Changes in Prescription and Illicit Stimulant Use in the United States, 2014 to 2018

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Abstract

Background: Over the past two decades, diagnosis of attention-deficit/hyperactivity disorder (ADHD) has significantly increased in the United States. ADHD is a neurodevelopmental disorder treated with amphetamine, methylphenidate, and lisdexamfetamine. In addition to pharmacotherapeutic use, stimulants have a high misuse potential. The purpose of this study was to analyze pharmacoepidemiological trends in both prescription and illicit stimulant distribution in the United States from 2014 through 2018.

Methods: Drug weight data was obtained from the Automation of Reports and Consolidated Orders System (ARCOS) retail drug summary reports and StreetRx.com in all 50 states for the following drugs: amphetamine, methylphenidate, and lisdexamfetamine. Mass of the stimulants in grams was corrected from population estimates from the U.S. Census Bureau, Population Division. The median values (20 mg/day/person for methylphenidate and amphetamine and 40 mg/day/person for lisdexamfetamine) were used for daily dose calculations.

Results: Average prescription distribution increased by 8.2% and 15.2% for lisdexamfetamine and amphetamine, respectively, from 2015 through 2018. Methylphenidate prescription distribution decreased by 5.5% during this period. Lisdexamfetamine average daily dose for all 50 states increased from 0.74 mg/day/person to 0.83 mg/day/person over the 4 years. Amphetamine daily dose increased from 2.92 mg/day/person to 3.62 mg/day/person. In contrast, methylphenidate daily dose decreased from 2014 through 2017, from 3.47 mg/day/person in 2014 to 3.23 mg/day/person in 2017. Diverted lisdexamfetamine, amphetamine, and methylphenidate distribution changed by an average of +0.24%, -0.04% and +0.35% across all 50 states, respectively.

Conclusion: From 2014 through 2018, the average prescription distribution and daily dose of amphetamine and lisdexamfetamine have increased throughout the United States, while methylphenidate prescription distribution and daily dose have decreased. Diverted stimulant distribution underwent modest changes. Efficacy, safety, and availability likely play an underlying role in these trends.

Introduction

The diagnosis of attention-deficit/hyperactivity disorder (ADHD) is increasing in the United States. ADHD is a neurodevelopmental disorder which presents in childhood with symptoms of hyperactivity, impulsivity, and/or inattention. Between 1997 and 2016, the prevalence of ADHD rose from 6.1% to 10.2% (1). The reason behind this significant increase remains unclear. One hypothesis is that there has been a change in physician and parental attitudes toward diagnosing attention disorders and pursuing treatment through medication (2). Stimulant based pharmacological therapy is indicated in the first-line treatment of ADHD in the U.S., along with behavioral therapy in younger children (3). Commonly used medications are amphetamine, methylphenidate, or lisdexamfetamine, and less commonly methamphetamine (4). The overall usage of stimulants has doubled in the last decade, with amphetamine distribution increasing 2.5-fold (5). The U.S. is somewhat unusual in that amphetamine is approved for use in 3- to 5-year-olds with ADHD. A report from the CDC documented instances of prescription stimulant use among 2-year-olds (6). A 2012 analysis of outpatient pediatric prescription drug trends found an increase in ADHD medication from 2002 through 2010, with methylphenidate being the most frequently prescribed treatment. The second most frequently prescribed treatment was amphetamine/dexamphetamine, although there began a slight decrease resulting in lower prescriptions in 2010 compared with 2002 (7). Methylphenidate usage peaked in 2012, subsequently declining (5). Analysis of lisdexamfetamine began in 2007 after FDA approval for treatment, thus resulting in an increase in prescriptions from 2007 through 2010 (7).

Alterations to catecholamine neurotransmitters are indicated in the pharmacology of ADHD. In general, stimulants prescribed to treat ADHD aim to increase dopamine and norepinephrine levels in regions of the brain with attentional function. While there are several elements to the mechanism of amphetamine, the drug works primarily to increase levels of extracellular dopamine and norepinephrine. This is accomplished by inhibiting reuptake in the synaptic cleft, particularly through inhibition of dopamine transporter and norepinephrine transporter. Methylphenidate directly inhibits these two transporters as well, while additionally agonizing serotonin receptors (8).

