PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Dynamic Changes in Methadone Utilization for Opioid Use Disorder Treatment: A Retrospective Observational Study During the COVID-19 Pandemic
AUTHORS	Kennalley, Amy; Fanelli, Jessica; Furst, John; Mynarski, Nicholas; Jarvis, Margaret; Nichols, Stephanie; McCall, Kenneth L.; Piper, Brian J.

VERSION 1 – REVIEW

REVIEWER	Wyse , Jessica J Oregon Health & Science University
REVIEW RETURNED	29-Jun-2023

GENERAL COMMENTS	Trends in Methadone Utilization for Opioid Use Disorder Treatment in the United States During the COVID-19 Pandemic This paper utilizes three data sources-the Data from the Drug Enforcement Administration's Automated Reports and Consolidated Ordering System, Medicaid's State Drug Utilization Data, and the US Census Bureau to investigate the distribution of methadone treatment across the US over time. This is an important and timely topic and data used are novel for this approach. My suggestions aim to enhance the clarity and contribution of the manuscript. Abstract: 1. Setting appears to describe a data source rather than the setting of the study (the US.) 2. I would think that the participants section should also include patients prescribed buprenorphine and dispensed methadone. Introduction 3. The introduction needs to be streamlined and organized. For instance, the second paragraph is very long and contains many distinct ideas. Authors should verify that each paragraph has a topic sentence that covers all topics discussed within a given paragraph. The final paragraph should clearly lay out the gaps in existing research that will be filled by this manuscript. 4. It would be helpful to clarify either in the introduction or methods (probably methods) what data are contained in each data sources. Methods 5. Can Authors more directly describe how the numerator and denominator were calculated for each analysis and how analyses were conducted? Authors should also clearly define each numerator and denominator (e.g., “percent change in methadone distribution” is not a clearly defined outcome). As written, the

	reader does not have enough information to understand what was done and thus it is hard to judge the reliability of the analyses and findings. 6. Does ARCOS exclude methadone used for pain? Results 7. Results are dense with numbers and listing of states. It would be helpful to synthesize and summarize results more in the write-up and refer to figures for additional detail. Unfortunately, I was unable to view most figures due to an error of some kind (unable to convert image) so cannot comment on them. 8. Page 8, line 32, could this be described in lay language? 9. Medicaid: Authors should consider discussing Medicaid policy coverage of Methadone in OTPs in the introduction to provide some context for the results to come. 10. The result that four states account for 64% of all methadone covered by Medicaid seems very unlikely. What about MA, PA, NY, CA? I know that Medicaid covers methadone in much larger states than those listed. Could there be a data error to account for this finding? See articles below. Lifesaving Addiction Treatment Out of Reach for Many Americans | The Pew Charitable Trusts (pewtrusts.org) New Methadone Treatment Regulations Should Be Complemented By Payment And Financing Reform | Health Affairs Discussion 11. Authors make many important and interesting points in the discussion. Writing here, too, could be reorganized in shorter paragraphs with topic sentences. Authors should verify that discussion points are clearly related to the paper's results. Some of the detail in the discussion could also be dropped for clarity.

REVIEWER	McKnight, Courtney New York University School of Medicine
REVIEW RETURNED	26-Jul-2023

GENERAL COMMENTS	The manuscript describes the findings from a national study which examined patterns of methadone distribution, the number of opioid treatment programs and Medicaid prescriptions for methadone in the United States from 2010-2021, a period which included a significant increase in opioid overdose mortality. Overall, the study provides important insights into methadone distribution and the prevalence of OTPs during this 10+ year period of the opioid epidemic, including trends in methadone distribution for the US as a whole, as well as highlighting important variability in methadone distribution by state. The authors have written a thoughtful and well-supported manuscript that underscores the critical need to expand access to methadone, particularly within the context of persistently high opioid overdose mortality rates. However, the manuscript would be significantly improved by including discussion of fentanyl and the important role that MMTPs can have in treating individuals using fentanyl. Overall comments: • It is a major oversight that there was almost no mention of fentanyl in the manuscript, despite the fact that the study time frame includes the period that fentanyl increased in the US, and the major impact fentanyl has had on opioid overdose mortality. I strongly recommend that the authors include a discussion of fentanyl, including (but not limited to) some of the following points: o Evidence that methadone patients significantly decreased their fentanyl use: https://onlinelibrary.wiley.com/doi/10.1111/add.16180

