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Evaluating opioid analgesic prescribing limits: A narrative review

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Abstract

Purpose: In response to the opioid crisis, opioid analgesic guidelines and prescribing limits have proliferated. The purpose of this narrative review is to examine evidence from studies evaluating the patient or public health impact of federal and state opioid analgesic prescribing guidelines and laws, describe gaps and challenges in current research, and highlight opportunities for improving future research.

Methods: We focused on evidence from a literature review covering 2013 through 2019. We identified 30 studies evaluating opioid analgesic thresholds based on federal policies and guidelines, state laws, and Medicaid state plans that attempt to influence the course of patient care at or when the limit is exceeded (e.g., prior authorization).

Results: Most studies evaluated changes in prescribing or dispensing patterns of opioid analgesics, largely finding decreases in prescribing after policy enactment. Fewer studies evaluated patient or public health outcomes beyond changes in prescribing and dispensing patterns; results were infrequently stratified by potentially important sociodemographic and clinical factors. No studies assessed the potential for adverse patient outcomes for which we have emerging evidence of harms.

Conclusions: We describe knowledge gaps and propose opportunities for future research to sufficiently assess the potential impact and unintended consequences of opioid analgesic prescribing laws, regulations, guidelines, and policies.

Plain Language Summary

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CONFLICT OF INTEREST

Dr. Compton reports long-term holdings in General Electric Company, 3M Companies and Pfizer, Incorporated, unrelated to the present work. Other authors have no competing interests to declare.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

Guidelines and prescribing limits on the use of opioids for treating pain (opioid analgesics) have increased in recent years. We identified 30 studies evaluating opioid analgesic limits based on federal policies and guidelines, state laws, and Medicaid state plans. Most studies evaluated changes in prescribing or dispensing patterns of opioid analgesics, mostly finding decreases in prescribing after the policy was started. Fewer studies evaluated patient or public health outcomes beyond changes in prescribing and dispensing patterns; results were infrequently reported separately by potentially important patient and clinical factors. No studies assessed the potential for patient harms for which we have early evidence. We describe knowledge gaps and propose opportunities for future research.

Keywords

opioid analgesic; prescribing limit

1 | INTRODUCTION

A root cause of the opioid crisis in the United States can be traced to increases in opioid analgesic (OA) prescribing that began in the mid-to-late 1990s. Between 1999 and 2010, the distribution of opioids in the United States increased four-fold, paralleled by a nearly four-fold increase in overdose deaths involving prescription opioids.[1] Increases in prescription opioid misuse and use disorder were also seen during this time.[2] In addition to the overall increase in the total number of opioid prescriptions and quantity of opioids prescribed, opioid prescribing changed, with opioids increasingly prescribed at higher doses, and concomitantly with benzodiazepines, now known risk factors for opioid overdose.[3-5] Risks of harms due to increased availability of opioids extended beyond patients prescribed opioids due to diversion of these medications for nonmedical use by others.[6] The opioid overdose crisis has rapidly shifted since 2010 from one driven by prescription opioid-involved overdose deaths to one driven by heroin and synthetic opioids such as illicit fentanyl, although prescription opioids continue to be involved in overdose deaths.[7,8]

In response to the risk of harms from opioid analgesic availability, an array of policy and clinical practice initiatives at multiple levels of the health system have been launched (Figure 1). At the federal level, a variety of agencies have implemented OA prescribing policies and guidelines. The Department of Veterans Affairs (VA) and Department of Defense (DoD) implemented OA prescribing limits starting in 2003, with updates to their Guideline in 2010 and 2017.[9] In March 2016, the Centers for Disease Control and Prevention (CDC) released its *Guideline for Prescribing Opioids for Chronic Pain* (CDC Guideline) for primary care clinicians treating adults with chronic pain.[10] Within their guideline on treating chronic pain were several recommendations for treating acute pain with OAs, including dose and duration thresholds. Other federal agencies, including the Bureau of Prisons, Centers for Medicare & Medicaid Services (CMS), and Indian Health Service have adopted components of the CDC Guideline as part of their recommendations for clinicians or as part of payment policies. At the state level, many states have enacted laws and regulations, and state Medicaid agencies have established guidelines intended to curb inappropriate OA prescribing (Table S1). Many prescribing limits at both federal and state levels provide professional judgment

exceptions or specific medical exceptions. The landscape is further complicated both by the multitude of other opioid policies implemented alongside prescribing limits (e.g., education and training requirements) and by myriad policies across levels of the health system (e.g., individual institution and insurance policies).

