

Pronounced Declines in Meperidine in the US: Is the End Imminent?

Lavinia R. Harrison¹, Rhudjerry E. Arnet^{1,2}, Anthony Soto Ramos^{1,2}, Poul A. Chinga^{1,3}, Trinidad R. Anthony^{1,4}, John M. Boyle¹, Kenneth L. McCall⁵, Stephanie D. Nichols⁶ and Brian J. Piper^{1,7}

¹Department of Medical Education, Geisinger Commonwealth School of Medicine, Scranton PA

²Department of Chemistry, University of Scranton, Scranton, PA

³Department of Biology, University of Scranton, Scranton, PA

⁴Department of Biology, Temple University, Philadelphia, PA

⁵Department of Pharmacy Practice, Binghamton University, Johnson City, NY

⁶Department of Pharmacy Practice, University of New England, Portland, ME

⁷Center of Pharmacy Innovation and Outcomes, Forty Fort, PA

Correspondence: Brian J. Piper, Ph.D., Department of Medical Education, Geisinger Commonwealth School of Medicine, Scranton PA, USA, bpiper@som.geisinger.edu

Abstract: Background: Once a widely used analgesic in the United States (US), meperidine offered an alternative to other opioids as a pain reliever. However, within the last two decades, meperidine has gone from a drug to be utilized only when patients exhibit atypical reactions to opioids (e.g., morphine and hydromorphone) to being taken off the World Health Organization List of Essential Medications and receiving strong recommendations for the overall avoidance. The aim of this study was to identify changes in meperidine distribution in the US and regional disparities as reported to the Drug Enforcement Administration's Automation of Reports and Consolidated Orders System (DEA ARCOS) and Medicaid. Methods: Data related to the meperidine distribution was obtained through ARCOS (2001 –2021) and Medicaid public use files (2016 –2021). Heat maps were used to visualize regional disparities in distribution by state. States outside a 95% confidence interval were statistically significant. Results: Meperidine distribution between 2001 and 2021 decreased by 97.4% ($R=-.97$, $P < .0001$). There was a 34-fold state-level difference in meperidine distribution between Arkansas (16.8 mg/10 persons) and Connecticut (0.5 mg/ 10 persons) in 2020. Meperidine distribution in 2020 was elevated in Arkansas, Mississippi, and Alabama. In 2021, Meperidine distribution was highest in Arkansas (1.67 /10 persons) and lowest in Connecticut (0.08 /10 persons). Total prescriptions of meperidine as reported by Medicaid decreased by 73.8% ($R= -0.67$, $P = 0.045$) between 2016 and 2021. Conclusion: We observed a decrease in the overall distribution of meperidine in the past two decades with similar recent declines in prescribing to Medicaid enrollees. The shortage of some parenteral formulations is an important contributor to these declines. This data may reflect plans to phase out the use of this opioid, especially in the many situations where preferred opioids are available.

Keywords: opiate; pain; neurotoxicity; misuse

1. Introduction

Although opioids are a highly effective class of drugs to reduce acute pain, their short and long-term risks are considerable including potentially fatal respiratory depression and developing opioid use disorder. Meperidine was originally synthesized in 1939 as an anticholinergic agent. It was soon after discovered to have analgesic properties [1]. The US Food and Drug Administration approved the use of meperidine for its analgesic properties in 1942 [2]. Meperidine was the most widely used opioid analgesic in the US in 1987, prescribed by approximately 60% of physicians for acute pain and by 22% for chronic pain [3]. Conversely, meperidine is categorized in the US as a schedule II-controlled substance with a "high potential for abuse", with use potentially leading to severe psychological or physical dependence[2]. Guidelines from 1992 indicated that meperidine was only to be used in healthy patients who have had adverse side effects from other opioids such as

morphine and hydromorphone (Table 1). The involvement of meperidine in the Libby Zion serotonin syndrome case [4] and a meperidine analog in the Barry Kidston dopamine neurotoxicity case promoted further reconsideration of the utility of this once ubiquitous agent[5]. Additionally, the medical dogma that meperidine was less likely to cause Sphincter of Oddi spasm compared with morphine, and thus the first line in acute pain associated with pancreatitis, was dispelled [6]. Thus, in light of the lack of clinical benefit over morphine and significant risks of adverse effects and drug interactions with meperidine, its risks clearly outweigh the benefits [7]. Meperidine was removed from the World Health Organization's Model List of Essential medicines in 2003. The American Geriatrics Society Beers Criteria voiced their opinion on the drug in 2012 recommending that meperidine use be avoided. In 2019 the American College of Obstetrics and Gynecology indicated that the use of meperidine generally is not recommended for peripartum analgesia (Supplemental Table 1).