Lisdexamfetamine is a prodrug that is converted in the body to d-amphetamine, which also inhibits the reuptake of dopamine and norepinephrine (9). While these medications benefit 70% of those diagnosed with ADHD, adverse side effects may include appetite loss, abdominal pain, headaches, and insomnia (3,10). However, the evidence base supporting the use of stimulants, and particularly methylphenidate, for ADHD has been characterized as “very weak” due to over-reliance on short-term (<12 weeks) studies, underestimation of the risk of harms, particularly in industry-supported trials,

and inadequate efforts to be blinded when the comparison group receives an inactive placebo (11). A well-powered (N = 190,559) epidemiological report from the laboratory of the former director of the National Institute of Drug Abuse (NIDA) determined that there was a nine-fold increase in basal ganglia and cerebellar disorders among those with a history of prescription stimulant use (12). Interestingly, the current NIDA director and colleagues determined that one-year of prescription methylphenidate (daily dose = 1 mg per kg of body weight) use resulted in an increase in dopamine transporter binding in the caudate and putamen (13) but it is too early to even speculate if this could contribute to neurodegenerative disease processes. Stimulants are used in the treatment of other conditions as well, such as narcolepsy and binge eating disorder, and can often be diverted for nonmedical use (14,15).

These pharmacotherapies are associated with significant abuse potential (16). Amphetamine, methylphenidate, and lisdexamfetamine are classified as Schedule II Controlled Substances, defined as having a high potential for abuse and possible adverse effects (17). Prescription drug diversion is defined as "the unlawful channeling of regulated pharmaceuticals from legal sources in the illicit market" (18). Stimulants, specifically methylphenidate, have been known to be commonly diverted drugs (19).

While it is possible to track the distribution of prescription medications used in the treatment of ADHD through national databases, it is more difficult to monitor the illicit use of these commonly abused medications. In order to gain a more complete understanding of the use of ADHD stimulants, our study further looked at the illicit distribution of stimulants. The Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System uses publicly reported submissions to surveil the diversion of prescription medications. This allows for clearer understanding of the street price of prescription and illicit drugs, the geographical distribution of such drugs, and the trends in misuse. The RADARS System's website, StreetRx.com, allows the public to anonymously submit information regarding which drugs users bought, the amount of that drug, as well as the date and location of their transaction (20). StreetRx.com also allows the public to access and rate this information, so that health officials can better understand the illegal market that exists for prescription drugs with the hopes of providing necessary outreach where needed.

The purpose of this study was to examine and analyze pharmacoepidemiologic trends in both prescribed and illicit stimulant usage in the United States from 2014 through 2018. We sought to specifically analyze the mass distribution per drug and daily dose for amphetamine, methylphenidate, and lisdexamfetamine. Although previous studies have analyzed the trends of stimulant usage (21), we aimed to further analyze these trends with the incorporation of data from drug diversion to better understand the usage patterns.

Methods

Procedures

Drug weight data was obtained from the Automation of Reports and Consolidated Orders System (ARCOS) retail drug summary reports for the years 2014 through 2017 in all 50 states for the following drugs: amphetamine, methylphenidate, and lisdexamfetamine. 2018 drug summary reports were obtained for lisdexamfetamine and amphetamine as well. The amphetamine and methylphenidate prescription distribution data reflect drugs of all enantiomers reported. The 2018 data have been temporarily excluded from the statistical reporting for methylphenidate and thus were not included in this analysis.

Additional drug weight data for illicit distribution was obtained from StreetRx.com through a Data Use Agreement between Geisinger Commonwealth School of Medicine and the Rocky Mountain Poison and Drug Safety department of the Denver Health and Hospital Authority. The date of submission, location of submission, generic name, and raw dose from 2015 through the end of 2018 was used for the following drugs: amphetamine, methylphenidate, and lisdexamfetamine. This study was approved by the Institutional Review Board of the University of New England.