Reports in recent years have indicated unintended harm to patients resulting from forced OA tapers or abrupt discontinuation associated with OA dosage and duration thresholds, including serious withdrawal symptoms, worsening pain outcomes, psychological distress, transitions to illicit opioids, overdose, and suicide.[11-16] Thus, while policies to improve appropriate OA prescribing are a key component of the response to the U.S. opioid crisis, these policies must balance goals of reducing OA-related harms, maximizing patient benefit, and avoiding unintended consequences.

In this narrative review, we briefly describe results from our literature review of published studies evaluating federal policies and guidelines as well as state laws on OA prescribing limits. To highlight potential unintended harms of prescribing limits that need formal evaluation in future studies, we describe selected comments made by patients, family members, and experts during public federal meetings or online submissions. Finally, we describe current research gaps and areas for future research to better understand the patient and public health impact of OA prescribing limits.

2 | METHODS

For this narrative review, we focused on federal policies and guidelines, state laws, and Medicaid state plans that establish OA prescribing limits for acute and/or chronic use. We defined a prescribing limit as a threshold of OA length, quantity, or dosage that attempts to influence the course of patient care at or when the limit is exceeded (e.g., prior authorization, urine drug testing, and safety-edits).

We conducted two comprehensive literature reviews of peer-reviewed literature evaluating OA prescribing limits (Table S2). First, we examined articles from our previously published systematic review of peer-reviewed literature from 2013 to May 2018[17] that examined a wide variety of interventions that may affect OA prescribing. Second, because of the rapid accumulation of data and findings, we extended the earlier review by examining literature published from 2018 through November 2019, using search terms associated with opioids and prescribing limits in PubMed, Embase, and Web of Science (Table S3). We screened articles from both reviews to determine appropriateness for inclusion. We included studies that evaluated the impact (i.e., prescription characteristics or provider, patient, and public health outcomes) of federal policies and guidelines and state laws with a requirement or recommendation for limiting OA prescription length or number of days supplied, quantity of dosage units prescribed, or dose measured in morphine milligram equivalents (MME). We also included studies evaluating the impact of policies and guidelines implemented at other levels of care if it was clear that the intervention included components of federal or state limits and guidelines on length, quantity, or dose of OA prescriptions. For example, we included studies evaluating interventions that include length, quantity, or dose components

of the CDC Guideline since components of this guideline have been adopted throughout the U.S. healthcare system.

2.1 | Role of the funding source

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3 | RESULTS

We identified 30 studies that evaluated the impact of federal and state OA prescribing limits on at least one of the following outcomes: prescribing patterns, patient health outcomes, patient and/or provider burden or satisfaction, or other patient or public health outcomes (Table S2). Nearly all studies (n = 29) evaluated changes in OA prescribing and/or dispensing before and after implementation of the prescribing limit (Figure 2). Most studies used insurance claims, PDMP dispensing data, or prescribing data. Most studies indicated that OA prescribing limits resulted in some reduction in OA prescribing and dispensing, often reported as reductions in MME.

Patient and public health outcomes, evaluated in less than half of the studies, included changes in patient-reported pain scores or quality of life,[18,19] unplanned access to additional medical care for pain or related issues,[20-25] concomitant opioid and benzodiazepine prescribing,[26-30] prescription opioid or heroin overdose hospitalizations or trends,[26,31,32] transition from acute to prolonged use after surgical procedures,[18,33-37] all-cause mortality,[18] patient retention rate,[28] and changes in number of prescribers or pharmacies.[26,31,38] One study also evaluated prescriber utilization of an electronic medical record (EMR) alert tool designed to facilitate compliance with OA prescribing limits.[21] No studies were identified that evaluated mental health changes, use of illicit substances, missed care, diversion, patient burden related to prescribing limits, or provider burden or satisfaction associated with prescribing limits.

4 | DISCUSSION

We identified important gaps and challenges to understanding the full impact of OA prescribing limits on patient or population health. The main gaps and challenges we identified are: 1) insufficient evaluation of patient outcomes, public health outcomes, and unintended consequences; 2) lack of stratification on patient factors, thus limiting applicability of findings to clinically important subgroups; and 3) methodologic challenges for assessment of trends and outcomes, such as adjusting for secular trends, isolating the impact of prescribing limit components among larger OA prescribing policies, and limitations of electronic healthcare data (e.g., administrative claims and EMR) (Table 1).