A prior pharmacoepidemiology report characterized changes in US meperidine distribution and use between 2001 and 2019. The total distribution of meperidine, as reported to the DEA, decreased precipitously between 2001 and 2019 [8]. However, four southern states: Arkansas, Alabama, Oklahoma, and Mississippi) showed the largest meperidine distribution when correcting for the population. Our goal here was to include updated information (2020 and 2021) as well as examine the changes among Medicaid recipients.

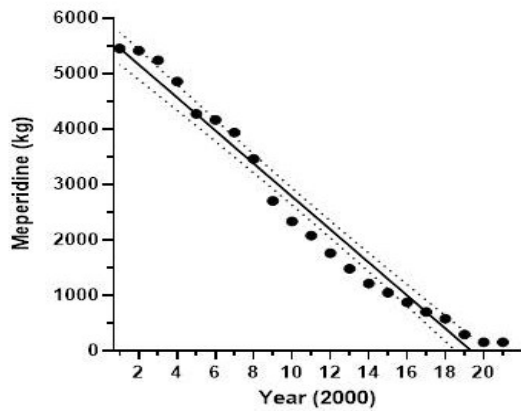
2. Materials and Methods

Procedures: Retail drug summary reports for all 50 states in the year 2020 and quarter one of the years 2021 were obtained using DEA's Automated of Reports and Consolidated Orders System (ARCOS) [9,10]. Although ARCOS reports on controlled substances by weight (rather than more standard measures like prescriptions), this has shown high correspondence with state Prescription Drug Monitoring Programs [9, 10]. Medicaid Prescriber Public Use Files were obtained for all 50 state totals in 2016-2021 [11].

Data Analysis: The total distribution of meperidine per state as reported to the DEA between 2001 and 2021 was corrected from population estimates from the American Community Survey for each year and state. States were ranked and values outside of 1.96 standard deviations from the average were considered statistically significant. Two choropleth maps were created for 2020 and 2021 using JMP statistical software and waterfall graphs were created using GraphPad Prism to visualize disparities in distribution. Linear regression was created using Prism to present the total distribution of meperidine by year. This was also completed for Medicaid prescriptions for 2016- 2021.

3. Results

A. Meperidine Total Distribution 2000-2021



B. Meperidine Total Distribution 2016-2021

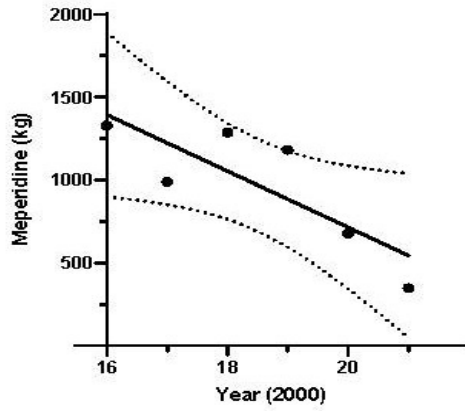


Figure 1. The total distribution of meperidine, as reported to the DEA by ARCOS between 2001 and 2021, decreased by 97.4%. A linear regression over time was significant ($R = -0.97$, $p < .0001$) (A). The total distribution of meperidine, as reported by Medicaid Prescriber public use file between 2016-2021 decreased by 73.8%. A linear regression of national distribution over time was significant ($R = -0.67$, $p = 0.045$) (B).

