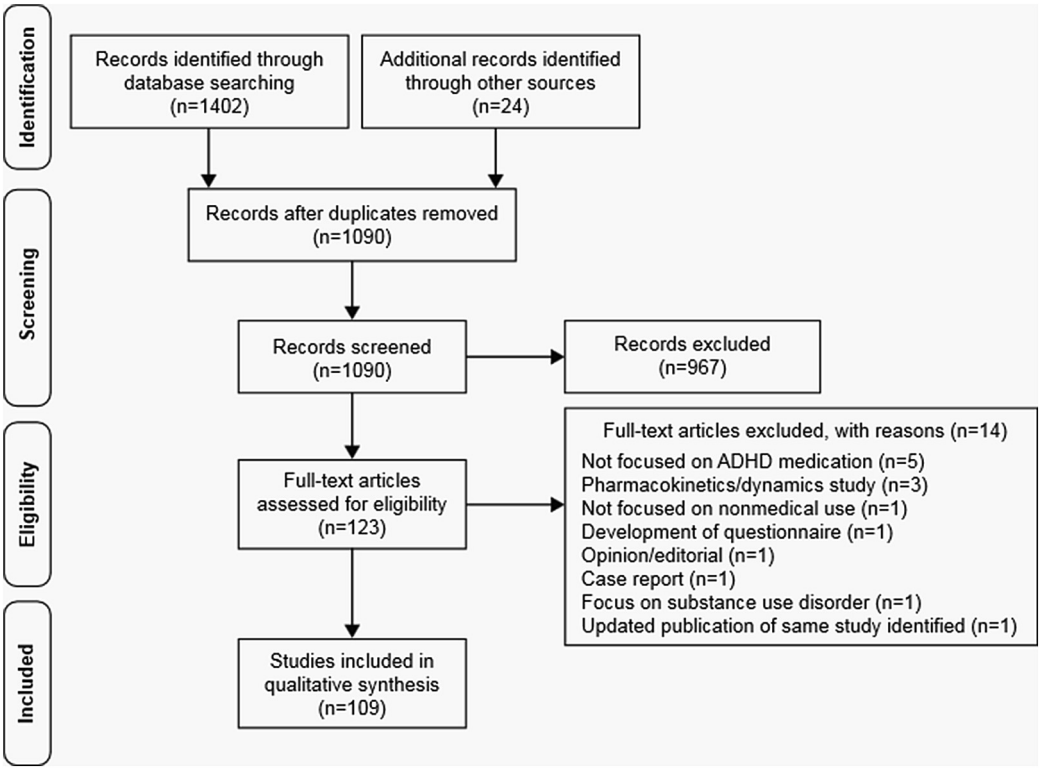
A total of 111 studies[2,9,11,13-120] met inclusion criteria (Figure 1).

### Epidemiology of Stimulant NMU and Diversion

We identified 86 studies addressing the epidemiology of NMU and/or diversion. Self-reported rates of NMU among samples of mainly adolescents and young adults varied dramatically depending on the definitions, methodology, and study population (Figure 2). Most studies used the term NMU, but this term may have referred to misuse, abuse, or both, or it was not clearly defined.[15,27,41,42,67] Several studies focused on diversion, with shopping behavior and feigning ADHD symptoms studied less often. US databases indicated an increase in reports of stimulant NMU during the past 25 years, particularly with AMP.[30,45,46,64,65,71] The only population-based estimate of NMU used data from the 2015–2016 National Survey on Drug Use and Health (NSDUH), finding that ~5 million (2.1%) adults (≥18 years old) had engaged in stimulant NMU at least once in the past year.[2] Details from individual studies are provided online (Tables S1, S2, S3, and S4, available online).

