PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (http://bmjopen.bmj.com/site/about/resources/checklist.pdf) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

| TITLE (PROVISIONAL) | Changes in Medical Use of Central Nervous System Stimulants Among US Adults, 2013-2018, a Cross-Sectional Study |
|---------------------|-----------------------------------------------------------------------------------------------------------|
| AUTHORS             | Moore, Thomas; Wirtz, Phillip; Kruszewski, Stefan; Alexander, G Caleb                                      |

VERSION 1 – REVIEW

| REVIEWER             | Haukka, Jari                                                                                     |
|----------------------|--------------------------------------------------------------------------------------------------|
|                      | University of Helsinki, Hjelt Institute, Public Health                                          |
| REVIEW RETURNED      | 11-Feb-2021                                                                                     |

| GENERAL COMMENTS     | Changes in Medical Use of Central Nervous System Stimulants Among US Adults, 2013-2018, a Cross-Sectional Study  |
|----------------------|-----------------------------------------------------------------------------------------------------------|
|                      | Journal: BMJ Open                                                                                  |
|                      | Manuscript ID bmjopen-2020-048528                                                                   |

This is an interesting and well written report of extremely important subject.

I have only few comments and suggestions.

1) In my opinion the most important possible source of bias is self-reporting bias.
I wonder if authors are interested in adding evaluation of size of this bias in different demographics (gender, age-group, ethnicity). At least part of differences may be explained by differences in reporting.

I think there are studies that have validated self-report using biological samples (including hair, urine, and saliva).

Discussion about subject will provide reader with more insight of validity of current report.

2) USA is a large country. I wonder if authors have checked if there is any geographical pattern in prevalence, or change of prevalence in medical use of CNS stimulants after demographic characteristics have been taken into account? Would there be enough data to make state-level map about age, gender etc. adjusted prevalence?
3) Statistical analysis should be reported more in detail and give references to methods used.

REVIEWER
Scherag, Andre
Universitätsklinikum Jena

REVIEW RETURNED
03-Mar-2021

GENERAL COMMENTS
In “Changes in Medical Use of Central Nervous System Stimulants Among US Adults, 2013-2018, a Cross-Sectional Study” Moore et al. analyze data from the US Medical Expenditure Panel Survey (MEPS). They focus on adults (age ≥19 years) who reported obtaining one or more prescriptions for amphetamine or methylphenidate products during two survey years, 2013 and 2018. The authors report the number of prescriptions obtained, the specific stimulant product, and the total treatment days of drug supplied. They summarize and conclude that “adult medical use of prescription stimulants increased markedly in 5 years and occurred in a population often reporting multiple mental or neurological disorders. Further action is needed to better understand and manage this new resurgence in use of drugs.”

This is an important topic and the results - even if they are only descriptive - of potential concern. Thus, they have to be as robust as possible. I have some major and minor remarks that I would like to see addressed in a revised version of this manuscript.

Major:
- please comment on why you select the years 2013 and 2018 – what about new approvals in this period or other events (such as changes in diagnoses, coding or coding systems)
- related to this please add U.S. national information on (changes in) diagnosis frequencies on those diseases listed in Table 4 (especially ADHD) but also regarding diseases related to amphetamine/methylphenidate use (especially related to the cardiovascular system)
- a strong argument for a true change is to see that there is a continuing increase every year; while you might highlight two cross-sectional views (i.e. 2013 and 2018), I would like to see figure for all the years
- please add the analysis code that you used for the data processing and analyses to the appendix
- related to analyses (page 8, line 3) you say you “imputed the median days” – who did you do that (maybe refer to the code?)
- for which of the “some analysis” did you categorize the products
- the U.S. population growth is considered as potential alternative explanation for the observed changes; please provide evidence what part of the change could be due to the growth (under a worst case scenario)
- when did the U.S. initiative to control the use of opioids start

Minor:
- page 6, line 38: please add the a reference
- page 7, line 31: please introduce the abbreviation “NDC”
- page 12, line 54: what is “thattilization”?

