Supplementary Material*

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Supplement 1. **Protocol**

Supplement 2. **Appendix Table**

* This supplementary material was provided by the authors to give readers further details on their article. The material was reviewed but not copyedited.

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Supplement 1
Protocol

A systematic review of the Effect of Prescription Drug Monitoring Programs on Nonfatal and Fatal Drug Overdoses

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Review question
Do states that implement a prescription drug monitoring program (PDMP) experience a change in nonfatal or fatal drug-related overdoses. For this review, we will consider the following classes of overdoses: drugs (in general), opioids (in general), and prescription opioids.
Do certain PDMP provisions differentially effect nonfatal and fatal overdoses?
Do PDMPs unintentionally increase heroin-related overdoses?

Searches
Systematic search strategy will be delineated in cooperation with a professional librarian and using a combination of the following terms listed below. Several electronic sources will be searched for eligible articles, including Medline (via Web of Science), Social Sciences Citation Index (Web of Science Core Collection), Current Contents Connects, and Science Citation Index. We will search ProQuest Dissertations for dissertations using the same search terms. Additionally, we will scan references from included articles to identify other potentially relevant studies.

Search Terms:
Program terms: Prescription drug monitoring program*, prescription drug polic*, opioid polic*, drug polic*, substance abuse polic*, substance use polic*
Outcome terms: Prescription drug*, overdose, opioid*, prescription opioid, heroin.
Data Range: Database source inception date to present

Types of study to be included
Inclusion criteria: We will include all studies that include exposure (i.e., PDMP implementation) and outcomes (i.e., nonfatal and fatal drug overdoses) regardless of design. Thus, studies that examine the pre- and post-implementation effect of PDMPs on the outcomes will be included. Only studies examining programs operating in the United States will be included. Articles written in English will be included. Only full text articles and dissertations will be considered. Exclusion criteria: No studies will be excluded based on study design.

Conditions or domain being studied
Temporal changes in nonfatal and fatal drug-related overdoses attributable to PDMPs.

Participants/population
Studies included will involve people living in the United States.

Intervention(s), exposure(s)
State implementation of a PDMP

Comparator(s)/control
Because 49 of 50 states have implemented a PDMP, studies may not have a true control group. If present, control groups will consist of states who have not yet implemented their PDMP at the

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time of study. While we will include studies that do not use a comparator control, such studies will be considered a lower level of evidence.

Primary outcome(s)
Nonfatal and fatal drug-related overdoses. Nonfatal drug-related overdoses, including poisonings, hospitalizations, or emergency department visits.

Secondary outcomes(s)
Adverse drug events related to heroin use or abuse, including overdose deaths, poisonings, hospitalizations, or emergency department visits

Data extraction
Upon completion of the search process, two authors will perform the study selection independently and then compared. If discrepancy arise and cannot be resolved, the first-author will be consulted. Titles and abstracts will be screened and excluded if irrelevance can be clearly seen at this step. After the title and abstract review, the full texts of all possibly relevant articles will be obtained and checked for eligibility. Subsequently, data will be extracted using a standardized spreadsheet independently by two members of the research team and the compared. If discrepancies exist, the first-author will review and make a final decision. The standardized spreadsheet will contain questions on the studies' methodology, such as (i) the characteristics of the publication (author, year, title); (ii) study design (country, study type, study population); (iii) characteristics of the intervention investigated (type of PDMP, specific operational characteristics); (iv) method of exposure assessment; (v) method of outcome assessment; (vi) statistical analyses; (vii) results; and (viii) any evidence of risk of bias in the single study. Information on effect estimates will be derived from primary articles. If the respective 95% confidence intervals are not available, authors will be contacted for further information.

Risk of bias (quality) assessment
Because of the nature of the question, we anticipate all evidence will be derived from observational studies. We will use the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I). The ROBINS-I is concerned with evaluating the risk of bias (RoB) in quantitative studies estimating the effectiveness of an intervention, which did not use randomization to allocate units. The ROBINS-I is based on the Cochrane RoB tool for randomized trials. The ROBINS-I will be used to evaluate the overall quality of the study and identify major risks of bias present in the study. Study quality will be independently evaluated by two authors and discrepancies will be resolved by the first author.

Strategy for data synthesis
We do not anticipate synthesizing data.

