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Medical Use and Combination Drug Therapy Among US Adult Users Of Central Nervous System Stimulants: A Cross-Sectional Analysis

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OBJECTIVE Examine patterns of adult medical use of amphetamine and methyphendate stimulant drugs, classified in the US as Schedule II Controlled Substances with a high potential for psychological or physical dependence.

DESIGN Cross-sectional study.

SETTING AND PARTICIPANTS Prescription drug claims for US adults, age 19-65, included in a commercial insurance claims database with 9.1 million continuously enrolled adults from October 1, 2019 through December 31, 2020. Stimulant use was defined as adults filling 1 or more prescriptions during calendar 2020.

PRIMARY AND SECONDARY OUTCOME MEASURES The primary outcome was an outpatient prescription claim, service date, and days' supply for CNS-active drugs. Combination-2 was defined as 60 days or more of combination treatment with a Schedule II stimulant and 1 or more additional CNS-active drugs. Combination-3 therapy was defined as the addition of 2 or more additional CNS-active drugs.

RESULTS Among 9 141 877 continuously enrolled adults, the study identified 276 223 individuals (3.0%) using Schedule II stimulants during 2020. They filled a median of 8 (interquartile range [IQR], 4-11) prescriptions for these stimulant drugs that provided 227 (IQR, 110-322) treatment days of exposure. Among this group, 125 781 (45.5%) combined use of 1 or more additional CNS active drugs for a median of 213 (IQR, 126-301) treatment days. Also, 66 996 (24.3%) stimulant users also used 2 or more additional CNS-active drugs for a median of 182 (IQR, 108-276) days. Among stimulants users, 131 485 (47.6%) were exposed to an antidepressant, 85 166 (30.8%) filled prescriptions for anxiety/sedative/hypnotic medications, and 54 035 (19.6%) received opioid prescriptions.

CONCLUSIONS A large proportion of adults using Schedule II stimulants are simultaneously exposed to 1 or more other CNS-active drugs, many with tolerance, withdrawal effects, or potential for non-medical use. There are no approved indications and limited clinical trial testing of these multi-drug combinations.

Strengths and Limitations of this Study

- This study of adult use of amphetame and methyphenidate stimulants uses a large commercial claims database with 20 million covered individuals designed for research use into US medical care issues.
- The study population for the primary outcome was large (n = 276 223) and contained extensive detail on each CNS-active prescription, including drug, drug class, strength and days' supply. This permitted evaluation of exposure for each day of 2020, and paid claims made it highly likely the drugs were dispensed.
- The commercially insured population assessed in this study may not represent all commercially insured adults, and omits those insured in state Medicaid programs, through other government programs, the uninsured, and adults over age 64.
- Although the MarketScan data set includes up to 4 diagnosis codes for each outpatient and emergency department encounter, the diagnoses cannot be directly linked to specific prescription drug claims and were not evaluated.

Amphetamines and the chemically related methylphenidate are central nervous system (CNS) stimulants in medical use for 85 years.[1] Their complex mechanisms of action have not been completely elucidated in 137 years since they were first synthesized,[2] but many stimulant effects are primarily result of increased release of dopamine and epinephrine. Its effects have led to multiple medical indications over the many decades, including nasal congestion, narcolepsy, appetite suppression, binge eating, depression, senile behavior, lethargy and attention deficit hyperactivity disorder (ADHD). In the US, risks of addiction and non-medical use have led to amphetamines and methylphenidate being classified (along with opioids and barbiturates), as Schedule II Controlled Substances. [3]

Over the years, many amphetamine and methylphenidate drug products have been created and marketed with various combinations salts, esters, and optical isomers. In July 2022, The US Food and Drug Administration (FDA) Orange Book [4] listed 272 approved drug products with amphetamine ingredients and 303 approved products with methylphenidate. These product totals also reflect various strengths, dosage forms and formulations.

Medical use of the CNS stimulants amphetamine and methylphenidate have been reported to be increasing among adults in observational studies. Using the US Medical Expenditure Survey Panel, a representative sample of all US households, we previously reported a 79% increase from 2013 to 2018 in the number of adults self-reporting prescriptions for these Schedule II stimulants. [5] A Center for Disease Control (CDC) study using the National Prescription Audit reported increased dispensing rates from 2014 to 2019 “driven by notable increases in adults over age 20.” [6] A 2022 study in the electronic health records of 70 million

patients in 52 health care organizations reported stimulant prescriptions increased by 250% from 2006-2016, with these substances increasingly dispensed to older individuals.[7]

Amphetamines are also frequently reported in overdose toxicity, recreational or other non-medical use. In Kentucky state report of fatal drug overdose toxicity in 2021, amphetamine products were ranked 4th among substances found in postmortem toxicology testing, behind fentanyl, 4-ANPP (fentanyl precursor), and illicit methamphetamine. In the Kentucky reports, amphetamine as a listed substance in overdose death toxicology increased from 20.2% of cases in 2017 to 42.0% in 2021.[8,9] The 2020 National Survey of Drug Use and Health estimated that 1.5 % (SE 0.12%) of adults 26 or older (3.2 million) reported misuse of medical stimulants, including both Schedule II and non-scheduled stimulant drugs.[10]

In this study we used a large commercial claims database with 20 million covered individuals to investigate the extent of medical use of these high-risk stimulants among adults and analyze combination therapy with other psychiatric drugs.

Methods

Data source

The data for this study were extracted from the MarketScan 2019 and 2020 Commercial Claims and Encounters Databases.[11] The study population was defined as adults age 19-64 who were continuously enrolled in an included commercial benefit plan from October 1, 2019 through December 31, 2020. Also required was a valid enrollment ID and a non-missing gender as reflected in the Annual Enrollment Summary and the Enrollment Detail tables. The MarketScan product contains de-identified individual data licensed for research use and was

exempt from review by at the Johns Hopkins University Bloomberg School of Public Health Institutional Review Board.

Identification of valid cases

From the study population we identified valid cases as any continuously enrolled adult filling at least one prescription for Schedule II stimulant drug during calendar 2020 as reflected in the Outpatient Pharmaceutical Claims table. For inclusion, the claims record had to include a valid National Drug Code, a service date in 2020, and a non-missing value for the days' supply. Valid claim records indicated a therapeutic class of stimulants (71) and a Drug Enforcement Administration (DEA) class 2. Cocaine is FDA-approved Schedule II stimulant but not indicated for outpatient treatment and no cases appeared in the claims data.

Assessment of drug exposure

We defined exposure as starting on the prescription service date and extending without interruption through the days' supply. To include exposure that occurred in 2020 but began with a prescription filled in 2019, we included any prescription claim filled in 2019 that included days' supply extending into 2020. Days' exposure was censored on December 31, 2020 even if days' supply extended into 2021. For the stimulant medications, we counted as one day of exposure even if more than 1 stimulant prescription was in effect.

Drug class and other drug-specific detail was extracted from the Micromedex Red Book[12] , which we linked to Commercial Claims database through National Drug Codes. CNS-active drug classes were defined as antidepressants, anxiolytics/sedatives/hypnotics, antipsychotics, opioids, anti-convulsants, and other CNS-active. Opioids that were not Schedule II were classified separately. We excluded non-steroidal anti-inflammatory drugs (NSAIDS) and non-opioid pain

medications that are active within and outside of the central nervous system, but are listed in the Red Book grouping of CNS-active drug products. Exposure to included CNS-active drugs was assessed in the same procedure as for the Schedule II stimulants except that we counted all CNS-active prescriptions that were in effect on any study day.

