Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities (SUPPORT) Act Section 7024

REPORT TO CONGRESS ON OPIOID PRESCRIBING LIMITATIONS

Table of Contents

Executive Summary

In this report, we provide an overview of federal and state laws and regulations that limit the length, quantity, or dosage of opioid analgesic prescriptions and review the available evidence evaluating these limits. As of April 2020, at least thirty-three states have adopted statutory limits on opioid analgesic prescriptions. We are not aware of any federal laws or regulations requiring opioid analgesic prescribing limits. However, federal guidelines and policies, such as the Centers for Disease Control and Prevention (CDC) Guideline for Prescribing Opioids for Chronic Pain, Veterans Affairs (VA)/Department of Defense (DOD) Pain Guideline, and Centers for Medicare & Medicaid Services (CMS) payment policies, have been used as the basis for many state laws and regulations, and therefore, are discussed in this report.

Published literature provide most of the evidence evaluating opioid analgesic prescribing limits at the federal and state level, to date. In our literature review, we identified twenty-nine studies published from 2013 through 2019 evaluating federal and state opioid analgesic prescribing limits. All published studies that we identified, except for one, evaluated changes in prescribing or dispensing of opioid analgesics after implementation of state opioid prescribing laws or federal guidelines. The majority of these studies described reductions in opioid analgesic prescribing or dispensing after implementation of prescribing limits. Thirteen studies evaluated outcomes beyond changes in prescribing and dispensing patterns, such as patient outcomes, patient burden, prescriber burden, or financial implications for insurance carriers. Among the studies evaluating patient outcomes (n=12), most showed no change or modest improvement in patient outcomes, such as no change in opioid analgesic prescription refill rates or unplanned visits to the office or emergency department (ED) due to insufficient pain control after implementation of the prescribing limit. However, one study found a small but statistically significant increase in pain scores after implementation of a prescribing limit in the context of post-surgical acute pain.[1] Patient burden was not well studied, and the most relevant information we obtained from these studies were impacts on healthcare contact for inadequate pain after the initial opioid prescription (e.g., 30-day hospital admissions, office visits, telephone calls). Unfortunately, this measure provided no information on the number of patients with inadequately treated pain who were unable to access healthcare after their initial visit. Prescriber burden or prescriber outcomes were also poorly studied, with only one study evaluating prescriber utilization of an electronic prescription suggestion list designed to help prescribers follow the new opioid analgesic prescribing limits.[2] No studies evaluated the impact of prescribing laws, regulations, policies, or guidelines on diversion or misuse of Schedule II – IV controlled substances other than prescription opioid analgesics.

We identified multiple gaps in the literature and opportunities for future studies. Most studies did not adjust for the decreasing trends in opioid analgesic prescribing already occurring before the implementation of prescribing limits, or control for other concurrent interventions that could impact opioid analgesic prescribing. Importantly, while measurement of prescribing and dispensing trends is an important first step in assessing the impact of prescribing limits, far fewer studies included other provider outcomes or patient health outcomes. In fact, only twelve of the studies included more informative outcomes to assess the effectiveness and unintended consequences of opioid analgesic prescribing limits such as patient health outcomes, refill rates/attempts, patient burden, prescriber burden, and public health outcomes. Further, no studies assessed other important patient outcomes such as suicidal ideation or mental health conditions, outcomes for which we have anecdotal evidence of harms from various public meetings and federal advisory committee meetings. Finally, it is worth noting that

[1] Chen Q, Hsia HL, Overman R, Bryan W, Pepin M, Mariano ER, Mudumbai SC, Buchheit T, Krishnamoorthy V, Good CB, Brookhart MA and Raghunathan K. Impact of an Opioid Safety Initiative on Patients Undergoing Total Knee Arthroplasty: A Time Series Analysis. *Anesthesiology.* 2019; 13: 369-380.

[2] Lowenstein M, Hossain E, Yang W, Grande D, Perrone J, Neuman MD, Ashburn M and Delgado MK. Impact of a State Opioid Prescribing Limit and Electronic Medical Record Alert on Opioid Prescriptions: a Difference-in-Differences Analysis. *J Gen Intern Med.* 2020 (epub 2019); 35 (3): 662-671.

many of the studies suffered from important methodological flaws that limit our ability to use them to enhance our understanding of the impact of prescribing limits on prescription, patient, provider, and health outcomes.

The lack of understanding regarding the impact of opioid analgesic prescribing limits on more meaningful patient outcomes is an important gap in our existing knowledge, but studies to assess these outcomes are generally more expensive and time-consuming to conduct than analyses of prescription patterns using "big data" sources like insurance claims. In addition, the most informative studies will require measurement of outcomes prior to implementation of the intervention for comparison and therefore, it may not be possible to accurately assess the impact of existing opioid analgesic prescribing limits on meaningful patient and provider outcomes. We recommend careful consideration of the evaluation phase prior to implementing new prescribing limits or changing existing prescribing limits so that meaningful outcomes can be assessed in the affected population before implementation for comparison. Other gaps can be addressed in future studies by using more sophisticated methods to control for existing secular trends in prescribing, by isolating the impact of prescribing limits within larger interventions around opioid analgesic prescribing, and by isolating the impact of state and federal prescribing limits from interventions from other organizations.

Ongoing efforts across the U.S. Department of Health and Human Services (HHS) are addressing some of these gaps in the evidence. For example, multiple HHS Agencies are collaborating to conduct a comprehensive literature review of studies evaluating opioid analgesic prescribing limits at all levels of care, such as those implemented within medical practices and those recommended by professional organizations. CMS has proposed requiring states to implement prospective safety edits in Medicaid pharmacy programs to better manage certain prescribing and dispensing of opioid analgesics. CMS is assessing the impact of such edits across a broad range of outcomes (e.g., incidence and/or prevalence of overdose related to prescription and/or illicit opioids; prevalence of opioid use disorders; medically necessary use of and access to opioids; misuse of opioids; resulting negative health outcomes such as suicide; increases in burden on providers and patients, and mitigation of such burden) by collecting Drug Utilization Survey data from states and managed care organizations.[3] The Indian Health Service (IHS) is assessing prescribing indices to evaluate the impacts of its policies as well as state mandates through the development of an IHS Opioid Surveillance dashboard on outcomes such as opioid use disorders and co-occurring disorders. The National Institute on Drug Abuse (NIDA) supports several research projects that include both qualitative and quantitative assessment of the impact of opioid analgesic prescribing limits on health outcomes (Appendix C). Outcomes associated with opioid misuse include overdose rates related to prescription and illicit opioids and ED visits/hospitalizations related to opioids. Outcomes associated with pain include substitution or concurrent utilization of non-opioid treatments, pain-related clinical outcomes, health care spending, and qualitative assessment of patient and clinician experiences. Unintended consequences are also being assessed, including patient suicidality and the impact on prescribing rates to historically underserved or high-risk populations, including racial/ethnic minorities and individuals living in socioeconomically disadvantaged and rural areas.

Overall, evidence from the published literature indicates that opioid analgesic prescribing limits are likely effective in decreasing the dose, quantity of dosage units, or number of opioid analgesic prescriptions. However, the impact of these prescribing limits on the patient, their pain level, their quality of life, and other important health outcomes has not been well studied and the limited evidence that is available shows mixed results. There is some limited evidence that prescribing limits may not affect some patient outcomes or might result in a decrease in unneeded refills and associated decrease in the number of patients transitioning to chronic opioid analgesic use after implementation. However, there is also evidence that patient outcomes such as effective pain management could be negatively affected. Most importantly, most of the current literature does not sufficiently evaluate patient outcomes in a rigorous manner, and many other important patient outcomes are not evaluated at all. Additionally, we have anecdotal evidence of negative impacts on some patient outcomes not included in the literature that we describe here, such as mental health conditions or suicidality, stigmatization, difficulty finding a provider, and increased patient burden. Other outcomes, such as prescriber burden, should also be more thoroughly studied. In

[3] Drug Utilization Review Annual Report. https://www.medicaid.gov/medicaid/prescription-drugs/drug-utilization-review/drug-utilization-review-annual-report/index.html (accessed August 21, 2020)

this report, we identify knowledge gaps and propose opportunities for future research to sufficiently understand the potential impact and unintended consequences of opioid analgesic prescribing laws, regulations, guidelines, and policies.

Section I. **Overview**

Section 7024 of the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act (SUPPORT Act) requires the following:

> Not later than 2 years after the date of enactment of this Act, the Secretary of Health and Human Services, in consultation with the Attorney General of the United States, shall submit to the Committee on Health, Education, Labor, and Pensions of the Senate and the Committee on Energy and Commerce of the House of Representatives a report on the impact of Federal and State laws and regulations that limit the length, quantity, or dosage of opioid prescriptions. Such report shall address--
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> (1) the impact of such limits on—
> (A) the incidence and prevalence of overdose related to prescription opioids;
> (B) the incidence and prevalence of overdose related to illicit opioids;
> (C) the prevalence of opioid use disorders;
> (D) medically appropriate use of, and access to opioids, including any impact on travel expenses and pain management outcomes for patients, whether such limits are associated with significantly higher rates of negative health outcomes, including suicide, and whether the impact of such limits differs based on the clinical indication for which opioids are prescribed;
>
> (2) whether such limits lead to a significant increase in burden for prescribers of opioids or prescribers of treatments for opioid use disorder, including any impact on patient access to treatment, and whether any such burden is mitigated by any factors such as electronic prescribing or telemedicine; and
>
> (3) the impact of such limits on diversion or misuse of any controlled substance in schedule II, III, or IV of section 202(c) of the Controlled Substances Act (21 U.S.C. 812(c)).

This report is organized into seven sections to provide detailed information on: 1) background, purpose, and structure of the report; 2) current landscape of opioid analgesic prescribing limits; 3) published literature assessing the impact of state and federal opioid analgesic laws, regulations, policies, and guidelines on specific outcomes; 4) other interventions commonly implemented alongside state and federal opioid analgesic prescribing limits; 5) challenges, gaps, and opportunities for evaluating opioid analgesic prescribing limits; 6) ongoing HHS efforts related to opioid analgesic prescribing limits; and 7) conclusions. The report also contains appendices that provide additional detail on state statutes and policies, the published literature reviewed in the report, ongoing HHS agency-specific activities, and a detailed description of the methodology used to identify published research for inclusion in the report.

The U.S. Department of Health and Human Services (HHS) prepared this report in response to Section 7024 of the SUPPORT Act, with assistance from the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the National Institutes of Health (NIH), and the Substance Abuse and Mental Health Services Administration (SAMHSA).

Section II. **Current Landscape of Opioid Analgesic Prescribing Limits**

The following reflects what is currently known about the existence of federal and state limitations on the length, quantity, and dosage of opioid analgesic prescriptions. For the purposes of this report, a prescribing limit was

defined as anything that would require an action at any point within the course of patient care (e.g., prior authorization, urine drug testing, safety-edits, Prescription Drug Monitoring Program (PDMP) checks) if the prescription exceeded any value of days supplied, morphine milligram equivalent (MME) or dosage units prescribed.

Section 2.01 Federal laws, regulations, policies, and guidelines

There are no federal laws or regulations that require opioid analgesic prescribing limits, but in recent years, multiple federal policies and guidelines have been implemented addressing opioid analgesic prescribing. The Department of Veterans Affairs (VA)[4] and Department of Defense (DOD) implemented opioid analgesic prescribing limits starting in 2003, with updates to their Guideline in 2010 and 2017.[5,6,7] In March 2016, the CDC released its *Guideline for Prescribing Opioids for Chronic Pain* (CDC Guideline) for primary care clinicians treating adults with chronic pain.[8] Hereafter, these guidelines will be referred to as the CDC Guideline. The CDC Guideline was developed based on review of scientific literature and input from subject matter experts. Other federal agencies, including the Bureau of Prisons, Centers for Medicare & Medicaid Services (CMS), and Indian Health Service (IHS) have adopted components of the CDC Guideline as part of their recommendations for clinicians or as part of payment policies (Appendix A, Table 1). Since the release of the CDC Guideline, many states have enacted laws, policies, or guidelines relates to opioid prescribing. Specifically, most states that have enacted opioid laws or guidelines focus on general prescribing limitations and provide certain exceptions for chronic pain treatment, similar to the CDC Guideline. It is important to note that the CDC Guideline was intended for clinicians practicing in primary care and treating patients with chronic pain; however, some organizations have implemented the CDC Guideline or components of the CDC Guideline outside of primary care settings, such as in oncology and pain medicine, which go beyond CDC recommendations.[9] In 2019, CDC published a perspective article encouraging closer adherence and decreased misapplication of the Guidelines.[10] In addition to these efforts, the Drug Enforcement Administration (DEA) also has regulatory controls that influence opioid analgesic prescribing more broadly, as healthcare providers are required to obtain a DEA Registration number before being able to prescribe opioid medications, and are also subject to DEA's Diversion Control Program activities.[11]

Section 2.02 State laws, regulations, policies, and guidelines

State laws, regulations, policies, and guidelines enacted to curb opioid analgesic nonmedical use, overdose, and other adverse outcomes include provisions that limit initial opioid analgesic prescriptions based on quantity, dose, or duration. In addition to laws, some state Medicaid agencies have also established guidelines for prescribing opioid analgesics. While these laws, statutes, and regulations are in many instances modeled after federal guidelines, specific requirements vary across states. These prescribing limits cover opioid analgesic prescriptions

[4] Note: The Department of Veterans Affairs will be referred to as the VA in this report unless referencing a program, policy, or guideline specifically created and implemented by the Veterans Health Administration (VHA).
[5] VA/DoD Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain. 2003. Available at: https://www.va.gov/painmanagement/docs/chronicpainguidelinesva2003.pdf (accessed May 5, 2020).
[6] VA/DoD Clincial Practice Guideline for Management of Opioid Therapy for Chronic Pain. 2010. Available at: https://www.va.gov/painmanagement/docs/cpg_opioidtherapy_summary.pdf (accessed August 21, 2020)
[7] VA/DoD Clinical Practice Guideline for Opioid Therapy for Chronic Pain. 2017. Available at: https://www.healthquality.va.gov/guidelines/Pain/cot/VADoDOTCPG022717.pdf (accessed August 21, 2020)
[8] Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *MMWR Recomm Rep*. 2016; 65: 1-49. DOI: http://dx.doi.org/10.15585/mmwr.rr6501e1
[9] Kroenke K, Alford DP, Argoff C, Canlas B, Covington E, Frank JW, Haake KJ, Hanling S, Hooten WM, Kertesz SG, Kravitz RL, Krebs EE, Stanos SP, Sullivan M. Challenges with implementing the Centers for Disease Control and Prevention opioid guideline: A consensus panel report. *Pain Medicine*. 2019; 20(4): 724-735.
[10] Dowell D, Haegerich T, Chou R. No shortcuts to safer opioid prescribing. *NEJM*. 2019; 380: 2285-2287.
[11] Drug Enforcement Administration. Diversion Control Program. https://www.deadiversion.usdoj.gov/

for new prescribing (patients who have not previously taken opioids) and patients with chronic pain, often with exceptions for professional judgement or certain medical conditions (Appendix A, Table 1).[12]

At least 33 states have adopted statutory limits on opioid analgesic prescriptions as of April 2020.[13] Specifically:

- Four states set statutory limits at three or four days for an opioid analgesic prescription (some with the same limits for dental, optometry, or emergency department (ED)/urgent care)
- Three states set statutory limits at five days
- Twenty-six states set statutory limits at seven days
- Nevada set statutory limits at fourteen days
- Most states offer professional judgment exceptions and specific exceptions for hospice, palliative care, cancer, or other chronic conditions.

Section 2.03 Other selected policies and guidelines

While not the focus of this report, it is worth noting that other policies and guidelines exist at the state level. Medical and Pharmacy Boards in some states including Alabama, Alaska, California, Indiana, Kentucky, and Maryland have adopted additional prescribing guidelines as have Departments of Workforce Services and Worker's Compensation programs in multiple states.

To provide further context on the federal and state laws, regulations, policies, and guidelines, in the Appendix of this report we provide a brief description of some of the opioid analgesic prescribing limits implemented by state and non-state organizations (Appendix A, Table 2).

Examples of other selected policies and guidelines from state and non-state entities include:

- Alabama Medical and Pharmacy Boards: Dental Board of Examiners: PDMP check required for: >7-day supply or >50 MME/day of opioid analgesics with additional limits on other patient or prescription situations[14]
- State Medical Board of Ohio: Maximum 7-day supply for initial acute care pain opioid analgesic prescriptions for adults.[15]

Section III. **Published Literature Assessing the Impact of State and Federal Opioid Analgesic Laws, Regulations, Policies, and Guidelines on Specific Outcomes**

Review Methods

A literature review covering peer-reviewed published literature from 2013 to May 2018 was previously published.[16] This literature review examined a wide variety of interventions that may affect opioid analgesic prescribing, and, for the purpose of this report, focused on studies that assessed the impact of opioid analgesic prescribing limits, including (but not necessarily limited to) an evaluation of prescribing laws, regulations, policies, and guidelines based on dose measured in MME, number of days supplied, or dosage units prescribed.

[12] Note: The authors of this report attempted to include the most accurate prescribing limits, but inaccuracies may occur due to factors such as updates to information after preparation of this report.
[13] National Conference of State Legislatures. Prescribing Policies: States Confront Opioid Overdose Epidemic. June 30, 2019. Available at: http://www.ncsl.org/research/health/prescribing-policies-states-confront-opioid-overdose-epidemic.aspx (accessed May 26, 2020).
[14] Alabama Medical and Pharmacy Boards. September 2018. Rule 270-x-2-.23, adopted pursuant to Code of Ala. 1975, §§ 20-2-54.1,
[15] State Medical Board of Ohio. 2017. Available at: https://med.ohio.gov/Publications/Recent-News/effective-december-29-phase-2-of-prescribing-opioids-for-acute-pain (accessed May 4, 2020).
[16] Haegerich TM, Jones CM, Cote PO, Robinson A, Ross L. Evidence for state, community and systems-level prevention strategies to address the opioid crisis. *Drug and Alcohol Dependence.* 2019; 204: 1-13.

This published literature review was updated for this report with peer-reviewed literature published from May 2018 through November 2019 (see Appendix B for updated methods and modified search string). In total, twenty-nine articles were identified that evaluated the effect of federal and state prescribing limits on at least one of the following outcomes: prescribing patterns, patient-reported health outcomes, patient and/or provider burden, or diversion or misuse of opioids. Patient populations and reasons for opioid analgesic prescriptions varied from patients on chronic opioid analgesic therapy to patients prescribed opioid analgesics for post-surgical pain.

The following sections describe the findings of these combined literature reviews, stratified by outcomes examined (Appendix A, Tables 3a and 3b). Although patient health outcomes are very important, we discuss prescribing patterns, dispensing patterns, and "high-risk" prescribing first, as these outcomes are the outcomes most commonly addressed in the current published literature.

Prescribing patterns, dispensing patterns, and "high-risk" prescribing

All of the studies identified in this report, except one, evaluated federal and state prescribing limits by examining opioid analgesic prescribing and dispensing patterns (e.g., prescription counts, dose, days' supply, or dosage units prescribed) before and after implementation of federal or state laws, regulations, policies, or guidelines. Thirteen studies also included other outcomes such as refill rates, measures of appropriate pain management, transition to chronic opioid analgesic use, and overdose rates in their evaluation. Most studies utilized insurance claims data or PDMP data to capture prescription dispensing data before and after implementation of the prescribing limit, while a limited number of studies utilized electronic medical records (EMR) or electronic health records (EHR) to capture written prescription information before and after implementation of the prescribing limit. Of the research conducted to date, the majority indicate that opioid analgesic prescribing limits implemented by federal agencies, states, and state Medicaid agencies, as well as the publication of the 2016 CDC Guideline resulted in a reduction in opioid analgesic prescribing or dispensing. Changes in prescribing or dispensing were often reported as changes in opioid daily dosage measured using MME. For example, Riggs et al., 2017 assessed the implementation of a four tablets/day and 120 tablets/30 days short-acting opioid analgesic quantity limit among Colorado Medicaid beneficiaries and found a 24 percent decrease in total daily dose in MME among patients who exceeded the quantity limit at baseline after the implementation of this policy.[17] A retrospective cohort study evaluated the change in total MME prescribed after the implementation of provider education efforts and a dose limit of 120 MME/day (prescribing limit based on 2010 Washington State legislation) in a University clinic in Oregon.[18] The study showed that after these interventions, there was a 24% decrease in average daily dose in MME among patients who had previously been prescribed over 120 MME/day for four consecutive months.

Other outcomes were also evaluated in insurance claims data, PDMP data, and/or EMR or EHR data by a limited number of studies, such as:

- use of non-opioid analgesic pain medications,[19,20,21,22]

[17] Riggs CS, Billups SJ, Flores S, Patel RJ, Heilmann MF and Milchak JL. Opioid use for pain management after implementation of a Medicaid short-acting opioid quantity limit. *Journal of Managed Care and Specialty Pharmacy.* 2017; 23 (3): 346-354.
[18] Weimer MB, Hartung DM, Ahmed S, Nicolaidis C. A chronic opioid therapy dose reduction policy in primary care. *Subst. Abus*. 2016; 37 (1): 141-147.
[19] Chen Q, Hsia HL, Overman R, Bryan W, Pepin M, Mariano ER, Mudumbai SC, Buchheit T, Krishnamoorthy V, Good CB, Brookhart MA and Raghunathan K. Impact of an Opioid Safety Initiative on Patients Undergoing Total Knee Arthroplasty: A Time Series Analysis. *Anesthesiology.* 2019; 13: 369-380.
[20] Karst AC, Hayes BF, Burka AT, Bean JR and Wallace, JL. Effect of the Centers for Disease Control and Prevention opioid prescribing guidelines on postsurgical prescribing among veterans. *Journal of the American College of Clinical Pharmacy*. 2019 (epub 2018); (2) 2: 155-160.
[21] Samimi P, Panza J, Heft J, Wang L and Adam R, Opioid prescriptions for female pelvic reconstructive surgery patients before and after implementation of Tennessee state legislation. *Female Pelvic Med and Reconstr Surg*. 2019: 1-4.
[22] Zipple, M and Braddock, A. Success of Hospital Intervention and State Legislation on Decreasing and Standardizing Postoperative Opioid Prescribing Practices. *J Am Coll Surg.* 2019; 229 (2): 158-163.

- "high-risk" prescribing and/or utilization[23,24,25,26] (e.g., concomitant opioid and benzodiazepine use,[27] prescribing of extended-release/long-acting opioid analgesics, prescribing additional opioid analgesics from the ED to patients already on opioids, use of multiple prescribers or pharmacies for opioid analgesic prescriptions), and
- tapering patients who were prescribed daily opioid analgesic doses or number dosage units above a prescribing limit down to or below the prescribing limit.[28,29,30,31]

Austin et al., 2019 evaluated the impact of the CDC Guideline and Washington State Interagency Guideline on Prescribing Opioids for Pain, and found a statistically significant decrease in the number of patients on higher opioid analgesic doses (above 50 and 90 MME per day[32]), with 29 percent of active patients fully tapered off of their chronic opioid analgesic therapy one year after implementation of the prescribing guidelines, as well as a decrease in the number of patients who received concomitant opioid analgesic and benzodiazepine therapy.[33] Other studies reported no impact of prescribing limits on opioid analgesic prescribing, dispensing, or the use of multiple prescribers or pharmacies, including Meara et al., 2016, which did not find an association between the implementation of state opioid analgesic prescribing laws and the percentage of Medicare beneficiaries with four or more prescribers or the percentage of Medicare beneficiaries filling opioid analgesic prescriptions with daily doses above 120 MME.[34] One study evaluating non-opioid analgesics found an increase in post-operative acetaminophen and nonsteroidal anti-inflammatory drug (NSAID) prescriptions, among other outcomes.[35] However, another study found no statistically significant change in the percentage of patients prescribed a non-opioid analgesic at discharge after minor carotid endarterectomy or endovascular aneurysm repair surgeries following the implementation of the CDC Guideline at the Veterans Affairs Tennessee Valley Healthcare System.[36]

Prescribing patterns, dispensing patterns, and "high-risk" prescribing: limitations

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[23] Losby JL, Hyatt JD, Kanter MH, Baldwin G, Matsuoka D. Safer and more appropriate opioid prescribing: a large healthcare system's comprehensive approach. *J Eval Clin Pract*. 2017: 1-7.
[24] Austin R C, Fusco CW, Fagan EB, Drake E, Pacious J, Dickens H, Galvin SL and Wilson CG. Teaching Opioid Tapering Through Guided Instruction. *Fam Med.* 2019; 51 (5): 434-437.
[25] Dayer LE, Breckling MN, Kling BS, Lakkad M, McDade ER and Painter JT. Association of the "CDC Guideline for Prescribing Opioids for Chronic Pain" With Emergency Department Opioid Prescribing. *J Emerg Med.* 2019; 57 (5): 597-602.
[26] Hartung DM, Kim H, Ahmed SM, Middleton L, Keast S, Deyo RA, Zhang K and McConnell KJ. Effect of a high dosage opioid prior authorization policy on prescription opioid use, misuse, and overdose outcomes. *Subst Abus*. 2018; 39 (2): 239-246.
[27] Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality, including profound sedation, respiratory depression, coma, and death.
[28] Weimer MB, Hartung DM, Ahmed S, Nicolaidis C. A chronic opioid therapy dose reduction policy in primary care. *Subst. Abus*. 2016; 37 (1): 141-147.
[29] Riggs CS, Billups SJ, Flores S, Patel RJ, Heilmann MF and Milchak JL. Opioid use for pain management after implementation of a Medicaid short-acting opioid quantity limit. *Journal of Managed Care and Specialty Pharmacy.* 2017; 23 (3): 346-354.
[30] Austin R C, Fusco CW, Fagan EB, Drake E, Pacious J, Dickens H, Galvin SL and Wilson CG. Teaching Opioid Tapering Through Guided Instruction. *Fam Med.* 2019; 51 (5): 434-437.
[31] US Department of Health and Human Services. HHS guide for clinicians on the appropriate dosage reduction or discontinuation of long-term opioid analgesics. https://www.hhs.gov/opioids/treatment/clinicians-guide-opioid-dosage-reduction/index.html (accessed August 24, 2020).
[32] Note: Studies may have different definitions of "high-dose" and "high-risk" doses and there is no established point in opioid analgesic dose after which the risk of adverse health outcomes increases (Coyle DT, Pratt CY, Ocran-Appiah J, Secora A, Kornegay C, Staffa J. Opioid analgesic dose and the risk of misuse, overdose, and deaths: a narrative review. *Pharmacoepidemiol Drug Saf.* 2018; 27: 464-472).
[33] Austin R C, Fusco CW, Fagan EB, Drake E, Pacious J, Dickens H, Galvin SL and Wilson CG. Teaching Opioid Tapering Through Guided Instruction. *Fam Med.* 2019; 51 (5): 434-437.
[34] Meara E, Horwitz, JR, Powell W, McClelland L, Zhou W, O'Malley AJ, Morden NE. State legal restrictions and prescription-opioid use among disabled adults. *N. Engl. J. Med.* 2016; 375 (1): 44-53.
[35] Chen Q, Hsia HL, Overman R, Bryan W, Pepin M, Mariano ER, Mudumbai SC, Buchheit T, Krishnamoorthy V, Good CB, Brookhart MA and Raghunathan K. Impact of an Opioid Safety Initiative on Patients Undergoing Total Knee Arthroplasty: A Time Series Analysis. *Anesthesiology.* 2019; 13: 369-380.
[36] Karst AC, Hayes BF, Burka AT, Bean JR and Wallace, JL. Effect of the Centers for Disease Control and Prevention opioid prescribing guidelines on postsurgical prescribing among veterans. *Journal of the American College of Clinical Pharmacy.* 2019 (epub 2018); (2) 2: 155-160.

Changes in prescribing and dispensing patterns were the most frequently assessed outcome for determining the impact of opioid analgesic prescribing limits. This is not surprising, as the reason for implementation of opioid analgesic prescribing limits is generally to avoid excess availability and consumption, and changes in prescribing behavior are usually the first indication that the prescribing limits are having any effect, making prescribing and dispensing patterns an appropriate target for measuring the impact of the limits. In addition, prescribing and dispensing data are widely available on large populations. Most studies found a decrease in measures of opioid analgesic prescribing or dispensing after a prescribing limit intervention. Additionally, a few studies found decreases in co-prescribing of opioids with benzodiazepines and mixed results with respect to changes in either the number of prescriptions or quantities of non-opioid analgesics prescribed. These studies used insurance claims data, PDMP data, and EMR or EHR data. These types of data often do not capture additional prescriptions written or filled outside of specific medical systems (EMR/EHR) or states (PDMP), prescriptions that were not paid for using a specific health insurance (insurance claims data), and the use of non-opioid analgesics for pain control (often over-the-counter). Although most studies showed decreases in opioid analgesic prescribing or dispensing, decreases in "high-risk" opioid prescribing, or some increases in non-opioid analgesic prescribing, these measures are only a first step in the evaluation of prescribing limits and, unfortunately, do not provide information on other important outcomes such as misuse or overdose. Prescribing and dispensing patterns do not provide sufficient information to assess whether the limits had a positive impact on patients and communities or whether reductions in prescribing and dispensing caused access issues or other negative impacts for patients.

Patient health outcomes

Evaluating the impact of prescribing limits on patient health outcomes is important to understand the benefits and harms to patients from enactment of prescribing limit laws, regulations, policies, and guidelines. Patient health outcomes include but are not limited to measures of appropriate pain management, mental health changes and other negative mental health outcomes, burden of care, nonmedical use, development of opioid use disorder, substitution with illicit drugs, fatal or nonfatal overdose, and death. These outcomes are key to determining the effectiveness of prescribing limits as well as identifying unintended consequences. However, they are also likely to vary based on existing recognized or unrecognized conditions such as opioid use disorder and mental health disorders. Previous research among VA patients found that having a diagnosis of substance use disorder or mental health condition was associated with an increased risk of fatal overdose or completed suicide after stopping treatment with opioids for any reason.[37] For this report, we assess refill rates[38] as a patient outcome, as many studies used this as a measure of appropriate pain management, noting, as described below, the significant limitations with this approach. Twelve studies analyzed the impact of a prescribing limit on one or more patient health outcomes. Among these, three studies analyzed changes in patient-reported pain control or quality of life and the impact of prescribing limits on the medically appropriate use of opioid analgesics,[39,40,41] while three

[37] Oliva EM, Bowe T, Manhapra A, Kertesz S, Hah JM, Henderson P, Robinson A, Paik M, Sandbrink F, Gordon AJ, Trafton JA. Associations Between Stopping Prescriptions for Opioids, Length of Opioid Treatment, and Overdose or Suicide deaths in US Veterans: Observational Evaluation. *BMJ*. 2020; 368: m283.

