Received: 7 May 2021 | Accepted: 10 May 2021

DOI: 10.1002/prp2.809

ORIGINAL ARTICLE

Declines and pronounced regional disparities in meperidine use in the United States

John M. Boyle[1] | Kenneth L. McCall[2] | Stephanie D. Nichols[2] | Brian J. Piper[1,3]

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

[2]Department of Pharmacy Practice, University of New England, Biddeford, ME, USA

[3]Center for Pharmacy Innovation and Outcomes, Precision Health Center, Danville, PA, USA

Correspondence
Brian J. Piper, Department of Medical Education, Geisinger Commonwealth School of Medicine, Scranton, PA, USA.
Email: bpiper@som.geisinger.edu; psy391@gmail.com

Funding information
Geisinger Commonwealth School of Medicine Summer Research Immersion Program; Health Resources and Services Administration, Grant/Award Number: D34HP31025; National Institute of Environmental Health Sciences, Grant/Award Number: T32 ES007060-31A1

Abstract

There have been increasing concerns about adverse effects and drug interactions with meperidine. The goal of this study was to characterize meperidine use in the United States. Meperidine distribution data were obtained from the Drug Enforcement Administration's Automated of Reports and Consolidated Orders System. The Medicare Part D Prescriber Public Use File was utilized to capture overall trends in national prescriptions in this observational report. Nationally, meperidine distribution decreased by 94.6% from 2001 to 2019. In 2019, Arkansas, Alabama, Oklahoma, and Mississippi saw significantly greater distribution when compared with the US state average of 9.27 mg per 10 persons (SD = 6.82). Meperidine distribution showed an 18-fold difference between the highest state (Arkansas = 36.8 mg) and lowest state (Minnesota = 2.1 mg). Five of the six states with the lowest distribution were in the Northeast. Meperidine distribution per state was correlated with the prevalence of adult obesity ($r(48) = +0.48$, $p < .001$). Family medicine and internal medicine physicians accounted for 28.9% and 20.5%, respectively, of meperidine total daily supply (TDS) in 2017. Interventional pain management (5.66) and pain management (3.48) physicians accounted for the longest TDS per provider. The use of meperidine declined over the last two decades. Meperidine varied by geographic region with south-central states, and those with more obesity, showing greater distribution. Primary care doctors continue to account for the majority of meperidine daily supply. Increasing knowledge of meperidine's undesirable adverse effects like seizures and serious drug–drug interactions is likely responsible for these pronounced reductions.

KEYWORDS
geriatrics, obesity, opiate, opioid

Abbreviations: ARCOS, Automated of Reports and Consolidated Orders System; DEA, Drug Enforcement Administration; IRB, institutional review board; PUF, Public Use File; TDS, total daily supply.

1 | INTRODUCTION

Meperidine was first synthesized in 1938 by Otto Eisleb as a novel anticholinergic.[1] Meperidine's analgesic properties were later discovered and it was approved by the US Food and Drug Administration in 1942.[2] Meperidine has an oral bioavailability of 30%–60% and about one-third the analgesic potency of morphine. This agent was the analgesic of choice in the United States in the latter half of the 20th century.[3] Opioids are employed for the abdominal pain resulting from acute pancreatitis, although meperidine did not produce greater benefits than buprenorphine.[4] Meperidine was thought to have an improved safety profile and lower potential for abuse compared to traditional opioids. However, it was later discovered that claims of decreased risk of addiction were untrue.[5] The US Drug Enforcement Administration (DEA) categorizes meperidine as a Schedule II controlled substance with a high potential for abuse, with use potentially leading to severe psychological or physical dependence.[6] The DEA has production quotas for Schedule II substances and the extent of any diversion is considered when establishing these annually.[7] Moreover, meperidine's misuse potential is higher than that of many other opioids due to its rapid onset of action.[8] Attempts at home synthesis of a meperidine analog in the Barry Kidston case resulted in MPTP which became an important research tool to study Parkinson's disease in experimental animals as the symptoms (akinetic movements, fixed facial expression, drooling, shuffling gait with varying degrees of tremor, a positive response to levodopa) and neuropathology (loss of dopaminergic neurons in the substantia nigra) showed many similarities with this neurodegenerative disease.[9,10]

