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Methodologic limitations of prescription opioid safety research and recommendations for improving the evidence base

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Abstract

Purpose: The ongoing opioid epidemic has claimed more than a quarter million Americans' lives over the past 15 years. The epidemic began with an escalation of prescription opioid deaths and has now evolved to include secondary waves of illicit heroin and fentanyl deaths, while the deaths due to prescription opioid overdoses are still increasing. In response, the Centers for Disease Control and Prevention (CDC) moved to limit opioid prescribing with the release of opioid prescribing guidelines for chronic noncancer pain in March 2016. The guidelines represent a logical and timely federal response to this growing crisis. However, CDC acknowledged that the evidence base linking opioid prescribing to opioid use disorders and overdose was grades 3 and 4.

Methods: Motivated by the need to strengthen the evidence base, this review details limitations of the opioid safety studies cited in the CDC guidelines with a focus on methodological limitations related to internal and external validity.

Results: Internal validity concerns were related to poor confounding control, variable misclassification, selection bias, competing risks, and potential competing interventions. External validity concerns arose from the use of limited source populations, historical data (in a fast-changing epidemic), and issues with handling of cancer and acute pain patients' data. We provide a nonexhaustive list of 7 recommendations to address these limitations in future opioid safety studies.

Conclusion: Strengthening the opioid safety evidence base will aid any future revisions of the CDC guidelines and enhance their prevention impact.

KEYWORDS

opioid overdose, opioid safety, opioid use disorders, pharmacoepidemiology, prescription opioids

1 | INTRODUCTION

There have been repeated and resolute efforts from policy makers, public health agencies, and the medical community to stem the opioid overdose epidemic. Yet, prescription opioid use in the United States tripled between 2000 and 2012,[1] heroin use doubled from 2000 to 2014,[2] and the overall opioid overdose death rate quadrupled over the same period.[3,4] The opioid epidemic claimed more than 250 000 American lives between 1999 and 2015.[5] Since 2012, the number of opioids prescribed has slightly declined; however, overdose deaths continue to increase.[6] In 2016 alone, more than 42 000 people lost their lives to opioid overdoses in the United States,[5] with fentanyl being the leading involved drug, followed by heroin, oxycodone, morphine, methadone, and hydrocodone.[5,7-9] Indiscriminate use and diversion of prescription opioids may predispose certain individuals to eventually use heroin and illicitly manufactured fentanyl.[2-4] An estimated 99 adolescents (12-17 years age) and 258 young adults (18-25 years age) become new users of heroin in the United States every day.[8] To limit unnecessary prescribing of opioids, the Centers for Disease Control and Prevention (CDC)

published opioid prescribing guidelines for chronic noncancer pain patients in March 2016.[10]

The CDC guidelines have had swift uptake with state licensing boards adopting them as the standard of care.[11] The guidelines are 1 of the most prominent initiatives by a federal agency and have strong potential for limiting opioid prescribing while maintaining appropriate pain management. However, the guidelines have been subject to criticism.[12,13] Notably, it has been argued that the guidelines are based on limited evidence,[12-14] also acknowledged in the guidelines themselves (grade 3 and 4 evidence).[10] Additionally, the majority of studies cited in the guidelines are limited to the association between opioid prescribing with overdose deaths.[10,14] The guidelines note, however, that while preventing overdose death is paramount, guidelines aimed at preventing prior outcomes like opioid use disorders (OUDs) are equally important in addressing the epidemic. Despite these limitations in the evidence base, the escalating magnitude of the opioid crisis required strong federal action. Therefore, the guidelines were developed by experienced pain medicine physicians and scientists by leveraging pragmatic pain management approaches and the best possible interpretations of the literature available at the time.

The guidelines' emphasis on chronic noncancer pain reflects the concern that most nonmedical use of opioid analgesics occurs in this population and many primary care providers feel inadequately prepared to manage chronic pain while minimizing OUD and overdose risks.[10] However, in doing so, the guidelines were forced to omit cancer pain patients and only made a brief note that 3 to 7 days of opioids might suffice for most acute and postsurgical pain. Moreover, the absence of evidence based on specific clinical subpopulations (eg, women, minorities, acute trauma, and elective surgery) or specific opioid formulations meant that the guidelines adopted a one-size-fits-all approach for the many pain-inducing conditions, regardless of pain etiology and biologic variation among patient subpopulations. Notably, there is a lack of data on effective noncancer pain management among African-Americans, which is concerning given mixed evidence on racial differences in pain and prescribing.[15-17] These critical research gaps need to be addressed if prescribing behavior is to become more evidence-based.