[38] Federal Regulations limit refills for controlled substances such that refills for controlled substance listed in Schedule II are prohibited and refills for controlled substances in Schedules III-V are allowed with some restrictions. Drug Enforcement Administration. Diversion Control Division Title 21 Code of Federal Regulations Part 1306. https://www.deadiversion.usdoj.gov/21cfr/cfr/2106cfrt.htm

[39] Weimer MB, Hartung DM, Ahmed S and Nicolaidis C. A chronic opioid therapy dose reduction policy in primary care. *Subst Abus*. 2016; 37 (1): 141-7.

[40] Aulet RM, Trieu V, Landrigan GP and Millay DJ. Changes in Opioid Prescribing Habits for Patients Undergoing Rhinoplasty and Septoplasty. *JAMA Facial Plast Surg*. 2019; 21 (6): 487-490.

[41] Chen Q, Hsia HL, Overman R, Bryan W, Pepin M, Mariano ER, Mudumbai SC, Buchheit T, Krishnamoorthy V, Good CB, Brookhart MA and Raghunathan K. Impact of an Opioid Safety Initiative on Patients Undergoing Total Knee Arthroplasty: A Time Series Analysis. *Anesthesiology.* 2019; 13: 369-380.

studies assessed opioid analgesic refills[42,43,44] and five studies assessed changes in unplanned telephone calls, clinic visits, or ED visits/admissions[45,46,47,48,49] as proxy measures for ineffective pain control. Two studies assessed the impact of prescribing limits on the transition from acute to chronic opioid analgesic use after surgical procedures,[50,51] three studies evaluated the impact of prescribing limits on prescription opioid or heroin overdose trends,[52,53,54] and one study evaluated the impact of prescribing limits on mortality rates up to one year after an inpatient discharge.[55]

The majority of studies that reported on pain management outcomes showed little to no change from before to after the prescribing limit was put into place. However, one study that evaluated the effect of Vermont's 2017 opioid analgesic prescribing law on post-operative opioid analgesic prescribing for general, orthopedic, gynecologic, urologic, or vascular procedures at the University of Vermont demonstrated a statistically significant decrease in the proportion of patients who received opioid analgesic refill prescriptions within 30 days of discharge from the hospital.[56] Another study evaluating the impact of the Veterans Health Administration's (VHA) Opioid Safety Initiative (OSI) and 100 MME/day opioid analgesic prescribing limit specifically on opioid analgesic prescribing for total knee arthroplasty procedures nationally showed a small but statistically significant increase in some pain scores after implementation of the OSI.[57] Studies that evaluated the impact of opioid analgesic prescribing limits on the transition from acute to chronic use after surgical procedures had mixed results, with one study demonstrating a statistically significant decrease in the number of patients transitioning to

[42]Aulet RM, Trieu V, Landrigan GP and Millay DJ. Changes in Opioid Prescribing Habits for Patients Undergoing Rhinoplasty and Septoplasty. *JAMA Facial Plast Surg*. 2019; 21 (6): 487-490.
[43] Lowenstein M, Hossain E, Yang W, Grande D, Perrone J, Neuman MD, Ashburn M and Delgado MK. Impact of a State Opioid Prescribing Limit and Electronic Medical Record Alert on Opioid Prescriptions: a Difference-in-Differences Analysis. *J Gen Intern Med*. 2020 (epub 2019); 35 (3): 662-671.
[44] MacLean CD, Fujii M, Ahern TP, Holoch P, Russell R, Hodges A and Moore J. Impact of Policy Interventions on Postoperative Opioid Prescribing. *Pain Med*. 2019 (epub 2018); 20 (6):1212-1218.
[45] Aulet RM, Trieu V, Landrigan GP and Millay DJ. Changes in Opioid Prescribing Habits for Patients Undergoing Rhinoplasty and Septoplasty. *JAMA Facial Plast Surg*. 2019; 21 (6): 487-490.
[46]Lowenstein M, Hossain E, Yang W, Grande D, Perrone J, Neuman MD, Ashburn M and Delgado MK. Impact of a State Opioid Prescribing Limit and Electronic Medical Record Alert on Opioid Prescriptions: a Difference-in-Differences Analysis. *J Gen Intern Med*. 2020 (epub 2019); 35 (3): 662-671.
[47] Potnuru P, Dudaryk R, Gebhard RE, Diez C, Velazquez OC, Candiotti KA and Epstein RH. Opioid prescriptions for acute pain after outpatient surgery at a large public university-affiliated hospital: Impact of state legislation in Florida. *Surgery*. 2019; 166 (3): 375-379.
[48] Zipple, M and Braddock, A. Success of Hospital Intervention and State Legislation on Decreasing and Standardizing Postoperative Opioid Prescribing Practices. *J Am Coll Surg*. 2019; 229 (2): 158-163.
[49] Zolin SJ, Ho VP, Young BT, Harvey AR, Beel KT, Tseng ES, Brown LR and Claridge JA. Opioid prescribing in minimally injured trauma patients: Effect of a state prescribing limit. *Surgery*. 2019; 166 (4): 593-600.
[50] Chen Q, Hsia HL, Overman R, Bryan W, Pepin M, Mariano ER, Mudumbai SC, Buchheit T, Krishnamoorthy V, Good CB, Brookhart MA and Raghunathan K. Impact of an Opioid Safety Initiative on Patients Undergoing Total Knee Arthroplasty: A Time Series Analysis. *Anesthesiology*. 2019; 13: 369-380.
[51] Reid DBC, Shah KN, Ruddell JH, Shapiro BH, Akelman E, Robertson AP, Palumbo MA, Daniels AH. Effect of narcotic prescription limiting legislation on opioid utilization following lumbar spine surgery. *The Spine Journal*. 2019 (epub 2018); 19: 717-725.
[52] Hartung DM, Kim H, Ahmed SM, Middleton L, Keast S, Deyo RA, Zhang K and McConnell KJ. Effect of a high dosage opioid prior authorization policy on prescription opioid use, misuse, and overdose outcomes. *Subst Abus*. 2018; 39 (2): 239-246.
[53] Meara E, Horwitz JR, Powell W, McCleland L, Zhou W, O'Malley A.J and Morden NE. State legal restrictions and prescription-opioid use among disabled adults. *N. Engl. J. Med*. 2016; 375 (1): 44-53.
[54] Sears JM, Fulton-Kehoe D, Schulman BA, Hogg-Johnson S and Franklin GM. Opioid Overdose Hospitalization Trajectories in States with and without Opioid-Dosing Guidelines. *Public Health Rep*. 2019; 134 (5): 567-576.
[55] Chen Q, Hsia HL, Overman R, Bryan W, Pepin M, Mariano ER, Mudumbai SC, Buchheit T, Krishnamoorthy V, Good CB, Brookhart MA and Raghunathan K. Impact of an Opioid Safety Initiative on Patients Undergoing Total Knee Arthroplasty: A Time Series Analysis. *Anesthesiology*. 2019; 13: 369-380.
[56] MacLean CD, Fujii M, Ahern TP, Holoch P, Russell R, Hodges A and Moore J. Impact of Policy Interventions on Postoperative Opioid Prescribing. *Pain Med*. 2019 (epub 2018); 20 (6): 1212-1218.
[57] Chen Q, Hsia HL, Overman R, Bryan W, Pepin M, Mariano ER, Mudumbai SC, Buchheit T, Krishnamoorthy V, Good CB, Brookhart MA and Raghunathan K. Impact of an Opioid Safety Initiative on Patients Undergoing Total Knee Arthroplasty: A Time Series Analysis. *Anesthesiology*. 2019; 13: 369-380.

chronic use after implementation of the VHA's OSI,[58] while another study found no difference in the proportion of patients who required opioid analgesics for a prolonged period post-operatively after implementation of Rhode Island's opioid prescribing law limiting initial prescriptions for opioid naïve patients to 30 MME/day (total of 150 MME) or 20 total doses.[59] Only one study demonstrated a decrease in prescription opioid or heroin overdoses in patients hospitalized for an opioid overdose after the implementation of new prescribing laws in three states when compared to five states without prescribing laws.[60] However, it is important to note that prescription opioid and heroin overdose trends were only analyzed through 2014, trends in overdose deaths were not captured in the study, and current trends in each state may be different. All-cause mortality rates up to one-year post-discharge for total knee arthroplasty demonstrated statistically significant decreases after enactment of the VHA's OSI nationally.[61]

We found no studies in the published scientific literature as of November 2019 that evaluated whether the impact of prescribing laws, regulations, policies, or guidelines varied based on the clinical indication for opioid analgesic treatment. This is an important consideration since opioid analgesic prescribing needs may be different by medical condition and other patient factors[62,63] and implementing prescribing limits may result in different outcomes by medical condition. Multiple studies evaluated outcomes among patients with acute pain. However, no single study compared the impacts from a prescribing limit among patient groups with different clinical indications for opioid analgesic treatment. Additionally, there were no published studies found in the scientific literature that evaluated the impact of state or federal opioid analgesic prescribing limit laws, regulations, policies, or guidelines on the incidence or prevalence of opioid use disorder.

Patient health outcomes: limitations

Our literature review identified multiple studies evaluating patient health outcomes. However, only three studies included an evaluation of the impact of prescribing limits specifically on self-reported outcomes such as pain control and quality of life. Among the studies that evaluated patient health outcomes, the results were mixed, and notably, lower opioid analgesic prescribing did not always translate to improved patient outcomes. Although patient health outcomes are essential for understanding the impact of prescribing limits, some can be hard to measure and difficult to collect. For example, although refills may be captured in electronic healthcare data,[64] refill attempts that were unsuccessful are not captured and it cannot be determined from these data if patients needed additional opioid analgesics to manage their pain appropriately but did not request a refill. Further, refills may reflect medically appropriate pain management for sequelae or unrelated medical condition and distinguishing between appropriate pain management and nonmedical use may not be possible. Mental health outcomes may be captured either by patient survey or using diagnosis codes in administrative data. However, mental health changes are likely most accurately captured through patient surveys, which are more difficult to reliably collect compared to large electronic healthcare-based measures. With respect to conversion from acute

[58] Chen Q, Hsia HL, Overman R, Bryan W, Pepin M, Mariano ER, Mudumbai SC, Buchheit T, Krishnamoorthy V, Good CB, Brookhart MA and Raghunathan K. Impact of an Opioid Safety Initiative on Patients Undergoing Total Knee Arthroplasty: A Time Series Analysis. *Anesthesiology.* 2019; 13: 369-380.

[59] Reid DBC, Shah KN, Ruddell JH, Shapiro BH, Akelman E, Robertson AP, Palumbo MA, Daniels AH. Effect of narcotic prescription limiting legislation on opioid utilization following lumbar spine surgery. *The Spine Journal*. 2019 (epub 2018); 19: 717-725.

[60] Sears JM, Fulton-Kehoe D, Schulman BA, Hogg-Johnson S and Franklin GM. Opioid Overdose Hospitalization Trajectories in States with and without Opioid-Dosing Guidelines. *Public Health Rep*. 2019; 134 (5): 567-576.

[61] Chen Q, Hsia HL, Overman R, Bryan W, Pepin M, Mariano ER, Mudumbai SC, Buchheit T, Krishnamoorthy V, Good CB, Brookhart MA and Raghunathan K. Impact of an Opioid Safety Initiative on Patients Undergoing Total Knee Arthroplasty: A Time Series Analysis. *Anesthesiology.* 2019; 13: 369-380.

[62] Thiels CA, Ubl DS, Yost KJ, Dowdy SC, Mabry TM, Gazelka HM, Cima RR, Habermann EB. Results of a prospective, multicenter initiative aimed at developing opioid-prescribing guidelines after surgery. *Ann Surg.* 2018; 268:457-468.

[63] Mundkur ML, Franklin JM, Abdia Y, Huybrechts KR, Patorno E, Gagne JJ, Meyer TE, Staffa J, Bateman BT. Days' supply of initial opioid analgesic prescriptions and additional fills for acute pain conditions treated in the primary care setting—United States, 2014. MMWR. 2019; 68:140-143.

[64] Note: Electronic healthcare data include administrative claims data and electronic medical record data. From: 2013 FDA's Guidance for Industry and FDA Staff: "Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data." May 2013. Available at: https://www.fda.gov/files/drugs/published/Best-Practices-for-Conducting-and-Reporting-Pharmacoepidemiologic-Safety-Studies-Using-Electronic-Healthcare-Data-Sets.pdf (accessed May 22, 2020).

opioid analgesic use to long-term use, it may be difficult in the research setting to determine if the transition to long-term use was warranted based on the condition or procedure causing the pain, the severity of the underlying condition or procedure, baseline chronic pain conditions, or other conditions/procedures not related to the initial prescription, instead of resulting from excess prescribing or signalling a transition to nonmedical use.

Patient burden

Implementation of prescribing laws, regulations, policies, and guidelines to impact opioid analgesic prescribing may inadvertently harm patients by increasing burdens to obtain appropriate medical care and necessary treatments. Prescribing limits may decrease patient access to appropriate opioid analgesic therapy by reducing the number of prescriptions, dosage units prescribed, or dose of opioid analgesics to levels that may not successfully manage their pain. Additionally, prescribing limits may reduce provider availability as primary care physicians may be reluctant to accept new patients with current opioid analgesic use.[65] Prescribing limits may require a patient to visit their provider more frequently to obtain new opioid analgesic prescriptions, which may further limit a patient's access with such burdens as additional travel expenses, picking up paper prescriptions, taking time off from work, additional co-payments for office visits and prescriptions, seeking care from other providers, and other issues. However, three studies found no statistically significant difference in healthcare contact after implementation of opioid prescribing limits.[66,67,68]

No studies were identified that evaluated missed care, increased travel time or expenses, or other limitations on access to opioid analgesics indirectly related to prescribing limits. Additionally, no studies were identified that evaluated the possible mitigation of patient burden through telemedicine or e-prescribing. Therefore, a complete understanding of the potential impact of prescribing limits on patient burden and mitigation of burden is unknown.

Patient burden: limitations

Potential patient burden from prescribing limits is poorly understood. The few studies evaluating follow-up care found no evidence that visits and phone calls for inadequate pain control increased after prescribing limits were enacted. However, it is not known how many patients in these studies experienced inadequate pain control or were not able to follow-up with their provider for additional medication to achieve adequate pain control. For example, it is unknown how many patients seeking initial contact for pain control were turned away by providers, requiring them to seek other providers or travel long-distance for a provider willing to treat their pain. Additionally, these studies focused on acute, post-surgical pain control which does not fully capture the spectrum of pain conditions impacted by the prescribing limits, including for persons who have chronic pain conditions such as low back pain, migraines, or neuropathic pain. No studies assessed the impact on patient burden for patients seeking therapy for chronic pain among the published epidemiologic studies captured in our literature review.

Prescriber burden and prescriber outcomes

Providers may also face burdens as a result of enactment of prescribing laws, regulations, policies, and guidelines. Potential burdens include but are not limited to additional office visits, paperwork, phone calls with pharmacies, fear or unease associated with prescribing outside a "guideline," and completing prior authorization forms to prescribe opioid analgesics. These potential burdens may also increase the costs for providers as a result of the work hours or staff required to care for patients and complete additional requirements. It is also possible that

[65] Lagisetty PA, Healy N, Garpestad C, Jannausch M, Tipirneni R, Bohnert AS. Access to primary care clinics for patients with chronic pain receiving opioids. *JAMA Network Open*. 2019; 2(7):e196928.
[66] Lowenstein M, Hossain E, Yang W, Grande D, Perrone J, Neuman MD, Ashburn M and Delgado MK. Impact of a State Opioid Prescribing Limit and Electronic Medical Record Alert on Opioid Prescriptions: a Difference-in-Differences Analysis. *J Gen Intern Med*. 2020 (epub 2019); 35 (3): 662-671.
[67] Zolin SJ, Ho VP, Young BT, Harvey AR, Beel KT, Tseng ES, Brown LR and Claridge JA. Opioid prescribing in minimally injured trauma patients: Effect of a state prescribing limit. *Surgery*. 2019; 166 (4): 593-600.
[68] Zipple, M and Braddock, A. Success of Hospital Intervention and State Legislation on Decreasing and Standardizing Postoperative Opioid Prescribing Practices. *J Am Coll Surg*. 2019; 229 (2): 158-163.

creating prescribing limits might create new prescribing norms and result in opioid analgesic prescriptions with longer durations if providers have already been writing opioid analgesic prescriptions for durations shorter than the enacted prescribing limit. There are reports that many primary care providers, for example, have stopped accepting new patients with chronic pain who are using opioid analgesics for pain management. Only one study assessed prescriber outcomes by evaluating the utilization of a tool designed to minimize prescriber burden related to prescribing limits. To facilitate compliance with New Jersey's prescribing law limiting all initial opioid analgesic prescriptions for opioid naive patients (someone who has not previously taken opioids) to a five day supply, University of Pennsylvania Health System (Penn Medicine) in New Jersey, located in the greater Philadelphia area, implemented an EMR alert that provided prescribers with a list of suggested dosing schedules for the chosen opioid analgesic that were consistent with the new prescribing limit.[69] Lowenstein et al., 2019 found that prescribers used this prescription suggestion list in 31 percent of all opioid analgesic orders and 49 percent of opioid analgesic orders with less than ten tablets after the EMR alert was implemented, potentially decreasing burden on providers while increasing their compliance with the new prescribing law.

Other provider outcomes that are important to consider with the implementation of prescribing limits include provider satisfaction and agreement with the limits, outcomes related to the excess burden, such as a reluctance to take on new patients with chronic pain disorders (particularly those already using opioid analgesics to control pain), or pressure to refer the patient to another provider, and fear of liability. No studies evaluating these prescriber outcomes were captured in our literature review.

Prescriber burden and prescriber outcomes: limitations
Very little information on prescriber burden and prescriber outcomes was found in our literature review. Studies are needed to better understand prescriber burden and prescriber outcomes resulting from implementation of prescribing limits.

Diversion or misuse of schedule II, III, or IV controlled substances
We found no studies in our literature review that evaluated the impact of prescribing laws, regulations, policies, or guidelines on diversion or misuse of Schedule II – IV controlled substances.

Section IV. **Other Interventions Commonly Implemented Alongside State and Federal Opioid Analgesic Prescribing Limits**

State and federal prescribing limit laws and regulations are surrounded by other interventions, including interventions implemented alongside the same law or regulation or other interventions implemented by non-governmental organizations, intended to alter opioid analgesic prescribing, reduce opioid misuse and opioid use disorder, and reduce opioid-related adverse health outcomes such as overdose. Interventions at all levels of care are often complex and involve multiple components. Interventions commonly implemented alongside state laws related to opioid analgesic prescribing limits include PDMPs, pain clinic laws, and policies and regulations implemented by state medical and pharmacy boards, departments of health, state Medicaid agencies, and state worker's compensation programs. These rules, policies, and regulations at the state level may include specific prescribing limits in addition to or supplementary to prescribing limit laws of the state. Additionally, as part of the DEA's Diversion Control Program, DEA sends updates to registrants alerting them to new matters of mutual interest, such as the CDC Guideline, which can greatly influence prescribing practices and lead to misapplication of guidelines beyond the intended scope. Additional interventions may be enacted only during emergencies or specific situations to temporarily change existing prescribing laws and regulations or create new prescribing laws and regulations that can impact opioid analgesic prescribing and dispensing. For example, during the COVID-19

[69] Lowenstein M, Hossain E, Yang W, Grande D, Perrone J, Neuman MD, Ashburn M and Delgado MK. Impact of a State Opioid Prescribing Limit and Electronic Medical Record Alert on Opioid Prescriptions: a Difference-in-Differences Analysis. *J Gen Intern Med*. 2020 (epub 2019); 35 (3): 662-671.

public health emergency, DEA adopted policies to allow prescribing of controlled substances without in-person interaction.[70] CMS also includes prospective safety edits and other policies in addition to prescribing limits for Medicare and Medicaid, potentially affecting levels of opioid analgesic prescribing.

Legislative interventions such as pain clinic laws or PDMPs can limit the dispensing of opioid analgesics. Pain clinic laws restrict the ability of prescribers to dispense opioid analgesics at the site of care, while PDMPs allow providers to view patient prescription history to identify and address problematic use. Studies have shown that pain clinic laws and PDMPs have been associated with significant decreases in opioid analgesic prescribing, prescription opioid analgesic overdoses, and prescription opioid analgesic overdose deaths. [71, 72, 73, 74, 75, 76, 77, 78, 79] Mandatory use of PDMPs has also been associated with a reduction in opioid analgesic prescribing and opioid-related inpatient stays and emergency department visits.[80, 81, 82, 83] However, at least one study did not find an association between the level of PDMP requirements (e.g., mandatory vs. no requirement) and patients being prescribed an opioid analgesic for chronic non-cancer pain.[84] Moreover, since multiple policies are often implemented simultaneously, there are often significant challenges in assessing the unique impact of specific state policies. Multiple state medical and pharmacy boards also have implemented prescribing limits and some of these interventions have been evaluated.[85,86,87] However, many of the gaps and challenges discussed in Section V also apply to these evaluations. Importantly, the 2019 report from the Pain Management Best Practices Inter-Agency Task Force emphasizes an individualized, patient-centered approach for treatment of pain, the use of various classes of medications, including opioid analgesics and non-opioid analgesicss, as part of a multi-disciplinary approach for chronic pain management.

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[70] DEA. How to prescribe controlled substances during the COVID-19 public health emergency. https://www.deadiversion.usdoj.gov/GDP/(DEA-DC-023)(DEA075)Decision_Tree_(Final)_33120_2007.pdf (accessed August 24, 2020)

[71] Chang HY, Lyapustina T, Rutkow L, Daubresse M, Richey M, Faul M, Stuart EA, Alexander GC. Impact of prescription drug monitoring programs and pill mill laws on high-risk opioid prescribers: A comparative interrupted time series analysis. *Drug and alcohol dependence.* 2016; 165:1-8.

[72] Rutkow L, Chang HY, Daubresse M, Webster DW, Stuart EA, Alexander GC. Effect of Florida's Prescription Drug Monitoring Program and Pill Mill Laws on Opioid Prescribing and Use. *JAMA Intern Med*. 2015; 175 (10): 1642-1649.

[73] Johnson H, Paulozzi L, Porucznik C, Mack K, Herter B. Decline in drug overdose deaths after state policy changes - Florida, 2010-2012. *MMWR. Morbidity and mortality weekly report*. 2014; 63 (26): 569-574.

[74] Kennedy-Hendricks A, Richey M, McGinty EE, Stuart EA, Barry CL, Webster DW. Opioid Overdose Deaths and Florida's Crackdown on Pill Mills. *Am J Public Health*. 2016; 106 (2): 291-297.

[75] Lyapustina T, Rutkow L, Chang HY, Daubresse M, Ramji AF, Faul M, Stuart EA, Alexander GC. Effect of a "pill mill" law on opioid prescribing and utilization: The case of Texas. *Drug and alcohol dependence.* 2016; 159: 190-197.

[76] Raji MA, Kuo YF, Chen NW, Hasan H, Wilkes DM, Goodwin JS. Impact of Laws Regulating Pain Clinics on Opioid Prescribing and Opioid-Related Toxicity Among Texas Medicare Part D Beneficiaries. *Journal of Pharmacy Technology*. 2017; 33 (2): 60-65.

[77] Pardo B. Do more robust prescription drug monitoring programs reduce prescription opioid overdose? *Addiction*. 2016; 112 (10): 1773-1783.

[78] Guy G, Zhang K. Effect of Florida's Prescription Drug Monitoring Program and Pain Clinic Laws on Nonfatal Opioid-Related Overdoses. *American Journal of Preventive Medicine.* 2020; 58 (5): 703-706.

[79] Fink DS, Schleimer JP, Sarvet A. et al. Association between prescription drug monitoring programs and nonfatal and fatal drug overdoses: A systematic review. *Ann Intern Med*. 2018; 168 (11): 783-790.

[80] Haffajee RL, Mello MM, Zhang F, Zaslavsky AM, Larochelle MR, Wharam JF. Four states with robust prescription drug monitoring programs reduced opioid dosages. *Health Affairs.* 2018; 37 (6): 964-974.

[81] Strickler GK, Zhang K, Halpin JF, Bohnert ASB, Baldwin GT and Kreiner PW. Effects of mandatory prescription drug monitoring program (PDMP) use laws on prescriber registration and use and on risky prescribing. *Drug Alcohol Depend*. 2019; 199: 1-9.

[82] Wen H, Hockenberry J, Jeng PJ, Bao Y. Prescription Drug Monitoring Program Mandates: impact on opioid prescribing and related hospital use. *Health Affairs.* 2019; 38 (9): 1550-1556.

[83] Dowell D, Zhang K, Noonan R, Hockenberry J. Mandatory provider review and pain clinic laws reduce the amounts of opioids prescribed and overdose death rates *Health Aff.* 2016; 35: 1876-1883.

[84] Lin HS, Wang Z, Boyd C, Simoni-Wastila L, Buu A. Associations between statewide prescription drug monitoring program (PDMP) requirement and physician patterns of prescribing opioid analgesics for patients with non-cancer chronic pain. Addictive Behaviors. 2018; 76:348-354.

[85] Austin R C, Fusco CW, Fagan EB, Drake E, Pacious J, Dickens H, Galvin SL and Wilson CG. Teaching Opioid Tapering Through Guided Instruction. *Fam Med.* 2019; 51 (5): 434-437.

[86] Al Achkar M, Grammis S, Revere D, MacKie P, Howard M, Gupta S. The effects of state rules on opioid prescribing in Indiana. *BMC Health Services Research*. 2018; 18: 1-7.

[87] Zolin SJ, Ho VP, Young BT, Harvey AR, Beel KT, Tseng ES, Brown LR and Claridge JA. Opioid prescribing in minimally injured trauma patients: Effect of a state prescribing limit. *Surgery*. 2019; 166 (4): 593-600.

Interventions are also implemented by non-governmental organizations, such as medical associations, health systems, insurers, or individual hospitals or health systems. This can aid in implementation, strengthen governmental policy, encourage compliance, or affect the behavior of both patients and providers. Strategies for implementation typically include the dissemination of national, state, local, or professional society clinical practice guideline recommendations. Dissemination can happen through provider education,[88,89,90,91,92] structured educational sessions (i.e., academic detailing[93]), and by providing clinical decision support at the point of care through integration within the EMR or EHR.[94,95] These are often based on guidelines and laws at the federal and state level with some variation or additional components and may include specific prescribing limits determined by the organization. One example are the limits set by the Mayo Clinic, which are specific to surgical procedures and patient factors.[96] Insurance companies also implement policies and limits on opioid analgesic prescriptions, such as those set by United Healthcare, which include dispensing limits, safety edits for concurrent use of drugs, and drug management programs for at risk patients.[97] In 2010, Kaiser Permanente Southern California implemented a suite of policies aimed at reframing the perception and treatment of chronic pain. These interventions aimed to reduce inappropriate opioid analgesic prescribing and included prescribing and dispensing policies; monitoring and follow-up processes; and clinical coordination through EHR integration. Losby et al., 2017 found that after these polices were enacted there was a 30 percent reduction in high dose opioid analgesic prescribing (≥120 MME/ day), a 98 percent reduction of prescriptions greater than 200 tablets/capsules, a 90 percent reduction in co-prescribing of benzodiazepines, and a 72 percent reduction in extended-release/long-acting opioid analgesic prescriptions.[98] Additional insurance interventions typically used to identify high-risk opioid analgesic prescribing include programs that lock-in patients to specific providers and pharmacies, as well as prior authorization policies that require prior approval of medication before reimbursement. While some

[88] Weimer MB, Hartung DM, Ahmed S and Nicolaidis C. A chronic opioid therapy dose reduction policy in primary care. *Subst Abus*. 2016; 37 (1): 141-7.
[89] Aulet RM, Trieu V, Landrigan GP and Millay DJ. Changes in Opioid Prescribing Habits for Patients Undergoing Rhinoplasty and Septoplasty. *JAMA Facial Plast Surg*. 2019; 21 (6): 487-490.
[90] MacLean CD, Fujii M, Ahern TP, Holoch P, Russell R, Hodges A and Moore J. Impact of Policy Interventions on Postoperative Opioid Prescribing. *Pain Med*. 2019 (epub 2018); 20 (6): 1212-1218.
[91] Potnuru P, Dudaryk R, Gebhard RE, Diez C, Velazquez OC, Candiotti KA and Epstein RH. Opioid prescriptions for acute pain after outpatient surgery at a large public university-affiliated hospital: Impact of state legislation in Florida. *Surgery.* 2019; 166 (3): 375-379.
[92] Zipple, M and Braddock, A. Success of Hospital Intervention and State Legislation on Decreasing and Standardizing Postoperative Opioid Prescribing Practices. *J Am Coll Surg.* 2019; 229 (2): 158-163.
[93] Chen Q, Hsia HL, Overman R, Bryan W, Pepin M, Mariano ER, Mudumbai SC, Buchheit T, Krishnamoorthy V, Good CB, Brookhart MA and Raghunathan K. Impact of an Opioid Safety Initiative on Patients Undergoing Total Knee Arthroplasty: A Time Series Analysis. *Anesthesiology.* 2019; 13: 369-380.
[94] Lowenstein M, Hossain E, Yang W, Grande D, Perrone J, Neuman MD, Ashburn M and Delgado MK. Impact of a State Opioid Prescribing Limit and Electronic Medical Record Alert on Opioid Prescriptions: a Difference-in-Differences Analysis. *J Gen Intern Med.* 2020 (epub 2019); 35 (3): 662-671.
[95] Losby JL, Hyatt JD, Kanter MH, Baldwin G, Matsuoka D. Safer and more appropriate opioid prescribing: a large healthcare system's comprehensive approach. *J Eval Clin Pract.* 2017: 1-7.
[96] Mayo Clinic. "Variation in postoperative opioid prescribing provides motivation for a more standardized approach." Available at: https://www.mayoclinic.org/medical-professionals/urology/news/variation-in-postoperative-opioid-prescribing-provides-motivation-for-a-more-standardized-approach/mac-20450573 (accessed May 1, 2020).
[97] 2020 Opioid Readiness: UnitedHealthcare Medicare Advantage and Prescription Drug Plans. Available at: https://www.uhcprovider.com/content/dam/provider/docs/public/resources/pharmacy/opioids/Pharmacy-opioid-qrg-2020.pdf (accessed April 30, 2020).
[98] Losby JL, Hyatt JD, Kanter MH, Baldwin G, Matsuoka D. Safer and more appropriate opioid prescribing: a large healthcare system's comprehensive approach. *J Eval Clin Pract.* 2017: 1-7.

evidence exists on the effectiveness of these polices,[99,100,101,102,103,104] not all policies are evaluated or have only been evaluated in limited ways.