Like all phenylpiperidine opioids, meperidine is a weak serotonin reuptake inhibitor. However, the most serious adverse effects associated with meperidine are due to its metabolite normeperidine which possesses agonist activity at the serotonin 5-HT_{2A} receptor. Thus, build-up of normeperidine via renal insufficiency or concurrent administration of meperidine with drugs possessing serotonergic activity (SSRIs, MAOIs, etc.) may precipitate serotonin syndrome.[11-14] Serotonin syndrome is marked by a triad of symptoms including altered mental status, neuromuscular abnormalities, and autonomic hyperactivity. In mild cases, the symptoms are generally limited to autonomic disturbances such as tachycardia, hypertension, and mydriasis, among others. If activity at serotonin receptors continues to increase, serotonin syndrome symptomatology may proceed to seizures, coma, rhabdomyolysis, metabolic acidosis, or even, in the unfortunate case of Libby Zion involving meperidine, phenelzine, and cocaine, death. The Zion case prompted calls for reductions in US resident hours.[15] While meperidine has a short half-life (2.5–4 h), its neurotoxic metabolite, normeperidine, has a half-life of 4–21 h.[16] Due to meperidine's relatively short duration of action, multiple daily doses are required for chronic pain control, leading to a build-up of normeperidine. This build up is exaggerated in patients with renal disease and in the elderly.[17] The 2012–2019 Beers Criteria strongly recommended avoiding meperidine in older adults.[18] Meperidine also was removed from the World Health Organization's Model List of Essential Medicines in 2003. With meperidine's prominent adverse effect profile and little added benefit compared to other analgesics, the question must be asked, why is this agent still being used in the United States? As no recent national pharmacoepidemiological studies have focused on meperidine, our goals were to characterize changes in meperidine distribution and use between 2001 and 2019, examine regional disparities in meperidine use as reported to the DEA, and determine meperidine prescriber characteristics using the Medicare Part D Public Use File (PUF). We hypothesized that there would be a reduction in meperidine distribution and use over the past two decades and sizable regional disparities. In addition, exploratory analyses were completed to (1) describe how the DEA's production quota for meperidine has changed during this interval; (2) identify the Medicare prescribers that continue to use meperidine; and (3) assess whether there was a correlation at the state level between the prevalence of obesity and meperidine use.

2 | MATERIALS AND METHODS

2.1 | Procedures

Volume of meperidine distributed was obtained in this longitudinal observational study from the DEA's Automated of Reports and Consolidated Orders System (ARCOS) retail drug summary reports for the years 2001 through 2019 in all 50 states. ARCOS is a comprehensive of Schedule II substance distribution in the United States. Prior research has shown a high correspondence between ARCOS and state prescription drug monitoring programs.[19,20] Data were obtained by state (Report 2) and retail type (Report 7).[21] The yearly final aggregate production quotas for meperidine and intermediates A–C was also obtained from 2001 through 2021.[22,23] The Medicare Part D Prescriber PUF was obtained for 2013 through 2017.[24] Medicare provided coverage for 17.4% of the US population in 2017.[25] The year 2017 was chosen because it is the last year for which data were available when data analysis was completed (July, 2020). The institutional review board (IRB) of the University of New England deemed these data sources to be exempt. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