VERSION 1 – AUTHOR RESPONSE

AUTHOR RESPONSE – VERSION 1
Reviewer: 1

1) In my opinion the most important possible source of bias is self-reporting bias. I wonder if authors are interested in adding evaluation of size of this bias in different demographics (gender, age-group, ethnicity). At least part of differences may be explained by differences in reporting.

I think there are studies that have validated self-report using biological samples (including hair, urine, and saliva).

Discussion about subject will provide reader with more insight of validity of current report.

We agree that self-reporting of stimulant prescriptions is an important limitation of this study and will expand our previous discussion of this topic. On the other hand, we cannot identify any factors that imply that possible self-reporting bias changed between the 2013 and 2018 survey years.

The MEPS survey design contains procedures to confirm the survey respondents' reports of dispensed outpatient prescriptions. The self-reports are confirmed with pharmacy records for the survey year.

An additional study compared the MEPS survey responses in 2011 with insurance claims data and reported a .97 agreement rate (k = .66) between the two data sources. However, the limitations of this study include a focus on insurance claims from the population 65 years and older and an early survey year.

That same study compared these results with other surveys in other countries or data systems and found the other studies had lower rates of agreement and variation among drugs. In two studies in the Netherlands, pharmacy records showed that 61%-67% of self-reports indicated the same number and types of drugs dispensed. The implication was that MEPS procedures were producing more accurate estimates of outpatient drug utilization than were previous studies in different systems conducted from 2004 to 2008.

None of these studies addressed a class of drugs with documented risks for recreational use, abuse, and diversion. As we state in the expanded limitations section of our discussion, we suspect that our self-reported data underestimate the extent of use but cannot report by how much.

2) USA is a large country. I wonder if authors have checked if there is any geographical pattern in prevalence, or change of prevalence in medical use of CNS stimulants after demographic characteristics have been taken into account? Would there be enough data to make state-level map about age, gender etc. adjusted prevalence?

Geographical variation in the US is an interesting topic. However, limitations of sample size for our study population in 2013 and 2018, combined with limited disclosure of respondent location in the MEPS survey, prevent this analysis from exploring regional differences in these sample data.

3) Statistical analysis should be reported more in detail and give references to methods used.

We have expanded the statistical analysis paragraphs to detail the methods used and provide references.
1. This is an important topic and the results - even if they are only descriptive - of potential concern. Thus, they have to be as robust as possible. I have some major and minor remarks that I would like to see addressed in a revised version of this manuscript.

We hope that we have addressed the specific issues below.

2. please comment on why you select the years 2013 and 2018 – what about new approvals in this period or other events (such as changes in diagnoses, coding or coding systems)

We selected 2018 as the most recent survey year for which the publicly available data were available. A 5-year time span was selected as a reasonable period in which to detect change.

However, another critical factor in selection of time periods relates to the underlying design of MEPS. The survey design does not permit the standard year-by-year trend-over-time. The design issue is as follows:

The household component of MEPS is conducted in a sequence of overlapping panels. A new cohort is selected each calendar year and then interviewed for 5 rounds over two-and-a-half years' time. Thus, any specific panel could appear in adjacent years.

The second question relates to external events that might have contributed to the estimates of increased use such as new approvals and changes in coding systems.

Concerning new approvals, as we reported in the introduction section, the stimulant drug products in this survey are among the oldest psychoactive medications in medical use. In the US system, we separated and reported 'brand name drugs' (lisdexamfetamine/Vyvanse and dexmethylphenidate/Focalin XR) and described any additional indications. We identified and reported one indication change in our study period: in 2015 lisdexamfetamine received an additional indication for binge eating. As we show in Table 2, the 5-year growth of brand-name lisdexamfetamine product was smaller than the many (less expensive) generic products in this drug category.