A. 2020 United States Meperidine Distribution
MG/Population

B. 2020 United States Meperidine Distribution
MG/Population

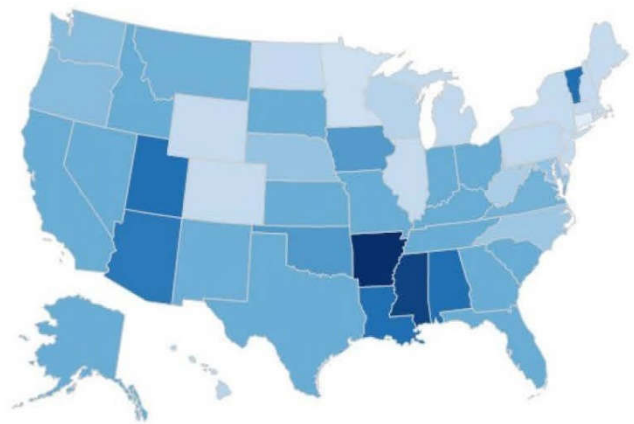
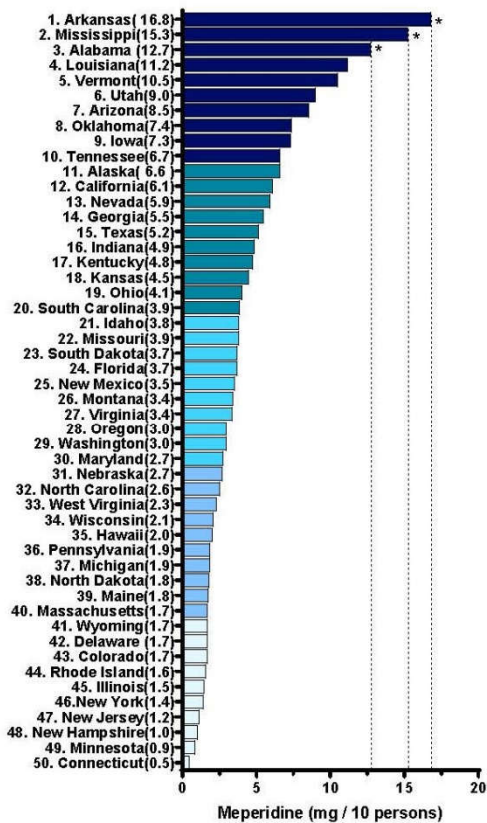
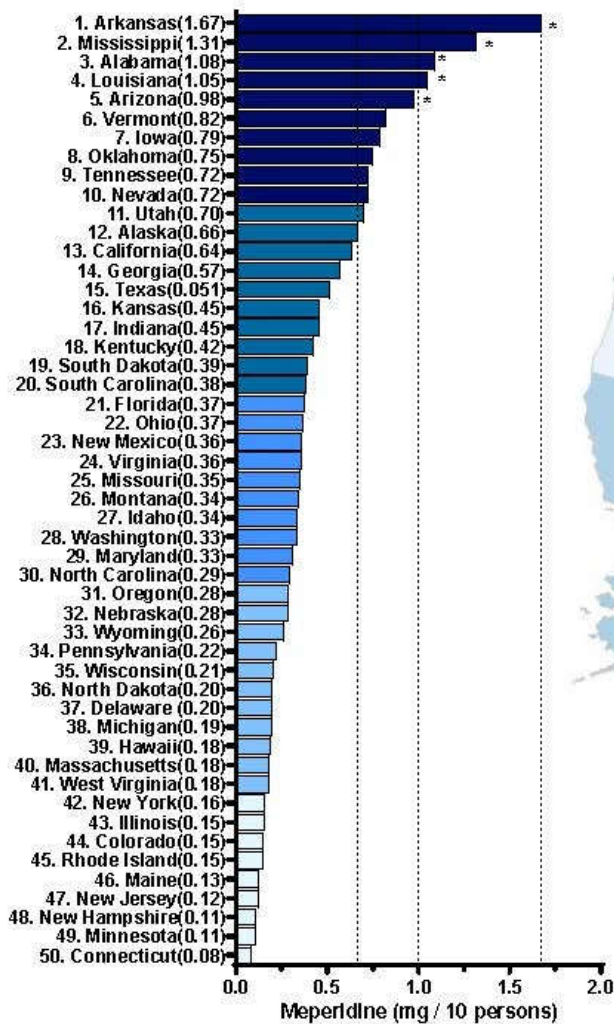


Figure 2. Pronounced regional variation was observed for 2020. Meperidine distribution was highest in Arkansas (16.8 mg/10 persons) and lowest in Connecticut (0.5 mg/10 persons), a 34-fold difference. Arkansas, Mississippi, and Alabama had significantly elevated meperidine relative to the state average (mean 4.5 ± 3.6) (A). Heatmap of meperidine distribution in the United States in 2020 (B).

A.2021 United States Meperidine Distribution
MG/Population ranked.