2.2 | Data analysis

ARCOS retail distribution was reported in the aggregate and by three specific categories: hospitals, pharmacies, and practitioners (DEA business activities A, B, and C, respectively). The DEA defines practitioners as "physician, dentist, veterinarian, or other individual licensed, registered, or otherwise permitted, by the United States or the jurisdiction in which he/she practices, to dispense a controlled substance in the course of professional practice, but does not include a pharmacist, a pharmacy, or an institutional practitioner".[26] Distribution data for teaching institutions, a category indicating non-human use, were not displayed separately due to minute and sporadic volumes and are available elsewhere.[26] The volume of meperidine distributed each year as reported by ARCOS was corrected with US Census Bureau population

estimates. States were ranked and values outside of 1.96 standard deviations from the average were considered statistically significant. As obesity is a risk factor for acute pancreatitis,[28] the prevalence of adult obesity per state in 2019 was obtained from the Centers for Disease Control and Prevention's Behavioral Risk Factor Surveillance System and correlated with per capita meperidine distribution.[28] Heat maps were created with Excel to visualize distribution disparities.

Medicare Part D PUF data were used to plot two variables over time, total daily supply (TDS) and total drug cost (TDC). TDS was defined as "The aggregate number of day's supply for which this drug was dispensed." TDC was defined as "The aggregate drug cost paid for all associated claims. This amount includes ingredient cost, dispensing fee, sales tax, and any applicable vaccine administration fees and is based on the amounts paid by the Part D plan, Medicare beneficiary, government subsidies, and any other third-party payers." In addition, for each year, TDS was examined by prescriber specialty. This allowed us to analyze which specialties accounted for the largest volume of the TDS. Finally, TDS for each specialty was divided by the number of Medicare providers in that specialty to calculate TDS per provider. Specialties with fewer than 200 Medicare prescribers were excluded from the analysis. Linear regressions over time and figures were completed with GraphPad Prism.

3 | RESULTS

The total distribution of meperidine, as reported to the DEA between 2001 and 2019, decreased by 94.6%. A linear regression of national distribution over time was significant ($R^2(18) = .978$, $p < .0001$, Figure 1A). The total population of the US increased by 15.1% during this interval (285.0–328.2 million). All states experienced appreciable decreases in meperidine distribution per capita during the period under review. Iowa (−87.5%), Vermont (−90.2%), and Arkansas (−92.2%) had the smallest reductions while Alaska (−97.7%), Connecticut (−98.0%), and Rhode Island (−98.1%) had the largest (Figure S1). Further analysis examined distribution by business activity. In 2001, hospitals and pharmacies each accounted for nearly half of meperidine distribution (49.0% and 49.3%, respectively) while practitioners were responsible for 1.7% of distribution. In 2019, distribution was similar for pharmacies (48.2%) but lower for hospitals (41.3%) and higher for practitioners (10.4%, Figure S2). The decline from 2001 to 2019 for practitioners (−67.2%) was less than that for pharmacies (−94.7%) and hospitals (−95.5%). Hospital reductions began in 2003 while those of pharmacies did not become pronounced until 2009 (Figure 1B).

Pronounced regional variation was observed in the 2019 meperidine distribution when corrected for population. Meperidine distribution was highest in Arkansas (36.8 mg/10 persons), which was 17.9-fold larger than in the lowest state (Minnesota = 2.1). Furthermore, regional analysis showed that three states near Arkansas (Alabama, Oklahoma, and Mississippi) represented the 2nd to 4th largest distribution per 10 persons (Figure S3). Meperidine distribution in each of these four states was significantly elevated relative to that of the average of the all-states average (Figure 2). This four-state region accounted for 13.8% of the meperidine distributed in 2019 although only 4.5% of the US population resided in these states. Five of the six states with the lowest distribution were in the Northeast.

An exploratory analysis was completed to determine whether there was an association between meperidine distribution and the prevalence of obesity per state in 2019. States with higher rates of obesity also had higher meperidine distribution ($R^2(48) = .230$, $p < .001$, Figure 3). This association was retained with the top four most prevalent states removed ($R^2(44) = .206$, $p < .005$). The DEA's aggregate production quota for meperidine decreased 91.6% between 2001 (10,168 kg) and 2020 (856.7 kg, Figure S4).