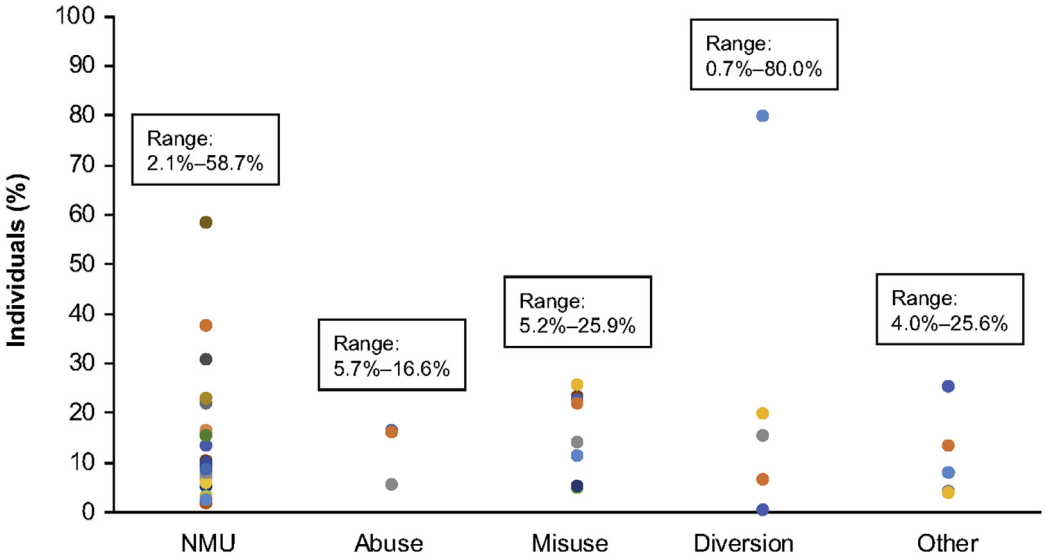
Most individuals who reported NMU (~50%–90%) obtained the medication from family or friends.[15,20,26,27,30,36,37,40,42,50,55,59,73,78,80,105,106,118] College peers are also an often-cited source,[98,101,104,118] although the peer supplying the medication is not always a friend.[118] Many individuals (4%–35%) reported NMU of their own prescription stimulant.[20,26,27,40,69,73,118] Individuals often gave or sold their medications to family or friends.[9,14,44,63,67,82,83,89,108] Finally, some individuals feign ADHD symptoms to receive a prescription from their health care provider.[80] In addition, 20% of US adults reporting past-year NMU indicated that they had obtained prescriptions fraudulently from a doctor.[80]

**FIGURE 1** Selection of Studies




*Note:* *ADHD = attention-deficit/hyperactivity disorder.*

**FIGURE 2** Percentages of Individuals Who Self-Reported Nonmedical Use and Diversion Among Population Samples




*Note:* *Each dot represents the percentage of respondents in each study who reported inappropriate use of stimulants; colors differentiate individual data points. Several references appear more than once because they reported a rate for more than one category and/or reported a rate for multiple age or stimulant-type categories. Terminology used by each study is applied here. Individual study details are available in Table S1, available online.*[9,11,15,18-22,27,31,32,42-44,50,52,54,55,58,61,63,72-77,80,82,84,93,95-100,103,105,109,118]
*NMU = nonmedical use.*

College students often reported that obtaining stimulants is "easy."[101,118] Only in a few studies did students report having even a "slightly difficult" time acquiring the medication.[36,40,104,105] Stimulant medication is often acquired without paying, sometimes through theft. When purchased, the cost is usually low.[13,15,37,105] Respondents infrequently cite a dealer/stranger[26,30,36,40,59,73,106] or the Internet as a source for obtaining stimulants.[30,59,80]

The most frequently reported route of administration is oral (52%–95%).[15,20,26,42,54,78,97,105,115] Among 15,876 adults and adolescents with AMP exposures who contacted the American Association of Poison Control Centers (AAPCC) from 2012 to 2016, a total of 11,923 exposures were classified as abuse. Of these, 93.6% were via oral administration, followed by 5.0% and 1.3% for nasal and intravenous routes, respectively.[115]

Snorting (insufflation) was indicated as a route of administration at least some of the time by 7% to 48% of US college students who reported NMU.[15,19,20,38,42,50,54,55,78,97,105] In one of the above studies, 1% to 6% and 1% to 11% of those reporting NMU endorsed smoking or injecting stimulants, respectively.[27] Similar proportions of oral and non-oral routes of administration were reported among 147,816 adolescents and adults being assessed for substance abuse treatment, with 38% of those reporting NMU endorsing snorting, 10% endorsing injecting, and 3% endorsing smoking.[26]

Based on the estimate that 5 million US adults misused stimulants during 2015 to 2016[2] and the rates of non-oral NMU described above,[27] we can estimate past-year non-oral NMU in US adults. As rates of insufflation range from 11% to 40%,[27] we estimate that ∼550,000 to 2 million US adults snort stimulants each year. Likewise, as smoking and injecting rates range from 1% to 6%[27] and from 1% to 11%, respectively,[27] we estimate that 50,000 to 300,000 and 50,000 to 550,000 US adults smoke or inject stimulants each year.

