BMJ Open

Changes in Medical Use of Central Nervous System Stimulants Among US Adults, 2013-2018, a Cross-Sectional Study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-048528
Article Type:	Original research
Date Submitted by the Author:	30-Dec-2020
Complete List of Authors:	Moore, Thomas; Johns Hopkins University Bloomberg School of Public Health, Epidemiology; The George Washington University Milken Institute of Public Health, Epidemiology Wirtz, Phillip; The George Washington University School of Business, Decision Sciences Kruszewski, Stefan; Johns Hopkins University Bloomberg School of Public Health, Center for Drug Safety and Effectiveness Alexander, G Caleb; Johns Hopkins University Bloomberg School of Public Health, Department of Epidemiology
Keywords:	EPIDEMIOLOGY, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Neurology < INTERNAL MEDICINE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Research

Changes in Medical Use of Central Nervous System Stimulants Among US Adults, 2013-2018: a Cross-Sectional Study

Thomas J. Moore, faculty associate [1,2]; Philip W. Wirtz, professor [3] ; Stefan P. Kruszewski, associate professor [1] ; G. Caleb Alexander, professor [1,4]

Author affiliations:

[1] The Center for Drug Safety and Effectiveness, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

[2] Department of Epidemiology, Milken Institute School of Public Health, The George Washington University, Washington, DC, USA

[3] Department of Decision Sciences, School of Business, The George Washington University, Washington, DC, USA

[4] Division of General Internal Medicine, Johns Hopkins Medicine, Baltimore, MD, USA

Correspondence to: Thomas J. Moore, 916 Prince St, Ste 102, Alexandria VA 22314. (tmoore86@jhmi.edu) ORCID ID 0000-0003-0994-836X

Abstract

Objective To assess the five-year changes in the adult medical use of central nervous system (CNS) stimulants with a substantial risk of dependence and evaluate the population characteristics of users and their medical and/or neurological conditions.

Design Cross-sectional study

Setting Annual US Medical Expenditure Survey, a stratified random sample of approximately 30 000 persons designed to produce national population estimates. It focuses on reported medical spending, use of medical services, population health status, and prescription medications.

Participants Adults age 19 years and older who reported obtaining one or more prescriptions for amphetamine or methylphenidate products during two survey years, 2013 and 2018.

Main Outcomes Measures The number of prescriptions obtained, the specific stimulant product, and the total treatment days of drug supplied.

Results In 2018 an estimated 4.1 million US adults (95% confidence interval 3.4 million - 4.8 million) reported obtaining prescriptions for CNS stimulants, having filled a mean of 7.3 (6.8-7.8) prescriptions with a mean of 226 (210 - 242) days' supply. Compared to 2013, the estimated number of adults reporting using CNS stimulants in 2018 increased by 1.8 million (1.0 million - 2.7 million) or 79.8%. Most 2018 adult stimulant users reported taking psychoactive medication for one or more mental, behavioral. or neurodevelopment disorders. Overall 77.8% (72.6% -

83.0%) reported some medication for adult attention deficit disorder (ADHD), 26.8% (22.2% - 31.5%) took medication for anxiety, 25.1% (19.9% - 30.3%) for depression, and 15.3% (9.8% - 20.8%) indicated drug treatment for other mental or neurological disorders. Adult CNS stimulant use was higher in females, in younger age cohorts, and among individuals of White race/ethnicity compared to their counterparts.

Conclusions and Relevance Adult medical use of prescription stimulants increased markedly in 5 years and occurred in a population often reporting multiple mental or neurological disorders. Further action is needed to better understand and manage this new resurgence in use of drugs with high risks of dependence.

Strengths and limitations of this study

- This study assesses the patterns of use and recent changes in US adult use of prescribed amphetamine and methylphenidate stimulants, widely used psychoactive drugs with a high risk of dependence.
- The source data for this study were extracted from an authoritative annual US health survey with extensive detail about the population, health status, medical treatments, and prescription drug use. Its survey design is intended to permit national population estimates and variance.
- Because the prescriptions are initially identified in household survey interviews, this self-reported use may underestimate actual prescriptions. While prescription data are then verified with pharmacies, respondents may underestimate their use over survey periods.
- Although these prescription stimulants have a decades-long history of diversion and abuse, this survey only captures self-reported medical use.

Introduction

The central nervous system (CNS) stimulants amphetamine and methylphenidate are among the oldest synthetic psychoactive medications still in widespread clinical use. The first amphetamine product (Benzedrine) was first marketed in 1933 for nasal congestion, and in 1937 for depression and narcolepsy;[1] in 1954 the US Food and Drug Administration (FDA) approved a methylphenidate product (Ritalin), which was marketed for depression, senile behavior, lethargy, and narcolepsy.[2]

Amphetamine and methylphenidate are potent and structurally related sympathomimetic amines with therapeutic mechanisms that remain unclear but stimulate the release of dopamine and norepinephrine primarily through inhibition of neuronal reuptake.[3] Currently, a large number of amphetamine products are licensed based on mixtures of various salts (saccharate, sulfate, aspartate), specific enantiomers (d-), extended release formulations, and a prodrug. Methylphenidate has fewer chemical variants, but is available in immediate and extended release formulations, d-enantiomer salt mixtures, and a transdermal patch. Multiple generics and brand name variants are available for both stimulants. Approved and off-label uses of these two CNS stimulants have evolved over the many decades of their use. Medical use for depression and weight loss declined in the 1950s and 1960s and these indications were repealed over concern about growing evidence of misuse and questions about effectiveness.[1] However, beginning in 1961 use in children expanded with FDA approval of indications for treating behavioral problems and later for attention deficit hyperactivity disorder (ADHD).[4] For many years new formulations were approved based on studies of ADHD in children. Starting in 2004 the FDA extended the ADHD indication to adults for some branded stimulants, (Adderall XR, Concerta, Vyvanse) and in 2015 approved a binge eating indication for lisdexamfetamine (Vyvanse).[5–7]

Throughout the decades since initial marketing the two stimulant products were approved for narcolepsy, and during that time off-label use was observed among persons using them to increase alertness or seeking to achieve cognitive enhancement.[8]

Amphetamine and methylphenidate have been long restricted globally because of addiction risks including a United Nations Convention on Psychotropic Substances and specific legal controls in many countries, including the United Kingdom, Canada, and Australia.[9–12] In the US, these stimulants are classified as Schedule II controlled substances, those declared to have "a high potential for abuse which may lead to severe psychological or physical dependence."[13] Other major Schedule II drugs include higher potency opioids and the barbiturates. Restrictions for this highest-risk class of licit psychoactive drugs include a Drug Enforcement Administration (DEA) license to prescribe, limitations on prescribed refills, monitoring at the state and federal levels, and secure pharmacy storage measures to prevent theft and diversion. In addition to risks of misuse and dependence, other adverse events associated with these stimulants include serious cardiovascular reactions, seizures, tics, tremors, aggression, manic symptoms, and psychosis.[5–7,14] Given that the increased use of prescription opioids continued for many years before declining in response to numerous public health initiatives, we examined most recent trends in exposure to the other widely used group of Schedule II drugs, the CNS stimulants amphetamine and methylphenidate.

Methods

We extracted the data for this study from the US Medical Expenditure Panel Survey (MEPS), a healthcare survey of individuals and households conducted annually since 1996 and published for research use by the Agency for Healthcare Research and Quality.[15] To assess change over five years, this study analyzed the 2013 and 2018 annual surveys. MEPS collects

data from a nationally representative sample of approximately 30 000 persons each year, and its multistage probability design supports estimates of population variance. The confidentiality of personal identifying information is protected by federal law and removed before survey data are released for public research use.[16] These de-identified public use data are exempt from review by the Johns Hopkins Bloomberg School of Public Health Institutional Review Board.

Identification of Medications

Population estimates of exposure to prescription drugs in MEPS begin with the household survey questionnaire and are then expanded with more detailed information collected from respondents' pharmacies.[17] Each annual data release contains a prescribed medicines file with records for approximately 325 000 prescriptions and multiple fields identifying the drug prescription detail. We used the following algorithm to standardize medications: if the record contained a National Drug Code, we matched it to the ingredient name in the National Library of Medicine RxNorm database;[18] for prescription records without an NDC we used the Multum Lexicon medication name, which is defined as the generic name most commonly used by physicians.[17] Medication names provided by respondents that were vague or described a class of drugs (e.g., stimulants, antidepressants) were excluded.

For this study we identified persons reporting any use of the following standardized generic medication names: amphetamine/dextroamphetamine, lisdexamfetamine, methylphenidate, and dexmethylphenidate. We excluded CNS stimulants that were not classified as Schedule II (e.g., atomoxetine), or those with utilization that was too infrequent to estimate in the MEPS data (prescription methamphetamine). The extent of each respondent's exposure was measured by calculating the number of prescriptions filled in the survey year and the total annual days' supply reported for these prescriptions. If the days' supply was missing for a prescription

we imputed the median days for that specific drug. For some analyses we also categorized the products into these two groups: amphetamine products and methylphenidate products.

This study population included all persons reporting that they were 19 years of age or older as last ascertained during the survey year. Other assessed population characteristics included sex, race/ethnicity, education, and marital status. Among those reporting exposure to Schedule II CNS stimulants, we also analyzed the mental health, neurological, or developmental conditions for which respondents indicated one or more of the following: (1) They had the condition during the survey year; (2) they took a prescribed medication for the condition; (3) they received medical treatment, defined as an office, outpatient, inpatient, or emergency department visit. The mental health conditions analyzed were identified by the following International Classification of Disease, 10th Revision (ICD-10) codes: ADHD (F90), Major depression (F32), Anxiety (F40, F41), Other neurological or mental conditions (all other ICD-10 codes in "F" series). The mental health condition information in the ICD-10 format was not available for the 2013 year, limiting our analysis to the 2018 survey year data.

Statistical Analysis

We estimated the exposed adult population totals, percentages, and 95% confidence intervals (CI) using the MEPS multistage probability design characteristics for the entire US population. Each survey observation included data on the sampling unit, the sampling stratum, and the specific sample weight for each observation. Populations, variance, and statistical significance within survey years were estimated using Taylor series linearization. Standard errors and confidence intervals were calculated based on the weighted estimates when available. A Z-test of two binomial proportions was used to compare the proportions across years. All analyses

were performed using SAS Version 9.4 (SAS Institute, Carey, North Carolina) and were conducted from July to October 2020.

Public and Patient Involvement

The public/patients were not involved in the design, conduct, or reporting of this study.

Results

Stimulant Population Characteristics

In 2018, an estimated 4.1 million US adults (95% confidence interval 3.4 million - 4.8 million) reported that they had filled 1 or more prescriptions for the CNS stimulants amphetamine or methylphenidate. Population characteristics are shown in Table 1. Use of these prescription stimulants skewed toward the younger age cohorts and the percentage reporting prescription use was highest among those age 19-24 years – 3.2% (1.7% - 4.8%) – and lowest among those age 65-85 years – 0.5% (0.3% - 0.7%). Utilization also varied substantially by race/ethnicity with 2.3% (1.8% - 2.8%) of Whites reporting use compared to 0.6% (0.3% - 1.0%) of Blacks, a more than 4-fold difference. CNS stimulant use was also higher in those with education beyond high school and among those never married compared to those currently or previously married.

CNS Stimulant Medication Use

In 2018, US adults filled an estimated 30.2 million prescriptions (27.9 million - 32.4 million) for CNS stimulants. Medication detail is shown in Table 2. These adults filled a mean of 7.3 (6.8 - 7.8) prescriptions during the survey year – which provided a mean of 226 (210 - 242) days' supply. Amphetamine products were more widely used among adults than methylphenidate products, accounting for 78.9% vs 21.1% of the 2018 prescription volume.