Analysis of Medicare data revealed that between 2013 and 2017, TDS of meperidine decreased by 30.3% while TDC increased by 34.9% ($948,702 in 2017). In 2017, Medicare family practice (28.9%) and internal medicine (20.5%) physicians accounted for the largest portion of meperidine TDS. However, interventional pain management (5.66) and pain management (3.48) physicians accounted for the longest TDS per provider compared to family medicine (0.69) and internal medicine (0.40). Further information is found in Figures S5–S9.

4 | DISCUSSION

Overall, the United States saw a decrease of nearly 95% in meperidine distribution between 2001 and 2019. Meperidine has played an

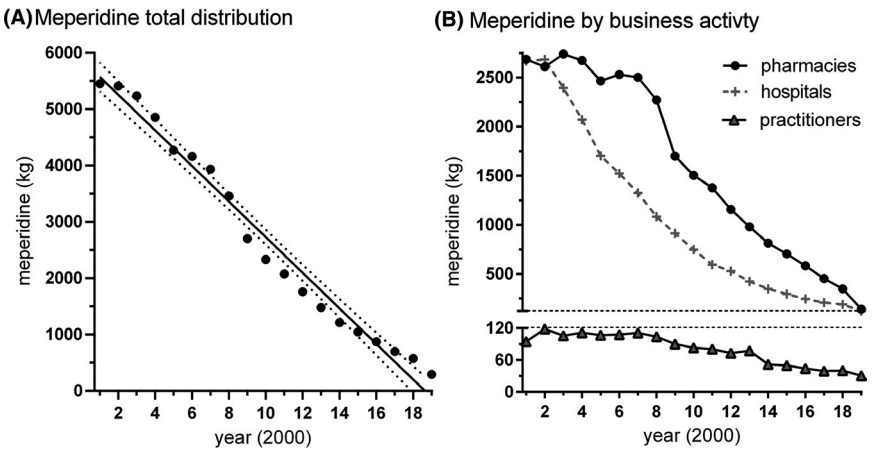

FIGURE 1 Meperidine total distribution in the United States by weight over time [$r(17) = -.989$, $p < .0001$] with 95% CI (A) and by business activity (B) from 2001 to 2019 as reported by the Drug Enforcement Administration's Automated Reports and Consolidated Orders System