We did identify a coding change that could have affected our results. In our screening of all reported MEPS methods changes from survey years 2013 to 2018 we found that in 2015 the MEPS surveys changed from identifying medical diagnosis codes from the International Classification of Diseases - 9 (ICD-9) to International Classification of Diseases - 10 (ICD-10).

As a result, our Table 4 (Mental, Neurological Conditions) does not contain comparisons between the 2013 and 2018 survey years.

3. Related to this please add U.S. national information on (changes in) diagnosis frequencies on those diseases listed in Table 4 (especially ADHD) but also regarding diseases related to amphetamine/methylphenidate use (especially related to the cardiovascular system)

As noted above we cannot compare diagnostic frequencies between 2013 and 2018 because the survey diagnosis codes changed in 2015 from ICD-9 to ICD-10, rendering comparisons between the two years problematical. This study is not designed to assess the cardiovascular risks of these stimulant medications, a separate but interesting topic given the adverse event profile of the study drugs.
4. A strong argument for a true change is to see that there is a continuing increase every year; while you might highlight two cross-sectional views (i.e. 2013 and 2018), I would like to see figure for all the years

This reviewer's concerns (and expanded above) revolve around the primary question: Could this large change in adult use of stimulants be an undetected artifact of changes in survey design or external factors?

While we agree with the reviewer that a year-by-year figure with appropriate confidence intervals would be informative and valuable, however, the survey design does not permit year-to-year comparisons. As noted, this is because each survey year includes overlapping separate panels of respondents from immediately adjacent years.

In addition, analysis of MEPS data from 2012 to 2017 also showed an increase over that earlier 5-year period, although smaller.

We also summarize these steps we have taken to ensure that our findings are not an artifact of changes in survey design or coding:

1) Our 2013 and 2018 comparisons show confidence intervals that accurately measure the uncertainty derived from the sample design. Notably, the growth in adults reporting stimulant use could be as small as 1 million adults and as large as 2.6 million adults; the differences are statistically significant and shown in Table 3.

2. Our 2013-2018 results confirm and extend key features of other published reports that analyze changes over time in adult ADHD diagnoses and treatment -- a related but by no means identical research question. Notably, 4 cited studies reported steady growth in treatment of adult ADHD from 1999 through 2016. An additional study in an integrated health system showed 57% of ADHD patients were also diagnosed with depression, consistent with our results in Table 4.

5. Please add the analysis code that you used for the data processing and analyses to the appendix.

We share this reviewer's objective that we provide sufficient information to support a reproducible analysis. Given a publicly available database and numerous investigators skilled in its use and publishing reports, our disclosure should be complete.

Because this data source is intended for health policy analysis, the tools to support analysis are already supported, described, and provided by the Agency for HealthCare Research and Quality on its web site for the survey. Notably the site provides, for each year, SAS code, STATA code, a codebook, complete variable definitions and frequency counts, and a series of statistical briefs and other materials to guide use.

Our disclosures are consistent with the many other peer-reviewed publications using the MEPS data.

Specific programming codes are too specialized to the SAS version, underlying platform, specific MEPS update, and other factors to be readily reproducible.

6. related to analyses (page 8, line 3) you say you “imputed the median days” – who did you do that (maybe refer to the code?!); for which of the “some analysis” did you categorize the products?
We have revised the methods section to be specific about how median days supply were imputed for missing values. We also expanded the analysis for which we combined brand name and generic products. The grouping and subgroups are shown in full detail in Table 2.

In addition, we have explained the reasons for grouping all amphetamine/dextroamphetamine and methylphenidate products in some tables.

7. The U.S. population growth is considered as potential alternative explanation for the observed changes; please provide evidence what part of the change could be due to the growth (under a worst case scenario)

We agree with the reviewer that population growth over the 5-year period could have contributed to the increase in adult utilization of the study drugs. We have reported and addressed increase in the U.S. adult population in the Results section:

"Meanwhile, the total adult US population was estimated to increase during the 5-year-period from 237.5 million to 248.4 million, an increase of 4.6%.