4.1 | Insufficient evaluation of patient outcomes, public health outcomes, and unintended consequences

Evidence from the published literature on federal policies, guidelines, and state laws indicates that OA prescribing limits may be effective in decreasing prescribing and dispensing of OAs. However, changes in prescribing and dispensing patterns are minimally informative for understanding whether an intervention improved patient and public health outcomes and/or introduced unintended consequences. Additional OA prescription fills and unplanned follow-up visits do not provide complete information on adequacy of pain management for patients, especially for those who do not or are unable to seek follow-up care or are denied additional OA prescriptions.

Public comments on the impact of opioid policies to decrease OA prescribing provided during public meetings as well as published qualitative studies describe outcomes that require additional research. For example, a 2020 Federal Register notice, Management of Acute and Chronic Pain: Request for Comment, received over 5000 comments.[39] Unintended consequences reported reflected patient frustrations surrounding accessing OA medications, increased stigmatization, quality of life challenges with untreated pain, mental health decompensation, transitioning to illicit substances, job loss, and increased disability.[40-45] However, few studies that met our inclusion criteria evaluated these or similar potential unintended consequences of OA prescribing limits. This demonstrates a need for including the perspectives of persons with lived experience, as information from patients who are directly affected by these policies is essential for understanding their impact. This also demonstrates a need for improved collaboration between policy researchers and clinicians and others working with populations potentially impacted by unintended consequences of these policies. For example, when evaluating a prescribing limit or intervention, researchers should consider partnering with harm reduction programs or substance use disorder treatment centers to identify if any changes in the population accessing these services may be associated with the policy change or intervention.

4.2 | Stratification by sociodemographic and clinical factors

The impact of OA prescribing limits on patient and public health outcomes likely differ by sociodemographic factors, provider specialty, primary source of payment (e.g., private insurance, Medicaid, Medicare, cash), or comorbidities such as mental health disorders or opioid use disorder. Some of these factors are known to affect OA prescribing independently from implementation of prescribing limits.[46,47] Some studies described the race and ethnicity of their populations, but many did not report stratified study results, leaving a major gap in our knowledge of the differential impact of OA prescribing limits.

4.3 | Methodologic challenges

Changes in OA prescribing and dispensing are a reasonable first target for evaluating the impact of OA prescribing limits, since changes in prescribing and dispensing may be the first indication that the prescribing limits have brought about change. Additionally, there is relative ease, lower costs, and less time associated with using retrospective prescribing and dispensing data captured from electronic healthcare data such as insurance claims.

Reductions in prescribing and dispensing identified using electronic healthcare data may be misleading because of the lack of linkages between different data systems. For example, as part of the Veterans Health Administration's (VHA) Opioid Safety Initiative, the VHA implemented guidelines to reduce high-dose OA prescribing with an individualized approach to slow tapering. They reported a 70 percent reduction in patients with opioid doses >100 MME/day subsequent to the intervention.[48] However, care received outside of the VA system was not captured in the VA data. Another example is the lack of linkages between different sources of payment for OA prescriptions, as single payer insurance claims would not capture cash payments or payments made through other insurance systems.

Accurate measurement of dose and duration of exposure using electronic healthcare data is also challenging. As part of clinically appropriate OA use, OA prescriptions in claims data may overlap as patients pick up prescriptions before their prior prescription ends, or patients may require multiple OA prescriptions at the same time, such as an extended-release medicine and an immediate-release option for breakthrough pain. In addition, attempts to standardize dose to MMEs using existing conversion tables may result in inaccuracies, as there is no clear single standard definition.[49,50] MMEs were originally developed for use as an adjunct to clinical judgment to inform a starting dose when switching patients between OAs, and conversion factors vary among different conversion tables, which can result in differences in the calculated dose in MMEs.

Granular clinical information, such as the severity of illness, and many patient behaviors are not captured or may be incomplete in electronic healthcare data systems. Many patient and provider outcomes can be more accurately captured utilizing prospective data collection than through retrospective review of electronic healthcare data. Prospective, systematic collection of patient and provider outcomes requires continued follow-up at standardized times and tools such as surveys. For robust evaluation, these surveys need to be completed before and after the intervention, requiring additional time and planning.

