Prescription drug monitoring programs: a response to the opioid epidemic

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Abstract

Background: The non-medical use of prescription opioids is a significant problem in the United States, with significant health and economic consequences. The nationwide implementation and expansion of prescription drug monitoring programs (PDMPs) has been utilized to reduce the incidence of doctor shopping, influence prescribing practices, and improve patient treatment decisions.

Objective: The purpose of this paper is to describe the available primary literature on prescription drug monitoring programs.

Methods: Peer reviewed research articles, literature reviews, and opinion articles on prescription drug monitoring programs from 2000 to 2017 were identified by searching PubMed/Medline, CINAHL, Embase, PsycInfo, using ‘prescription drug monitoring programs’ OR ‘PDMP’ OR ‘prescription monitoring programs’ AND ‘opioids’ as search terms or MeSH terms. Article bibliographies were also search manually for applicable papers.

Results: Nineteen primary research articles were included for analysis. Evidence of impact of prescription drug monitoring programs on opioid-related outcomes is inconclusive.

Conclusions: As PDMP implementation continues to expand, there needs to be continued focus on specific PDMP characteristics to determine what is the most effective at reducing opioid-related outcomes.

Key Words: prescription monitoring programs, diversion, drug, prescription drug abuse, controlled substances

Background

Importance and impact

Pain is a serious health issue that affects more patients than heart disease, cancer and diabetes mellitus combined.[1,2] It is the most commonly cited reason that Americans utilize the healthcare system; it is also the current leading cause of disability and remains a major contributor to healthcare costs.[2] As a result, there has been an expansion in pharmacologic treatments for pain and the rates of controlled substance prescriptions for pain, specifically opioids, have increased.[3] Analyses performed by the United States Food and Drug Administration (FDA) found that between 1998 and 2010, retail opioid sales have increased by 242%.[4,5] Studies have shown that the increased prescribing rate of opioids is correlated with a significant rise in misuse, addiction, and opioid-related overdoses.

The Centers for Disease Control and Prevention (CDC) describes the upsurge in opioid-related overdose deaths in three distinct waves. The first wave began in the early 1990s and is characterized by the rise in opioid prescriptions, with a subsequent increase in prescription opioid-related overdose deaths. The second wave is marked by the rise in heroin-related overdose deaths that began in 2010. Lastly, the third wave in 2013 is distinguished by the increase in synthetic opioid-related overdose deaths, particularly those involving illicitly-manufactured fentanyl.[6] In 2010, opioid-related overdose deaths substantially surpassed deaths from any other drug class.[7] By 2016, death rates related to opioids, including prescription opioids, heroin, and illicitly-manufactured fentanyl, had increased five-fold since 1999.[6]

Doctor shopping

The rise in popularity and utilization of opioids is accompanied by an upsurge in drug diversion activities.[8] In 2008, the United States Department of Justice found that doctor shopping is a principle method for obtaining controlled substances for illegitimate (non-medical) use.[9,10] The term "doctor shopping" describes patients that receive multiple prescriptions for controlled substances from multiple providers.[11] According to a 2013 report from the Substance Abuse and Mental Health Services Administration (SAMHSA), only 3.1 percent of survey respondents indicated doctor shopping as a source of obtaining prescription pain relievers for non-medical use.[12] The latest available data from the National Survey on Drug Use and Health in the United States showed that there were 11.5 million non-medical users of prescription opioids in 2016, a greater than ten percent increase from 2002.[13,14]

A study conducted by the United States Government Accountability Office (GAO) found that over 170,000 Medicare beneficiaries received prescriptions for controlled substances from five or more medical providers. Of those Medicare beneficiaries, 600 received prescriptions from 21 to 87 medical providers. The results of this 2008 study lead to the 2011 testimony of GAO managing director, Gregory Kutz, to conclude that the United States government has been supporting and disguising an addiction to prescription drugs.[10]

The economic burden of prescription drug diversion is estimated to be approximately $72 billion per year. Financial costs are associated with increased healthcare costs, productivity loss, criminal activity, and incarceration.[15,16] In 2016, in response to the rapid increase in drug diversion and abuse, the United States Office of National Drug Control Policy (ONDC) called for a 15% reduction in prescription drug abuse and diversion with a recommendation to expand prescription drug monitoring programs nationwide.[17]

Prescription drug monitoring programs

In the 1990s, prior to the prevalence of electronic databases, the United States had a paper-prescription monitoring program, known as 'triplicate prescriptions' or 'multiple copy prescriptions'. It required medical providers to use triplicate prescription pads for controlled substances, with one copy going to the pharmacy, one to the prescribing provider, and one to the state. Providers could access a patient's controlled substance prescription history after submitting a written request in the mail. Due to this lengthy process, triplicate prescriptions do not allow for real-time assessment of a patient's controlled substance dispensing history. Because paper programs were time-consuming, burdensome, and expensive, they were ultimately considered ineffective against drug diversion activities.[18]

Prescription drug monitoring programs (PDMPs) replaced paper programs and were started in the United States in 2003. They serve to function as easily-accessible statewide electronic databases that collect prescribing and dispensing data of controlled substances. Pharmacists are required to enter prescriptions of controlled substances, as specified by the governing state, into the database. Registered medical providers can conveniently access patient data to check the quantity and types of controlled substances prescribed for patients by other providers.[18,19]

As of 2017, all 50 states and Washington D.C. have operational PDMPs. Missouri's PDMP remains the only program that is not operational state-wide.[20] This paper seeks to describe published peer-reviewed scientific literature focused on prescription drug monitoring programs. Existing literature will be reviewed to discuss: the impact of prescription drug monitoring programs on (1) the prescribing practices of opioids, (2) patient behavior, and (3) opioid-related population health outcomes.