B. 2021 United States Meperidine
Distribution MG/Population heatmap.

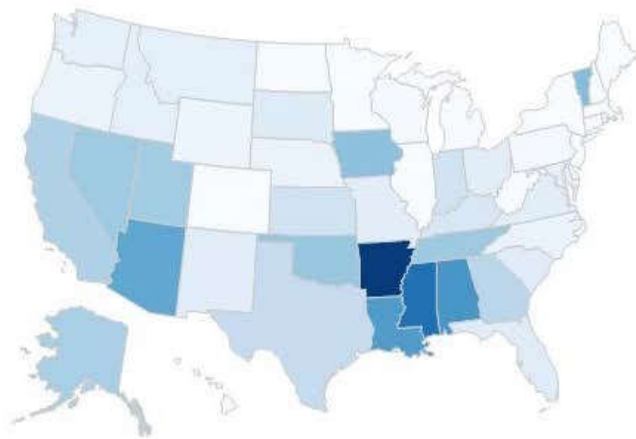


Figure 3. Pronounced regional variation was also observed for 2021 (A). Meperidine distribution was highest in Arkansas (1.67 mg/10 persons) and lowest in Connecticut (0.08 mg/10 persons). Arkansas, Mississippi, Alabama, Louisiana, and Arizona had significantly elevated meperidine relative to the state average (mean 4.4 ± SD 3.3). Heatmap of meperidine distribution in the United States in 2021 (B).

4. Discussion

The United States had an overall decrease of 97.4% between 2001 and 2021 in meperidine. While it is no surprise that meperidine continued to decrease, the reported distribution of meperidine for 2021 was lower than expected. One key factor is declines in production including the cessation of some formulations. Pfizer discontinued Demerol 100 mg/mL 20 mL vials in April 2021 [12]. In addition, Demerol 50 mg/mL 2 mL ampules are on long-term back order and the company estimated release date of February 2023 [12]. When comparing the use of meperidine in the US to those of Canada, there was an overall

decrease in the use of oral meperidine from 2005 to 2010 but a ten-fold difference between the highest (Newfoundland) and lowest (Quebec) provinces [13].

Although meperidine distribution in the US continues to decrease, there was a 34-fold difference between the highest and lowest states in 2020. Codeine, another low potency opioid, showed a four-fold difference, and oxymorphone a 27-fold difference [14]. Arkansas [16.8 mg/10 persons], Mississippi [15.3 mg/10 persons], and Alabama [12.7 mg/10 persons] were the highest distributors in 2020 and were significantly elevated relative to the national average. This is consistent with earlier data [8]. Similar to 2019, in 2020 meperidine varied by geographic region with south-central states, and those with more obesity, showing greater distribution [8]. As of 2020, Arkansas [36.4%; ranked number 9], Mississippi [39.7% ranked number 1], and Alabama [39% ranked number 3] was ranked as the top ten highest adult obesity rates in the US [15]. Colorado has the lowest at 24.2%; and was in the lower ranking distributors at number 43. (F.2a)[15].

The signature benefit of meperidine usage over other opioids was that it was purported to not cause spasms in the Sphincter of Oddi. Once this was disproven, the adverse effects of increased seizure risks and serotonin syndrome greatly outweighed any benefits of use for this weak opioid (Supplemental Table 1). Meperidine now primarily serves as an option for patients who may have special considerations such as allergies to morphine or those that cannot use fentanyl or other alternatives. Although it may still be a bit premature, it is tempting to speculate whether meperidine will remain a rarely used Schedule II substance like cocaine [16] or methamphetamine [17] or join the ranks of heroin and propoxyphene that were discontinued in the US.

This study is not without limitations. Although a modest amount, meperidine is also distributed by veterinarians to non-human animals, and this is reported to ARCOS. However, the use of meperidine at veterinary teaching institutions was negligible [18] and the temporal pattern in Medicaid was similar to ARCOS. Although controlled substances can be sent by mail order pharmacies across state lines beginning in 2020 [4], there was a high degree of similarity in state rankings of meperidine distribution for 2019 [8] and 2020 so we believe this had little impact on our findings of pronounced geographic differences.

5. Conclusions

Recent pharmacoepidemiologic studies of opioid use and regional distribution patterns are vital to informing opioid stewardship programs. This research can be accessed to develop intervention plans [19] to phase out the use of meperidine in situations when it is not necessary. This can be done by producing a steady supply of alternatives and working with state agencies to make other options more readily available. Intervention plans may involve educating providers, including anesthesiologists, in continued use areas about the lack of benefits of prescribing meperidine. The use of meperidine will continue to follow its decreasing trend as the further appreciation of its lack of superiority over other opioids and increased understanding of elevated risks reaches all prescribers in the US and beyond.