As further described in Section V, disentangling multiple components from prescribing limits and other laws, regulations, policies, and guidelines and the complexity of these interventions makes evaluating prescribing limits very challenging.

Section V. **Challenges, Gaps, and Opportunities for Evaluating Opioid Analgesic Prescribing Limits**

Section 5.01 Challenges and gaps

Our assessment of the published literature highlights the need for additional studies that rigorously evaluate the impact of laws, regulations, policies, and guidelines that limit opioid analgesic prescriptions. Of note, we identified multiple challenges and gaps associated with evaluating the impact of these limits that should be addressed in future studies. The main challenges and gaps identified were:

1) Challenges with interpreting observational epidemiologic studies
2) Gaps in the evaluation of important health outcomes and differences in these outcomes by sociodemographic and clinical factors
3) Challenges in isolating the impact of individual laws, regulations, policies, and guidelines
4) Gaps in high quality published studies: scientific rigor greatly varies across published studies
5) Challenges applying findings of individual studies to the larger populations impacted by the law, regulation, policy, or guideline, and
6) Challenges comparing the impact of different prescribing limits, as they are highly variable.

1) Challenges with interpreting observational epidemiologic studies

Observational epidemiologic studies are studies where treatment or intervention is not assigned or randomized using a study protocol. These studies provide an essential tool for answering questions of public health importance, and they provide a way to evaluate an intervention when randomization is either unethical or impractical. However, lack of randomization presents opportunities for bias and incorrect conclusions if the study is not well designed or the results are not correctly interpreted. Observational epidemiologic studies should be interpreted with a full appreciation of the strengths and limitations of the study design.

Challenges with interpreting studies using electronic healthcare data

Administrative claims data and electronic medical and health records data allow for the rapid assessment of large numbers of patients. However, the depth of information is usually limited and dependent on the quality and quantity of data entered into the system. With these data, we can only see what has been included within the system (either the payer system or the electronic medical records within the medical group); medical care and

[99] Skinner AC, Ringwalt C, Naumann RB, Roberts AW, Moss LA, Sachdeva N, Weaver MA, Farley J. Reducing opioid misuse: evaluation of a Medicaid controlled substance lock-in program. *J. Pain.* 2016; 17 (11): 1150–1155.
[100] Morden NE, Zerzan JT, Rue TC, Heagerty PJ, Roughead EE, Soumerai SB, Ross-Degnan D, Sullivan SD. Medicaid prior authorization and controlled release oxycodone. *Med. Care*. 2008; 46 (6): 573–580.
[101] Garcia MC, Dodek AB, Kowalski T, Fallon J, Lee SH, Iademarco MF, Auerbach J, Bohm MK. Declines in opioid prescribing after a private insurer policy change- Massachusetts, 2011-2015. *MMWR Morb Mortal Wkly Rep.* 2016; 65: 1125-1131.
[102] Barre L, Oliver B, Alexander-Scott N, McCormick M, Elmaleh R and McDonald JV. Impact of state regulations on initial opioid prescribing behavior in Rhode Island. *Rhode Island Medical Journal*. 2019: 24-26.
[103] Garcia MM, Lenz K, Greenwood BC, Angelini MC, Thompson T, Clements KM, Mauro RP and Jeffrey PL. Impact of Sequential Opioid Dose Reduction Interventions in a State Medicaid Program Between 2002 and 2017. *J Pain.* 2019; 20 (8): 876-884.
[104] Hartung DM, Kim H, Ahmed SM, Middleton L, Keast S, Deyo RA, Zhang K and McConnell KJ. Effect of a high dosage opioid prior authorization policy on prescription opioid use, misuse, and overdose outcomes. *Subst Abus*. 2018; 39 (2): 239-246.

prescriptions received outside of the system are not usually visible. Granular clinical information, such as severity of illness, and most patient behaviors are not collected. Other single payer systems, such as VA, have similar advantages and disadvantages to a single payer medical group that currently uses a unique electronic medical record system; data are available for a large number of patients, but we are unable to see what is happening outside of the single payer system, and patient behaviors are also not usually captured. For example, as part of the VHA's OSI, the VHA implemented guidelines to reduce high-dose opioid analgesic prescribing with an individualized approach to slow tapering. They reported a 70 percent reduction in patients with opioid doses >100 MME subsequent to the intervention.[105] However, the decrease in patients with high doses may not tell the whole story; if the patient receives care outside of the VA system, it will not be captured in the VA data. This limitation with using single payer or single medical group data from the VA system was discussed during a recent FDA Advisory Committee meeting: "…if [the patients] get the medication from outside and it's not paid for by the VA system, if they go externally, no, that's not captured."[106] One of the panel members discussed her experience with patients from the VA seeking treatment for pain: "The data that was presented by the VA, I found incredibly amazing and also have a very hard time to reconcile with what I see in my clinical practice, which was an onslaught of patients, who previously got their care from the VA on high-dose opioids, now going through their other insurance in order to get care and to get someone to take over their medications."[107]

Another common problem in interpreting studies of opioid analgesic use in electronic healthcare data is that the patients' adherence to the prescription is unknown. It is also very difficult to measure dose using MME in prescription dispensing data because there can be overlapping prescriptions (e.g., a patient picks up the next opioid analgesic prescription early, a patient has multiple prescribed opioid analgesics at the same time), and algorithms for calculating opioid dosage (i.e., MME) vary.

Challenges with ecological study design

One type of observational study design used for understanding the effect of a policy change in a large population is the ecological study design. The ecological study design takes a high-level approach, using information available at the population level instead of the individual level. However, factors not accounted for in an analysis could affect the results, and any interpretation should be made carefully. For example, Davis et al., 2019, used the DEA's Automation of Reports and Consolidated Orders System (ARCOS) data to evaluate the impact of prescribing limits on opioid analgesic prescribing through the examination of the volume of opioids distributed in eleven different states before and after implementation of the opioid prescribing law in that state.[108] The authors found no clear connection between prescribing laws and the volume of opioids distributed before and after the intervention. However, since ARCOS data do not capture what patients are actually prescribed or dispensed, this data source may not be the most appropriate data source to evaluate the impact of prescribing limits on opioid analgesic prescribing and dispensing patterns or other patient or provider outcomes.

2) Gaps in the evaluation of important health outcomes and differences in these outcomes by sociodemographic and clinical factors

Most of the studies identified in our literature review evaluated changes in prescribing and/or dispensing patterns of prescription opioid analgesics after implementation of a prescribing limit. Changes in prescribing are an important first step in measuring adherence to the intervention but are relatively uninformative for the overall goal of improving patient and public health outcomes. Few studies evaluated more informative outcomes, particularly

[105] Presentation for the Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee. Sandbrink, F. June 11, 2019. Slide 16. Available at: https://www.fda.gov/media/128871/download (accessed May 5, 2020).

[106] Joint Meeting of the Drug and Risk Management Advisory Committee (DSaRM) and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC). Comment: Sandbrink, F. June 11, 2019. Transcript page 433. Available at: https://www.fda.gov/media/130640/download (accessed May 4, 2020).

[107] Joint Meeting of the Drug and Risk Management Advisory Committee (DSaRM) and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC). Comment: Jowza, M. June 12, 2019. Transcript page 213. Available at: https://www.fda.gov/media/130641/download (accessed May 6, 2020).

[108] Davis CS, Piper BJ, Gertner AK and Rotter JS. Opioid Prescribing Laws Are Not Associated with Short-term Declines in Prescription Opioid Distribution. *Pain Med*. 2020 (epub 2019); 21 (3): 532-537.

patient health outcomes or prescriber outcomes. Additionally, most studies did not stratify results by sociodemographic or clinical factors (e.g., medical conditions, comorbidities). Examples of patient-reported outcomes of interest include patient-reported opioid analgesic use, non-opioid analgesic use, opioid analgesic misuse, leftover opioid analgesic tablets, number of refills requested, pain scores, unscheduled follow-up visits for pain, quality of life, suicidal ideation, behavioral health status (e.g. depression, anxiety), stigmatization, difficulty finding a provider and patient satisfaction. Examples of provider outcomes include barriers to prescribing and fear of liability. The lack of studies assessing patient and provider outcomes is not surprising considering the relative ease and low expense of collecting prescribing and dispensing data compared with the difficulty and expense of collecting patient and provider outcomes. Opioid analgesic *prescribing data* are routinely maintained in electronic medical records and can be queried retrospectively for evaluating an intervention. Opioid analgesic prescription *dispensing data* are available to be queried retrospectively through PDMPs, insurance claims data sources, and private vendors that purchase and nationally project opioid analgesic prescriptions dispensed based on pharmacy data.

However, most *patient-reported outcomes*, such as pain scores, cannot be collected retrospectively unless they were previously recorded in the electronic medical or health record, and they are often missing from patient records. Prospective, systematic collection of patient-reported outcomes requires continued follow-up at standardized times as well as the use of tools such as patient surveys administered to at least a subset of the study population. *Provider-reported outcomes*, such as new prescribing burdens associated with the implementation of prescribing limits, can usually only be collected prospectively using tools such as surveys, as provider-burdens are not otherwise documented. To robustly evaluate an intervention, these surveys need to be completed before and after the intervention, requiring additional time and planning. Furthermore, it may be impossible to assess the impact of the existing federal and state prescribing limits on these more informative outcomes since they were most likely not collected prior to implementation.

Patient and provider outcomes are necessary not only for a complete evaluation of the potential effectiveness of the intervention but are also important for assessing potential unintended consequences of limiting opioid analgesic prescribing. Potential unintended consequences for patients could include forced tapers and dose reduction, denial of prescriptions, decreased pain control, increased disability, transition to illicit drug use or other substance use, and negative mental health outcomes such as depression, suicidal ideation, anxiety, social isolation, job loss, and completed suicide. Further, misapplication of prescribing limits, such as the misapplication of the CDC Guideline in oncology and pain medicine, could result in unintended consequences. Potential unintended consequences for prescribers may include a "chilling effect" or fear of liability, as well as barriers to prescribing, such as additional time requirements to complete extra documentation and prior authorization forms. During multiple comment periods at various public hearings and meetings, individual accounts of these unintended consequences have been shared by the public as well as from experts in pain medicine. During a June 2019 FDA Advisory Committee meeting, one guest speaker described the importance of patient-centered and evidence-based opioid analgesic prescribing. The guest speaker noted that "there has been a broad misinterpretation of the CDC guidelines, so patients are being force-tapered to zero or tapered to predefined doses. There's a failure to account for individual differences when de-prescribing, and a failure to monitor, protect, and to be flexible and meet the individual needs of the patient." The guest speaker also described potential risks of de-prescribing, including suicidal ideation and completed suicide and the need for research for better understanding these risks.[109] During a May 2019 public meeting for the Pain Management Best Practices Inter-Agency Task Force, comments from the public and pain management patient testimonials described multiple unintended consequences of limiting opioid analgesics, including being stigmatized as a drug-seeker, being rejected from multiple providers, thoughts of suicide and hopelessness, and a need for patient-centered care.[110] A 2020 Federal Register notice, Management of

[109] Joint Meeting of the Drug and Risk Management Advisory Committee (DSaRM) and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC). June 11, 2019. Transcript pages 389-410. Guest Speaker Presentation. Available at: https://www.fda.gov/media/130640/download (accessed May 6, 2020).
[110] Pain Management Best Practices Inter-Agency Task Force, Public Meeting #3, May 9-10, 2019. (Day 1 Summary pg 3, 6). https://www.hhs.gov/sites/default/files/pmtf-public-meeting-3-day-1-summary-05-09-2019_508.pdf

Acute and Chronic Pain: Request for Comment, received over 5,000 comments.[111] Many of these comments reflected frustrations from patients about challenges in accessing opioid analgesic medications.[112] Rigorous evaluations to assess patient and provider outcomes are needed because it is unclear how frequently these serious problems are encountered.

Additional challenges are associated with evaluating the impact of prescribing limits on other important outcomes such as nonmedical use, substance use disorders, and overdose. These outcomes may develop in patients as a result of their own opioid analgesic prescriptions, but can also develop in community members through diversion, and it may be difficult to measure or link these outcomes to the initial opioid analgesic prescription source. These outcomes may also develop on longer time scales and are affected by a multitude of known and unknown factors, both at the individual and the community levels, leading to significant difficulty in attributing these outcomes to a single intervention.[113] However, rigorous evaluation of these individual and community outcomes is important since one of the main goals of these prescribing limits is to reduce nonmedical use, substance use disorders, and overdose involving prescription opioid analgesics.

Finally, the important outcomes described above may vary by factors such as patient race/ethnicity, income geographic area, urbanicity, physician specialty, primary source of payment (private insurance, Medicare, Medicaid, cash) or chronic conditions or comorbidities, such as mental disorders or opioid use disorder. Some of these outcomes are known to affect opioid analgesic prescribing independently from implementation of prescribing limits.[114,115,116] Some studies reported race/ethnicity of their populations, but few stratified their study outcomes by race/ethnicity. This is a major gap in the literature since diseases such as sickle cell disease disproportionately affect African Americans and policies involving prescribing limits should consider the potential for exacerbating any racial disparities and stigma. In one qualitative study, patients with sickle cell disease reported increased stigmatization for opioid analgesic use and difficulty filling opioid analgesic prescriptions at the pharmacy post CDC Guideline.[117] One study investigating opioid analgesic prescribing in Indiana after implementation of new emergency rules found differential effects of the emergency rule by gender, age, and payer (Medicare or Medicaid vs private insurance).[118]

3) Challenges in isolating the impact of individual laws, regulations, policies, and guidelines

Existing trends and external interventions

When evaluating the impact of opioid analgesic prescribing limits, controlling for changes in overall prescribing trends over time at local, state, and federal levels is crucial to isolating the impact of the limit. Although national outpatient opioid analgesic prescribing and dispensing rates have continued to decline since 2012, research shows

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[111] Federal Register. Management of Acute and Chronic Pain: Request for Comment. https://www.federalregister.gov/documents/2020/04/17/2020-08127/management-of-acute-and-chronic-pain-request-for-comment (accessed August 24, 2020)

[112] Board of Scientific Counselors of the National Center for Injury Prevention and Control. July 22, 2020. Management of Acute and Chronic Pain: Opportunities for Stakeholder Engagement and Public Comment. https://www.cdc.gov/injury/pdfs/bsc/Lee_FINAL_BSC_07_07_2020-508-r.pdf (accessed August 24, 2020)

[113] Drug Safety and Risk Management and Anesthetics and Analgesic Drug Products Advisory Committees. May 3 and May 4, 2016. Available at: https://www.fda.gov/media/100444/download and https://www.fda.gov/media/100451/download (accessed May 6, 2020).

[114] García MC, Heilig CM, Lee SH, et al. Opioid Prescribing Rates in Nonmetropolitan and Metropolitan Counties Among Primary Care Providers Using an Electronic Health Record System — United States, 2014–2017. MMWR Morb Mortal Wkly Rep 2019; 68:25–30. DOI: http://dx.doi.org/10.15585/mmwr.mm6802a1

[115] Lund BC, Oh ME, Hadlandsmyth K, Mosher HJ. Regional and rural-urban variation in opioid prescribing in the Veterans Health Administration. Military Medicine. 2019; 184 (11/12):894.

[116] Lin HC, Boyd C, Simoni-Wastila L, Buu A. Association between statewide prescription drug monitoring program (PDMP) requirement and physician patterns of prescribing opioid analgesics for patients with non-cancer chronic pain. *Addictive Behaviors*. 2018; 76:348-354.

[117] Sinha CB, Bakshi N, Ross D, Krishnamurti L. Management of chronic pain in adults living with sickle cell disease in the era of opioid epidemic: a qualitative study. *JAMA Network Open*. 2019; 2:e194410.

[118] Al Achkar M, Grammis S, Revere D, MacKie P, Howard M, Gupta S. The effects of state rules on opioid prescribing in Indiana. *BMC Health Services Research*. 2018; 18: 1-7.

that there was an accelerated decrease following the publication of the CDC Guideline in March 2016.[119] The existing or background trends in opioid analgesic prescribing and dispensing make it difficult to evaluate the impact of a specific prescribing law, regulation, guideline, or limit. Most studies were unable to account for existing trends prior to their evaluated interventions. For example, most studies face the challenge of disentangling state and local policies from the trend that was already occurring and accelerated in the period after publication of the CDC Guideline. Additional external interventions at all levels of care can affect trends in the outcomes evaluated and should be accounted for in analyses as well. Utilizing certain study designs and statistical methods can assist with accounting for these external factors and trends. For example, Davis et al., 2019 evaluated prescribing laws enacted from 2016-2017 in multiple states.[120] In an attempt to control for external trends and interventions, such as the CDC Guideline from 2016, the authors compared the states with laws enacted during this time to states without laws enacted during this time period.

Internal components and interventions

Accounting for multiple components occurring within the same intervention is especially difficult as it can be complicated or sometimes impossible to disentangle the effect of one component from another. Many laws and regulations intended to decrease opioid analgesic prescribing consist of multiple other components in addition to the prescribing limit. For example, opioid prescribing laws passed in Vermont in July 2017 also contained requirements for providers to check the Vermont Prescription Monitoring System, provide patient education about the risks of taking opioids, and obtain signed consent forms prior to prescribing opioids to treat acute pain. Implementation of multiple components at the same time makes it difficult to isolate the effect of the opioid analgesic prescribing limit on important patient, provider, and health outcomes.[121]

Timing of the law

An additional challenge exists with interpreting results from studies of the impact of prescribing limits due to the timing of the enactment and implementation of the law and period of evaluation. Time between enactment and implementation of a law can vary, and changes in the behavior of providers and patients can occur prior to the actual implementation of the law. Studies should account for changes in behavior during the period between enactment and implementation. However, most of the studies that were identified in our literature searches did not distinguish between the date when the prescribing law was enacted and when it was actually implemented, and therefore did not account or control for these pre-implementation changes in behavior. This further complicates the interpretation of individual studies and comparison between studies.

4) Gaps in high quality published studies: scientific rigor greatly varies across published studies

Published scientific studies can vary greatly in their scientific rigor. Although not included in this report, we found many articles merely describing an outcome after an intervention with no statistical comparison or context provided. These were excluded from our literature review as we required there to be some formal evaluation or comparison of outcomes between the time before and after implementation of the prescribing limit. Among the studies that we included for this report, some studies included comparator groups that were not affected by the prescribing limit, used innovative methods (e.g., interrupted time series analysis) to account for potential confounding factors such as existing trends in prescribing, or took advantage of "natural experiments," providing strong evidence of the potential effects of opioid analgesic prescribing laws, regulations, policies, and guidelines. An example of a natural experiment was conducted by Lowenstein et al., 2019. This study compared outcomes between two populations within the same health system (University of Pennsylvania Health System) with different prescribing limits: a population in New Jersey with a five-day limit for all acute opioid analgesic prescriptions and a population in Pennsylvania with a seven day limit for prescription opioid analgesics for some

[119] Bohnert ASB, Guy GP Jr, Losby JL. Opioid prescribing in the United States before and after the Centers for Disease Control and Prevention's 2016 opioid guideline. *Ann Intern Med.* 2018; 169: 367-375.

[120] Davis CS, Piper BJ, Gertner AK and Rotter JS. Opioid Prescribing Laws Are Not Associated with Short-term Declines in Prescription Opioid Distribution. *Pain Med*. 2020 (epub 2019); 21 (3): 532-537.

[121] Aulet RM, Trieu V, Landrigan GP and Millay DJ. Changes in Opioid Prescribing Habits for Patients Undergoing Rhinoplasty and Septoplasty. *JAMA Facial Plast Surg*. 2019; 21 (6): 487-490.

settings such as EDs and urgent care.[122] Other studies provided only a descriptive comparison of outcomes pre- and post-intervention without any substantial statistical analysis.

Sample size is also an important factor to consider. Sample size is often related to the study design and types of outcomes collected. Studies using administrative claims data collecting only prescription information often have large sample sizes, while studies collecting more informative outcomes via prospective survey data on patients or prescribers tend to have smaller study populations. Additionally, studies are limited by the size of the population which they are studying. Studies conducted within a single surgical specialty or at a single institution are often limited by the patient population or patient volume. Consequently, some study conclusions were strongly supported by rigorous methodologies and a substantial sample size while others were weakly supported with a small sample size and limited methods that did not account for factors which could affect the results. This variation made it difficult to compare results between studies as conclusions should be weighted according to the strength of the study design.

5) Challenges applying findings of individual studies to the larger populations impacted by the law, regulation, policy, or guideline

Many studies found in the literature searches evaluated the implementation of opioid analgesic prescribing laws, regulations, policies, and guidelines at a single institution, medical practice or specialty, or within a specific population. Evaluation of prescribing laws, regulations, policies, and guidelines within these types of locations and populations provide a limited view into the potential outcomes associated with the law for the broader affected population. For example, studies evaluating outcomes among a population of patients with post-surgical pain from one specific procedure represent only a limited subgroup of the population needing treatment for acute pain state-wide. In contrast, studies that evaluate the impact of laws at the population level such as at the state level do not provide insight into how the impacts might vary across patients with different pain conditions.

6) Challenges comparing the differences in impact between prescribing limits as they are highly variable

Major variations between prescribing limits found in different laws, regulations, policies, and guidelines also pose a challenge when evaluating their effects on important outcomes. Prescribing limits vary by the types of drugs covered, the amount or duration of the medication for which a limit has been established, whether it is for acute pain, chronic pain, or both, whether it is an initial prescription or subsequent prescriptions, the ages of patients or medical diagnoses that are automatically excluded from the prescribing limit, and type of authority of the prescriber to override the limit. These variations make comparisons between interventions difficult. Further, there is little to no information about how federal and state opioid analgesic prescribing laws, regulations, policies, and guidelines are implemented and enforced, as it is often the responsibility of organizations, medical practices, and other healthcare providers to become compliant with the prescribing limits, and this information is not often provided by these groups or in the current scientific literature. The lack of this information makes a national evaluation or assessment of their effectiveness challenging.

Section 5.02 Opportunities

Awareness of the challenges and gaps in research on prescribing limits provides opportunities for future studies.

First and foremost, studies should be designed to prospectively collect meaningful patient, provider, and community outcomes. These outcomes are the most relevant for improving public health and for ensuring that the impact of these prescribing limits is for the benefit of patients and supports public health. These studies should also collect potential unintended consequences, such as increased or untreated pain, mental health decompensation, social impact, and suicidal ideation or completion resulting from severe untreated pain. Studies to evaluate these outcomes must be planned before the prescribing limits are implemented so that investigators

[122] Lowenstein M, Hossain E, Yang W, Grande D, Perrone J, Neuman MD, Ashburn M and Delgado MK. Impact of a State Opioid Prescribing Limit and Electronic Medical Record Alert on Opioid Prescriptions: a Difference-in-Differences Analysis. *J Gen Intern Med*. 2020 (epub 2019); 35 (3): 662-671.

can collect information on patient, provider, and community outcomes before and after implementation of the prescribing limits. Such studies may no longer be possible for existing prescribing limits but can be prospectively designed to assess the impact of any modifications to the prescribing limits (including the process for exceptions). Further, formal descriptive or qualitative studies of unintended consequences could still be very useful for identifying potential unintended consequences to be addressed with other interventions or modifications to existing prescribing limits. Prospective studies using patient- and provider-reported outcomes are relatively expensive to conduct and will require careful consideration of sufficient sample size and representativeness of the entire population to provide reliable information.

Second, studies should employ innovative epidemiological and statistical methods to control for potential biases. Specific analytic methods might include interrupted time series analyses, propensity score matching, and non-intervention comparator groups. Additionally, interventions should be implemented with evaluation in mind; programs could stagger the components of the intervention to build in time for outcome measurement related to specific components, such as a prescribing limit. For example, one study by Garcia et al., 2019 evaluated three sequential decreases in opioid limits implemented by Massachusetts Medicaid.[123] Studies should provide a clear description of the timing of the enactment relative to the implementation of the law and account for this period in their interpretation of the results. Studies should also include information on the level of enforcement of the prescribing laws since different degrees of enforcement may contribute to variations in uptake and implementation. Additionally, there have been declines in overdose deaths involving prescription opioid analgesics in recent years.[124,125] Future research is needed to disentangle any contribution to the declining overdose deaths from specific opioid analgesic prescribing limits from other factors that may have resulted in changes in overdose deaths, such as increasing naloxone use, expansion of medication treatment for opioid use disorder, changes in the illciti drug supply, and changing patterns of polysubstance use.

Additionally, research is needed to examine the differential impact of laws with variable components. For example, studies should be conducted to determine how effective a seven-day limit is compared to a 30-day limit. Similarly, research is needed to examine the impact of these laws on different populations and by patient demographics and clinical characteristics as previously mentioned. Patient factors such as race/ethnicity, income, urbanicity, existing chronic conditions, such as opioid use disorder should be considered as factors which might result in differential effects of the prescribing limits on the outcomes assessed.

Section VI. Ongoing HHS Efforts Related to Opioid Analgesic Prescribing Limits

Ongoing efforts across HHS are addressing some of these gaps in evidence about the impact of laws, regulations, policies, and guidelines that limit opioid analgesic prescriptions. As described above, a significant amount of research to date on the impact of prescribing limits has assessed changes in prescribing patterns, but far fewer studies have assessed health outcomes. Evaluating prescribing alone, however, does not reflect the capacity of these policies to reduce opioid misuse and overdose, nor does it capture unintended consequences such as impeded pain care or increased suicidality. Many current efforts are specifically tailored to address these open questions and are already building on the opportunity to deploy innovative methods to determine the impact of different prescribing limit approaches on meaningful patient, provider and community outcomes.

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[123] Garcia MM, Lenz K, Greenwood BC, Angelini MC, Thompson T, Clements KM, Mauro RP and Jeffrey PL. Impact of Sequential Opioid Dose Reduction Interventions in a State Medicaid Program Between 2002 and 2017. *J Pain.* 2019; 20 (8): 876-884.
[124] Wilson N, Kariisa M, Seth P, Smith H IV, Davis NL. Drug and Opioid-Involved Overdose Deaths — United States, 2017–2018. *MMWR Morb Mortal Wkly Rep.* 2020; 69: 290–297. DOI: http://dx.doi.org/10.15585/mmwr.mm6911a4
[125] Ahmad FB, Rossen LM, Sutton P. Provisional drug overdose death counts. National Center for Health Statistics. 2020. Designed by LM Rossen, A Lipphardt, FB Ahmad, JM Keralis, and Y Chong: National Center for Health Statistics Dashboard: 12 Month-ending Provisional Number of Drug Overdose Deaths by Drug or Drug Class. Updated May 3, 2020. Available at: https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm#dashboard (accessed June 12, 2020).

Evidence Review
Multiple HHS agencies are collaborating to assemble the body of evidence on policies to reduce opioid analgesic prescribing, including on health outcomes associated with the treatment of pain. They are conducting a systematic literature review of published observational studies that evaluate the impact of opioid analgesic prescribing guidelines containing a specific threshold of days' supply, dose, or tablet quantity, and other associated interventions intended to reduce opioid analgesic prescribing. Evaluated outcomes include but are not limited to: prescription characteristics, prescribing habits, patient-reported consumption, and patient-reported outcomes. This project is expected to be completed in June 2021 and will also identify gaps in the literature and provide recommendations for further research.

Evaluation
CMS is focusing on prescribing policies to achieve a broad range of health outcomes, including the incidence and/or prevalence of all overdoses related to prescription and/or illicit opioids; prevalence of opioid use disorder; medically appropriate use of and access to opioids; nonmedical use of opioids; and resulting negative health outcomes such as suicide, increases in burden on providers and patients, and mitigation of such burden. Pursuant to amendments made by section 1004 of the SUPPORT Act, CMS has proposed a rule to implement prospective safety edits and automated claims review processes to better manage prescribing and dispensing of opioid analgesics through the Medicaid program, and to report on these efforts in their annual drug utilization review reports required under section 1927(g) of the Social Security Act. Furthermore, CMS is collecting data about these safety edits and other drug utilization data from state Medicaid programs and Medicaid managed care organizations. These Drug Utilization Review surveys[126] were distributed to all state Medicaid Fee-for Service (FFS) and managed care programs on April 1, 2020, and results will be posted November 2020 on Medicaid.gov. Pursuant to Section 1004 of the SUPPORT Act[127], a report to Congress will be submitted by October 2021. CMS has also included several quality measures in the Medicaid Adult Core Set related to opioid analgesic prescribing practices and opioid treatment. State reporting on Medicaid Adult Core Set measures is currently voluntary.[128]

While CMS does not regulate prescribing limits in the Medicare Part D program, CMS has implemented several opioid-related policies to reduce overutilization of opioid analgesics, including retrospective drug utilization reviews, drug management programs, and opioid safety edits at the point-of-sale. CMS began this Medicare opioid overutilization policy in 2013 and enhanced these policies over time. CMS continues to track the impact of these policies using various data sources, such as plan-reported data and prescription drug event (PDE) records. Additional information and initial results are available in the Improving Drug Utilization Review Controls in Medicare Part D sections in the 2019 and 2020 Final Call Letters, and in multiple HPMS memos. [129,130,131,132,133]

[126] State Drug Utilization Review Reporting. https://www.medicaid.gov/medicaid/prescription-drugs/drug-utilization-review/state-drug-utilization-review-reporting/index.html (accessed August 21, 2020).
[127] SUPPORT for Patients and Communities Act. https://www.govinfo.gov/content/pkg/BILLS-115hr6enr/pdf/BILLS-115hr6enr.pdf (accessed August 10, 2020).
[128] Adult Health Care Quality Measures. https://www.medicaid.gov/medicaid/quality-of-care/performance-measurement/adult-and-child-health-care-quality-measures/adult-health-care-quality-measures/index.html (accessed August 10, 2020).
[129] Announcement of Calendar Year (CY) 2019 Medicare Advantage Capitation Rates and Medicare Advantage and Part D Payment Policies and Final Call Letter. Available at: https://www.cms.gov/files/document/cy-2020-opioid-safety-edits-reminders-and-recommendations.pdf (accessed June 3, 2020).
[130] Announcement of Calendar Year (CY) 2020 Medicare Advantage Capitation Rates and Medicare Advantage and Part D Payment Policies and Final Call Letter. Available at: https://www.cms.gov/Medicare/Health-Plans/MedicareAdvtgSpecRateStats/Downloads/Announcement2020.pdf (accessed June 3, 2020).
[131] Additional Guidance on Contract Year 2019 Formulary-Level Opioid Point-of-Sale Safety Edits. Date: October 23, 2018. Available at: https://mopa.memberclicks.net/assets/docs/Opioid_SafetyEdit_Memo_10232018%20%28002%29.pdf (accessed June 3, 2020).
[132] Frequently Asked Questions (FAQs) about Formulary-Level Opioid Point-of-Sale (POS) Safety Edits. May 13, 2019. Available at: https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/Frequently-Asked-Questions-about-Contract-Year-2019-Formulary-Level-Opioid-Point-of-Sale-Safety-Edits.pdf (accessed June 3, 2020).
[133] Contract Year (CY) 2020 Opioid Safety Edit Reminders and Recommendations. December 9, 2019. Available at: https://www.cms.gov/files/document/cy-2020-opioid-safety-edits-reminders-and-recommendations.pdf (accessed June 3, 2020).

