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Proposed Healthcare Initiatives to Mitigate Opioid Risk and Advance Safety of Pain Management

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KEYWORDS: Opioid, abuse-deterrent, overutilization, naloxone, pharmacist, prescriber

INTRODUCTION

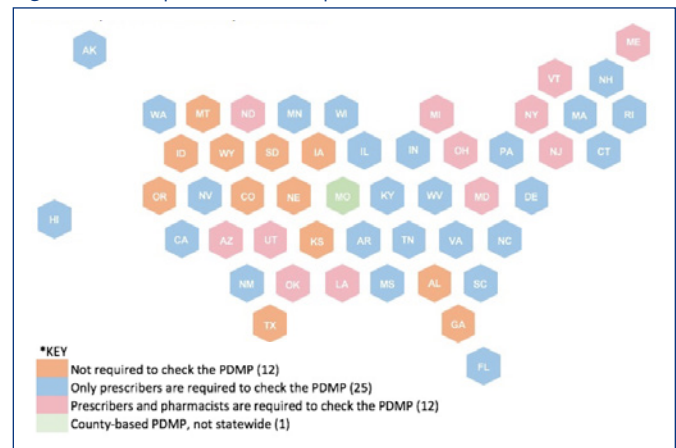
Between 1999 and 2017 more than 400,000 people died due to an opioid-related death from both prescription and illicit use.¹ Opioid overdose can occur as a result of accidental misuse of a legitimate prescription or as a result of intentional drug abuse, and it is among the most preventable public health threats facing the United States. Numerous initiatives and strategies have been proposed and implemented to help with the growing opioid issue. This report aims to provide insight into programs and products available in the United States which address mitigation strategies to promote safe and appropriate opioid prescribing.

PRESCRIPTION DRUG MONITORING PROGRAM (PDMP)

The prescription drug monitoring program (PDMP) is an electronic database used to track controlled substance prescriptions in each state. This database logs controlled drug prescription information including location, prescriber, and payment source. PDMP content, access, and utilization varies from state to state; however, they share the common goal of tracking the use of potentially abused medications and utilizing the data to implement positive change. Prescribers and pharmacists access the PDMP to obtain information about a patient's past medication history for controlled substances. The information included in a PDMP report allows for assessment of risks when issuing a new prescription, and also alerts the healthcare professional to recent prescription opioid use. This information may potentially serve as a deciding factor regarding opioid issuance, dosage, and duration of therapy. In Rhode Island, prescribers must check the PDMP prior to prescribing a controlled substance to a patient for the first time and if the patient remains on therapy it is recommended to check the PDMP every 3 months. For pharmacists in Rhode Island, it is recommended that they check the PDMP before dispensing a controlled prescription to a patient for the first time and every 3 months thereafter, if the patient remains on long-term therapy. For

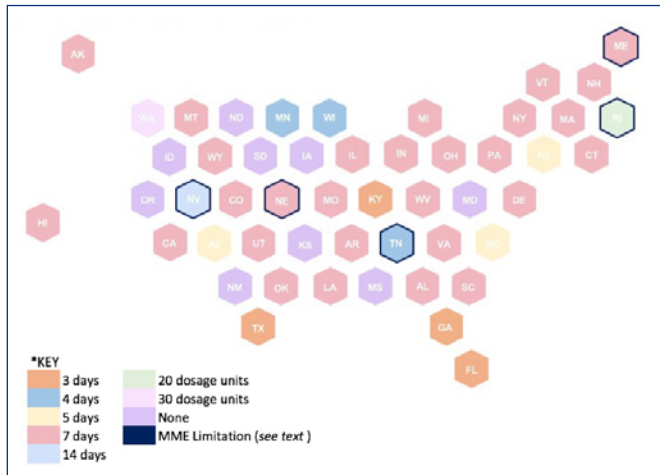
both prescribers and pharmacists in Rhode Island it is also suggested to check the PDMP before prescribing or dispensing a benzodiazepine or central nervous system-sedating medication.² All 50 states currently utilize a PDMP system. (Figure 1).