In this brief review, we examine characteristics of studies cited in the CDC guidelines that specifically addressed the impact of prescription opioids on OUD and overdoses (fatal or nonfatal). We refer to these studies as opioid safety studies and differentiate them from studies evaluating the efficacy of opioids for pain relief. We examine concerns related to internal and external validity in these studies (as noted in the guidelines[10] and a previous systematic review[14]) and provide recommendations to overcome these limitations in future research, so that refined guidelines can take advantage of a stronger and deeper evidence base.

KEY POINTS

- Prescribing guidelines for chronic noncancer pain medication has been developed and is being adopted nationwide to mitigate the growing incidence of opioid use disorders and overdose deaths.
- These guidelines have to rely on the current evidence base for prescription opioid safety, which includes studies with multiple internal and external validity-related limitations.
- Utilization of "big data" resources, superior computing power, and employment of advanced epidemiologic and statistical methods is needed to strengthen the opioid safety evidence base.

2 | METHODS

We examined all the studies cited in the CDC guidelines to identify opioid safety studies for further review. We classified opioid safety studies as those that evaluate the association of opioid prescribing patterns with harmful effects of prescription opioids including fatal and nonfatal overdoses; OUD identified as misuse, abuse, or dependence; or other side effects related to activity, sleep, mood, or bowel dysfunction. We also included studies that examined the association of opioid prescribing patterns with opioid abstinence, emergency department visits, and all cause-mortality. The studies were independently evaluated by 3 co-authors, and information was entered in tabular format by using a common template that included study identifiers, design, data sources, data years, exposures (opioid prescribing), opioid safety outcomes studied, and potential internal and external validity concerns. The resulting data were then reviewed by co-authors as a group, and overall limitations of the evidence base and outline of the results were determined.

3 | RESULTS

3.1 | Study characteristics

We found 27 opioid safety studies cited in the CDC guidelines which assessed associations between opioid prescribing and safety outcomes (Table 1) such as fatal overdoses (n = 10)[24,27-29,32,34,37,38,41,42]; nonfatal overdoses (n = 5)[24,36,39,40,44]; OUDs, including opioid or substance misuse, abuse, or dependence (n = 7)[21-23,25,30,31,35]; and other outcomes including opioid abstinence; side effects related to activity, sleep, mood, or bowel dysfunction; emergency visits; and all-cause mortality (n = 6).[18-20,26,33,43]

3.2 | Study design and population characteristics

The study designs included 6 randomized controlled trials (RCTs),[18,20,22,26,30,33] 1 prospective cohort,[19] 12 retrospective cohort,[21,23-25,29,35,37-40,43,44] 2 case-cohort,[27,40] 5 case-control,[17,32,34,36,42] and 3 cross-sectional studies (2 combined with retrospective cohorts)[23,31,32] (Table 1). Most studies were conducted among chronic noncancer pain patients (n = 15)[19-26,30,33,35,39,40,43,44]; however, some studies were conducted among all opioid users including cancer and acute pain patients (Table 1). The studies varied in new or prevalent user designs (Table 1).[45] Only 5 studies utilized data after 2010[31,34,36,38,44]; the remaining represented earlier data (Table 1). Data sources included prescription monitoring programs (PMPs), US Veterans Health Administration (VHA), health insurance (claims),

TABLE 1 Characteristics of studies[a] examining opioid prescribing for chronic pain