## Risk Factors and Motivations for NMU of Stimulants

*Risk Factors.* Figure 3 presents statistically significant predictors of past-year or lifetime NMU. NMU is most common among adults aged 18 to 25 years.[27,30] In a study of 4,297 US adults, those aged 18 to 25 years were significantly more likely to report NMU than those aged 26 to 49 years.[80] Among middle and high school students, those in higher grades were more likely to engage in NMU than those in lower grades.[74] NMU of MPH was reported more frequently by students in 10th grade (4.6%) and 12th grade (5%) compared with 8th grade (2.7%), even after controlling for demographic factors.[74] Similar age-related trends have been observed in college-aged students.[22,73]

With some exceptions,[20,74,80] most studies find male students to be at greater risk for NMU than female students, across all age groups.[13,17,22,30,40,42,45,46,48,53,54,73,81,84,91,102] Those who report NMU are more likely to be white.[17,18,20,22,30,40,42,72-74,77,84,102] For example, a survey of 4,572 US high-school seniors found the lifetime prevalence of NMU to be 11.2% among white students, 5.6% among Hispanic students, and 2.9% among African American students.[77] Surveys of 12,237 students in the 8th, 10th, and 12th grades found that white students were 6 times more likely than African American students to report NMU.[74]

There is an inverse correlation between grade point average (GPA) and NMU.[20,73,74] A study of 9,161 college students found that those with GPAs <3.5 had significantly greater odds of misusing stimulants than other students.[73] Longitudinal data show that academic difficulties lead to NMU of stimulants as students try to keep up academically.[18] Among college students, those associated with fraternities or sororities are more likely than others to report NMU.[22,73,84,85,104]

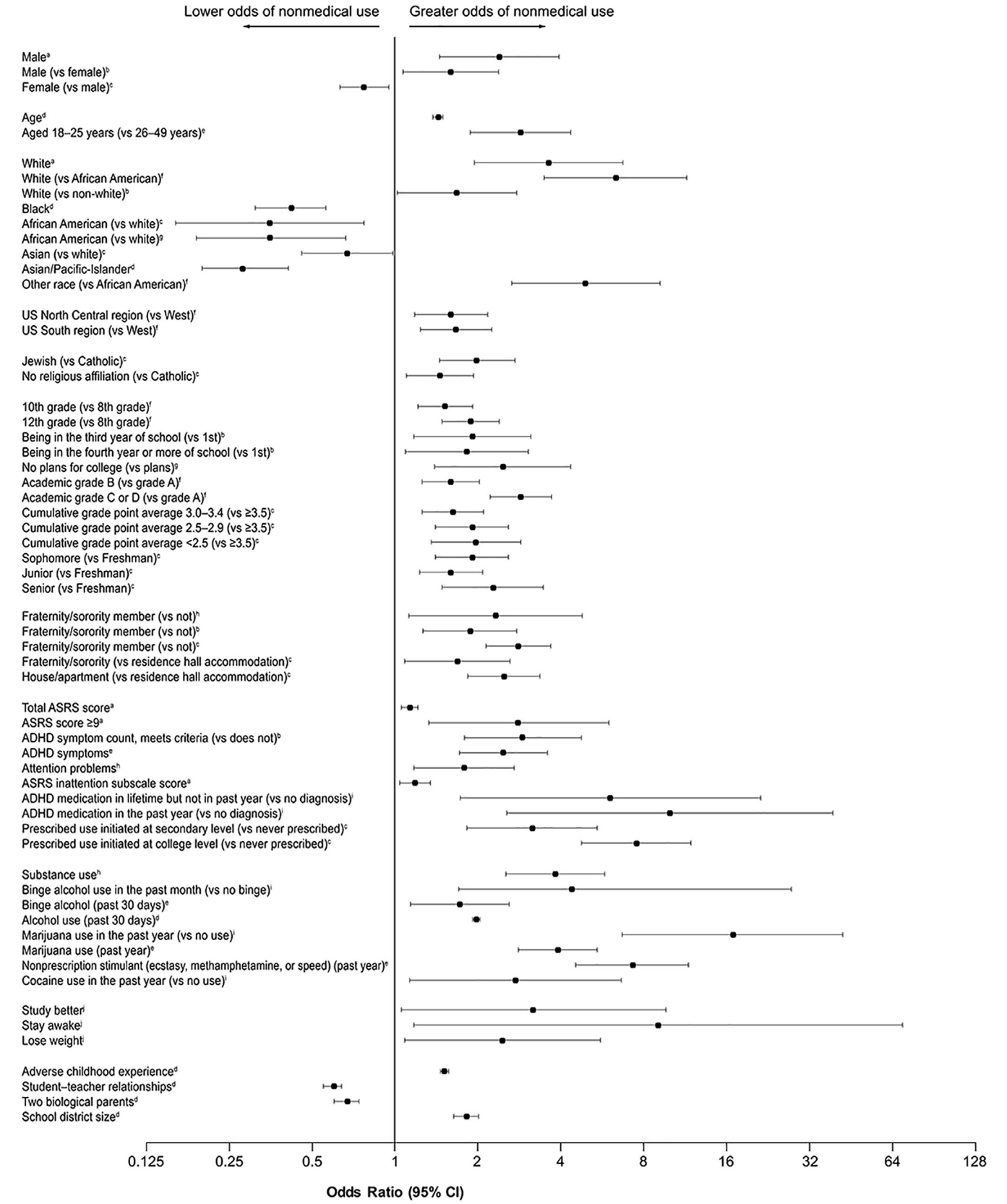
Individuals who report NMU have higher levels of ADHD symptoms than those who do not,[9,17,18,22,57,81,84,99,101,106] although the self-report nature of the data cannot rule out confounding from malingering. A longitudinal study of college students found that 17% of those reporting NMU had high levels of self-reported ADHD symptoms.[17] A national cross-sectional survey of more than 4,000 US adults found similar results. However, a small minority of studies did not find an association between ADHD symptoms and NMU.[55,89,103]

