

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

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ABSTRACT

Objective Examine patterns of adult medical use of amphetamine and methylphenidate stimulant drugs, classified in the USA 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 years, included in a commercial insurance claims database with 9.1 million continuously enrolled adults from 1 October 2019, through 31 December 2020. Stimulant use was defined as adults filling one or more stimulant prescriptions during calendar 2020.

Outcome measures The primary outcome was an outpatient prescription claim, service date and days' supply for central nervous system (CNS)-active drugs. Combination-2 was defined as 60 days or more of combination treatment with a Schedule II stimulant and one 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 (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 one or more additional CNS active drugs for a median of 213 (IQR, 126–301) treatment days. Also, 66 996 (24.3%) stimulant users used two or more additional CNS-active drugs for a median of 182 (IQR, 108–276) days. Among stimulant 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.

Conclusion A large proportion of adults using Schedule II stimulants are simultaneously exposed to one 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 central nervous system-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 programmes, through other government programmes, the uninsured and adults over age 64 years.
- ⇒ Although the MarketScan data set includes up to four 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 synthesised,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 behaviour, lethargy and attention deficit hyperactivity disorder (ADHD). In the USA, 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 Book⁴ 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 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 healthcare organisations reported stimulant prescriptions increased by 250% from 2006 to 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 fourth 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 analyse combination therapy with other psychiatric drugs.

METHODS

Data source

The data for this study were extracted from the Market-Scan 2019 and 2020 Commercial Claims and Encounters Databases.¹¹ The study population was defined as adults aged 19–64 years who were continuously enrolled in an included commercial benefit plan from 1 October 2019 through 31 December 2020. Also required was a valid enrolment ID and a non-missing gender as reflected in the Annual Enrolment Summary and the Enrolment 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 31 December 2020, even if the days' supply extended into 2021. For the stimulant medications, we counted as 1 day of exposure even if more than one 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 and non-opioid pain medications that are active within and outside of the CNS 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 one 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 fourth 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 one or more additional CNS-active drugs. The robustness of this definition was evaluated through calculating the

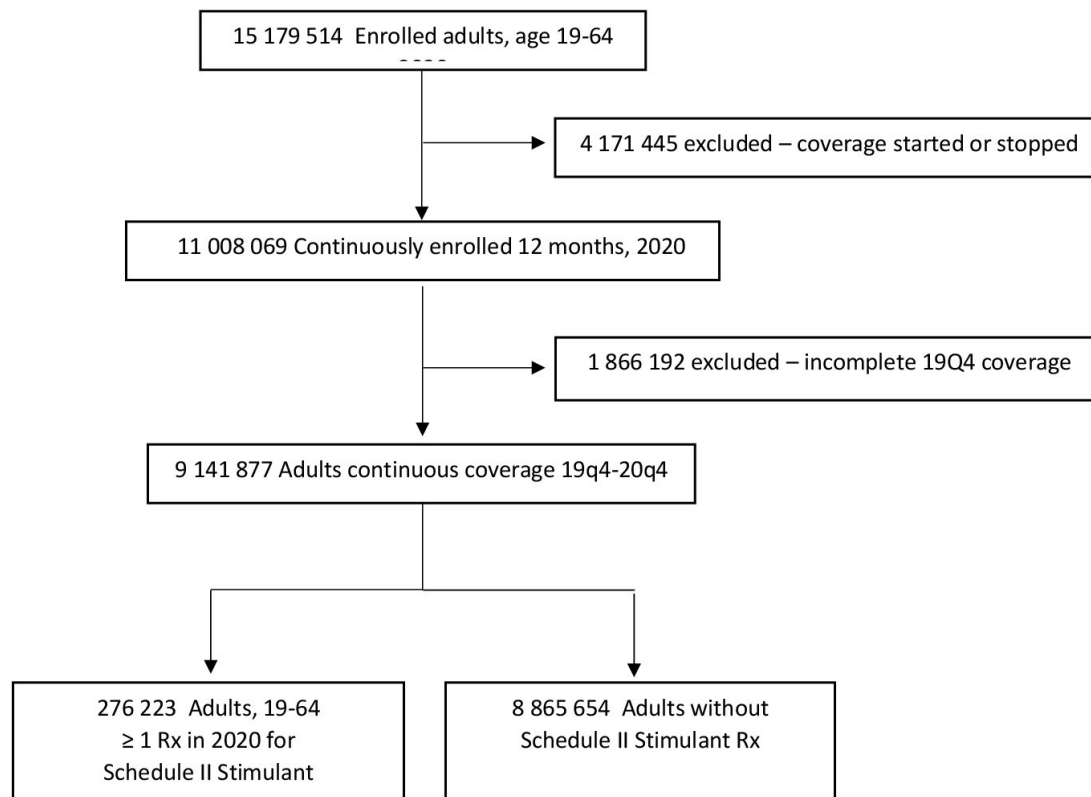


Figure 1 Commercially insured adult population prescribed Schedule II stimulants, 2020. Source: MarketScan Research Databases, 2019–2020, commercially insured adults, age 19–64 years. Schedule II stimulants include amphetamine and methylphenidate drug products.

number of treatment days in 2020 in which the Combination-2 definition applied. Combination-3 was defined similarly, except it required two 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 V.9.4 (SAS Institute) 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 years with continuous coverage for outpatient drug claims from 1 October 2019 through 21 December 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

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 (years)		
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 years. Schedule II stimulants include amphetamine and methylphenidate drug products. CNS, central nervous system.