Author, Year	Data Source	Data Years	Population	Study Design	Assessed Health Outcome(s)
Tennant, 1982[18]	1 clinic	1979-1981	Opioid-dependent patients	RCT	Opioid abstinence
Ralphs, 1994[19]	1 hospital (UK)		CNCP patients, prevalent opioid users	Prospective cohort	Opioid abstinence
Allan, 2005[20]	Multicenter (UK)		CNCP patients, new opioid users	RCT	Bowel dysfunction
Reid, 2002[21]	1 VHA hospital, 1 primary care hospital (Connecticut)	1997-1998	CNCP patients, new and prevalent opioid users	Retrospective cohort	Opioid abuse behaviors
Cowan, 2005[22]	1 pain clinic (London)		CNCP patients, new opioid users	RCT	Psychological dependence, drug craving
Banta-Green, 2009[23]	1 integrated group clinic (Washington state)	Pre-2009	CNCP patients, prevalent users	Retrospective cohort/surveys	Opioid misuse
Dunn, 2010[24]	Claims (Washington state)	1997-2005	CNCP patients, new and prevalent opioid users	Retrospective cohort	Fatal and nonfatal opioid overdose
Sullivan, 2010[25]	Claims (private and Arkansas Medicaid)	2000-2004	CNCP patients, new and prevalent opioid users	Retrospective cohort	Opioid misuse score
Wild, 2010[26]	Multisite (North America and Europe)		CNCP patients, new opioid users	RCT	Activity, sleep, mood, ED visits, side effects
Bohnert, 2011[27]	VHA	2004-2008	All new and prevalent opioid users	Case-cohort	Fatal opioid overdose
Gomes, 2011[28]	Ontario PDBP	1997-2006	All new and prevalent opioid users	Case–control	Fatal opioid overdose
Gomes, 2011[29]	Ontario PDBP	2003-2008	All new and prevalent opioid users	Cross-sectional; retrospective cohort	Fatal opioid overdose
Naliboff, 2011[30]	1 VHA hospital (California)	2001-2004	CNCP patients, prevalent opioid users referred for long-term management	RCT	Substance misuse
Cicero, 2012[31]	US MAT programs	2009-2012	MAT patients	Cross-sectional	Oxycontin and opioid misuse
Paulozzi, 2012[32]	New Mexico PMP	2006-2008	All new and prevalent opioid users	Case-control	Fatal opioid overdose
Mitra, 2013[33]	1 pain clinic (Australia)		CNCP patients, new opioid users	RCT	Activity, sleep, mood, ED visits, side effects
G Baumblatt, 2014[34]	Tennessee PMP	2007-2011	All new and prevalent opioid users	Case-control	Fatal opioid overdose
Edlund, 2014[35]	Claims (HealthCore Integrated Research Database)	2000-2005	CNCP patients, new opioid users	Retrospective cohort	Abuse, dependence
Zedler, 2014[36]	VHA	2010-2012	All new and prevalent opioid users	Case-control	Nonfatal opioid overdose
Dasgupta, 2015[37]	North Carolina PMP	2010	All new and prevalent opioid users	Retrospective cohort	Fatal opioid overdose
Jones, 2015[38]	DAWN-ED	2004-2011	All new and prevalent opioid users	Retrospective cohort	Fatal opioid overdose
Liang, 2015[39]	Claims (Aetna)	2009-2012	CNCP patients, new and prevalent opioid users	Retrospective cohort	Nonfatal drug overdose
Miller, 2015[40]	VHA	2000-2009	CNCP patients, new opioid users	Retrospective cohort	Nonfatal drug overdose
Park, 2015[41]	VHA	2004-2009	All new and prevalent opioid users	Case-cohort	Fatal drug overdose
Bohnert, 2016[42]	VHA	2004-2009	All new opioid users	Case–control	Fatal opioid overdose
Gaither, 2016[43]	Veterans Aging Cohort	2000-2010	CNCP patients, new opioid users with	Retrospective cohort	All-cause mortality

(Continues)

TABLE 1 (Continued)

Author, Year	Data Source	Data Years	Population	Study Design	Assessed Health Outcome(s)
			history of long-term opioid therapy		
Turner, 2015[44]	Claims (Aetna)	2009-2012	CNCP patients, new and prevalent opioid users	Retrospective cohort	Nonfatal drug overdose

Abbreviations: CNCP, chronic noncancer pain; Co-Benzo, benzodiazepines co-prescribed with opioids; ED, emergency department; DAWN, Drug Abuse Warning Network; MAT, medication-assisted treatment. NCP, noncancer pain; PDBP, public drug benefit program; PMP, prescription monitoring program; RCT, randomized controlled trial; Rx, prescription; UK, United Kingdom; VA, Veterans Administration; VHA, Veterans Health Administration.