NMU has also been associated with use of other substances and substance-use disorders.[17,18,27,29,31,36,43,50,57,59,72,73,77,83,84,87,89,102,106,108,120] In a population sample of 6,103 adults who reported past-year NMU, concurrent abuse was most frequently reported for alcohol (64.2%), followed by marijuana (43.6%), cocaine (10.6%), tranquilizers/sedatives (8.8%), hallucinogens (8.4%), heroin (2.5%), inhalants (2.3%), and pain relievers (2.1%).[29] A study of 2,203 adolescents and another of 984 college students reported similar results.[18,31]

Some studies have found that individuals who report NMU are more likely to have eating disorders.[51,59,109] For example, among 707 college students without a prescription for stimulants, respondents who used stimulants for weight loss had more symptoms of eating disorders than those who did not.[59]

*Motivations.* Academic motivations were cited by 50% to 89% of college students who reported NMU and were the most common motivations in almost every

**FIGURE 3** Significant Predictors of Prescription Stimulant Nonmedical Use



survey.[13,15,20,22,36,37,40,42,50,53,54,78,81,83,84,94,96-98,101,104,118] The desire to be more productive was cited by 40% of those reporting NMU in a survey of 4,297 US adults.[80] The desire to enhance academic or work performance was cited by 38% to 57% of those reporting NMU among a representative sample of 10,000 US adults.[27] The above figures are in line with the acknowledged motivation for NMU. However, the second most commonly cited reason for NMU is recreation. Approximately 2% to 31% of college students reported "getting high" as a motivation for NMU.[13,15,36,40,49,55,83,97,101,118,120] A survey of 4,580 college students found that 31% of those reporting NMU did so to "get high." This motivation varies by race; in one study, African American students did not report getting high as a motive.[97]

In all, 17% to 31% of college students reported NMU of stimulants because they were curious or wanted to experiment.[15,20,53,97,118] Among college students who reported NMU, other motivations were enhancing the effects of alcohol, enhancing social situations, and helping them socialize.[37,84,101,118] Enhancing wakefulness while partying or going out with friends was also a motivation for NMU among college students.[15,20,36,37,40,42,54,81]

Two surveys of US college students found that among those without ADHD who reported NMU of stimulants (n = 591 and 585), 12%[13] and 4%[40] did so to self-medicate undiagnosed ADHD. A survey of 180 parents found that those with suspected or diagnosed ADHD were 2.6 times more likely to have been tempted to use or to have used their child's stimulants.[9]

Weight loss is also a motivation for NMU, with rates among US college populations ranging from 3.5% to 11.7%.[2,13,58,59] Among 448 US college-aged women who were either at risk for or who had an eating disorder, 17% reported that the primary reason for NMU was controlling their weight or body shape.[51]

### Outcomes of Stimulant NMU

Stimulant NMU is associated with the same adverse effects reported in clinical trials (Table S5, available online).[13,55,83,84] These effects include headache, stomachache, irritability, feeling sad, reduced appetite, sleep difficulties, and dizziness. These effects were slightly higher among prescription holders compared with nonprescription holders. For example, among 299 US college students reporting NMU, the percentage of individuals reporting an unwanted effect was substantially higher among those with a prescription compared with those without a prescription.[55]

*Medical Outcomes.* The NMU of stimulants places a substantial burden on health care facility use.[30,45,46,64,65,71,90,115] Data from the Drug Abuse Warning Network (DAWN) found that the number of emergency room (ER) visits related to NMU by adults increased from 5,212 in 2005 to 15,585 in 2010; there was no increase in visits by children.[71] NSDUH and DAWN data from 2006 to 2011 found that ER visits involving AMP increased by 67% and 156%, respectively. There was not a comparable change in ER visits for MPH; among adolescents, trends remained stable or decreased.[30] A study of 15,629 adults and adolescents with AMP exposures reported to poison control centers found greater rates of admission to health care facilities among individuals who abused versus those who did not abuse AMP.[115] Among those who abused AMP, half of admissions were to a critical care unit.[115]