Stimulant exposure

We evaluated patterns of stimulant use with day-by-day exposure during calendar 2020. Treatment days were the sum of every day in 2020 with 1 or more stimulant prescription in effect, including prescriptions that were initiated in 2019 but still had days of supply extending into 2020. Prescription starts in 2020 were defined as any valid case with no days stimulant exposure in the 4th quarter of 2019. Prescription stops were defined as by-day assessments that showed no exposure for at least the final 31 days in 2020.

Combination treatment assessment

The Combination-2 outcome variable was defined as 60 days or more exposure to both stimulants and 1 or more additional CNS-active drugs. The robustness of this definition was evaluated through calculating the number of treatment days in 2020 in which the combination-2 definition applied. Combination-3 was defined similarly, except it required 2 or more additional CNS-active drugs' exposure for 60 days or longer. We also evaluated specific drug combinations of stimulants and other classes of CNS-active drug, but included any use of the other classes during 2020.

Statistical analysis

We calculated full population descriptive statistics for the MarketScan data set without need to estimate sampling variation, confidence intervals or other measures of statistical uncertainty. We

used SAS Version 9.4 (SAS Institute, Cary, NC) for Linux and conducted the analysis from January to August 2022.

Results

The study population was 9 141 877 US commercially insured adults age 19-64 with continuous coverage for outpatient drug claims from October 1, 2019 through December 21, 2020. Figure 1 shows the selection of the study population among the MarketScan commercially-insured adult population with coverage for all or part of 2020. Among this group, 276 223 adults (3.0%) filled at least one prescription claim for a Schedule II stimulant. Demographic characteristics of the stimulant vs. non-stimulant adult population are shown in Table 1. The population skewed towards the younger age groups with a prevalence of 4.57% in the age 19-34 years group declining to 1.36% among those age 55-64 years. Utilization was also higher among females (3.32%) compared to males (2.7%). Another notable difference was seven-fold higher utilization of all prescription drugs among the Schedule II stimulant group compared to the non-stimulant population. The stimulant group accounted for a median (interquartile range [IQR]) of 21 (IQR, 12-36) prescription claims in 2020, compared to 4 (IQR, 0-14) among non-stimulant adults.

Utilization of Schedule II stimulants

Utilization of the Schedule II stimulants was intensive. The exposed population was dispensed Schedule II stimulant drugs to provide for a median 227 days (IQR, 110-322) treatment in 2020, including prescriptions that were dispensed in 2019 but with a supply that extended into 2020. Schedule II stimulant utilization is shown in Table 2. Among the adults, amphetamine products accounted for 86.4% of the 2.2 million stimulant prescriptions vs for 13.6% of prescriptions methylphenidate products. Stimulant product detail is shown in Table 3.

Combination treatment results

Among 276 223 adults exposed to Schedule II stimulants in the study year, 125 781 (45.5%) were in the combination-2 group, meaning they were exposed to both stimulants and at least 1 additional CNS-active drug for 60 days or more. Although the combination-2 definition required only 60 days of simultaneous exposure, this group accounted for a median (IQR) of 213 (IQR, 126-301) combination treatment days. Details are shown in Table 4. In addition, 66 996 adults or 24.3% had prescription claims indicating combination-3, or exposure to stimulants plus 2 or more additional CNS-active drugs for a median (IQR) of 182 (IQR, 108-276) days.

Differences by sex and age group

Combined use of stimulants with other CNS-active drugs was more commen among females 82 556 (52.6%) compared to males, 43 225 (36.2%). As shown in Figure 2, combined use increased by age group, with 34.7% of age 19-34 years rising to 63.2% among those age 55-64 years.

Specific drug combinations

Among the adults, 47.6% were also taking antidepressants for 1 or more days during the study year, 30.8% were taking an anxiolytic/sedative/hypnotic, and 15.5% were also exposed to Schedule II opioids. The utilization of non-stimulant CNS-active drugs are shown by drug class in Table 5. The top 20 specific non-stimulant drugs are shown in Table 6 and reinforce the by-class analysis showing antidepressant and anxiolytic/sedative/hypnotics as the most frequently administered combinations.

Discussion

Using a large commercial claims database we found a 3% prevalence of adults age 19-64 years who were exposed to Schedule II stimulants for a median (IQR) of 227 days (IQR, 110-322) during 2020. Among these 276 223 individuals, 45.5% had 60 days or more of stimulant use combined with 1 or more additional CNS-active drugs, including 24.3% taking 2 or more additional CNS-active drugs. Approximately one-half (47.6%) of stimulante users were also taking an antidepressants during the year while nearly one-third (30.8%) were also taking anxiolytics/sedatives/hypnotics. The stimulant-exposed patient population utilized a median (IQR) of 15 (IQR, 9-26) prescriptions for drugs active in the CNS.

Utilization of these Schedule II stimulants may have been restrained by the US Drug Enforcement Administration (DEA) and state-level restrictions on the drugs with high potential for physiological or psychological dependence. This includes licensing of providers, a ban on refills without a direct or telemedicine encounter, monitoring of provider prescribing, and controls to prevent diversion from dispensing pharmacies.[13]

Limitations

While this study relies on a population of 9.1 million adults, this commercially insured population may not represent all commercially insured adults, and omits those insured in state Medicaid programs, through other government programs, the uninsured, and adults over age 64. This study also assumed that the entire days' supply was taken as prescribed. However, the large number of days' treatment and timely renewals suggests that for these stimulants, non-adherence was relatively uncommon. Although the MarketScan data set includes up to 4 diagnosis codes for each outpatient and emergency department encounter, the diagnoses cannot be directly linked to specific prescription drug claims and were not evaluated. Since many providers will not

accept a drug claim for a Schedule II stimulant without an on-label diagnosis of ADHD, we expected large numbers of this diagnosis were present.

Conclusion

Amphetamine utilization in adults has waxed and waned over many decades and is now making a comeback as monotherapy for adult ADHD and in combination with treatments for depression and anxiety. Given risks of addiction, dependence and non-medical use, physicians should monitor the ongoing need, assess results, and be alert to patient requests for these medications.

Contributers: Mr. Moore had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Moore, Wirtz, Alexander

Acquisition, analysis, or interpretation of data: Moore, Wirtz, Alexander

Drafting of the manuscript: Moore, Curran

Critical revision of the manuscript for important intellectual content: Alexander, Wirtz, Curran

Statistical analysis: Wirtz, Moore

Administrative, technical, or material support: Curran, Alexander

Supervision: Moore

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests: Dr. Alexander is past Chair and a current member of FDA's Peripheral and Central Nervous System Advisory Committee; is a co-founding Principal and equity holder in Monument Analytics, a health care consultancy whose clients include the life sciences industry as well as plaintiffs in opioid litigation, for whom he has served as a paid expert witness; and is a past member of OptumRx's National P&T Committee. These arrangements have been reviewed and approved by Johns Hopkins University in accordance with its conflict of interest policies.

Data availability statement: Data for this study were extracted from the MarketScan 2019 and 2020 Commercial Claims and Encounters Databases which was accessed under license and not publicly available.

Patient and Public Involvement: Neither patients nor the public were involved in the design, conduct, of this study or drafting of this manuscript.