Figure 1. State Specific PDMP Requirements³



INITIAL OPIOID PRESCRIBING LIMITS BY STATE

States have begun restricting the total daily amount (mg) of opioid prescribed and quantities dispensed by pharmacies. Furthermore, more stringent restrictions have been placed when the opioid is prescribed for the first time, defined as the initial fill. The designation of 'initial fill' is determined by review of the PDMP records, and is typically defined by absence of a prescription for an opioid medication within a specified amount of time (i.e. preceding 30 or 60 days). Limits range from a specific day supply to certain dosage units based on morphine milligram equivalents (MMEs), with the most common being a 7-day limit on initial fill of an opioid (Figure 2). Currently there are four states with a 3-day supply limit, three states with a 4-day supply limit, three states with a 5-day supply limit, 29 states with a 7-day supply limit, one state with a 14-day supply limit and nine states with no limit. Washington state law limits initial opioid prescriptions to no more than 30 dosage units and Oregon does not have a law that limits initial opioid prescriptions; however, the health authority recommends no more than a 7-day trial. Maine has implemented a 100 MME/day limit,

Figure 2. State Specific Opioid Prescribing Limits⁴

Tennessee has implemented a 60 MME/day limit, Nevada has implemented a 90 MME/day limit, and Nebraska has implemented a 50 MME/day limit. Rhode Island defines their initial opioid prescribing limit as 30 MME per day for a maximum of 20 dosage units.⁵

Although the states themselves are implementing limits on initial opioid fills, third-party payers may also limit initial fills to a pre-determined day supply. For example, Anthem, Inc. was among the first to limit patient's first fill of opioids to a 7-day supply.⁶ Similarly, in 2018 CVS Caremark[®] also placed a 7-day supply limit on opioid prescriptions for an acute condition in which patients had not received opioids in the past 90 days.⁷

NALOXONE ACCESSIBILITY

Pharmacologically, naloxone is a mu-opioid antagonist that displaces opioids that are bound at mu-opioid receptor sites. The physiological response to using this drug is immediate reversal of respiratory suppression and it is available in injectable and intranasal formulations. Almost all states have enacted Good Samaritan laws which protect citizens from legal implications when administering naloxone to a person in need. Good Samaritan laws are vital to protect both parties to ensure that patients receive access to care without concern for prosecution. The majority of states allow pharmacists to dispense naloxone to patients without a prescription if deemed fit, with the exception of Connecticut, Idaho, Nebraska, and Oregon.⁸

Eight states require co-prescribing of naloxone when a patient is prescribed an opioid, and under specific conditions. For example, Arizona requires co-prescribing if the prescription issued exceeds 90 MME per day.⁹ In California, prescribers must offer a prescription for naloxone if the prescription dosage for the patient is 90 or more MMEs per day,

if the patient is concurrently using an opioid and benzodiazepine, or if the patient is deemed as having an increased risk for overdose, which could include history of substance use disorder or returning to a high dose of medication when the patient is no longer as tolerant to that dose.¹⁰ New Mexico requires a naloxone prescription with any opioid prescription exceeding a 5 day supply.¹¹ In Rhode Island, co-prescribing is mandatory under 3 different scenarios: the patient is taking 50 or more MME per day, the patient is taking opioid and benzodiazepine concurrently, or when prescribing an opioid to a patient who has a history of opioid use disorder.⁵ Vermont requires co-prescribing for patients on 90 or more MME per day, or if the patient is using an opioid and benzodiazepine concurrently.¹² Virginia requires co-prescribing if the patient's daily MME exceeds 120, or if the patient is using an opioid and benzodiazepine concurrently.¹³ In Washington, prescribers must provide naloxone prescription when patient exceeds 50 MME per day.¹⁴ Florida requires naloxone to be co-prescribed when a patient is being treated with a Schedule II controlled substance for a traumatic injury with an Injury Severity Score of 9 or greater.¹⁵