*Note: ADD = attention deficit disorder; ADHD = attention-deficit/hyperactivity disorder; ASRS = Adult ADHD Self-Report Scale; NMU = nonmedical use.*

[a]*Characteristics associated with persistent NMU of prescription stimulants (at least once per year for 4 consecutive years) in first-time, first-year college students who did not have an ADHD diagnosis (large, public, mid-Atlantic university; N = 112).*[17]

[b]*Characteristics associated with NMU of prescription stimulants in the past year in undergraduate students with and without a stimulant prescription (large, public, southeastern US university; N = 900). Models controlled for comorbid oppositional defiant disorder.*[22]

[c]*Factors associated with illicit use of prescription stimulants (lifetime) in undergraduate students (large midwestern university; N = 9,161).*[73]

[d]*Characteristics associated with NMU of prescription medications for ADHD and ADD in the past year in public-school students (2013 Minnesota Student Survey; N = 1,957). Models adjusted for age, sex, race/ethnicity, poverty status, family structure, past 30-day alcohol use, and school district location/size.*[119]

[e]*Factors associated with NMU of prescription stimulants in the past year in 10,000 US adults (aged 18–49 years).*[27]

[f]*Factors associated with illicit methylphenidate use in the past year in 8th, 10th, and 12th grade US high school students (Monitoring the Future Study; N = 12,237). Analyses controlled for grade level, sex, race, region, academic grade, and urbanicity.*[74]

[g]*Associations with the illicit use (lifetime) of prescription stimulants in middle and high school students (Detroit public schools; N = 1,337). Odds ratios adjusted for all other predictive variables in the model.*[72]

[h]*Predictors of NMU of prescription stimulants in undergraduates (one private and one public university in southeastern United States; N = 843).*[85]

[i]*Correlates of NMU of prescription stimulants in the past year in US adults (aged 18–49 years; N = 4,297). All characteristics listed were included as covariates.*[80]

[j]*Beliefs held about the properties of prescription stimulants associated with NMU of prescription stimulants in undergraduate students without an ADHD diagnosis (private liberal arts college, New England; N = 336).*[25]

**TABLE 1** Medical Outcomes Associated With Exposures to Prescription Stimulants[a]

| Study | Sample Period | Sample Size (N) | Stimulant | Not Followed, n (%) | No Effect, n (%) | Minor Effect, n (%) | Moderate Effect, n (%) | Major Effect, n (%) | Death, n (%) |
|---|---|---|---|---|---|---|---|---|---|
| King *et al.*, 2018[b] [62] | 2000–2014 | 72,267 | MPH | 31,276 (43.3) | 20,948 (29.0) | 10,465 (14.5) | 5,778 (8.0) | 169 (0.2) | 1 (<0.1) |
| King *et al.*, 2018[b] [62] | 2000–2014 | 69,642 | AMP | 22,674 (32.6) | 21,439 (30.8) | 12,232 (17.6) | 7,974 (11.4) | 302 (0.4) | 2 (<0.1) |
| Klein-Schwartz, 2003[c] [64] | 1993–1999 | 12,917 | MPH | — | 7,786 (60.3) | 3,713 (28.7) | 1,385 (10.7) | 33 (0.3) | 0 |
| Klein-Schwartz and McGrath, 2003[d] [65] | 1993–1999 | 759 | MPH | — | 189 (24.9) | 318 (41.9) | 245 (32.3) | 7 (0.9) | 0 |
| Forrester, 2006[e] [45] | 1998–2004 | 189 | MPH | — | 54 (28.6) | 69 (36.5)[g] | 55 (29.1)[g] | 11 (5.8)[g] | 0 |
| Forrester, 2007[f] [46] | 1998–2004 | 244 | AMP | — | 56 (23.0) | 93 (38.1) | 89 (36.5)[g] | 6 (2.5) | 0 |

*Note: Dashes indicate data that were not reported. Intentional exposures include suicide attempt, abuse, misuse, or unknown. AMP = amphetamine formulation; MPH = methylphenidate formulation.*

[a]*American Association of Poison Control Centers National Poison Data System definitions: "not followed" includes those judged as nontoxic exposure and minimal clinical effects possible; "no effect" includes cases with no symptoms as a result of the exposure. The remaining effects are defined as minor (some symptoms, no residual disability or disfigurement), moderate (pronounced, prolonged symptoms), major (symptoms that are life-threatening or produce significant disability or disfigurement), or deaths.*