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Table 1. Characteristics of Commercially Insured Adult Population Exposed and Not Exposed to Schedule II Stimulants in 2020

	Schedule II stimulant	Not exposed
Insured adults, No. (%)	276 223 (3.0)	8 865 654 (97.0)
Sex		
Male	119 271 (2.7)	4 299 018 (97.3)
Female	156 952 (3.3)	4 566 636 (96.7)
Age group		
19-34	128 257 (4.6)	2 680 706 (95.4)
35-44	66 387 (3.4)	1 889 361 (96.6)
45-64	51 658 (2.4)	2 128 239 (97.6)
55-64	29 921 (1.4)	2 167 348 (98.6)
Prescription claims, median (IQR)		
Total prescriptions	21 (12-36)	4 (0-14)
CNS prescriptions	12 (7-21)	0 (0-1)

Table 2. Patterns of Use of Schedule II Stimulants in 2020

Adult use, No. (%)	
All users	276 223 (100.0)
Continuous	157 081 (56.9)
New starts	79 407 (28.8)
Stopped	67 469 (24.4)
Exposure, median (IQR)	
Treatment days,	227 (110-322)
Stimulant prescriptions	8 (4-11)
Total CNS-active prescriptions	15 (9-26)

Table 3. Schedule II Stimulant Products Used in 2020

	Prescriptions	Persons
	No. (%)	No. (%)[a]
Drug name		
Amphetamine products		
Amphetamine & combinations	1 429 450 (64.8)	183 019 (66.3)
Lisdexamfetamine	452 415 (20.5)	66 844 (24.2)
Dextroamphetamine	26 681 (1.2)	4 243 (1.5)
Methamphetamine[b]	211 (<0.1)	44 (<0.1)
Methylphenidate products		
Methylphenidate	262 191 (11.9)	42 089 (15.2)
Dexmethylphenidate	36 645 (1.7)	6 446 (2.3)

a Percent totals by person do not add to 100 due to patients taking multiple stimulants
b Prescription drug product only (excludes illicit street drugs)

Table 4. Combination Therapy in 2020 Among Schedule II Stimulant Users

	Combination-2[a]		Combination-3[b]	
	----Yes----	----No----	----Yes----	----No----
	No. (%)	No. (%)	No. (%)	No. (%)
All Users	125 781 (45.5)	150 442 (54.5)	66 996 (24.3)	209 227 (75.7)
Gender				
Male	43 225 (36.2)	76 046 (63.8)	20 708 (17.4)	98 563 (82.6)
Female	82 556 (52.6)	74 396 (47.4)	46 288 (29.5)	110 664 (70.5)
Age Group				
19-34	44 549 (34.7)	83 708 (65.3)	20 371 (15.9)	107 886 (84.1)
35-44	32 608 (49.1)	33 779 (50.9)	17 277 (26.0)	49 110 (74.0)
45-64	29 708 (57.5)	21 950 (42.5)	17 452 (33.8)	34 206 (66.2)
55-64	18 916 (63.2)	11 005 (36.8)	11 896 (39.8)	18 025 (60.2)
Exposure pattern, median (IQR)				
Stimulant treatment days	271(179-335)	173(60-300)	283 (194-338)	202 (90-313)
Combination therapy days	213 (126-301)	0 (0-5)	182 (108-276)	0 (0-4)
Non-stimulant CNS prescriptions	11 (6-20)	0 (0-1)	18 (12-27)	1 (0-5)

a ≥ 60 days use of stimulant + at least 1 other CNS-active drug
b ≥60 days use of stimulant + at least 2 other CNS-active drugs

Table 5. Other CNS-active Drugs by Drug Class in 2020

	Prescriptions	Persons
	No. (%)	No. (%)[a]
Drug class		
Anti-convulsant	225 592 (10.3)	38 112 (13.8)
Antidepressant	987 582 (45.1)	131 485 (47.6)
Antipsychotic	143 611 (6.6)	22 650 (8.2)
Anxiolytic/sedative/hypnotic	540 619 (24.7)	85 166 (30.8)
CNS other	75 613 (3.5)	14 558 (5.3)
Opioids other	48 257 (2.2)	11 322 (4.1)
Opioids Schedule II	149 368 (6.8)	42 713 (15.5)
Stimulant other	19 705 (0.9)	4 368 (1.6)

a Percent totals by person do not add to 100 due to patients taking multiple medications

Table 6. Top 20 Non-stimulant CNS-Active Drugs[a]

		Prescriptions	Persons
		No. (%)	No. (%)
	Drug name		
1	Bupropion	198 943 (9.1)	37 356 (13.5)
2	Alprazolam	140 253 (6.4)	26 184 (9.5)
3	Escitalopram	129 450 (5.9)	26 088 (9.4)
4	Sertraline	120 656 (5.5)	23 550 (8.5)
5	Fluoxetine	111 486 (5.1)	20 528 (7.4)
6	Trazodone	96 148 (4.4)	21 774 (7.9)
7	Clonazepam	94 430 (4.3)	16 690 (6.0)
8	Zolpidem tartrate	86 409 (3.9)	13 956 (5.1)
9	Lamotrigine	84 145 (3.8)	13 722 (5.0)
10	Hydrocodone & combinations	75 943 (3.5)	28 570 (10.3)
11	Gabapentin	75 482 (3.4)	16 922 (6.1)
12	Duloxetine HCL	73 046 (3.3)	12 572 (4.6)
13	Venlafaxine HCL	66 938 (3.1)	10 790 (3.9)
14	Oxycodone & combinations	57 807 (2.6)	17 698 (6.4)
15	Lorazepam	54 379 (2.5)	13 276 (4.8)
16	Buspirone	47 563 (2.2)	11 659 (4.2)
17	Citalopram	47 207 (2.2)	9 250 (3.3)
18	Aripiprazole	46 918 (2.1)	9 290 (3.4)
19	Hydroxyzine	39 066 (1.8)	14 444 (5.2)
20	Quetiapine	37 615 (1.7)	6 912 (2.5)

a Drugs are ranked by number of prescriptions

Figure 1. Commercially Insured Adult Population Prescribed Schedule 2 Stimulants, 2020