	o Evidence that methadone is protective against mortality due to overdose among individuals using fentanyl who were retained in methadone for 12 months compared to those stopping methadone before one year: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10347815/ o There is some evidence that methadone may be preferred to buprenorphine for individuals who are using fentanyl: META PHI Methadone treatment for people who use fentanyl: Recommendations. o Given the increased prevalence of fentanyl in the US during the study period, the authors should include some discussion of this, particularly related to the need to increase accessibility to methadone treatment in order to help reduce opioid overdose mortality • In the background section, it may be useful to cite the small proportion of people with OUD who receive MOUD: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2790432 Suggested line edits: *All page numbers listed below refer to the number in the upper left hand corner of the pdf document, not the page number in the upper right hand corner* 1. P.8 line 30-31: Sentence beginning with "Data were similarly…" – there is a missing word or phrase after this 2. P.8 line 32: Add "were" between Heatmaps and created 3. P.8 line 33-34: Add "were" between analysis and completed 4. P.9 line 16-17: please provide the 5 states that had a decrease in distribution of methadone between 2010-2020 and the 3 states that had no change in parentheses? 5. P.9 line 24-25: add "of methadone" after "national average distribution" and "for OUD" 6. P.9 line 26-27: please provide the names of the 11 states that had a decrease in distribution of methadone between 2015-2020 7. P.11 line 40-41: Traveling methadone treatment would also be useful for states/locales with a limited number of methadone programs, regardless of urbanicity

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Jessica J Wyse , Oregon Health & Science University

Reviewer 1's Comment	Author Response	Edit
Abstract:		
1. Setting appears to describe a data source rather than the setting of the study (the US.)	Changed the setting to the US.	Page 2 – tracked changes "Unit ed States."
2. I would think that the participants section should also include patients prescribed buprenorph ine and dispensed methadone.	Updated participants section.	Page 2 – tracked changes "Patients who were dispensed methadone at US Opioid Treatment Programs."

Introduction:		
3. The introduction needs to be streamlined and organized. For instance, the second paragraph is very long and contains many distinct ideas. Authors should verify that each paragraph has a topic sentence that covers all topics discussed within a given paragraph. The final paragraph should clearly lay out the gaps in existing research that will be filled by this manuscript.	Major revisions to restructure and streamline the introduction with an addition to addressing the gaps in research.	End of Introduction: “This manuscript aims to address the paucity of research on methadone for OUD treatment over the past decade and during the COVID-19 pandemic. The impact of COVID-19-related policies on individuals with OUD is poorly understood, and this manuscript seeks to shed light on this important area of research. The use of both ARCOS and SDUD databases provide a comprehensive picture of the distribution and utilization of methadone for the OUD treatment over the past decade. Together, it is critical to examine the changes in methadone distribution during the COVID-19 pandemic to determine whether there are national or regional barriers to accessing this evidence-based pharmacotherapy.”
4. It would be helpful to clarify either in the introduction or methods (probably methods) what data are contained in each data sources.	Added “per state” to clarify ARCOS data. Reorganized sentence to hopefully clarify Medicaid data.	Page 7-Materials and Methods: “The quantities of methadone distributed (in grams) per state were obtained from the ARCOS yearly drug summary reports for 2010, 2015, 2019, 2020 and 2021.” Also Added “Medicaid Ddata was collected for methadone covered by Medicaid inin the year 2020 for all 50 states and DC using a filtered download from the

		SDUD [36]. This data from Medicaid was the methadone reimbursements for use for OUD.”
Methods:		
5. Can Authors more directly describe how the numerator and denominator were calculated for each analysis and how analyses were conducted? Authors should also clearly define each numerator and denominator (e.g., “percent change in methadone distribution” is not a clearly defined outcome). As written, the reader does not have enough information to understand what was done and thus it is hard to judge the reliability of the analyses and findings.	Added clarification.	Methods added “For all 50 states, the milligrams of methadone per person for the years 2010, 2015, 2020 was calculated. This this calculation is the “amount distributed” per year in the following equation: percentage change = (Amount distributed in later year - Amount distributed in earlier year) / Amount distributed in earlier year * 100.”
6. Does ARCOS exclude methadone used for pain?	Yes, comment added in tracked changes document, methadone distrib uted to OTPs is classified here as methadone for OUD. Added clarification.	Methadone distributed to OTPs, in the ARCOS database, was classified as an OUD treatment which excluded all methadone for pain.
Results:		
7. Results are dense with numbers and listing of states. It would be helpful to synthesize and summarize results more in the write-up and refer to figures for additional detail. Unfortunately, I was unable to view most figures due to an error of some kind (unable to convert image) so	Added summary sentences to each paragraph.	Results: “These findings show that methadone distribution in the US has increased significantly over the past decade, with most states showing increases.” “In conclusion, methadone distribution increased from 2015 to 2020, with significant