Data analysis

Using ARCOS data, mass of the stimulants in grams was corrected from population estimates from the U.S. Census Bureau, Population Division for each year and state. Percent changes between consecutive pairs of years were calculated for the years 2015-2018. Outliers were identified using Grubbs' Test on GraphPad Prism. Average daily dose calculations were completed for amphetamine, methylphenidate, and lisdexamfetamine for all 50 states for the years 2014 through 2018, with the exception of methylphenidate daily dose for 2018. These calculations used the median values of 20 mg/day/person for methylphenidate and amphetamine and 40 mg/day/person for lisdexamfetamine (21). Figures were created using GraphPad Prism to plot the mean prescription distribution with standard error of mean (SEM) for each drug during their respective years. Heat maps were created using Excel to map the percent changes in total prescription distribution of amphetamine and lisdexamfetamine from 2015 through 2018 and from 2015 through 2017 for methylphenidate.

Using data from StreetRx.com, the raw dose in milligrams was totaled for each drug according to year and state to determine the total quantity in milligrams of amphetamine, methylphenidate, and lisdexamfetamine during the years of 2015 through 2018. The mass of the stimulants in milligrams was similarly corrected from population estimates from the U.S. Census Bureau, Population Division for each state. Percent changes between consecutive pairs of years were calculated for each drug. Figures were created using GraphPad Prism to plot the mean illicit distribution with standard error of mean (SEM) for each drug from 2015 through 2018.

Paired t-tests were completed using GraphPad Prism to analyze the statistical significance of yearly changes. For each drug's ARCOS data, a paired t-test was conducted to compare the daily dose value of each year, 2015 through 2018, relative to 2014 values. Paired t-tests were also conducted using the total distributed mass of each drug, comparing the 2015 through 2018 values to the 2014 value. The exception was methylphenidate, for which the final year tested was 2017. For each drug's StreetRx data, paired t-tests were employed

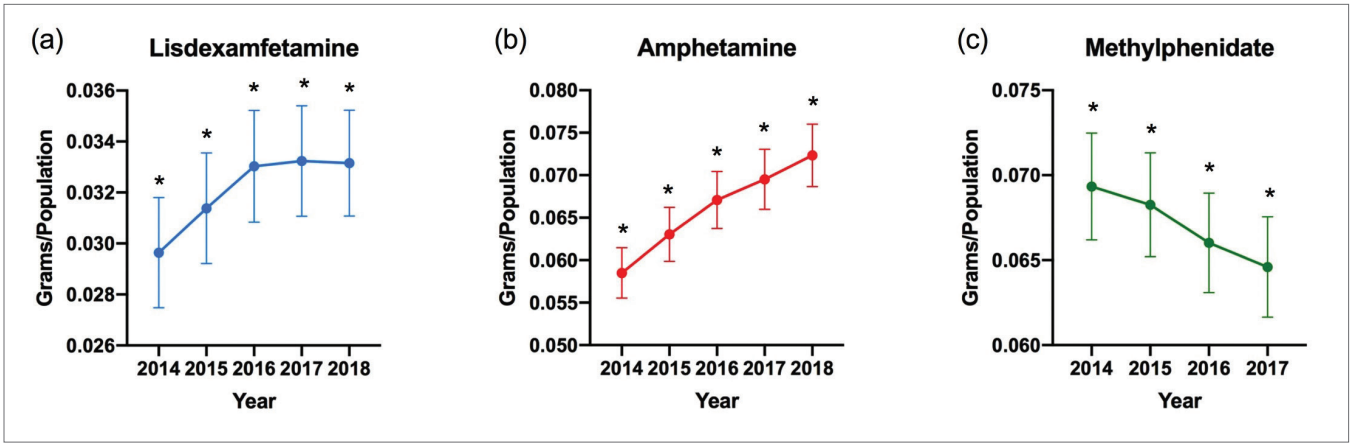

Figure 1. Total prescription distribution in grams of lisdexamfetamine (A), amphetamine (B), and methylphenidate (C) for all 50 states from 2014 through 2017/18 as reported by the Drug Enforcement Administration's Automated Reports and Consolidated Orders System.