In addition to CMS, IHS is assessing prescribing indices to evaluate the impacts of its policies as well as state mandates through the development of an IHS Opioid Surveillance dashboard. Outcomes to be evaluated may include the prevalence of opioid use disorders, prevalence of co-occurring disorders, and use of non-pharmacologic approaches to pain management.

Research

The National Institute on Drug Abuse (NIDA) supports several research projects that include both qualitative and quantitative assessment of the impact of prescribing limits on health outcomes. Outcomes associated with opioid misuse include overdose rates related to prescription and illicit opioids and ED visits/hospitalizations related to opioids. Outcomes associated with pain include substitution of non-opioid analgesic treatments, pain-related clinical outcomes, healthcare spending, and qualitative assessment of patient and clinician experiences. Unintended consequences are also being assessed, including patient suicidality and the impact on prescribing rates to historically underserved or high-risk populations. NIDA supported research remains mindful of the challenges in analyzing the heterogeneous landscape of policy change and implementation, and studies have been designed to include control conditions and advanced analytic approaches to improve understanding of effects specific to a given policy change. For example, Oregon Medicaid curbed coverage of opioid analgesics for acute back pain while simultaneously expanding coverage of nonpharmacologic health services for back pain. Researchers investigating the impact of this policy[134] on patient outcomes will use data from Utah Medicaid enrollees as a comparator; a similar approach in identifying comparator states without similar provisions will be used to assess the impact of New Jersey legislation[135] limiting initial opioid analgesic prescriptions to five days, requiring use of pain management contracts with patients, and expanding access to medications to treat opioid use disorder. Another project will employ a mixed-methods approach to disentangle the causal effects of each of four different types of laws on high-risk opioid analgesic prescribing.[136] Finally, qualitative information collected from patients and providers[137] is targeted to address the need for evidence about the impact of opioid analgesic prescribing limits on patient and provider burden and experience not captured in claims data or the electronic health record. The completion dates of these projects range from 2021-2023.

In addition to determining the impact of prescribing limits on the treatment of acute pain and the experience of new patients with pain, assessing the impact of policy change on patients previously maintained on opioid analgesics is an important component of ensuring adequate pain care. FDA has funded a study to evaluate the effect of opioid analgesic tapering and/or discontinuation on patient outcomes, including suicidality and unintentional overdose. This study is expected to be completed in 2022. The Agency for Healthcare Research and Quality (AHRQ) is also conducting a study titled: "Chronic Pain, Public Policy, and the Dynamics of Prescription Opioid Use, 2014-2017," which will evaluate changes in both the initiation of and persistence of prescription opioid versus non-opioid pain relievers, with results stratified by presence of conditions associated with chronic pain. A draft for internal AHRQ review is expected in Spring 2020. In addition, CDC is conducting research to examine how state laws limiting the duration of acute pain opioid analgesic prescriptions have affected dispensed initial opioid analgesic prescriptions. This work focuses on initial opioid analgesic prescriptions, as the characteristics of a new prescription written to an opioid naïve individual may be risk factors for unnecessary long-term opioid analgesic use. This work examines the impact of laws with limits of various lengths (i.e. ≤ 7

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[134] Research Portfolio online Reporting Tools. NIH. Project number 5R01DA044284-02. Implementation, Outcomes, and Cost of a Novel Medicaid Policy to Reduce Opioids for Back Pain. Available at: https://projectreporter.nih.gov/project_info_description.cfm?aid=9762070&icde=49197011&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball= (accessed June 3, 2020).

[135] Research Portfolio online Reporting Tools. NIH. Project number 5R01DA047347-02. Opioid Overdoses among Medicaid Beneficiaries: Predictors, Outcomes, and State Policy Effects. Available at: https://projectreporter.nih.gov/project_info_description.cfm?aid=9876989&icde=49194853 (accessed June 3, 2020).

[136] Research Portfolio online Reporting Tools. NIH. Project number 3R01DA044987-03S1. An Evaluation of State Laws Intended to Curb High-Risk Opioid Prescribing. Available at: https://projectreporter.nih.gov/project_info_description.cfm?aid=9954385&icde=49190629 (accessed June 3, 2020).

[137] Research Portfolio online Reporting Tools. NIH. Project number 1R21DA049861-01. Impact of SB 273 on West Virginia Patients, Providers, and Overall Prescription Rates of Opiate Medications. Available at: https://projectreporter.nih.gov/project_info_description.cfm?aid=9869148&icde=49190666&ddparam=&ddvalue=&ddsub=&cr=121&csb=default&cs=ASC&pball= (accessed June 15, 2020).

days and >7 days) on multiple potential changes in opioid analgesic prescribing including the duration of the prescriptions, quantity of pills prescribed, and daily and total MME. CDC has also determined that an update of the CDC Guideline is warranted based on three systematic reviews conducted by AHRQ on the evidence base for chronic pain treatment. Two additional systematic reviews on treatments for acute pain are expected to be available in late 2020, which will help inform the decision of whether to further expand the CDC Guideline into the treatment of acute pain. The CDC Guideline update development process will include results from these systematic reviews and a public comment period through the Federal Register once an update or expansion is drafted. Given these projected activities, a CDC Guideline update would potentially be released in 2022.

For a table of ongoing work see Appendix C.

Section VII. **Conclusions**

While at least thirty-three states have laws or regulations limiting the dose, duration, or quantity of opioid analgesics for some patients (based on adopted statuatory limits), we are aware of no federal laws or regulations requiring opioid analgesic prescribing limits. However, federal guidelines and policies, such as the CDC Guideline for primary care practitioners, VA/DOD Pain Guideline, and CMS payment policies, have been used as the basis for many state laws and regulations. State and federal laws, regulations, policies, and guidelines often have additional components to prescribing limits such as PDMP checks, pain clinic laws, urine drug testing, and patient contracts. Other organizations are also requiring or recommending limits to opioid analgesic prescriptions and contributing to changes in patient care, such as pharmacies, payers, medical and pharmacy associations and organizations, hospitals and health systems, and medical and pharmacy boards.

Among the twenty-nine studies evaluating prescribing limits and reviewed for the purposes of this report, most assessed changes to opioid analgesic prescription or dispensing patterns after implementation of prescribing limits and generally reported decreasing trends in the dose, duration, and quantity of opioid analgesic prescriptions after implementation of prescribing limits. Thirteen studies evaluated outcomes beyond changes in prescribing and dispensing, such as patient outcome, patient burden, prescriber burden, or financial implications for insurance. Among the studies evaluating patient outcomes (n=12), most showed no change or modest improvement in patient outcomes after implementation of the prescribing limit and one study found a small but statistically significant increase in pain scores after implementation of the prescribing limit. Most studies did not adjust for any decreases in opioid analgesic prescribing already occurring before the implementation of prescribing limits or control for other interventions that could impact opioid analgesic prescribing. Importantly, while measurement of prescription and dispensing trends is a critical first step in assessing the impact of prescribing limits, far fewer studies included other patient, provider, or health outcomes. In fact, only twelve of the studies included more informative outcomes to assess the effectiveness and unintended consequences of prescribing limits such as patient health outcomes, refill rates/attempts, patient burden, prescriber burden, and public health outcomes. Results from these studies are mixed, and notably, lower levels of opioid analgesic prescribing did not always translate to improved patient outcomes. Finally, it is worth noting that many of the studies suffered from methodological flaws that limit our ability to use them to enhance our understanding of the impact of prescribing limits on prescription, patient, provider, and health outcomes.

The lack of understanding of the impact of prescribing limits on these more meaningful outcomes is an important gap in our existing knowledge, but studies to assess these outcomes are generally more expensive and time-consuming than analyses of prescription patterns using “big data” sources like insurance claims. In addition, the most informative studies will require measurement of outcomes prior to implementation of the intervention for comparison and may therefore not be possible to assess with respect to existing prescribing limits. We recommend careful consideration of the evaluation phase prior to implementing new prescribing limits or changing existing prescribing limits so meaningful outcomes can be assessed in the affected population before implementation for comparison. Other gaps can be addressed in future studies by using more sophisticated methods to control for existing trends in prescribing, by isolating the impact of prescribing limits within larger

interventions around opioid analgesic prescribing, and by isolating the impact of state and federal prescribing limits from other interventions.

As part of its overarching work to address the opioid crisis, HHS has ongoing efforts designed to help fill some of the research gaps identified in this report, including disentangling the independent effects of multiple components of state legislation (NIDA), assessing the impact of prescribing limits on meaningful patient outcomes like suicidal ideation (FDA) and opioid use disorder (IHS and CMS), assessing the impact of various levels of prescribing limits on multiple opioid dispensing measures (CDC), patient and provider experiences (NIDA) and burden (CMS), public health outcomes like overdose (NIDA), and healthcare spending (NIDA), and evaluating changes in both the initiation of and persistence of use of opioid versus prescription non-opioid pain relievers (AHRQ).

Appendices

Appendix A. Table 1. Landscape of Federal and State Opioid Analgesic Prescribing Limits: Laws, Regulations, Policies, and Guidelines

Federal Agencies and States	Date[a]	Prescribing Limits[b]	Restrictions/Exceptions and Other Components	Reference/Prescribing Limit Rationale[c]	Published Study References[c]
Federal Agencies					
Bureau of Prisons	June 2018	**Days' Supply:** 3-day supply or less for most opioid prescriptions to treat acute pain; more than a 7-day supply will rarely be needed **MME:** Lowest effective dose; use caution when prescribing any opioid ≥ 50 MME/day, and avoid prescribing any opioid ≥ 90 MME/day without first consulting a pain management specialist **Dose:** Codeine 30-60 mg or oxycodone 5-10 mg ONLY for breakthrough severe dental pain not controlled by maximum therapeutic doses of an NSAID or ibuprofen	Only one prescriber for all controlled substances; exclusions for cancer pain patients	CDC Guideline for Prescribing Opioids for Chronic Pain; Hersh, 2011; VA/DoD Clinical Practice Guideline for Management of Opioid Therapy for Chronic Pain, 2010	
CDC[d]	March 18, 2016	**Days' Supply:** 3-day supply for most opioid prescriptions for acute pain; greater than 7-day supply will rarely be needed to treat acute pain **MME:** Lowest effective dose; use caution when prescribing any opioid ≥ 50 MME/day, and avoid prescribing any opioid ≥ 90 MME/day without careful justification **Tapering:** Decrease by 10% of original dose per week; slower tapers may be appropriate for patients taking opioids chronically; rapid tapers over 2-3 weeks recommended for patients with severe adverse events (e.g., overdose)	Guideline recommendations focused on opioid prescribing for chronic pain treated by primary care physicians in outpatient settings; applies to patients ≥ 18 years; not for MAT for opioid use disorder; when initiating opioid therapy, IR opioids should be prescribed first	Review of scientific literature and input from subject matter experts	Young et al., 2018 Austin et al., 2019 Dayer et al., 2019
CMS	January 1, 2019	**Days' Supply:** Medicare Part D: 7-day supply for all initial opioid prescriptions for opioid naïve patients **MME:** Part D safety edits to be implemented based on a cumulative 90 MME/day across all opioid prescriptions	Allows for exclusions for long-term care, hospice care, palliative/end-of-life care, and cancer patients; allows for exclusions for patients on MAT; recommends an exemption from day's supply	CDC Guideline for Prescribing Opioids for Chronic Pain in primary care settings	

Federal Agencies and States	Date[a]	Prescribing Limits[b]	Restrictions/Exceptions and Other Components	Reference/Prescribing Limit Rationale[c]	Published Study References[c]
			and MME opioid safety edits for sickle cell disease patients		
IHS	February 2018	**Days' Supply:** 3-day supply for most opioid prescriptions for nontraumatic, nonsurgical acute pain; greater than 7-day supply will rarely be needed **MME:** Lowest effective dose; all patients on ≥30 MME/day for >60 days should be evaluated for conversion to an ER/LA opioid; use caution when prescribing any opioid ≥ 50 MME/day, and avoid prescribing any opioid ≥ 90 MME/day without careful justification **Co-prescribing:** Consider prescribing naloxone for all patients on opioids chronically at doses >50 MME/day; avoid co-prescribing opioids and benzodiazepines whenever possible	Allows for exclusions for cancer patients, perioperative pain, palliative care, end-of-life care, hospice care, pregnant women, or inpatient pain management	CDC Guidelines for Prescribing Opioids for Chronic Pain; Model Policy on the Use of Opioid Analgesics in the Treatment of Chronic pain	
	July 6, 2016	**PDMP Check**: >7-day supply for new patients to treat acute pain, when progressing from acute to chronic pain therapy, and at least every 3 months while being treated for chronic pain; all pharmacists must check the PDMP prior to dispensing a prescription for a controlled substance, and every 3 months prior to dispensing a chronic controlled substance prescription for CII-CIV medications		HHS Opioid Initiative	
VA/DoD	February 2017	**Days' Supply:** for all patients on > 90 days of opioid therapy for *chronic pain*, re-evaluate treatment plan and risks/benefits of continuing therapy; for *acute pain*, use IR opioids and reassess opioid therapy no later than 3-5 days after initiating treatment **MME:** Lowest effective dose; avoid prescribing any opioid ≥ 90 MME/day for chronic pain and evaluate for tapering or discontinuation; individual dosing guidelines for each opioid API **Tapering:** Tapering treatment plan should be individualized, and could include a 5-20% reduction in original dose per week to per	Avoid initiating long-term opioid therapy for chronic pain unless all other therapies have been explored; avoid long-term opioid therapy for pain in patients with untreated substance use disorder or patients < 30 years; avoid ER/LA opioids for acute pain, as an as-needed medication, or for initiation of long-term therapy; avoid concurrent use of benzodiazepines and opioids whenever possible; chronic	2010 VA/DoD Clinical Practice Guideline for Management of Opioid Therapy for Chronic Pain; systematic review of scientific literature	

Federal Agencies and States	Date[a]	Prescribing Limits[b]	Restrictions/Exceptions and Other Components	Reference/Prescribing Limit Rationale[c]	Published Study References[c]
		month, depending on dose and individual patient characteristics	pain guidance does not provide recommendations for children/adolescents, acute pain, or end-of-life care		
	October 19, 2016	**PDMP Check**: > 5-day supply and yearly	Patients under hospice care are excluded		
	May 2010	**MME:** Lowest effective dose with one medication at a time; avoid transdermal fentanyl in opioid-naïve patients; start with IR opioids for intermittent pain; use an opioid with long duration of action to treat continuous pain; re-evaluate treatment at > 200 MME/day	For adult (≥ 18 years) chronic pain patients; excludes end-of-life care, cancer patients, and serious/life-threatening illnesses	2003 VA/DoD Clinical Practice Guideline for Management of Opioid Therapy for Chronic Pain; APS/AAPM 2009 guideline; systematic review of scientific literature	Chen et al., 2019
	March 2003	**MME:** Lowest effective dose of one opioid medication at a time; start with IR opioids for intermittent pain; use an opioid with long duration of action to treat continuous pain **Tapering:** For non-addicted patients, decrease by 20-50% of original dose/week; slower tapers may be appropriate for patients taking opioids chronically	For chronic, non-cancer pain patients	Systematic review of scientific literature and input from subject matter experts	
States					
Alabama					
Law		No relevant prescribing law found as of April 2020.			
Medicaid	December 2, 2019	**MME:** Hard limit: cumulative daily opioid dose may not exceed 200 MME/day. Daily cumulative limit will decrease every 4 months by 50 MME until it reaches CDC recommendation of 90 MME per day.	Exceptions for cancer patients, long-term care, hospice patients. Accumulation policy prevents beneficiaries from having more than a 14-day supply of opioids on hand.	Alabama Medicaid	

Federal Agencies and States	Date[a]	Prescribing Limits[b]	Restrictions/Exceptions and Other Components	Reference/Prescribing Limit Rationale[c]	Published Study References[c]
		Prior Authorization: required for all cumulative daily opioid doses between 150 MME/day and 200 MME/day			
	August 1, 2019	**MME:** Hard limit: cumulative daily opioid dose may not exceed 250 MME/day **Prior Authorization:** required for all cumulative daily opioid doses between 200 MME/day and 250 MME/day	Exceptions for cancer patients, long-term care, hospice patients	Alabama Medicaid	
	November 1, 2018	**Days' Supply:** 7-day supply for all IR opioid prescriptions for all opioid naïve (no opioid claim in past 180 days) adults (≥19 years); 5-day supply for all IR opioid prescriptions for all opioid naïve children (≤18 years) **MME:** 50 MME/day per claim for all IR opioid prescriptions for opioid naïve patients **Prior Authorization:** PA required for refills of remaining quantities and/or new opioid prescriptions filled within 180 days of initial opioid naïve claim	Restrictions for minors; exceptions for cancer patients, long-term care, hospice patients	Alabama Medicaid	
Alaska					
Law	July 25, 2017 October 24, 2017 - (Only Optometrists)	**Days' Supply:** 7-day supply for all initial outpatient opioid prescriptions by physicians, dentists, veterinarians, physician assistants, and nurse practitioners; 4-day supply for all initial outpatient opioid prescriptions written by optometrists	Restrictions for minors. Professional judgement exceptions; exceptions for chronic pain management, cancer patients, palliative care, substance abuse, access to care restrictions, travel restrictions	AK Stat § 08.64.363; 08.72.276	
Medicaid	June 1, 2020	**MME:** Cumulative daily opioid dose may not exceed 250 MME/day; individual MME limits for specific APIs **Quantity:** Individual quantity limits for specific APIs **Prior Authorization:** PA required for all cumulative daily doses above 250 MME/day; individual PA requirements for specific APIs	Exceptions for cancer patients, long-term care, hospice patients	Alaska Medicaid http://manuals.medicaidalaska.com/docs/dnld/Alaska_Medicaid_Pharmacy_Update_April2020.pdf	
	March 2, 2020	**MME:** Cumulative daily opioid dose may not exceed 250 MME/day; individual MME limits for specific APIs	Exceptions for cancer patients, long-term care, hospice patients	Alaska Medicaid http://manuals.medicaidalaska.co	

Federal Agencies and States	Date[a]	Prescribing Limits[b]	Restrictions/Exceptions and Other Components	Reference/Prescribing Limit Rationale[c]	Published Study References[c]
		Quantity: Individual quantity limits for specific APIs **Prior Authorization:** PA required for all cumulative daily doses above 250 MME/day; individual PA requirements for specific APIs		m/docs/dnld/Update_Alaska_Medicaid_Pharmacy_Update_Jan2020.pdf	
	October 1, 2019	**MME:** Cumulative daily opioid dose may not exceed 300 MME/day; individual MME limits for specific APIs **Quantity:** Individual quantity limits for specific APIs **Prior Authorization:** PA required for all cumulative daily doses above 300 MME/day; individual PA requirements for specific APIs	Exceptions for cancer patients, long-term care, hospice patients	Alaska Medicaid	
	November 2018	**Day's Supply:** 7-day supply for all Medicaid patients		Alaska Medicaid	
Arizona					
Law	April 26, 2018	**Days' Supply:** All initial CII opioid prescriptions: 5-day supply except for following surgical procedures; 14-day supply following surgical procedures **MME:** All CII opioid prescriptions must not exceed 90 MME/day Co-prescribing: Must prescribe Naloxone or other opioid antagonists with all new opioid prescriptions > 90 MME/day **PDMP Check:** Eliminated the exemption of not checking the CSPMP if prescribing for ≤ 5 days when CSPMP was reviewed in the previous 30 days	Professional judgement exceptions; exceptions for cancer patients, hospice patients, end-of life or palliative care, skilled nursing facility care, burn patients, trauma patients, MAT for substance use disorder; board-certified pain physicians may write for opioid prescriptions > 90 MME/day without consultation	Ariz. Rev. Stat. Ann. § 32-3248	
Medicaid		Follows state prescribing law.		Arizona Medicaid	
Arkansas					
Law	August 15, 2018	**Days' Supply:** 7-day supply for all initial opioid prescriptions **MME:** Lowest effective dose	Professional judgement exceptions, exceptions for cancer, palliative care, nursing home, emergency situation	Ark. Admin. Code 060.00.1-223	

Federal Agencies and States	Date[a]	Prescribing Limits[b]	Restrictions/Exceptions and Other Components	Reference/Prescribing Limit Rationale[c]	Published Study References[c]
Medicaid	March 14, 2018	**Days' Supply:** 7-day supply for all initial opioid prescriptions with corresponding limit of 6 tablets a day **MME:** 50 MME/day		Arkansas Medicaid	
California					
Law		No relevant prescribing law found as of April 2020.			
Medicaid		30-day supply limit for naïve patients			
Colorado					
Law	May 21, 2018	**Days' Supply:** 7-day supply for all opioid prescriptions for patients who haven't received an opioid prescription in the past 12 months	Exceptions for surgical pain, cancer, palliative care	Colo. Rev. Stat. Ann. § 12-30-109	
Medicaid	November 15, 2018	**Days' Supply:** 4-day, 24 pill limit for dental patients. 7-day, 56 pill limit for opioid naïve patients and more complex dental procedures. 120 pills per 30 days for non-naïve patients. MME: 200 MME per day		Colorado Medicaid	
	August 1, 2014	**Days' supply:** Maximum of 4 tablets per day or 120 tablets for 30 days of short-acting opioids		Colorado Medicaid	Riggs et al., 2017
Connecticut					
Law	July 1, 2016	**Days' Supply:** 7-day supply for all initial opioid prescriptions for adults; 5-day supply for all opioid prescriptions for minors	Restrictions for minors; professional judgement exceptions for cancer, palliative care, substance abuse.	Conn. Gen. Stat. Ann. § 20-14o	
Medicaid		No specific guidelines found as of April 2020.			
Delaware					
Law	April 1, 2017	**Days' Supply:** 7-day supply for all initial opioid analgesic prescriptions for adults	Restrictions for minors; professional judgement exceptions	Del. Admin. Code Chapter 24-0001 § 9.0	Davis et al., 2019
Medicaid		Follows state prescribing law.		Delaware Medicaid	
Florida					

Federal Agencies and States	Date[a]	Prescribing Limits[b]	Restrictions/Exceptions and Other Components	Reference/Prescribing Limit Rationale[c]	Published Study References[c]
Law	July 1, 2018	**Days' Supply:** 3-day supply for all CII opioid prescriptions; 7-day supply if certain specific conditions are met	Professional judgement exceptions	Fla. Stat. Ann. § 456.44	
Medicaid		Follows state prescribing law.		Florida Medicaid	
Georgia					
Law		No relevant prescribing law found as of April 2020.			
Medicaid		30-day supply limit for naïve patients			
Hawaii					
Law	July 5, 2019	**Day's Supply:** 7-day supply for concurrent CII opioid/benzodiazepine prescriptions, with certain exceptions	Exceptions for patients suffering from terminal illness; post-operative care, chronic pain management, substance abuse, cancer, palliative care or hospice care	Haw. Rev. Stat. Ann. § 329-38	
	July 1, 2017	**Days' Supply:** 7-day supply for concurrent CII opioid/benzodiazepine prescriptions, with certain exceptions	Exceptions for post-operative care, chronic pain management, substance abuse, cancer, palliative care or hospice care	Haw. Rev. Stat. Ann. § 329-38	
	July 1, 2016	**Days' Supply:** 30-day supply for all CII opioid prescriptions		Haw. Rev. Stat. § 329-38	Davis et al., 2019
Medicaid		30-day supply limit for naïve patients; dental formulary has 4-day supply maximum			
Idaho					
Law		No relevant prescribing law found as of April 2020.			
Medicaid		34-day supply limit for naïve patients			
Illinois					
Law	January 1, 2012	**Days' Supply:** 30-day supply for all prescriptions for all CII substances. Physicians may issue multiple prescriptions (3 sequential 30-day supplies) for CII substances, authorizing up to 90-day supply if certain conditions met.		720 Ill. Comp. Stat. 570/312(a)	
Medicaid		No specific guidelines found as of April 2020.			
Indiana					
Law	July 1, 2017	**Days' Supply:** 7-day supply for all initial opioid prescriptions for adults	Restrictions for minors; professional judgement exceptions for cancer, post-surgical pain, palliative care	Ind. Code § 25-1-9.7-2	Davis et al., 2019

Federal Agencies and States	Date[a]	Prescribing Limits[b]	Restrictions/Exceptions and Other Components	Reference/Prescribing Limit Rationale[c]	Published Study References[c]
Medicaid		7-day supply limit for naïve patients.			
Iowa					
Law		No relevant prescribing law found as of April 2020.			
Medicaid	July 1, 2018	**MME:** PA required for ≥200 MME per day. Gradually decreased to ≥90 MME per day	Exceptions for cancer and end of life care	Iowa Medicaid	
Kansas					
Law		No relevant prescribing law found as of April 2020.			
Medicaid		**Days' Supply:** 7-day limit for initial prescriptions **MME:** <90 MME per day	Exceptions for cancer, sickle cell, palliative care	Kansas Medicaid	
Kentucky					
Law	June 27, 2019	**Days' Supply:** 3-day supply for all prescriptions for all CII substances	Exception for patients in palliative care**;** professional judgement exceptions for cancer, chronic pain, surgical pain, hospice exceptions	Ky. Rev. Stat. Ann. § 218A.205(3)(b)	
	June 29, 2017	**Days' Supply:** 3-day supply for all prescriptions for all CII substances	Professional judgement exceptions for cancer, chronic pain, surgical pain, hospice exceptions	Ky. Rev. Stat. Ann. § 218A.205(3)(b)	Davis et al., 2019
	September 1, 2012	**Day's Supply:** Required all state licensing boards to limit the dispensing of any CII or CIII substance containing hydrocodone to a 48-hour supply		Ky. Rev. Stat. Ann. § 218A.205(3)(b)	
Medicaid		No specific guidelines found as of April 2020.			
Louisiana					
Law	August 1, 2017	**Days' Supply:** 7-day supply for all initial opioid prescriptions for adults	Restrictions for minors; professional judgement exceptions for chronic pain, cancer diagnosis, palliative care, substance abuse	La. Stat. Ann. § 40:978(G)	
Medicaid	September 12, 2017	**MME:** ≤ 90 MME per day		Louisiana Medicaid	
	July 10, 2017	**Days' Supply:** 7-day supply for naïve recipients		Louisiana Medicaid	
Maine					

Federal Agencies and States	Date[a]	Prescribing Limits[b]	Restrictions/Exceptions and Other Components	Reference/Prescribing Limit Rationale[c]	Published Study References[c]
Law	June 16, 2017	**Day's Supply:** 7-day supply for all opioid prescriptions **MME:** 100 MME/day for all opioid prescriptions	Surgical pain exceptions	32 Maine Rev. Stat. Ann. §3300-F(2)(B)	
	January 1, 2017	**Days' Supply:** 7-day supply for all opioid prescriptions **MME:** 100 MME/day for all opioid prescriptions	If an opioid product is labeled by FDA to be dispensed only in a stock bottle that exceeds a 7-day supply as prescribed, then up to a 14-day supply can be dispensed. Exceptions for cancer treatment, palliative care, hospice care	32 Maine Rev. Stat. Ann. §3300-F	
Medicaid	September 1, 2017	**Prior Authorization:** Prior authorization is required for all acute pain opioid analgesic prescriptions after 7 days of treatment within a calendar year		MaineCare Benefits Manual	
Maryland					
Law	May 25, 2017	**MME:** Lowest effective dose for all opioid prescriptions	Cancer, hospice, palliative care, substance abuse and chronic pain exceptions	Md. Code Ann., Health Occ. § 1-223	Davis et al., 2019
Medicaid	July 1, 2018	**MME:** Prior authorization required for opioids> 90 MME/day; 30-day supply for naïve patients		Maryland Medicaid	
Massachusetts					
Law	March 14, 2016	**Days' Supply:** 7-day supply for all initial opioid prescriptions for adults	Restrictions for minors; professional judgement exceptions for chronic pain management, cancer, palliative care	Mass. Ann. Laws ch. 94C, § 19D	
Medicaid	March 2016	**MME:** Hard limit of 120 mg MED/day **Prior Authorization:** Prospective PAs for all opioid prescriptions above 120 mg MED/day		Massachusetts Medicaid (MassHealth)	Garcia et al., 2019
	April 2014	**MME:** Hard limit of 240 mg MED/day **Prior Authorization:** Prospective PAs for all opioid prescriptions above 240 mg MED/day		Massachusetts Medicaid (MassHealth)	Garcia et al., 2019

Federal Agencies and States	Date[a]	Prescribing Limits[b]	Restrictions/Exceptions and Other Components	Reference/Prescribing Limit Rationale[c]	Published Study References[c]
	October 2004	**MME:** Hard limit of 360 mg MED/day for fentanyl patch, oxycodone CR, morphine, methadone, meperidine, hydromorphone, levorphanol, and oxymorphone **Prior Authorization:** Prospective PAs for all fentanyl patch, oxycodone CR, morphine, methadone, meperidine, hydromorphone, levorphanol, and oxymorphone prescriptions above 360 mg MED/day		Massachusetts Medicaid (MassHealth)	Garcia et al., 2019
	April 2003	**MME:** Hard limit of 360 mg MED/day for fentanyl patch and oxycodone CR **Prior Authorization:** Prospective PAs for all fentanyl patch and oxycodone CR prescriptions above 360 mg MED/day		Massachusetts Medicaid (MassHealth)	Garcia et al., 2019
	January 1, 2002	**Prior authorization** required for prescriptions above identified dose limits: 240 mg per day of oxycodone ER, 200 micrograms per day of fentanyl, 360 mg per day of morphine ER, and 120 mg per day of methadone.			Garcia et al., 2014
Michigan					
Law	July 1, 2018	**Days' Supply:** 7-day supply for all opioid prescriptions within a 7-day period	Restrictions for minors	Mich. Comp. Laws Ann. § 333.7333b	Zipple et al., 2019
Medicaid		7-day supply limit for naïve patients			
Minnesota					
Law	July 1, 2019	**Days' Supply:** 7-day supply for all opioid analgesic/narcotic pain reliever prescriptions; 4-day supply for all opioid analgesics/narcotic pain reliever prescriptions for dental or refractive surgery pain	Restrictions for minors; professional judgement exceptions for cancer, palliative care, surgical pain	Minn. Stat. Ann. § 152.11, Subd. 4.	
	July 1, 2017	**Days' Supply:** 4-day supply for all opioid analgesic/narcotic pain reliever prescriptions for dental or refractive surgery pain	Restrictions for minors; professional judgement exceptions for cancer, palliative care, surgical pain	Minn. Stat. Ann. § 152.11 Subd. 4b	Davis et al., 2019
Medicaid		7-day supply limit for naïve patients			
Mississippi					
Law		Miss. Code Ann. §73-43-11 authorizes the State Board of Medical Licensure to promulgate certain rules. *See Appendix A Table 2.*			