Change in Utilization

Reported use of these CNS simulants increased during the 5 years from the 2013 to the 2018 annual MEPS survey. Survey-to-survey changes are shown in Table 3. The estimated number of adults increased from 2.3 million (1.8 million - 2.8 million) in 2013 to 4.1 million (3.4 million - 4.8 million) in 2018. During that period, adult exposure increased by an estimated 1.8 million adults ($t = 4.35$, $p < 0.01$), or an increase of 79.8%. Examined by sex, the largest increase occurred among females, who accounted for 1.3 million of 1.8 million (72.1%) of the 5-year growth (difference, $t = 5.39$, $p < 0.01$). Male use increased by 0.5 million, a 38.9% nominal increase that was not statistically significant ($t = 1.86$, $p = 0.063$). Change in use by age was concentrated in two cohorts, age 25-44 years and age 45-64. Among those age 25-44, an additional 0.88 million (0.39 million - 1.37 million) reported stimulant use from 2013 to 2018 ($t = 3.55$, $p < 0.01$), or an increase of 85.2%. Among those age 45-64 years, estimated stimulant use increased by 0.59 million ($t = 3.81$, $p < 0.01$), or 100.7%. Among those in the youngest age cohort, age 19-24 years, the initial rate of utilization in 2013 was the highest of any age group (3.2%) but the increases were smaller, a nominal increase of 33.4% that was not statistically significant ($t = 0.91$, $p = 0.365$). Meanwhile, the total adult US population was estimated to increase during the 5-year-period from 237.5 million to 248.4 million, an increase of 4.6%.

The growth in stimulant prescriptions was concentrated in the amphetamine products, which was estimated to increase 119.2% from 10.9 million in 2013 to 23.8 million in 2018 ($t = 10.46$, $p < 0.01$). Growth in use of methylphenidate products was slower, an estimated 39.4% increase ($t = 2.27$, $p = 0.023$).

Medical Conditions

Stimulant users frequently reported taking medications for a variety of mental, neurological, and developmental conditions. The 2018 survey results are shown in Table 4.

Among those exposed to the stimulants 77.8% (72.6% - 83.0%) indicated they took medication for ADHD, 26.8% (22.2% - 31.5%) reported anxiety medication, 25.1% (19.9% - 30.3%) said they had taken drugs for depression, and 15.3% (9.8% - 20.8%) indicated drug therapy for other mental or neurological conditions. As shown in Table 4, similar percentages reported a medical visit for the reported condition, and/or indicated a medical condition, regardless of whether it was treated with drugs or a medical visit. Overall, 40.6% (34.9% - 46.3%) of those reporting stimulant use indicated they were taking medication for anxiety, depression, or both.

Discussion

In this study we have shown that US adult exposure to prescription CNS stimulants with risk of dependence is substantial – an estimated 4 .1 million adults in 2018 – and has grown by approximately 80% over five years. The total number of prescriptions dispensed grew even faster, an increase of approximately 96%. Medication and treatment for depression, anxiety, and other mental conditions were common. Those adults reporting use represented a population that was younger, had higher educational attainment, and was more likely to be unmarried. While use remained more frequent in the youngest age cohort, the largest percentage increases occurred in adults age 25 and older.

The most frequently reported disorder was ADHD. These data confirm, and extend to more recent years, results of previous studies indicating increasing diagnosis and drug treatment of adults for ADHD covering time periods from 1999 through 2016.[19–22] One study of adults with ADHD in a large integrated health system also reported high rates of comorbid depression and anxiety.[19] Another study of ADHD diagnosis and treatment based on office-visit data in an earlier 5-year period (2008-2009 to 2012-2013) reported a 36.4% increase.[22] Our analysis

differs from these studies in that the primary focus was to assess the exposure to stimulant drugs for any medical purpose, given the varied off-label and on-label uses over many decades.

While we did not assess safety in this study, some patterns of use raise issues that warrant further investigation. Notably, given that amphetamine stimulants are reported to cause anxiety in 10% to 50% of patients and methylphenidate in 10% to 30%,[23](p323) we observed that anxiety was the second most frequently reported mental condition reported, accounting for 31.2% of exposed adults. Combination therapy with antidepressants also warrants further investigation given that many antidepressant drugs are associated not only with adverse effects of anxiety and insomnia, but also dullness and flat affect.[3] (p 410) None of the major antidepressants are FDA-approved for use in combination therapy with Schedule II stimulants.

Finally, the growing use of these stimulants should renew interest in updating, characterizing, and managing the risks of this drug class. There are three concerns warranting investigation. First, these data show that use of CNS stimulants is overwhelmingly in long-term, with a median of 226 days' supply. Second, the skew towards use in younger age groups raises the question of whether or when those prescribed stimulants for ADHD in childhood or adolescence should be discontinued as they grow older. Third, while the estimates are not comparable, the major government survey of drug use and mental health for 2018[24] reported that the total number of adults estimated to make *non-medical* use of CNS stimulants was higher that our total of adults with self-reported *medical* use. Other studies indicate widespread use in hopes of achieving cognitive enhancement.[8]

This study also has limitations. Although MEPS is the largest publicly available survey providing data on the US use of drugs, our population estimates are derived from two random samples of modest size. A source of potential bias was thattilization was self-reported and might

underestimate true exposure because of possible non-medical use, poor recollection, or beginning therapy part-way through the survey year. During the period, the US adult population increased by 4.6%, which could contribute to increased use. While we could report the mental and neurological conditions such as ADHD and anxiety and whether medication was prescribed, we could not link these conditions to specific stimulant medications or combinations of medications. The intended medical purpose of various medications was further confounded because some widely used medications are indicated for multiple conditions (for example, paroxetine and sertraline are approved for both depression and social anxiety disorder) and because it is uncertain whether combinations were used intentionally in off-label combinations, or unintentionally.

Conclusions

Adult reporting medical use of those stimulants with the highest risk of misuse and dependence increased markedly in 5 years and occurred in a population often reporting multiple neurological or mental disorders. Given that the epidemic in use of prescription opioids continued for years before public health initiatives began to control use, understanding and managing this new resurgence in a class of drugs with a decades-long history of problems should be a public health priority. Physicians seeing patients who request prescriptions for these stimulants should assess with care the risks, benefits, and medical need.

Contributors: All the coauthors contributed to the study concept and design and to critical revision of the manuscript for important intellectual content. All coauthors have approved the final manuscript. TJM drafted the manuscript and is the guarantor. PWW and TJM provided the statistical analysis. The corresponding author attests that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted.

Competing Interests: All authors have completed the ICJME uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare GCA is former Chair of FDA's Peripheral and Central Nervous System Advisory Committee, serves as a paid advisor to IQVIA, serves on the advisory board of MesaRx Innovations, is a member of OptumRx's National P&T Committee; and holds equity in Monument Analytics, a consultancy that provides services to the life sciences industry as well as to plaintiffs in opioid litigation. These arrangements have been reviewed and approved by Johns Hopkins University in accordance with its conflict of interest policies. SPK is Psychiatric Medical Director for Mazzitti & Sullivan, a private counseling service for addiction and mental health.

Funding: None.

Data sharing: All of the data for this study are publicly available from the US Agency for Healthcare Quality and Research.

Ethical approval: This study reports de-identified personal data protected by US federal law and published for unrestricted public research use; institutional review board approval is not required.

Transparency statement: TJM affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

References

1 Rasmussen N. America's First Amphetamine Epidemic 1929–1971: A Quantitative and Qualitative Retrospective With Implications for the Present. *Am J Public Health* 2008;**98**:974–85. doi:10.2105/AJPH.2007.110593

2 Myers RL. *The 100 Most Important Chemical Compounds : A Reference Guide*. Westport, CT: : Greenwood Press 2007.

3 Brunton L, Knollmann B, Hilal-Dandan R. *Goodman and Gilman's The Pharmacological Basis of Therapeutics, 13th Edition*. 13th Edition. New York: : McGraw-Hill Education / Medical 2017.

4 Mayes R, Bagwell C, Erkulwater J. ADHD and the Rise in Stimulant Use Among Children. *Harv Rev Psychiatry* 2008;**16**:151–66.

5 ADDERALL XR (dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine sulfate and amphetamine aspartate capsule, extended release) [package insert]. Lexington, MA: : Shire LLC, a Takeda company 2019.

6 CONCERTA (methylphenidate hydrochloride tablet, extended release) [package insert]. Titusville, NJ: : Janssen Pharmaceuticals, Inc. 2013.

7 VYVANSE (lisdexamfetamine dimesylate capsule) [package insert]. Lexington, MA: : Shire LLC, a Takeda company 2019.

8 Carlier J, Giorgetti R, Varì MR, *et al.* Use of cognitive enhancers: methylphenidate and analogs. *Eur Rev Med Pharmacol Sci* 2019;**23**:3–15. doi:10.26355/eurrev_201901_16741

9 International Drug Control Conventions. U. N. Off. Drugs Crime. 2013.https://www.unodc.org/unodc/en/commissions/CND/conventions.html (accessed 14 Dec 2020).

10 Misuse of drugs legislation | Department of Health. Dep. Health U. K. 2015.https://www.health-ni.gov.uk/articles/misuse-drugs-legislations (accessed 10 Dec 2020).

11 Consolidated Federal Laws of Canada, Controlled Drugs and Substances Act. Gov. Can. Justice Laws Website. 2019.https://laws-lois.justice.gc.ca/eng/acts/c-38.8/ (accessed 14 Oct 2020).

12 Poisons Standard October 2017. Aust. Gov. Fed. Regist. Legis. 2017.https://www.legislation.gov.au/Details/F2017L01285/Html/Text, http://www.legislation.gov.au/Details/F2017L01285 (accessed 10 Dec 2020).

13 Controlled Substance Schedules. US Dep. Justice Drug Enforc. Adm. Divers. Control Div. 2020.https://www.deadiversion.usdoj.gov/schedules/#define (accessed 23 Sep 2020).

14 RITALIN (methylphenidate hydrochloride tablet) [package insert]. East Hanover, NJ: : Novartis Pharmaceuticals Corporation 2019.

15 Medical Expenditure Panel Survey Background. Agency Healthc. Res. Qual. MEPS Med. Expend. Panel Surv. 2019.https://meps.ahrq.gov/mepsweb/about_meps/survey_back.jsp (accessed 23 Sep 2020).

16 MEPS HC-204 2018 Full Year Population Characteristics. Rockville, MD: : Agency for Healthcare Research and Quality, Center for Financing, Access, and Cost Trends 2020.

17 MEPS HC-206A: 2018 Prescribed Medicines. Rockville, MD: : Agency for Healthcare Research and Quality, Center for Financing, Access, and Cost Trends 2020.

18 RxNorm Overview. US Natl. Libr. Med. Unified Med. Lang. Syst. UMLS Web Site. 2018.https://www.nlm.nih.gov/research/umls/rxnorm/ (accessed 17 Apr 2018).

19 Chung W, Jiang S-F, Paksarian D, *et al.* Trends in the Prevalence and Incidence of Attention-Deficit/Hyperactivity Disorder Among Adults and Children of Different Racial and Ethnic Groups. *JAMA Netw Open* 2019;**2**:e1914344. doi:10.1001/jamanetworkopen.2019.14344

20 Zhu Y, Liu W, Li Y, *et al.* Prevalence of ADHD in Publicly Insured Adults. *J Atten Disord* 2018;**22**:182–90. doi:10.1177/1087054717698815

21 Wei Y-JJ, Zhu Y, Liu W, *et al.* Prevalence of and Factors Associated With Long-term Concurrent Use of Stimulants and Opioids Among Adults With Attention-Deficit/Hyperactivity Disorder. *JAMA Netw Open* 2018;**1**:e181152. doi:10.1001/jamanetworkopen.2018.1152

22 Fairman KA, Peckham AM, Sclar DA. Diagnosis and Treatment of ADHD in the United States: Update by Gender and Race. *J Atten Disord* 2020;**24**:10–9. doi:10.1177/1087054716688534

23 Tisdale JE, Miller DA. *Drug-Induced Diseases: Prevention, Detection, and Management*. 3rd Edition. Bethesda, Maryland: : Amer Soc of Health System 2018.

24 Lipari RN. Key Substance Use and Mental Health Indicators in the United States: Results from the 2018 National Survey on Drug Use and Health. Rockville, MD: : Substance Abuse and Mental Health Services Administration 2018. https://www.samhsa.gov/data/sites/default/files/cbhsq-

reports/NSDUHNationalFindingsReport2018/NSDUHNationalFindingsReport2018.pdf (accessed 10 Oct 2020).