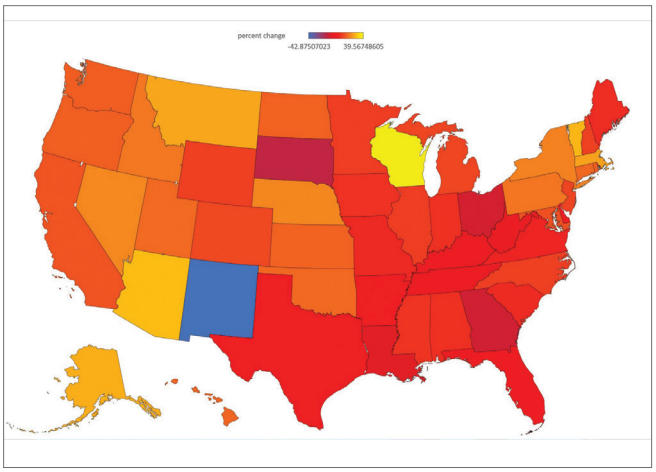

Figure 2. Percent change in lisdexamfetamine distribution from 2015 through 2018. The total mass in grams of lisdexamfetamine distributed as reported by the Drug Enforcement Administration's Automated Reports and Consolidated Orders System has been corrected for population.

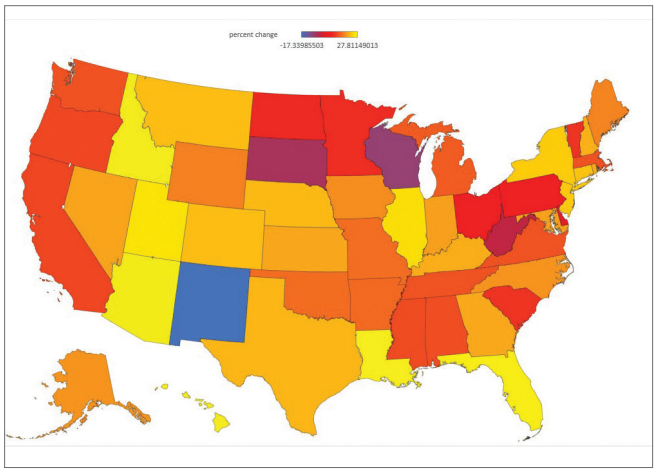

Figure 3. Percent change in amphetamine distribution from 2015 through 2018. The total mass in grams of amphetamine distributed as reported by the Drug Enforcement Administration's Automated Reports and Consolidated Orders System has been corrected for population.

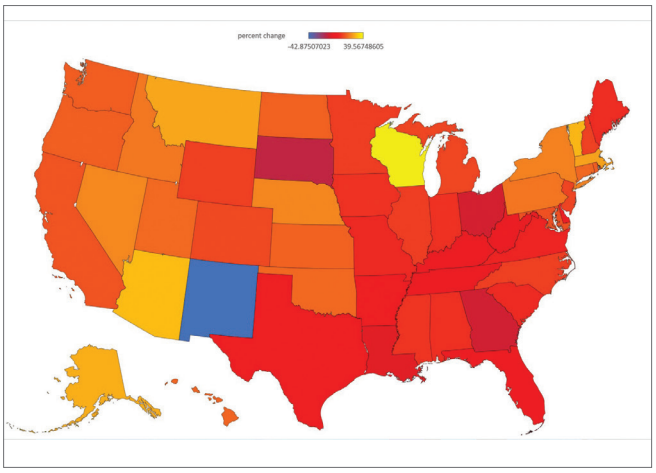

Figure 4. Percent change in methylphenidate distribution from 2015 through 2017. The total mass in grams of methylphenidate distributed as reported by the Drug Enforcement Administration's Automated Reports and Consolidated Orders System has been corrected for population.

for analysis of the total diverted drug mass, comparing the 2016 through 2018 values to the 2015 value. Additionally, the percent change calculation comparing the 2015 value to the 2018 value was done using both the ARCOS and the StreetRx data for each drug.