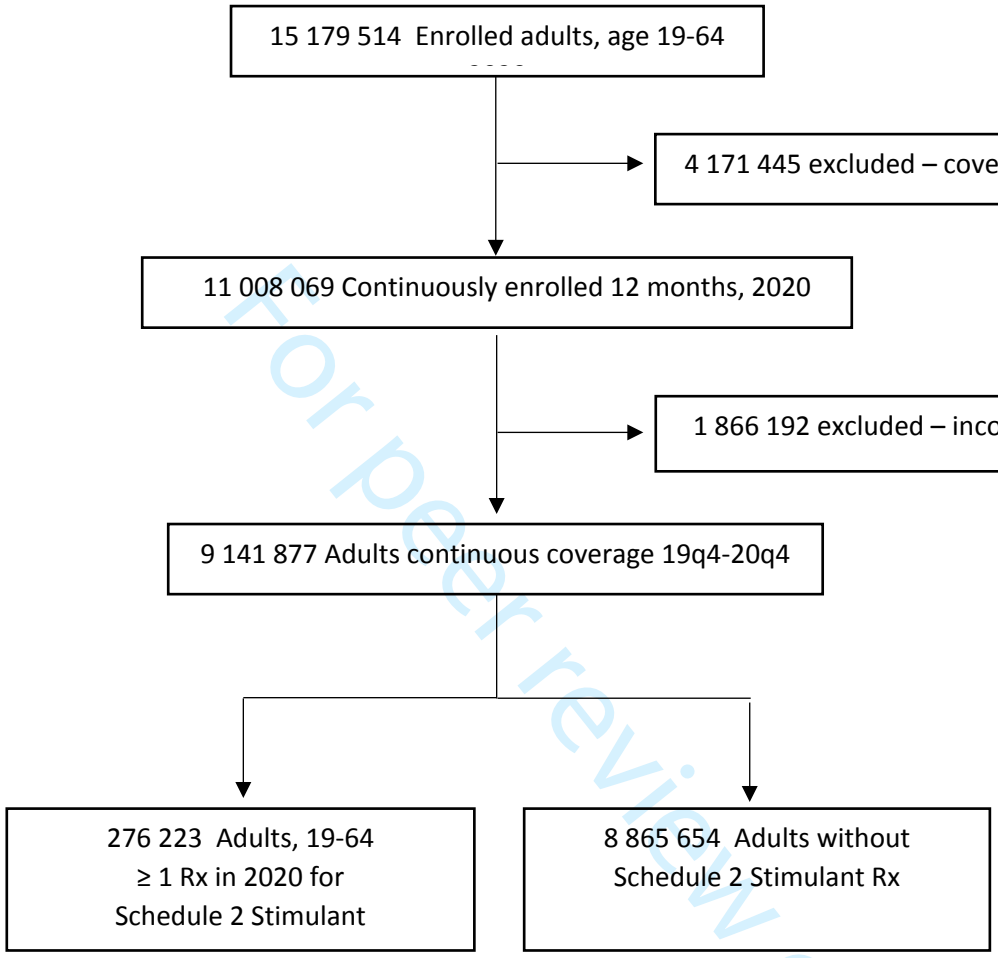
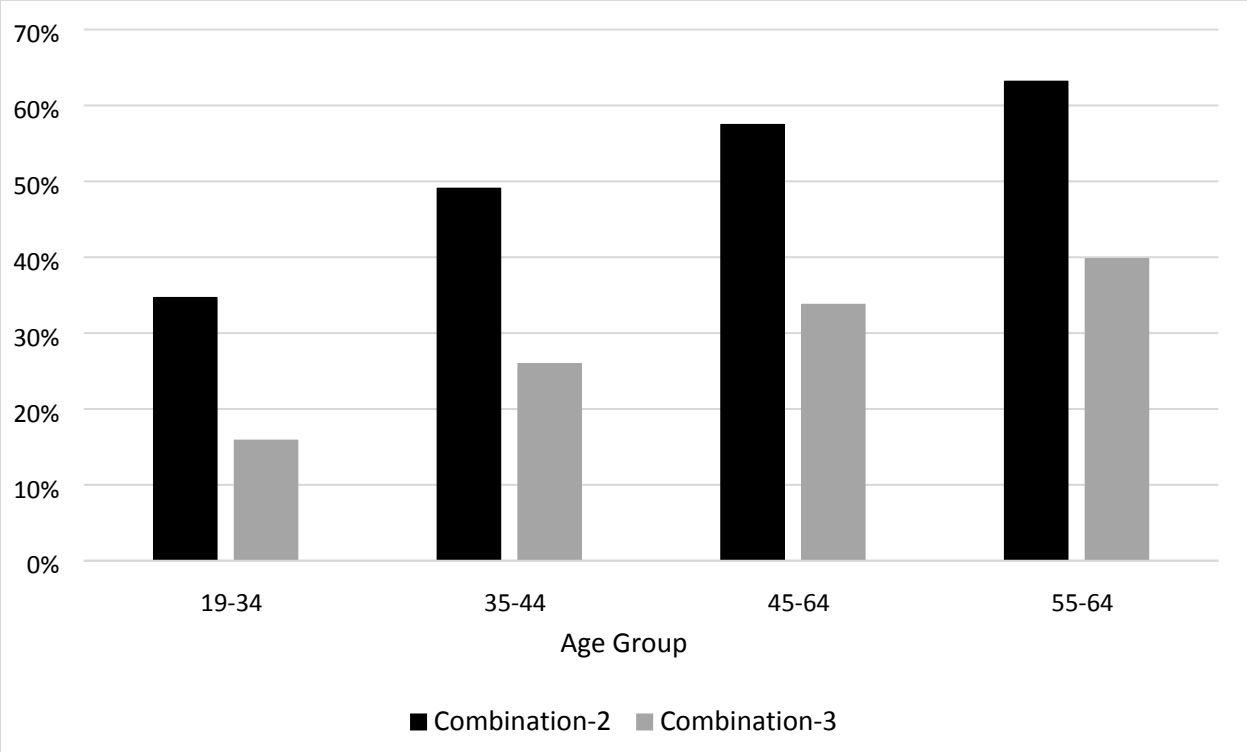


Figure 2. Prevalence of Combination Therapy among Stimulant Users by Age Group[a]



a Exposure to stimulants declines by age group as shown in Table 1 but combination therapy increases

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	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-8
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	5-8
		(*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	6-7
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	*6-7*
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	Fig.1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	NA
		(*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 *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	A population

	(e) Describe any sensitivity analyses	None

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	Fig 1
		(b) Give reasons for non-participation at each stage	Fig 1
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	None
		(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	*Table 2*
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	8
		(*b*) Report category boundaries when continuous variables were categorized	9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	none
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-10
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	10-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
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.

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Medical use and combination drug therapy among US adult users of central nervous system stimulants: a cross-sectional analysis

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Objective: Examine patterns of adult medical use of amphetamine and methylphenidate stimulant drugs, classified in the US as Schedule II Controlled Substances with a high potential for psychological or physical dependence.

Design: Cross-sectional study.

Setting and participants: Prescription drug claims for US adults, age 19-64, included in a commercial insurance claims database with 9.1 million continuously enrolled adults from October 1, 2019, through December 31, 2020. Stimulant use was defined as adults filling 1 or more stimulant prescriptions during calendar 2020.

Outcome measures: The primary outcome was an outpatient prescription claim, service date, and days' supply for CNS-active drugs. Combination-2 was defined as 60 days or more of combination treatment with a Schedule II stimulant and 1 or more additional CNS-active drugs. Combination-3 therapy was defined as the addition of 2 or more additional CNS-active drugs. Using service date and days' supply, we examined the number of stimulant and other CNS-active drugs for each of the 366 days of 2020.

Results: Among 9 141 877 continuously enrolled adults, the study identified 276 223 individuals (3.0%) using Schedule II stimulants during 2020. They filled a median of 8 (interquartile range [IQR], 4-11) prescriptions for these stimulant drugs that provided 227 (IQR, 110-322) treatment days of exposure. Among this group, 125 781 (45.5%) combined use of 1 or more additional CNS active drugs for a median of 213 (IQR, 126-301) treatment days. Also, 66 996 (24.3%) stimulant users also used 2 or more additional CNS-active drugs for a median of 182 (IQR, 108-276) days. Among stimulants users, 131 485 (47.6%) were exposed to an antidepressant, 85 166

(30.8%) filled prescriptions for anxiety/sedative/hypnotic medications, and 54 035 (19.6%) received opioid prescriptions.

Conclusions: A large proportion of adults using Schedule II stimulants are simultaneously exposed to 1 or more other CNS-active drugs, many with tolerance, withdrawal effects, or potential for non-medical use. There are no approved indications and limited clinical trial testing of these multi-drug combinations, and discontinuation may be challenging.