Table 1: Adult Demographic Characteristics and Population Estimates, 2013, 2018

	2013 US Adult Population	Taking Schedule II CNS stimulants				2018 US Adult Population	Taking Schedule II CNS stimulants			
		Number	95% CI		(%)		Number	95% CI		(%)
Sample size	25 999	187			0.7	22 592	312			1.4
Weighted total	237 542 474	2 296 473	1 793 935	2 799 011	1.0	248 422 599	4 128 752	3 414 679	4 842 825	1.7
Gender										
Male	114 248 604	1 315 701	957 355	1 674 048	1.2	119 882 386	1 827 177	1 393 945	2 260 410	1.5
Female	123 293 870	980 772	706 623	1 254 920	0.8	128 540 213	2 301 574	1 882 252	2 720 897	1.8
Age group										
19-24	26 118 821	578 917	349 554	808 281	2.2	24 075 889	772 502	400 828	1 144 176	3.2
25-44	81 793 471	1 033 683	724 965	1 342 401	1.3	86 681 356	1 914 712	1 514 676	2 314 747	2.2
45-64	83 167 154	581 227	387 805	774 649	0.7	83 002 693	1 166 798	930 809	1 402 788	1.4
65-85	46 463 029	102 646	22 645	182 647	0.2	54 662 660	274 739	160 564	388 915	0.5
Race/ethnicity										
Hispanic	35 671 675	99 783	42 216	157 350	0.3	40 404 296	286 699	137 849	435 548	0.7
White	155 869 496	1 991 331	1 519 826	2 462 836	1.3	155 534 457	3 508 558	2 868 675	4 148 442	2.3
Black	27 243 504	85 026	34 260	135 791	0.3	29 399 571	188 157	88 320	287 995	0.6
Asian	13 016 744	12 152	0	26 575	0.1	15 222 103	4 702		13 994	0
Multiple/other	5 741 056	108 181	31 355	185 007	1.9	7 862 172	140 636	39 820	241 452	1.8
Education										
Less than 12 years	31 831 465	152 491	41 377	263 604	0.5	29 281 941	205 801	91 374	320 228	0.7
High school	63 162 840	427 477	231 253	623 700	0.7	69 557 184	679 812	465 308	894 315	1
Some college	73 555 386	853 103	556 308	1 149 898	1.2	65 099 328	1 588 589	1 138 409	2 038 770	2.4
College (16 years)	41 972 988	497 804	312 628	682 980	1.2	50 233 073	1 037 728	777 809	1 297 646	2.1
> College	25 382 768	328 152	188 049	468 256	1.3	32 182 381	595 711	378 295	813 127	1.9
Marital status										
Married	126 006 314	873 147	602 927	1 143 366	0.7	127 963 174	1 538 405	1 220 135	1 856 675	1.2
Widow/sep/divorced	47 913 352	296 835	143 947	449 723	0.6	51 490 812	723 526	502 261	944 790	1.4
Never married	62 532 999	1 126 492	790 959	1 462 024	1.8	68 963 284	1 866 821	1 370 429	2 363 213	2.7

Table 2. Adult Reported Prescriptions for Schedule II Stimulants 2013, 2018

	2013				2018			
	Number	95% CI		(%)	Number	95% CI		(%)
Sample size	1 247				2 336			
All Schedule II stimulants (weighted)	15 412 693	13 927 848	16 897 539		30 150 428	27 929 702	32 371 154	
Amphetamine products	10 859 022	9 461 363	12 256 680	70.5	23 803 206	21 847 712	25 758 700	78.9
Amphetamine / Dextroamphetamine	8 628 463	7 321 851	9 935 075	56	19 173 869	17 229 361	21 118 377	63.6
Lisdexamfetamine	2 230 558	1 672 254	2 788 863	14.5	4 629 337	3 888 062	5 370 612	15.4
Methylphenidate products	4 553 672	3 796 140	5 311 204	29.5	6 347 222	4 984 163	7 710 281	21.1
Methylphenidate	4 303 540	3 561 713	5 045 367	27.9	5 886 552	4 346 483	7 426 621	19.5
Dexmethylphenidate	250 132	0	534 579	1.6	460 670	166 583	754 756	1.5
Prescriptions per patient (mean, 95% CI)	6.7	6.1	7.4		7.3	6.8	7.8	
Annual days supply (mean, 95% CI)	208	187	229		226	210	242	

Table 3. Changes in Schedule II CNS stimulant use, 2013, 2018

	Persons, number who took CNS stimulants							
	2013	2018	Difference	95% CI		t	p	Change t1-t2,(%)
All Adults	2 296 473	4 128 752	1 832 279	1 006 626	2 657 932	4.35	< 0.01	79.8
Gender								
Male	1 315 701	1 827 177	511 476	- 28 416	1 051 368	1.86	0.063	38.9
Female	980 772	2 301 574	1 320 802	840 273	1 801 333	5.39	< 0.01	134.7
Age Group								
19-24	578 917	772 502	193 585	- 224 956	612 126	0.91	0.365	33.4
25-44	1 033 683	1 914 712	881 029	394 685	1 367 372	3.55	< 0.01	85.2
45-64	581 227	1 166 798	585 571	284 399	886 745	3.81	< 0.01	100.7
65-85	102 646	274 739	172 093	35 088	309 099	2.46	0.014	167.7
	Stimulant prescriptions, number dispensed							
	2013	2018	Difference	95% CI		t	p	Change t1-t2,(%)
All Schedule II stimulants	15 412 693	30 150 428	14 737 735	12 105 049	17 370 420	10.97	< 0.01	95.6
Amphetamine products	10 859 022	23 803 206	12 944 184	10 518 473	15 369 896	10.46	< 0.01	119.2
Methylphenidate products	4 553 672	6 347 222	1 793 550	244 341	3 342 759	2.27	0.023	39.4

Table 4. Adult Schedule II Stimulant Users Mental, Neurological Conditions, 2018

	Reported medication			Reported medical visit[a]			Reported condition		
	(%)	95% CI		(%)	95% CI		(%)	95% CI	
Mental, neurological condition									
ADHD	77.8	72.6	83.0	79.3	73.3	85.4	79.3	73.3	85.4
Anxiety	26.8	22.2	31.5	31.2	26.3	36.2	31.2	26.3	36.2
Depression	25.1	19.9	30.3	28.3	22.8	33.8	28.3	22.8	33.8
Other mental	15.3	9.8	20.8	19.8	14.3	25.3	19.8	14.3	25.3
Anxiety and/or depression	40.6	34.9	46.3	45.0	39.3	50.8	45.0	39.3	50.8

Abbreviations: ADHD, Attention deficit hyperactivity disorder.
a Medical visit = Includes office, inpatient, outpatient, or emergency department

Changes in Medical Use of Central Nervous System Stimulants Among US Adults, 2013-2018, a Cross-Sectional Study

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6-7
Methods			
Study design	4	Present key elements of study design early in the paper	6-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7-8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-8*
Bias	9	Describe any efforts to address potential sources of bias	12-13
Study size	10	Explain how the study size was arrived at	6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	7-8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	8-9

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6-8. Table 1
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9, table 1
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	*9-12*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-12, Table 2-4
		(*b*) Report category boundaries when continuous variables were categorized	Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12-13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NONE

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Changes in Medical Use of Central Nervous System Stimulants Among US Adults, 2013-2018, a Cross-Sectional Study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-048528.R1
Article Type:	Original research
Date Submitted by the Author:	13-May-2021
Complete List of Authors:	Moore, Thomas; Johns Hopkins University Bloomberg School of Public Health, Center for Drug Safety and Effectiveness; The George Washington University Milken Institute of Public Health, Department of Epidemiology Wirtz, Phillip; The George Washington University School of Business, Department of Decision Sciences Kruszewski, Stefan; Johns Hopkins University Bloomberg School of Public Health, Center for Drug Safety and Effectiveness Alexander, G Caleb; Johns Hopkins University Bloomberg School of Public Health, Department of Epidemiology
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	EPIDEMIOLOGY, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Neurology < INTERNAL MEDICINE, MENTAL HEALTH, Adult psychiatry < PSYCHIATRY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Original research

Changes in Medical Use of Central Nervous System Stimulants Among US Adults, 2013-2018, a Cross-Sectional Study

Thomas J Moore [1,2], Philip W Wirtz [3], Stefan P. Kruszewski [1], G. Caleb Alexander [1,4]

Author affiliations:

[1] The Center for Drug Safety and Effectiveness, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, USA

[2] Department of Epidemiology, Milken Institute School of Public Health, The George Washington University, Washington, DC, USA

[3] Department of Decision Sciences, School of Business, The George Washington University, Washington, DC, USA

[4] Division of General Internal Medicine, Johns Hopkins Medicine, Baltimore, MD, USA

Correspondence to: Thomas J Moore, 916 Prince St, Ste 102, Alexandria VA 22314. (tmoore86@jhmi.edu) ORCID ID 0000-0003-0994-836X

ABSTRACT

Objective To assess the 5-year changes in the adult medical use of central nervous system (CNS) stimulants with higher risk of dependence and evaluate the population characteristics of users and their medical and/or neurological conditions.

Design Cross-sectional study

Setting Annual US Medical Expenditure Survey, a stratified random sample of approximately 30 000 persons designed to produce national population estimates. It focuses on reported medical spending, medical services used, health status, and prescription medications.

Participants Adults age 19 years and older who reported obtaining one or more prescriptions for amphetamine or methylphenidate products during two survey years, 2013 and 2018.

Main outcomes measures Prescriptions obtained, the specific stimulant product, and annual treatment days of drug supplied.

Results In 2018 an estimated 4.1 million US adults (95% confidence interval 3.4 million - 4.8 million) reported prescriptions for CNS stimulants, having filled a mean of 7.3 (6.8-7.8) prescriptions with a mean of 226 (210 - 242) days' supply. Compared to 2013, the estimated number of adults reporting using CNS stimulants in 2018 increased by 1.8 million (1.0 million - 2.7 million) or 79.8%. Most 2018 adult stimulant users reported taking psychoactive medication for one or more mental, behavioral, or neurodevelopment disorders. Overall 77.8% (72.6% - 83.0%) reported some medication for adult attention deficit disorder (ADHD), 26.8% (22.2% -

31.5%) took medication for anxiety, 25.1% (19.9% - 30.3%) for depression, and 15.3% (9.8% - 20.8%) indicated drug treatment for other mental or neurological disorders. Adult CNS stimulant use was higher in females, in younger age cohorts, and among individuals of White race/ethnicity.

Conclusions Adult medical use of prescription stimulants increased markedly in 5 years and occurred in a population often reporting multiple mental or neurological disorders. Further action is needed to understand and manage this new resurgence in drugs with high risks of dependence.

Strengths and limitations of this study

- This analysis of adult use of prescription amphetamine and methylphenidate stimulants is based on the largest publicly available annual US health survey conducted annually since 1996.
- While the utilization of these stimulant drug products in 2013 and 2018 was self-reported in an annual household survey, the prescription detail was confirmed in pharmacy records.
- The annual, federally funded survey was designed to support health policy analysis; its multistage probability design supports population estimates and confidence intervals for the entire US population.
- With an overall survey random sample of approximately 30 000 households and 365 000 dispensed prescriptions for each year, the number of cases indicating the study drug products was modest.
- Given stimulant drugs with a higher risk of psychological or physical dependence, as well as risks of non-medical use, the self-reporting feature of this survey could result in underestimating actual exposure among adults.