Most prescribing interventions include multiple components, and it can be complicated or sometimes impossible to disentangle the effect of each individual component. One option is to stagger implementation of the individual components of an intervention to allow time for outcome measurement related to the specific components. To do this, researchers need to work closely with policy makers so that the evaluation is considered a critical component of policy implementation and is considered as early in the policy development process as possible. Outcomes that are more distal to the intervention, such as development of substance use disorders, may be especially difficult to attribute to one specific intervention. Prospective studies of long duration with repeated follow-up via tools such as surveys and more complex epidemiological study designs and analyses may be necessary to accurately measure the impact of interventions on more distal outcomes. Differences in the timing between enactment and implementation of OA prescribing limits and the period of evaluation, and differences in enforcement provide additional challenges to interpreting study results. For example, behavioral changes may occur during gaps in time between the enactment and implementation of a law. Further, often there is limited information about how limits are enforced once implemented, as it is often the responsibility of organizations, medical practices, and other healthcare providers to ensure compliance. Many of the studies

we examined did not take into consideration differences in enactment and implementation dates, preimplementation changes in behavior, or the level of enforcement or compliance with the limits to more accurately measure the impact of these policies on patient and public health outcomes.

Although national outpatient OA prescribing and dispensing rates had already been declining since 2012, there was an accelerated decrease following the publication of the CDC Guideline in March 2016.[30] Most studies we identified faced the challenge of disentangling the impact of prescribing limits in their state from secular trends resulting from multiple concurrent efforts to address the opioid crisis[51] as well as changes in illicit opioid use patterns. A broad understanding of the direction and impact of multiple policy interventions is valuable. In addition, disentangling the impact of a specific threshold is critical in certain instances, for example, when making decisions about a specific numeric threshold such as quantity or MME limits. Finally, substantial variations among prescribing limits, including but not limited to the type or chronicity of pain, pose a challenge when trying to compare the effects of different thresholds on important outcomes.

Many studies included in our review evaluated the implementation of OA prescribing limits within a single institution or medical practice, or within a specific population, thus providing a limited view of the impact across the broader population potentially affected by these policies. For example, studies evaluating outcomes among patients with post-surgical pain from one specific procedure represent only a limited subgroup of the population needing treatment for acute pain. In contrast, studies that evaluate the population-level effects of laws, such as at a state level, do not provide insight into how the effects might vary across patients with different pain conditions. An evidence-base of research at multiple patient- and population- levels is needed to understand the contribution of clinical and patient factors (i.e., effect measure modifiers) to the impact of the policy, for example, the positive and negative impacts of the policy in specific clinical situations (e.g., post-surgical vs. primary care) and with specific patient factors (e.g., sociodemographic, urbanicity, social support). Policy makers should consider whether the various patient and clinical factors have been sufficiently studied when synthesizing results from multiple evaluations about the policy impact.

4.4 | Responses to methodologic challenges

The multiple methodologic challenges highlighted in this narrative review present opportunities for future research. For example, to overcome challenges with isolating the impact of the intervention or unclear implementation times, researchers must carefully control for existing trends using innovative epidemiological methods and quasiexperimental designs, such as interrupted time series analysis,[52] and methods that incorporate a comparison group or transition period. The literature we reviewed included some examples, such as including assessment of a control group,[21] use of interrupted time series analysis,[30,38] and incorporating the period of adoption or policy implementation in the evaluation,[22,26] among others. Limitations in measurement of dose and duration can be partially addressed by varying the decision rules surrounding prescription gaps, overlaps, and assumptions about how patients may use medications that are taken as needed in

algorithms used to calculate dose and duration. Comparative effectiveness studies could be designed to compare different prescribing limits, and any variations between interventions should be clearly documented and accounted for when comparing the successes, harms, and potential unintended consequences. Finally, multiple studies examining the impact of a prescribing limit may be needed at different levels of the healthcare system to fully characterize the impact of these laws and policies.

5 | STRENGTHS AND LIMITATIONS

This narrative review presents a comprehensive review of the literature covering recent years to inform conclusions about the gaps, methodologic challenges, and future opportunities for studies evaluating OA prescribing limits. Many methodologic challenges we describe in this review are consistent with those previously described in the literature[53,54]; however, our review includes additional challenges for consideration and suggestions for improving future research. In addition, our review expands on such previous work by identifying patient and public health outcomes potentially impacted by prescribing limits with little or no published quantitative evaluations.