Analysis of subgroups or subsets
We do not anticipate having sufficient studies for quantitative subgroup analysis. We will consider variation in findings between studies qualitatively based on characteristics of study, setting, and outcomes.

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Conflicts of interest
None known

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Appendix Table 1. Observational Studies Estimating the Association between Prescription Drug Monitoring Programs on Nonfatal and Fatal Overdoses

Study, Publication Year (Reference)	Study Design	Intervention	Outcome data source (Study Years)	State(s)	Risk of Bias	Summary of outcome(s) and direction of results	
						Nonfatal Outcomes (N=4)	Fatal Outcomes (N=13)
Maughan, 2015 (31)	Difference-in-differences estimation (GEE) with adjustment for metropolitan area factors	PDMP operational	Opioid ED visits from Drug Abuse Warning Network (DAWN) (2004 to 2011)	11 Multi-state metropolitan areas[a]	Serious	**PDMP Operational** There was no change in the rate of opioid-related ED visits (mean difference 0.8 visits [95% CI, -3.7 to 5.2] per 100,000 residents per quarter).	N/A
Bachhuber, 2016 (30)	Difference-in-differences estimation (GEE) with adjustment for metropolitan area factors	PDMP operational	Benzodiazepine ED visits from Drug Abuse Warning Network (DAWN) (2004 to 2011)	11 Multi-state metropolitan areas[a]	Serious	**PDMP Operational** There was no change in the rate of benzodiazepine-related ED visits (mean difference 0.9 [95% CI, -0.09 to 1.9] visits per 100,000 residents per quarter.	N/A
Brown, 2017 (23)	Interrupted time series without control state	Mandatory use of the program	Prescription opioid ED and inpatient admissions (ICD9 codes 965.00, 965.02, 965.09, E850, E850.1; ICD10 codes T40.0, T40.2, T40.3) and Heroin ED and inpatient admissions (ICD9 codes 965.01, E850.00; ICD10 codes T40.1) Prescription opioid- and heroin-related ED and inpatient admissions (ICD9 codes 965.00, 965.02, 965.09, 965.01, E850,	New York	Critical	**Mandatory use of the Program** There was no change in the rate of prescription opioid-related ED visits and inpatient admissions (F = 1.04; P = .37): The rate of prescription opioid-related ED visits and inpatient admissions switched from an increasing rate of events per quarter during the pre-implementation period (b = 9.5; P = .37) to a flat rate of events per quarter during the post-implementation period (b = -.01; P = .983). There was an increase in the quarterly rate of heroin-related ED visits and inpatient admissions (F = 14.2; P < .001); The post-implementation slope for heroin-related ED visits and	**Mandatory Use of the System** Mandatory use of PDMP was associated with an increase in the quarterly rate of prescription opioid- and heroin-related overdose deaths (F = 5.75; p= .01): The post-implementation slope of combined prescription opioid- and heroin-related deaths increased from 38.3 events per 100,000 (p < .001) to 98.8 events per 100,000 (p < .001)

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			E850.00, E850.1; ICD10 codes T40.0, T40.1, T40.2, T40.3)			inpatient admissions increased from 30 events per 100,000 ($P < .001$) to 101.9 events per 100,000 ($P < .001$)	
Pauly, 2018 (28)	Difference-in-differences estimation (GEE) with adjustment for state area factors	PDMP operational, monitoring schedule V drugs, frequency of reports, proactive reports (PDMP analyzes data proactively) versus reactive (PDMP only responds to data requests), mandatory use of the system	Prescription opioid inpatient or ED visit from Truven Health Marketscan administrative claims data (2004-2014)	50 U.S. states	Serious	**PDMP Operational** Prescription opioid-related inpatient and ED visits decreased 31% (aRR, 0.69; 95% CI, 0.56 to 0.87). **Monitoring Schedule V Drugs** Monitoring Schedules II-IV and Schedules II-V were associated with a 43% decrease (aRR, 0.57; 95% CI, 0.44 to 0.74) and 32% decrease (aRR, 0.68; 95% CI, 0.54 to 0.86), respectively. Monitoring Schedule II only or Schedules II-III did not change overdose rates (aRR, 0.72; 95% CI, 0.43 to 1.19). **Data Reporting Frequency** Weekly or daily data uploads were associated with a 40% (aRR, 0.60; 95%CI: 0.47 to 0.76) and 44% (aRR, 0.56; 95%CI: 0.45 to 0.70) decrease in opioid-related deaths, respectively. Monthly data reporting did not change overdose rates (aRR, 0.87; 95% CI, 0.69 to 1.11). **Proactive reports** Proactive reporting was associated with a 30% decrease (aRR, 0.60; 95% CI, 0.55 to 0.88). **Mandatory Use of the System** Mandatory use of the system was associated with a 42% decrease (aRR, 0.58; 95% CI, 0.44 to 0.78).	N/A
Paulozzi, 2011 (34)	Difference-in-differences estimation (GEE) with adjustment for	PDMP operational	Drug OD (ICD-10 codes X40-44, Y10-Y14) and Prescription opioid OD (ICD-10 codes	50 U.S. states	Moderate	N/A	**PDMP Operational** Nonsignificant change in drug overdose mortality rate ($b = 0.10$; $P = .50$) and opioid overdose mortality rate ($b = 0.09$; $P = .34$).