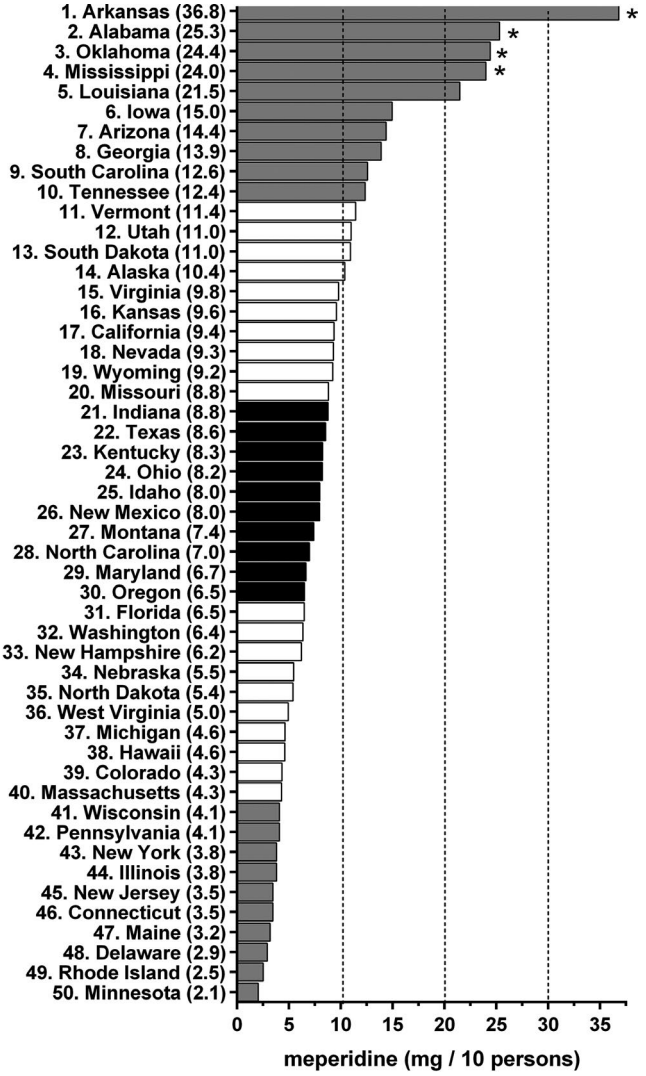

FIGURE 2 Meperidine distribution per 10 persons by state in 2019 as reported by the Drug Enforcement Administration's Automated Reports and Consolidated Orders System. *$p < .05$ versus the average (9.28 ± 6.82)

important role in the history of US medicine and pain management. The Kidston case involving Parkinsonian symptoms following synthesis of a meperidine analog attracted considerable attention.[9,10] Meperidine's ability to induce a lethal serotonin syndrome when combined with other drugs in the Zion case changed the training of medical residents.[15] The American Pain Society began advocating for restricted meperidine use in the late 1990s.[29] Although hospitals, pharmacies, and practitioners have decreased their use substantially, individual practitioners have done so at a reduced rate compared to hospitals and pharmacies. Continuing education may be indicated for these providers in order to address this problem. As the DEA's final aggregate production quotas for meperidine (856.7 kg) for 2021 are a 55.2% reduction relative to 2018,[22,23] this may provide an added impetus to encourage healthcare systems to consider alternative agents.

While the large overall decrease in meperidine use as reported to the DEA was not unexpected,[19] the pronounced geographic variance

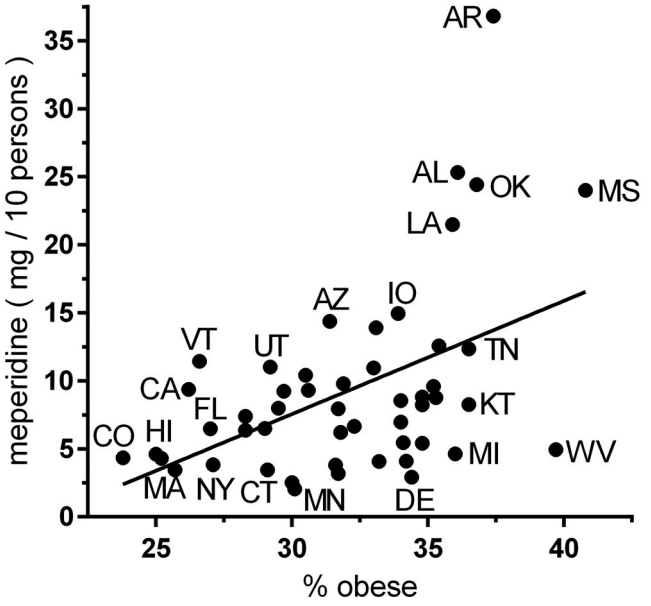

FIGURE 3 Scatterplot depicting the association of percent obesity according to the Behavioral Risk Factor Surveillance System[29] by meperidine distribution per 10 persons per state in 2019 as reported by the Drug Enforcement Administration's Automated Reports and Consolidated Orders System ($r(48) = +.479$, $p < .001$)