[a]Studies cited in, and used to inform, national opioid prescribing guideline.[10]

electronic health records (EHRs), and death records. These sources contain different levels of information; eg, EHR, claims, and PMP do not have complete death data, whereas death records do not have opioid exposure information. While linkage may solve some issues, other properties of these data and studies may result in validity concerns, as discussed below.

3.3 | Threats to internal validity

A major internal validity issue in research is lack of exchangeability. This refers to the imbalance of potential confounders between exposure groups. Lack of exchangeability gives rise to confounding or selection bias. Lack of exchangeability is typically of minimal concern in large, well-conducted RCTs.[20,22,30] However, it is a concern in small sample RCTs with selective withdrawals, which was as seen in 3 of the 6 RCTs (Table 2).[26,30,33]

Lack of exchangeability is a major concern in observational studies and requires the use of statistical methods to be addressed. This poses several challenges for opioid safety studies. First, depending on the data source used, there may be a lack of confounder information. For example, PMP and death records may not include diagnostic and substance use disorder histories. While linkage of these 2 sources allows for good exposure assessment[37] and for examining associations between opioid dispensing and overdose deaths, it does not allow us to establish causal relationships between prescription opioids and opioid safety outcomes because of inadequate confounding control.[28,29,32,34,37] Second, even when confounder information is available from sources like VHA, claims, and EHR, failing to identify and control for all appropriate confounders can lead to biased effect estimates.[19,21,23-25,27,35,36,38-44] To illustrate this concept, we developed a directed acyclic graph (DAG) representing the association between prescription opioids and OUD (Figure 1). In Figure 1, the covariates presented in boxes are potential confounders which, if controlled for, will eliminate measured or known confounding, although there may be other confounders that are unknown or unmeasured .[46] However, several of the observational studies cited in the guidelines failed to account for some or all of these well-known confounders (Figure 1).[19,21,23-25,27,35,36,38-44] Third, in some of the reviewed studies, investigators controlled for multiple confounders and interpreted all coefficient estimates from the single multivariable model as causal effects.[20,23,25,27,35,36] This results in so called "table 2 fallacy," a term that refers to improper interpretations of effect estimates and potential selection bias.[47] Fourth, most studies failed to account for time-varying opioid exposure and confounding by indication (eg, patient selection for abuse-deterrent formulations).

In addition to confounding, measurement error due to misclassification of outcome, exposure, or covariates can also lead to a lack of internal validity.[48,49] For example, researchers frequently express concern that ICD-9/10 codes for opioid dependence and abuse lack sensitivity and underestimate OUD (outcome misclassification), claims data also do not capture out-of-pocket prescriptions (exposure misclassification), all prescribed medications (EHR) are not filled (exposure misclassification), and all filled medications (PMP, claims) are not consumed (exposure misclassification). Other measurement error issues include considering all opioid medications as equianalgesic equivalents without consideration to specific formulations (exposure misclassification). For example, most observational studies combined immediate release and extended release opioids by converting them into morphine milligram equivalents, without examining effect measure modification by formulation. Such information is beneficial to regulators like the US Food and Drug Administration. Similarly, inconsistencies in correctly identifying the substance involved in overdose deaths may lead to outcome misclassification. For example, heroin rapidly metabolizes to morphine potentially rendering the overdose indistinguishable from prescription opioid overdoses. Even as these limitations exist, they are infrequently discussed and not addressed in the cited studies (Table 2).

An additional source of bias in both observational and randomized studies is selection bias.[50,51] For example, many observational studies used prevalent opioid user designs (includes both new and current users),[19,21,23-25,27-32,34,36-39,41,44] as opposed to study design in which the comparison group was limited to new opioid initiators (so-called "new user comparator" designs). The use of prevalent opioid user designs is likely to introduce survival bias resulting from inclusion of individuals who did not have severe adverse events (eg, fatal overdose) from initial opioid exposures. This can lead to under-ascertainment of adverse events that occur early in opioid therapy.[45] Additionally, selection bias can result from differential withdrawal or dropout from the study.[18,23,26,33]