Strengths and limitations of this study

- This study of adult use of amphetamine and methylphenidate stimulants uses a large commercial claims database with 20 million covered individuals designed for research use into US medical care issues.
- The study population for the primary outcome was large (n = 276 223) and contained extensive detail on each CNS-active prescription, including drug, drug class, strength, and days' supply, permitting evaluation of exposure for each day of 2020.
- The commercially insured population assessed in this study may not represent all commercially insured adults, and omits those insured in state Medicaid programs, through other government programs, the uninsured, and adults over age 64.
- Although the MarketScan data set includes up to 4 diagnosis codes for each outpatient and emergency department encounter, the diagnoses cannot be directly linked to specific prescription drug claims and were not evaluated.

Introduction

Amphetamines and the chemically related methylphenidate are central nervous system (CNS) stimulants in medical use for 85 years.[1] Their complex mechanisms of action have not been completely elucidated in 137 years since they were first synthesized,[2] but many stimulant effects are primarily the result of increased release of dopamine and norepinephrine. Their effects have led to multiple medical indications over the many decades, including nasal congestion, narcolepsy, appetite suppression, binge eating, depression, senile behavior, lethargy, and attention deficit hyperactivity disorder (ADHD). In the US, risks of addiction and non-medical use have led to amphetamines and methylphenidate being classified (along with opioids and barbiturates), as Schedule II Controlled Substances.[3]

Over the years, many amphetamine and methylphenidate drug products have been created and marketed with various combinations, salts, esters, and optical isomers. In July 2022, The US Food and Drug Administration (FDA) Orange Book [4] listed 272 approved drug products with amphetamine ingredients and 303 approved products with methylphenidate. These product totals also reflect various strengths, dosage forms, and formulations.

Medical use of the CNS stimulants amphetamine and methylphenidate has been reported to be increasing among adults in observational studies. Using the US Medical Expenditure Survey Panel, a representative sample of all US households, we previously reported a 79% increase from 2013 to 2018 in the number of adults self-reporting prescriptions for these Schedule II stimulants.[5] A Centers for Disease Control (CDC) study using the National Prescription Audit reported increased dispensing rates from 2014 to 2019 “driven by notable increases in adults over age 20.” [6] A 2022 study in the electronic health records of 70 million

patients in 52 health care organizations reported stimulant prescriptions increased by 250% from 2006-2016, with these substances increasingly dispensed to older individuals.[7]

Amphetamines are also frequently reported in overdose toxicity, recreational or other non-medical use. In a Kentucky state report of fatal drug overdose toxicity in 2021, amphetamine products were ranked 4th among substances found in postmortem toxicology testing, behind fentanyl, 4-ANPP (fentanyl precursor), and illicit methamphetamine. In the Kentucky reports, amphetamine as a listed substance in overdose death toxicology increased from 20.2% of cases in 2017 to 42.0% in 2021.[8,9] The 2020 National Survey of Drug Use and Health estimated that 1.5 % (SE 0.12%) of adults 26 or older (3.2 million) reported misuse of medical stimulants, including both Schedule II and non-scheduled stimulant drugs.[10]

In this study, we used a large commercial claims database with 20 million covered individuals to investigate the extent of medical use of these high-risk stimulants among adults and analyze combination therapy with other psychiatric drugs.

Methods

Data source

The data for this study were extracted from the MarketScan 2019 and 2020 Commercial Claims and Encounters Databases.[11] The study population was defined as adults age 19-64 who were continuously enrolled in an included commercial benefit plan from October 1, 2019, through December 31, 2020. Also required was a valid enrollment ID and a non-missing gender as reflected in the Annual Enrollment Summary and the Enrollment Detail tables.

Identification of valid cases

From the study population we identified valid cases as any continuously enrolled adult filling at least one prescription for a Schedule II stimulant drug during calendar 2020 as reflected in the Outpatient Pharmaceutical Claims table. For inclusion, the claims record had to include a valid National Drug Code, a service date in 2020, and a non-missing value for the days' supply. Valid claim records indicated a therapeutic class of stimulants (71) and a Drug Enforcement Administration (DEA) class 2. Cocaine is an FDA-approved Schedule II stimulant but not indicated for outpatient treatment, and no cases appeared in the claims data.

Assessment of drug exposure

We defined exposure as starting on the prescription service date and extending without interruption through the days' supply. To include exposure that occurred in 2020 but began with a prescription filled in 2019, we included any prescription claim filled in 2019 that included days' supply extending into 2020. Days' exposure was censored on December 31, 2020, even if the days' supply extended into 2021. For the stimulant medications, we counted as one day of exposure even if more than 1 stimulant prescription was in effect on that day.

Drug class and other drug-specific details were extracted from the Micromedex RED BOOK,[12] which we linked to the Commercial Claims database through National Drug Codes. CNS-active drug classes were defined as antidepressants, anxiolytics/sedatives/hypnotics, antipsychotics, opioids, anti-convulsants, and other CNS-active drugs. Opioids that were not Schedule II were classified separately. We excluded non-steroidal anti-inflammatory drugs (NSAIDs) and non-opioid pain medications that are active within and outside of the central nervous system but are listed in the RED BOOK grouping of CNS-active drug products. Exposure to included CNS-active drugs was assessed in the same procedure as for the Schedule

II stimulants except that we counted all CNS-active prescriptions that were in effect on any study day.

Stimulant exposure

We evaluated patterns of stimulant use with day-by-day exposure during calendar 2020. Treatment days were the sum of every day in 2020 with 1 or more stimulant prescriptions in effect, including prescriptions that were initiated in 2019 but still had days of supply extending into 2020. Prescription starts in 2020 were defined as any valid case with no days of stimulant exposure in the 4th quarter of 2019. Prescription stops were defined as by-day assessments that showed no exposure for at least the final 31 days in 2020.

Combination treatment assessment

The Combination-2 outcome variable was defined as 60 days or more of exposure to both stimulants and 1 or more additional CNS-active drugs. The robustness of this definition was evaluated through calculating the number of treatment days in 2020 in which the Combination-2 definition applied. Combination-3 was defined similarly, except it required 2 or more additional CNS-active drugs' exposure for 60 days or longer. We also evaluated specific drug combinations of stimulants and other classes of CNS-active drugs but included any use of the other classes during 2020.

Statistical analysis

We calculated full population descriptive statistics for the MarketScan data set without the need to estimate sampling variation, confidence intervals, or other measures of statistical uncertainty. We used SAS Version 9.4 (SAS Institute, Cary, NC) for Linux and conducted the analysis from January to August 2022.

Public and patient involvement

None.

Results

The study population was 9 141 877 US commercially insured adults age 19-64 with continuous coverage for outpatient drug claims from October 1, 2019, through December 21, 2020. Figure 1 shows the selection of the study population among the MarketScan commercially insured adult population with coverage for all or part of 2020. Among this group, 276 223 adults (3.0%) filled at least one prescription claim for a Schedule II stimulant. Demographic characteristics of the stimulant vs. non-stimulant adult population are shown in Table 1. The population skewed towards the younger age groups with a prevalence of 4.6% in the age 19-34 years group declining to 1.4% among those age 55-64 years. Utilization was also higher among females (3.3%) compared to males (2.7%). Another notable difference was seven-fold higher utilization of all prescription drugs among the Schedule II stimulant group compared to the non-stimulant population. The stimulant group accounted for a median (interquartile range [IQR]) of 21 (IQR, 12-36) number of prescription claims in 2020, compared to 4 (IQR, 0-14) among non-stimulant adults.