A key limitation of this review is that we focus solely on federal and state OA prescribing limits. As mentioned above, local factors may also play a role in influencing prescribing and dispensing practices. Healthcare systems, insurers, pharmacy chains, and pharmacy benefit managers may have unique rules or practices related to prescribing. Local jurisdictions may have their own approaches that vary from state or federal approaches. Yet, federal and state OA prescribing limits serve as a platform for many of these local efforts and are therefore an important target for assessment.

6 | CONCLUSIONS

Gaps and challenges in the current literature highlight the need to improve scientific research on the impact of OA prescribing limits to ensure positive health outcomes while minimizing unintended negative consequences. We provide multiple suggestions for improving evaluations of prescribing limits and overcoming challenges. First, in addition to studies that examine retrospective electronic healthcare data, studies should be designed to prospectively collect meaningful patient, provider, and community outcomes not readily captured in electronic healthcare data, with assessments stratified by sociodemographic and clinical factors. Second, researchers should consider partnering with harm reduction programs or substance use disorder treatment centers and include perspectives of persons with lived experience in their evaluations. Third, when possible, researchers should collaborate with policy makers to ensure appropriate evaluation plans are developed prior to the implementation of OA prescribing limits. Fourth, researchers should employ innovative epidemiological and statistical methods to control for existing secular trends as well as account for the timing of enactment and level of enforcement and implementation of the intervention. Finally, as several types of studies contribute to the evidence-base and no single study should be interpreted in isolation, researchers should work with policy makers to ensure that the evidence-base, and not a single study, is used to inform the development OA prescribing limits.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DISCLAIMER

The findings and conclusions in this article are those of the authors and do not necessarily represent the official positions of the U.S. Food and Drug Administration, the Centers for Disease Control and Prevention, the National Institute on Drug Abuse, the National Institutes of Health, or the U.S. Department of Health and Human Services.

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Key Points

- Opioid analgesic prescribing policies have proliferated in recent years, and careful evaluation of their impact on important patient and public health outcomes is imperative.
- Most studies evaluating the impact of federal and state guidelines and laws on opioid analgesic prescribing have assessed only prescribing and dispensing characteristics and have not assessed patient or public health outcomes.
- Many gaps in knowledge exist, constraining our overall understanding of the patient and public health impact of opioid analgesic prescribing limits.
- Studies should be designed to collect meaningful patient, provider, and community outcomes with assessments stratified by sociodemographic and clinical factors.

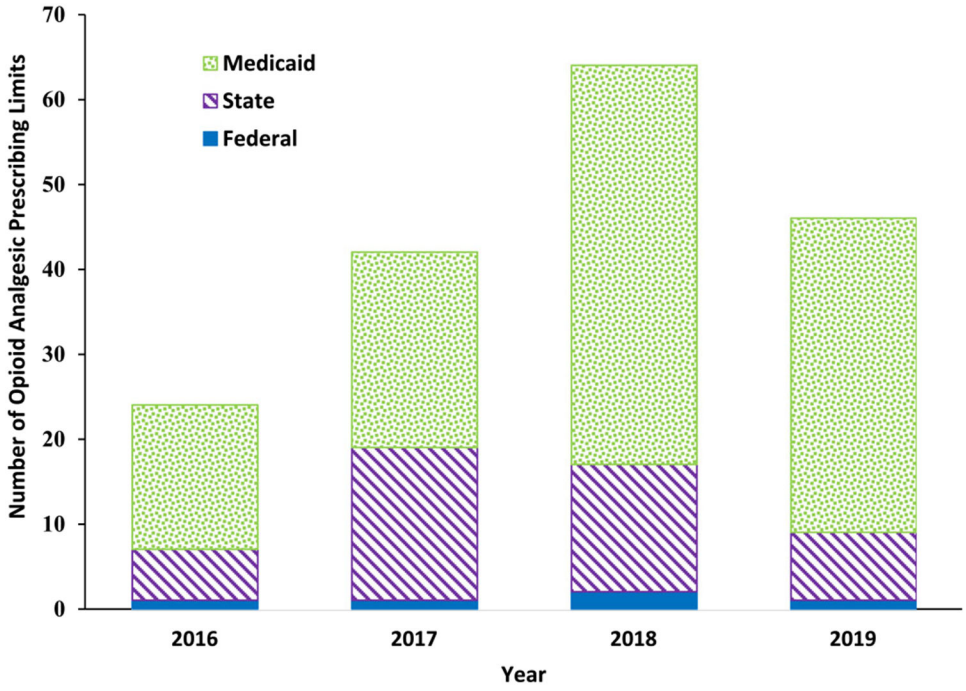

FIGURE 1.