Lastly, competing interventions and competing outcomes (competing risks) may also lead to a lack of internal validity. Competing interventions (eg, policy change or Naloxone access) may predict both the receipt of opioid prescriptions and opioid safety outcomes (eg, overdose), thereby confounding the relationship between opioid prescribing and opioid safety outcomes. On the other hand, not accounting for competing risks (eg, death due to other causes) may introduce immortal person-time into some studies[52] (person-time during which

TABLE 2 Internal and external validity concerns in studies[a] examining opioid prescribing for chronic pain

Author, Year	Lack of Internal Validity				Small Sample Size (Lack of External Validity)
	Incomplete or no Adjustment for Confounding	Potential Measurement Error or Misclassification		Potential Selection Bias (Due Lost to Follow or Nonresponse)	
		Exposure	Outcome		
Tennant, 1982[18]				16/21 from the first study arm dropped out in first 3 weeks of follow-up and 1/21 from the second arm	Total 42 patients
Ralphs, 1994[19]	X		X		
Allan, 2005[20]					
Reid, 2002[21]	X	X	X		27 opioid abuse behavior patients
Cowan, 2005[22]					10 CNCP patients
Banta-Green, 2009[23]	X	X	X	57% nonresponders who were more likely to be male, younger, and received high opioid doses	
Dunn, 2010[24]	X	X			51 ODs
Sullivan, 2010[25]	X	X			
Wild, 2010[26]				46% intervention and 35% control participants completed the study	
Bohnert, 2011[27]	X	X			
Gomes, 2011[28]	X	X			
Gomes, 2011[29]	X	X			
Naliboff, 2011[30]			X		
Cicero, 2012[31]	X				
Paulozzi, 2012[32]	X	X			
Mitra, 2013[33]	X			16 of 46 participants withdrew (8 in each group)	Total 46 patients
G Baumblatt, 2014[34]	X	X			
Edlund, 2014[35]	X	X	X		
Zedler, 2014[36]	X	X	X		
Dasgupta, 2015[37]	X	X			
Jones, 2015[38]	X				
Liang, 2015[39]	X	X	X		
Miller, 2015[40]	X	X	X		37 ODs in long acting opioid group
Park, 2015[41]	X	X			
Bohnert, 2016[42]	X	X			
Gaither, 2016[43]	X	X			
Turner, 2015[44]	X	X	X		

Abbreviations: CNCP, chronic noncancer pain; OD, opioid overdose.

[a]Studies cited in, and used to inform national opioid prescribing guidelines.[10]

the outcome cannot occur), leading to underestimation of overall risk measures. The US Food and Drug Administration has also acknowledged similar concerns in studies evaluating impact of abuse deterrent opioid formulations on OUD and overdoses.[53]

3.4 | Threats to external validity

While studies that lack internal validity automatically lack external validity, there are additional considerations that may help improve external validity or generalizability of studies.

Lack of generalizability may result from different data generating mechanisms or source populations. For example, 7 studies cited in the guidelines utilized data from 1 specific hospital.[18,19,21-23,30,33] Such data are only generalizable to the specific geographic catchment area and the practices of physicians and staff at that hospital. Similarly, data generated from the VHA, a single state, or another country, as used in 21 studies cited in the guidelines,[18-25,27-30,32-34,36,37,40-43] might not generalize to the broader US population. Moreover, small sampled studies, even from nationwide sources, may not represent the source population from which the sample arises.[18,21,22,24,33,40] Small sample sizes can also lead to nonpositivity (ie, not having exposed and unexposed subjects for each combination of observed confounders) and threaten internal validity.

Outdated or historical data when not used along with current data also threaten external validity. Some studies cited in the CDC guidelines included data from the 1980s and 1990s,[18,19,21,24,28] the majority utilized data up to 2010,[20-30,32,35,37,40-43] and only a few used data after 2010,[31,33,36,39,44] but none went beyond 2012. As the opioid