Federal Agencies and States	Date[a]	Prescribing Limits[b]	Restrictions/Exceptions and Other Components	Reference/Prescribing Limit Rationale[c]	Published Study References[c]
Medicaid	August 1, 2019	**Days' Supply:** Prescriptions for naïve patients can be filled for a maximum of two 7-day supplies in a 30-day period. **MME:** ≥ 90 MME will require documentation.	Exceptions for cancer of sickle-cell disease	Mississippi Medicaid	
Missouri					
Law	August 28, 2018	**Days' Supply:** 7-day supply for all initial opioid prescriptions	Professional judgement exceptions	Mo. Ann. Stat. § 195.080(2)	
	Pre-1989	**Days' Supply:** 30-day supply		Mo. Rev. Stat. 195.080(2)	
Medicaid		7-day supply limit for naïve patients			
Montana					
Law	October 1, 2019	**Days' Supply:** 7-day supply for all initial opioid prescriptions	Professional judgment exceptions for chronic pain, palliative care, cancer	Mont. Code Ann. 37-2-108	
Medicaid		Follows state prescribing law.			
Nebraska					
Law	July 19, 2018	**Days' Supply:** 7-day supply for all opioid prescriptions for minors only	Minor restrictions, professional judgement exceptions	Neb. Rev. St. § 38-1,145	
Medicaid	October 1, 2016	**Days' Supply:** 150 tablets or capsules per 30 days for short acting opioids **MME:** 50 MME/day for all initial opioid prescriptions		Nebraska Medicaid	
Nevada					
Law	October 1, 2019	**Days' Supply:** 30-day supply for all initial CII-CIV prescriptions to treat pain associated with sickle-cell disease	Allows for an exemption for sickle-cell disease	Nevada Laws Ch. 349 (A.B. 254)	
	June 3, 3019	**Days' Supply:** 14-day supply for all initial CII-CIV prescriptions to treat acute pain **MME:** 90 MME/day for all initial opioid prescriptions to treat acute pain	Professional judgement exceptions for cancer, palliative care	Nevada Laws Ch. 346 (A.B. 239); N.R.S. 639.2391	
	January 1, 2018	**Days' Supply:** 14-day supply for all initial CII-CIV prescriptions **MME:** 90 MME/day for all initial opioid prescriptions		N.R.S. 639.2391	Davis et al., 2019

Federal Agencies and States	Date[a]	Prescribing Limits[b]	Restrictions/Exceptions and Other Components	Reference/Prescribing Limit Rationale[c]	Published Study References[c]
Medicaid	May 2017	Requires prior authorization to exceed 7-day supply or 60 MME per day or 13 prescriptions in a rolling 12-month period		Nevada Medicaid	
New Hampshire					
Law	January 1, 2017	**Days' Supply:** 7-day supply for all opioid prescriptions from the ED, urgent care, and walk-in clinic; limited duration for all opioids **MME:** Lowest effective dose	Allows for professional judgement exceptions	N.H. Code Admin. R. Med. 502	
Medicaid	June 2016	**Prior Authorization:** Prior beneficiaries reaching a daily MME of 100 or more to receive prior authorization to continue with that dose; prior authorization required by all Medicaid fee-for-service plans for all long-acting narcotics and methadone when prescribed for pain		New Hampshire Medicaid and Healthy Families, Reference Number: NH.PPA.12	
New Jersey					
Law	May 16, 2017	**Days' Supply:** 5-day supply for all initial opioid prescriptions and all CII substances **MME:** Lowest effective dose of IR opioids	Professional judgment exceptions	N.J. Stat. Ann. § 24:21-15.2	Davis et al., 2019 Lowenstein et al., 2019
Medicaid		No specific guidelines found as of April 2020.			
New Mexico					
Law		No relevant prescribing law found as of April 2020.			
Medicaid		No specific guidelines found as of April 2020.			
New York					
Law	July 22, 2016	**Days' Supply:** 7-day supply for all initial CII-CIV opioid prescriptions	Exceptions for cancer, chronic pain, hospice or palliative care	N.Y. Pub. Health L. § 3331(5)(b)	Davis et al., 2019
Medicaid		Follows state prescribing law.			
North Carolina					
Law	January 2, 2018	**Days' Supply:** 5-day supply for all initial targeted controlled substance prescriptions; 7-day supply for all initial targeted controlled substance prescriptions for post-operative pain	Allows for surgical pain exceptions	N.C. Gen. Stat. § 90-106(a3)	
Medicaid	January 2, 2018	Prior approval required for > 5-day supply for all initial targeted controlled substance prescriptions; 7-day supply for all initial targeted controlled substance prescriptions for post-operative pain		North Carolina Medicaid	

Federal Agencies and States	Date[a]	Prescribing Limits[b]	Restrictions/Exceptions and Other Components	Reference/Prescribing Limit Rationale[c]	Published Study References[c]
	August 27, 2017	Prior approval required for > 120 MME; > 14-day supply		North Carolina Medicaid	
North Dakota					
Law		No relevant prescribing law found as of April 2020.			
Medicaid		No specific guidelines found as of April 2020.			
Ohio					
Law	August 31, 2017	**Days' Supply:** 7-day supply for all initial opioid analgesic prescriptions; 5-day supply for all initial opioid analgesic prescriptions for minors **MME:** ≤ an average of 30 MME/day for all initial opioid analgesic prescriptions	Restrictions for minors; exceptions for hospice, palliative care, cancer; surgical pain	Ohio Admin. Code 4731-11-13 (adopted pursuant to ORC. Ann. 3719.062)	Davis et al., 2019
Medicaid		Follows state prescribing law.			
Oklahoma					
Law	May 21, 2019	**Days' Supply:** Allow for an additional, subsequent 7-day supply opioid prescription if very specific criteria are met	Criteria for additional opioid prescription: major surgical procedure/ "confined to home" status, subsequent prescription is provided on the same day as the initial prescription and contains a "do not fill until" date, subsequent prescription is dispensed no more than 5 days after the "do not fill" date	Okla. Stat. Ann. tit. 63, § 2-309I (Amended)	
	November 1, 2018	**Days' Supply:** 7-day supply for all initial opioid prescriptions **MME:** Lowest effective dose	Restrictions for minors; allows for surgical pain exceptions	Okla. Stat. Ann. tit. 63, § 2-309I	
Medicaid		No specific guidelines found as of April 2020.			
Oregon					
Law		No relevant prescribing law found as of April 2020.			
Medicaid	June 10, 2019	**MME:** ≥ 120 MME requires prior authorization; 30-day supply limit for naïve patients.		Oregon Medicaid	Hartung et al., 2018
Pennsylvania					
Law	January 3, 2017	**Days' Supply:** 7-day supply for all opioid prescriptions for adults from the ED, urgent	Exceptions for acute medical condition, cancer patients, palliative care	35 Pa. Cons. Stat. § 873.3	

Federal Agencies and States	Date[a]	Prescribing Limits[b]	Restrictions/Exceptions and Other Components	Reference/Prescribing Limit Rationale[c]	Published Study References[c]
		care, or hospital observation settings; 7-day supply for all opioid prescriptions for minors			
Medicaid		7-day supply limit for naïve patients			
Rhode Island					
Law	January 2, 2020	**MME: C**onsider consultation with a Pain Medicine Physician for all chronic pain opioid prescriptions ≥ 90 MME/day **Co-Prescribing:** Co-prescribe naloxone for all patients with opioid prescriptions ≥ 50 MME/day (individually or in aggregate) or when also prescribed a benzodiazepine within the past 30 days	Added requirement that prescribers must have a conversation with a patient or minor patient's parent prior to prescribing any opioid	216 RI Admin. Code 20-20-4.4 (Amended, Adopted pursuant to R.I. Gen Session Laws 21-28-3.01)	
	July 2, 2018	**MME: C**onsider consultation with a Pain Medicine Physician for all chronic pain opioid prescriptions ≥ 90 MME/day **Co-Prescribing:** Co-prescribe naloxone for all patients with opioid prescriptions ≥ 50 MME/day (individually or in aggregate) or when also prescribed a benzodiazepine within the past 30 days		216 RI Admin. Code 20-20-4.4 (Amended, Adopted pursuant to R.I. Gen Session Laws 21-28-3.01)	
	March 22, 2017	**Quantity:** Maximum of 20 doses for all initial opioid prescriptions **MME:** 30 MME/day for all initial opioid prescriptions **Formulation:** Prohibited from prescribing ER/LA opioids for all initial opioid prescriptions for opioid naïve patients (no opioid prescription in prior 30 days)	Restrictions for minors; exemptions for chronic pain patients, cancer patients, palliative care	216 RI Admin. Code 20-20-4.4 (Adopted pursuant to R.I. Gen Session Laws 21-28-3.01)	Barre et al., 2019; Reid et al., 2019 Clin Orthop Relat Res; Reid, 2019 J of Ortho Trauma; Reid, 2019 J of Bone and Joint Surg; Reid, 2019 The Spine Journal; Reid, 2018
Medicaid		10-day supply limit for naïve patients.			
South Carolina					

Federal Agencies and States	Date[a]	Prescribing Limits[b]	Restrictions/Exceptions and Other Components	Reference/Prescribing Limit Rationale[c]	Published Study References[c]
Law	July 16, 2018	**Days' Supply:** 7-day supply for all initial opioid prescriptions	Exceptions for surgical pain, cancer, chronic pain, hospice care, palliative care, sickle cell disease	S.C. Code Ann. § 44-53-360(j)(1)	
Medicaid	May 1, 2018	**Days' Supply:** 5-day supply or **MME:** 90 MME daily	Professional judgment exceptions; exceptions for chronic pain, cancer, palliative care, sickle cell disease	South Carolina Medicaid	
South Dakota					
Law		No relevant prescribing law found as of April 2020.			
Medicaid	October 1, 2019	**Days' Supply:** 7-day supply for all initial opioid prescriptions **MME:** 90 MME daily; 60 MME for initial prescribers. Following tapering schedule used for new or renewal prescriptions: Oct 1, 2018: 300 MMEs Nov 1, 2018: 270 MMEs Dec 1, 2018: 240 MMEs Jan 1, 2019: 220 MMEs Feb 1, 2019: 200 MMEs Mar 1, 2019: 180 MMEs April 1, 2019: 160 MMEs May 1, 2019: 140 MMEs June 1, 2019: 130 MMEs July 1, 2019: 120 MMEs Aug 1, 2019: 110 MMEs Sept 1, 2019: 100 MMEs Oct 1, 2019: 90 MMEs		South Dakota Medicaid	
Tennessee					
Law	July 1, 2018	**Days' Supply:** 3-day supply for all opioid prescriptions **MME:** 180 MME/dose	Allows for professional judgement exceptions	Tenn. Code Ann. § 63-1-164	Samimi et al., 2019
	October 1, 2013	**Days' Supply:** 30-day supply for all opioid or benzodiazepine prescriptions		Tenn. Code Ann. § 53-11-308€	
Medicaid	February 2019	**MME:** ≥ 60 MME for first time or non-chronic opioid users		Tennessee Medicaid	
Texas					

Federal Agencies and States	Date[a]	Prescribing Limits[b]	Restrictions/Exceptions and Other Components	Reference/Prescribing Limit Rationale[c]	Published Study References[c]
Law	September 1, 2019	**Days' Supply:** 10-day supply for acute pain prescriptions	Exceptions for cancer care, hospice, end of life and palliative care	V.T.C.A., Health & Safety Code § 481.07636	
Medicaid	January 2018	**Days' Supply:** Avoid prescribing more than a 3-day supply (or 20 pills) of low-dose, short acting opioids for acute pain; 7-day limit for initial acute prescription. **MME:** ≥200 MME; to taper down to ≥ 90 MME by January 1, 2019	Additional recommendations for post-acute pain period and chronic opioid therapy	Texas Medicaid	
Utah					
Law	May 9, 2017	**Days' Supply:** 7-day supply for all CII and CIII opioid prescriptions	Prescribing limit restriction is for dispensers, not prescribers; restrictions for minors; surgical pain exceptions	Utah Code Ann. §§ 58-37-6(7)(f)	
Medicaid	July 1, 2019	**Days' Supply:** Follows state prescribing law. **MME:** ≤ 90 MME for naïve patients, ≤ 150 MME for "experienced" opioid users	Minor restrictions; cancer exceptions	Utah Medicaid	
Vermont					
Law	July 1, 2017	**Days' Supply and MME:** For opioid naive pts, first prescription in non-healthcare setting ***additional cutoffs and rules for chronic pain (starting at 90 MME/day)*** Adults (≥18 years): • Minor Pain: Prescription total MME = 0; Avg. daily MME = 0 • Moderate Pain: Prescription total MME: 0-3 days = 72 MME, 1-5 days = 120 MME; Avg. daily MME = 24 MME/day • Severe Pain: Prescription total MME: 0-3 days = 96 MME, 1-5 days = 160 MME; Avg. daily MME = 32 MME/day • Extreme pain: Prescription total MME: 7-day max=350 MME; Avg. daily MME = 50 MME/day Children (0-17 years): • Minor Pain: Prescription total MME = 0, Avg. daily MME = 0	Dependent on age and pain severity; Prescription total MME is the maximum limit (mandatory), Average daily MME is a suggestion to allow for tapering; can only prescribe up to 7 days if the reason is clearly documented in the medical record; additional cutoffs and rules for chronic pain (starting at 90 MME/day) DOH Rule Exclusions: Acute Pain: significant/severe trauma, complex surgical interventions (e.g., spinal surgery), prolonged inpatient care due to post-op complications, MAT, not-opioid naive	VT DOH Rule based adopted pursuant to 18 V.S.A. § 4289 (e), Section 14(e) of Act 75 (2013) and Section 2a of Act 173 (2016).	Aulet et al., 2019; MacLean et al., 2019

Federal Agencies and States	Date[a]	Prescribing Limits[b]	Restrictions/Exceptions and Other Components	Reference/Prescribing Limit Rationale[c]	Published Study References[c]
		• Moderate to Severe Pain: Prescription total MME: 0-3 days = 72 MME; Avg. daily MME = 24 MME/day	Chronic Pain: cancer, patients in nursing homes, terminal illness, hospice care		
Medicaid		7-day supply limit for naïve patients.			
Virginia					
Law	March 15, 2017	**Days' Supply:** 7-day supply for all CII-CIV opioid prescriptions; 14 days for surgical procedures	Professional judgement exceptions	18 VAC 85-21-40	
Medicaid		Follows state prescribing law.			
Washington					
Law	January 1, 2019	**Days' Supply:** 7-day supply for all opioid prescriptions	Professional judgement exceptions	Wash. Admin. Code 246-919-885 (adopted pursuant to ARCW § 18.22.800)	
Medicaid	November 1, 2019	**Days' Supply:** 7-day supply **MME:** 120 MME/day	Restrictions for persons under 21; professional judgment exceptions, exceptions for cancer, hospice, end of life or palliative care	Washington Medicaid	
Washington, DC					
Law		No relevant prescribing law found as of April 2020.			
Medicaid	October 1, 2019	**Prior Authorization:** PA required for all new opioid prescriptions with >7-day supply or >90 MME; PA *may* be required for all opioid prescriptions with >7-day supply or >90 MME for chronic pain patients		DC Fee-for-Service Medicaid	
	October 1, 2019	**Days' Supply:** No more than 7-day supply **MME:** ≤90 MME *For patients already prescribed opioid analgesics (chronic pain)		DC Fee-for-Service Medicaid	
	April 1, 2019	**Days' Supply:** No more than 7-day supply **MME:** ≤180 MME * For patients already prescribed opioid analgesics (chronic pain)		DC Fee-for-Service Medicaid	

Federal Agencies and States	Date[a]	Prescribing Limits[b]	Restrictions/Exceptions and Other Components	Reference/Prescribing Limit Rationale[c]	Published Study References[c]
	October 1, 2018	**Days' Supply:** No more than 7-day supply **MME:** ≤300 MME * For patients already prescribed opioid analgesics (chronic pain)		DC Fee-for-Service Medicaid	
	October 1, 2018	**Days' Supply:** No more than 7-day supply **MME:** ≤90 MME *Initial opioid analgesic prescription; opioid naïve patient		DC Fee-for-Service Medicaid	
West Virginia					
Law	June 7, 2018	**Days' Supply:** 7-day supply for all initial CII opioid prescriptions; 4-day supply for all CII opioid prescriptions from the ED or urgent care; 3-day supply for all CII opioid prescriptions from dentists and optometrists; 30-day supply for all other CII opioid prescriptions **MME:** Lowest effective dose	Restrictions for minors	W. Va. Code, § 16-54-4	
Medicaid		Follows state prescribing law.			
Wisconsin					
Law	April 2017	**PDMP Check:** Review the PDMP for greater than a 3-day's supply as part of the HOPE agenda		Enacted by the Controlled Substance Board pursuant to Wis. Stat. § 961.385	
Medicaid	January 1, 2011	No more than 5 prescription fills per calendar month; 30-day supply limit for naïve patients	Exceptions for nursing home or hospice care		
Wyoming					
Law	Effective: July 1, 2019	**Days' Supply:** 7-day supply in 7-day period for acute pain for opioid naïve patients		WY Stat. § 35-7-1030	
Medicaid		No specific guidelines found as of April 2020.			

MME, morphine milligram equivalents; mg, milligram; NSAID, nonsteroidal anti-inflammatory drugs; CDC, Centers for Drug Control and Prevention; MAT, medication-assisted treatment; IR, immediate release; CMS, Centers for Medicare and Medicaid Services; IHS, Indian Health Services; ER/LA, extended release/long-acting; PDMP, prescription drug monitoring program; CII, Schedule II controlled substance; CIV, Schedule IV controlled substance; HHS, Health and Human Services; API, active pharmaceutical ingredient; VA, Veterans Affairs; DoD, Department of Defense; APS, American Pain Society; AAPM, Academy of Pain Medicine; PA, prior authorization; CSPMP, Controlled Substances Prescription Monitoring Program; FDA, Food and Drug Administration; CR, controlled-release; ED, emergency department; CIII, Schedule III controlled substance; DOH, Department of Health;
Note: This table includes the most recent information we were able to locate on the various state statutes and policies as of April 2020. It is possible that relevant information was not identified in our review.
Note: Gray text indicates prescribing limits carried from previous laws
[a] Effective date unless otherwise specified
[b] Please refer to Section II for the definition of a prescribing limit for the purposes of this report
[c] References noted below

[d] Policy or Guideline

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Appendix A. Table 2. Examples of Opioid Analgesic Prescribing Limits from Selected State Medical and Pharmacy Boards and Other Selected Organizations

Selected Organizations	Date[a]	Prescribing Limits	Restrictions/Exceptions and Other Components	Program Basis	Published Study References[b]
Medical and Pharmacy Boards					
Alabama Medical and Pharmacy Boards: Dental Board of Examiners	September 9, 2018	**PDMP Check:** > 7-day supply or > 50 MME/day, for any patient prescribed ≥ 3 acute pain medicine prescriptions within 90 days, and any patients on chronic opioid or benzodiazepine therapy	**Patient Evaluation and Risk Stratification:** All dentists must document the use of risk and mitigation strategies prior to writing a controlled substance prescription for > 7-day supply or > 50 MME/day, for any patient prescribed ≥ 3 acute pain medicine prescriptions within 90 days, and any patients on chronic opioid or benzodiazepine therapy	Rule 270-x-2-.23, adopted pursuant to Code of Ala. 1975, §§ 20-2-54.1, 20-2-214(b), 34-9-43(a)(10)	
Alabama Medical and Pharmacy Boards: Board of Medical Examiners; State Board of Pharmacy	March 9, 2017	**PDMP Check**: All prescribers must check the PDMP at least twice per year for all opioid prescriptions > 30 MME/day and all sedative-hypnotic prescriptions > 3 LME/day; all prescribers must check the PDMP on the same day prior to writing any opioid prescription for > 90 MME/day and any sedative-hypnotic prescription for > 5 LME/day	Allows for exemptions to the PDMP check for nursing home or hospice patients, cancer patients, or intra-operative care	Rule 540-x-4-.09, adopted pursuant to Code of Ala. 1975, §§34-24-53, 34-24-336, 20-2-54, 20-2-214	
California Medical Board	November 2014	**Days' Supply:** Initiating opioid therapy: therapeutic trial for (usually) no longer than 45 days with specific		Medical Board of California Guidelines for Prescribing Controlled Substances for Pain (sections of the guideline are based upon CDC recommendations)	

Selected Organizations	Date[a]	Prescribing Limits	Restrictions/Exceptions and Other Components	Program Basis	Published Study References[b]
		evaluation points. Special caution when prescribing more than 90 days **MME:** Caution (yellow flag warning) prescribing doses above 80 MED/day. Consider referring to specialist at higher doses			
Indiana Medical Licensing Board	December 15, 2013	**Days' supply**: Patients with more than three consecutive months with >60 opioid pills per month or MME >15 per day.		Indiana Medical Board Emergency Rule: P.L. 185-2013 (SEA 246)	Al Achkar et al., 2018
	November 1, 2014	Same as above		Indiana Medical Board Final Rule: LSA Document #14-289	Al Achkar et al., 2018
Kentucky Medical Boards	November 15, 2017	**Days' Supply:** 3-day supply for all initial prescriptions for CII substances; 3-day supply of a CII substance or a 7-day supply of a non-CII substance for all patients being discharged from the ED **MME:** Refer patients to addiction management and/or taper for all patients on opioid doses >50 MME/day or have concurrent opioid and benzodiazepine use without evidence of benefit	Exceptions for cancer patients, single doses for diagnostic tests/procedures, a CII substance prescribed as part of a narcotic treatment program, any CII substance prescribed immediately prior to/during/within 14 days after major surgery or significant trauma with a maximum of a 14-day supply	201 KAR 9:260	

Selected Organizations	Date[a]	Prescribing Limits	Restrictions/Exceptions and Other Components	Program Basis	Published Study References[b]
Mississippi State Board of Medical Licensure	2018	**Days' Supply:** Limit prescription for acute pain to 3-10 days. **MME:** Lowest effective dose of immediate release opioids for acute pain; use of long acting opioids for acute pain prohibited. Strive to keep doses <50 MME and avoid doses > 90 MME	Exceptions for cancer	Part 2640 Chapter 1 Rules adopted pursuant to Miss. Code Ann. §73-43-11	
State Medical Board of Ohio	August 2017 and December 2017	**Days' Supply:** Maximum of 7-day supply for all initial acute pain opioid prescriptions for adults **MME:** Average of 30 MED/day; maximum of 210 MED	Cancer, end-of-life care/ hospice care, palliative care, medication-assisted treatment for addiction	https://med.ohio.gov/Publications/Recent-News/effective-december-29-phase-2-of-prescribing-opioids-for-acute-pain (accessed May 4, 2020)	Zolin et al., 2019
Washington State Medical Directors' Group	2015	**Days' Supply:** For acute and chronic (non-cancer) pain, prescribe in multiples of a 7-day supply **MME:** Lowest effective dose	Guidelines for prescribing to minors; cancer survivors, older adults, during pregnancy	Interagency Guideline for Prescribing Opioids for Pain, available at: https://agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf (accessed August 24, 2020)	Austin, 2019
	March 2007; updated in 2010	**MME:** Avoid prescribing a cumulative opioid dose above 120 MME/day without seeking a pain medicine consultation **Tapering:** Decrease original dose by 10% per week		Washington State Agency Medical Directors' Group	Weimer, 2016
Health Systems, Insurance and Hospital Practices					

Selected Organizations	Date[a]	Prescribing Limits	Restrictions/Exceptions and Other Components	Program Basis	Published Study References[b]
Kaiser Permanente Southern California	January 1, 2010	**Days' supply**: Maximum of 30 days for OxyContin and Opana prescriptions, maximum daily doses of 40 mg for methadone, and maximum of 200 pills per prescription of opioid-acetaminophen combination products.		The Safe and Appropriate Opioid Prescribing program https://permanente.org/road-safe-appropriate-opioid-prescribing/ (accessed August 24, 2020)	Losby et al., 2017
Mayo Clinic	Updated March 2018	**Quantity and/or MME limits** for post-operative pain for a variety of surgical procedures (general surgery, surgical oncology, urology, CRS, and vascular, thoracic, and endocrine surgical procedures) *Guidelines vary depending on the type of surgical procedure AND clinical and patient factors shown to influence opioid use after discharge		Mayo Clinic Surgical Outcomes Program Recommendations for Adult Discharge Opioid Prescriptions Mayo Clinic Urology postoperative opioid prescribing guidelines for opioid-naive patients (found as a link in an article located at: https://www.mayoclinic.org/medical-professionals/urology/news/variation-in-postoperative-opioid-prescribing-provides-motivation-for-a-more-standardized-approach/mac-20450573) (accessed August 24, 2020)	
Oregon Health & Science University: General Internal Medicine Clinic	May 15, 2012	**MME:** Maximum of 120mg MED/day for chronic opioid therapy to treat chronic non-cancer pain. New patients on >120mg MED/day required to be tapered (encouraged time frame of 3-6 months).		Washington Opioid Dosing Legislation – HB 2876, 2010; Washington State Agency Medical Directors' Group – Interagency Guideline on Opioid dosing for Chronic Non-cancer Pain: 2010 Update http://www.oregonpainguidance.org/app/content/uploads/2015/04/OHSU_Opioid_Guideline_1-14.pdf (accessed May 4, 2020)	Weimer et al., 2016

Selected Organizations	Date[a]	Prescribing Limits	Restrictions/Exceptions and Other Components	Program Basis	Published Study References[b]
		Exceptions on individual patient basis only**Error! Bookmark not defined.**			
Blue Cross Massachusetts	July 1, 2012	**Prior Authorization:** Prior authorization required for new short-acting opioid prescriptions with more than a 30-day supply.		Blue Cross Quality and Safety Measures in Opioid Management https://www.bluecrossma.com/bluelinks-for-employers/whats-new/special-announcements/opioid-management.html (accessed August 24, 2020)	Garcia et al., 2016

MME, morphine milligram equivalent; PDMP, prescription drug monitoring program; LME, Lorazepam milligram equivalency; mg, milligram; MED, morphine equivalent dose; CDC, Centers for Disease Control and Prevention; CII, Schedule II controlled substance; CRS, colorectal surgery

[a] Effective date unless otherwise specified

[b] See below for full references

Note: Prescribing limits in this table represent only selected limits.