INTRODUCTION

The central nervous system (CNS) stimulants amphetamine and methylphenidate are among the oldest synthetic psychoactive medications still in widespread clinical use. The amphetamine product Benzedrine was first marketed in 1933 for nasal congestion, and in 1937 for depression and narcolepsy;[1] in 1954 the US Food and Drug Administration (FDA) approved a methylphenidate product (Ritalin), which was marketed for depression, senile behavior, lethargy, and narcolepsy.[2]

Amphetamine and methylphenidate are potent and structurally related sympathomimetic amines with therapeutic mechanisms that remain unclear but stimulate the release of dopamine and norepinephrine primarily through inhibition of neuronal reuptake.[3] Currently, a large number of amphetamine products are licensed based on mixtures of various salts (saccharate, sulfate, aspartate), specific enantiomers (d-), extended release formulations, and a prodrug. Methylphenidate has fewer chemical variants, but is available in immediate and extended release formulations, d-enantiomer salt mixtures, and a transdermal patch. Multiple generics and brand name variants are available for both stimulants. Approved and off-label uses of these two CNS stimulants have evolved over the many decades. Medical use for depression and weight loss declined in the 1950s and 1960s and these indications were repealed over concern about growing evidence of misuse and questions about effectiveness.[1] However, beginning in 1961 use in children expanded with FDA approval of indications for treating behavioral problems and later for attention deficit hyperactivity disorder (ADHD).[4] For many years new formulations were approved based on studies of ADHD in children. Starting in 2004, the FDA extended the ADHD indication to adults for some branded stimulants, (Adderall XR, Concerta, Vyvanse) and in 2015 approved a binge eating indication for lisdexamfetamine (Vyvanse).[5–7] Throughout the

decades since initial marketing the two stimulant products were approved for narcolepsy, and during that time off-label use was observed among persons using them to increase alertness or seeking to achieve cognitive enhancement.[8]

Amphetamine and methylphenidate have been long restricted globally because of addiction risks including a United Nations Convention on Psychotropic Substances and specific legal controls in many countries, including the United Kingdom, Canada, and Australia.[9–12] In the US, these stimulants are classified as Schedule II Controlled Substances, those declared to have "a high potential for abuse which may lead to severe psychological or physical dependence."[13] Other major Schedule II drugs include higher potency opioids and the barbiturates. Restrictions for this highest-risk class of licit psychoactive drugs include a Drug Enforcement Administration (DEA) license to prescribe, limitations on prescribed refills, monitoring at the state and federal levels, and secure pharmacy storage measures to prevent theft and diversion. In addition to risks of misuse and dependence, other adverse events associated with these stimulants include serious cardiovascular reactions, seizures, tics, tremors, aggression, manic symptoms, and psychosis.[5–7,14] Given that the increased use of prescription opioids continued for many years before declining in response to numerous public health initiatives, we examined the most recent trends in exposure to the other widely used group of Schedule II drugs, the CNS stimulants amphetamine and methylphenidate.

METHODS

We extracted the data for this study from the US Medical Expenditure Panel Survey (MEPS), a healthcare survey of individuals and households conducted annually since 1996 and published for research use by the Agency for Healthcare Research and Quality.[15] To assess change over 5 years, this study analyzed the 2013 and 2018 annual surveys. MEPS collects data

from a nationally representative sample of approximately 30 000 persons each year, and its multistage probability design supports estimates and variance of the US population. The confidentiality of personal identifying information is protected by federal law and removed before survey data are released for public research use.[16] These de-identified public use data are exempt from review by the Johns Hopkins Bloomberg School of Public Health Institutional Review Board.

Identification of medications

Population estimates of exposure to prescription drugs in MEPS begin with the household survey questionnaire and are then expanded with more detailed information collected from respondents' pharmacies.[17] Each annual data release contains a prescribed medicines file with records for approximately 325 000 prescriptions and multiple fields identifying the drug prescription detail. We used the following algorithm to standardize medications: if the record contained a National Drug Code (NDC), we matched it to the ingredient name in the National Library of Medicine RxNorm database;[18] for prescription records without an NDC we used the Multum Lexicon medication name, which is defined as the generic name most commonly used by physicians.[17] Medication names provided by respondents that were vague or described a class of drugs (e.g., stimulants, antidepressants) were excluded. The outpatient medications identified by survey respondents were then confirmed in pharmacy records which also provided additional detail about each dispensed prescription for the survey year.[19]

For this study we identified persons reporting any use of the following standardized generic medication names: amphetamine/dextroamphetamine, lisdexamfetamine, methylphenidate, and dexmethylphenidate. Notably, lisdexamfetamine and dexmethyphenidate are newer brand name drugs without generics. Amphetamine/dextroamphetamine and

methylphenidate describe multiple generic products. The objective of analyzing the two newer brand name products separately was to measure any effects of marketing and promotion, as compared to generics. We excluded CNS stimulants that were not classified as Schedule II (e.g., atomoxetine), or those with utilization that was too infrequent to estimate in the MEPS data (prescription methamphetamine). The extent of each respondent's exposure was measured by calculating the number of prescriptions filled in the survey year and the total annual days' supply reported for these prescriptions. If the days' supply was missing for a prescription, we imputed the days' supply based on median days supply for that drug (e.g. lisdexamfetamine) among respondents with non-missing values. For some analyses we also combined the four products into these two groups: amphetamine and methylphenidate products.

This study population included all persons reporting that they were 19 years of age or older as last ascertained during the survey year. Other assessed population characteristics included sex, race/ethnicity, education, and marital status. Among those reporting exposure to Schedule II CNS stimulants, we also analyzed the mental health, neurological, or developmental conditions for which respondents indicated one or more of the following: (1) They had the condition during the survey year; (2) they took a prescribed medication for the condition; (3) they received medical treatment, defined as an office, outpatient, inpatient, or emergency department visit. The mental health conditions analyzed were identified by the following International Classification of Disease, 10th Revision (ICD-10) codes: ADHD (F90), Major depression (F32), Anxiety (F40, F41), Other neurological or mental conditions (all other ICD-10 codes in the "F" series). The mental health condition information in the ICD-10 coding format was not available for the 2013 year, limiting this analysis to the 2018 survey year data.

Statistical analysis

We estimated the exposed adult population totals, percentages, and 95% confidence intervals (CI) using the MEPS multistage probability design characteristics for the entire US population in accordance with the survey statistical methods documentation.[20] Each survey observation included data on the sampling unit, the sampling stratum, and the specific sample weight for each observation. Populations, variance, and statistical significance within survey years were estimated using Taylor series linearization. Standard errors and confidence intervals were calculated based on the weighted estimates when available. A Z-test of two binomial proportions was used to compare the proportions across years. All analyses were performed using SAS Version 9.4 (SAS Institute, Carey, North Carolina) and were conducted from July to October 2020.

Public and patient involvement

The public/patients were not involved in the design, conduct, or reporting of this study.

RESULTS

Stimulant population characteristics

In 2018, an estimated 4.1 million US adults (95% confidence interval 3.4 million - 4.8 million) reported that they had filled 1 or more prescriptions for the CNS stimulants amphetamine or methylphenidate. Population characteristics are shown in Table 1. Use of these prescription stimulants skewed toward the younger age cohorts and the percentage reporting prescription use was highest among those age 19-24 years – 3.2% (1.7% - 4.8%) – and lowest among those age 65-85 years – 0.5% (0.3% - 0.7%). Utilization also varied substantially by race/ethnicity with 2.3% (1.8% - 2.8%) of Whites reporting use compared to 0.6% (0.3% - 1.0%) of Blacks, a more than 4-fold difference. CNS stimulant use was also higher in those with

education beyond high school and among those never married compared to those currently or previously married.

CNS stimulant medication use

In 2018, US adults filled an estimated 30.2 million prescriptions (27.9 million - 32.4 million) for CNS stimulants. Medication detail is shown in Table 2. These adults filled a mean of 7.3 (6.8 - 7.8) prescriptions during the survey year – which provided a mean of 226 (210 - 242) days' supply. Amphetamine products were more widely used among adults than methylphenidate products, accounting for 78.9% vs 21.1% of the 2018 prescription volume.

Change in utilization

Reported use of these CNS simulants increased during the 5 years from the 2013 to the 2018 annual MEPS survey. Survey-to-survey changes are shown in Table 3. The estimated number of adults increased from 2.3 million (1.8 million - 2.8 million) in 2013 to 4.1 million (3.4 million - 4.8 million) in 2018. During that period, adult exposure increased by an estimated 1.8 million adults ($t = 4.35$, $p < 0.01$), or an increase of 79.8%. Examined by sex, the largest increase occurred among females, who accounted for 1.3 million of 1.8 million (72.1%) of the 5-year growth (difference, $t = 5.39$, $p < 0.01$). Male use increased by 0.5 million, a 38.9% nominal increase that was not statistically significant ($t = 1.86$, $p = 0.063$). Change in use by age was concentrated in two cohorts, age 25-44 years and age 45-64. Among those age 25-44, an additional 0.88 million (0.39 million - 1.37 million) reported stimulant use from 2013 to 2018 ($t = 3.55$, $p < 0.01$), or an increase of 85.2%. Among those age 45-64 years, estimated stimulant use increased by 0.59 million ($t = 3.81$, $p < 0.01$), or 100.7%. Among those in the youngest age cohort, age 19-24 years, the initial rate of utilization in 2013 was the highest of any age group (3.2%) but the increases were smaller, a nominal increase of 33.4% that was not statistically

significant (t = 0.91, p = 0.365). Meanwhile, the total adult US population was estimated to increase during the 5-year-period from 237.5 million to 248.4 million, an increase of 4.6%.

The growth in stimulant prescriptions was concentrated in the amphetamine products, which were estimated to increase 119.2% from 10.9 million in 2013 to 23.8 million in 2018 (t = 10.46, p < 0.01). Growth in use of methylphenidate products was slower, an estimated 39.4% increase (t = 2.27, p = 0.023).

Medical conditions

Stimulant users frequently reported taking medications for a variety of mental, neurological, and developmental conditions. The 2018 survey results are shown in Table 4. Among those exposed to the stimulants 77.8% (72.6% - 83.0%) indicated they took medication for ADHD, 26.8% (22.2% - 31.5%) reported anxiety medication, 25.1% (19.9% - 30.3%) said they had taken drugs for depression, and 15.3% (9.8% - 20.8%) indicated drug therapy for other mental or neurological conditions. As shown in Table 4, similar percentages reported a medical visit for the reported condition, and/or indicated a medical condition, regardless of whether it was treated with drugs or a medical visit. Overall, 40.6% (34.9% - 46.3%) of those reporting stimulant use indicated they were taking medication for anxiety, depression, or both.

DISCUSSION

In this study we have shown that US adult exposure to prescription CNS stimulants with risk of dependence is substantial – an estimated 4 .1 million adults in 2018 – and has grown by approximately 80% over 5 years. The total number of prescriptions dispensed grew even faster, an increase of approximately 96%. Medication and treatment for depression, anxiety, and other mental conditions were common. Those adults reporting stimulant use represented a population that was younger, had higher educational attainment, and was more likely to be unmarried.

While use remained more frequent in the youngest age cohort, the largest percentage increases occurred in adults age 25 and older.

The most frequently reported disorder was ADHD. These data confirm, and extend to more recent years, results of previous studies indicating increasing diagnosis and drug treatment of adults for ADHD covering time periods from 1999 through 2016.[21–24] One study of adults with ADHD in a large integrated health system also reported high rates of comorbid depression and anxiety.[21] Another study of ADHD diagnosis and treatment based on office-visit data in an earlier 5-year period (2008-2009 to 2012-2013) reported a 36.4% increase.[24] Our analysis differs from these studies in that the primary focus was to assess the exposure to stimulant drugs for any medical purpose, given the varied off-label and on-label uses over many decades.

While we did not assess safety in this study, some patterns of use raise issues that warrant further investigation. Notably, given that amphetamine stimulants are reported to cause anxiety in 10% to 50% of patients and methylphenidate in 10% to 30%,[25](p323) we observed that anxiety was the second most frequently reported mental condition reported, accounting for 31.2% of exposed adults. Combination therapy with antidepressants also warrants further investigation given that many antidepressant drugs are associated not only with adverse effects of anxiety and insomnia, but also dullness and flat affect.[3] (p 410) None of the major antidepressants are FDA-approved for use in combination therapy with Schedule II stimulants.