**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 years. Schedule II stimulants include amphetamine and methylphenidate drug products. CNS, central nervous system.

declining to 1.4% among those age 55–64 years. Utilisation was also higher among females (3.3%) compared with males (2.7%). Another notable difference was seven-fold higher utilisation of all prescription drugs among the Schedule II stimulant group compared with the non-stimulant population. The stimulant group accounted for a median (IQR) of 21 (IQR, 12–36) number of prescription claims in 2020 compared with 4 (IQR, 0–14) among non-stimulant adults.

Utilisation of Schedule II stimulants

Utilisation 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 utilisation 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 one 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 two 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 with males, 43 225 (36.2%). As shown in

Table 3 Schedule II stimulant products used in 2020

Drug name	Prescriptions	Persons
	No (%)	No (%)*
Amphetamine products		
Amphetamine and 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†	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)

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

*Per cent totals by person do not add to 100 due to patients taking multiple stimulants.

†Prescription drug product only (excludes illicit street drugs).

[figure 2](#), combined use increased by age group, with 34.7% of those 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 one 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 utilisation of non-stimulant CNS-active drugs is shown by drug class in [table 5](#). The top 20 specific non-stimulant drugs are shown in online supplemental 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 one or more additional CNS-active drugs, including 24.3% taking two 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 utilised a median of 15 (IQR, 9–26) prescriptions for drugs active in the CNS.

Utilisation of these Schedule II stimulants may have been restrained by the US 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,

Table 4 Combination therapy in 2020 among Schedule II stimulant users

	Combination-2*		Combination-3†	
	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 (years)				
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)

Source: MarketScan Research Databases, 2019–2020, commercially insured adults, age 19–64 years. Schedule II stimulants include amphetamine and methylphenidate drug products.
 *≥60 days' use of stimulant+at least one other CNS-active drug.
 †≥60 days' use of stimulant+at least two other CNS-active drugs.
 CNS, central nervous system.

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 utilised reveals several new patterns. First, once treatment started, most patients become long-term users—75% of patients continued throughout the 1-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

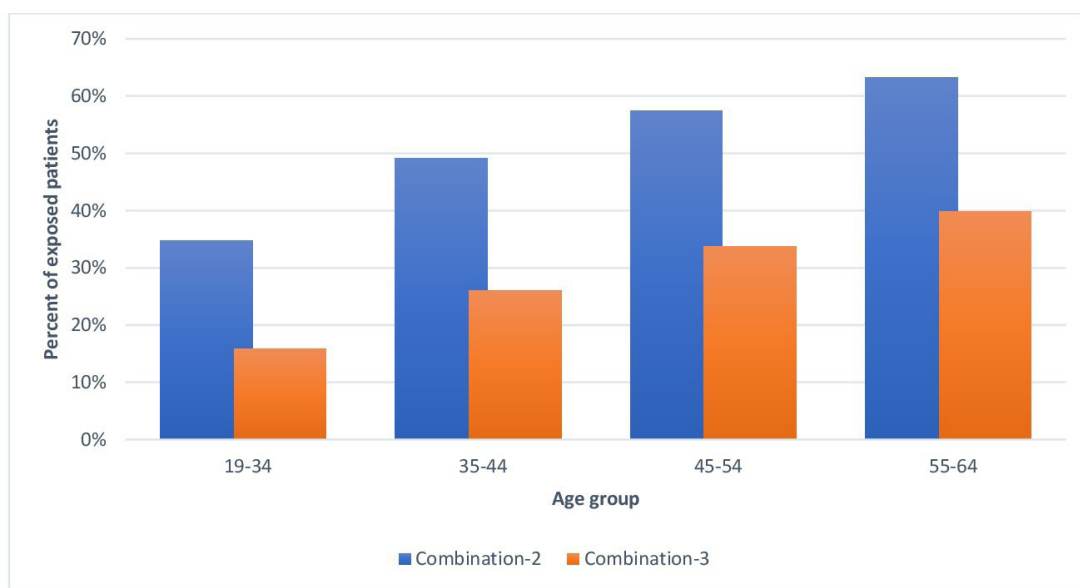


Figure 2 Prevalence of combination therapy among stimulant users by age group, 2020 combination therapy with stimulants and one or more other psychiatric drugs (n=121 781, Combination-2) or two or more other psychiatric drugs (n=66 996, Combination-3); MarketScan Research Databases, 2019–2020, outpatient pharmaceutical claims.

**Table 5** Other CNS-active drugs by drug class among those exposed to Schedule II stimulants in 2020

Drug class†	Prescriptions	Persons
	No (%)	No (%)*
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)

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

*Per cent totals by person do not add to 100 due to patients taking multiple medications.

†Drug classes defined in Micromedex RED BOOK for 2020. CNS, central nervous system.

these drugs in combination therapy with one or more other psychiatric drugs, including 24.3% in combination therapy with two 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 programmes, through other government programmes, the uninsured and adults over age 64 years. 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 four 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 utilisation beyond the approved use as monotherapy for adult ADHD. Nearly half were prescribed one 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 two or more drugs with different withdrawal effects may be challenging.

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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.

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Competing interests GCA 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 healthcare 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 competing interests.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. 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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