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	state area factors		T40.2, T40.3, or T40.4) from multiple cause of death mortality files produced by the National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention (1999-2005)				
Kim, 2013 (19)	Difference-in-differences estimation with state and year fixed effects and adjustment for state area factors	PDMP operational, proactive (PDMP analyzes data proactively) versus reactive (PDMP only responds to data requests), interstate sharing, frequency of reports, housing agency, non-schedules monitored	Drug OD (ICD-10 codes X40-44, Y10-Y14, X60-X64) and Prescription opioid OD (ICD-10 codes T40.2, T40.3, or T40.4) from multiple cause of death mortality files produced by the National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention (1999-2008)	50 U.S. states and Washington D.C.	Moderate	N/A	**PDMP Operational** There was no change in opioid-related mortality rates. **Proactive Reports** There was no change in opioid-related mortality rates. **Interstate Sharing** Opioid-related mortality rates decreased 24% (IRR, 0.76; 95% CI, 0.61 to 0.97). **Frequency of Reports** There was no change in opioid-related mortality rates. **Housing Agency** There was no change in opioid-related mortality rates. **Non-Scheduled Drugs Monitored** Monitoring of non-scheduled drugs was associated with a 28% reduction (IRR, 0.72; 95% CI, 0.52, 0.98) in opioid-related deaths.
Li, 2014 (35)	Difference-in-differences estimation	PDMP operational,	Drug OD (ICD-10 codes X40-44, Y10-Y14) from multiple	50 U.S. states and	Serious	N/A	**PDMP Operational**

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	(GEE) with adjustment for state area factors		cause of death mortality files produced by the National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention (1999-2008)	Washington D.C.			Drug-related overdoses increased 11% (aRR, 1.11; 95% CI, 1.02 to 1.21)
Delcher, 2015 (29, 36)	Interrupted time series with control state	PDMP operational	Oxycodone OD and heroin OD as reported to the Florida Medical Examiners Commission (2003-2012)	Florida	Serious	N/A	**PDMP Operational** The number of oxycodone-related deaths declined by 24.7 deaths (95% CI, -42.9 to -6.4) per month and heroin-related deaths increased by 1.26 deaths (95% CI, 0.56 to 1.97) per month after Florida's implementation of their PDMP.
Radakrishnan, 2015 (21)	Difference-in-differences estimation with state and year fixed effects and adjustment for state area factors	PDMP operational	Prescription opioid OD (ICD-10 codes T40.2, T40.3, or T40.4) from multiple cause of death mortality files produced by the National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention (1999-2010)	50 U.S. states and Washington D.C.	Low	N/A	**PDMP Operational** There was no change in mean opioid-related deaths (0.05; 95% CI, -0.14 to 0.24) or heroin-related deaths (-0.03; 95% CI, -0.33 to 0.28).
Kilby, 2015 (32)	Difference-in-differences estimation with state and year fixed effects and adjustment for state area factors	PDMP operational	Prescription opioid OD (ICD-10 codes T40.2, T40.3, or T40.4) and heroin-related OD (T40.1) from multiple cause of death mortality files produced by the National Center for	38 U.S. states	Moderate		**PDMP Operational** PDMP implementation was associated with a 12.5% decline (95% CI, -0.23 to -0.02) in prescription overdose deaths, a nonsignificant decrease in opioid-related mortality rate (-0.8, 95% CI, -0.19 to 0.04), and an increase in heroin overdose deaths in the