Finally, the growing use of these stimulants should renew interest in updating, characterizing, and managing the risks of this drug class. There are three concerns warranting investigation. First, these data show that use of CNS stimulants is overwhelmingly in long-term, with a median of 226 days' supply. Second, the skew towards use in younger age groups raises the question of whether or when those prescribed stimulants for ADHD in childhood or

adolescence should be discontinued as they grow older. Third, while the estimates are not comparable, the major government survey of drug use and mental health for 2018[26] reported that the total number of adults estimated to make *non-medical* use of CNS stimulants was higher that our total of adults with self-reported *medical* use. Other studies indicate widespread use in hopes of achieving cognitive enhancement.[8]

This study also has limitations. Although MEPS is the largest publicly available survey providing data on the US use of prescription drugs, our population estimates are derived from two random samples of modest size. A source of potential bias was that utilization was self-reported and might underestimate true exposure because of possible non-medical use, poor recollection, or beginning therapy part-way through the survey year. However, most self-reported medications were confirmed in pharmacy records and additional detail about each prescription collected from pharmacy records. While a validation study of this issue reported good agreement between self-reports and pharmacy records, the stimulant controlled substance drugs were not assessed in that study, and agreement could differ. During the period, the US adult population increased by 4.6%, which could contribute to increased use. While we could report the mental and neurological conditions such as ADHD and anxiety and whether medication was prescribed, we could not link these conditions to specific stimulant medications or combinations of medications. The intended medical purpose of various medications was further confounded because some widely used medications are indicated for multiple conditions (for example, paroxetine and sertraline are approved for both depression and social anxiety disorder) and because it is uncertain whether combinations were used intentionally in off-label combinations, or unintentionally.

CONCLUSIONS

Adult reporting medical use of those stimulants with the highest risk of misuse and dependence increased markedly in 5 years and occurred in a population often reporting multiple neurological or mental disorders. Given that the epidemic in use of prescription opioids continued for years before public health initiatives began to control use, understanding and managing this new resurgence in a class of drugs with a decades-long history of problems should be a public health priority. Physicians seeing patients who request prescriptions for these stimulants should assess with care the risks, benefits, and medical need.

Contributors: All the coauthors (TJM,PWW,SPK,CGA) contributed to the study concept and design and to critical revision of the manuscript for important intellectual content. All coauthors have approved the final manuscript. TJM drafted the manuscript and is the guarantor. PWW and TJM provided the statistical analysis. The corresponding author attests that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted.

Competing Interests: All authors have completed the ICJME uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare GCA is former Chair of FDA's Peripheral and Central Nervous System Advisory Committee, serves as a paid advisor to IQVIA, serves on the advisory board of MesaRx Innovations, is a member of OptumRx's National P&T Committee; and holds equity in Monument Analytics, a consultancy that provides services to the life sciences

industry as well as to plaintiffs in opioid litigation. These arrangements have been reviewed and approved by Johns Hopkins University in accordance with its conflict of interest policies. SPK is Psychiatric Medical Director for Mazzitti & Sullivan, a private counseling service for addiction and mental health.

Funding: None.

Data sharing: All of the data for this study are publicly available from the US Agency for Healthcare Research and Quality.

Ethical approval: This study reports de-identified personal data protected by US federal law and published for unrestricted public research use; institutional review board approval is not required.

Transparency statement: TJM affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

References

1 Rasmussen N. America's First Amphetamine Epidemic 1929–1971: A Quantitative and Qualitative Retrospective with Implications for the Present. *American Journal of Public Health* 2008;**98**:974–85. doi:10.2105/AJPH.2007.110593

2 Myers RL. *The 100 Most Important Chemical Compounds : A Reference Guide*. Westport, CT: Greenwood Press 2007.

3 Brunton L, Knollmann B, Hilal-Dandan R. *Goodman and Gilman's The Pharmacological Basis of Therapeutics, 13th Edition*. 13th Edition. New York: McGraw-Hill Education / Medical 2017.

4 Mayes R, Bagwell C, Erkulwater J. ADHD and the Rise in Stimulant Use Among Children. *Harvard Review of Psychiatry* 2008;**16**:151–66.

5 ADDERALL XR (dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine sulfate and amphetamine aspartate capsule, extended release) [package insert]. Lexington, MA: Shire LLC, a Takeda company 2019.

6 CONCERTA (methylphenidate hydrochloride tablet, extended release) [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc. 2013.

7 VYVANSE (lisdexamfetamine dimesylate capsule) [package insert]. Lexington, MA: Shire LLC, a Takeda company 2019.

8 Carlier J, Giorgetti R, Varì MR, *et al.* Use of cognitive enhancers: methylphenidate and analogs. *Eur Rev Med Pharmacol Sci* 2019;**23**:3–15. doi:10.26355/eurrev_201901_16741

9 International Drug Control Conventions. United Nations : Office on Drugs and Crime. 2013.https://www.unodc.org/unodc/en/commissions/CND/conventions.html (accessed 14 Dec 2020).

10 Misuse of drugs legislation | Department of Health. Department of Health, United Kingdom. 2015.https://www.health-ni.gov.uk/articles/misuse-drugs-legislations (accessed 10 Dec 2020).

11 Consolidated Federal Laws of Canada, Controlled Drugs and Substances Act. Government of Canada Justice Laws Website. 2019.https://laws-lois.justice.gc.ca/eng/acts/c-38.8/ (accessed 14 Oct 2020).

12 Poisons Standard October 2017. Australian Government Federal Register of Legislation. 2017.https://www.legislation.gov.au/Details/F2017L01285/Html/Text, http://www.legislation.gov.au/Details/F2017L01285 (accessed 10 Dec 2020).

13 Controlled Substance Schedules. U.S. Department of Justice, Drug Enforcement Administration, Diversion Control Division. 2020.https://www.deadiversion.usdoj.gov/schedules/#define (accessed 23 Sep 2020).

14 RITALIN (methylphenidate hydrochloride tablet) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation 2019.

15 Medical Expenditure Panel Survey Background. Medical Expenditure Panel Survey, Agency for Healthcare Research and Quality. 2019.https://meps.ahrq.gov/mepsweb/about_meps/survey_back.jsp (accessed 23 Sep 2020).

16 MEPS HC-204 2018 Full Year Population Characteristics. Medical Expenditure Panel Survey, Agency for Healthcare Research and Quality. 2020.https://meps.ahrq.gov/mepsweb/data_stats/download_data_files_detail.jsp?cboPufNumber=HC-204 (accessed 3 Apr 2021).

17 MEPS HC-206A: 2018 Prescribed Medicines. Medical Expenditure Panel Survey, Agency for Healthcare Research and Quality. 2020.https://meps.ahrq.gov/mepsweb/data_stats/download_data_files_detail.jsp?cboPufNumber=HC-206A (accessed 3 Apr 2021).

18 RxNorm Overview. U.S. National Library of Medicine Unified Medical Language System (UMLS) web site. 2018.https://www.nlm.nih.gov/research/umls/rxnorm/ (accessed 17 Apr 2018).

19 MEPS Topics: Prescription Drugs. Medical Expenditure Panel Survey, Agency for Healthcare Research and Quality. 2019.https://meps.ahrq.gov/mepsweb/data_stats/MEPS_topics.jsp?topicid=14Z-1 (accessed 23 Sep 2020).

20 Machlin S, Yu W, Zodet M. Computing Standard Errors for MEPS Estimates. Medical Expenditure Panel Survey, Agency for Healthcare Research and Quality. 2005.https://meps.ahrq.gov/mepsweb/survey_comp/standard_errors.jsp (accessed 10 May 2021).

21 Chung W, Jiang S-F, Paksarian D, *et al.* Trends in the Prevalence and Incidence of Attention-Deficit/Hyperactivity Disorder Among Adults and Children of Different Racial and Ethnic Groups. *JAMA Netw Open* 2019;**2**:e1914344. doi:10.1001/jamanetworkopen.2019.14344

22 Zhu Y, Liu W, Li Y, *et al.* Prevalence of ADHD in Publicly Insured Adults. *J Atten Disord* 2018;**22**:182–90. doi:10.1177/1087054717698815

23 Wei Y-JJ, Zhu Y, Liu W, *et al.* Prevalence of and Factors Associated With Long-term Concurrent Use of Stimulants and Opioids Among Adults With Attention-Deficit/Hyperactivity Disorder. *JAMA Netw Open* 2018;**1**:e181152. doi:10.1001/jamanetworkopen.2018.1152

24 Fairman KA, Peckham AM, Sclar DA. Diagnosis and Treatment of ADHD in the United States: Update by Gender and Race. *J Atten Disord* 2020;**24**:10–9. doi:10.1177/1087054716688534

25 Tisdale JE, Miller DA. *Drug-Induced Diseases: Prevention, Detection, and Management*. 3rd Edition. Bethesda, Maryland: Amer Soc of Health System 2018.

26 Lipari RN. Key Substance Use and Mental Health Indicators in the United States: Results from the 2018 National Survey on Drug Use and Health. Rockville, MD: Substance Abuse and Mental Health Services Administration 2018. https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHNationalFindingsReport2018/NSDUHNationalFindingsReport2018.pdf (accessed 10 Oct 2020).

Table 1: Adult Demographic Characteristics and Population Estimates, 2013, 2018

	2013 US Adult Population	Taking Schedule II CNS stimulants				2018 US Adult Population	Taking Schedule II CNS stimulants			
		Number	95% CI		(%)		Number	95% CI		(%)
Sample size	25 999	187			0.7	22 592	312			1.4
Weighted total	237 542 474	2 296 473	1 793 935	2 799 011	1.0	248 422 599	4 128 752	3 414 679	4 842 825	1.7
Gender										
Male	114 248 604	1 315 701	957 355	1 674 048	1.2	119 882 386	1 827 177	1 393 945	2 260 410	1.5
Female	123 293 870	980 772	706 623	1 254 920	0.8	128 540 213	2 301 574	1 882 252	2 720 897	1.8
Age group										
19-24	26 118 821	578 917	349 554	808 281	2.2	24 075 889	772 502	400 828	1 144 176	3.2
25-44	81 793 471	1 033 683	724 965	1 342 401	1.3	86 681 356	1 914 712	1 514 676	2 314 747	2.2
45-64	83 167 154	581 227	387 805	774 649	0.7	83 002 693	1 166 798	930 809	1 402 788	1.4
65-85	46 463 029	102 646	22 645	182 647	0.2	54 662 660	274 739	160 564	388 915	0.5
Race/ethnicity										
Hispanic	35 671 675	99 783	42 216	157 350	0.3	40 404 296	286 699	137 849	435 548	0.7
White	155 869 496	1 991 331	1 519 826	2 462 836	1.3	155 534 457	3 508 558	2 868 675	4 148 442	2.3
Black	27 243 504	85 026	34 260	135 791	0.3	29 399 571	188 157	88 320	287 995	0.6
Asian	13 016 744	12 152	0	26 575	0.1	15 222 103	4 702		13 994	0
Multiple/other	5 741 056	108 181	31 355	185 007	1.9	7 862 172	140 636	39 820	241 452	1.8
Education										
Less than 12 years	31 831 465	152 491	41 377	263 604	0.5	29 281 941	205 801	91 374	320 228	0.7
High school	63 162 840	427 477	231 253	623 700	0.7	69 557 184	679 812	465 308	894 315	1
Some college	73 555 386	853 103	556 308	1 149 898	1.2	65 099 328	1 588 589	1 138 409	2 038 770	2.4
College (16 years)	41 972 988	497 804	312 628	682 980	1.2	50 233 073	1 037 728	777 809	1 297 646	2.1
> College	25 382 768	328 152	188 049	468 256	1.3	32 182 381	595 711	378 295	813 127	1.9
Marital status										
Married	126 006 314	873 147	602 927	1 143 366	0.7	127 963 174	1 538 405	1 220 135	1 856 675	1.2
Widow/sep/divorced	47 913 352	296 835	143 947	449 723	0.6	51 490 812	723 526	502 261	944 790	1.4
Never married	62 532 999	1 126 492	790 959	1 462 024	1.8	68 963 284	1 866 821	1 370 429	2 363 213	2.7