In addition, we refer to this factor in the Discussion section paragraph about limitations:

"During the period, the US adult population increased by 4.6%, which could contribute to increased use."

8. When did the U.S. initiative to control the use of opioids start?

This is an interesting question but difficult to answer specifically. The opioid crisis is a complex and multi-faceted epidemic that has evolved over more than two decades. Because of this, there has not been a highly uniform or coordinated "start" of initiatives to address it, and of course, such efforts have originated within both the private and public sectors and at local, state and federal levels.

Minor:
- page 6, line 38: please add the a reference
- page 7, line 31: please introduce the abbreviation “NDC”
- page 12, line 54: what is “thattilization”?

We have made these corrections.

References
1. MEPS Topics: Prescription Drugs. US Medical Expenditure Panel Survey, Agency for Healthcare Research and Quality.
https://www.meps.ahrq.gov/mepsweb/data_stats/MEPS_topics.jsp?topicid=14Z-1)
2. Hill, S.C., Roemer, M., Stagnitti, M.N. Outpatient Prescription Drugs: Data Collection and Editing in the 2011 Medical Expenditure Panel Survey. Methodology Report #29. March 2014. Agency for Healthcare Research and Quality, Rockville, MD.
http://www.meps.ahrq.gov/mepsweb/data_files/publications/mr29/mr29.shtml
3. MEPS-HC Panel Design and Data Collection Process. US Medical Expenditure Panel Survey, Agency for Healthcare Research and Quality.
https://www.meps.ahrq.gov/mepsweb/survey_comp/hc_data_collection.jsp
4. Amphetamine Use Expands. QuarterWatch: Monitoring FDA MedWatch Reports. Institute for Safe Medication Practices. December 2019. https://www.ismp.org/resources/scope-injury-therapeutic-drugs

5. Download Data Files, Documentation and Codebooks. Medical Expenditure Panel Survey, Agency for Healthcare Research and Quality. https://www.meps.ahrq.gov/mepsweb/data_stats/download_data_files.jsp

### VERSION 2 – REVIEW

| REVIEWER          | Haukka, Jari                  |
|-------------------|-------------------------------|
|                   | University of Helsinki, Hjelt Institute, Public Health |
| REVIEW RETURNED   | 20-May-2021                   |

**GENERAL COMMENTS**

- Checklist of observational study is lacking.
- It is advised to register also observational studies. it is possible to register observational study in clinicaltrials.gov or similar.

| REVIEWER          | Scherag, Andre                |
|-------------------|-------------------------------|
|                   | Universitatsklinikum Jena    |
| REVIEW RETURNED   | 31-May-2021                   |

**GENERAL COMMENTS**

- I thank the authors for addressing most of my concerns. However, I do not understand why the authors do not want to share their SAS analysis code. Since the data and data preprocessing is publicly usable, the analysis code is THEIR contribution and as important as the manuscript. In order to forster reproducibility, the analysis code has to be added to the appendix.

### VERSION 2 – AUTHOR RESPONSE

**Reviewer: 1**  
Dr. Jari Haukka, University of Helsinki, Hjelt Institute

**Comments to the Author:**
1. Checklist of observational study is lacking.

**Response:** This reviewer may not have received the completed STROBE checklist that was submitted with the original manuscript and resubmitted with revision #1.

2. It is advised to register also observational studies. it is possible to register observational study in clinicaltrials.gov or similar.

**Response:** Registration of observational studies involving human subjects with ClinicalTrials.gov is required in some settings, and optional in others. This study does not involve human subjects, but rather the analysis of publicly available, de-identified survey data published for search use by anyone. However, if the manuscript is accepted the full details of this study will be fully available in open access through BMJ journals and through the National Library of Medicine PubMed index. In addition, the corresponding author will register this study (if published) with his ORCID ID, which will link it to other observational studies by this author.
Reviewer: 2  
Prof. Andre Scherag, Universitätsklinikum Jena

I thank the authors for addressing most of my concerns. However, I do not understand why the authors do not want to share their SAS analysis code. Since the data and data preprocessing is publicly usable, the analysis code is THEIR contribution and as important as the manuscript. In order to foster reproducibility, the analysis code has to be added to the appendix.