Results

Total mass distribution and daily dosage (ARCOS data set)

Lisdexamfetamine prescription distribution increased by +8.2% on average from 2015 through 2018 (Figure 1A). Wisconsin had the largest increase in prescription distribution, +39.6% (Figure 2). Amphetamine prescription distribution increased by an average per state of +15.2% from 2015 through 2018 across all 50 states (Figure 1B). Arizona saw the largest increase in prescription distribution, +27.8% (Figure 3). Methylphenidate prescription distribution decreased by -5.5% from 2015 through 2017 (Figure 1C). New Mexico had the largest decrease, -24.3% (Figure 4). New Mexico consistently showed

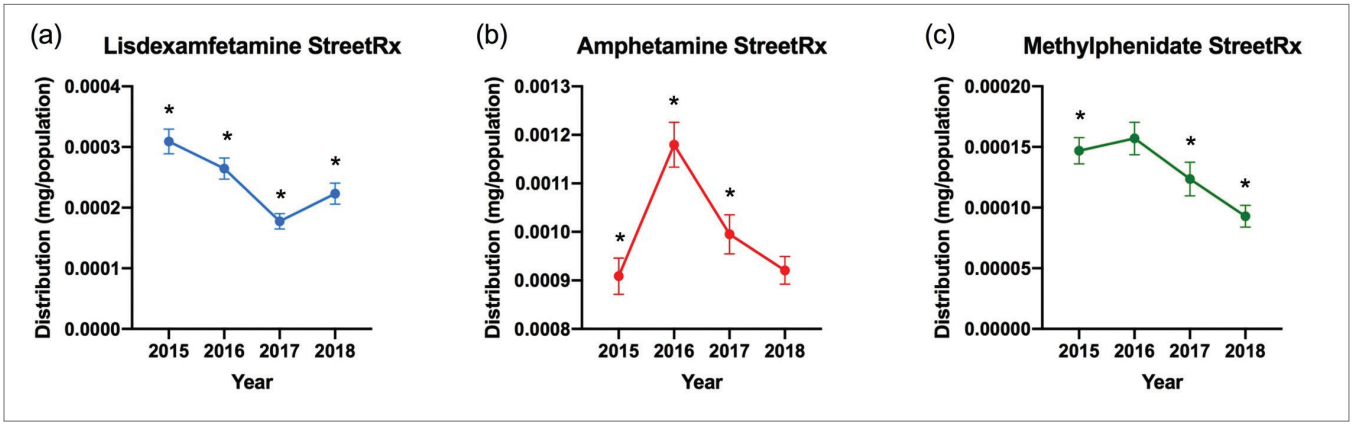

Figure 5. Total diverted distribution as reported by StreetRx in milligrams of lisdexamfetamine (A), amphetamine (B), and methylphenidate (C) for all 50 states from 2015-2018.

the largest decrease in prescription stimulant distribution during the time periods studied. New Mexico prescription distribution decreased by -17.3%, -42.9%, and -24.3% for amphetamine, lisdexamfetamine, and methylphenidate respectively, and was considered a statistically significant outlier (Grubbs' p <0.05).

Lisdexamfetamine daily dose increased from 0.7410 mg/day/person in 2014 to 0.8289 mg/day/person in 2018. This reflects the mild increase in prescription distribution of lisdexamfetamine. Amphetamine daily dose increased from 2014 to 2018, with an average across all 50 states of 2.9249 mg/day/person in 2014, compared to 3.6168 mg/day/person in 2018. In contrast, methylphenidate daily dose decreased from 2014-2017, with an average of 3.4667 mg/day/person in 2014, compared to 3.2299 mg/day/person in 2017.

