

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Medical use and combination drug therapy among US adult users of central nervous system stimulants: a cross-sectional analysis
AUTHORS	Moore, Thomas; Wirtz, Phillip; Curran, Jill; Alexander, G Caleb

VERSION 1 – REVIEW

REVIEWER	Zuckerman, Diana National Center for Health Research
REVIEW RETURNED	15-Feb-2023

GENERAL COMMENTS	<p>This is a well-designed study with interesting and important results. I found the results to be very disturbing and believe they deserve public attention. BMJ should publish this article after much needed revisions -- I called them minor revisions but others may disagree. The main problem is that the Discussion section does not discuss the findings, it just repeats the same statistics that were previously presented in the Results section. Instead, it should explain why the results are important, what are the implications for the practice of medicine, public health, public policy, or whatever the authors want to tackle. The Conclusions section also needs to be revised: it is only two sentences, both of which raise issues that don't belong there because they were not raised previously -- and probably should have been discussed in the Discussion section.</p>
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REVIEWER	Piper, Brian Geisinger Commonwealth School of Medicine, Medical Education BJP was (2019-21) part of an osteoarthritis research team supported by Pfizer and Eli Lilly.
REVIEW RETURNED	24-Feb-2023

GENERAL COMMENTS	<p>The manuscript "Medical Use and Combination Drug Therapy Among US Adult Users Of Central Nervous System Stimulants: A Cross-Sectional Analysis" addresses a timely and important question, is cautiously analyzed, and interpreted.</p> <p>General concerns</p> <p>A. Do you have trustworthy information on patient race/ethnicity? Its curious to analyze that data by age and sex but not race. Was the % using stimulants higher among Whites? Were Whites also at greater risk of combination use? If you have this information in your de-identified file, the literature on disparities with stimulants should be set-up in the intro. If these race/ethnicity differences are less prominent in a commercially insured population, that's important too!</p>
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	<p>B. The discussion would greatly benefit with a meaty paragraph that describes the “so what” of these findings. Why does the audience care about adult polypharmacy with stimulants? Is it because they are receiving drugs that are not well studied for long-term use or based on research of very low quality (DOI: 10.1136/ebmed-2017-110716)? Are you concerned about the potential of drug interactions?</p> <p>Minor points</p> <p>Line 13: Do you have a citation for the mechanism (e.g. Stahl’s Essential Psychopharmacology)? Am more used to seeing discussion of norepinephrine instead of epinephrine.</p> <p>Its odd that the intro doesn’t include at least a brief nod to the COVID-19 pandemic and expanded use of telemedicine.</p> <p>https://www.wsj.com/articles/dea-investigating-adhd-telehealth-provider-done-11663239601 https://www.reuters.com/business/healthcare-pharmaceuticals/walmart-cvs-halt-filling-prescriptions-controlled-substances-by-cerebral-done-2022-05-26/</p> <p>Page 9 Line 37: reporting to the hundredths (2.7X%)</p> <p>Page 11 L 13: stimulant (no e)</p> <p>Page 11 L 15: antidepressant (singular)</p> <p>P 12 L 16: An ever increasing portion of primary care (where presumably the vast majority of stimulants are coming from) are from NP and PAs. Instead of “physicians”, consider the more inclusive “health care providers”</p> <p>From Table 2, it appeared that stimulant users received it for 227 / 365 days (62.1% of the year). However, the authors interpret this as “the large number of days treatment” (page 11, line 45-46). For ADHD and narcolepsy, would expect 12 month use as 9 month for ADHD has fallen out of fashion. Consider digging more into the stimulant adherence literature.</p> <p>References could use light attention to detail (e.g. non-proper nouns in article titles in citation #1 in lower-case).</p> <p>Figures and tables should be free-standing and include enough information so that, without reading the rest of the manuscript, the reader could get the main idea. Table 1-6 and Fig 2 captions should include the name of the database.</p> <p>Fig 2 should also have a label on the Y-axis. Combination-2 and Combination-3 should be defined in the caption too. Was this figure created in Excel? Since this is an open-access online journal, color gets more attention than black and white. For future projects, consider using professional graphing software (e.g. GraphPad Prism).</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Diana Zuckerman, National Center for Health Research