Utilization of Schedule II stimulants

Utilization of the Schedule II stimulants was intensive. The exposed population was dispensed Schedule II stimulant drugs to provide for a median 227 days (IQR, 110-322) of treatment in 2020, including prescriptions that were dispensed in 2019 but with a supply that extended into 2020. Schedule II stimulant utilization is shown in Table 2. Among the adults, amphetamine

products accounted for 86.4% of the 2.2 million stimulant prescriptions vs 13.6% of prescriptions for methylphenidate products. Stimulant product detail is shown in Table 3.

Combination treatment results

Among 276 223 adults exposed to Schedule II stimulants in the study year, 125 781 (45.5%) were in the Combination-2 group, meaning they were exposed to both stimulants and at least 1 additional CNS-active drug for 60 days or more. Although the Combination-2 definition required only 60 days of simultaneous exposure, this group accounted for a median of 213 (IQR, 126-301) combination treatment days. Details are shown in Table 4. In addition, 66 996 adults or 24.3% had prescription claims indicating Combination-3, or exposure to stimulants plus 2 or more additional CNS-active drugs for a median of 182 (IQR, 108-276) days.

Differences by sex and age group

Combined use of stimulants with other CNS-active drugs was more common among females 82 556 (52.6%) compared to males, 43 225 (36.2%). As shown in Figure 2, combined use increased by age group, with 34.7% of age 19-34 years rising to 63.2% among those age 55-64 years.

Specific drug combinations

Among the adults, 47.6% were also taking antidepressants for 1 or more days during the study year, 30.8% were taking an anxiolytic/sedative/hypnotic, and 15.5% were also exposed to Schedule II opioids. The utilization of non-stimulant CNS-active drugs are shown by drug class in Table 5. The top 20 specific non-stimulant drugs are shown in Supplementary Table 1 and reinforce the by-class analysis showing antidepressants and anxiolytic/sedative/hypnotic drugs as the most frequently administered combinations.

Discussion

Using a large commercial claims database we found a 3% prevalence of adults age 19-64 years who were exposed to Schedule II stimulants for a median of 227 days (IQR, 110-322) during 2020. Among these 276 223 individuals, 45.5% had 60 days or more of stimulant use combined with 1 or more additional CNS-active drugs, including 24.3% taking 2 or more additional CNS-active drugs. Approximately one-half (47.6%) of stimulant users were also taking an antidepressant during the year, while nearly one-third (30.8%) were also taking anxiolytics/sedatives/hypnotics. The stimulant-exposed patient population utilized a median of 15 (IQR, 9-26) prescriptions for drugs active in the CNS.

Utilization of these Schedule II stimulants may have been restrained by the US Drug Enforcement Administration (DEA) and state-level restrictions on the drugs with high potential for physiological or psychological dependence. This includes licensing of providers, a ban on refills without a direct or telemedicine encounter, monitoring of provider prescribing, and controls to prevent diversion from dispensing pharmacies.[13]

These findings add new public health concerns to those raised by our previous study reporting a 79% increase in stimulant use in adults over a 5-year period.[5] This more detailed profile of *how* these stimulants are being utilized reveals several new patterns. First, once treatment started, most become long-term users–75% of patients continued throughout the one-year period. This underscores the possible risks of non-medical use and dependence that have warranted the classification of these drugs as having a high potential for psychological or physical dependence and their prominent appearance in toxicology drug rankings of fatal overdose cases. Second, these data reveal an additional medical use for amphetamine and

methylphenidate products beyond their primary approved use as monotherapy for adult ADHD. Nearly half the exposed population was being prescribed these drugs in combination therapy with 1 or more other psychiatric drugs, including 24.3% in combination therapy with 2 or more additional psychiatric drugs. Third, these combination therapy results identify patients who may be getting stimulants or other psychiatric drugs as part of a prescribing cascade. For example, 9.5% of the population getting a potent stimulant of the CNS were also taking alprazolam, an anxiolytic/sedative/hypnotic drug. These data do not indicate which intervention may have come first—a stimulant added to compensate for excess sedation from the benzodiazepine, or the alprazolam added to calm excessive CNS stimulation and/or insomnia from the stimulants or other drugs. Since, in addition, alprazolam itself has a boxed warning for "abuse, misuse, and addiction," as well as dependence, and withdrawal reactions,[14] this complicates any discontinuation of either or both drugs. In addition, 15.5% of stimulant patients were also taking DEA Schedule II opioids.

Limitations

While this study relies on a population of 9.1 million adults, this commercially insured population may not represent all commercially insured adults, and it omits those insured in state Medicaid programs, through other government programs, the uninsured, and adults over age 64. This study also assumed that the entire days' supply was taken as prescribed. However, the median of 227 days of treatment and timely renewals suggests that for these stimulants, non-adherence was relatively uncommon. Although the MarketScan data set includes up to 4 diagnosis codes for each outpatient and emergency department encounter, the diagnoses cannot be directly linked to specific prescription drug claims and were not evaluated. Since many

providers will not accept a drug claim for a Schedule II stimulant without an on-label diagnosis of ADHD, we suspected that large numbers of this diagnosis were present.

Conclusion

This real-world-evidence profile of amphetamine and methylphenidate use in a large adult population reveals new patterns of utilization beyond the approved use as monotherapy for adult ADHD. Nearly half were prescribed 1 or more additional psychiatric drugs. Little scientific evidence is available to assess the risks and benefits of combination therapy with multiple psychiatric drugs. In addition, many combination therapy drugs had their own elevated risks of psychological or physical dependence or non-medical use. Discontinuation of 2 or more drugs with different withdrawal effects may be challenging.

Ethics approval: The data in this study were de-identified for research use and publication under the licensing agreement. It is exempt from review and approval by the Johns Hopkins University Bloomberg School of Public Health Institutional Review Board.

Contributors: Mr. Moore had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Concept and design:* Moore, Wirtz, Alexander. *Acquisition, analysis, or interpretation of data:* Moore, Wirtz, Alexander. *Drafting of the manuscript:* Moore, Curran. *Critical revision of the manuscript for important intellectual content:* Alexander, Wirtz, Curran. *Statistical analysis:* Wirtz, Moore. *Administrative, technical, or material support:* Curran, Alexander. *Supervision:* Moore.

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Competing interests: Dr. Alexander is past Chair and a current member of FDA's Peripheral and Central Nervous System Advisory Committee; is a co-founding Principal and equity holder in Monument Analytics, a health care consultancy whose clients include the life sciences industry as well as plaintiffs in opioid litigation, for whom he has served as a paid expert witness; and is a past member of OptumRx's National P&T Committee. These arrangements have been reviewed and approved by Johns Hopkins University in accordance with its conflict of interest policies. The other authors declare no completing interests.

Data availability statement: Data for this study were extracted from the MarketScan 2019 and 2020 Commercial Claims and Encounters Databases which were accessed under license and not publicly available.

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FIGURE LEGENDS

Figure 1. Commercially insured adult population prescribed Schedule II stimulants, 2020
Source: MarketScan Research Databases, 2019-2020, commercially insured adults, age 19-64. Schedule II stimulants include amphetamine and methylphenidate drug products.