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Appendix A. Table 3a. Articles from Systematic Literature Review Conducted by CDC Covering 2013 to May 2018

First author, year [a]	Prescribing limit (length, quantity, dosage) [b]	Intervention description	Design	Outcome	Findings
Meara et al., 2016	• Prescribing regulations limiting days' supply and quantity across states	• Implementation: Prescribing limits with additional requirements: o Doctor shopping o Examinations o Identification requirement o Pharmacist verification o Tamper-resistant prescription forms o PDMP checks o Pain clinic laws	• Retrospective cohort study • Time-frame: 2006 – 2012 • Study Population: Disabled Medicare beneficiaries < 65 years	• Prescribing Patterns: o Opioid prescription characteristics • Patient health outcomes o Overdose: prescription opioids	• The adoption of controlled substance laws was not associated with the percentage of beneficiaries filling opioid prescriptions with high daily doses or the percentage treated for nonfatal prescription-opioid overdoses • Limitations: Data on disabled fee-for-service Medicare beneficiaries who have higher rates of opioid use; article relies on hospital and emergency department claims data
Weimer et al., 2016	• 120 MME/day	• Oregon Health & Science University Internal Medicine and Geriatrics (OHSU IMC) • Date: May 2012 • Implementation: Opioid dosing limitation policy in combination with a provider education program	• Time-series • Time-frame: May 2011 – August 2013 • Location: Oregon Health & Science University General Internal Medicine Clinic • Data Source: OHSU IMC electronic health records • Study Population: OHSU IMC patients who are receiving chronic opioids	• Prescribing Patterns: o Opioid prescription characteristics o Tapering • Patient Health Outcomes: o Pain management o Other health outcomes: quality of life	• After policy adoption, the average dose declined by 64 MME/day • Among patients on high dose opioids, 37% tapered their doses below 120 MME/day • There were no significant differences in pain or quality of life after the intervention was implemented • Limitations: Small sample size based on a single clinic; some data collected were for clinical, not research, purposes
Riggs et al., 2017	• 4 tablets/day or 120 tablets for 30 days of short-acting opioids	• Colorado Medicaid • Date: August 2014 • Implementation: Pharmacy benefit change limiting the quantity of short-acting opioids that could be reimbursed	• Before-after • Time-frame: May 2014 – March 2015 • Location: Colorado • Data Source: Colorado Medicaid claims • Study Population: 54,000 Medicaid-eligible patients at	• Prescribing Patterns: o Opioid prescription characteristics o Tapering	• 3% reduction in total daily dose was observed among the study population after implementation • 24% reduction in total daily dose was observed among patients who exceeded the quantity limit at baseline • No change in the proportion of patients receiving more than 120 MME/day or the

First author, year [a]	Prescribing limit (length, quantity, dosage) [b]	Intervention description	Design	Outcome	Findings
			Kaiser Permanente Colorado integrated care delivery system		proportion of patients receiving long-acting opioids • Limitations: lack of control group; some reductions were likely the result of compliance efforts upon the laws' enaction unclear if reduction will be sustained
Losby et al., 2017	• 30-day supply for OxyContin and Opana prescriptions • 40 mg/day for methadone • 200 tablets per prescription of opioid-acetaminophen combination products	• Kaiser Permanente Southern California • Date: Stepwise approach from 2010 to 2015 • Implementation: Electronic health record integration of prescribing and dispensing policies, monitoring and follow-up processes, and clinical coordination	• Before-after • Time-frame: January 2010 – December 2015 • Location: California • Data Source: Patient data from Kaiser Permanente Southern California pharmacy data system and electronic health record • Study Population: Kaiser Permanente Southern California members age 18 years or older excluding cancer, hospice, and palliative care patients	• Prescribing Patterns: o Opioid prescription characteristics o "High-risk" opioid use	• 30% reduction in high-dose opioid prescriptions • 98% reduction in prescriptions with greater than 200 tablets • 90% decrease in the combination of an opioid prescription with benzodiazepines and carisoprodol • 72% reduction in the prescribing of long-acting/extended-release opioids • 95% reduction in prescriptions of brand name opioid-acetaminophen combination products • Methadone prescribing did not increase during the study period • Limitations: Long-term health outcomes not measured; did not have a comparison group; health system implemented many interventions simultaneously and the relative contribution of a single intervention is unknown and might not be generalizable across states
Al Achkar et al., 2018	• Three consecutive months with >60 opioid tablets/month or >15 MME/day	• Indiana emergency prescribing rules • Date: December 2013 • Implementation: For all patients above the prescribing limit, prescribers required to: o Evaluate opioid recipients for psychiatric conditions o Review the PDMP o Perform regular drug screenings	• Time-series • Time-frame: January 2011 – November 2014 • Location: Indiana • Data Source: Indiana PDMP • Study Population: Individuals dispensed opioids between	• Prescribing Patterns: o Opioid prescription characteristics	• Significant decrease in the total MME of opioids dispensed after policy implementation • Decline in both the number of prescribers and number of day supply • The effect of the policy differed by patient gender, age, and payer • Limitations: analysis is limited in its ability to determine causality; prescriber zip codes capture location of prescriber's residence or practice; impact on access-to-

First author, year [a]	Prescribing limit (length, quantity, dosage) [b]	Intervention description	Design	Outcome	Findings
		○ Obtain a signed controlled-substance agreement	January 1, 2011 through November 6, 2014		appropriate treatment and care involving opioid alternatives could not be evaluated; and did not explore link of daily opioid dose impact on overdose and death
Garcia et al., 2016	• Prior authorization for new short-acting opioid prescriptions with >30-day supply	• Blue Cross Blue Shield of Massachusetts (BCBSMA) • Date: June 2015 • Implementation: Comprehensive opioid utilization policy: ○ Treatment plans ○ Risk assessments ○ Patient-provider agreements ○ Single pharmacy dispensing ○ Prior authorization ○ Mail-order ban	• Time-series • Time-frame: 2011 – 2015 • Location: Massachusetts • Data Source: BCBSMA claims • Study Population: BCBSMA members	• Prescribing Patterns: ○ Opioid prescription characteristics	• 6% to 9% annual decline in the percentage of members on short-acting and long-acting opioid prescriptions and in opioid prescribing rates compared with the pre-implementation period • Limitations: Non-oncology opioid prescriptions might be underestimated by the inclusion of oncology members; external factors affecting prescribing rates could not be evaluated
Garcia et al., 2014	• Prior authorization for prescriptions greater than: ○ 240 mg/day of oxycodone ER ○ 200 mcg/day of fentanyl ○ 360 mg/day of morphine ER ○ 120 mg/day of methadone	• Massachusetts Medicaid • Date: October 2002 • Implementation: Initiative focused on dose and therapeutic alternatives	• Time-series • Time-frame: 2002 – 2005 • Location: Massachusetts • Data Source: Massachusetts Medicaid claims • Study Population: MassHealth members enrolled in Massachusetts Medicaid pharmacy benefit	• Prescribing Patterns: ○ Opioid prescription characteristics • Other: ○ Change in therapy costs	• 17.8% decrease in the number of Medicaid members utilizing long-acting opioids and a 4.1% decrease in the overall number of claims for long-acting opioids • Average daily dose declined in methadone and morphine ER and increased in oxycodone ER and fentanyl transdermal system • The overall cost of long-acting opioids decreased 8% • Limitations: Morphine equipotent ratio is used to determine or calculate the oral morphine equivalent doses and these doses are not universally agreed upon and time between the implementation of changes and evaluation of outcomes when it comes to cost benefit

CDC, Centers for Disease Control and Prevention; PDMP, prescription drug monitoring program; MME, morphine milligram equivalent; mg, milligram; ER, extended-release; OHSU IMC, Oregon Health & Science University Internal Medicine and Geriatrics; BCBSMA, Blue Cross Blue Shield of Massachusetts

[a] See references below

[b] Please see Appendix A, Table 1 and 2 for further details on the source and other components of the opioid analgesic prescribing limit

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Appendix A. Table 3b. Articles from Updated Literature Review Conducted by FDA Covering May 2018 to November 2019

First author, Year[a]	Prescribing limit (length, quantity, dosage)[b]	Intervention description	Design	Outcome	Findings
Aulet et al., 2019	• Adults: o Minor pain: no opioids o Moderate pain: maximum average of 24 MME/day for 5 days o Severe pain: maximum average of 32 MME/day for 5 days o Extreme pain: maximum average of 50 MME/day for 7 days • Children: o Minor pain: no opioids o Moderate to severe pain: maximum average of 24 MME/day for 3 days • Initial acute pain opioid prescription • Opioid naïve patients • PDMP look-up at >10 opioid tablets	• Vermont law, Vermont Department of Health rule governing prescribing limits of opioids for acute pain • Date: July 1, 2017 • Implementation: Prescribers required to: o Check state's PMS o Provide patient education on risks of opioid use o Obtain signed informed consent o Prescribe fewest number of pain pills for shortest duration possible	• Retrospective case control • Time-frame: Prior to July 2017 – after July 2017; Intervention: July 1, 2017 • Location: University of Vermont Medical Center • Data Source: o EMR – Patient information o VPMS – Opioid prescription fills • Study Population: Rhinoplasty and/or septoplasty with or without turbinate reduction surgical patients >14 years	• Prescribing Patterns: o Opioid prescription characteristics • Patient Health Outcomes: o Pain management	• No significant change in number of refills prescribed, phone calls for pain, or pain complaints at post-operative visits • Mean number of pills prescribed significantly decreased from 18.2 to 9.7 • Mean MME significantly decreased from 130.9 to 73.1 • Limitations: Small sample size (pre-intervention N=40, post-intervention N=40); unclear what prescribing limits were used; length of pre-intervention and post-intervention time-frames are unclear
Austin et al., 2019	• Caution prescribing >50 MED	• CDC Guidelines; Washington State Interagency Guideline	• Retrospective chart review	• Prescribing Patterns:	• Percent of patients on ≥90 MED and ≥50 MED decreased significantly

First author, Year[a]	Prescribing limit (length, quantity, dosage)[b]	Intervention description	Design	Outcome	Findings
	• Maximum of 90 MED • Taper if over the limit • Chronic pain	on Prescribing Opioids for pain • Dates: o CDC Guidelines: March 18, 2016 o Washington State Interagency Guideline: June 2015 • Implementation: o Academic detailing for all prescribers o Resident physicians required to spend 4 half-days at interdisciplinary pain clinic, one chronic pain group medical visit yearly	• Time-frame: Prior to July 2016 – July 2017; Intervention: July 2016 • Location: University of North Carolina Health Sciences at the Mountain Area Health Education Center • Data Source: EMR for patient and opioid prescription information • Study Population: Chronic opioid analgesic therapy (COT) patients	o Opioid prescription characteristics o Tapering o "High-risk" opioid use	• Mean MED not significantly different for baseline cohort and patients who remained on COT • 29% of active patients were tapered off COT • Number of patients on concomitant benzodiazepines decreased from 212 to 131 • Limitations: Does not include patient-reported outcomes; no description of etiology of chronic pain or actual tapering strategy used
Barre et al., 2019	• Maximum of 20 doses and 30 MME/day • Initial acute pain opioid prescription • Opioid naïve patients	• Rhode Island Department of Health Regulations • Date: March 2017 • Implementation: o Letters sent to all prescribers o Prior authorization required for all initial opioid analgesic prescriptions to treat acute pain in opioid naïve patients that exceed the prescribing limit	• Retrospective, pre/post • Time-frame: January 2017 – December 2017; Intervention #1 (letters): April 2017; Intervention #2 (prior authorization): July 2017 • Location: Rhode Island • Data Source: PDMP • Study Population: Patients prescribed initial opioid prescriptions for acute pain	• Prescribing Patterns: o Opioid prescription characteristics	• Percent of initiate opioid analgesic prescriptions >30 MME/day significantly decreased for April 2017 (40% to 22%) and July 2017 (22% to 13%) • Percent of initiate opioid analgesic prescriptions >20 doses significantly decreased from 46% to 16% for April 2017. No change noted for July 2017 • Limitations: Does not include details about study sample sizes, prescribers, or patients; does not include patient-reported outcomes
Chen et al., 2019	• 100 mg MME/day • High dose: 200 mg MME/day	• Opioid Safety Initiative • Dates: o Piloted in Minnesota VA Health Care System in 2011	• Interrupted time-series • Time-frame: January 2010 – December 2015; Intervention: October 2013	• Prescribing Patterns: o Opioid prescription characteristics	• Small but statistically significant increases in some pain scores pre- to post-OSI implementation • Statistically significant decreases in chronic post-operative opioid analgesic use and new initiation of chronic post-operative opioid

First author, Year[a]	Prescribing limit (length, quantity, dosage)[b]	Intervention description	Design	Outcome	Findings
		○ Implemented in all VHAs nationwide by October 2013 • Implementation: ○ Academic detailing for all prescribers to disseminate guidelines ○ Electronic dashboards providing audit and feedback tools for prescribing behaviors	• Location: VHAs nationally • Data Source: Corporate Data Warehouse (EMR): detailed info on patient characteristics, pain scores, prescriptions • Study Population: All veterans who underwent total knee arthroplasty	○ Non-opioid or adjunct pain medications • Patient Health Outcomes: ○ Pain management ○ Transition from acute to chronic use ○ Death	analgesic use from pre- to post-OSI implementation • Statistically significant decreases in mortality rates within 30 days, 90 days, and 365 days of discharge from pre- to post-OSI implementation • Post-operative acetaminophen and NSAID prescriptions increased post-OSI implementation • Limitations: No linkage between procedures, actual prescribing habits/amounts, and patient-reported outcomes; multiple components to intervention
Davis et al., 2019	• NV: 14 days, 90 MME/day • HI: 30 days • MD: lowest effective dose • NJ: lowest effective dose • NY: 7 days or less • DE: 7 days or less • IN: 7 days or less • KY: 7 days or less • MN: 7 days or less • OH: 7 days or less, 30 MME/day • VT: 7 days or less, 24 MME/day for moderate pain, 50 MME/day for extreme pain • All limits are on initial opioid prescriptions	• Opioid prescribing laws enacted in 3rd quarter of 2016: ○ HI, NY • Opioid prescribing laws enacted in 2nd quarter of 2017: ○ DE, MD, NJ, NV • Opioid prescribing laws enacted in 3rd quarter of 2017: ○ IN, KY, MN, OH, VT • Control States: ○ CO, DC, FL, IA, ID, KS, MI, MS, MT, ND, NE, OK, OR, SD, WA, WY	• Retrospective, ecological • Time-frame: 2015 – 2018 (quarterly data for eight opioids); January 2016 – December 2017 for states that adopted opioid prescribing laws • Location: Twenty-six states and Washington, D.C. • Data Source: DEA ARCOS • Study Population: ○ Intervention group: Eleven states that enacted opioid prescribing laws without enactment or modification of PDMP laws ○ Control group: Fifteen states and Washington D.C. that didn't enact an opioid prescribing	• Prescribing Patterns: ○ Opioid prescription characteristics	• Control states: Volume of opioid distributed: overall average morphine gram equivalents (MGE) decreased by 23% from 1st quarter of 2015 to 4th quarter of 2017; buprenorphine volume increased by 44% during the same time period • Intervention states: Volume of opioid distributed: overall average morphine gram equivalents (MGE) decreased by 22% to 25% across the study period • In states that enacted opioid prescribing laws, there was no clear changes in the trend of volume of opioid distributed around the time of law enactment • Limitations: ARCOS data is the sale of every opioid analgesic medication by distributors to retail pharmacies, hospitals/clinics, and medical providers. It does not actually look at what was prescribed or dispensed to patients. Data are converted from grams per 100,000 persons into morphine gram equivalents. It is difficult to tell exactly what happened in each state, as analyses are grouped by which quarter the states enacted laws. Does not include any patient-reported outcomes.

First author, Year[a]	Prescribing limit (length, quantity, dosage)[b]	Intervention description	Design	Outcome	Findings
			law or enact/modify a PDMP law		
Dayer et al., 2019	• Acute pain: should not preferably exceed 3-day supply • Use caution when prescribing opioid analgesics above 50 MME/day • Avoid prescribing above 90 MME/day without careful consideration and justification • Avoid co-prescribing opioid and benzodiazepine prescriptions	• CDC Guideline • Date: March 18, 2016	• Retrospective cohort • Time-frame: January 2015 – June 2017; Intervention: March 2016; Washout period: January 2016 – June 2016 • Location: Level 1 trauma Emergency Department at an academic medical center in Arkansas • Data Source: EHR and Arkansas Clinical Data Repository at UAMS • Study Population: Adult patients ≥ 18 years who were prescribed an opioid upon discharge from the emergency department	• Prescribing Patterns: o Opioid prescription characteristics o "High-risk" opioid use	• Small but statistically significant decrease in average MEDD and days' supply after enactment of CDC guidelines • The percent of patients who already had an opioid prescription that were prescribed an opioid upon discharge decreased significantly from 18.7% to 15.0% • The percent of patients prescribed an opioid upon discharge with a concomitant benzodiazepine prescription decreased significantly from 2.5% to 1.6% • Limitations: Did not control for secular trends or potential confounding factors; limited generalizability; results were statistically significant, but it is unclear how clinically meaningful the differences are; does not include patient-reported outcomes
Garcia et al., 2019	• Prior authorization for all opioid prescriptions > 120 mg MED/day	• MassHealth - Massachusetts Medicaid • Dates: o April 2003/October 2004: Prior authorization for 360 mg MED (fentanyl patch and oxycodone CR first, then expanded) o April 2014: Prior authorization for 240 mg MED	• Retrospective claims • Time-frame: January 2002 – March 2017; Interventions: April 2003, October 2004, April 2014, March 2016 • Location: Massachusetts • Data Source: Massachusetts Medicaid enrollment and pharmacy claims • Study Population: Adult patients ages 18-64 with ≥1 schedule II opioid analgesic MassHealth pharmacy claim	• Prescribing Patterns: o Opioid prescription characteristics	• Average daily MED decreased 55.8% from the peak in October – December 2003 • Percent of patients exceeding the original high dose limit of 360 mg MED peaked in October – December 2003, and overall, decreased 87.3% from the beginning to the end of the study period, with similar trajectories for high dose thresholds of 240 mg MED (79.8% reduction) and 120 mg MED (75.2% reduction) • Limitations: Does not include any patient-reported outcomes; intervention was implemented in multiple phases over a 13-year period; limited generalizability

First author, Year[a]	Prescribing limit (length, quantity, dosage)[b]	Intervention description	Design	Outcome	Findings
		○ March 2016: Prior authorization for 120 mg MED • Implementation: Three sequential and progressive opioid high dose prior authorization interventions with review by a clinical pharmacist and peer-to-peer outreach to determine if prior authorization criteria are met			
Hartung et al., 2018	• Prior authorization for non-combination opioid prescriptions >120 mg/day MED	• Oregon Medicaid fee-for-service program • Dates: ○ April 2012: Prior authorization for long-acting opioid prescriptions >120 mg/day MED ○ June2012: Prior authorization for short-acting opioid prescriptions >120 mg/day MED • Implementation: Prior authorization required for all initial opioid prescriptions above limit; re-authorization required every six months for approved patients	• Retrospective • Time-frame: January 2011- December 2013 • Data Source: Oregon Medicaid administrative claims • Study Population: ○ Intervention group: Oregon ○ Control group: Colorado	• Prescribing Patterns: ○ Opioid prescription characteristics ○ "High-risk" opioid use • Patient Health Outcomes: ○ Overdose: prescription opioids	• Decrease in the monthly probability of an opioid over 120 mg/day MED and small increase in opioid prescriptions less than 61 mg/day MED • No significant change in high-risk use indicators, except slight decline in monthly probability of multiple pharmacy use • No significant changes in opioid-related emergency department visits or hospitalizations, including for opioid overdose • Limitations: Colorado was used as a control state due to author preference, but other interventions occurred in that state during 2011-2013
Karst et al., 2018	• <3-day supply of opioids	• CDC Guideline was implemented by the Veterans Affairs	• Retrospective chart review • Time-frame: Pre-guideline: July 2015 –	• Prescribing Patterns:	• Significant decrease in the mean MME prescribed and in the mean number of days of opioid therapy prescribed

First author, Year[a]	Prescribing limit (length, quantity, dosage)[b]	Intervention description	Design	Outcome	Findings
	• Acute pain care (including minor surgeries)	Tennessee Valley Healthcare System • Date: CDC Guideline: March 18, 2016 • Implementation: o Recommend <3 days of opioid therapy for acute pain, with an emphasis on individualized care o Post-surgical opioid prescribing education at monthly surgical orientations	December 2015; Post-guideline: July 2016 – December 2016; Post-education: October 2017 – March 2018 • Data Source: Single-center opioid prescribing data • Study Population: Adult patients discharged following minor carotid endarterectomy or endovascular aneurysm repair	o Opioid prescription characteristics o Non-opioid or adjunct pain medications	• No significant percent change for prescribed non-opioid therapy at discharge • Decrease in percent of patients prescribed >300 morphine equivalents from the pre- to post-guideline • Increase in the percent of patients prescribed <200 morphine equivalents • Limitations: small sample size (Pre-guideline: N=24; post-guideline: N=22)
Lowenstein et al., 2020	• 5-day supply maximum • Initial prescription for all schedule II substances or any opioid medication	• New Jersey Law • Dates: o Law passed: February 2017 o Law implemented: May 2017 • Implementation: EMR Best Practices Alert was displayed for prescribers in New Jersey if new prescription exceeded 5-day limit	• Difference-in-differences • Time-frame: Pre-period: May 2016 - May 2017; Transition period (law but no EMR edit): May 2017 - July 2017; Post-period: July 2017 - March 2018 • Location: o Intervention group: Ambulatory, non-teaching practices (family medicine, internal medicine, OB/GYN, cardiology) within University of Pennsylvania Health System (Penn Medicine) in New Jersey in the greater Philadelphia area o Control group: Unexposed practices	• Prescribing Patterns: o Opioid prescription characteristics • Patient Health Outcomes: o Pain management • Prescriber Burden: o Prescribing opioids	• Decline in mean MME and quantity per index prescription in both groups (intervention and control) • No significant difference in rate of opioid refills within 30 days of a new opioid prescription in New Jersey or Pennsylvania between pre- and post-intervention periods • Adjusted analyses: o Total MME for new prescriptions declined more in New Jersey compared to Pennsylvania practices o No significant difference in opioid refills, 30-day admissions, emergency department/clinic visits, or telephone calls to practices pre- to post-intervention compared to controls • Prescribers used the opioid analgesic prescription suggestion list in 31% of opioid orders after the alert was put into place overall in New Jersey, and in 49% of orders with <10 tablets • Limitations: Limited generalizability

First author, Year[a]	Prescribing limit (length, quantity, dosage)[b]	Intervention description	Design	Outcome	Findings
			(same practice types) in the Penn Medicine health system in Pennsylvania • Data Source: EMR • Study Population: Patients who received a new opioid prescription at intervention or control locations		
MacLean et al., 2019	Acute pain: • PDMP look-up at >10 opioid tablets • Minor pain: no opioids recommended • Moderate pain: maximum average of 24 MME/day for 5 days • Severe pain: maximum average of 32 MME/day for 5 days • Extreme pain: maximum average of 50 MME/day for 7 days	• Vermont law, Vermont Department of Health rule governing prescribing limits of opioids for acute pain • Date: July 1, 2017 • Implementation: Prescribers required to: o Check state's PMS o Provide patient education on risks of opioid use o Obtain signed informed consent o Prescribe fewest number of pain pills for shortest duration possible; alert reminders o Hospital-level policies focused on prescriber and staff education of prescribing limits	• Retrospective • Time-frame: Baseline: July 2016 – December 2016; Adoption: January 2017 – June 2017; Post-rule: July 2017 – December 2017 • Location: University of Vermont Medical Center • Data Source: EMR • Study Population: Adult patients after general, orthopedic, gynecologic, urologic or vascular surgery	• Prescribing Patterns: o Opioid prescription characteristics • Patient Health Outcomes: o Pain management	• Significant decline (40%) in median MME prescribed at discharge from baseline to post-rule • Significant decline in the proportion of patients prescribed additional opioids <30 days after discharge • Significant decline in the median 30-day MME prescribed • Strengths: Study allowed for an "adoption" period between baseline and post-rule period • Limitations: Lack of patient health outcomes other than refills
Potnuru et al., 2019	• 3-day supply of schedule II opioids; allowance for up to maximum of 7	• Florida Law: House Bill 21 • Dates:	• Retrospective cohort • Time-frame: Baseline: July 2017 – February 2018; Interim: March	• Patient Health Outcomes: o Pain management	• No significant difference in emergency department visits within 7 or 30 days after hospital discharge pre- to post-law

First author, Year[a]	Prescribing limit (length, quantity, dosage)[b]	Intervention description	Design	Outcome	Findings
	days if certain criteria are met • Acute pain	o Passed: March 2, 2018 o Implemented: July 1, 2018 • Implementation: o 2-hour education course for providers o Consult PDMP for each patient o Documentation required for exceeding 3-day supply	2018 – June 2018; Law implemented: July 2018 – December 2018 • Location: Large public university-affiliated hospital in Florida • Data Source: EMR • Study Population: Adult patients ≥ 18 years who underwent one of six common outpatient surgical procedures (cholecystectomy, appendectomy, hernia repair, hysterectomy, mastectomy, lymph node dissection)	• Prescribing Patterns: o Opioid prescription characteristics	• Statistically significant decrease in the overall number of opioid prescriptions and opioid prescriptions with >3-day supply pre- to post-law • Statistically significant decreases in total and daily opioid prescribed (MME) pre-to post-law • Limitations: Limited generalizability; limited patient-reported outcomes; no documentation of why patients visited the emergency department after discharge
Reid et al., 2019 (The Spine Journal)	• >30 MME/day (>150 total MME) or >20 total doses • Initial opioid prescription • Opioid naïve patients	• Rhode Island state law • Dates: o Passed: June 28, 2016 o Implemented: April 17, 2017	• Retrospective, pre/post • Time-frame: Pre-law: January 2016 – June 2016; Post-law: June 2017 – December 2017 • Location: Rhode Island • Data Source: o Claims data o PDMP data • Study Population: Patients undergoing three common lumbar surgeries	• Prescribing Patterns: o Opioid prescription characteristics • Patient Health Outcomes: o Prolonged post-operative opioid use	• Compared to the pre-law period, the post-law period showed significant declines in the number of pills and total MME in first post-operative prescription • Post-law, post-operative total number of opioid prescriptions filled <30 days significantly increased while the total mean MME filled significantly decreased • No significant difference in mean MME filled 30-90 days • No difference in proportion of patients requiring prolonged post-operative opioids • Pre-operative use of opioids (<30 days of surgery) is a strong predictor of prolonged (30-90 days) post-operative opioid use • Limitations: Inability to assess actual pills consumed; inability to account for opioids dispensed during hospitalization
Reid et al., 2019 (Clin Orthop Relat Res)	• >30 MME/day (>150 total MME) or >20 total doses	• Rhode Island state law • Dates: o Passed: June 28, 2016	• Retrospective cohort • Time-frame: Pre-law: January 2016 – June	• Prescribing Patterns:	• Decreased dosage (MME) for first postoperative prescription in post-law cohort,

First author, Year[a]	Prescribing limit (length, quantity, dosage)[b]	Intervention description	Design	Outcome	Findings
	• Initial opioid prescription following a surgical procedure • Opioid naïve patients	o Implemented: April 17, 2017	2016; Post-law: June 2017 – December 2017 • Location: Large, multi-specialty orthopedic group in Rhode Island • Data Source: o Internal billing records o PDMP • Study Population: All patients undergoing primary total hip or total knee arthroplasty (THA or TKA)	o Opioid prescription characteristics	• Decreased 30-day cumulative dosage (MME) in post-law cohort but there were slightly more prescriptions in the first 30-days post-law • No difference in 30 to 90-day cumulative dosage, no difference by surgery type • Strengths: Gap in time between the pre-law and post-law evaluation phases reduced potential confounding due to voluntary practice changes after passage of the law but before implementation • Limitations: 20% of initially identified patients were excluded for not meeting predefined criteria or due to incomplete data; inability assess actual pills consumed; inability of PDMP to account for opioids dispensed during hospitalization, at rehabilitation facilities, or at nursing facilities
Reid et al., 2019 (J of Bone and Joint Surg)	• >30 MME/day (>150 total MME) or >20 total doses • Initial opioid prescription following a surgical procedure • Opioid naïve patients	• Rhode Island state law • Dates: o Passed: June 28, 2016 o Implemented: April 17, 2017	• Retrospective cohort • Time-frame: Pre-law: January 2016 – June 2016; Post-law: June 2017 – December 2017 • Location: Large, multi-specialty orthopedic group in Rhode Island • Study Population: All patients undergoing one of six primary orthopedic procedures	• Prescribing Patterns: o Opioid prescription characteristics	• Initial post-surgery prescription: decline in number of pills and dosage (MME) in post-law period • 30-days post-surgery: small increase in cumulative number of prescriptions and decline in dosage (MME) in post-law cohort • 30-90 days post-surgery: decline in dosage (MME) in post-law cohort • Limitations: Inability to assess actual pills consumed; inability of PDMP to account for opioids dispensed during hospitalization, at rehabilitation facilities, or at nursing facilities
Reid et al., 2019 (J of Ortho Trauma)	• >30 MME/day (>150 total MME) or >20 total doses • Initial opioid prescription • Opioid naïve patients	• Rhode Island state law • Dates: o Passed: June 28, 2016 o Implemented: April 17, 2017	• Retrospective cohort • Time-frame: Pre-law: January 2016 – June 2016; Post-law: June 2017 – December 2017 • Location: Level I-academic trauma center • Data Source: o Medical chart review	• Prescribing Patterns: o Opioid prescription characteristics	• Decline in mean number of opioid pills and dosage (MME) in initial prescription post-law period • ≤30 days post-surgery, small increase in number of opioid prescriptions filled but a 29% reduction in cumulative dosage (MME) in post-law period • Limitations: Unmeasured confounders; inability to assess actual pills consumed; inability of PDMP to account for opioids

First author, Year[a]	Prescribing limit (length, quantity, dosage)[b]	Intervention description	Design	Outcome	Findings
			○ Operative billing databases ○ PDMP • Study Population: All patients undergoing isolated fixation of six common fracture types		dispensed during hospitalization, at rehabilitation facilities, or at nursing facilities
Reid et al., 2019 (The Spine Journal)	• >30 MME/day (>150 total MME) or >20 total doses • Initial opioid prescription • Opioid naïve patients	• Rhode Island state law • Dates: ○ Passed: June 28, 2016 ○ Implemented: April 17, 2017	• Retrospective cohort • Time-frame: Pre-law: December 2015 – June 2016; Post-law: June 2017 – December 2017 • Data Source: ○ EMR ○ PDMP • Study Population: Patients undergoing primary elective 1-3 level anterior cervical decompression fusion surgeries	• Prescribing Patterns: ○ Opioid prescription characteristics	• Decrease in number of opioid pills and MME in initial prescription in post-law cohort • No difference in number of opioid prescriptions filled in 30-day post-operative period • Decrease in cumulative 30-day dosage (MME) in post-law • No difference in dosage between the cohorts after 30-day post-operative period • Limitations: Unmeasured confounders; inability to assess actual pills consumed; inability of PDMP to account for opioids dispensed during hospitalization, at rehabilitation facilities, or at nursing facilities
Samimi et al., 2019	• Informed consent required for all opioid prescriptions >3-day supply and >180 MME	• Tennessee House Bill No. 1831 • Date: July 1, 2018 • Implementation: In order to exceed prescribing limit, prescribers required to: ○ Document evaluation of the patient ○ Patient consent (including risk to pregnancy) ○ Record alternative pain treatments considered and reason for opioid use	• Retrospective, pre/post • Time-frame: Pre-law: January 2018 – June 2018; Post-law: July 2018 – December 2018 • Location: Single institution and surgical division • Data Source: EMR • Study Population: females ≥18 years undergoing pelvic reconstructive surgery	• Prescribing Patterns: ○ Opioid prescription characteristics ○ Non-opioid or adjunct pain medications	• Overall decrease in the median opioid dosage prescribed at discharge in the post-law cohort, but no difference in number of opioid tablets prescribed • No difference in number of patients prescribed NSAIDs, but number of NSAID tablets increased • Limitations: Minimal time allowed for prescribers to change behaviors; does not account for opioids received while inpatient; does not account for confounding factors; small sample size

First author, Year[a]	Prescribing limit (length, quantity, dosage)[b]	Intervention description	Design	Outcome	Findings
Sears et al., 2019	Three states: • Colorado: increase vigilance and consider pain consult at >120 mg MEDD; avoid >200 mg MEDD • Utah: Increase clinical vigilance and consider pain consult at >120-200 mg MEDD • Washington: Document functional improvement or seek pain consult at >120 mg MEDD	• Colorado: Division of Workers' Compensation o February 2012 guidelines (enforceable through state rules) • Utah: Department of Health o March 2009 (voluntary guidelines) • Washington: Agency Medical Directors' Group and other organizations o March 2007 (voluntary guidelines)	• Retrospective, pre/post • Timeframe: 2001 – 2014 • Location: Convenience sample of eight states • Data Source: Inpatient hospital discharge records • Study Population: o Three guideline states: Colorado, Utah, Washington o Five comparator states: Arizona, California, Michigan, New Jersey, South Carolina	• Patient Health Outcomes: o Overdose: prescription opioids and heroin	• Compared to the five comparator states, all three intervention states had a decreasing trend in prescription opioid overdoses and combined heroin and prescription opioid overdoses after intervention • Utah and Colorado also had a decreasing trend in heroin overdoses after intervention • Limitations: Convenience sample so potential for biases; different populations in the intervention states (injured workers or general population; interventions occurred at different times; data from hospital discharge data and ICD-9 codes were used to define overdose, so an overdose was only captured if recorded in claims data
Young et al., 2018	• 7-day supply for all opioid prescriptions	• CDC Guideline • Date: CDC Guideline: March 18, 2016 • Implementation: o Prescriber education (PowerPoint presentation and supplemental handouts on CDC Guideline) o Monitor patients' prescription history o Monitor prescribing behavior	• Prospective cohort • Time-frame: Pre-intervention: Eight weeks; Post-intervention: weeks 1-4 and weeks 5-8 • Location: Four urgent care settings in Rhode Island • Data Source: PDMP • Study Population: Opioid prescribing profiles of fourteen urgent care physicians	• Prescribing Patterns: o Opioid prescription characteristics	• Compared to the pre-intervention period, on average, a significant decline of 2.43 opioid prescriptions per provider per week was observed in the post-intervention weeks 5-8 period • No significant decline was observed between the pre-intervention period and the post-intervention weeks 1-4 period or between the post-intervention periods weeks 1-4 and 5-8 • Limitations: Limited generalizability and small sample size (pilot implemented at four urgent care centers staffed by fourteen providers)
Zipple and Braddock, 2019	• One-week supply of opioid analgesics (equal to 210 OME) • Opioid naïve patients	• Michigan state legislation • Date: July 2018 • Implementation: o State law:	• Retrospective • Time-frame: Pre-intervention: January 2015 – December 2017; Post-intervention: July 2018 – October 2018	• Prescribing Patterns: o Opioid prescription characteristics	• For the five most common surgeries, a 60-70% reduction in the average prescribed OME was observed from the pre- to post-intervention period • Significant increase in percentage of patients discharged with non-opioid pain medication