Methods

Search strategies

The primary objective of this paper is to identify, review, and describe the available evidence regarding the impact of prescription drug monitoring programs on opioid-related outcomes. Peer-reviewed research articles, literature reviews, and opinion articles on prescription drug monitoring programs were identified by initially searching PubMed/Medline. CINAHL, Embase, and PsycInfo were used as alternative databases. The majority of literature on prescription drug monitoring programs were primarily published between 2001 and 2012.[21] To ensure inclusion of relevant studies, articles published between 2000 and 2017 were included in the search. The keywords and MeSH terms used were: "prescription drug monitoring programs", "PDMP", and "opioid". The initial search results yielded 166 unique articles. Systematic reviews, commentaries, editorials, and non-United States studies were excluded. Nineteen relevant articles and studies were identified using this approach. An additional five articles were identified and reviewed from manually searching article references for applicable papers. Most studies were excluded from our analysis because of their editorial nature. Several studies were also excluded because their impact analyses combined prescription opioids with other controlled substances, such as benzodiazepines.

Table 1. Summary of Search Methods

Primary objective:	Describe available literature regarding impact of prescription drug monitoring programs on the following opioid-related outcomes: (1) opioid-prescribing behavior, (2) patient behavior, and (3) opioid-related health outcomes.
Keywords, MeSH terms:	"prescription drug monitoring programs" OR "PDMP" OR "prescription monitoring programs" AND "opioid" Additional studies were identified using article references.
Published dates:	1/1/2000-12/31/2017
Inclusion criteria:	English language, human, original primary research, direct assessment of outcomes related to impact of PDMP implementation.

Study selection:	Abstracts and titles were reviewed, and irrelevant and duplicate articles were identified. Systematic reviews, commentaries, and non-United States studies were excluded.

Data synthesis and analysis

The full text of original articles that met inclusion criteria were reviewed and examined. Articles were divided into three distinct categories: the impact of PDMPs on (1) opioid prescribing behavior, (2) patient behavior, and (3) opioid-related health outcomes. Among the articles identified, a wide range of research design and primary endpoint variables were employed. To prevent the author from excluding relevant and important study findings, a decision was made to use a data chart to summarize research findings.

Results

Table 2. Characteristics of Included Studies.

First Author, Year	Study Period	Setting	Data Source
Domain 1: Impact of PDMPs on opioid prescribing behavior			
Bao, 2016	2001-2010	24 states	National Ambulatory Medical Care Survey
Moyo, 2017	2007-2012	10 states	Opioid prescription claims among Medicare beneficiaries
Wen, 2017	2011-2014	46 states	Medicaid drug utilization data
Baehren, 2010	2008	Single-center ED[a] (Toledo, OH)	Study-specific pre- and post-PDMP[a] review survey
Weiner, 2013	2011-2013	2 urban trauma centers (Massachusetts)	Study-specific pre- and post-PDMP review survey
Paulozzi, 2011[b]	1999-2005	50 states and Washington D.C.	Automation of Reports and Consolidated Orders System
Brady, 2014	1999-2008	50 states and Washington D.C.	Automation of Reports and Consolidated Orders System
Rasubala, 2015	2012-2014	New York	Electronic medical records at dental urgent care center
Rutkow, 2015	2010-2012	Florida, Georgia	IMS Health LifeLink LRx database
Brown, 2017[b]	2010-2015	New York	Automation of Reports and Consolidated Orders System
Chang, 2016	2010-2012	Florida, Georgia	IMS Health LifeLink LRx database
Simoni-Wastila, 2012	2007	50 states and Washington D.C.	Coordination of Benefits Market Scan claims data
Domain 2: Impact of PDMPs on patient behavior			

First Author, Year	Study Period	Setting	Data Source
Meara, 2016[b]	2006-2012	50 states and Washington D.C.	Medicare medical claims data
Surratt, 2014	2010-2011	Florida	RADARS[a] System
Reifler, 2012[b]	2003-2009	50 states and Washington D.C.	RADARS System Poison Center and Opioid Treatment surveillance databases
Ali, 2017	2004-2014	50 states and Washington D.C.	National Survey of Drug Use and Health
Domain 3: Impact of PDMPs on population health outcomes			
First Author, Year	**Study Period**	**Setting**	**Data Source**
Li, 2014	1999-2008	50 states and Washington D.C.	National Center for Health Statistics database
Meara, 2016 [b]	2006-2012	50 states and Washington D.C.	Medicare medical claims data
Patrick, 2016	1999-2013	35 states	LawAtlas database, WONDER[a] database
Pardo, 2017	1999-2014	50 states and Washington D.C.	WONDER database
Paulozzi, 2011[b]	1999-2005	50 states and Washington D.C.	National Center for Health Statistics
Reisman, 2009	1997-2003	50 states and Washington D.C.	Treatment Episode Data Sets
Reifler, 2012 [b]	2003-2009	50 states and Washington D.C.	RADARS System Poison Center and Opioid Treatment surveillance databases
Delcher, 2015	2003-2012	Florida	Florida Medical Examiners Commission
Maughan, 2015	2004-2011	11 multi-state metropolitan areas	Drug Abuse Warning Network
Brown, 2017 [b]	2010-2015	New York	Statewide Planning and Research Cooperative System
Young, 2017	1999-2014	50 states and Washington D.C.	National Center for Health Statistics database and WONDER database
Phillips, 2017	2011-2014	50 states and Washington D.C.	WONDER database