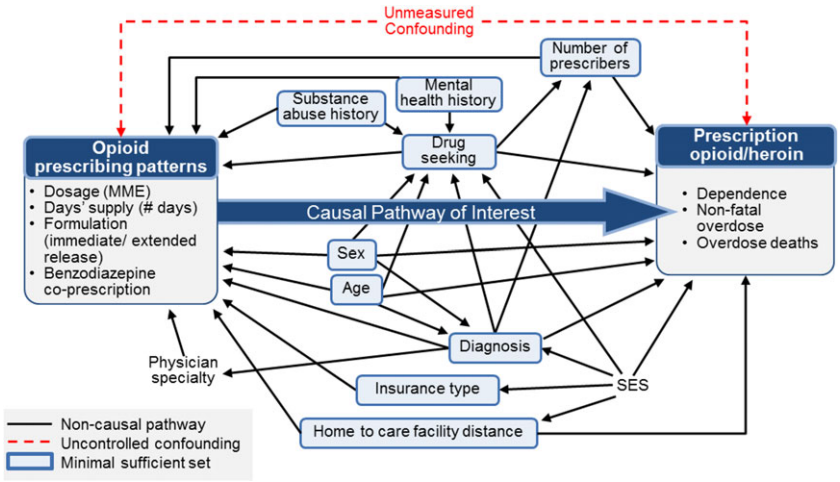

FIGURE 1 Example DAG showing key pathways to consider in future studies [Colour figure can be viewed at wileyonlinelibrary.com]

epidemic is rapidly changing, more recent data would improve generalizability to current conditions, thereby improving effectiveness of the guidelines.

Finally, exclusion of cancer pain patients, or inclusion of cancer pain patients but reporting 1 summary estimate for the whole population, may reduce generalizability. Cancer pain is generally long lasting and often requires high doses of opioid analgesics to be relieved. The exclusion of these patients means results can only be generalized to noncancer pain patients, eliminating a large and important segment of the opioid-using population. On the other hand, some studies included both cancer and noncancer pain patients but only presented overall effect estimates.[27-29,32,34,36-38,41,42] Doing so may reduce generalizability to both cancer as well as noncancer pain patients because of potential heterogeneity of effects between the 2 groups. The overall summary estimate, even if unbiased (internally valid) for the entire sample, may be too large or too small for either cancer or noncancer patients. Similarly, pooling estimates from opioid patients suffering with distinct chronic or acute pain conditions may limit generalizability. Furthermore, the practice of identifying and excluding cancer patients varies between studies. For example, some studies included skin cancer patients but excluded patients with other types of cancer.[22,23,27,31] Previous studies have shown that White race is associated with a higher incidence of skin cancer,[54] pain,[55] receiving opioids,[56,57] and experiencing overdose.[36] Therefore, selective inclusion of skin cancers (or selective exclusion of other cancers) could lead to selection bias, threatening both internal and external validity.

4 | DISCUSSION AND RECOMMENDATIONS

Centers for Disease Control and Prevention's opioid prescribing guidelines constitute a logical and timely response by a federal agency to a rapidly escalating public health crisis. However, we identified several internal and external validity concerns in the opioid safety evidence base, which if addressed in subsequent studies may allow future guidelines to ensure ideal balance between limiting overprescribing and providing appropriate pain management. Many of these concerns arise commonly in observational studies. Internal validity concerns resulted from incomplete confounder information, inability to identify and control for pertinent confounders, or inappropriate confounding control methods (time-varying confounding and table 2 fallacy). Additionally, variable misclassification, selection bias due to the prevalent users, and competing risks threatened internal validity among these studies. Limited source populations, timeliness of data, and issues in the handling of cancer pain patient data were the most common threats to external validity. These limitations are persistent in the literature. We reviewed 6 additional opioid safety studies that were published after the CDC guidelines (until December 31, 2016) and 1 study previously published but not cited in the guidelines; these studies shared similar limitations.[58-64]

The emergence of big data science, access to large healthcare databases, modern epidemiological methods, and large-scale computing power provide means to address many of these limitations. Such methods are already being utilized in HIV, cancer, and pharmacoepidemiology research but remain underutilized in opioid safety or drug use disorder research. Below, we detail some key recommendations and resources that may be useful in planning and conducting future opioid safety research (Table 3).