ABUSE-DETERRENT FORMULATIONS

In 2017, more than 190 million opioid prescriptions were dispensed from outpatient retail pharmacies; however of those, only about 3.8 million were written for an abuse-deterrent formulation (ADF).¹⁶ There are various mechanisms utilized to develop abuse-deterrent formulations: physical/chemical barriers, agonist/antagonist combinations, aversion, delivery systems and new molecular entities or prodrugs.^{1,17} Through the addition of agents such as gel or microspheres, physical/chemical barriers make it significantly more difficult to abuse a drug through injecting, chewing, crushing, or snorting. There are currently seven abuse-deterrent opioids commercially available that utilize a physical/chemical barrier formulation: Oxycontin[®], Xtampza[®] ER, Morphabond[™] ER, Hysingla[™] ER, Arymo[™] ER, ZoHydro[®] ER and RoxyBond[™] IR (Table 1). In a review of 15 pre-market studies, several ADFs showed improvement in endpoint scores when compared to their non-ADF counterparts. For example, Hysingla[™] ER was shown to have a noticeable effect on the primary endpoints, drug-liking and likelihood of taking the drug again, when compared to hydrocodone, and the same can be said for Embeda[®] when compared to morphine sulfate.¹⁸

The mechanism of action for drugs that use an agonist/antagonist formulation is such that the antagonist component of the drug is released only when the drug is tampered with, or taken via a non-oral route. The antagonist portion would displace the opioid agonist from the receptor, precipitating a withdrawal syndrome.

Table 1.

DRUG	FORMULATION	MECHANISM OF ACTION
Oxycontin®	Physical/chemical barrier	Oxycodone formulated using high- molecular- weight polyethylene oxide as the tablets outer coating to resist crushing. Also becomes a viscous gel to resist use via needles/IV.
Xtampza® ER	Physical/chemical barrier	Oxycodone formulated with DETERx® technology, which incorporates oxycodone into fatty acid and wax microspheres resulting in slow diffusion- controlled drug release.
Morphabond™ ER	Physical/chemical barrier	Morphine sulfate formulated with SentryBond™ technology, which retains extended- release properties if manipulated and becomes viscous to resist use via needles/IV.
Hysingla™ ER	Physical/chemical barrier	Hydrocodone bitartrate formulated with Resistec™, which hardens the tablet to increase difficulty of manipulation and becomes viscous when dissolved.
Arymo™ ER	Physical/chemical barrier	Morphine sulfate formulated using a polymer matrix to make it more difficult to cut, crush, grind or break.
Embeda®	Agonist/antagonist combo	Morphine sulfate + naltrexone HCl. The naltrexone is stored at core of the pill in a sequestering membrane and is only released when capsule is manipulated.
ZoHydro® ER	Physical/chemical barrier	A combination of 20% IR and 80% ER hydrocodone bitartrate formulated with BeadTek®, which forms a viscous gel if capsule is crushed or dissolved.
Roxybond™ IR*	Physical/chemical barrier	Oxycodone formulated with SentryBond™ technology to make release lower and slower when manipulated. Also becomes viscous to resist use via needles/IV.

*First and only immediate release abuse-deterrent formulation

MEDICARE PART D OPIOID OVERUTILIZATION POLICY

In 2019, Medicare implemented the Part D Opioid Overutilization Policy. This policy is primarily focused on encouraging interdisciplinary collaboration and coordination in order to improve universal patient care across providers.¹⁹ The primary areas of the policy include pharmacy alliance data, drug management programs, day supply limits, and opioid care coordination alerts.

Pharmacy alliance data has three focal points: prevention of new cases of opioid overutilization, treatment of existing patients, and proper utilization of data. To prevent new cases, inappropriate prescribing must be identified, non-opioid treatments must be promoted, and opioid use disorder diagnoses must be enhanced. When treating existing pain patients, it has been recommended to offer a broad range of treatment options and to continuously implement updated practices. This data enables healthcare professionals to recognize opioid prescribing patterns and to monitor the effectiveness and safety of treatment.²⁰

Drug management programs (DMP) proactively aid the healthcare professional in identifying patients who may be at risk for misuse, abuse or potential overdose when prescribed an opioid or benzodiazepine. Once identified, the Part D plan will contact the prescriber to determine medical necessity or potential risk for abuse. Medicare also determines if the patient may benefit from the implementation of a DMP to manage their prescriptions. Three major DMPs are patient-specific, point-of-sale claim edit (POS), pharmacy limitation, and prescriber limitation. Once a patient's insurance performs a case review and gives approval, POS can be used to limit the amount of frequently abused drugs that can be dispensed to a patient. Pharmacy limitation requires

a patient to fill all prescriptions for frequently abused drugs at a specific pharmacy of their choosing. Prescriber limitation requires a patient to obtain all medications of potential misuse from a sole provider, and contractual agreements between prescriber and patient may be utilized.