Comments to the Author:

This is a well-designed study with interesting and important results. I found the results to be very disturbing and believe they deserve public attention. BMJ should publish this article after much needed revisions -- I called them minor revisions but others may disagree. The main problem is that the Discussion section does not discuss the findings, it just repeats the same statistics that were previously presented in the Results section. Instead, it should explain why the results are important, what are the implications for the practice of medicine, public health, public policy, or whatever the authors want to tackle. The Conclusions section also needs to be revised: it is only two sentences, both of which raise issues that don't belong there because they were not raised previously -- and probably should have been discussed in the Discussion section.

We agree with this critique. The discussion section has been more than doubled in length to focus on the public health and clinical implications of these data. Also, we have replaced the conclusions section entirely.

Reviewer: 2

Dr. Brian Piper, Geisinger Commonwealth School of Medicine

Comments to the Author:

The manuscript "Medical Use and Combination Drug Therapy Among US Adult Users Of Central Nervous System Stimulants: A Cross-Sectional Analysis" addresses a timely and important question, is cautiously analyzed, and interpreted.

General concerns

A. Do you have trustworthy information on patient race/ethnicity? Its curious to analyze that data by age and sex but not race. Was the % using stimulants higher among Whites? Were Whites also at greater risk of combination use? If you have this information in your de-identified file, the literature on disparities with stimulants should be set-up in the intro. If these race/ethnicity differences are less prominent in a commercially insured population, that's important too!

This is an interesting question. Unfortunately racial or ethnic information are not included in the Marketscan data. However, our previous study in the Medical Expenditure Survey population disclosed large racial and ethnic differences.

In this previous study we showed that whites were approximately 3 times more likely to be taking Schedule II stimulants compared to either Hispanic or Black persons. Asian utilization was so small that the confidence intervals included zero. The citation:

Moore, Thomas J., Phillip W. Wirtz, Stefan P. Kruszewski, and G. Caleb Alexander. "Changes in Medical Use of Central Nervous System Stimulants among US Adults, 2013 and 2018: A Cross-Sectional Study." *BMJ Open* 11, no. 8 (August 13, 2021): e048528. <https://doi.org/10.1136/bmjopen-2020-048528>.

B. The discussion would greatly benefit with a meaty paragraph that describes the "so what" of these findings. Why does the audience care about adult polypharmacy with stimulants? Is it because they are receiving drugs that are not well studied for long-term use or based on research of very low quality (DOI: 10.1136/ebmed-2017-110716)? Are you concerned about the potential of drug interactions?

We agree with this recommendation, which reinforces the recommendation of Reviewer #1. As we stated above:

The discussion section has been more than doubled in length to focus on the public health and clinical implications of these data. Similar to interactions, we discuss the problems raised by widespread simultaneous use of sedatives and stimulants. Also, we have replaced the conclusions section entirely.

Minor points

Line 13: Do you have a citation for the mechanism (e.g. Stahl's Essential Psychopharmacology)? Am more used to seeing discussion of norepinephrine instead of epinephrine.

We agree that norepinephrine is a better term to discuss the complex and incomplete understanding of the mechanism. We have made this change.

Our cited source is “New insights into the mechanism of action of amphetamines” (#2). There is likely a whole paper examining the uncertainties and unusual effects of these 137-year old drugs. The one we cite is just a good start.

Its odd that the intro doesn't include at least a brief nod to the COVID-19 pandemic and expanded use of telemedicine.

<https://nam02.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.wsj.com%2Farticles%2Fdea-investigating-adhd-telehealth-provider-done-11663239601&data=05%7C01%7Ctmooore86%40jhmi.edu%7Cda87c18db2be40ebc2fc08db1b37f02a%7C9fa4f438b1e6473b803f86f8aedf0dec%7C0%7C0%7C638133699307672276%7CUnknown%7CTWFPbGZsb3d8eyJWljoimc4wLjAwMDAiLCJQljoiv2luMzliLCJBTil6lk1haWwiLCJXVCi6Mn0%3D%7C3000%7C%7C%7C&sdata=G0AFuHRwHEXt2B0CglTu%2Bx0sAS8tSQLvN6TbbexGDS8%3D&reserved=0>