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			Health Statistics (NCHS) at the Centers for Disease Control and Prevention (1999-2013)				first year after introduction, but the association reverses and becomes negative (nonsignificant) in years 2 through 4.
Patrick, 2016 (27)	Difference-in-differences estimation with state fixed effects and adjustment for state area factors	PDMP operational, monitoring of nonscheduled drugs, frequency of reports, mandatory registration or use of the program	Drug OD (ICD-10 codes X40-44, Y10-Y14, X60-X64) and Prescription opioid OD (ICD-10 codes T40.2, T40.3, or T40.4) from multiple cause of death mortality files produced by the National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention (1999-2013)	34 U.S. States	Moderate	N/A	**PDMP Operational** PDMP implementation was associated with a decrease of 1.12 opioid-related overdose deaths (95% CI, -1.68 to -0.55) per 100,000 population annually after implementation **Non-Scheduled Drugs Monitored** Monitoring of non-scheduled drugs was associated with a decrease of 0.55 opioid-related overdose deaths (95% CI, -1.02 to -0.08) per 100,000 population annually after implementation **Frequency of Reports** Data updated at least weekly was associated with a decrease of 0.82 opioid-related overdose deaths (95% CI, -1.25 to -0.38) per 100,000 population annually after implementation **Mandatory Use of the System** Mandatory use or registration of PDMP was associated with a nonsignificant change in opioid-related death rates (0.30 opioid-related deaths [95% CI: -0.27, 0.87] per 100,000 population)
Birk, 2017 (20)	Difference-in-differences estimation with state and year fixed effects	PDMP operational, mandatory use of the program;	Opioid OD (ICD-10 codes X40-44, Y10-Y14, X60-X64, X85) and Prescription opioid OD (ICD-10	50 U.S. states	Low	N/A	**PDMP Operational** PDMP implementation was associated with a nonsignificant change in opioid mortality rate (IRR: 0.94; 95% CI: -0.48, 1.15)

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	and adjustment for state area factors	provider access to data	codes T40.0, T40.1, T40.2, T40.3, T40.4, or T40.6) from multiple cause of death mortality files produced by the National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention (1999-2012)				**Mandatory Use of the System** Mandatory use of the system was associated with a 33% reduction (IRR: 0.66; 95% CI: 0.43, 1.02). **Can use the System** PDMPs that allow, not require, provider access was associated with a nonsignificant change in opioid-related deaths
Nam, 2017 (33)	Difference-in-differences estimation with state and year fixed effects and adjustment for state area factors	PDMP operational	Drug OD (ICD-10 codes X40-44, X60-X64, X85, Y10-Y14), legal narcotics (T40.2-40.4), legal narcotics and benzodiazepines (T40.2-T40.4, T42.4), opioids (T40.2), Methadone (T40.3), other synthetic narcotics (T40.4), cocaine (T40.5), benzodiazepines (T42.4) from multiple cause of death mortality files produced by the National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention (1999-2014)	35 U.S. states	Moderate	N/A	**PDMP Operational** PDMP implementation was associated with a nonsignificant change in deaths from drug overdose (RD, 0.08; 95% CI, -0.89 to 1.04), legal narcotics (RD, 0.02; 95% CI, -0.81 to 0.84), legal narcotics and benzodiazepines (RD, 0.08; 95% CI, -0.75 to 0.90), illicit drugs (RD, -0.03; 95% CI, -0.62 to 0.56), opioids (RD, -0.11; 95% CI, -0.57 to 0.34), methadone (RD, 0.17; 95% CI, -0.47 to 0.82), other synthetic narcotics (RD, -0.14; 95% CI, -0.43 to 0.15), cocaine (RD, 0.04; 95% CI, -0.40 to 0.48), or benzodiazepines (RD, -0.20; 95% CI, -0.68 to 0.27)
Meinhofer, 2017 (22)	Difference-in-differences estimation with	PDMP operational, provider	Prescription opioid OD (ICD-10 codes X40-44, X60-X64,	50 U.S. States	Moderate	N/A	**PDMP Operational** PDMP implementation was associated with a nonsignificant