Total mass distribution (diverted, StreetRx)

Diverted lisdexamfetamine distribution decreased by an average of -0.2376% across all 50 states (Figure 5A). Montana showed the largest decrease of -0.9375%, while Michigan showed the smallest decrease of -0.01872%. Rhode Island contrastingly showed the largest increase of +1.328%. Diverted amphetamine distribution increased by an average of +0.0417% from 2015-2018 across all 50 states (Figure 5B). Iowa showed the largest increase of +0.4779% and Connecticut showed the smallest increase of +0.0047%. In contrast, Alaska showed the largest decrease of -0.2095%. Diverted methylphenidate distribution decreased by an average of -0.3453% across all 50 states (Figure 5C). New Mexico showed the largest decrease of -0.8372%, while Kentucky showed the smallest decrease of -0.0608%. In contrast, Alaska showed the largest increase of +0.6883%.

Paired t-tests comparing the total mass of illicit distribution for prescription stimulants showed that the change in mass was statistically significant for every year compared to 2014 (p <0.0001). This included the years 2015 through 2018 for amphetamine and lisdexamfetamine and 2015 through 2017 for methylphenidate. Paired t-tests comparing the daily dose values showed that the change in daily dose was statistically significant for every year compared to 2014 (p <0.0001). This included the years 2015 through 2018 for amphetamine and lisdexamfetamine and 2015 through 2017 for methylphenidate. Paired t-tests comparing the total mass of illicit distribution for stimulants showed varying significance through the years 2015 through 2018. For amphetamine, the change in total mass of illicit distribution was statistically significant in 2016 and 2017 compared to 2015, but not in 2018. For methylphenidate, the change in total mass of illicit distribution was statistically significant in 2017 and 2018 compared to 2015, but not in 2016. For lisdexamfetamine, the change in total mass of illicit distribution was statistically significant for every

Drug Name	*Years Compared*	*95% Confidence Interval*	*Mean of Differences*	*P-Value*	*Significance (Yes/No)*
Amphetamine	2014 vs 2015	0.1991 to 0.2548	0.2269	<0.0001	Yes
	2014 vs 2016	0.3698 to 0.4892	0.4295	<0.0001	Yes
	2014 vs 2017	0.4595 to 0.6432	0.5513	<0.0001	Yes
	2014 vs 2018	0.5737 to 0.8101	0.6919	<0.0001	Yes
Lisdexamfetamine	2014 vs 2015	0.03543 to 0.05169	0.04356	<0.0001	Yes
	2014 vs 2016	0.06786 to 0.1017	0.08477	<0.0001	Yes
	2014 vs 2017	0.06452 to 0.1154	0.08995	<0.0001	Yes
	2014 vs 2018	0.05514 to 0.1207	0.08791	<0.0001	Yes
Methylphenidate	2014 vs 2015	-0.07768 to -0.02965	-0.05366	<0.0001	Yes
	2014 vs 2016	-0.2140 to -0.1176	-0.1658	<0.0001	Yes
	2014 vs 2017	-0.2847 to -0.1891	-0.2369	<0.0001	Yes

Table 1. T-Test results comparing ARCOS daily dose drug values between years

Drug Name	Years Compared	95% Confidence Interval	Mean of Differences	P-Value	Significance (Yes/No)
Amphetamine	2014 vs 2015	0.003981 to 0.005096	0.004539	<0.0001	Yes
	2014 vs 2016	0.007396 to 0.009783	0.008590	<0.0001	Yes
	2014 vs 2017	0.009190 to 0.01286	0.01103	<0.0001	Yes
	2014 vs 2018	0.01147 to 0.01620	0.01384	<0.0001	Yes
Lisdexamfetamine	2014 vs 2015	0.001417 to 0.002068	0.001742	<0.0001	Yes
	2014 vs 2016	0.002714 to 0.004067	0.003391	<0.0001	Yes
	2014 vs 2017	0.002581 to 0.004615	0.003598	<0.0001	Yes
	2014 vs 2018	0.002206 to 0.004827	0.003516	<0.0001	Yes
Methylphenidate	2014 vs 2015	-0.001554 to -0.0005930	-0.001073	<0.0001	Yes
	2014 vs 2016	-0.004281 to -0.002352	-0.003316	<0.0001	Yes
	2014 vs 2017	-0.005693 to -0.003782	-0.004737	<0.0001	Yes