was surprising. The identification of the Arkansas, Alabama, Oklahoma, and Mississippi region is crucial to understand meperidine's pharmacoepidemiological trends and presents a target for further mitigation of meperidine use. The reason for the exaggerated meperidine use in this region is unclear. However, we do know that this agent is "indicated" in the setting of acute pancreatitis.[30] Traditional medical education has taught that meperidine mitigates spasm at the sphincter of Oddi compared to other opioids. Following this logic, meperidine should be employed in the setting of acute pancreatitis. Although surgeons have been following this practice for decades, there is actually no evidence to support the claim that meperidine does not cause sphincter spasm. Furthermore, no comparative studies have been conducted to evaluate outcomes in patients with acute pancreatitis administered traditional opiates such as morphine versus meperidine.[30] Although it is difficult to ascertain rates of acute pancreatitis by region in the United States, it is possible to study risk factors on a geographic basis. Risk factors associated with acute pancreatitis include alcohol use, tobacco use, and obesity.[31,32] Obesity is also a risk factor for the development of severe acute pancreatitis.[33] Mississippi has the highest rate of obesity in the United States, with an adult rate of 40.8%, and Arkansas, Alabama, and Oklahoma each have obesity rates over 36%.[28] A statistically significant association was identified between rates of obesity and meperidine distribution. However, this intriguing correlation should be viewed as tentative until verified using electronic medical records. The 18-fold difference in meperidine use between the highest-utilizing and lowest-utilizing states is comparable to the 20-fold difference identified for buprenorphine [34] and larger than the 5-fold difference in the per capita morphine milligram equivalent for 10 opioids.[18]

Medicare Part D data indicated that TDS decreased substantially from 2013 to 2017. This is exactly what we would expect to see after examining the nationwide trends per ARCOS. However, Medicare Part D data also revealed that the TDC increased 34.9% over the same period to over $900,000. The reason for the divergent trend in TDC compared to TDS is unclear. It is possible that the increasing drug cost of meperidine is due to policies [35,36] that discourage its use. Analysis of Medicare Part D data revealed that family medicine and internal medicine specialties contributed the greatest proportion of TDS. This is most likely because many physicians in the United States practice in primary care. Moreover, the two largest specialties in the realm of primary care are family medicine and internal medicine. In 2010, 21.5% of primary care doctors practiced internal medicine while 38.2% practiced family medicine.[20] Although the large volume of TDS coming from these specialties is likely accounted for by their large physician populations, internists and family medicine providers may still represent a target for continuing education to encourage reduced meperidine use. When accounting for the physician population specifically, we found that pain specialists practicing interventional pain management and pain management specialists accounted for the largest volume of TDS per provider. However, it is important to note that they contribute a modest amount of TDS to the sum. Furthermore, these specialists undergo extensive training that may better inform them of risk versus reward when prescribing meperidine relative to primary care physicians.

There are some strengths and limitations to this study. ARCOS is a comprehensive and publicly available data source frequently used in research.[19,20,27,35,37] Meperidine is used for acute pain in non-humans. Although the portion of non-human meperidine use is miniscule,[27,38] this modest subset cannot readily be isolated from the total for the pharmacy business activity. The use of each state's adult prevalence of obesity as a proxy for pancreatitis, although plausible,[28,39] should be verified with future studies including examining obesity, or quantifying visceral adipose tissue at a patient, instead of population, level. There is the possibility that state-level differences in adherence to current evidence-based pharmacotherapeutic practices could be a confounding factor. Medicare served almost 60 million beneficiaries in 2017.[25] Another limitation of this study was the lack of full prescribing patterns to compare all meperidine distributions across specialties with the Medicare Part D PUF. Of course, the Medicare findings may not generalize to other younger patient populations. Additional studies using data from other health insurance providers or electronic medical records can help elucidate further insights into who continues to use meperidine and for which conditions.

5 | CONCLUSIONS

While the use of meperidine continues to decrease across the United States, the reduction has not been consistent in all areas or within all specialties; therefore, our analysis has revealed possible areas for further mitigation efforts. The evidence is clear that meperidine puts patients at increased risk with little to no added benefit compared to other opioids. Targeted education for healthcare systems in the four-state region identified (Arkansas, Alabama, Oklahoma, and Mississippi) may lead to improved patient safety.

ACKNOWLEDGMENTS

JMB was supported by the Geisinger Commonwealth School of Medicine Summer Research Immersion Program. BJP was supported by the Health Resources and Services Administration (D34HP31025). The National Institute of Environmental Health Sciences (T32 ES007060-31A1) provided software used for figure construction. Technical assistance was provided by Lavinia R. Harrison, Trinidy R. Anthony, Josiah K. Charles, and Iris Johnston.