Table 2. Adult Reported Prescriptions for Schedule II Stimulants 2013, 2018

	2013				2018			
	Number	95% CI		(%)	Number	95% CI		(%)
Sample size	1 247				2 336			
All Schedule II stimulants (weighted)	15 412 693	13 927 848	16 897 539		30 150 428	27 929 702	32 371 154	
Amphetamine products	10 859 022	9 461 363	12 256 680	70.5	23 803 206	21 847 712	25 758 700	78.9
Amphetamine / Dextroamphetamine	8 628 463	7 321 851	9 935 075	56	19 173 869	17 229 361	21 118 377	63.6
Lisdexamfetamine	2 230 558	1 672 254	2 788 863	14.5	4 629 337	3 888 062	5 370 612	15.4
Methylphenidate products	4 553 672	3 796 140	5 311 204	29.5	6 347 222	4 984 163	7 710 281	21.1
Methylphenidate	4 303 540	3 561 713	5 045 367	27.9	5 886 552	4 346 483	7 426 621	19.5
Dexmethylphenidate	250 132	0	534 579	1.6	460 670	166 583	754 756	1.5
Prescriptions per patient (mean, 95% CI)	6.7	6.1	7.4		7.3	6.8	7.8	
Annual days supply (mean, 95% CI)	208	187	229		226	210	242	

Table 3. Changes in Schedule II CNS stimulant use, 2013, 2018

	Persons, number who took CNS stimulants							
	2013	2018	Difference	95% CI		t	p	Change t1-t2,(%)
All Adults	2 296 473	4 128 752	1 832 279	1 006 626	2 657 932	4.35	< 0.01	79.8
Gender								
Male	1 315 701	1 827 177	511 476	- 28 416	1 051 368	1.86	0.063	38.9
Female	980 772	2 301 574	1 320 802	840 273	1 801 333	5.39	< 0.01	134.7
Age Group								
19-24	578 917	772 502	193 585	- 224 956	612 126	0.91	0.365	33.4
25-44	1 033 683	1 914 712	881 029	394 685	1 367 372	3.55	< 0.01	85.2
45-64	581 227	1 166 798	585 571	284 399	886 745	3.81	< 0.01	100.7
65-85	102 646	274 739	172 093	35 088	309 099	2.46	0.014	167.7
	Stimulant prescriptions, number dispensed							
	2013	2018	Difference	95% CI		t	p	Change t1-t2,(%)
All Schedule II stimulants	15 412 693	30 150 428	14 737 735	12 105 049	17 370 420	10.97	< 0.01	95.6
Amphetamine products	10 859 022	23 803 206	12 944 184	10 518 473	15 369 896	10.46	< 0.01	119.2
Methylphenidate products	4 553 672	6 347 222	1 793 550	244 341	3 342 759	2.27	0.023	39.4

Table 4. Adult Schedule II Stimulant Users Mental, Neurological Conditions, 2018

	Reported medication			Reported medical visit[a]			Reported condition		
	(%)	95% CI		(%)	95% CI		(%)	95% CI	
Mental, neurological condition									
ADHD	77.8	72.6	83.0	79.3	73.3	85.4	79.3	73.3	85.4
Anxiety	26.8	22.2	31.5	31.2	26.3	36.2	31.2	26.3	36.2
Depression	25.1	19.9	30.3	28.3	22.8	33.8	28.3	22.8	33.8
Other mental	15.3	9.8	20.8	19.8	14.3	25.3	19.8	14.3	25.3
Anxiety and/or depression	40.6	34.9	46.3	45.0	39.3	50.8	45.0	39.3	50.8

Abbreviations: ADHD, Attention deficit hyperactivity disorder.
a Medical visit = Includes office, inpatient, outpatient, or emergency department

Changes in Medical Use of Central Nervous System Stimulants Among US Adults, 2013-2018, a Cross-Sectional Study

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6-7
Methods			
Study design	4	Present key elements of study design early in the paper	6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7-8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-8*
Bias	9	Describe any efforts to address potential sources of bias	12-13
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	7-8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	8-9

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6-8. Table 1
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9, table 1
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	*9-12*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-12, Table 2-4
		(*b*) Report category boundaries when continuous variables were categorized	Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12-13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NONE

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Changes in Medical Use of Central Nervous System Stimulants Among US Adults, 2013-2018, a Cross-Sectional Study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-048528.R2
Article Type:	Original research
Date Submitted by the Author:	12-Jul-2021
Complete List of Authors:	Moore, Thomas; Johns Hopkins University Bloomberg School of Public Health, Center for Drug Safety and Effectiveness; The George Washington University Milken Institute of Public Health, Department of Epidemiology Wirtz, Phillip; The George Washington University School of Business, Department of Decision Sciences Kruszewski, Stefan; Johns Hopkins University Bloomberg School of Public Health, Center for Drug Safety and Effectiveness Alexander, G Caleb; Johns Hopkins University Bloomberg School of Public Health, Department of Epidemiology
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	EPIDEMIOLOGY, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Neurology < INTERNAL MEDICINE, MENTAL HEALTH, Adult psychiatry < PSYCHIATRY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Original research

Changes in Medical Use of Central Nervous System Stimulants Among US Adults, 2013-2018, a Cross-Sectional Study

Thomas J Moore [1,2], Philip W Wirtz [3], Stefan P. Kruszewski [1], G. Caleb Alexander [1,4]

Author affiliations:

[1] The Center for Drug Safety and Effectiveness, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, USA

[2] Department of Epidemiology, Milken Institute School of Public Health, The George Washington University, Washington, DC, USA

[3] Department of Decision Sciences, School of Business, The George Washington University, Washington, DC, USA

[4] Division of General Internal Medicine, Johns Hopkins Medicine, Baltimore, MD, USA

Correspondence to: Thomas J Moore, 916 Prince St, Ste 102, Alexandria VA 22314. (tmoore86@jhmi.edu) ORCID ID 0000-0003-0994-836X

ABSTRACT

Objective To assess the 5-year changes in the adult medical use of central nervous system (CNS) stimulants with higher risk of dependence and evaluate the population characteristics of users and their medical and/or neurological conditions.

Design Cross-sectional study

Setting Annual US Medical Expenditure Survey, a stratified random sample of approximately 30 000 persons designed to produce national population estimates. It focuses on reported medical spending, medical services used, health status, and prescription medications.

Participants Adults age 19 years and older who reported obtaining one or more prescriptions for amphetamine or methylphenidate products during two survey years, 2013 and 2018.

Main outcomes measures Prescriptions obtained, the specific stimulant product, and annual treatment days of drug supplied.

Results In 2018 an estimated 4.1 million US adults (95% confidence interval 3.4 million - 4.8 million) reported prescriptions for CNS stimulants, having filled a mean of 7.3 (6.8-7.8) prescriptions with a mean of 226 (210 - 242) days' supply. Compared to 2013, the estimated number of adults reporting using CNS stimulants in 2018 increased by 1.8 million (1.0 million - 2.7 million) or 79.8%. Most 2018 adult stimulant users reported taking psychoactive medication for one or more mental, behavioral, or neurodevelopment disorders. Overall 77.8% (72.6% - 83.0%) reported some medication for adult attention deficit disorder (ADHD), 26.8% (22.2% -

31.5%) took medication for anxiety, 25.1% (19.9% - 30.3%) for depression, and 15.3% (9.8% - 20.8%) indicated drug treatment for other mental or neurological disorders. Adult CNS stimulant use was higher in females, in younger age cohorts, and among individuals of White race/ethnicity.

Conclusions Adult medical use of prescription stimulants increased markedly in 5 years and occurred in a population often reporting multiple mental or neurological disorders. Further action is needed to understand and manage this new resurgence in drugs with high risks of dependence.

Strengths and limitations of this study

- This analysis of adult use of prescription amphetamine and methylphenidate stimulants is based on the largest publicly available annual US health survey conducted annually since 1996.
- While the utilization of these stimulant drug products in 2013 and 2018 was self-reported in an annual household survey, the prescription detail was confirmed in pharmacy records.
- The annual, federally funded survey was designed to support health policy analysis; its multistage probability design supports population estimates and confidence intervals for the entire US population.
- With an overall survey random sample of approximately 30 000 households and 365 000 dispensed prescriptions for each year, the number of cases indicating the study drug products was modest.
- Given stimulant drugs with a higher risk of psychological or physical dependence, as well as risks of non-medical use, the self-reporting feature of this survey could result in underestimating actual exposure among adults.

INTRODUCTION

The central nervous system (CNS) stimulants amphetamine and methylphenidate are among the oldest synthetic psychoactive medications still in widespread clinical use. The amphetamine product Benzedrine was first marketed in 1933 for nasal congestion, and in 1937 for depression and narcolepsy;[1] in 1954 the US Food and Drug Administration (FDA) approved a methylphenidate product (Ritalin), which was marketed for depression, senile behavior, lethargy, and narcolepsy.[2]

Amphetamine and methylphenidate are potent and structurally related sympathomimetic amines with therapeutic mechanisms that remain unclear but stimulate the release of dopamine and norepinephrine primarily through inhibition of neuronal reuptake.[3] Currently, a large number of amphetamine products are licensed based on mixtures of various salts (saccharate, sulfate, aspartate), specific enantiomers (d-), extended release formulations, and a prodrug. Methylphenidate has fewer chemical variants, but is available in immediate and extended release formulations, d-enantiomer salt mixtures, and a transdermal patch. Multiple generics and brand name variants are available for both stimulants. Approved and off-label uses of these two CNS stimulants have evolved over the many decades. Medical use for depression and weight loss declined in the 1950s and 1960s and these indications were repealed over concern about growing evidence of misuse and questions about effectiveness.[1] However, beginning in 1961 use in children expanded with FDA approval of indications for treating behavioral problems and later for attention deficit hyperactivity disorder (ADHD).[4] For many years new formulations were approved based on studies of ADHD in children. Starting in 2004, the FDA extended the ADHD indication to adults for some branded stimulants, (Adderall XR, Concerta, Vyvanse) and in 2015 approved a binge eating indication for lisdexamfetamine (Vyvanse).[5–7] Throughout the

decades since initial marketing the two stimulant products were approved for narcolepsy, and during that time off-label use was observed among persons using them to increase alertness or seeking to achieve cognitive enhancement.[8]

Amphetamine and methylphenidate have been long restricted globally because of addiction risks including a United Nations Convention on Psychotropic Substances and specific legal controls in many countries, including the United Kingdom, Canada, and Australia.[9–12] In the US, these stimulants are classified as Schedule II Controlled Substances, those declared to have "a high potential for abuse which may lead to severe psychological or physical dependence."[13] Other major Schedule II drugs include higher potency opioids and the barbiturates. Restrictions for this highest-risk class of licit psychoactive drugs include a Drug Enforcement Administration (DEA) license to prescribe, limitations on prescribed refills, monitoring at the state and federal levels, and secure pharmacy storage measures to prevent theft and diversion. In addition to risks of misuse and dependence, other adverse events associated with these stimulants include serious cardiovascular reactions, seizures, tics, tremors, aggression, manic symptoms, and psychosis.[5–7,14] Given that the increased use of prescription opioids continued for many years before declining in response to numerous public health initiatives, we examined the most recent trends in exposure to the other widely used group of Schedule II drugs, the CNS stimulants amphetamine and methylphenidate.

METHODS

We extracted the data for this study from the US Medical Expenditure Panel Survey (MEPS), a healthcare survey of individuals and households conducted annually since 1996 and published for research use by the Agency for Healthcare Research and Quality.[15] To assess change over 5 years, this study analyzed the 2013 and 2018 annual surveys. MEPS collects data

from a nationally representative sample of approximately 30 000 persons each year, and its multistage probability design supports estimates and variance of the US population. The confidentiality of personal identifying information is protected by federal law and removed before survey data are released for public research use.[16] These de-identified public use data are exempt from review by the Johns Hopkins Bloomberg School of Public Health Institutional Review Board.