Table 2. T-Test results comparing ARCOS total prescription distribution between years

Drug Name	Years Compared	95% Confidence Interval	Mean of Differences	P-Value	Significance (Yes/No)
Amphetamine	2015 vs 2016	0.0002261 to 0.0003161	0.0002711	<0.0001	Yes
	2015 vs 2017	3.967e-005 to 0.0001328	8.625e-005	0.0005	Yes
	2015 vs 2018	-2.746e-005 to 5.136e-005	1.195e-005	0.5452	No
Lisdexamfetamine	2015 vs 2016	-7.022e-005 to -1.904e-005	-4.463e-005	0.0010	Yes
	2015 vs 2017	-0.0001709 to -9.261e-005	-0.0001318	<0.0001	Yes
	2015 vs 2018	-0.0001167 to -5.529e-005	-8.598e-005	<0.0001	Yes
Methylphenidate	2015 vs 2016	-1.002e-005 to 3.005e-005	1.001e-005	0.3201	No
	2015 vs 2017	-4.253e-005 to -4.331e-006	-2.343e-005	0.0172	Yes
	2015 vs 2018	-6.999e-005 to -3.809e-005	-5.404e-005	<0.0001	Yes

Table 3. T-Test results comparing StreetRx total Illicit distribution between years

year, 2016 through 2018, compared to 2015. Results and statistical analysis for ARCOS daily dose values and total illicit distribution are summarized in Tables 1 and 2, respectively. Statistical analysis for StreetRx total illicit distribution is summarized in Table 3.

Discussion

The average amphetamine prescription distribution increased across all 50 states from 2014 through 2018. Lisdexamfetamine prescription distribution increased from 2014 through 2017; however, it showed a very slight decrease in 2018. In contrast, methylphenidate prescription distribution decreased throughout all years. Methylphenidate daily dose was higher than amphetamine daily dose in 2014, but this trend reversed by 2017. Amphetamine daily dose was higher than methylphenidate daily dose in 2017. Amphetamine and methylphenidate both had a higher total prescription distribution and daily dose (mg/day/person) compared with lisdexamfetamine across 2014 through 2018.

The etiology of these trends remains unclear, yet the efficacy, safety, and availability of these different pharmacotherapies may play a role. Both amphetamine and methylphenidate work by increasing dopamine and norepinephrine synaptic availability in cortical and subcortical regions which are associated with ADHD pathology (8). A possible explanation for why amphetamine-based therapy is expanding could be due to superior efficacy. A 2010 meta-analysis showed that amphetamine-based treatments for ADHD proved to be significantly more efficacious than methylphenidate-based treatments (22). When asked to evaluate the potential of methylphenidate to be added to the World Health Organization's List of Essential Medications, uncertainties about the benefit-to-harm ratio resulted in a negative decision which was unanimous (11). Furthermore, lisdexamfetamine prescription distribution may be increasing because it is potentially a safer version of amphetamine-based therapy. Lisdexamfetamine is a prodrug which must be processed in the liver to transform into the therapeutically active metabolite, d-amphetamine (9). Many parameters determine the abuse potential of a substance. One of these parameters is the time to reach peak plasma concentration, T_{max} (23). It is commonly known that drugs of abuse are intentionally administered via routes that decrease T_{max} (e.g., insufflation, intravenous). Lisdexamfetamine cannot be administered via a route that bypasses first-pass hepatic metabolism, as this step is necessary to transform it into its active metabolite. This greatly decreases the possibility of using certain routes of administration that would decrease T_{max}. In theory, a misuser could attempt to convert the lisdexamfetamine to d-amphetamine via incubation with a proteolytic enzyme like trypsin that cleaves at the carboxy terminal of lysine residues. This would prepare the drug for administration via routes which sidestep first pass hepatic metabolism. Our group has not found any reports of this sort of at-home chemistry taking place. However, misuse by taking multiple oral doses continues to be reported (19). When compared with instant release d-amphetamine, lisdexamfetamine has been shown to have a lower score on the Drug Rating Questionnaire-Subject Liking Scale in patients with a history of stimulant abuse (24). Our group has shown that stimulant diversion increased from 2015 through 2018. Increasing diversion and stimulant abuse is cause for concern. Clinicians may be more likely to prescribe a drug with a lower misuse profile such as lisdexamfetamine,

which may explain the increase seen in lisdexamfetamine prescription distribution, or this may be due to increased usage for binge eating disorder.