First author, Year[a]	Prescribing limit (length, quantity, dosage)[b]	Intervention description	Design	Outcome	Findings
	• Acute post-operative pain	▪ Opioid prescribing limit ▪ Provider awareness and consent form ▪ Mandatory PDMP review o Concurrent hospital intervention: ▪ MI-OPEN limits the number of post-operative opioids to 75 OME ▪ Educational campaign posting dosing recommendations throughout postoperative areas and on pocket cards for staff ▪ Lectures on the opioid epidemic also provided to residents	• Location: Michigan community-based hospital • Data Source: EMR • Study Population: Post-operative patients	o Non-opioid or adjunct pain medications • Patient Health Outcomes o Pain management	from pre- (7% in 2015, 17.3 in 2016, 23.5% in 2017) to post- (31.5% in 2018) intervention period • No emergency department or hospital readmissions for pain management were observed • Limitations: Decrease observed in pre-intervention period; pre-intervention included only twelve surgeons; no mention of the number of post-intervention number of surgeons
Zolin et al., 2019	• Adults: 7-day supply with an average of 30 MED per day; no more than 210 MED • Initial opioid prescription • Acute pain	• State Medical Board of Ohio • Date: August 2017	• Retrospective, serial cross-sectional • Time-frame: May 2015 – May 2018 (cross-sectional data collected yearly in May) • Location: Level 1 trauma center • Data Source: Trauma Registry • Study Population: Minimally injured adult trauma patients	• Prescribing patterns: o Opioid prescription characteristics o Non-opioid or adjunct pain medications • Patient Health Outcomes: o Pain management	• Overall decrease in opioid prescription frequency and MED at discharge • No change in most 30-day outcomes (30-day follow-up, phone call for pain, emergency department return for pain, clinical follow-up, days to earliest follow-up, post-discharge MED) • No significant change in the frequency or total of non-opioid or adjunct pain medication prescriptions at discharge • Limitations: Small sample size; limited study duration (30- day period for each of the four years); 30-day follow-up unavailable for half the cohort; authors note that many of these outcomes were decreasing prior to the Ohio

First author, Year[a]	Prescribing limit (length, quantity, dosage)[b]	Intervention description	Design	Outcome	Findings
					law and their study cannot demonstrate a statistically significant decrease that is directly attributable to this law

FDA, Food and Drug Administration; MME, morphine milligram equivalent; PDMP, prescription drug monitoring program; PMS, prescription monitoring system; EMR, electronic medical record; VPMS, Vermont prescription monitoring system; N, number; MED, morphine equivalent daily; CDC, Centers for Disease Control and Prevention; COT, chronic opioid analgesic therapy; mg, milligram; VA, Veterans Affairs; VHA, Veterans Health Administration; EMR, electronic medical record; OSI, Opioid Safety Initiative; NSAID, nonsteroidal anti-inflammatory drug; NV, Nevada; HI, Hawaii; MD, Maryland; NJ, New Jersey; NY, New York; DE, Delaware; IN, Indiana; KY, Kentucky; MN, Minnesota; OH, Ohio; VT, Vermont; CO, Colorado; DC, District of Columbia; FL, Florida; IA, Iowa; ID, Idaho; KS, Kansas; MI, Michigan; MS, Mississippi; MT, Montana; ND, North Dakota; NE, Nebraska; OK, Oklahoma; OR, Oregon; SD, South Dakota; WA, Washington; WY, Wyoming; DEA, Drug Enforcement Administration; ARCOS, Automation of Reports and Consolidated Orders System; MGE, morphine gram equivalent; EHR, electronic health record; UAMS, University of Arkansas for Medical Sciences; MEDD, morphine equivalent daily dose; CR, controlled-release; OB/GYN, obstetrics and gynecology; THA, total hip arthroplasty; TKA, total knee arthroplasty; No., number; ICD-9, International Classification of Diseases, 9th Revision; OME, oral morphine equivalent; MI-OPEN, Michigan Opioid Prescribing Engagement Network

[a] See references below

[b] Please see Appendix A, Table 1 and 2 for further details on the source and other components of the opioid analgesic prescribing limit

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Appendix B. Table 1. Methods: Updated Literature Review Conducted by FDA Covering May 2018 to November 2019

Criteria used for updated literature review covering May 2018 to November 2019	
Inclusion	Full-text, peer-reviewed observational epidemiologic published articles evaluating federal or state laws, regulations, guidelines, or policies on prescription opioid analgesic limits or policies based on federal or state laws, regulations, guidelines, or policies.
Exclusion	Studies conducted on populations outside of the United States, published in languages other than English, conference abstracts, non-peer-reviewed literature
Time period	May 2018 to November 2019 Note: this time period was selected to cover the end of the time period from the previous search (May 2018) to the month when analysis was started for this report (November 2019)
Databases	PubMed, Embase, Web of Science
Search string (PubMed)	((((((((((((opioid[tw] OR opioids[tw] OR analgesic[tw] OR analgesics[tw] OR opiate[tw] OR opiates[tw] OR opioid[majr])))) AND ((opioid[ti] OR opioids[ti] OR analgesic[ti] OR analgesics[ti] OR opiate[ti] OR opiates[ti] OR prescribe[ti] OR prescribing[ti] OR prescription[ti] OR prescriptions[ti] OR “prescribing limits”[ti] OR “prescription drug monitoring program”[ti] OR “prescription drug monitoring programs”[ti] or PDMP[ti])))) AND ((opioid[tw] OR opioids[tw] OR analgesic[tw] OR analgesics[tw] OR opiate[tw] OR opiates[tw])))) AND ((pill[tw] OR pills[tw] OR dose[tw] OR doses[tw] OR dosing[tw] OR dosage[tw] OR tablet[tw] OR tablets[tw] OR day[tw] OR days[tw] OR unit[tw] OR units[tw] OR MME[tw] OR MED[tw] OR “order set”[tw] OR “milligram morphine equivalent”[tw] OR “morphine equivalent dosing”[tw] OR distribut*[tw] OR dispense*[tw] OR dispensing[tw] OR supply[tw] OR supplied[tw] OR supplies[tw] OR supplying[tw] OR prescribe*[tw] OR prescribing[tw] OR prescription[tw] OR prescriptions[tw] OR "administration and dosage"[tw] OR "prevention and control"[tw] OR “pain score”[tw] OR “pain scores”[tw] OR “pain relief”[tw] OR “pain control”[tw] OR “patient satisfaction”[tw] OR satisfaction[tw] OR “opioid-related death”[tw] OR “opioid related death”[tw] OR “opioid poisoning”[tw] OR overdose[tw] OR refill[tw] OR refills[tw] OR misuse[tw] OR “drug misuse”[tw] OR abuse[tw] OR “drug abuse”[tw] OR “non-medical use”[tw] OR “non medical use”[tw] OR addiction[tw] OR dependence[tw] OR “substance use disorder”[tw] OR SUD[tw] OR “opioid use disorder”[tw] OR OUD[tw] OR “overdose death”[tw] OR “opioid overdose death”[tw] OR “overdose related hospitalization”[tw] OR “overdose reversal”[tw] OR “opioid overdose reversal”[tw] OR withdrawal[tw] OR “non-fatal overdose”[tw] OR “non fatal overdose”[tw] OR diversion[tw] OR “drug diversion”[tw] OR poisoning[tw] OR mortality[tw] OR death[tw] OR suicide[tw] OR “extra-medical”[tw] OR “unintended misuse”[tw] OR recreational[tw] OR “adverse effects”[tw] OR “adverse effect”[tw] OR “unintended consequences”[tw] OR “unintended consequence”[tw] OR “patient harm”[tw] OR “patient harms”[tw] OR “negative health outcomes”[tw] OR “negative health outcome”[tw] OR “pain management”[tw] OR “patient pain management”[tw] OR function[tw] OR “lifestyle change”[tw] OR “lifestyle changes”[tw] OR disability[tw] OR “activities of daily living”[tw] OR ADLs[tw] OR fatality[tw] OR fatalities[tw] OR functionality[tw] OR “disability-adjusted life year”[tw] OR “disability-adjusted life years”[tw] OR DALY[tw] OR DALYS[tw] OR “quality-adjusted life year”[tw] OR “quality-adjusted life years”[tw] OR QALY[tw] OR QALYs[tw] OR “health-adjusted life year”[tw] OR “health-adjusted life years”[tw] OR HALY[tw] OR HALYs[tw] OR “prescription opioid overdose”[tw] OR “illicit opioid overdose”[tw] OR “heroin overdose”[tw] OR “fentanyl overdose”[tw] OR decompensation[tw] OR depression[tw] OR anxiety[tw] OR “self-harm”[tw] OR “self harm”[tw] OR “self-poisoning”[tw] OR “self poisoning”[tw] OR “self-injury”[tw] OR “self injury”[tw] OR “post-traumatic

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mouflons[tw] OR ovis[tw] OR goats[tw] OR goat[tw] OR capra[tw] OR capras[tw] OR rupicapra[tw] OR chamois[tw] OR haplorhini[tw] OR monkey[tw] OR monkeys[tw] OR anthropoidea[tw] OR anthropoids[tw] OR saguinus[tw] OR tamarin[tw] OR tamarins[tw] OR leontopithecus[tw] OR hominidae[tw] OR ape[tw] OR apes[tw] OR pan[tw] OR paniscus[tw] OR "pan paniscus"[tw] OR bonobo[tw] OR bonobos[tw] OR troglodytes[tw] OR "pan troglodytes"[tw] OR gibbon[tw] OR gibbons[tw] OR siamang[tw] OR siamangs[tw] OR nomascus[tw] OR symphalangus[tw] OR chimpanzee[tw] OR chimpanzees[tw] OR prosimians[tw] OR "bush baby"[tw] OR prosimian[tw] OR "bush babies"[tw] OR galagos[tw] OR galago[tw] OR pongidae[tw] OR gorilla[tw] OR gorillas[tw] OR pongo[tw] OR pygmaeus[tw] OR "pongo pygmaeus"[tw] OR orangutans[tw] OR pygmaeus[tw] OR lemur[tw] OR lemurs[tw] OR lemuridae[tw] OR horse[tw] OR horses[tw] OR pongo[tw] OR equus[tw] OR cow[tw] OR calf[tw] OR bull[tw] OR chicken[tw] OR chickens[tw] OR gallus[tw] OR quail[tw] OR bird[tw] OR birds[tw] OR quails[tw] OR poultry[tw] OR poultries[tw] OR fowl[tw] OR fowls[tw] OR reptile[tw] OR reptilia[tw] OR reptiles[tw] OR snakes[tw] OR snake[tw] OR lizard[tw] OR lizards[tw] OR alligator[tw] OR alligators[tw] OR crocodile[tw] OR crocodiles[tw] OR turtle[tw] OR turtles[tw] OR amphibian[tw] OR amphibians[tw] OR amphibia[tw] OR frog[tw] OR frogs[tw] OR bombina[tw] OR salientia[tw] OR toad[tw] OR toads[tw] OR "epidalea calamita"[tw] OR salamander[tw] OR salamanders[tw] OR eel[tw] OR eels[tw] OR fish[tw] OR fishes[tw] OR pisces[tw] OR catfish[tw] OR catfishes[tw] OR siluriformes[tw] OR arius[tw] OR heteropneustes[tw] OR sheatfish[tw] OR perch[tw] OR perches[tw] OR percidae[tw] OR perca[tw] OR trout[tw] OR trouts[tw] OR char[tw] OR chars[tw] OR salvelinus[tw] OR "fathead minnow"[tw] OR minnow[tw] OR cyprinidae[tw] OR carps[tw] OR carp[tw] OR zebrafish[tw] OR zebrafishes[tw] OR goldfish[tw] OR goldfishes[tw] OR guppy[tw] OR guppies[tw] OR chub[tw] OR chubs[tw] OR tinca[tw] OR barbels[tw] OR barbus[tw] OR pimephales[tw] OR promelas[tw] OR "poecilia reticulata"[tw] OR mullet[tw] OR mullets[tw] OR seahorse[tw] OR seahorses[tw] OR mugil curema[tw] OR "atlantic cod"[tw] OR shark[tw] OR sharks[tw] OR catshark[tw] OR anguilla[tw] OR salmonid[tw] OR salmonids[tw] OR whitefish[tw] OR whitefishes[tw] OR salmon[tw] OR salmons[tw] OR sole[tw] OR solea[tw] OR "sea lamprey"[tw] OR lamprey[tw] OR lampreys[tw] OR pumpkinseed[tw] OR sunfish[tw] OR sunfishes[tw] OR tilapia[tw] OR

	tilapias[tw] OR turbot[tw] OR turbots[tw] OR flatfish[tw] OR flatfishes[tw] OR sciuridae[tw] OR squirrel[tw] OR squirrels[tw] OR chipmunk[tw] OR chipmunks[tw] OR suslik[tw] OR susliks[tw] OR vole[tw] OR voles[tw] OR lemming[tw] OR lemmings[tw] OR muskrat[tw] OR muskrats[tw] OR lemmus[tw] OR otter[tw] OR otters[tw] OR marten[tw] OR martens[tw] OR martes[tw] OR weasel[tw] OR badger[tw] OR badgers[tw] OR ermine[tw] OR mink[tw] OR minks[tw] OR sable[tw] OR sables[tw] OR gulo[tw] OR gulos[tw] OR wolverine[tw] OR wolverines[tw] OR minks[tw] OR mustela[tw] OR llama[tw] OR llamas[tw] OR alpaca[tw] OR alpacas[tw] OR camelid[tw] OR camelids[tw] OR guanaco[tw] OR guanacos[tw] OR chiroptera[tw] OR chiropteras[tw] OR bat[tw] OR bats[tw] OR fox[tw] OR foxes[tw] OR iguana[tw] OR iguanas[tw] OR "xenopus laevis"[tw] OR parakeet[tw] OR parakeets[tw] OR parrot[tw] OR parrots[tw] OR donkey[tw] OR donkeys[tw] OR mule[tw] OR mules[tw] OR zebra[tw] OR zebras[tw] OR shrew[tw] OR shrews[tw] OR bison[tw] OR bisons[tw] OR buffalo[tw] OR buffaloes[tw] OR deer[tw] OR deers[tw] OR bear[tw] OR bears[tw] OR panda[tw] OR pandas[tw] OR "wild hog"[tw] OR "wild boar"[tw] OR fitchew[tw] OR fitch[tw] OR beaver[tw] OR beavers[tw] OR jerboa[tw] OR jerboas[tw] OR capybara[tw] OR capybaras[tw])))) AND “2009/01/01”[Date - Entrez] : “2019/11/14”[Date – Entrez]) AND English[lang])
Search string (Embase)	('opioid'/exp/mj OR opioids:ti,ab OR 'opiate'/exp/mj OR opiates:ti,ab OR analgesic:ti,ab OR analgesics:ti,ab) AND (opioid:ti OR opioids:ti OR analgesic:ti OR analgesics:ti OR opiate:ti OR opiates:ti OR prescribe:ti OR prescribing:ti OR prescription:ti OR prescriptions:ti OR 'prescribing limits':ti OR 'prescription drug monitoring program':ti OR 'prescription drug monitoring programs':ti OR pdmp:ti) AND (pill:ti,ab OR pills:ti,ab OR dose:ti,ab OR doses:ti,ab OR dosing:ti,ab OR dosage:ti,ab OR tablet:ti,ab OR tablets:ti,ab OR day:ti,ab OR days:ti,ab OR unit:ti,ab OR units:ti,ab OR mme:ti,ab OR med:ti,ab OR 'order set':ti,ab OR 'milligram morphine equivalent':ti,ab OR 'morphine equivalent dosing':ti,ab OR distribute:ti,ab OR distributed:ti,ab OR distributes:ti,ab OR distribution:ti,ab OR dispense:ti,ab OR dispensed:ti,ab OR dispenses:ti,ab OR dispensing:ti,ab OR supply:ti,ab OR supplied:ti,ab OR supplies:ti,ab OR supplying:ti,ab OR prescribe:ti,ab OR prescribed:ti,ab OR prescribes:ti,ab OR prescribing:ti,ab OR prescription:ti,ab OR prescriptions:ti,ab OR 'administration and dosage':ti,ab OR 'prevention and control':ti,ab OR 'pain score':ti,ab OR 'pain scores':ti,ab OR 'pain relief':ti,ab OR 'pain control':ti,ab OR 'patient satisfaction':ti,ab OR satisfaction:ti,ab OR 'opioid-related death':ti,ab OR 'opioid related death':ti,ab OR 'opioid poisoning':ti,ab OR overdose:ti,ab OR refill:ti,ab OR refills:ti,ab OR misuse:ti,ab OR 'drug misuse':ti,ab OR abuse:ti,ab OR 'drug abuse':ti,ab OR 'non-medical use':ti,ab OR 'non medical use':ti,ab OR addiction:ti,ab OR dependence:ti,ab OR 'substance use disorder':ti,ab OR sud:ti,ab OR 'opioid use disorder':ti,ab OR oud:ti,ab OR 'overdose death':ti,ab OR 'opioid overdose death':ti,ab OR 'overdose related hospitalization':ti,ab OR 'overdose reversal':ti,ab OR 'opioid overdose reversal':ti,ab OR withdrawal:ti,ab OR 'non-fatal overdose':ti,ab OR 'non fatal overdose':ti,ab OR diversion:ti,ab OR 'drug diversion':ti,ab OR poisoning:ti,ab OR mortality:ti,ab OR death:ti,ab OR suicide:ti,ab OR 'extra-medical':ti,ab OR 'unintended misuse':ti,ab OR recreational:ti,ab OR 'adverse effects':ti,ab OR 'adverse effect':ti,ab OR 'unintended consequences':ti,ab OR 'unintended consequence':ti,ab OR 'patient harm':ti,ab OR 'patient harms':ti,ab OR 'negative health outcomes':ti,ab OR 'negative health outcome':ti,ab OR 'pain management':ti,ab OR 'patient pain management':ti,ab OR function:ti,ab OR 'lifestyle change':ti,ab OR 'lifestyle changes':ti,ab OR disability:ti,ab OR 'activities of daily living':ti,ab OR adls:ti,ab OR fatality:ti,ab OR fatalities:ti,ab OR functionality:ti,ab OR 'disability-adjusted life year':ti,ab OR 'disability-adjusted life years':ti,ab OR daly:ti,ab OR dalys:ti,ab OR 'quality-adjusted life year':ti,ab OR 'quality-adjusted life years':ti,ab OR qaly:ti,ab OR qalys:ti,ab OR 'health-adjusted life year':ti,ab OR 'health-adjusted life years':ti,ab OR haly:ti,ab OR halys:ti,ab OR 'prescription opioid overdose':ti,ab OR 'illicit opioid overdose':ti,ab OR 'heroin overdose':ti,ab OR 'fentanyl overdose':ti,ab OR decompensation:ti,ab OR depression:ti,ab OR anxiety:ti,ab OR 'self-harm':ti,ab OR 'self harm':ti,ab OR 'self-poisoning':ti,ab OR 'self poisoning':ti,ab OR 'self-injury':ti,ab OR 'self injury':ti,ab OR 'post-traumatic stress disorder':ti,ab OR 'posttraumatic stress disorder':ti,ab OR ptsd:ti,ab OR 'psychiatric comorbidity':ti,ab OR 'psychiatric comorbidities':ti,ab OR 'mental illness':ti,ab OR 'mental health condition':ti,ab OR 'mental health conditions':ti,ab OR 'prescriber burden':ti,ab OR 'burden for prescribers':ti,ab OR 'prescriber satisfaction':ti,ab OR 'prescribers satisfaction':ti,ab OR 'prescriber practice':ti,ab OR 'prescriber attitudes':ti,ab OR 'prescribers attitudes':ti,ab OR 'prescriber beliefs':ti,ab OR 'prescribers beliefs':ti,ab OR 'prescriber preference':ti,ab OR 'prescribers preference':ti,ab OR 'prescriber preferences':ti,ab OR 'prescribers preferences':ti,ab OR 'prescriber adoption':ti,ab OR 'survey of prescriber':ti,ab OR 'survey of prescribers':ti,ab OR 'prescriber feedback':ti,ab OR 'access to opioids':ti,ab OR 'patient access':ti,ab OR 'travel expenses':ti,ab OR 'impact on travel':ti,ab OR 'access to care':ti,ab OR 'access to treatment':ti,ab OR 'patient burden':ti,ab OR 'cost of care':ti,ab

	OR 'costs of care':ti,ab OR 'doctor shopping':ti,ab OR 'doctor-shopping':ti,ab OR 'pharmacy shopping':ti,ab OR 'pharmacy-shopping':ti,ab OR 'drug seeking':ti,ab OR 'drug-seeking':ti,ab OR 'doctor pharmacy shopping':ti,ab OR 'doctor-pharmacy shopping':ti,ab OR 'doctor and pharmacy shopping':ti,ab OR dps:ti,ab OR 'opioid substitution':ti,ab OR nonmedical:ti,ab OR heroin:ti,ab OR fentanyl:ti,ab OR 'illicit substance':ti,ab OR kratom:ti,ab OR loperamide:ti,ab OR 'transition to illicit':ti,ab OR stimulants:ti,ab OR methamphetamine:ti,ab OR cocaine:ti,ab OR cannabis:ti,ab OR marijuana:ti,ab OR cannabinoid:ti,ab OR cbd:ti,ab OR 'medication assisted treatment':ti,ab OR mat:ti,ab OR 'medication-assisted treatment':ti,ab OR 'opioid substitution therapy':ti,ab OR ost:ti,ab OR 'opioid-substitution therapy':ti,ab OR 'methadone maintenance treatment':ti,ab OR mmt:ti,ab OR 'methadone-maintenance treatment':ti,ab OR 'x waiver':ti,ab OR waiver:ti,ab OR 'x-waiver':ti,ab OR buprenorphine:ti,ab OR suboxone:ti,ab OR 'buprenorphine-naloxone':ti,ab OR subutex:ti,ab OR sublocade:ti,ab OR zubsolv:ti,ab OR bunavail:ti,ab OR cassipa:ti,ab OR methadone:ti,ab OR methadose:ti,ab OR dolophine:ti,ab OR 'opioid agonist':ti,ab OR 'opioid agonist treatment':ti,ab OR naloxone:ti,ab OR narcan:ti,ab OR evzio:ti,ab OR naltrexone:ti,ab OR vivitrol:ti,ab OR 'opioid antagonist':ti,ab OR 'opioid antagonists':ti,ab OR 'sedative hypnotic':ti,ab OR 'sedative-hypnotic':ti,ab OR 'sedative/hypnotic':ti,ab OR 'sedative hypnotics':ti,ab OR 'sedative-hypnotics':ti,ab OR 'sedative/hypnotics':ti,ab OR benzodiazepine:ti,ab OR benzodiazepines:ti,ab OR alprazolam:ti,ab OR xanax:ti,ab OR chlordiazepoxide:ti,ab OR librium:ti,ab OR clobazam:ti,ab OR onfi:ti,ab OR sympazan:ti,ab OR clonazepam:ti,ab OR klonopin:ti,ab OR clorazepate:ti,ab OR tranxene:ti,ab OR diazepam:ti,ab OR valium:ti,ab OR diastat:ti,ab OR estazolam:ti,ab OR prosom:ti,ab OR flurazepam:ti,ab OR lorazepam:ti,ab OR ativan:ti,ab OR midazolam:ti,ab OR versed:ti,ab OR oxazepam:ti,ab OR quazepam:ti,ab OR doral:ti,ab OR temazepam:ti,ab OR restoril:ti,ab OR triazolam:ti,ab OR halcion:ti,ab OR 'z-drug':ti,ab OR 'z drug':ti,ab OR 'z-drugs':ti,ab OR 'z drugs':ti,ab OR eszopiclone:ti,ab OR lunesta:ti,ab OR zaleplon:ti,ab OR sonata:ti,ab OR zolpidem:ti,ab OR ambien:ti,ab OR edluar:ti,ab OR intermezzo:ti,ab OR zolpimist:ti,ab OR bupropion:ti,ab OR aplenzin:ti,ab OR wellbutrin:ti,ab OR forfivo:ti,ab OR zyban:ti,ab OR 'cns depressant':ti,ab OR 'cns depressants':ti,ab OR 'central nervous system depressant':ti,ab OR acetaminophen:ti,ab OR apap:ti,ab OR tylenol:ti,ab OR 'nonsteroidal anti-inflammatory drugs':ti,ab OR nsaids:ti,ab OR 'nonsteroidal anti-inflammatory drug':ti,ab OR nsaid:ti,ab OR ibuprofen:ti,ab OR advil:ti,ab OR motrin:ti,ab OR naproxen:ti,ab OR aleve:ti,ab OR naprosyn:ti,ab OR aspirin:ti,ab OR asa:ti,ab OR 'cox-2 inhibitor':ti,ab OR 'cox-2 inhibitors':ti,ab OR 'cox-ii inhibitor':ti,ab OR 'cox-ii inhibitors':ti,ab OR celebrex:ti,ab OR celecoxib:ti,ab OR gabapentinoid:ti,ab OR gabapentinoids:ti,ab OR gabapentin:ti,ab OR neurontin:ti,ab OR gralise:ti,ab OR horizant:ti,ab OR pregabalin:ti,ab OR lyrica:ti,ab OR 'muscle relaxant':ti,ab OR 'muscle relaxants':ti,ab OR carisoprodol:ti,ab OR soma:ti,ab OR cyclobenzaprine:ti,ab OR flexeril:ti,ab OR amrix:ti,ab OR fexmid:ti,ab OR 'selective serotonin reuptake inhibitor':ti,ab OR 'selective serotonin reuptake inhibitors':ti,ab OR ssri:ti,ab OR ssris:ti,ab OR citalopram:ti,ab OR escitalopram:ti,ab OR fluoxetine:ti,ab OR fluvoxamine:ti,ab OR paroxetine:ti,ab OR sertraline:ti,ab OR vilazodone:ti,ab OR 'serotonin-norepinephrine reuptake inhibitor':ti,ab OR 'serotonin-norepinephrine reuptake inhibitors':ti,ab OR 'selective serotonin-norepinephrine reuptake inhibitor':ti,ab OR 'selective serotonin-norepinephrine reuptake inhibitors':ti,ab OR snri:ti,ab OR snris:ti,ab OR ssnri:ti,ab OR ssnris:ti,ab OR desvenlafaxine:ti,ab OR duloxetine:ti,ab OR levomilnacipran:ti,ab OR milnacipran:ti,ab OR venlafaxine:ti,ab OR 'physical therapy':ti,ab OR massage:ti,ab OR acupuncture:ti,ab OR 'alternative treatments':ti,ab OR 'alternative therapies':ti,ab OR 'cognitive behavioral therapy':ti,ab OR cbt:ti,ab OR 'opioid-sparing':ti,ab OR 'opioid sparing':ti,ab OR deprescribing:ti,ab OR 'dose reduction':ti,ab OR 'opioid replacement':ti,ab OR 'opioid augmentation':ti,ab OR tapering:ti,ab OR flagging:ti,ab OR 'mitigate burden':ti,ab OR 'minimize burden':ti,ab OR 'reduce burden':ti,ab OR burden:ti,ab OR 'harm reduction':ti,ab) AND (limit:ti,ab OR limits:ti,ab OR limited:ti,ab OR limiting:ti,ab OR reduce:ti,ab OR reduced:ti,ab OR reduces:ti,ab OR reducing:ti,ab OR reduction:ti,ab OR reductions:ti,ab OR restrict:ti,ab OR restricted:ti,ab OR restricts:ti,ab OR restriction:ti,ab OR restrictions:ti,ab OR decrease:ti,ab OR decreased:ti,ab OR decreases:ti,ab OR decreasing:ti,ab OR diminish:ti,ab OR diminished:ti,ab OR diminishing:ti,ab OR taper:ti,ab OR tapering:ti,ab OR tapered:ti,ab OR cutoff:ti,ab OR 'cut-off':ti,ab OR cutoffs:ti,ab OR 'cut-offs':ti,ab) AND (evaluate:ti,ab OR evaluates:ti,ab OR evaluation:ti,ab OR evaluations:ti,ab OR evaluated:ti,ab OR examine:ti,ab OR examines:ti,ab OR examined:ti,ab OR analyze:ti,ab OR analyzed:ti,ab OR analysis:ti,ab OR analyses:ti,ab OR assess:ti,ab OR assessed:ti,ab OR assessment:ti,ab OR appraise:ti,ab OR appraised:ti,ab OR appraises:ti,ab OR investigate:ti,ab OR investigated:ti,ab OR investigates:ti,ab OR investigation:ti,ab OR investigations:ti,ab OR compare:ti,ab OR compares:ti,ab OR compared:ti,ab OR comparing:ti,ab OR comparison:ti,ab OR comparisons:ti,ab OR comparative:ti,ab OR 'pre-implementation':ti,ab OR 'post-implementation':ti,ab OR 'pre-intervention':ti,ab OR 'post-intervention':ti,ab OR 'pre-post':ti,ab OR 'interrupted time-series':ti,ab OR 'interrupted time series':ti,ab OR impact:ti,ab) AND (policy:ti,ab OR policies:ti,ab OR