Number of newly enacted federal, state, and medicaid opioid analgesic prescribing limits with a days' supply, dose (MME), or quantity restriction, by Year.[a] *Source:* See Table S1.[a] The newly enacted prescribing limits displayed in Figure 1 are restricted to opioid analgesic prescribing limits with a days' supply, dose, or quantity restriction, often with requirements for some action (e.g., prior authorization, point of sale edits) at the limits. These limits are not cumulative, and some may be updates to opioid analgesic prescribing limits enacted in previous years. This figure is intended to provide context to illustrate the large number of policies enacted during the last 4 years; it is not representative of the increase in cumulative opioid analgesic prescribing limits over time. Limits on benzodiazepine and opioid analgesic co-prescribing were included if the limit was based on a days' supply, dose, or quantity restriction for the opioid analgesic. We did not include general requirements for PDMP checks or naloxone co-prescribing laws (requirements prior to prescribing any opioid analgesic), or universal prior authorizations (e.g., prior authorization required prior to prescribing any long-acting opioid analgesic). Prescribing limits for medications for opioid use disorder (e.g., buprenorphine/naloxone, methadone) were not included. We included PDMP checks triggered by a specific OA prescribing limit. Best practices documents or guidelines from state workgroups or professional associations were not included. Federal agencies, states, and state Medicaid programs that enacted more than one opioid analgesic prescribing limit with a days' supply, dose, or quantity component in 1 year were only counted once for that specific year

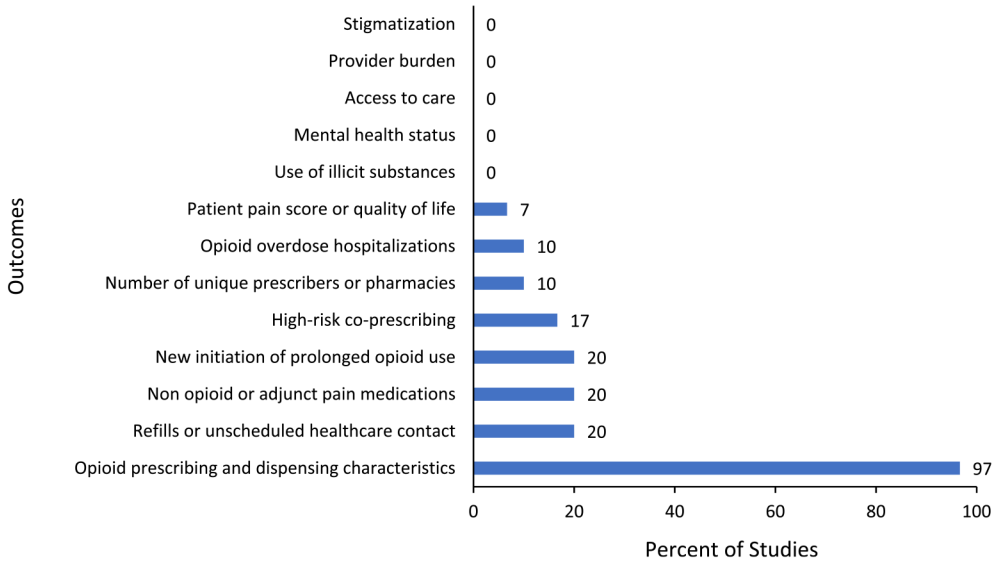

FIGURE 2.