[a] *ED* emergency department; *PDMP* prescription drug monitoring program; *RADARS* research, abuse, diversion, and addiction-related surveillance; *WONDER* wide-ranging online data for epidemiologic research
[b] Article findings address more than one domain of opioid-related outcomes.

Research Findings

The following tables provide a summary of the articles reviewed. A data chart was formulated to extract outcome measures, study design, primary study findings, and whether the study provides findings indicative of a significant impact on opioid-related outcomes. The articles were further subdivided based on key domains of impact: (1) opioid prescribing behavior, (2) patient behavior, and (3) opioid-related health outcomes.

Table 3. Studies of Prescription Drug Monitoring Program Impact on Opioid Prescribing Behavior (Domain 1)

First Author, Year	Outcome Measure	Design/Methods	Findings	Evidence for PDMP Impact
Bao, 2016 [22]	▪ Prescription of at least one Schedule II[a] opioid analgesic ▪ Prescription of at least one opioid of any kind.	**Comparison:** 24 PDMP[b] states **Control:** non-PDMP states **Time:** 2011-2014 **Statistical method:** linear probability regression model	PDMP implementation was associated with a greater than 30% reduction in the rate of prescribing Schedule II opioids.	Yes
Moyo, 2017 [23]	▪ Monthly total opioid volume ▪ Mean daily MME[b] dose per prescription ▪ Number of opioid prescriptions dispensed ▪ Total opioid volume dispensed	**Comparison:** 14 PDMP states **Control:** 5 geographically proximal non-PDMP states **Time:** 2007-2012 **Statistical method:** interrupted time-series regression analyses	PDMP implementation was associated with reduced monthly total opioid volume (-2.36 kg/month) and no changes in mean MMEs or opioid prescriptions dispensed compared to non-PDMP states.	Yes
Wen, 2017 [24]	▪ Number of filled prescriptions (both new prescriptions and refills) ▪ Amount of pre-rebate Medicaid spending on prescription opioids	**Comparison:** PDMP states with registration or use mandates **Control:** PDMP states with no mandates **Time:** 2007-2012 **Statistical method:** linear regression model	PDMP mandates of any kind (either registration or use) were associated a nine to ten percent reduction in population-adjusted numbers of Schedule II opioids.	Yes
Baehren, 2010 [25]	▪ Change in opioid prescription writing from predicted before PDMP database review	**Comparison:** ED provider assessment post-PDMP review **Control:** ED provider assessment pre-PDMP review **Time:** Jun – Jul 2008 **Statistical method:** descriptive statistics	After reviewing patient in PDMP, overall opioid prescribing was altered for 41% of patients. In cases of altered management, 61% resulted in fewer or no opioid medications prescribed compared with pre-PDMP assessment.	Yes

Weiner, 2013 [26]	▪ Change in opioid prescription writing from predicted before PDMP database review	**Comparison:** ED provider assessment post-PDMP review **Control:** ED provider assessment pre-PDMP review **Time:** 2011-2013 **Statistical method:** multiple logistic regression analysis	ED providers changed plans to prescribe opioids in 9.5% of cases, with 6.5% of patients receiving opioids not previously planned.	No
Paulozzi, 2011 [27]	▪ MME rates of opioid consumption	**Comparison:** 19 PDMP states **Control:** 31 non-PDMP states **Time:** 1999-2005 **Statistical method:** linear regression models for multiple parallel time series (panel regression)	PDMP and non-PDMP states had almost identical mean MME rates each year and over the entire study period. MME rates from Schedule III opioids were significantly higher (about 20 MME/person) in PDMP states compared with non-PDMP states.[b]	No
		Comparison: 13 proactive[c] PDMP states **Control:** 6 non-proactive PDMP states **Time:** 1999-2005 **Statistical method:** linear regression models for multiple parallel time series (panel regression)	Proactive PDMP states did not have lower MME rates than other PDMP states. Analysis for individual states showed that three states had significantly lower use of prescription opioid drugs.	No
Brady, 2014 [28]	▪ MME of opioids dispensed per person	**Comparison:** 31 PDMP states **Control:** 19 non- PDMP states **Time:** 1999-2008 **Statistical method:** linear regression model	There was no statistically significant difference in MMEs dispensed with and without PDMPs. Effect varied markedly by state (significantly fewer in nine states, no significant effect in 14 states, and a significant increase in eight states).	No
		Comparison: PDMP states with certain characteristics[d] **Control:** PDMP states without certain characteristics. **Time:** 1999-2008 **Statistical method:** linear regression model	The amount of MMEs dispensed was less in PDMPs with the following features: ▪ Governed by state health departments. ▪ No statutory requirements for committee oversight. ▪ No laws that explicitly impose no expectation on providers to access statewide electronic PDMP data.	No