	regulation:ti,ab OR regulations:ti,ab OR state:ti,ab OR states:ti,ab OR guideline:ti,ab OR guidelines:ti,ab OR guidance:ti,ab OR guidances:ti,ab OR protocol:ti,ab OR protocols:ti,ab OR intervention:ti,ab OR law:ti,ab OR pdmp:ti,ab OR 'prescription drug monitoring program':ti,ab OR 'prescription drug monitoring programs':ti,ab OR cdc:ti,ab OR evaluate*:ti,ab OR evaluation:ti,ab OR evaluated:ti,ab OR rule:ti,ab OR rules:ti,ab OR 'opioid prescribing guideline':ti,ab OR 'opioid prescribing guidelines':ti,ab OR 'electronic prescribing':ti,ab OR 'e-prescribing':ti,ab OR 'e prescribing':ti,ab OR eprescribing:ti,ab OR 'e-prescribe':ti,ab OR 'e-rx':ti,ab OR erx:ti,ab OR telemedicine:ti,ab OR telehealth:ti,ab OR 'remote medicine':ti,ab) NOT (cell:ti,ab OR 'cell line':ti,ab OR cellular:ti,ab OR tissue:ti,ab OR 'in vitro':ti,ab OR spectroscopic:ti,ab OR spectrometer:ti,ab OR spectrophotometry:ti,ab OR 'transformation products':ti,ab OR synthesized:ti,ab OR 'gene variants':ti,ab OR plant:ti,ab) NOT ((animals:ti,ab OR animal:ti,ab OR 'pogona vitticeps':ti,ab OR mice:ti,ab OR mus:ti,ab OR mouse:ti,ab OR murine:ti,ab OR woodmouse:ti,ab OR rats:ti,ab OR rat:ti,ab OR murinae:ti,ab OR muridae:ti,ab OR cottonrat:ti,ab OR cottonrats:ti,ab OR hamster:ti,ab OR hamsters:ti,ab OR cricetinae:ti,ab OR rodentia:ti,ab OR rodent:ti,ab OR rodents:ti,ab OR pigs:ti,ab OR pig:ti,ab OR swine:ti,ab OR swines:ti,ab OR piglets:ti,ab OR piglet:ti,ab OR boar:ti,ab OR boars:ti,ab OR 'sus scrofa':ti,ab OR ferrets:ti,ab OR ferret:ti,ab OR polecat:ti,ab OR polecats:ti,ab OR 'mustela putorius':ti,ab OR 'guinea pigs':ti,ab OR 'guinea pig':ti,ab OR cavia:ti,ab OR callithrix:ti,ab OR marmoset:ti,ab OR marmosets:ti,ab OR cebuella:ti,ab OR hapale:ti,ab OR octodon:ti,ab OR chinchilla:ti,ab OR chinchillas:ti,ab OR gerbillinae:ti,ab OR gerbil:ti,ab OR gerbils:ti,ab OR jird:ti,ab OR jirds:ti,ab OR merione:ti,ab OR meriones:ti,ab OR rabbits:ti,ab OR rabbit:ti,ab OR hares:ti,ab OR hare:ti,ab OR diptera:ti,ab OR flies:ti,ab OR fly:ti,ab OR dipteral:ti,ab OR drosphila:ti,ab OR drosophilidae:ti,ab OR cats:ti,ab OR cat:ti,ab OR carus:ti,ab OR felis:ti,ab OR nematoda:ti,ab OR nematode:ti,ab OR nematodes:ti,ab OR sipunculida:ti,ab OR dogs:ti,ab OR dog:ti,ab OR canine:ti,ab OR canines:ti,ab OR canis:ti,ab OR sheep:ti,ab OR sheeps:ti,ab OR mouflon:ti,ab OR mouflons:ti,ab OR ovis:ti,ab OR goats:ti,ab OR goat:ti,ab OR capra:ti,ab OR capras:ti,ab OR rupicapra:ti,ab OR chamois:ti,ab OR haplorhini:ti,ab OR monkey:ti,ab OR monkeys:ti,ab OR anthropoidea:ti,ab OR anthropoids:ti,ab OR saguinus:ti,ab OR tamarin:ti,ab OR tamarins:ti,ab OR leontopithecus:ti,ab OR hominidae:ti,ab OR ape:ti,ab OR apes:ti,ab OR pan:ti,ab OR paniscus:ti,ab OR 'pan paniscus':ti,ab OR bonobo:ti,ab OR bonobos:ti,ab OR troglodytes:ti,ab OR 'pan troglodytes':ti,ab OR gibbon:ti,ab OR gibbons:ti,ab OR siamang:ti,ab OR siamangs:ti,ab OR nomascus:ti,ab OR symphalangus:ti,ab OR chimpanzee:ti,ab OR chimpanzees:ti,ab OR prosimians:ti,ab OR 'bush baby':ti,ab OR prosimian:ti,ab OR 'bush babies':ti,ab OR galagos:ti,ab OR galago:ti,ab OR pongidae:ti,ab OR gorilla:ti,ab OR gorillas:ti,ab OR 'pongo pygmaeus':ti,ab OR orangutans:ti,ab OR pygmaeus:ti,ab OR lemur:ti,ab OR lemurs:ti,ab OR lemuridae:ti,ab OR horse:ti,ab OR horses:ti,ab OR pongo:ti,ab OR equus:ti,ab OR cow:ti,ab OR calf:ti,ab OR bull:ti,ab OR chicken:ti,ab OR chickens:ti,ab OR gallus:ti,ab OR quail:ti,ab OR bird:ti,ab OR birds:ti,ab OR quails:ti,ab OR poultry:ti,ab OR poultries:ti,ab OR fowl:ti,ab OR fowls:ti,ab OR reptile:ti,ab OR reptilia:ti,ab OR reptiles:ti,ab OR snakes:ti,ab OR snake:ti,ab OR lizard:ti,ab OR lizards:ti,ab OR alligator:ti,ab OR alligators:ti,ab OR crocodile:ti,ab OR crocodiles:ti,ab OR turtle:ti,ab OR turtles:ti,ab OR amphibian:ti,ab OR amphibians:ti,ab OR amphibia:ti,ab OR frog:ti,ab OR frogs:ti,ab OR bombina:ti,ab OR salientia:ti,ab OR toad:ti,ab OR toads:ti,ab OR 'epidalea calamita':ti,ab OR salamander:ti,ab OR salamanders:ti,ab OR eel:ti,ab OR eels:ti,ab OR fish:ti,ab OR fishes:ti,ab OR pisces:ti,ab OR catfish:ti,ab OR catfishes:ti,ab OR siluriformes:ti,ab OR arius:ti,ab OR heteropneustes:ti,ab OR sheatfish:ti,ab OR perch:ti,ab OR perches:ti,ab OR percidae:ti,ab OR perca:ti,ab OR trout:ti,ab OR trouts:ti,ab OR char:ti,ab OR chars:ti,ab OR salvelinus:ti,ab OR 'fathead minnow':ti,ab OR minnow:ti,ab OR cyprinidae:ti,ab OR carps:ti,ab OR carp:ti,ab OR zebrafish:ti,ab OR zebrafishes:ti,ab OR goldfish:ti,ab OR goldfishes:ti,ab OR guppy:ti,ab OR guppies:ti,ab OR chub:ti,ab OR chubs:ti,ab OR tinca:ti,ab OR barbels:ti,ab OR barbus:ti,ab OR pimephales:ti,ab OR promelas:ti,ab OR 'poecilia reticulata':ti,ab OR mullet:ti,ab OR mullets:ti,ab OR seahorse:ti,ab OR seahorses:ti,ab OR mugil) AND curema:ti,ab OR 'atlantic cod':ti,ab OR shark:ti,ab OR sharks:ti,ab OR catshark:ti,ab OR anguilla:ti,ab OR salmonid:ti,ab OR salmonids:ti,ab OR whitefish:ti,ab OR whitefishes:ti,ab OR salmon:ti,ab OR salmons:ti,ab OR sole:ti,ab OR solea:ti,ab OR 'sea lamprey':ti,ab OR lamprey:ti,ab OR lampreys:ti,ab OR pumpkinseed:ti,ab OR sunfish:ti,ab OR sunfishes:ti,ab OR tilapia:ti,ab OR tilapias:ti,ab OR turbot:ti,ab OR turbots:ti,ab OR flatfish:ti,ab OR flatfishes:ti,ab OR sciuridae:ti,ab OR squirrel:ti,ab OR squirrels:ti,ab OR chipmunk:ti,ab OR chipmunks:ti,ab OR suslik:ti,ab OR susliks:ti,ab OR vole:ti,ab OR voles:ti,ab OR lemming:ti,ab OR lemmings:ti,ab OR muskrat:ti,ab OR muskrats:ti,ab OR lemmus:ti,ab OR otter:ti,ab OR otters:ti,ab OR marten:ti,ab OR martens:ti,ab OR martes:ti,ab OR weasel:ti,ab OR badger:ti,ab OR badgers:ti,ab OR ermine:ti,ab OR mink:ti,ab OR sable:ti,ab OR sables:ti,ab OR gulo:ti,ab OR gulos:ti,ab OR wolverine:ti,ab OR wolverines:ti,ab OR minks:ti,ab OR mustela:ti,ab OR llama:ti,ab OR llamas:ti,ab OR alpaca:ti,ab OR alpacas:ti,ab OR camelid:ti,ab OR camelids:ti,ab OR guanaco:ti,ab OR

	guanacos:ti,ab OR chiroptera:ti,ab OR chiropteras:ti,ab OR bat:ti,ab OR bats:ti,ab OR fox:ti,ab OR foxes:ti,ab OR iguana:ti,ab OR iguanas:ti,ab OR 'xenopus laevis':ti,ab OR parakeet:ti,ab OR parakeets:ti,ab OR parrot:ti,ab OR parrots:ti,ab OR donkey:ti,ab OR donkeys:ti,ab OR mule:ti,ab OR mules:ti,ab OR zebra:ti,ab OR zebras:ti,ab OR shrew:ti,ab OR shrews:ti,ab OR bison:ti,ab OR bisons:ti,ab OR buffalo:ti,ab OR buffaloes:ti,ab OR deer:ti,ab OR deers:ti,ab OR bear:ti,ab OR bears:ti,ab OR panda:ti,ab OR pandas:ti,ab OR 'wild hog':ti,ab OR 'wild boar':ti,ab OR fitchew:ti,ab OR fitch:ti,ab OR beaver:ti,ab OR beavers:ti,ab OR jerboa:ti,ab OR jerboas:ti,ab OR capybara:ti,ab OR capybaras:ti,ab) AND english:la AND [1-1-2009]/sd NOT [15-11-2019]/sd
Search string (Web of Science)	(TS=(opioid OR opioids OR opiate OR opiates OR analgesic OR analgesics) AND TI=(opioid OR opioids OR analgesic OR analgesics OR opiate OR opiates OR prescribe OR prescribing OR prescription OR “prescribing limits” OR “prescription drug monitoring program” OR “prescription drug monitoring programs” OR PDMP) AND TS=(pill OR pills OR dose OR doses OR dosing OR dosage OR tablet OR tablets OR day OR days OR unit OR units OR MME OR MED OR “order set” OR “milligram morphine equivalent” OR “morphine equivalent dosing” OR distribute OR distributed OR distributes OR distribution OR dispense OR dispensed OR dispenses OR dispensing OR supply OR supplied OR supplies OR supplying OR prescribe OR prescribed OR prescribes OR prescribing OR prescription OR prescriptions OR "administration and dosage" OR "prevention and control" OR “pain score” OR “pain scores” OR “pain relief” OR “pain control” OR “patient satisfaction” OR satisfaction OR “opioid-related death” OR “opioid related death” OR “opioid poisoning” OR overdose OR refill OR refills OR misuse OR “drug misuse” OR abuse OR “drug abuse” OR “non-medical use” OR “non medical use” OR addiction OR dependence OR “substance use disorder” OR SUD OR “opioid use disorder” OR OUD OR “overdose death” OR “opioid overdose death” OR “overdose related hospitalization” OR “overdose reversal” OR “opioid overdose reversal” OR withdrawal OR “non-fatal overdose” OR “non fatal overdose” OR diversion OR “drug diversion” OR poisoning OR mortality OR death OR suicide OR “extra-medical” OR “unintended misuse” OR recreational OR “adverse effects” OR “adverse effect” OR “unintended consequences” OR “unintended consequence” OR “patient harm” OR “patient harms” OR “negative health outcomes” OR “negative health outcome” OR “pain management” OR “patient pain management” OR function OR “lifestyle change” OR “lifestyle changes” OR disability OR “activities of daily living” OR ADLs OR fatality OR fatalities OR functionality OR “disability-adjusted life year” OR “disability-adjusted life years” OR DALY OR DALYS OR “quality-adjusted life year” OR “quality-adjusted life years” OR QALY OR QALYs OR “health-adjusted life year” OR “health-adjusted life years” OR HALY OR HALYs OR “prescription opioid overdose” OR “illicit opioid overdose” OR “heroin overdose” OR “fentanyl overdose” OR decompensation OR depression OR anxiety OR “self-harm” OR “self harm” OR “self-poisoning” OR “self poisoning” OR “self-injury” OR “self injury” OR “post-traumatic stress disorder” OR “posttraumatic stress disorder” OR PTSD OR “psychiatric comorbidity” OR “psychiatric comorbidities” OR “mental illness” OR “mental health condition” OR “mental health conditions” OR “prescriber burden” OR “burden for prescribers” OR “prescriber satisfaction” OR “prescribers’ satisfaction” OR “prescriber practice” OR “prescriber attitudes” OR “prescribers’ attitudes” OR “prescriber beliefs” OR “prescribers’ beliefs” OR “prescriber preference” OR “prescribers’ preference” OR “prescriber preferences” OR “prescribers’ preferences” OR “prescriber adoption” OR “survey of prescriber” OR “survey of prescribers” OR “survey of prescribers’” OR “prescriber feedback” OR “access to opioids” OR “patient access” OR “travel expenses” OR “impact on travel” OR “access to care” OR “access to treatment” OR “patient burden” OR “cost of care” OR “costs of care” OR “doctor shopping” OR “doctor-shopping” OR “pharmacy shopping” OR “pharmacy-shopping” OR “drug seeking” OR “drug-seeking” OR “doctor pharmacy shopping” OR “doctor-pharmacy shopping” OR “doctor and pharmacy shopping” OR DPS OR “opioid substitution” OR nonmedical OR heroin OR fentanyl OR “illicit substance” OR kratom OR loperamide OR “transition to illicit” OR stimulants OR methamphetamine OR cocaine OR cannabis OR marijuana OR cannabinoid OR CBD OR “Medication Assisted Treatment” OR MAT OR “medication-assisted treatment” OR “opioid substitution therapy” OR OST OR “opioid-substitution therapy” OR “methadone maintenance treatment” OR MMT OR “methadone-maintenance treatment” OR “X waiver” OR waiver OR “X-waiver” OR buprenorphine OR suboxone OR “buprenorphine-naloxone” OR Subutex OR Sublocade OR Zubsolv OR Bunavail OR Cassipa OR methadone OR Methadose OR Dolophine OR “opioid agonist” OR “opioid agonist treatment” OR naloxone OR Narcan OR Evzio OR naltrexone OR Vivitrol OR “opioid antagonist” OR “opioid antagonists” OR “sedative hypnotic” OR “sedative-hypnotic” OR “sedative/hypnotic” OR “sedative hypnotics” OR “sedative-hypnotics” OR “sedative/hypnotics” OR benzodiazepine OR benzodiazepines OR alprazolam OR Xanax OR chlordiazepoxide OR Librium OR clobazam OR Onfi OR Sympazan OR

	clonazepam OR Klonopin OR clorazepate OR Tranxene OR diazepam OR Valium OR Diastat OR estazolam OR Prosom OR flurazepam OR lorazepam OR Ativan OR midazolam OR Versed OR oxazepam OR quazepam OR Doral OR temazepam OR Restoril OR triazolam OR Halcion OR “z-drug” OR “z drug” OR “z-drugs” OR “z drugs” OR eszopiclone OR Lunesta OR zaleplon OR Sonata OR zolpidem OR Ambien OR Edluar OR Intermezzo OR Zolpimist OR bupropion OR Aplenzin OR Wellbutrin OR Forfivo OR Zyban OR “CNS depressant” OR “CNS depressants” OR “central nervous system depressant” OR Acetaminophen OR APAP OR Tylenol OR “nonsteroidal anti-inflammatory drugs” OR NSAIDs OR “nonsteroidal anti-inflammatory drug” OR NSAID OR ibuprofen OR Advil OR Motrin OR naproxen OR Aleve OR Naprosyn OR aspirin OR ASA OR “COX-2 inhibitor” OR “COX-2 inhibitors” OR “COX-II inhibitor” OR “COX-II inhibitors” OR Celebrex OR celecoxib OR gabapentinoid OR gabapentinoids OR gabapentin OR Neurontin OR Gralise OR Horizant OR pregabalin OR Lyrica OR “muscle relaxant” OR “muscle relaxants” OR carisoprodol OR Soma OR cyclobenzaprine OR Flexeril OR Amrix OR Fexmid OR “selective serotonin reuptake inhibitor” OR “selective serotonin reuptake inhibitors” OR SSRI OR SSRIs OR citalopram OR escitalopram OR fluoxetine OR fluvoxamine OR paroxetine OR sertraline OR vilazodone OR “serotonin-norepinephrine reuptake inhibitor” OR “serotonin-norepinephrine reuptake inhibitors” OR “selective serotonin-norepinephrine reuptake inhibitor” OR “selective serotonin-norepinephrine reuptake inhibitors” OR SNRI OR SNRIs OR SSNRI OR SSNRIs OR desvenlafaxine OR duloxetine OR levomilnacipran OR milnacipran OR venlafaxine OR “physical therapy” OR massage OR acupuncture OR “alternative treatments” OR “alternative therapies” OR “cognitive behavioral therapy” OR CBT OR “opioid-sparing” OR “opioid sparing” OR deprescribing OR “dose reduction” OR “opioid replacement” OR “opioid augmentation” OR tapering OR flagging OR “mitigate burden” OR “minimize burden” OR “reduce burden” OR burden OR “harm reduction”) AND TS=(limit OR limits OR limited OR limiting OR reduce OR reduced OR reduces OR reducing OR reduction OR reductions OR restrict OR restricted OR restricts OR restriction OR restrictions OR decrease OR decreased OR decreases OR decreasing OR diminish OR diminished OR diminishing OR taper OR tapering OR tapered OR cutoff OR “cut-off” OR cutoffs OR “cut-offs”) AND TS=(evaluate OR evaluates OR evaluation OR evaluations OR evaluated OR examine OR examines OR examined OR analyze OR analyzed OR analysis OR analyses OR assess OR assessed OR assessment OR appraise OR appraised OR appraises OR investigate OR investigated OR investigates OR investigation OR investigations OR compare OR compares OR compared OR comparing OR comparison OR comparisons OR comparative OR “pre-implementation” OR “post-implementation” OR “pre-intervention” OR “post-intervention” OR “pre-post” or “interrupted time-series” OR “interrupted time series” OR impact) AND TS=(policy OR policies OR regulation OR regulations OR state OR states OR guideline OR guidelines OR guidance OR guidances OR protocol OR protocols OR intervention OR law OR PDMP OR “prescription drug monitoring program” OR “prescription drug monitoring programs” OR CDC OR evaluate* OR evaluation OR evaluated OR rule OR rules OR “opioid prescribing guideline” OR “opioid prescribing guidelines” OR “electronic prescribing” OR “e-prescribing” OR “e prescribing” OR Eprescribing OR “e-prescribe” OR “e-Rx” OR eRx OR telemedicine OR Telehealth OR “remote medicine”) NOT TS=(cell OR "cell line" OR cellular OR tissue OR "in vitro" OR spectroscopic OR spectrometer OR spectrophotometry OR "transformation products" OR synthesized OR "gene variants" OR plant) NOT TS=(animals OR animal OR "Pogona vitticeps" OR mice OR mus OR mouse OR murine OR woodmouse OR rats OR rat OR murinae OR muridae OR cottonrat OR cottonrats OR hamster OR hamsters OR cricetinae OR rodentia OR rodent OR rodents OR pigs OR pig OR swine OR swines OR piglets OR piglet OR boar OR boars OR "sus scrofa" OR ferrets OR ferret OR polecat OR polecats OR "mustela putorius" OR "guinea pigs" OR "guinea pig" OR cavia OR callithrix OR marmoset OR marmosets OR cebuella OR hapale OR octodon OR chinchilla OR chinchillas OR gerbillinae OR gerbil OR gerbils OR jird OR jirds OR merione OR meriones OR rabbits OR rabbit OR hares OR hare OR diptera OR flies OR fly OR dipteral OR drosphila OR drosophilidae OR cats OR cat OR carus OR felis OR nematoda OR nematode OR nematoda OR nematode OR nematodes OR sipunculida OR dogs OR dog OR canine OR canines OR canis OR sheep OR sheeps OR mouflon OR mouflons OR ovis OR goats OR goat OR capra OR capras OR rupicapra OR chamois OR haplorhini OR monkey OR monkeys OR anthropoidea OR anthropoids OR saguinus OR tamarin OR tamarins OR leontopithecus OR hominidae OR ape OR apes OR pan OR paniscus OR "pan paniscus" OR bonobo OR bonobos OR troglodytes OR "pan troglodytes" OR gibbon OR gibbons OR siamang OR siamangs OR nomascus OR symphalangus OR chimpanzee OR chimpanzees OR prosimians OR "bush baby" OR prosimian OR "bush babies" OR galagos OR galago OR pongidae OR gorilla OR gorillas OR pongo OR pygmaeus OR "pongo pygmaeus" OR orangutans OR pygmaeus OR lemur OR lemurs OR lemuridae OR horse OR horses OR pongo OR equus OR cow OR calf OR bull OR chicken OR chickens OR gallus OR quail OR bird OR birds OR quails OR poultry OR poultries OR fowl OR fowls OR reptile OR reptilia OR reptiles OR

	snakes OR snake OR lizard OR lizards OR alligator OR alligators OR crocodile OR crocodiles OR turtle OR turtles OR amphibian OR amphibians OR amphibia OR frog OR frogs OR bombina OR salientia OR toad OR toads OR "epidalea calamita" OR salamander OR salamanders OR eel OR eels OR fish OR fishes OR pisces OR catfish OR catfishes OR siluriformes OR arius OR heteropneustes OR sheatfish OR perch OR perches OR percidae OR perca OR trout OR trouts OR char OR chars OR salvelinus OR "fathead minnow" OR minnow OR cyprinidae OR carps OR carp OR zebrafish OR zebrafishes OR goldfish OR goldfishes OR guppy OR guppies OR chub OR chubs OR tinca OR barbels OR barbus OR pimephales OR promelas OR "poecilia reticulata" OR mullet OR mullets OR seahorse OR seahorses OR mugil curema OR "atlantic cod" OR shark OR sharks OR catshark OR anguilla OR salmonid OR salmonids OR whitefish OR whitefishes OR salmon OR salmons OR sole OR solea OR "sea lamprey" OR lamprey OR lampreys OR pumpkinseed OR sunfish OR sunfishes OR tilapia OR tilapias OR turbot OR turbots OR flatfish OR flatfishes OR sciuridae OR squirrel OR squirrels OR chipmunk OR chipmunks OR suslik OR susliks OR vole OR voles OR lemming OR lemmings OR muskrat OR muskrats OR lemmus OR otter OR otters OR marten OR martens OR martes OR weasel OR badger OR badgers OR ermine OR mink OR minks OR sable OR sables OR gulo OR gulos OR wolverine OR wolverines OR minks OR mustela OR llama OR llamas OR alpaca OR alpacas OR camelid OR camelids OR guanaco OR guanacos OR chiroptera OR chiropteras OR bat OR bats OR fox OR foxes OR iguana OR iguanas OR "xenopus laevis" OR parakeet OR parakeets OR parrot OR parrots OR donkey OR donkeys OR mule OR mules OR zebra OR zebras OR shrew OR shrews OR bison OR bisons OR buffalo OR buffaloes OR deer OR deers OR bear OR bears OR panda OR pandas OR "wild hog" OR "wild boar" OR fitchew OR fitch OR beaver OR beavers OR jerboa OR jerboas OR capybara OR capybaras)) AND LANGUAGE: (English) Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan=2009-2019

Appendix C. Table 1. Ongoing Efforts to Implement and Evaluate Opioid Analgesic Prescribing Limits by Federal Agencies

Federal Agency	Project Description and Projected Completion
Agency for Healthcare Research Quality	Upcoming paper using MEPS data titled: "Chronic Pain, Public Policy, and the Dynamics of Prescription Opioid Use, 2014-2017." May evaluate changes in both the initiation of and persistence of opioid versus prescription non-opioid pain relievers, with results stratified by presence of conditions associated with chronic pain. Draft for internal AHRQ review expected in Spring 2020.
Centers for Disease Control and Prevention	Conducting research to examine how state laws limiting the duration of acute pain opioid prescriptions have affected dispensed initial opioid prescriptions. This work examines the impact of laws with limits of various lengths (i.e. ≤ 7 days and >7 days) on multiple potential changes in opioid prescribing including the duration of the prescriptions, quantity of pills prescribed, and daily and total MME.
Centers for Medicare & Medicaid Services	Under SUPPORT Act Section 1004 and Section 1927 of the Social Security Act, CMS has proposed to require Opioid Prospective Safety Edits on prescription days' supply, MME, tablet quantities, and early/duplicate refills, require retrospective reviews on opioid prescription characteristics and concurrent utilization of opioids and benzodiazepines and/or antipsychotics, and require programs to monitor for antipsychotic medication use in children and potential fraud or abuse of controlled substances. Drug Utilization Review surveys help trend what states are doing (prospectively/retrospectively/current programs) to help curb inappropriate prescribing and dispensing of medication, including opioids. Responses help to develop and implement means for states to have better oversight of their providers to comply with federal law. Outcomes to be evaluated include the incidence and/or prevalence of overdose related to prescription and/or illicit opioids, prevalence of opioid use disorders, medically appropriate use of and access to opioids, nonmedical use of opioids, resulting negative health outcomes such as suicide, increases in burden on providers and patients, and mitigation of such burden. Surveys sent to states and MCOs on April 1, 2020; results will be posted November 2020, and report to Congress by October 2021.
Centers for Medicare & Medicaid Services	Under Federal Regulation 42 CFR 423.153(c)(2), Medicare Part D sponsors are implementing soft and hard opioid safety edit thresholds (not prescribing limits) at the point-of-sale. Data have been collected for plan years 2017-2020 using prescription drug event and plan-reported data to evaluate the effect of opioid safety edits on the medically appropriate use of and access to opioids. Results are available in the Improving Drug Utilization Review Controls in Medicare Part D sections in the 2019 and 2020 Final Call Letters, and in multiple HPMS memos (Additional Guidance on Contract Year 2019 Formulary-Level Opioid Point-of-Sale Safety Edits (dated October 23, 2018), Frequently Asked Questions (FAQs) about Formulary-Level Opioid Point-of-Sale (POS) Safety Edits (dated May 13, 2019), and Contract Year (CY) 2020 Opioid Safety Edit Reminders and Recommendations (dated December 9, 2019)).
Food and Drug Administration	Funded a study to evaluate the effect of opioid tapering and/or discontinuation on patient outcomes, including suicidality and unintentional overdose. Expected study completion in 2022.
Multiple (National Institutes of Health, National Institute on Drug Abuse, Centers	Systematic literature review of published observational studies that evaluate the impact of the implementation of opioid analgesic prescribing guidelines containing a specific threshold of days' supply, dose, or tablet quantity, and other associated interventions intended to reduce opioid prescribing. Evaluated outcomes include but are not limited to: prescription characteristics (e.g., days' supply, dose, tablet counts), prescribing habits (e.g., number of prescriptions), patient-reported consumption, and patient-reported

Federal Agency	Project Description and Projected Completion
for Disease Control and Prevention, Food and Drug Administration)	outcomes (e.g., pain control, function, satisfaction, refills). Project will also focus on identifying gaps in the literature and provide recommendations for further research. Expected completion June 2021.
Indian Health Services	IHS Opioid Surveillance dashboard is in development. Includes thirteen measures focused on assessing prescribing indices to evaluate the impacts of Agency policies as well as state mandates. Outcomes to be evaluated may include the prevalence of opioid use disorders, prevalence of co-occurring disorders, and non-pharmacologic approaches to pain management. No estimated date for project completion.
National Institutes of Health, National Institute on Drug Abuse	Project by Johns Hopkins University (R01DA044987) aims to disentangle the independent effects of four types of state legislation (PDMP enrollment, mandatory PDMP queries, opioid prescribing limits, pill mill laws) on high-risk opioid prescribing and substitution of non-opioid pain treatments using qualitative interviews and claims data. Outcomes to be evaluated include substitution of non-opioid pain treatments among individuals diagnosed with non-cancer chronic pain. Study protocol published in Implementation Science in February 2018.
National Institutes of Health, National Institute on Drug Abuse	Project by Rutgers, The State University of New Jersey (R01DA047347) will evaluate the effects of New Jersey legislation (limits on opioid prescribing, use of pain management contracts, and expanded access to medication-assisted treatment for opioid use disorder) on overdose risk through analyses of large-scale Medicare data. Project completion expected January 21, 2023; results may be published after project completion.
National Institutes of Health, National Institute on Drug Abuse	Project by West Virginia University (R21DA049861) will examine, using qualitative and quantitative approaches in a de-adoption framework, the effect of West Virginia opioid prescribing limits (SB 273) on actual prescribing habits and availability of opioids in the state. Plan to evaluate the impact of state legislation on pain patient experiences and the prescribing practices and experiences of clinicians. Project completion expected August 21, 2021; results may be published after project completion.
National Institutes of Health, National Institute on Drug Abuse	Project by the RAND Corporation (R21DA045983) will analyze claims data to assess the ramifications of New York and Maine mandatory use of electronic prescriptions on overprescribing, "doctor-shopping," opioid misuse and overdose, as well as emergency department visits and inpatient hospitalizations. Plan to evaluate the impact of e-prescribing on incidence and/or prevalence of overdose related to prescription and/or illicit opioids. Project completion expected April 30, 2021; results may be published after project completion.
National Institutes of Health, National Institute on Drug Abuse	Project by the RAND Corporation (R01DA045055) will assess the impact of state policies across the country on overall opioid prescribing rates and appropriate/inappropriate prescribing, using Medicare claims for disabled beneficiaries and IQVIA data covering approximately 88% of prescriptions filled in the United States. Plan to evaluate how policies affect opioid prescription fills for historically underserved and high-risk populations. Project completion expected December 21, 2022; results may be published after project completion.
National Institutes of Health, National Institute on Drug Abuse	A project by Oregon Health & Science University (R01DA044284) will assess effects of an Oregon Medicaid policy (to reduce coverage of opioid medications for back pain) on back pain related clinical outcomes, as indicated by advanced imaging and/or need for surgery, overall healthcare service utilization and total health care spending for back-pain or opioid-related health care visits, prescription drugs, and non-pharmacologic services. Project completion expected May 31, 2023; results may be published after project completion.

MEPS, Medical Expenditure Panel Survey; AHRQ, Agency for Healthcare Research Quality; MME, morphine milligram equivalents; SUPPORT, Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment; CMS, Centers for Medicare and Medicaid Services; MCO, Managed Care Organization; CFR, Code of Federal Regulations; HPMS, Health Plan Management System; FAQs, frequently asked questions; POS, point-of-sale; CY, contract year; IHS, Indian Health Service; PDMP, prescription drug monitoring program; RAND, Research and Development; e-prescribing, electronic prescribing