Percent of studies evaluating the impact of federal or state-level opioid analgesic prescribing limits on opioid prescribing and dispensing characteristics and select outcomes, 2013–2019. Total studies included: $N = 30$; studies may include additional outcomes not captured in this figure (e.g., metrics on tapering, all-cause mortality, provider use of an electronic list for preferred prescriptions). Number of studies and examples of outcomes included in each category: (1) Stigmatization ($n = 0$): patient-reported feeling of stigmatization by healthcare provider or other; (2) provider burden ($n = 0$): provider-reported satisfaction, burden, or time requirements; (3) access to care ($n = 0$): challenges with accessing medical care to address acute or chronic pain (e.g., inability to find a provider or to make or attend appointments, financial restrictions preventing payment for medical visits or multiple prescriptions); (4) mental health status ($n = 0$): patient-reported changes in mental health (e.g., depression, anxiety, suicidal ideation); (5) use of illicit substances ($n = 0$): patient-reported use of illicit opioids (e.g., illicit fentanyl, heroin) or other substances to manage pain; (6) patient pain scores or quality of life ($n = 2$): patient self-reported pain score or quality of life on Likert Scale; (7) opioid overdose hospitalizations ($n = 3$): emergency department visits and hospitalizations due to overdose involving opioids; (8) number of unique prescribers or pharmacies ($n = 3$): number of unique prescribers or use of multiple pharmacies; (9) high-risk co-prescribing ($n = 5$): measures of opioid analgesic and benzodiazepine overlapping prescriptions; (10) new initiation of prolonged opioid use ($n = 6$): postoperative opioid use among new initiates; (11) non-opioid or adjunct pain medications ($n = 6$): prescribing and use of NSAIDs or other adjunct pain medications; (12) refills or unscheduled healthcare contact ($n = 6$): measures of additional opioid analgesic prescriptions, follow-up visits or phone calls, emergency department visits (some studies specified for pain); (13) opioid prescribing and dispensing characteristics ($n = 29$): changes in dose, quantity of tablets, number of patients with an opioid prescription, number or percent over a specific dose, number of opioid prescribers, changes in prescribing extended-release/long-acting opioids, prescription opioid distribution, and other related outcomes

TABLE 1

Methodologic challenges in evaluating the impact of opioid analgesic prescribing limits

Challenge	Details and examples	Possible opportunities for future research
A single data system may not capture the full picture of a patient's experience	Reductions in prescribing and dispensing may be exaggerated if patients go outside of a single payer system or use cash to obtain opioid analgesic prescriptions due to limits within the single payer system	Consider linked data systems or data systems that capture all prescriptions (e.g., PDMP)
No single standard method, and wide variation in measurements of dose, duration, or quantity of opioid analgesic used by the patient across methods	Overlapping or concurrent opioid analgesic prescriptions and medications taken as needed; multiple ways to calculate MME	Consider patient surveys to assess total number of tablets used and to obtain more information on prescriptions; vary decision rules used to calculate patient use
Important patient information may not be captured in electronic healthcare data	Many electronic healthcare data systems are not designed to capture information needed (e.g., severity of illness, patient behaviors, patient satisfaction, unaddressed pain, difficulty accessing treatment, feelings of stigmatization)	Consider patient surveys and other prospective data collection tools
Difficulty disentangling multiple components of an intervention	Most prescribing limits are implemented along with other components, such as provider education or required PDMP checks	Stagger implementation of interventions Collaborate with policy makers and encourage the implementation of interventions in a manner that allows for understanding the impact, such as staggered interventions
Distal outcomes difficult to connect to an intervention	Important outcomes such as substance use disorder develop over longer time period and are often a result of multiple factors	Consider prospective studies of long duration or select intermediate endpoints that are early markers of the distal outcomes of interest or on the causal pathway
Need to account for differences in level of enforcement	Stronger enforcement may result in greater changes in outcomes	Level of enforcement should be clearly described and assessed as a component of the prescribing limit
Time difference between enactment and implementation	Behavioral changes may start prior to intervention implementation, not allowing for a clear pre-intervention comparison period	Time between enactment and implementation should be clearly defined; any pre-implementation changes should be noted; other comparators may need to be considered if substantial preimplementation behavior change is identified; consider sensitivity analyses to vary intervention time points or allow for a transition period
Difficulty disentangling effect of the intervention from secular trends	Many external factors to consider: opioid analgesic prescribing has been decreasing in recent years, multiple policies at all levels have been implemented, and changes in public understanding may affect outcomes	Control for existing trends using innovative epidemiologic methods, and use appropriate comparator groups
Lack of representation of the broader population or important sociodemographic and clinical subgroups	Impact of opioid analgesic prescribing limits are often evaluated among narrow populations such as patients experiencing post-surgical pain from a specific procedure at a single institution	Multiple studies needed at different levels of the healthcare system and in varied populations representing important sociodemographic and clinical subgroups

Abbreviations: MME, morphine milligram equivalents; PDMP, Prescription Drug Monitoring Program.