DISCLOSURE

BJP is a member of an osteoarthritis research team supported by Pfizer and Eli Lilly. The other authors have no relevant disclosures.

ETHICS APPROVAL

Not applicable.

PATIENT CONSENT

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

PRIOR POSTINGS

A preprint was posted at MedRxIV 2 December 2020 at: https://www.medrxiv.org/content/10.1101/2020.11.30.20241182v1

DATA AVAILABILITY STATEMENT

The datasets generated during and analyzed during the current study are available in the ARCOS repository, at: https://www.deadiversion.usdoj.gov/arcos/retail_drug_summary/ and the Medicare repository, at: https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Medicare-Provider-Charge-Data/Part-D-Prescriber

ORCID

Brian J. Piper https://orcid.org/0000-0002-2295-445X

REFERENCES

1. Michaelis M, Schölkens B, Rudolphi K. An anthology from Naunyn-Schmiedeberg's archives of pharmacology. *Naunyn Schmiedebergs Arch Pharmacol*. 2007;375(2):81-84.
2. Fischer J, Ganellin CR. *Analogue-Based Drug Discovery*. Hoboken, NJ: John Wiley & Sons; 2006:52X.
3. Kaiko RF, Foley KM, Grabinski PY, et al. Central nervous system excitatory effects of meperidine in cancer patients. *Ann Neurol*. 1983;13(2):180-185.
4. Basurto Ona X, Rigau Comas D, Urrútia G. Opioids for acute pancreatitis pain. *Cochrane Database Syst Rev*. 2013;7(DCOO9179):1-3.
5. Latta KS, Ginsberg B, Barkin RL. Meperidine: a critical review. *Am J Ther*. 2002;9(1):53-68.