[b]*Clinical outcomes associated with MPH or AMP intentional and unintentional exposures in children and adolescents aged <20 years.*

[c]*Clinical outcomes associated with intentional and unintentional MPH exposures in children and adolescents.*

[d]*Clinical outcomes associated with MPH abuse exposures (with or without other substances) in adolescents aged 10–19 years.*

[e]*Clinical outcomes associated with MPH abuse exposures in children, adolescents, and adults.*

[f]*Clinical outcomes associated with AMP abuse exposures in children, adolescents, and adults.*

[g]*Denotes statistically significant greater rate of clinical outcomes versus nonabuse exposures.*

Although the majority of stimulant NMU reported to poison control centers was associated with no medical effects or minor toxicity, a notable percentage was associated with adverse medical outcomes (Table 1). Regional and national database analyses found that MPH and AMP were associated with clinically significant effects in approximately 35% of NMU exposures in adolescents.[45,46,65,90] These effects were defined as moderate (pronounced, prolonged symptoms) or major (symptoms that are life-threatening or produce significant disability or disfigurement) and included deaths. The severity of stimulant exposures appears to have increased over time; the percentage of adolescent poison control calls associated with clinically significant effects rose from 30% to 43% from 1998 to 2005.[90]

Data from poison control centers show a significantly greater risk of adverse medical outcomes among adults and adolescents abusing AMP versus nonabusers of AMP. This risk varied by route of administration. For example, the odds of dying were 13 times greater among nasal abusers (3 of 598 died [0.5%]) and 22 times greater among intravenous abusers (2 of 164 died [1.2%]) versus nonabusers (1 of 3,953 died [0.03%]).[115] Mean numbers of adverse medical outcomes were highest for intravenous use (2.95), followed by nasal (2.46) and oral (2.17) use, and by nonabuse exposures (1.57).[115]

*Academic Outcomes.* Although improving academic performance is an often-cited motivation for NMU, stimulant NMU has not been shown to improve academic performance in those without a diagnosis of ADHD.[81] A longitudinal study of 8,362 adolescents found that 35-year-old individuals who reported NMU during adolescence were less likely than others to have earned a college degree. In contrast, the prescribed use of stimulants was not associated with lower educational attainment.[76] In a 2-year study of 898 undergraduates without ADHD, GPAs significantly increased for students who did not engage in NMU but not for those who reported NMU.[16]

## Methods to Reduce the NMU of Stimulants

A survey of 826 US pediatricians found that 46% and 44% reported that they educated adolescent patients on health and legal risks of stimulant NMU "often" or "very often," respectively[33,34]; 40% provided no education regarding diversion and NMU when patients began college.[34] Many pediatricians did not often use prevention strategies, even when they suspected NMU or diversion.[33] However, 89% prescribed long-acting stimulants and 27% prescribed nonstimulants (atomoxetine or α2 agonists) to prevent NMU often or very often, with both percentages increasing when NMU or diversion were suspected.[33] Another study found that 25% and 48% of surveyed physicians did not

feel qualified to educate on the health or legal consequences of NMU and diversion, respectively.[113]

Challenging unrealistic expectations of performance enhancement may reduce NMU.[11] A study of 96 stimulant-naïve college students with at least 2 risk factors for NMU found that challenging the positive expectancies of NMU successfully altered perceptions about stimulant effects, but a deterrent effect was not maintained after 6 months.[111] A single-college study showed that students assigned to read information about the negative academic or health effects of NMU reported the lowest willingness to use stimulants; however, long-term effects on actual use were not measured.[94]

A study of 2,313 college students followed over four semesters found that when health care providers asked their patients about diversion, the students were less willing to engage in the behavior.[38] Thus, it may be beneficial to question college-aged patients if they ever share, or feel pressure to share, their stimulants.[38] This may be particularly helpful for patients at high risk for NMU.[38] In addition, it has been recommended that college students who misuse stimulants be carefully screened for ADHD and substance use disorder, because risk for these conditions may be elevated in students with stimulant NMU.[106]

Very little is known about the effectiveness of institutional policies as a potential tool for addressing the NMU of stimulants. Aikins *et al.*[121] examined the academic integrity policies and alcohol/drug use policies of 200 institutions of higher education. They found 191 academic integrity policies, but only one of these addressed the NMU of stimulants. Among 200 alcohol/drug use policies, 198 addressed the NMU of stimulants. The authors point out that this approach essentially treats NMU only as a legal issue, not as an issue of academic integrity. It is possible that defining NMU of stimulants for cognitive enhancement as a form of academic dishonesty could be a deterrent, but no research has addressed that issue. Also, because the use of stimulants as cognitive enhancers is, in part, a reaction to societal pressures to seek high levels of achievement and to overcome personal shortcomings at all costs,[122] changing this culture of high expectations could reduce the demand for performance-enhancing drugs.