Identification of medications

Population estimates of exposure to prescription drugs in MEPS begin with the household survey questionnaire and are then expanded with more detailed information collected from respondents' pharmacies.[17] Each annual data release contains a prescribed medicines file with records for approximately 325 000 prescriptions and multiple fields identifying the drug prescription detail. We used the following algorithm to standardize medications: if the record contained a National Drug Code (NDC), we matched it to the ingredient name in the National Library of Medicine RxNorm database;[18] for prescription records without an NDC we used the Multum Lexicon medication name, which is defined as the generic name most commonly used by physicians.[17] Medication names provided by respondents that were vague or described a class of drugs (e.g., stimulants, antidepressants) were excluded. The outpatient medications identified by survey respondents were then confirmed in pharmacy records which also provided additional detail about each dispensed prescription for the survey year.[19]

For this study we identified persons reporting any use of the following standardized generic medication names: amphetamine/dextroamphetamine, lisdexamfetamine, methylphenidate, and dexmethylphenidate. Notably, lisdexamfetamine and dexmethyphenidate are newer brand name drugs without generics. Amphetamine/dextroamphetamine and

methylphenidate describe multiple generic products. The objective of analyzing the two newer brand name products separately was to measure any effects of marketing and promotion, as compared to generics. We excluded CNS stimulants that were not classified as Schedule II (e.g., atomoxetine), or those with utilization that was too infrequent to estimate in the MEPS data (prescription methamphetamine). The extent of each respondent's exposure was measured by calculating the number of prescriptions filled in the survey year and the total annual days' supply reported for these prescriptions. If the days' supply was missing for a prescription, we imputed the days' supply based on median days supply for that drug (e.g. lisdexamfetamine) among respondents with non-missing values. For some analyses we also combined the four products into these two groups: amphetamine and methylphenidate products.

This study population included all persons reporting that they were 19 years of age or older as last ascertained during the survey year. Other assessed population characteristics included sex, race/ethnicity, education, and marital status. Among those reporting exposure to Schedule II CNS stimulants, we also analyzed the mental health, neurological, or developmental conditions for which respondents indicated one or more of the following: (1) They had the condition during the survey year; (2) they took a prescribed medication for the condition; (3) they received medical treatment, defined as an office, outpatient, inpatient, or emergency department visit. The mental health conditions analyzed were identified by the following International Classification of Disease, 10th Revision (ICD-10) codes: ADHD (F90), Major depression (F32), Anxiety (F40, F41), Other neurological or mental conditions (all other ICD-10 codes in the "F" series). The mental health condition information in the ICD-10 coding format was not available for the 2013 year, limiting this analysis to the 2018 survey year data.

Statistical analysis

We estimated the exposed adult population totals, percentages, and 95% confidence intervals (CI) using the MEPS multistage probability design characteristics for the entire US population in accordance with the survey statistical methods documentation.[20] Each survey observation included data on the sampling unit, the sampling stratum, and the specific sample weight for each observation. Populations, variance, and statistical significance within survey years were estimated using Taylor series linearization. Standard errors and confidence intervals were calculated based on the weighted estimates when available. A Z-test of two binomial proportions was used to compare the proportions across years. All analyses were performed using SAS Version 9.4 (SAS Institute, Carey, North Carolina) and were conducted from July to October 2020.

Public and patient involvement

The public/patients were not involved in the design, conduct, or reporting of this study.

RESULTS

Stimulant population characteristics

In 2018, an estimated 4.1 million US adults (95% confidence interval 3.4 million - 4.8 million) reported that they had filled 1 or more prescriptions for the CNS stimulants amphetamine or methylphenidate. Population characteristics are shown in Table 1. Use of these prescription stimulants skewed toward the younger age cohorts and the percentage reporting prescription use was highest among those age 19-24 years – 3.2% (1.7% - 4.8%) – and lowest among those age 65-85 years – 0.5% (0.3% - 0.7%). Utilization also varied substantially by race/ethnicity with 2.3% (1.8% - 2.8%) of Whites reporting use compared to 0.6% (0.3% - 1.0%) of Blacks, a more than 4-fold difference. CNS stimulant use was also higher in those with

education beyond high school and among those never married compared to those currently or previously married.

CNS stimulant medication use

In 2018, US adults filled an estimated 30.2 million prescriptions (27.9 million - 32.4 million) for CNS stimulants. Medication detail is shown in Table 2. These adults filled a mean of 7.3 (6.8 - 7.8) prescriptions during the survey year – which provided a mean of 226 (210 - 242) days' supply. Amphetamine products were more widely used among adults than methylphenidate products, accounting for 78.9% vs 21.1% of the 2018 prescription volume.

Change in utilization

Reported use of these CNS simulants increased during the 5 years from the 2013 to the 2018 annual MEPS survey. Survey-to-survey changes are shown in Table 3. The estimated number of adults increased from 2.3 million (1.8 million - 2.8 million) in 2013 to 4.1 million (3.4 million - 4.8 million) in 2018. During that period, adult exposure increased by an estimated 1.8 million adults ($t = 4.35$, $p < 0.01$), or an increase of 79.8%. Examined by sex, the largest increase occurred among females, who accounted for 1.3 million of 1.8 million (72.1%) of the 5-year growth (difference, $t = 5.39$, $p < 0.01$). Male use increased by 0.5 million, a 38.9% nominal increase that was not statistically significant ($t = 1.86$, $p = 0.063$). Change in use by age was concentrated in two cohorts, age 25-44 years and age 45-64. Among those age 25-44, an additional 0.88 million (0.39 million - 1.37 million) reported stimulant use from 2013 to 2018 ($t = 3.55$, $p < 0.01$), or an increase of 85.2%. Among those age 45-64 years, estimated stimulant use increased by 0.59 million ($t = 3.81$, $p < 0.01$), or 100.7%. Among those in the youngest age cohort, age 19-24 years, the initial rate of utilization in 2013 was the highest of any age group (3.2%) but the increases were smaller, a nominal increase of 33.4% that was not statistically

significant (t = 0.91, p = 0.365). Meanwhile, the total adult US population was estimated to increase during the 5-year-period from 237.5 million to 248.4 million, an increase of 4.6%.

The growth in stimulant prescriptions was concentrated in the amphetamine products, which were estimated to increase 119.2% from 10.9 million in 2013 to 23.8 million in 2018 (t = 10.46, p < 0.01). Growth in use of methylphenidate products was slower, an estimated 39.4% increase (t = 2.27, p = 0.023).

Medical conditions

Stimulant users frequently reported taking medications for a variety of mental, neurological, and developmental conditions. The 2018 survey results are shown in Table 4. Among those exposed to the stimulants 77.8% (72.6% - 83.0%) indicated they took medication for ADHD, 26.8% (22.2% - 31.5%) reported anxiety medication, 25.1% (19.9% - 30.3%) said they had taken drugs for depression, and 15.3% (9.8% - 20.8%) indicated drug therapy for other mental or neurological conditions. As shown in Table 4, similar percentages reported a medical visit for the reported condition, and/or indicated a medical condition, regardless of whether it was treated with drugs or a medical visit. Overall, 40.6% (34.9% - 46.3%) of those reporting stimulant use indicated they were taking medication for anxiety, depression, or both.

DISCUSSION

In this study we have shown that US adult exposure to prescription CNS stimulants with risk of dependence is substantial – an estimated 4 .1 million adults in 2018 – and has grown by approximately 80% over 5 years. The total number of prescriptions dispensed grew even faster, an increase of approximately 96%. Medication and treatment for depression, anxiety, and other mental conditions were common. Those adults reporting stimulant use represented a population that was younger, had higher educational attainment, and was more likely to be unmarried.

While use remained more frequent in the youngest age cohort, the largest percentage increases occurred in adults age 25 and older.

The most frequently reported disorder was ADHD. These data confirm, and extend to more recent years, results of previous studies indicating increasing diagnosis and drug treatment of adults for ADHD covering time periods from 1999 through 2016.[21–24] One study of adults with ADHD in a large integrated health system also reported high rates of comorbid depression and anxiety.[21] Another study of ADHD diagnosis and treatment based on office-visit data in an earlier 5-year period (2008-2009 to 2012-2013) reported a 36.4% increase.[24] Our analysis differs from these studies in that the primary focus was to assess the exposure to stimulant drugs for any medical purpose, given the varied off-label and on-label uses over many decades.

While we did not assess safety in this study, some patterns of use raise issues that warrant further investigation. Notably, given that amphetamine stimulants are reported to cause anxiety in 10% to 50% of patients and methylphenidate in 10% to 30%,[25](p323) we observed that anxiety was the second most frequently reported mental condition reported, accounting for 31.2% of exposed adults. Combination therapy with antidepressants also warrants further investigation given that many antidepressant drugs are associated not only with adverse effects of anxiety and insomnia, but also dullness and flat affect.[3] (p 410) None of the major antidepressants are FDA-approved for use in combination therapy with Schedule II stimulants.

Finally, the growing use of these stimulants should renew interest in updating, characterizing, and managing the risks of this drug class. There are three concerns warranting investigation. First, these data show that use of CNS stimulants is overwhelmingly in long-term, with a median of 226 days' supply. Second, the skew towards use in younger age groups raises the question of whether or when those prescribed stimulants for ADHD in childhood or

adolescence should be discontinued as they grow older. Third, while the estimates are not comparable, the major government survey of drug use and mental health for 2018[26] reported that the total number of adults estimated to make *non-medical* use of CNS stimulants was higher that our total of adults with self-reported *medical* use. Other studies indicate widespread use in hopes of achieving cognitive enhancement.[8]

This study also has limitations. Although MEPS is the largest publicly available survey providing data on the US use of prescription drugs, our population estimates are derived from two random samples of modest size. A source of potential bias was that utilization was self-reported and might underestimate true exposure because of possible non-medical use, poor recollection, or beginning therapy part-way through the survey year. However, most self-reported medications were confirmed in pharmacy records and additional detail about each prescription collected from pharmacy records. While a validation study of this issue reported good agreement between self-reports and pharmacy records, the stimulant controlled substance drugs were not assessed in that study, and agreement could differ. During the period, the US adult population increased by 4.6%, which could contribute to increased use. While we could report the mental and neurological conditions such as ADHD and anxiety and whether medication was prescribed, we could not link these conditions to specific stimulant medications or combinations of medications. The intended medical purpose of various medications was further confounded because some widely used medications are indicated for multiple conditions (for example, paroxetine and sertraline are approved for both depression and social anxiety disorder) and because it is uncertain whether combinations were used intentionally in off-label combinations, or unintentionally.

CONCLUSIONS

Adult reporting medical use of those stimulants with the highest risk of misuse and dependence increased markedly in 5 years and occurred in a population often reporting multiple neurological or mental disorders. Given that the epidemic in use of prescription opioids continued for years before public health initiatives began to control use, understanding and managing this new resurgence in a class of drugs with a decades-long history of problems should be a public health priority. Physicians seeing patients who request prescriptions for these stimulants should assess with care the risks, benefits, and medical need.

Contributors: All the coauthors (TJM,PWW,SPK,CGA) contributed to the study concept and design and to critical revision of the manuscript for important intellectual content. All coauthors have approved the final manuscript. TJM drafted the manuscript and is the guarantor. PWW and TJM provided the statistical analysis. The corresponding author attests that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted.

Competing Interests: All authors have completed the ICJME uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare GCA is former Chair of FDA's Peripheral and Central Nervous System Advisory Committee, serves as a paid advisor to IQVIA, serves on the advisory board of MesaRx Innovations, is a member of OptumRx's National P&T Committee; and holds equity in Monument Analytics, a consultancy that provides services to the life sciences

industry as well as to plaintiffs in opioid litigation. These arrangements have been reviewed and approved by Johns Hopkins University in accordance with its conflict of interest policies. SPK is Psychiatric Medical Director for Mazzitti & Sullivan, a private counseling service for addiction and mental health.

Funding: None.

Data sharing: All of the data for this study are publicly available from the US Agency for Healthcare Research and Quality. Key SAS code is available upon reasonable request.

Ethical approval: This study reports de-identified personal data protected by US federal law and published for unrestricted public research use; institutional review board approval is not required.

Transparency statement: TJM affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

References

1 Rasmussen N. America's First Amphetamine Epidemic 1929–1971: A Quantitative and Qualitative Retrospective with Implications for the Present. *American Journal of Public Health* 2008;**98**:974–85. doi:10.2105/AJPH.2007.110593

2 Myers RL. *The 100 Most Important Chemical Compounds : A Reference Guide*. Westport, CT: Greenwood Press 2007.

3 Brunton L, Knollmann B, Hilal-Dandan R. *Goodman and Gilman's The Pharmacological Basis of Therapeutics, 13th Edition*. 13th Edition. New York: McGraw-Hill Education / Medical 2017.

4 Mayes R, Bagwell C, Erkulwater J. ADHD and the Rise in Stimulant Use Among Children. *Harvard Review of Psychiatry* 2008;**16**:151–66.