1. Utilize large data resources from multiple states to increase generalizability (external validity). For example, EHR data from multiple health-care systems and large insurance claims data encompassing multiple states represent larger source populations,

TABLE 3 Key recommendations for future research on opioid safety

#	Recommendation
1	Utilize big data sources; eg, EHR-insurance claims.
2	Link multiple large data sources; eg, EHR-death records, EHR-Claims-PMP-death records.
3	Use DAGs to identify potential confounders; eg, Figure 1.
4	Examine misclassification of opioid exposures and harms.
5	Utilize modern analytic methods to improve validity; eg, MSM, G-formula, IV.
6	Examine EMM and biologic interaction due to cancer, acute pain, and for clinical subpopulations.
7	Conduct sensitivity analysis and quantitative bias analysis.

Abbreviations: DAG, directed acyclic graph; EHR, electronic health records; EMM, effect measure modification; IV, instrumental variable; MSM, marginal structural models; PMP, prescription monitoring program.

thereby providing greater generalizability, as opposed to localized use of data, like 1 hospital or 1 state.[18,19,21-23,30,33] In addition, EHRs provide more patient-level information, allowing better confounding control (internal validity).

2. Link multiple data sources to harness detailed covariate information (internal validity). For example, linking EHR and claims data with PMP and death data (eg, state death records or National Death Index) could allow for longitudinal follow-up (claims and PMP) and detailed covariate and outcome information (EHR). Thus, linkage could help to identify and control for variable misclassification, reduce loss-to-follow up, and improve identification of competing risks (internal validity).
3. Utilize a DAG[33] to identify potential confounders in exposure-outcome relationships (internal validity). Directed acyclic graphs are causal diagrams that graphically represent an exposure-outcome relationship (based on a specific research question) and their associations with other covariates. They are typically developed by using existing literature, expert advice, and consensus among investigators. Figure 1 shows an example DAG that we developed to examine the association between opioid prescribing practices and OUD. Use of DAGs can help researchers distinguish between causal and noncausal pathways between an exposure (opioid prescribing) and outcome (OUD, overdose, and overdose death), including identification of noncausal pathways due to confounding.[65] Using this information, a minimally sufficient set of adjustment variables can be determined to control for all known confounding.
4. Utilize longitudinal study designs and modern epidemiologic and analytic methods to examine the causal effect of opioids on OUDs in observational data. For example, methods like marginal structural models using inverse probability of treatment weighting[66] and g-formula[67,68] could allow for effect estimation of time-varying opioid exposure-outcome relationships, while controlling for time-varying confounding (internal validity). Additionally, instrumental variable approaches under a natural experiment[69] could allow for improved estimation of the effect of opioid exposure on OUDs.
5. Consider examining effect measure modification or even biologic interaction[70] due to cancer rather than excluding cancer pain patients or pooling them with noncancer pain patients. This type of research could then inform the need (or lack thereof) for different guidelines for cancer pain and chronic noncancer pain patients. Similarly, it will be valuable to examine effect measure modification for separate clinical subpopulations and acute pain, which could allow specialized guidelines, eg, for postsurgical pain control, acute injuries, and specific diagnoses.
6. Conduct validation studies to quantify the extent of exposure and outcome misclassification[43] in opioid safety studies, especially for claims and EHR data sources. For example, researchers could link claims data to EHR, then conduct EHR chart reviews, followed by patient interviews, to examine misclassification of OUD, as well as exposure misclassification by being able to discern between opioid prescriptions, fills, claims, and actual consumption.
7. Use epidemiologic tools like sensitivity analyses or quantitative bias analyses[71,72] to examine the level of unmeasured bias (eg, confounding, selection, and misclassification) involved in the generated evidence and its impact on effect estimates. Results from validation studies noted above may be useful to inform parameter estimates used in such analyses. Where possible, sensitivity and quantitative bias analyses should also be used to evaluate and correct covariate misclassification.[48]

These recommendations are not exhaustive and do not overcome all limitations present in the opioid safety literature. Conversely, not all recommendations may be needed for all studies. Depending on the exact research question, target population, nature of the data, and analytic techniques specific to a study, researchers may need to take additional steps to strengthen internal validity and improve generalizability of results. The CDC guidelines represent the best possible distillation of the available evidence and an eminently reasonable federal response. However, strengthening the evidence base to address the limitations noted in this review will assist in the formulation of any revision of the guidelines, allowing for more refinement of recommendations and potentially even greater prevention impact.

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