Several studies examined the issue of ADHD malingering in relation to NMU of stimulants. Motivated individuals can fake ADHD by underperforming on psychological measures[112] and overreporting symptoms.[117] Some performance validity tests[110] and symptom validity tests[116] may be reasonably effective at discriminating feigned from genuine ADHD, but this issue has not been adequately investigated to date.

## DISCUSSION

Unlike the current situation with opioid NMU in the United States, the NMU of stimulants has not yet reached epidemic proportions. Nonetheless, the high prevalence and adverse outcomes associated with NMU of stimulants raises concerns for specific subpopulations, especially young adults and college students. Physicians who prescribe stimulants or work with high-risk populations should consider taking preventive measures, especially for high-risk subgroups. Colleges and universities should consider universal education of incoming students. As the publication dates for many of the identified studies indicate, the warning signs of a potential stimulant NMU crisis have been signaling for at least a decade. These signs regarding the prevalence of stimulant NMU, routes of administration, and outcomes are evident in the main findings from this systematic review.

Our review shows that the prevalence of prescription stimulant NMU ranges from 2.1% to 58.7%, depending on study design, population, and definition used. Although NMU often represents sporadic attempts at performance enhancement or brief experimentation, such use carries potentially serious risks, especially for cardiac events among nonmedical users who have not been screened for preexisting cardiac conditions. This concern is supported by data from Poison Control Centers indicating that NMU has been associated with serious health outcomes including critical care hospitalizations, suicide, and other causes of death. Although the most adverse outcomes are rare, trends in NMU suggest they may increase, given that the NMU of AMP has increased over time (although NMU of MPH has remained constant or decreased).

College students have been the most frequently studied population.[37] Data for other age groups and for young adults who do not attend college are lacking. This is an important gap in the literature, because rates of and reasons for NMU vary by age. The sparse data for other young adults and adolescents indicate a substantial prevalence of NMU. We know almost nothing about the NMU of stimulants in older adults. Because advancing age is also associated with cardiovascular disease, it is possible that NMU may lead to a higher rate of adverse medical outcomes in older patients compared with younger patients.

Although most NMU of stimulants is via oral administration, a substantial minority occurs via non-oral routes. Based on the data reviewed, we computed that approximately 550,000 to 2 million US adults administer stimulants intranasally; 50,000 to 300,000 smoke stimulants; and 50,000 to 550,000 inject stimulants.[27] Although relevant supporting data are sparse, non-oral routes of administration appear to greatly increase the risks for severe and/or

potentially catastrophic outcomes.[115] One suspects that non-oral NMU could be a gateway to the non-oral use of illicit drugs, but no data are available to address that issue.

### Using Education to Prevent NMU and Diversion of Stimulants

Patient education is the first-line treatment for NMU and diversion, yet many clinicians do not educate patients about the health or legal consequences of these activities and do not feel qualified to do so.[34,113] There are several goals of patient education. Patients need to learn the medical and legal consequences of diverting their medication or using it in a nonprescribed manner. It may be useful to teach patients with ADHD that diversion of their medications is a felony and that diversion could be fatal when diverted to a person who is medically at risk for cardiovascular disease.

Education about NMU and diversion of stimulants is relevant for all ages. Although young children are unlikely to divert medications, their medications can be diverted and misused by their parents or older siblings. Patients and parents need to learn how to protect their medications (eg, not carrying extra pills, keeping medications hidden and locked away). To reduce diversion, patients can be taught specific responses when friends or siblings request their medications. Patient and parent education benefits from repetition and use of more than one modality (eg, discussions with health care professionals, printed handouts). It is especially important to address these issues just before patients leave for college.

Preventive strategies should also focus on nonpatient populations at risk of NMU, most notably high school and college students and other young adult populations. A major emphasis is to correct common misperceptions about NMU. College students overestimate the prevalence of misuse in peers, which may normalize the behavior and make them more likely to engage in NMU.[20,38,94] The excuse that "everyone is doing it" is simply not true. Also, the message that NMU does not improve academic performance may be helpful. NMU and diversion in college might also be reduced if colleges and universities defined the NMU of stimulants for cognitive enhancement as a form of academic dishonesty, with appropriate sanctions. This approach would potentially be relevant to many students and could be communicated in writing and verbally to all incoming students during orientation.