The patterns of illicit stimulant use per the StreetRx data are vaguer and more modest compared to the trends in prescription stimulant distribution obtained from ARCOS. The trends in amphetamine and methylphenidate diversion paralleled one another, with an increase from 2015 through 2016, followed by a subsequent decline through 2018. Lisdexamfetamine, however, showed a consistent decline from 2015 through 2017, followed by an increase in 2018. The average mass of diverted amphetamine was greater in 2018 compared to 2015. Conversely, the average mass of diverted methylphenidate and lisdexamfetamine were smaller in 2018 versus 2015. This indicates a decrease in the misuse of methylphenidate and lisdexamfetamine. The decrease in methylphenidate misuse could potentially be explained by overall phasing out of methylphenidate due to lower efficacy (17). Although the United States federal government defines all three stimulants as Schedule II Controlled Substances, it is known that lisdexamfetamine carries a lower abuse profile (19). Additionally, lisdexamfetamine has been shown to have a lower score on the Drug Rating Questionnaire-Subject Liking Scale (24). This could explain the downward trend in lisdexamfetamine misuse. The superior efficacy of amphetamine could be the major reason why both amphetamine prescription distribution and illicit distribution increased overall from 2015 through 2018. Additionally, the total milligrams per population values for amphetamine are much larger than the values for methylphenidate and lisdexamfetamine.

It is difficult to understand illicit drug use to the same extent at which prescription drug use can be understood, but it is vital to a community's health and well-being to attempt analysis and to hypothesize possible etiologies. The trends found in illicit stimulant use in this study can, in a way, be explained by the trends in prescription stimulant use. While the trends do not directly mirror one another, inferences can be made as to why these variations are seen.

Limitations

One limitation in this study was the lack of complete 2018 drug summary report data for the drugs analyzed. As mentioned previously, 2018 data was unavailable from ARCOS reporting for methylphenidate. Having a lack of data for methylphenidate made it difficult to compare trends among the drugs for 2018, the most current data set available. Further studies will need to be done comparing amphetamine, methylphenidate, and lisdexamfetamine with complete data for 2018. The ARCOS dataset does not provide the indication for use. Other data sources will be needed to determine whether there were changes in use for specific indications or among demographic groups, including for obesity or binge eating disorder, for adult ADHD, including during pregnancy, or among 2- to 5-year-olds (6).

Another limitation is that StreetRx.com is user-submitted data, therefore, potential trends may not have been elucidated due to lack of self-reporting or inaccurate submissions. Socioeconomic status and user accessibility likely influence the amount of submissions received from various U.S. regions. It should also be taken into consideration that StreetRx.com is only able to collect the data that the public is willing to submit. It may seem unusual to some to disclose information regarding one's own participation in illegal activity.

Conclusion

In recent years, the average prescription distribution and daily dose of lisdexamfetamine and amphetamine have increased throughout the United States. The prescription distribution and daily dose of methylphenidate contrastingly decreased during this time period. States and regions of the country varied greatly in the degree of total prescription distribution change of each stimulant medication. New Mexico showed the largest decrease in all three stimulants studied and proved to be an outlier upon statistical analysis. We hypothesize that amphetamine prescription distribution may have increased due to its superior efficacy and lisdexamfetamine prescription distribution may have increased because it is potentially a safer version of amphetamine-based therapy. We also hypothesize that amphetamine illicit distribution may have increased due to effectiveness reasons, while methylphenidate and lisdexamfetamine illicit distribution may have decreased due to decreased availability and less abuse potential, respectively. Further research may unveil possible additional reasons for the trends found in this analysis.

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Disclosures

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