Rasubala, 2015 [29]	▪ Frequency of opioid prescriptions ▪ Quantity of opioid prescriptions	**Comparison:** post-PDMP implementation in a single dental urgent care in New York (NY) State **Control:** pre-PDMP implementation in a single dental urgent care in NY State **Time:** 2012-2014 **Statistical method:** descriptive statistics	Compared to pre-PDMP, the odds for a patient to receive opioid analgesics was reduced by 58% (OR[b] 0.42) in the first three-months post-PDMP and 72% (OR 0.28) in the second three-months post-PDMP. By the end of the study, the total absolute quantity of opioids prescribed was reduced by 78%.	Yes
Rutkow, 2015 [30]	▪ Total opioid volume supply (MME doses) ▪ Mean MME per transaction ▪ Days' supply per transaction ▪ Total number of opioid prescriptions dispensed	**Comparison:** Florida (PDMP and pill mill laws[e]) **Control:** Georgia (no PDMP and pill mill laws) **Time:** 2010-2012 **Statistical method:** interrupted time-series analysis	When comparing pre-PDMP and post-PDMP periods in Florida, total opioid volume in FL was significantly reduced (2.5 kg/month). Mean MME per transaction was significantly reduced (0.45 mg/month). There was no apparent effect on days' supply per transaction or on total number of opioid prescriptions dispensed.	Yes
Chang, 2016 [31]		**Comparison:** high-risk prescribers[f] in Florida (PDMP and pill mill laws[e]) **Control:** low-risk prescribers in Florida, Georgia **Time:** 2010-2012 **Statistical method:** interrupted time-series analysis	When comparing the impact of PDMPs on high-risk providers versus low-risk providers, there was clinically significant reductions in monthly trends in the following outcomes: ▪ Number of patients with an opioid prescription (-536 patients/month) ▪ Average MME per transaction (-0.88 MME/month/transaction) ▪ Total opioid volume (-3.88 kg/month) ▪ Number of opioid prescriptions (-847 prescriptions/month)	Yes
Brown, 2017 [32]	▪ Annual MME of opioids ▪ Total number of opioid prescriptions dispensed	**Comparison:** post-PDMP **Control:** pre-PDMP **Time:** 2010-2015 **Statistical method:** interrupted time-series analysis	There was a significant decline in distribution of MMEs prior to PDMP implementation with a significant increase following implementation. Not enough data was available to draw a conclusion about the trend in the number of opioid prescriptions filled post-PDMP implementation.	No

Simoni-Wastila, 2012 [33]	▪ Odds of receiving opioid prescription	**Comparison:** 28 PDMP states **Control:** 22 non-PDMP states **Time:** 2007 **Statistical method:** logistic regression analysis	Among analgesic users, the odds of receiving Schedule II opioids was lowest in states with combined electronic PDMPs and serialized prescription overlay (OR 0.54), followed by states with only electronic PDMPs (OR 0.76) relative to non-PDMP states.	Yes

[a] Controlled substances are divided into five schedules with Schedule I having the highest potential for abuse and strictest regulations and Schedule V having the lowest potential for abuse. In 2014, the Drug Enforcement Agency (DEA) reclassified a major subclass of Schedule III opioids (combination drugs containing hydrocodone, such as Vicodin and Lortab) to Schedule II.
[b] *PDMP* prescription drug monitoring program; *MME* morphine milligram equivalent; *ED* emergency department; *OR* odds ratio
[c] Proactive PDMPs are defined as those generating reports for prescribers, dispensers, or law enforcement authorities without being solicited.
[d] Individual PDMP characteristics that were compared were (1) the PDMP governing agency, (2) the statutory requirements for committee oversight, and (3) presence of explicit laws that impose no expectation on providers.
[e] Pill mill laws required clinics to register with the state and have a physician-owner, created inspection requirements, and established prescribing and dispensing requirements and prohibitions for physicians at these clinics.
[f] High-risk providers were identified as providers in the top fifth percentile of opioid volume during four consecutive calendar quarters.

Domain 1 findings: PDMP impact on opioid prescribing behavior

Our literature search identified 11 studies that investigated the efficacy of prescription drug monitoring programs on opioid prescribing behavior (Table 3). The effect of PDMPs on opioid prescribing behavior is one of the most studied of the three domains we investigated. There was an expansive time period covered by these studies, ranging from as early as 1999 to as late as 2015. In quantifying changes in opioid prescribing behavior, total opioid volumes and the number of opioid prescriptions dispensed were commonly used as primary outcome measures. Routinely, opioids were converted to their morphine milligram equivalents (MME) to adjust for differences in opioid potency. Overall, findings were mixed on whether the implementation of prescription drug monitoring programs were associated with significant reduction in opioid prescribing behavior.