Two organizations provide free online and downloadable information about misuse and diversion that can supplement educational approaches taken by clinicians or school personnel. Children and Adults with Attention Deficit Hyperactivity Disorder (CHADD) is an ADHD advocacy group that provides information at: chadd.org/for-parents/medication-abuse-and-diversion/. The Coalition to Prevent ADHD Medication Misuse (CPAMM) is a group of organizations representing the medical community, mental health advocacy groups, college administrators, collegiate student leaders, and the pharmaceutical industry; it provides information and printable patient/parent handouts at: cpamm.org/about-us/.

### Prescribing Medications for ADHD When Diversion or NMU of Stimulants Is a Concern

When embedded in an appropriate educational approach, modifications to stimulant therapy can be useful for reducing NMU. One idea is to prescribe long-acting stimulants, which have lower abuse potential than immediate-release stimulants.[33,34] But, because long-acting stimulants are still susceptible to NMU (eg, some individuals may use them for performance enhancement), the nonstimulants (atomoxetine or $\alpha 2$ agonists) should be given a greater priority than they would for the average patient. If an acceptable level of efficacy can be obtained, nonstimulants are ideal because they are typically not diverted or misused.

Our review uncovered several safeguards that prescribers can implement in routine care to reduce the likelihood of NMU of stimulants, although each approach is associated with challenges. Ideally, physicians should implement a medication contract that describes the risks of NMU and diversion and commits the patient to avoiding these problems within the context of a well-defined treatment program. However, managing a medication contract and handling breaches of these commitments can be difficult. Enforcement can be especially effective if implemented by colleges via clearly defined rules. Reducing the number of pills per prescription (eg, weekly versus monthly supplies) decreases the patient's supply for diversion and NMU. However, limiting the number of pills per prescription could also lead to lapses in treatment and would seem to penalize individuals who do not misuse their medications. Using pill counts (when patients should still have pills remaining) can help physicians to detect diversion or NMU, but not in all cases. The AAP recommends that clinicians monitor symptoms and prescription refill requests for signs of misuse and diversion.[6] That is certainly prudent.

Prescription drug monitoring programs (now available in all states) help physicians to identify patients seeking stimulant prescriptions from multiple sources. We do not know of any mandated training initiatives focused on prevention of NMU. One program currently in development aims to produce strategies for primary care providers to reduce the diversion of prescription stimulants.[123] Future

initiatives could help to increase knowledge about NMU and the motivations and personality traits associated with NMU.

### Goals for Future Research

More research is urgently needed. The published literature about the NMU of stimulants is in its infancy. It is almost entirely descriptive, with very little published about the effectiveness of specific interventions to prevent or treat NMU of stimulants or their diversion. We especially need research to study nonpharmacologic approaches to these problems. For example, cognitive behavior therapy modules could be developed to specifically focus on the cognitive and behavioral skills needed to prevent stimulant NMU and diversion.

Future research should adopt the US FDA definitions of abuse and misuse so there is consistent terminology across studies and publications. Furthermore, future work should develop NMU detection tools and should validate interventions designed to mitigate risk. Future work should also develop tools that clinicians could use to screen for NMU. Clinicians need such tools so that prevention and treatment strategies can be targeted to those at highest risk for stimulant NMU. Such tools would likely determine whether patients fit the known risk profile or motivational tendencies for NMU of stimulants and might also aid in detection of malingering. We found no studies of methods or tools specific to identifying stimulant NMU. Such tools would be very useful for clinical work and research, although toxicology screens are available for use when substance abuse is suspected.

Several limitations affect our conclusions. Many studies used self-report questionnaires and/or interviews, which are prone to underreporting because of the stigma and potential negative consequences associated with NMU. Most studies were conducted among college students. Regional and national databases are frequently used to assess NMU, yet they cannot estimate population prevalence.[124] Moreover, these databases lack insights into key details, such as motivation and intent. Data from poison control centers and DAWN provide useful insights but are inherently biased, because all cases analyzed are those in which an individual has contacted the center or has been admitted to a hospital. Thus, individuals who die from stimulant overdoses before contacting emergency services are not entered into these databases, nor are those individuals who are fearful of exposing their NMU or who experience minor unwanted effects.

This review benefits from a broad scope and consolidates the literature on NMU across study designs, countries, and ages. However, this comprehensive approach is also a limitation. Because of the heterogeneity of included studies, a meta-analysis was not appropriate, and comparing studies is difficult. As is the case with all systematic reviews, certain foci in the literature may have been missed by our search strategy.

The NMU of prescription stimulants is highly prevalent. Wide variations in the definition of NMU call for consistent nomenclature and associated changes to surveys and databases to consistently and comprehensively collect data relevant to stimulants. Although stimulant NMU has not reached epidemic levels, many warning signs from prevalence and outcomes studies call for health care professionals, their organizations, colleges and universities, patient advocacy groups, and other stakeholders to address this growing public health problem.

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