5 ADDERALL XR (dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine sulfate and amphetamine aspartate capsule, extended release) [package insert]. Lexington, MA: Shire LLC, a Takeda company 2019.

6 CONCERTA (methylphenidate hydrochloride tablet, extended release) [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc. 2013.

7 VYVANSE (lisdexamfetamine dimesylate capsule) [package insert]. Lexington, MA: Shire LLC, a Takeda company 2019.

8 Carlier J, Giorgetti R, Varì MR, *et al.* Use of cognitive enhancers: methylphenidate and analogs. *Eur Rev Med Pharmacol Sci* 2019;**23**:3–15. doi:10.26355/eurrev_201901_16741

9 International Drug Control Conventions. United Nations : Office on Drugs and Crime. 2013.https://www.unodc.org/unodc/en/commissions/CND/conventions.html (accessed 14 Dec 2020).

10 Misuse of drugs legislation | Department of Health. Department of Health, United Kingdom. 2015.https://www.health-ni.gov.uk/articles/misuse-drugs-legislations (accessed 10 Dec 2020).

11 Consolidated Federal Laws of Canada, Controlled Drugs and Substances Act. Government of Canada Justice Laws Website. 2019.https://laws-lois.justice.gc.ca/eng/acts/c-38.8/ (accessed 14 Oct 2020).

12 Poisons Standard October 2017. Australian Government Federal Register of Legislation. 2017.https://www.legislation.gov.au/Details/F2017L01285/Html/Text, http://www.legislation.gov.au/Details/F2017L01285 (accessed 10 Dec 2020).

13 Controlled Substance Schedules. U.S. Department of Justice, Drug Enforcement Administration, Diversion Control Division. 2020.https://www.deadiversion.usdoj.gov/schedules/#define (accessed 23 Sep 2020).

14 RITALIN (methylphenidate hydrochloride tablet) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation 2019.

15 Medical Expenditure Panel Survey Background. Medical Expenditure Panel Survey, Agency for Healthcare Research and Quality. 2019.https://meps.ahrq.gov/mepsweb/about_meps/survey_back.jsp (accessed 23 Sep 2020).

16 MEPS HC-204 2018 Full Year Population Characteristics. Medical Expenditure Panel Survey, Agency for Healthcare Research and Quality. 2020.https://meps.ahrq.gov/mepsweb/data_stats/download_data_files_detail.jsp?cboPufNumber=HC-204 (accessed 3 Apr 2021).

17 MEPS HC-206A: 2018 Prescribed Medicines. Medical Expenditure Panel Survey, Agency for Healthcare Research and Quality. 2020.https://meps.ahrq.gov/mepsweb/data_stats/download_data_files_detail.jsp?cboPufNumber=HC-206A (accessed 3 Apr 2021).

18 RxNorm Overview. U.S. National Library of Medicine Unified Medical Language System (UMLS) web site. 2018.https://www.nlm.nih.gov/research/umls/rxnorm/ (accessed 17 Apr 2018).

19 MEPS Topics: Prescription Drugs. Medical Expenditure Panel Survey, Agency for Healthcare Research and Quality. 2019.https://meps.ahrq.gov/mepsweb/data_stats/MEPS_topics.jsp?topicid=14Z-1 (accessed 23 Sep 2020).

20 Machlin S, Yu W, Zodet M. Computing Standard Errors for MEPS Estimates. Medical Expenditure Panel Survey, Agency for Healthcare Research and Quality. 2005.https://meps.ahrq.gov/mepsweb/survey_comp/standard_errors.jsp (accessed 10 May 2021).

21 Chung W, Jiang S-F, Paksarian D, *et al.* Trends in the Prevalence and Incidence of Attention-Deficit/Hyperactivity Disorder Among Adults and Children of Different Racial and Ethnic Groups. *JAMA Netw Open* 2019;**2**:e1914344. doi:10.1001/jamanetworkopen.2019.14344

22 Zhu Y, Liu W, Li Y, *et al.* Prevalence of ADHD in Publicly Insured Adults. *J Atten Disord* 2018;**22**:182–90. doi:10.1177/1087054717698815

23 Wei Y-JJ, Zhu Y, Liu W, *et al.* Prevalence of and Factors Associated With Long-term Concurrent Use of Stimulants and Opioids Among Adults With Attention-Deficit/Hyperactivity Disorder. *JAMA Netw Open* 2018;**1**:e181152. doi:10.1001/jamanetworkopen.2018.1152

24 Fairman KA, Peckham AM, Sclar DA. Diagnosis and Treatment of ADHD in the United States: Update by Gender and Race. *J Atten Disord* 2020;**24**:10–9. doi:10.1177/1087054716688534

25 Tisdale JE, Miller DA. *Drug-Induced Diseases: Prevention, Detection, and Management*. 3rd Edition. Bethesda, Maryland: Amer Soc of Health System 2018.

26 Lipari RN. Key Substance Use and Mental Health Indicators in the United States: Results from the 2018 National Survey on Drug Use and Health. Rockville, MD: Substance Abuse and Mental Health Services Administration 2018. https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHNationalFindingsReport2018/NSDUHNationalFindingsReport2018.pdf (accessed 10 Oct 2020).

Table 1: Adult Demographic Characteristics and Population Estimates, 2013, 2018

	2013 US Adult Population	Taking Schedule II CNS stimulants				2018 US Adult Population	Taking Schedule II CNS stimulants			
		Number	95% CI		(%)		Number	95% CI		(%)
Sample size	25 999	187			0.7	22 592	312			1.4
Weighted total	237 542 474	2 296 473	1 793 935	2 799 011	1.0	248 422 599	4 128 752	3 414 679	4 842 825	1.7
Gender										
Male	114 248 604	1 315 701	957 355	1 674 048	1.2	119 882 386	1 827 177	1 393 945	2 260 410	1.5
Female	123 293 870	980 772	706 623	1 254 920	0.8	128 540 213	2 301 574	1 882 252	2 720 897	1.8
Age group										
19-24	26 118 821	578 917	349 554	808 281	2.2	24 075 889	772 502	400 828	1 144 176	3.2
25-44	81 793 471	1 033 683	724 965	1 342 401	1.3	86 681 356	1 914 712	1 514 676	2 314 747	2.2
45-64	83 167 154	581 227	387 805	774 649	0.7	83 002 693	1 166 798	930 809	1 402 788	1.4
65-85	46 463 029	102 646	22 645	182 647	0.2	54 662 660	274 739	160 564	388 915	0.5
Race/ethnicity										
Hispanic	35 671 675	99 783	42 216	157 350	0.3	40 404 296	286 699	137 849	435 548	0.7
White	155 869 496	1 991 331	1 519 826	2 462 836	1.3	155 534 457	3 508 558	2 868 675	4 148 442	2.3
Black	27 243 504	85 026	34 260	135 791	0.3	29 399 571	188 157	88 320	287 995	0.6
Asian	13 016 744	12 152	0	26 575	0.1	15 222 103	4 702		13 994	0
Multiple/other	5 741 056	108 181	31 355	185 007	1.9	7 862 172	140 636	39 820	241 452	1.8
Education										
Less than 12 years	31 831 465	152 491	41 377	263 604	0.5	29 281 941	205 801	91 374	320 228	0.7
High school	63 162 840	427 477	231 253	623 700	0.7	69 557 184	679 812	465 308	894 315	1
Some college	73 555 386	853 103	556 308	1 149 898	1.2	65 099 328	1 588 589	1 138 409	2 038 770	2.4
College (16 years)	41 972 988	497 804	312 628	682 980	1.2	50 233 073	1 037 728	777 809	1 297 646	2.1
> College	25 382 768	328 152	188 049	468 256	1.3	32 182 381	595 711	378 295	813 127	1.9
Marital status										
Married	126 006 314	873 147	602 927	1 143 366	0.7	127 963 174	1 538 405	1 220 135	1 856 675	1.2
Widow/sep/divorced	47 913 352	296 835	143 947	449 723	0.6	51 490 812	723 526	502 261	944 790	1.4
Never married	62 532 999	1 126 492	790 959	1 462 024	1.8	68 963 284	1 866 821	1 370 429	2 363 213	2.7

Table 2. Adult Reported Prescriptions for Schedule II Stimulants 2013, 2018

	2013				2018			
	Number	95% CI		(%)	Number	95% CI		(%)
Sample size	1 247				2 336			
All Schedule II stimulants (weighted)	15 412 693	13 927 848	16 897 539		30 150 428	27 929 702	32 371 154	
Amphetamine products	10 859 022	9 461 363	12 256 680	70.5	23 803 206	21 847 712	25 758 700	78.9
Amphetamine / Dextroamphetamine	8 628 463	7 321 851	9 935 075	56	19 173 869	17 229 361	21 118 377	63.6
Lisdexamfetamine	2 230 558	1 672 254	2 788 863	14.5	4 629 337	3 888 062	5 370 612	15.4
Methylphenidate products	4 553 672	3 796 140	5 311 204	29.5	6 347 222	4 984 163	7 710 281	21.1
Methylphenidate	4 303 540	3 561 713	5 045 367	27.9	5 886 552	4 346 483	7 426 621	19.5
Dexmethylphenidate	250 132	0	534 579	1.6	460 670	166 583	754 756	1.5
Prescriptions per patient (mean, 95% CI)	6.7	6.1	7.4		7.3	6.8	7.8	
Annual days supply (mean, 95% CI)	208	187	229		226	210	242	

Table 3. Changes in Schedule II CNS stimulant use, 2013, 2018

	Persons, number who took CNS stimulants							
	2013	2018	Difference	95% CI		t	p	Change t1-t2,(%)
All Adults	2 296 473	4 128 752	1 832 279	1 006 626	2 657 932	4.35	< 0.01	79.8
Gender								
Male	1 315 701	1 827 177	511 476	- 28 416	1 051 368	1.86	0.063	38.9
Female	980 772	2 301 574	1 320 802	840 273	1 801 333	5.39	< 0.01	134.7
Age Group								
19-24	578 917	772 502	193 585	- 224 956	612 126	0.91	0.365	33.4
25-44	1 033 683	1 914 712	881 029	394 685	1 367 372	3.55	< 0.01	85.2
45-64	581 227	1 166 798	585 571	284 399	886 745	3.81	< 0.01	100.7
65-85	102 646	274 739	172 093	35 088	309 099	2.46	0.014	167.7
	Stimulant prescriptions, number dispensed							
	2013	2018	Difference	95% CI		t	p	Change t1-t2,(%)
All Schedule II stimulants	15 412 693	30 150 428	14 737 735	12 105 049	17 370 420	10.97	< 0.01	95.6
Amphetamine products	10 859 022	23 803 206	12 944 184	10 518 473	15 369 896	10.46	< 0.01	119.2
Methylphenidate products	4 553 672	6 347 222	1 793 550	244 341	3 342 759	2.27	0.023	39.4

Table 4. Adult Schedule II Stimulant Users Mental, Neurological Conditions, 2018

	Reported medication			Reported medical visit[a]			Reported condition		
	(%)	95% CI		(%)	95% CI		(%)	95% CI	
Mental, neurological condition									
ADHD	77.8	72.6	83.0	79.3	73.3	85.4	79.3	73.3	85.4
Anxiety	26.8	22.2	31.5	31.2	26.3	36.2	31.2	26.3	36.2
Depression	25.1	19.9	30.3	28.3	22.8	33.8	28.3	22.8	33.8
Other mental	15.3	9.8	20.8	19.8	14.3	25.3	19.8	14.3	25.3
Anxiety and/or depression	40.6	34.9	46.3	45.0	39.3	50.8	45.0	39.3	50.8

Abbreviations: ADHD, Attention deficit hyperactivity disorder.
a Medical visit = Includes office, inpatient, outpatient, or emergency department

Changes in Medical Use of Central Nervous System Stimulants Among US Adults, 2013-2018, a Cross-Sectional Study

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6-7
Methods			
Study design	4	Present key elements of study design early in the paper	6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7-8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-8*
Bias	9	Describe any efforts to address potential sources of bias	12-13
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	7-8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	8-9

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6-8. Table 1
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9, table 1
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	*9-12*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-12, Table 2-4
		(*b*) Report category boundaries when continuous variables were categorized	Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12-13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NONE

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.