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	state and year fixed effects and adjustment for state area factors	access to data, mandatory use of the system	X85, Y10-Y14) and prescription opioid OD (ICD-10 codes T40.2-T40.4), benzodiazepines (T42.4), cocaine (T40.5), and heroin (T40.1) from multiple cause of death mortality files produced by the National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention (1999-2013)				change in deaths from prescription opioid deaths (aIRR: 0.97; 95% CI: 0.83, 1.14), benzodiazepine deaths (aIRR: 1.06; 95% CI: -0.91, 1.24), heroin deaths (aIRR: 1.00; 95% CI: -0.82, 1.22), and cocaine deaths (aIRR: 1.04; 95% CI: 0.91, 1.19) **Mandatory Use of the System** Required use of the system was associated with a 12.2% reduction (95% CI: 5.0%, 18.8%) in prescription opioid deaths and a 15.6% reduction (95% CI: 1.3%, 27.9%) in benzodiazepine deaths; Required use of the system was associated with 39% increase (95% CI: 1.10, 1.76) in heroin deaths and 20% increase (95% CI: 0.98, 1.46) in cocaine deaths **Can use the System** PDMPs that allow, not require, provider access was associated with a nonsignificant change in prescription opioid deaths, benzodiazepine deaths, heroin deaths, and cocaine deaths.
Phillips, 2017 (24)	Difference-in-differences estimation (GEE) with adjustment for state area factors	Mandatory use of the program	Prescription opioid OD (ICD-10 codes T40.2-T40.4, X40-X44, X60-X64, Y10-Y14) from multiple cause of death mortality files produced by the National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention (2006-2014)	50 U.S. states and Washington D.C.	Critical	N/A	**Mandatory Use of the System** Required PDMP use was associated with an increase of 11.4% (95% CI, 1.03 to 1.20) in mean age-adjusted opioid-related mortality (P = 0.005)

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Dowell, 2016 (25)	Difference-in-differences estimation with state and year fixed effects and adjustment for state area factors	PDMP w/ mandatory review + pain clinic law	Drug OD (ICD-10 codes X40-44, X60-X64, X85, Y10-Y14) heroin (T40.1), and prescription opioids (T40.2-T40.4) from multiple cause of death mortality files produced by the National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention (2006-2013)	38 U.S. states	Serious	N/A	**Mandatory Use of the System + Pain Clinic Law** Required PDMP use plus pain clinic laws was associated with a reduction in the prescription opioid death rate of 1.2 per 100,000 population ($p < .05$) and combined drug overdose rate of -1.1 per 100,000 population ($p < .05$); Required PDMP use plus pain clinic laws was not associated with reductions in heroin death rates.
Pardo, 2016 (26)	Difference-in-differences estimation with state and year fixed effects and adjustment for state area factors	PDMP robustness (a weighted sum of state PDMP characteristics where weights were assigned based on extant evidence, or expert judgement)	Prescription opioid OD (ICD-10 codes X40-44, X60-X64, X85, Y10-Y14) and prescription opioids (T40.2-T40.4) from multiple cause of death mortality files produced by the National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention (2006-2014)	50 U.S. states and Washington D.C.	Serious	N/A	**PDMP Robustness** A 1-point increase in average PDMP score was associated with a 1.5% reduction (95% CI: -0.003, -0.3) in prescription opioid deaths compared to states without a PDMP. PDMP scoring in the 3rd quartile was associated with a 18% reduction (95% CI: -0.02, -0.34) in prescription opioid deaths compared to states without a PDMP.

Abbreviations: aRR = adjusted rate ratio; CI = confidence interval; ED = emergency department; GEE = generalized estimating equation; IRR = incidence rate ratio; OD = overdose; PDMP = prescription drug monitoring program; RD = rate difference.

[a] Boston (Massachusetts, New Hampshire), Chicago (Illinois, Wisconsin, Indians), Denver (Colorado), Detroit (Michigan), Houston (Texas), Miami-Dade County (Florida), Minneapolis-St. Paul (Minnesota, Wisconsin), New York City (New York), Phoenix (Arizona), San Francisco (California), and Seattle (Washington).

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