Nine out of the 11 studies included were observational studies that extracted data from a diverse set of databases to analyze opioid trends in relation to PDMP implementation. Four studies obtained their findings by comparing PDMP states to non-PDMP states in the same time interval. Four studies employed a before-and-after design that evaluated changes in opioid dispensing rates as a response to PDMP implementation. Rutkow et al. and Chang et al. used a combination of both study designs. In both studies, the opioid dispensing rates in Florida were compared pre- and post-PDMP implementation.[31] Georgia, which had neither an established PDMP nor pill mill legislation at the time, was used as a control for additional comparison.

Two experimental studies evaluated the effect of PDMP review on opioid prescribing practices in an emergency department (ED) setting.[25,26] Despite being conducted in different geographic locations and in different time periods, both study designs were strikingly similar. In both studies, ED providers were asked about anticipated pain prescriptions pre- and post-review of a patient's PDMP data. The primary outcome measure was the frequency of change in opioid prescriptions after review of patient PDMP data. Interestingly, despite the similarities in methodology, the findings were remarkably different. Baehren et al. demonstrated that utilization of PDMPs resulted in a significant reduction in the opioid prescriptions; 61% of patients received fewer or no opioids prescribed compared with pre-PDMP predictions.[25] Conversely, Weiner and colleagues could not show that PDMP review resulted in any significant reduction in opioid prescribing behavior.[26] In Weiner et al.'s experiment, only 9.5% of ED cases showed a modification in opioid prescribing, with 6.5% of patients actually receiving more opioids than previously planned.[26]

There were three studies identified that specifically examined the effectiveness of certain PDMP characteristics in changing opioid prescribing behavior.[24,27,34] Wen et al. described the effectiveness of mandates that required provider registration or use; all mandates were associated with a nine to ten percent reduction in Schedule II opioid prescriptions. Interestingly, there was no significant difference in the effect between mandates that required registration versus mandates that required utilization. Paulozzi et al.'s study revealed that states that proactively generated PDMP reports for providers, dispensers, and law enforcement did not have any significant reduction in total opioid volume rates when compared to other PDMP states.[27] Lastly, Brady et al. evaluated three distinct PDMP characteristics: (1) the governing agency, (2) the statutory requirements for committee oversight, and (3) the presence of laws that explicitly impose no expectation on providers to use PDMPs.[34] In this study, there was a reduction of opioids dispensed when PDMPs were governed by state health departments, when there was no statutory requirement for committee oversight, or when there was no explicit provision in the law that exempted providers from the obligation of accessing the state PDMP database.

Table 4. Studies of Prescription Drug Monitoring Program Impact on Patient Behavior (Domain 2)

First Author, Year	Outcome Measure	Design/Methods	Findings	Evidence for PDMP Impact
Meara, 2016 [35]	▪ Annual prevalence of beneficiaries with four or more opioid prescribers ▪ Annual prevalence of prescriptions yielding a daily MME[a] of more than 120 mg	**Comparison:** post-PDMP[a] states **Control:** pre-PDMP states **Time:** 2006-2012 **Statistical method:** logistic regression modeling	In the post-PDMP period within a state, no significant reduction was seen in patients with four or more opioid prescribers (-0.14 percentage points). No significant decline was seen with a daily MME of more than 120 mg (0.27 percentage points).	No

Surratt, 2014 [36]	▪ Diversion rates for each opioid class	**Comparison:** post-PDMP in Florida **Control:** pre-PDMP in Florida **Time:** 2009-2012 **Statistical method:** multilevel logistic regression modeling	Significant declines were observed in the average diversion rates for oxycodone (slope -1.31), morphine (slope -0.13), and methadone (slope -0.23). The diversion rate for hydrocodone also trended downward but did not reach statistical significance.	Yes
Reifler, 2012 [37]	▪ Number of cases of intentional exposure to opioids	**Comparison:** PDMP states **Control:** non-PDMP states **Time:** 2003-2009 **Statistical method:** logistic regression modeling	Compared to states with PDMPs, states without PDMPs had a 0.2% increase in intentional opioid exposures per quarter.	Yes
Ali, 2017 [38]	▪ Non-medical opioid use in the past year ▪ Number of respondents who received opioids for non-medical use from two or more prescribers	**Comparison:** 36 PDMP states **Control:** 14 non-PDMP states **Time:** 2004-2014 **Statistical method:** logistic regression modeling	Having an operational PDMP is associated with a reduction of approximately 10 days of non-medical opioid use in the past year. PDMPs are associated with a 56% reduction in receipt of nonmedical opioids from two or more doctors.	Yes
		Comparison: PDMP states with mandatory enrollment or access laws **Control:** PDMP states without mandatory enrollment or access laws **Time:** 2004-2014 **Statistical method:** logistic regression modeling	There is a reduction of approximately 20 days of non-medical opioid use in the past year if the PDMP has provisions that require mandatory enrollment *and* access by providers. PDMPs with mandatory access provision is associated with an 80% reduction in the odds of having two or more doctors as a source of non-medical opioids.	Yes

[a] *MME* morphine milligram equivalent; *PDMP* prescription drug monitoring programs

Domain 2 findings: PDMP impact on patient behavior

There were only four studies identified that evaluated the effect of PDMPs on patient behavior (Table 4). Each study used a different primary outcome measure to quantify changes in patient behavior. These measures included incidence of intentional opioid exposures, opioid diversion rates, and the number of beneficiaries with multiple opioid prescribers. The time period covered by these studies ranged from 2003 to 2014. Two studies compared PDMP states to non-PDMP states in the same time period. Two studies used a before-and-after design, with one study that compared pre- and post-PDMP implementation in only a single state, Florida.