<https://nam02.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.reuters.com%2Fbusiness%2Fhealthcare-pharmaceuticals%2Fwalmart-cvs-halt-filling-prescriptions-controlled-substances-by-cerebral-done-2022-05-26%2F&data=05%7C01%7Ctmooore86%40jhmi.edu%7Cda87c18db2be40ebc2fc08db1b37f02a%7C9fa4f438b1e6473b803f86f8aedf0dec%7C0%7C0%7C638133699307672276%7CUnknown%7CTWFPbGZsb3d8eyJWljoimc4wLjAwMDAiLCJQljoiv2luMzliLCJBTil6lk1haWwiLCJXVCi6Mn0%3D%7C3000%7C%7C%7C&sdata=esndYNRDj2UCQvrwNsArXfY94KjdH%2ByuBT8ZtYN4EMI%3D&reserved=0>

This is an important issue that is being addressed elsewhere. We discuss the telemedicine startups in a STAT First Opinion piece: “Dangerous loophole for drug ads needs to be closed.”

<https://www.statnews.com/2023/01/26/drug-ads-dangerous-drug-advertising-loophole/>

This op-ed was also cited and expanded in a March 1, 2023 opinion piece by Jessica Grose in the New York Times

<https://www.nytimes.com/2023/03/01/opinion/ketamine-ads-depression-anxiety.html>

We believe we would need 2021-2 drug claims data to examine a direct effect of the 2020 regulatory change.

Page 9 Line 37: reporting to the hundredths (2.7X%)

We have fixed the inconsistent decimals. However we have changed all to decimal tenths to make it identical to table 1.

Page 11 L 13: stimulant (no e)

Corrected.

Page 11 L 15: antidepressant (singular)

Corrected.

P 12 L 16: An ever increasing portion of primary care (where presumably the vast majority of stimulants are coming from) are from NP and PAs. Instead of “physicians”, consider the more inclusive “health care providers”

We agree. In this case the sentence with “physicians” was deleted in the revision.

From Table 2, it appeared that stimulant users received it for 227 / 365 days (62.1% of the year). However, the authors interpret this as “the large number of days treatment” (page 11, line 45-46). For ADHD and narcolepsy, would expect 12 month use as 9 month for ADHD has fallen out of fashion. Consider digging more into the stimulant adherence literature.

To clarify we have replaced the adjective “large” with the specific data a median of 227 days.

References could use light attention to detail (e.g. non-proper nouns in article titles in citation #1 in lower-case).

We have rechecked our citations. However, our policy for titles is to use the capitalization and punctuation style of the original journal. These appear to be inconsistent across the medical literature.

Figures and tables should be free-standing and include enough information so that, without reading the rest of the manuscript, the reader could get the main idea. Table 1-6 and Fig 2 captions should include the name of the database.

We have added the name of the database to each of the tables. We also added additional detail to the tables and figures support stand-alone status.

Fig 2 should also have a label on the Y-axis. Combination-2 and Combination-3 should be defined in the caption too. Was this figure created in Excel? Since this is an open-access online journal, color gets more attention than black and white. For future projects, consider using professional graphing software (e.g. GraphPad Prism).

We have revised Figure 2 to add color, label the Y-axis clearly and provide a complete description and include the database description in the caption.

VERSION 2 – REVIEW

REVIEWER	Zuckerman, Diana National Center for Health Research
REVIEW RETURNED	01-Apr-2023

GENERAL COMMENTS	This is a well written, important study based on an enormous dataset. As noted in the manuscript, these types of data raise questions that can't be answered, but raising the questions is in itself important. In response to my earlier criticisms, the Discussion section is now very good and the Conclusion section is also improved. I also agree with the changes that the authors made in response to the suggestions of Reviewer #2.
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REVIEWER	Piper, Brian Geisinger Commonwealth School of Medicine, Medical Education BJP was (2019-21) part of an osteoarthritis research team supported by Pfizer and Eli Lilly.
REVIEW RETURNED	13-Mar-2023

GENERAL COMMENTS	My prior concerns have been addressed.
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