Author Contributions: All authors have read and agreed to the published version of the manuscript.

Data Availability Statement: All data is publicly available from the the US Drug Enforcement Administration and the Centers for Medicare and Medicaid Services [11]. Extracted information is available at MedRxiv.

Acknowledgments: Iris Johnston provided technical support. This investigation was supported by the Health Resources and Services Administration (D34HP31025).

Conflicts of Interest: BJP was (2019-21) part of an osteoarthritis research team supported by Pfizer and Eli Lilly. The other authors have no disclosures.

References

1. Latta KS, Ginsberg B, Barkin RL. Meperidine: a critical review. *Am J Ther.* 2002;9(1):53-68. doi:10.1097/00045391-200201000-00010
2. Drug Enforcement Administration. Established aggregate production quotas for Schedule I and II Controlled Substances and assessment of annual needs for the List I chemicals ephedrine, pseudoephedrine, and phenylpropanolamine for 2021. <https://www.federalregister.gov/documents/2020/11/30/2020-26289/established-aggregate-production-quotas-for-schedule-i-and-ii-controlled-substances-and-assessment>.
3. Armstrong PJ, Bersten A. Normeperidine toxicity. *Anesth Analg.* 1986 May;65(5):536-8. PMID: 3963440.
4. Lerner BH. A life-changing case for doctors in training. *The New York Times.* <https://www.nytimes.com/2009/03/03/health/03zion.html>. Published March 3, 2009.
5. Langston, J. W. (2017). *The MPTP story.* *Journal of Parkinson's disease.* Retrieved March 30, 2022, from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5345642/>
6. McLoughlin MT, Mitchell RM. Sphincter of Oddi dysfunction and pancreatitis. *World J Gastroenterol.* 2007;13(47):6333-6343. doi:10.3748/wjg.v13.i47.6333.
7. Buck ML. Is meperidine the drug that just won't die? *J Pediatr Pharmacol Ther.* 2011;16(3):167-169. doi:10.5863/1551-6776-16.3.167
8. Boyle JM, McCall KL, Nichols SD, Piper BJ. Declines and pronounced regional disparities in meperidine use in the United States. *Pharmacol Res Perspect.* 2021;9(4):e00809. doi:10.1002/prp2.809
9. Piper BJ, Shah DT, Simoyan OM, McCall KL, Nichols SD. Trends in medical use of opioids in the U.S., 2006-2016. *Am J Prev Med.* 2018;54(5):652-660.
10. Bokhari F, Mayes R, Scheffler RM. An analysis of the significant variation in psychostimulant use across the U.S. *Pharmacoepidemiol Drug Saf.* 2005;14(4):267-275. doi: 10.1002/pds.980
11. Medicare Provider Utilization and Payment Data: Part D Prescriber. Centers for Medicare & Medicaid Services. <https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Medicare-Provider-Charge-Data/Part-D-Prescriber>. Accessed November 23, 2020.
12. Drug shortage detail: Meperidine hydrochloride injection. ASHP. <https://www.ashp.org/drug-shortages/current-shortages/drug-shortage-detail.aspx?id=347&loginreturnUrl=SSOCheckOnly>.
13. Fischer B, Jones W, Krahn M, Rehm J. Differences and over-time changes in levels of prescription opioid analgesic dispensing from retail pharmacies in Canada, 2005-2010. *Pharmacoepidemiol Drug Saf.* 2011;20(12):1269-77. doi: 10.1002/pds.2190.
14. Madera, JD, Ruffino, AE, Feliz, A, McCall, KL, and Piper, BJ, 2021. Declines and pronounced regional disparities in prescription opioid use in the United States. *MedRxiv.* doi: <https://doi.org/10.1101/2021.12.02.21266660>
15. Robert Wood Johnson Foundation. Adult obesity rates. The state of childhood obesity. <https://stateofchildhoodobesity.org/adult-obesity/>.
16. Armbruster YC, Banas BN, Feickert KD, England SE, Moyer EJ, Christie EL, Chughtai S, Giuliani TJ, Halden RU, Graham JH, McCall KL, Piper BJ. Decline and pronounced regional disparities in medical cocaine usage in the United States. *J Pharm Technol.* 2021 Dec;37(6):278-285. doi: 10.1177/87551225211035563. Epub 2021 Jul 30.
17. Piper BJ, Ogden CL, Simoyan OM, Chung DY, Caggiano JF, Nichols SD, McCall KL. Trends in use of prescription stimulants in the United States and Territories, 2006 to 2016. *PLoS One.* 2018 Nov 28;13(11):e0206100. doi: 10.1371/journal.pone.0206100.
18. Piper BJ, McCall KL, Kogan LR, Hellyer P. Assessment of controlled substance distribution to U.S. veterinary teaching institutions from 2006 to 2019. *Front Vet Sci.* 2020;7:615646. Published 2020 Dec 18. doi:10.3389/fvets.2020.615646.
19. Fisher JE, Zhang Y, Sketris I, Johnston G, Burge F. The effect of an educational intervention on meperidine use in Nova Scotia, Canada: A time series analysis. *Pharmacoep Drug Saf* 2012; 21:177-183.