The findings from the three studies were varied. Meara et al. showed that PDMP implementation was not correlated with any significant decrease in the amount of Medicare beneficiaries with four or more opioid providers.[35] Ali et al. also demonstrated similar findings with more compelling reductions in doctor shopping associated with PDMPs with mandatory access laws.[38] However, Reifler et al. found a 0.2% quarterly increase in intentional opioid exposure cases in states without PDMPs compared to states with a PDMP.[37] In comparing opioid diversion rates in Florida, Surrat et al. observed a decrease in the average diversion rates for oxycodone, morphine, and methadone.[36] There was also an observable decrease in hydrocodone diversion rates, but not enough to reach statistical significance.

Table 5. Studies of Prescription Drug Monitoring Program Impact on Population Health Outcomes (Domain 3)

First Author, Year	Outcome Measure	Design/Methods	Findings	Evidence for PDMP Impact

Li, 2014 [28]	▪ Drug overdose mortality	**Comparison:** 31 PDMP[a] states **Control:** 20 non-PDMP states **Time:** 1999-2008 **Statistical method:** multilevel negative binomial logistic regression modeling	PDMPs were associated with an 11% increase in drug overdose mortality, with the greatest increase seen in PDMPs that imposed no expectation on practitioners.[b] Impact of PDMPs on drug overdose mortality varied across states, ranging from 35% decrease (Michigan) to a more than three-fold increase (Nevada).	No
Meara, 2016 [35]	▪ Number of non-fatal prescription opioid overdoses	**Comparison:** pre-PDMP states **Control:** post-PDMP states **Time:** 2006-2012 **Statistical method:** logistic regression modeling	The association between PDMPs and rates of non-fatal prescription-opioid overdose was not significant.	No
Patrick, 2016 [39]	▪ Annual rate of opioid-related overdose deaths	**Comparison:** PDMP states **Control:** non-PDMP states **Time:** 1999-2003 **Statistical method:** interrupted time-series linear regression model	States that implemented a PDMP had a lower opioid-related overdose death rate (6.19 per 100,000), compared to non-PDMP states (6.50 per 100,000). There was an associated 1.12 decline in opioid-related overdose deaths per 100,000 after PDMP implementation.	Yes
		Comparison: PDMP states that monitored at least four drug schedules **Control:** PDMP states that monitored less than four drug schedules **Time:** 1999-2003 **Statistical method:** interrupted time-series linear regression model	PDMPs that monitored four or more drug schedules were associated with a 0.55 reduction in opioid-related overdose deaths per 100,000.[c]	Yes
		Comparison: PDMP states that updated data at least weekly **Control:** PDMP states that did not update data at least weekly **Time:** 1999-2003 **Statistical method:** interrupted time-series linear regression model	PDMPs that updated data at least weekly were associated with a 0.82 reduction in opioid-related overdose deaths per 100,000.[c]	Yes

		Comparison: PDMP states with registration or use mandates **Control:** PDMP states without registration or use mandates **Time:** 1999-2003 **Statistical method:** interrupted time-series linear regression model	State requirements for registration with or use of PDMP did not show significant effect on opioid-related overdose deaths.[c]	No
Pardo, 2017 [40]	▪ Opioid death rates	**Comparison:** PDMP states that were categorized based on strength using a points-based system[d] **Control:** non-PDMP states **Time:** 1999-2014 **Statistical method:** two-way fixed-effects model	There was a one percent reduction in opioid death rates for each point assigned to a state's PDMP strength score. PDMP states with strength scores in the third quartile[e] were associated with an 18% reduction in opioid death rates compared to states with no PDMP.	Yes
Paulozzi, 2011 [27]	▪ Rate of drug overdose mortality ▪ Rate of opioid overdose mortality	**Comparison:** 19 PDMP states **Control:** 31 non-PDMP states **Time:** 1999-2005 **Statistical method:** linear regression models for multiple parallel time series (panel regression)	The differences between PDMP and non-PDMP states were not statistically significant for either mean drug overdose and opioid-related overdose mortality rates.	No
Reisman, 2009 [41]	▪ Inpatient prescription opioid treatment admissions	**Comparison:** 14 PDMP states **Control:** 36 non-PDMP states **Time:** 1997-2003 **Statistical method:** time-series linear regression model	PDMP states have lower increases in opioid admissions during study period and the gap widened with each successive year. A patient admitted to an inpatient drug abuse rehabilitation in a PDMP state was less likely to be admitted for prescription opioid drug abuse (OR 0.775)[a].	Yes
Reifler, 2012 [37]	▪ Number of opioid treatment admissions	**Comparison:** PDMP states **Control:** non-PDMP states **Time:** 2003-2009 **Statistical method:** logistic regression modeling	Opioid treatment admissions increase 4.9% in non-PDMP states and 2.6% in PDMP states	Yes