Figure 2. Prevalence of combination therapy among stimulant users by age group, 2020
Combination therapy with stimulants and 1 or more other psychiatric drugs (n = 121 781, Combination-2) or 2 or more other psychiatric drugs (n = 66 996, Combination-3); MarketScan Research Databases, 2019-2020, Outpatient Pharmaceutical Claims.

Table 1. Characteristics of commercially insured adult population exposed and not exposed to Schedule II stimulants in 2020

	Schedule II stimulant	Not exposed
Insured adults, No. (%)	276 223 (3.0)	8 865 654 (97.0)
Sex		
Male	119 271 (2.7)	4 299 018 (97.3)
Female	156 952 (3.3)	4 566 636 (96.7)
Age group		
19-34	128 257 (4.6)	2 680 706 (95.4)
35-44	66 387 (3.4)	1 889 361 (96.6)
45-54	51 658 (2.4)	2 128 239 (97.6)
55-64	29 921 (1.4)	2 167 348 (98.6)
Prescription claims, median (IQR)		
Total prescriptions	21 (12-36)	4 (0-14)
CNS prescriptions	12 (7-21)	0 (0-1)

Source: MarketScan Research Databases, 2019-2020, commercially insured adults, age 19-64. Schedule II stimulants include amphetamine and methylphenidate drug products.

Table 2. Patterns of use of Schedule II stimulants in 2020

Adult use, No. (%)	
All users	276 223 (100.0)
Continuous	157 081 (56.9)
New starts	79 407 (28.8)
Stopped	67 469 (24.4)
Exposure, median (IQR)	
Treatment days	227 (110-322)
Stimulant prescriptions	8 (4-11)
Total CNS-active prescriptions	15 (9-26)

Source: MarketScan Research Databases, 2019-2020, commercially insured adults, age 19-64. Schedule II stimulants include amphetamine and methylphenidate drug products.

Table 3. Schedule II stimulant products used in 2020

	Prescriptions	Persons
	No. (%)	No. (%)[a]
Drug name		
Amphetamine products		
Amphetamine & combinations	1 429 450 (64.8)	183 019 (66.3)
Lisdexamfetamine	452 415 (20.5)	66 844 (24.2)
Dextroamphetamine	26 681 (1.2)	4 243 (1.5)
Methamphetamine[b]	211 (<0.1)	44 (<0.1)
Methylphenidate products		
Methylphenidate	262 191 (11.9)	42 089 (15.2)
Dexmethylphenidate	36 645 (1.7)	6 446 (2.3)

a Percent totals by person do not add to 100 due to patients taking multiple stimulants
b Prescription drug product only (excludes illicit street drugs)
Source: MarketScan Research Databases, 2019-2020, commercially insured adults, age 19-64. Schedule II stimulants include amphetamine and methylphenidate drug products.

Table 4. Combination Therapy in 2020 among Schedule II stimulant users

	Combination-2[a]		Combination-3[b]	
	----Yes----	----No----	----Yes----	----No----
	No. (%)	No. (%)	No. (%)	No. (%)
All Users	125 781 (45.5)	150 442 (54.5)	66 996 (24.3)	209 227 (75.7)
Gender				
Male	43 225 (36.2)	76 046 (63.8)	20 708 (17.4)	98 563 (82.6)
Female	82 556 (52.6)	74 396 (47.4)	46 288 (29.5)	110 664 (70.5)
Age Group				
19-34	44 549 (34.7)	83 708 (65.3)	20 371 (15.9)	107 886 (84.1)
35-44	32 608 (49.1)	33 779 (50.9)	17 277 (26.0)	49 110 (74.0)
45-54	29 708 (57.5)	21 950 (42.5)	17 452 (33.8)	34 206 (66.2)
55-64	18 916 (63.2)	11 005 (36.8)	11 896 (39.8)	18 025 (60.2)
Exposure pattern, median (IQR)				
Stimulant treatment days	271(179-335)	173(60-300)	283 (194-338)	202 (90-313)
Combination therapy days	213 (126-301)	0 (0-5)	182 (108-276)	0 (0-4)
Non-stimulant CNS prescriptions	11 (6-20)	0 (0-1)	18 (12-27)	1 (0-5)

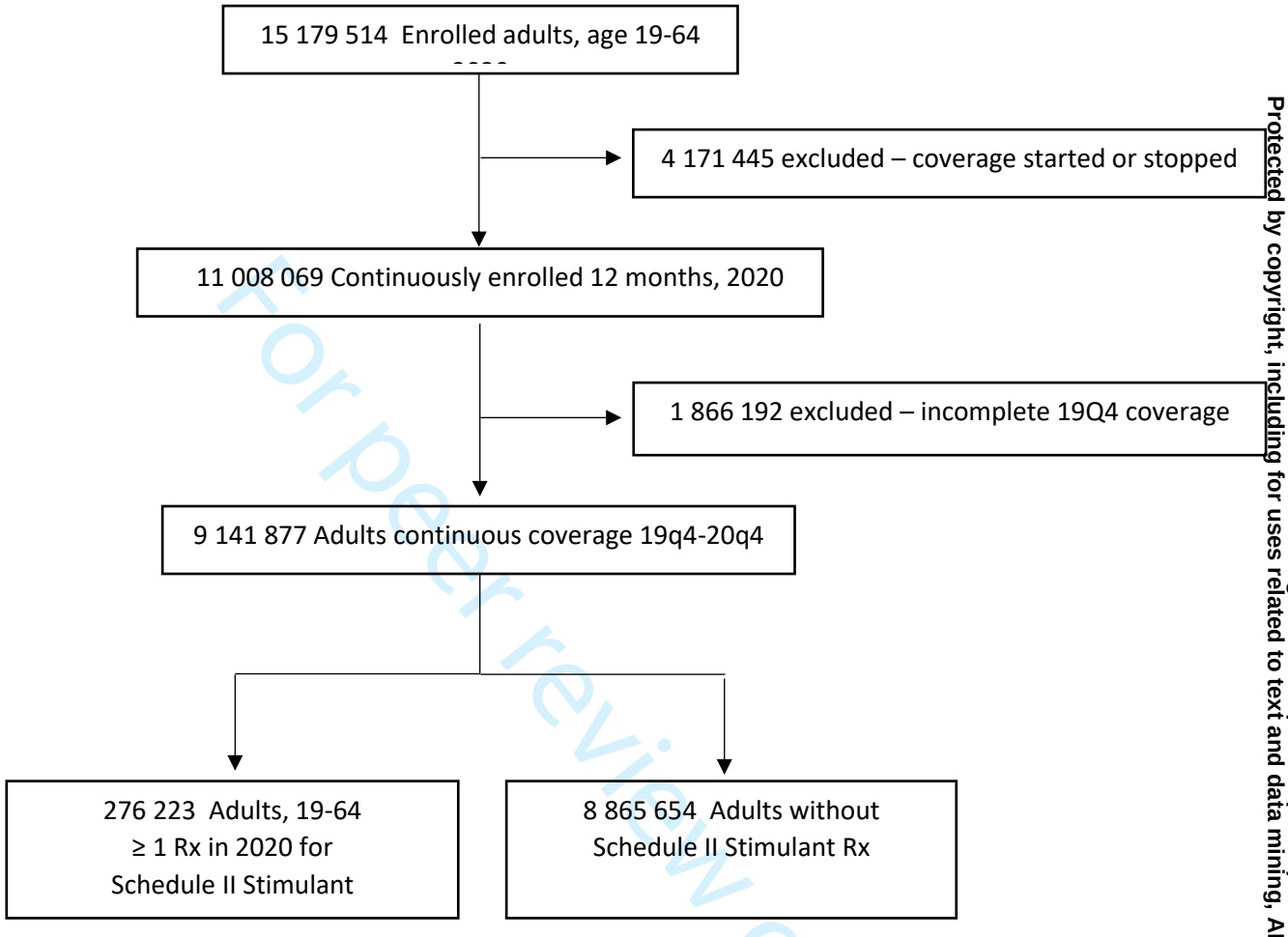
a ≥ 60 days' use of stimulant + at least 1 other CNS-active drug
b ≥60 days' use of stimulant + at least 2 other CNS-active drugs
Source: MarketScan Research Databases, 2019-2020, commercially insured adults, age 19-64. Schedule II stimulants include amphetamine and methylphenidate drug products.