The most recent Medicare policy also enacted an initial 7-day supply limit for opioid-naïve patients and an opioid care coordination alert. The goal of a limiting day supply limit is to reduce long-term opioid use in patients who initially receive a prescription for treatment of acute pain. The opioid care coordination alert is intended to advise the pharmacist to consult the prescriber when a patient's overall daily oral morphine equivalence exceeds 90 mg, to confirm appropriate use.

FDA OPIOID ACTION PLAN

The FDA has recognized opioid abuse, dependence, and overdose as a public health crisis in the United States. In response, the Administration unveiled their Opioid Action Plan in 2016, which sought to establish advisory committees, propose appropriate regulatory activities and policy development, with goals of improving the science of pain management and fostering communication and collaboration across fields.

The FDA aimed to establish an expert advisory committee that would review new opioid drug applications that are not manufactured as abuse-deterrent formulations. In addition, a pediatric advisory committee is intended to review and generate recommendations on labeling of opioids in regards to the pediatric population.²¹

Extended-release and long-acting opioid formulations are currently subject to a Risk Evaluation and Mitigation

Strategy (REMS) program. The FDA expanded REMS programs to include not only product-specific materials, but also educational programs in pain management. Training and education has been expanded to include more members of the health care team, rather than solely prescribers. Immediate release opioid labeling will expand to include any additional warning and safety information that is available, with the overall goal of this initiative being to promote safer prescribing practices of immediate release opioid formulations.

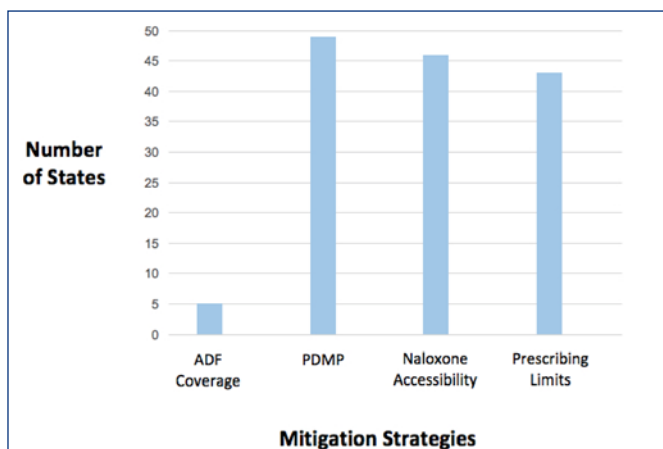
The development of ADFs has become a major area of interest in the pharmaceutical industry. The issue still persists, however, that the currently available ADFs are brand name products. This may pose a significant financial burden which limits their access for use. In response to the need to increase accessibility of opioid ADFs, the FDA has issued a high priority draft guidance to encourage the approval of generics.

The availability of naloxone varies from state to state. As outlined in the FDA's 2018 Strategic Policy roadmap, over-the-counter (OTC) naloxone is being reviewed to allow for expanded access.²² States such as Rhode Island have approved the purchase of OTC naloxone and data from 2016-2018 correlated the reduction in opioid-overdose related deaths to the increased availability of naloxone during this time.²³

CURRENT USE OF STRATEGIES

The use of the PDMP remains the most common mitigation strategy in the US. Naloxone accessibility has also improved; however, further efforts are needed to increase access across all 50 states. Most states are implementing prescribing limits on initial opioid prescription fill quantities. Lastly, affordability and further access to ADF products is needed to aid in combating the opioid crisis. (Figure 3) While no single approach will be sufficient to mitigate opioid risks while balancing appropriate use, a strategy that considers multiple possible approaches is needed to improve the health care landscape regarding opioid safety.

Figure 3. Nationwide Current Implementations of Mitigation Strategies



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Disclosure

The authors report no conflicts of interest in this work. Jayne Pawasauskas is a consultant for Heron Therapeutics and Mallinckrodt Pharmaceuticals.

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