cannot comment on them.		increases in most states." "Overall, the distribution in was stable from 2019 to 2020, with significant increases in two states and decreases in three states." "In summary, methadone distribution declined from 2019 to 2021, with significant decreases in four states and increase in one state." "Therefore, the distribution was relatively uniform in 2021, with significant elevations in Rhode Island, Delaware, Connecticut, and Vermont." "To sum up, the number of OTPs distributing methadone increased significantly from 2010 to 2021 but plateaued in 2021. The number of OTPs per million persons per state also increased significantly, but there was no significant increase from 2020 to 2021." "In conclusion, methadone prescribing for Medicaid patients varied widely across states, with the top four states curiously accounting for over 60% of all prescriptions."

8. Page 8, line 32, could this be described in lay language?	Not sure what text to change. If anything is unclear we can refine.	No change.
9. Medicaid: Authors should consider discussing Medicaid policy coverage of Methadone in OTPs in the introduction to provide some context for the results to come.	Added more context to the introduction.	Page 6 Introduction: added “However, not all states have equal coverage of medications, which can lead to discrepancies in the prescription numbers reflected by the SDUD. There is variation among states regarding methadone coverage, which in turn affects prescribing methadone patterns [47].”
10. The result that four states account for 64% of all methadone covered by Medicaid seems very unlikely. What about MA, PA, NY, CA? I know that Medicaid covers methadone in much larger states than those listed. Could there be a data error to account for this finding? See articles below. Lifesaving Addiction Treatment Out of Reach for Many Americans | The Pew Charitable Trusts (pewtrusts.org) New Methadone Treatment Regulations Should Be Complemented By Payment And Financing Reform | Health Affairs	Added a clearer voice of caution in interpreting data in the results section as well as the discussion.	Page 10 Results: tracked changes “Four states reporting zero values suggest that some data may be missing from the SDUD database. Discussion: “However, the substantial state-level inhomogeneity of methadone as reported by Medicaid should be viewed carefully and warrants further study. A reported value of zero for four state could possibly be explained by factors such as states not reporting data or changes in how states report this data over time.”
Discussion:		
11. Authors make many important and interesting points in the discussion. Writing here, too, could be reorganized in shorter	Major edits to reorganize the discussion section.	See tracked changes for discussion edits and reorganization.

paragraphs with topic sentences. Authors should verify that discussion points are clearly related to the paper's results. Some of the detail in the discussion could also be dropped for clarity.		

Reviewer: 2
Dr. Courtney McKnight, New York University School of Medicine

Reviewer 2's Comment	**Author Response**	**Edit**
1. P.8 line 30-31: Sentence beginning with "Data were similarly…" – there is a missing word or phrase after this	Fixed grammar.	Materials and Methods: Page 7 "Data were similarly analyzed to examine…"
2. P.8 line 32: Add "were" between Heatmaps and created	Added.	Materials and Methods: Page 7 "Heatmaps were created…"
3. P.8 line 33-34: Add "were" between analysis and completed	Added.	Materials and Methods: Page 7 "…analysis were completed…"
4. P.9 line 16-17: please provide the 5 states that had a decrease in distribution of methadone between 2010-2020 and the 3 states that had no change in parentheses?	Added.	Results: Page 8 "… five states a decrease (DC, Florida, Maine, Tennessee, and West Virginia), and three states showing no change (North Dakota, South Dakota, and Wyoming)."
5. P.9 line 24-25: add "of methadone" after "national average distribution" and "for OUD"	Added.	Results: Page 8 "…national average distribution of methadone for OUD…"
6. P.9 line 26-27: please provide the names of the 11 states that had a decrease in distribution of methadone between 2015-2020	Added	Results: Page 8 "…), with thirty-eight states increasing but eleven states decreasing (Alabama, Florida, Georgia, Kansas, Maine, Minnesota, Missouri, Nebraska, New Hampshire, South Dakota, and Texas)."
7. P.11 line 40-41: Traveling methadone treatment would also be useful for states/locales with a limited number of methadone programs, regardless of urbanicity	Added	Discussion: Page 10 "…for rural areas but also useful for zip codes with a limited number of methadone programs."
However, the manuscript would be significantly improved by including discussion of fentanyl and the important role that MMTPs can have in treating individuals using fentanyl.	Added paragraph in intro with suggested sources.	Introduction "Methadone is a safe and effective treatment for OUD in fentanyl users and is the preferred medication over buprenorphine in this population. Methadone treatment is associated with a significant decrease in illicit drug use, including fentanyl. However, it is important to start with a higher dose of methadone than in people who are not using fentanyl