Delcher, 2015 [42]	▪ Oxycodone-caused deaths	**Comparison:** post-PDMP in Florida **Control:** pre-PDMP in Florida **Time:** 2003-2012 **Statistical method:** logistic regression modeling	In Florida, there was a 25% decline in oxycodone-caused deaths after PDMP implementation. For a system-wide increase of one PDMP query per provider, oxycodone-caused deaths declined at a rate of 0.229 persons per month.	Yes
Maughan, 2015 [43]	▪ Rates of opioid-related ED[a] visits	**Comparison:** 11 post-PDMP metropolitan areas in the United States **Control:** 11 pre-PDMP metropolitan areas in the United States **Time:** 2004-2011 **Statistical method:** logistic regression modeling	Rates of opioid-related ED visits increased in all metropolitan areas, and the increase was similar when grouped by year of PDMP implementation.	No
Brown, 2017 [32]	▪ Prescription opioid dose overdoses	**Comparison:** post-PDMP implementation **Control:** pre-PDMP implementation **Time:** 2010-2015 **Statistical method:** interrupted time-series analysis	There was no significant difference in the prescription opioid overdose slopes after PDMP implementation compared to before PDMP implementation.	No
Nam, 2017 [44]	▪ Prescription drug overdose mortality rates	**Comparison:** PDMP states **Control:** non-PDMP states **Time:** 1999-2014 **Statistical method:** logistic regression modeling	PDMPs were not associated with reductions in prescription opioid overdose mortality rates relative to expected rates in non-PDMP states. PDMPs were associated with increased mortality rates, but associations were not statistically significant.	No
Phillips, 2017 [45]	▪ Mean age-adjusted opioid-related mortality	**Comparison:** PDMP states **Control:** non-PDMP states **Time:** 2011-2014 **Statistical method:** interrupted time-series analysis	PDMPs were associated with an increase of 11.4% in mean age-adjusted opioid-related mortality. For every additional year since enactment, mortality rate increased by 5.8% for states with a PDMP compared to states without a PDMP.	No

[a] *PDMP* prescription drug monitoring programs; *PDAP* prescription drug abuse policy system; *OR* odds ratio; *ED* emergency department

[b] Of the 31 implemented PDMPs included in the study, 11 contained provisions exempting providers from the obligation to access the state PDMP database.
[c] West Virginia was excluded in this analysis because it was an extreme outlier, with an opioid-related overdose death rate nearly twice as high as that of the next highest state. It also implemented a program early in the study period.
[d] Specific features of PDMPs were assigned a score from zero to four based on the strength of evidence provided by analytic studies. For example, requirements for providers to check PDMPs prior to prescribing were assigned four points, while features that required law enforcement access were only allotted one point.
[e] PDMP strength scores were collapsed into four different quartiles (scores 1-7=1, scores 8-10=2, scores 11-13=3; and scores 14-21=4).

Domain 3 findings: PDMP impact on opioid-related population health outcomes

Database results yielded 12 studies that assessed the effect of PDMPs on opioid-related population health outcomes (Table 5). Primary outcome measures in these studies were commonly related to opioid-related mortality rates. Opioid mortality rates were derived from a variety of different databases, including but not limited to the National Center for Health Statistics and Medicare claims data(Table 2). The years covered by these studies ranged from 1999 to 2015. Eight studies compared PDMP states to non-PDMP states in the same time period. Only four studies used a before-and-after design that compared opioid population health outcomes pre- and post-PDMP implementation. Similar to the other domains, the results of PDMP effects on opioid-related health outcomes were mixed.

Of the seven studies that looked at opioid-related drug mortality rates, four studies did not support an association of PDMPs with a reduction in opioid overdose mortality rates (Table 5).[27,28] Using data from the National Center for Health Statistics, Li et al. revealed that there was an 11% increase in drug overdose mortality in PDMP states compared to non-PDMP states. However, in Li's study, the impact of PDMPs on opioid-related overdose mortality had wide variability across states (Table 5).[28]

There were three studies that used opioid-related admissions and/or ED visits as the primary outcome measure (Table 5). In two studies that directly compared PDMP states to non-

PDMP states, PDMP states were associated with lower rates of opioid-related treatment admissions.[37,41] However, Maughan and colleague's study on 11 metropolitan areas pre- and post-PDMP implementation showed no significant reduction in opioid-related ED visits when PDMPs were enacted.[43]

In their respective papers, Patrick and Pardo delved further in evaluating the effectiveness of specific PDMP characteristics.[39,40] Patrick et al. showed that certain PDMP characteristics, such as the monitoring of at least four drug schedules and requiring weekly system updates, were associated with reduction in opioid-related deaths.[39] Conversely, there was no statistically significant effect of PDMP registration and use mandates on opioid-related deaths.[39]

In a unique approach, Pardo et al. designed a strength-based point system to assess the cumulative effect of specific PDMP characteristics on opioid-death rates.[40] Certain PDMP features were assigned a score from zero to four based on strength of evidence from prior research. The highest score of four was assigned to characteristics that were considered to have strong evidence-based backing. After considering all the features of each drug monitoring programs, each PDMP was given a summative strength score and categorized into different quartiles (Table 5). Pardo's research demonstrated that PDMP states with strength scores in the third quartile (scores of 11-13) were associated with an 18% reduction in opioid death rates compared to states with no PDMP.[40]