Table 5. Other CNS-active Drugs by Drug Class among those exposed to Schedule II stimulants in 2020

	Prescriptions	Persons
	No. (%)	No. (%)[a]
Drug class[b]		
Anticonvulsant	225 592 (10.3)	38 112 (13.8)
Antidepressant	987 582 (45.1)	131 485 (47.6)
Antipsychotic	143 611 (6.6)	22 650 (8.2)
Anxiolytic/sedative/hypnotic	540 619 (24.7)	85 166 (30.8)
CNS other	75 613 (3.5)	14 558 (5.3)
Opioids other	48 257 (2.2)	11 322 (4.1)
Opioids Schedule II	149 368 (6.8)	42 713 (15.5)
Stimulant other	19 705 (0.9)	4 368 (1.6)

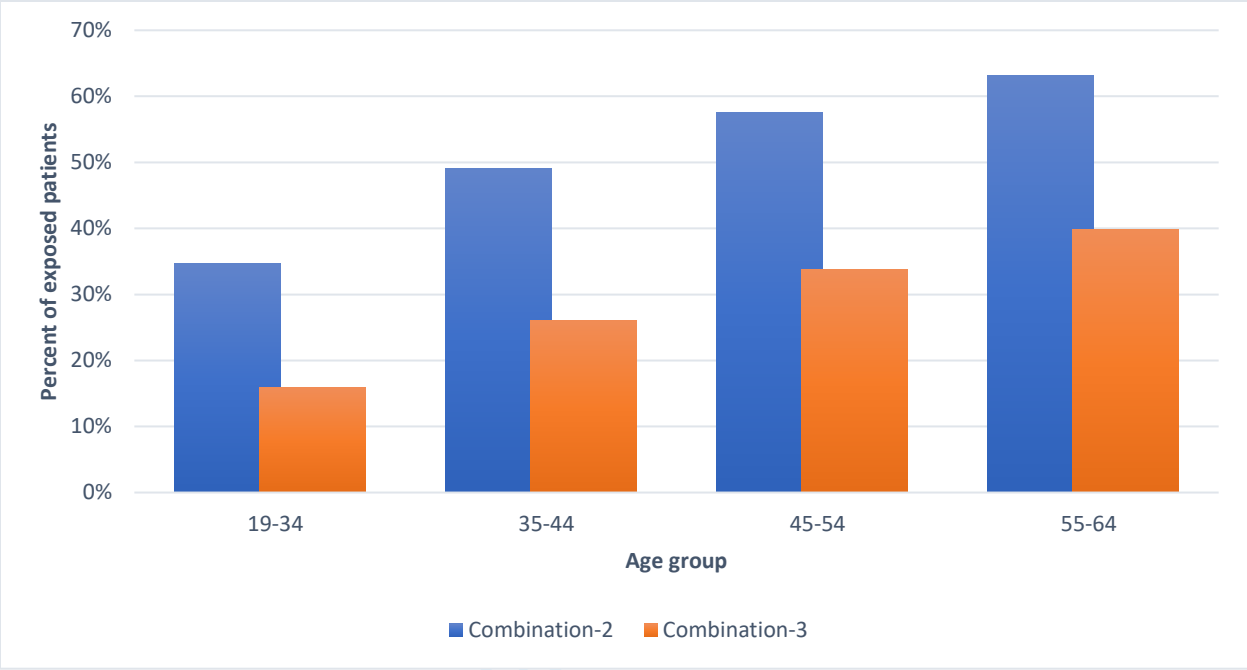
a Percent totals by person do not add to 100 due to patients taking multiple medications
b Drug classes defined in Micromedex RED BOOK for 2020.
Source: MarketScan Research Databases, 2019-2020, commercially insured adults, age 19-64. Schedule II stimulants include amphetamine and methylphenidate drug products.

Figure 1 Commercially insured adult population prescribed Schedule II stimulants, 2020



Source: MarketScan Research Databases, 2019-2020, commercially insured adults, age 19-64. Schedule II stimulants include amphetamine and methylphenidate drug products.

Figure 2 Prevalence of combination therapy among stimulant users by age group, 2020



Combination therapy with stimulants and 1 or more other psychiatric drugs (n = 121 781, Combination-2) or 2 or more other psychiatric drugs (n = 66 996, Combination-3); MarketScan Research Databases, 2019-2020, Outpatient Pharmaceutical Claims.

Supplementary Table 1 Top 20 non-stimulant CNS-active drugs among those exposed to Schedule II stimulants[a]

		Prescriptions	Persons
		No. (%)	No. (%)
	Drug name		
1	Bupropion	198 943 (9.1)	37 356 (13.5)
2	Alprazolam	140 253 (6.4)	26 184 (9.5)
3	Escitalopram	129 450 (5.9)	26 088 (9.4)
4	Sertraline	120 656 (5.5)	23 550 (8.5)
5	Fluoxetine	111 486 (5.1)	20 528 (7.4)
6	Trazodone	96 148 (4.4)	21 774 (7.9)
7	Clonazepam	94 430 (4.3)	16 690 (6.0)
8	Zolpidem tartrate	86 409 (3.9)	13 956 (5.1)
9	Lamotrigine	84 145 (3.8)	13 722 (5.0)
10	Hydrocodone & combinations	75 943 (3.5)	28 570 (10.3)
11	Gabapentin	75 482 (3.4)	16 922 (6.1)
12	Duloxetine HCL	73 046 (3.3)	12 572 (4.6)
13	Venlafaxine HCL	66 938 (3.1)	10 790 (3.9)
14	Oxycodone & combinations	57 807 (2.6)	17 698 (6.4)
15	Lorazepam	54 379 (2.5)	13 276 (4.8)
16	Buspirone	47 563 (2.2)	11 659 (4.2)
17	Citalopram	47 207 (2.2)	9 250 (3.3)
18	Aripiprazole	46 918 (2.1)	9 290 (3.4)
19	Hydroxyzine	39 066 (1.8)	14 444 (5.2)
20	Quetiapine	37 615 (1.7)	6 912 (2.5)

a Non-stimulant psychiatric drugs are ranked by number of prescriptions
Source: MarketScan Research Databases, 2019-2020, commercially insured adults, age 19-64. Schedule II stimulants include amphetamine and methylphenidate drug products.

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	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-8
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	5-8
		(*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	6-7
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	*6-7*
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	Fig.1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	NA
		(*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 *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	A population

	(e) Describe any sensitivity analyses	None

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	Fig 1
		(b) Give reasons for non-participation at each stage	Fig 1
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	None
		(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	*Table 2*
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	8
		(*b*) Report category boundaries when continuous variables were categorized	9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	none
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-10
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	10-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
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.