		(Guide_MethadoneForFentanyl.pdf (metaphi.ca) (https://onlinelibrary.wiley.com/doi/10.1111/add.16180).. Patients with OUD who are using fentanyl are at increased risk of overdose and relapse, but methadone treatment can significantly reduce this risk. Additionally, patientwho test positive for fentanyl use at the start of methadone treatment are just as likely to achieve remission as patients who test negative for fentanyl use. Methadone may also be protective against fentanyl overdose deaths (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10347815/).. These findings suggest that methadone is a valuable tool for treating OUD in fentanyl users."
It is a major oversight that there was almost no mention of fentanyl in the manuscript, despite the fact that the study time frame includes the period that fentanyl increased in the US, and the major impact fentanyl has had on opioid overdose mortality. I strongly recommend that the authors include a discussion of fentanyl, including (but not limited to) some of the following points: o Evidence that methadone patients significantly decreased their fentanyl use: https://onlinelibrary.wiley.com/doi/10.1111/add.16180 o Evidence that methadone is protective against mortality due to overdose among individuals using fentanyl who were retained in methadone for 12 months compared to those stopping methadone before one year: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10347815/ o There is some evidence that methadone may be preferred to buprenorphine for individuals who are using fentanyl: META PHI Methadone treatment for people who use fentanyl: Recommendations. o Given the increased prevalence of fentanyl in the US during the study period, the authors should include some discussion of this, particularly related to the need to increase accessibility to methadone treatment in order to help reduce opioid overdose mortality	Added the suggested references to the manuscript.	References: 4. Mauro, P.M.; Gutkind, S.; Annunziato, E.M.; Samples, H. Use of Medication for Opioid Use Disorder Among US Adolescents and Adults With Need for Opioid Treatment, 2019. JAMA Netw Open. 2022, 5(3), e223821; DOI:10.1001/jamanetworkopen.2022.3821. 12. Centers for Disease Control and Prevention. Available online: https://www.cdc.gov/nchs/nvss/index.htm (accessed on 30 September 2023). 13. Pande, L.J.; Arnett, R.A.; Piper, B.J. An Examination of the Complex Pharmacological Properties of the Non-Selective Opioid Modulator Buprenorphine. Pharmaceutics 2023-in press. 25. Bromley, L.; Kahan, M.; Regenstreif, L.; Srivastava, A.; Wyman, J. Methadone treatment for people who use fentanyl: Recommendations. Available online: www.metaphi.ca (accessed 25 September 2023). 26. Saloner, B.; Whitley, P.; Dawson, E.; Passik, S.; Gordon, A.J.; Stein, B.D. Polydrug use among patients on methadone medication treatment: Evidence from urine drug testing to inform

• In the background section, it may be useful to cite the small proportion of people with OUD who receive MOUD: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2790432		patient safety. Addiction. 2023, 118(8), 1549–1556; https://doi.org/10.1111/add.16180. 27. Stone, A.C.; Carroll, J.J.; Rich, J.D.; Green, T.C. One year of methadone maintenance treatment in a fentanyl endemic area: Safety, repeated exposure, retention, and remission. J Subst Abuse Treat. 2020; DOI: 10.1016/j.jsat.2020.108031. 56. Benito, R.A.; Michael H Gatusky, Mariah W Panoussi, Kenneth L McCall, Anisa S Suparmanian, Brian J Piper. Thirteen-fold variation between states in clozapine prescriptions to United States Medicaid patients. medRxiv. 2022; DOI:10.1101/2022.04.03.22273352. 57. Alexia G. Aguilar , Burke A. Beauregard , Christopher P. Conroy , Yashoda T. Khatiwoda , Shantia M. E. Horsford , Stephanie D. Nichols & Brian J. Piper (2023) Pronounced Regional Variation in Esketamine and Ketamine Prescribing to US Medicaid Patients, Journal of Psychoactive Drugs, DOI: 10.1080/02791072.2023.2178558