Discussion

The current literature evaluating the theoretical benefits of prescription drug monitoring programs are well-described but are poorly studied. Evaluation of prescription drug monitoring programs is predicated on the premise that increased monitoring and reporting of opioid prescriptions will be associated with corresponding changes in opioid-related outcomes. High-risk drug-seeking behavior, such as obtaining prescriptions from multiple providers or multiple pharmacies, can be identified with the utilization of PDMPs. When these behavior patterns are recognized, providers are subsequently expected to reduce their opioid prescribing, thus decreasing misuse and diversion and ultimately decreasing opioid-related mortality and morbidity. Therefore, opioid-related outcomes can be categorized into domains that include changes in provider opioid-prescribing behavior, overall opioid supply, drug diversion activities, and opioid-related morbidity and mortality outcomes.

Review of current literature reveals mixed effects of prescription drug monitoring programs on opioid-related outcomes. The wide discrepancy in results is likely due to study-related factors, such as differences in outcome measurements, study design (across-state versus within-state comparisons), data sources, exposures, and statistical approaches. It is these same factors that make it difficult to make direct comparisons between study results.

Additionally, PDMP characteristics vary considerably across states in both legislated components and implementation strategies. Legislated components include the state-mandated frequency in which data is entered into the system, the ease of accessing information, the types of providers allowed and/or required to register, and the amount of training providers receive in the utilization of their state's system. Another factor that complicates review is that drug monitoring programs were enacted across states at different times, resulting in variable levels of provider experience and comfort with their state's program.

Limitations

Conducting a well-designed randomized controlled trial to assess the effectiveness of PDMPs is challenging. Thus, observational cohort studies are increasingly utilized. The strength of observational studies is limited because of susceptibility to bias due to the confounding factors. As such, sophisticated multivariable techniques are often required to account for these factors. The employment of different analytical approaches across different papers makes it difficult to directly compare results from multiple studies.

Given the variability of the state-specific features of each drug monitoring program, it is difficult to assess whether results can be attributed to the establishment of PDMPs and not to other possible causes. For example, Florida's prescription drug monitoring program and pill mill laws were enacted at the same time. The individual effect of PDMPs in Florida cannot be accurately determined because it cannot be separated from the effect of concurrent pill mill legislation. In another example, states with stricter use mandates might have a more rapid growth in the opioid epidemic compared to other states. Without sufficient analytic control such confounding factors could lead to biased results, and researchers may fail to find an effect of mandates, even if one exists.[24]

Furthermore, in comparisons of PDMP states to non-PDMP states, state-to-state variability in impact (i.e., heterogeneity of effects) can mask important findings.[23] In Li et al.'s study, there was an observed 11% increase in opioid-related overdose mortality in PDMP states. However, further analysis showed that the impact of PDMPs on opioid mortality varied widely across states, ranging from a 35% decrease in Michigan to a greater than three-fold increase in Nevada. Significant state-to-state variability could also be seen in Brady et al.'s study.[34] In studying the impact of PDMPs on total opioids dispensed, Brady and colleagues showed a significant reduction in MMEs dispensed in nine states and a significant increase in eight states.

Directions for future research

Although PDMPs across states are similar in basic elements, many characteristics of these programs vary from state to state. Given the heterogeneity of state-specific characteristics of any single drug monitoring program, it is difficult to generalize that the findings in one state will hold for other states and at other periods of time. On the other hand, the inconsistency between PDMP characteristics among states can provide valuable insight on specific features that are more effective at impacting opioid-related behaviors.

There were several authors in this review that attempted to address the effectiveness of specific PDMP characteristics. However, in reality, most programs implement multiple features and it is difficult to discern the individual effectiveness of a specific feature. Pardo's approach of utilizing a strength-based scoring system for PDMPs was unique. Points were designated to specific features based on the strength of evidence-based research. However, if data was not available, PDMP characteristics were allotted points based on the opinions of a committee of doctors and experts. While Pardo's approach attempts to account for the cumulative effects of multiple PDMP characteristics, his system is at higher risk for bias once points are no longer allotted based on evidenced-based research. For this reason, how different PDMP features impact opioid-related outcomes require closer scrutiny.

There has been much effort in assessing the potential benefits of prescription drug monitoring programs. However, there is minimal focus on its potential harms. The most frequently touted argument against drug monitoring programs is referred to as the "chilling effect". The "chilling effect" refers to the hesitance or resistance of providers to prescribe opioid analgesics even to appropriate candidates, leaving patients seeking illegitimate means to manage their pain.[24,46] All of the studies reviewed in this paper did not include data to determine the appropriateness of opioid prescribing or non-prescribing. There is a paucity of research directed toward whether prescription drug monitoring programs have a negative impact on a patient's pain management needs.

Conclusion

Literature surrounding drug monitoring programs remains relatively nascent. As PDMP implementation and widespread program reform continues to expand and evolve over time, there needs to be continued research on the impact of specific program characteristics to determine what is most effective at reducing opioid-related outcomes. Development of a more sophisticated and universal analysis of these programs will provide an evidenced-based foundation to help establish drug monitoring programs that reaches their full potential in reducing opioid-related harms across the country.

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