Response: We propose to follow the best practices policy of a recent publications in BMJ Open that addressed the code sharing issue. We will add a statement that we will provide key analytical code on a reasonable request.

To ensure we were following best practices we examined data sharing and code sharing disclosures for the 5 most recent epidemiology publications in BMJ Open that featured statistical/data programming (as versus literature reviews). One study offered to share key programming code on reasonable request. The other 4 studies did not mention or reference the programming code. None included actual programming code.

In addition, we believe that no public purpose would be served publication of approximately 1,000 pages of SAS code used for this study. It was developed by coauthors TJM and PWW to meet the unique requirements of two specific (and different) annual data releases of the Medical Expenditure Panel Survey. The analysis was tailored to the particular pharmaceutical properties, drug class information and other unique characteristics of the stimulant drugs under study. In addition, for verification, we used two independently developed pieces of code to ensure that our results were consistent.

Simply rerunning this code on another machine would not facilitate true reproducibility and would involve wasting hours trying to determine how various blocks of code actually worked. A better approach to reproducibility would be to use publicly available resources, SAS code, and codebooks available from the US Agency for Healthcare Research and Quality as cited in the manuscript.

Data Sharing and Disclosure in 5 recent BMJ Open epidemiology studies

Rudisill, Toni Marie, and Motao Zhu. “Challenges of Enforcing Cellphone Use While Driving Laws among Police in the USA: A Cross-Sectional Analysis.” BMJ Open 11, no. 6 (June 1, 2021): e049053. https://doi.org/10.1136/bmjopen-2021-049053.

Data availability statement: [No code reference] No additional data are available.

Brønnum-Hansen, Henrik, Olof Östergren, Lasse Tarkiainen, Åsmund Hermansen, Pekka Martikainen, Kjetil A. van der Wel, and Olle Lundberg. “Changes in Life Expectancy and Lifespan Variability by Income Quartiles in Four Nordic Countries: A Study Based on Nationwide Register Data.” BMJ Open 11, no. 6 (June 1, 2021): e048192. https://doi.org/10.1136/bmjopen-2020-048192.

Data availability statement: [No code reference] No data are available.

Houben, E., L. Broeders, E. a. P. Steegers, and R. M. C. Herings. “Cohort Profile: The PHARMO Perinatal Research Network (PPRN) in the Netherlands: A Population-Based Mother–Child Linked Cohort.” BMJ Open 10, no. 9 (September 1, 2020): e037837. https://doi.org/10.1136/bmjopen-2020-037837.

Data availability statement: [No code reference] Data are available upon reasonable request.
Gao, Le, Miriam T. Y. Leung, Xue Li, Celine S. L. Chui, Rosa S. M. Wong, Shiu Lun Au Yeung, Edward W. W. Chan, et al. “Linking Cohort-Based Data with Electronic Health Records: A Proof-of-Concept Methodological Study in Hong Kong.” *BMJ Open* 11, no. 6 (June 1, 2021): e045868. https://doi.org/10.1136/bmjopen-2020-045868.

Data availability statement: [No mention of code]   Data are available upon reasonable request.

Ruan, Yibing, Stephen D. Walter, Priyanka Gogna, Christine M. Friedenreich, and Darren R. Brenner. “Simulation Study on the Validity of the Average Risk Approach in Estimating Population Attributable Fractions for Continuous Exposures.” *BMJ Open* 11, no. 7 (July 1, 2021): e045410. https://doi.org/10.1136/bmjopen-2020-045410.

Data availability statement:  Code: “R code for simulation and exposure datasets from ComPARe study are available.” Data were also available upon reasonable request.