6. US Drug Enforcement Administration. Drug scheduling. https://www.dea.gov/drug-scheduling. Accessed November 24, 2020.
7. Drug Enforcement Administration. Controlled Substance quotas. Final rule. *Fed Regist*. 2018;83:32784-32790.
8. Walker DJ, Zacny JP. Subjective, psychomotor, and physiological effects of cumulative doses of opioid mu agonists in healthy volunteers. *J Pharmacol Exp Ther*. 1999;289(3):1454-1464.
9. Buchanan JF, Brown CR. 'Designer drugs'. A problem in clinical toxicology. *Med Toxicol Adverse Drug Exp*. 1988;3:1-7.
10. Langston JW. The MPTP story. *J Parkinson's Dis*. 2017;7:S11-S19.
11. Tissot TA. Probable meperidine-induced serotonin syndrome in a patient with a history of fluoxetine use. *Anesthesiology*. 2003;98(6):1511-1512.
12. Fox MA, Jensen CL, Murphy DL. Tramadol and another atypical opioid meperidine have exaggerated serotonin syndrome behavioural effects, but decreased analgesic effects, in genetically deficient serotonin transporter (SERT) mice. *Int J Neuropsychopharmacol*. 2009;12(8):1055-1065.
13. Weiner AL. Meperidine as a potential cause of serotonin syndrome in the emergency department. *Acad Emerg Med*. 1999;6(2):156-158.
14. Guo SL, Wu TJ, Liu CC, Ng CC, Chien CC, Sun HL. Meperidine-induced serotonin syndrome in a susceptible patient. *Br J Anaesth*. 2009;103(3):369-370. https://doi.org/10.1093/bja/aep167
15. Volpi-Abadie J, Kaye AM, Kaye AD. Serotonin syndrome. *Ochsner J*. 2013;13(4):533-540.
16. Moy KV, Ma JD, Best BM, Atayee RS. Factors impacting variability of the urinary normeperidine-to-meperidine metabolic ratio in patients with chronic pain. *J Anal Toxicol*. 2014;38(1):1-7.
17. Parmar MS, Parmar KS. Management of acute and post-operative pain in chronic kidney disease. *F1000Res*. 2013;2:28.
18. American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2019;67(4):674-694.
19. 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.
20. 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.
21. ARCOS Retail Drug Summary Reports. Drug Enforcement Administration Department of Justice, Diversion Control Division. https://www.deadiversion.usdoj.gov/arcos/retail_drug_summary/. Accessed November 23, 2020.
22. US Drug Enforcement Administration. Final adjusted 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 2018. https://www.deadiversion.usdoj.gov/fed_regs/quotas/2018/fr1210.htm. Accessed November 28, 2020.
23. 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. Accessed November 28, 2020.
24. 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.
25. Statistica. Percentage of people covered by Medicare in the United States from 2000 to 2019. https://www.statista.com/statistics/200962/percentage-of-americans-covered-by-medicare/. Accessed April 28, 2021.
26. Part 1300.01 Definitions Relating to Controlled Substances, Drug Enforcement Administration Department of Justice, Diversion Control Division. https://www.deadiversion.usdoj.gov/21cfr/cfr/1300/1300_01.htm. Accessed April 22, 2021.
27. Piper BJ, McCall KL, Kogan L, Hellyer P. Assessment of controlled substance distribution to U.S. Veterinary Teaching Institutions from 2006 to 2019. *Front Vet Sci*. 2006;2021(7):615646.
28. Vege SS. Management of acute pancreatitis. In: Whitcomb DC, Grover S, eds. UpToDate. Philadelphia, PA.: Wolters Kluwer Health; https://www.uptodate.com/contents/management-of-Acute-pancreatitis?search=acute%20pancreatitis&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H3. Accessed November 26, 2020.
29. Adult Obesity Prevalence Maps. Behavioral Risk Factor Surveillance System 2019, Prevalence of self-reported obesity among U.S. adults. Centers for Disease Control and Prevention website. https://www.cdc.gov/obesity/data/prevalence-maps.html. Accessed November 25, 2020.
30. American Pain Society. *Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain*. Glenview, IL: American Pain Society; 1999.
31. Thompson DR. Narcotic analgesic effects on the sphincter of Oddi: a review of the data and therapeutic implications in treating pancreatitis. *Am J Gastroenterol*. 2001;96(4):1266-1272.
32. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. *Gastroenterology*. 2013;144(6):1252-1261.
33. Khatua B, El-Kurdi B, Singh VP. Obesity and pancreatitis. *Curr Opin Gastroenterol*. 2017;33(5):374-382.
34. Katuchova J, Bober J, Harbulak P, et al. Obesity as a risk factor for severe acute pancreatitis patients. *Wien Klin Wochenschr*. 2014;126(7-8):223-227.
35. Vermont ED Directors. Opiate prescribing guidelines for Vermont emergency departments. https://legislature.vermont.gov/Documents/2016/WorkGroups/Senate%20Health%20and%20Welfare/Bills/S.201/W~Dr.%20Mark%20Depman~Opioid%20Presribing%20Guidelines~1-27-2016.pdf. Accessed May 6, 2021.
36. Emergency Department Opioid Abuse Work Group. Washington Emergency Department opioid prescribing guidelines. https://www.wsha.org/wp-content/uploads/narcotic_edopioidabuseguidelinesfinal.pdf. Accessed May 6, 2021.
37. Pashmineh Azar AR, Cruz-Mullane A, Podd JC, et al. Rise and regional disparities in buprenorphine utilization in the United States. *Pharmacoepidemiol Drug Saf*. 2020;29:1-8.
38. Kogan L, Hellyer P, Rishniw M, Schoenfeld-Tacher R. The US opioid epidemic and its impact on US general practice veterinarians. *Front Veterinary Sci*. 2019;6:222.
39. Kuan LL, Dennison AR, Garcea G. Association of visceral adipose tissue on the incidence of acute pancreatitis: a systematic review. *Pancreatology*. 2020;20:1056-1061.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: 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:e00809. https://doi.org/10.1002/prp2.809