Supplementary Materials:

Supplemental Table 1. Guidelines and other influential documents with cautions on the use of meperidine.

Year	Document	Information
1992	Agency for Health Care Policy and Research ¹	Meperidine should be used only for very brief courses in otherwise healthy patients who have demonstrated an unusual reaction like local histamine release at the infusion site or an allergic response during treatment with other opioids such as morphine or hydromorphone
2002	World Health Organization Essential Medications ²	Pethidine (meperidine) listed in injection and tablet formulations
2003	World Health Organization Essentials Medications ³	Pethidine (meperidine) no longer listed
2004	Institute of Safe Medication Practices, Canada ⁴	Oral meperidine should be removed from the formulary of healthcare facilities. Parental meperidine should have a limited duration of 48 hours. Avoid use of meperidine among elderly.
2012	American Geriatrics Society Beers Criteria ⁵	Strong recommendation based on high-quality evidence to avoid meperidine. Not an effective oral analgesic in dosages commonly used, may cause neurotoxicity, safer alternatives available
2015	American Geriatrics Society Beers Criteria ⁶	Strong recommendation based on moderate quality evidence to avoid meperidine, especially in individuals with chronic kidney disease. Not effective oral analgesic in dosages commonly used; may have higher risk of neurotoxicity, including delirium, than other opioids, safer alternatives available
2019	American Geriatrics Society Beers Criteria ⁷	Strong recommendation based on moderate quality evidence to avoid meperidine. Not effective in dosages commonly used; may have higher risk of neurotoxicity, including delirium, than other opioids, safer alternatives available
2019	American College of Obstetrics and Gynecology ⁸	The use of meperidine generally is not recommended for peripartum analgesic because its active metabolite, normeperidine, has a prolonged half-life in adults and a half-life of up to 72 hours in the neonate

Supplemental Citations

1. Clinical Practice Guideline Number 1: Acute pain management: Operative or medical procedures and trauma. Clinical practice guideline. Rockville, Md: Agency for Health Care Policy and Research, US Dept of Health and Human Services; 1992. AHCPR publication 92-0032.

2. WHO Model List (revised April 2002). Accessed 11/27/2020 at:

<https://apps.who.int/iris/bitstream/handle/10665/67335/a76618.pdf;jsessionid=EB8AA9ECBECA1F01743B09AC720AD913?sequence=1>

-
3. WHO Model List (revised April 2003). Accessed 11/27/2020 at:
<https://apps.who.int/iris/bitstream/handle/10665/68168/a80290.pdf?sequence=1>
 4. ISMP Canada Safety Bulletin – Meperidine (Demerol®): Issues in medication safety; 2004. <http://www.ismp-canada.org/download/safetyBulletins/ISMPCSB2004-08.pdf>. Accessed September 13, 2022.
 5. American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2012;60(4):616-631.
 6. American Geriatrics Society Beers Criteria Update Expert Panel. American Geriatrics Society 2015 updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2015;63(11):2227-2246.
 7. 2019 American Geriatrics Society Beers Criteria Expert Panel. American Geriatrics Society 2019 Updated Beers Criteria for potentially inappropriate medication use in older adults. *JAGS* 2019; 67:674-694.
 8. American College of Obstetricians and Gynecologists (ACOG). ACOG practice bulletin no. 209: obstetric analgesia and anesthesia. *Obstet Gynecol.* 2019;133(3):e208-e225.