Opioids: Current and Future Directions for Addressing the Crisis

Scott K. Winiecki, MD
Safe Use Initiative Team Lead
Professional Affairs and Stakeholder Engagement Staff (PASES)
Center For Drug Evaluation and Research (CDER)
U.S. Food and Drug Administration

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Disclosures

- I have nothing to disclose.

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Objectives

- Review the current scope of the opioid crisis
- Learn effects of opioids on the brain and body
- Discuss FDA's role
  - FDA's Opioid Action Plan
- Discuss interventions by states
  - Prescription Drug Monitoring Programs
- Consider possible future directions
  - Need for organizational change

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No direction on Doctor's only on Med. company's

Where are we now?

- Almost 2 million Americans abused or were dependent on prescription opioids in 2014.[1]
- An estimate 10 million people used prescription opioids for non-medical use in 2014.[2]
- There were 33,091 overdoes deaths in the U.S. in 2015 from opioids.[3]
  - For perspective, this is about the average attendance of a NY Yankees game (33,027).[4]

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Prescribed Opioids pose a Risk beyond the Patient who receives the Prescription

- Among people who abuse prescription opioids, most get them
  - From a friend or relative for free (55%)
  - Prescribed by a physician (20%)
  - Bought from a friend or relative (11%)[5]
- Among new heroin users, about **three out of four** report abusing prescription opioids before using.[6]

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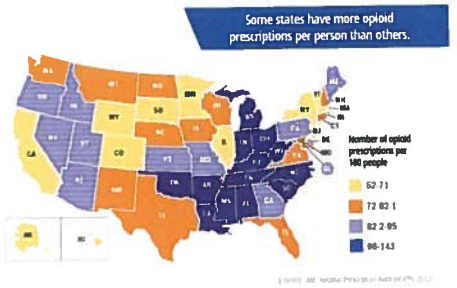
Opioid Prescribing Varies Widely



Map, see ref. 7

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Are we "Winning" the Battle?

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Progress is being made

- Prescriptions for opioid painkillers decreased in 2013, 2014, and 2015.[8]
- In 2015: the number of "narcotic prescriptions dispensed" decreased 16.6%.[9]

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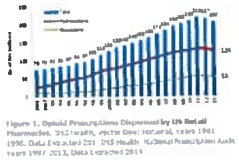
But we still have much to do

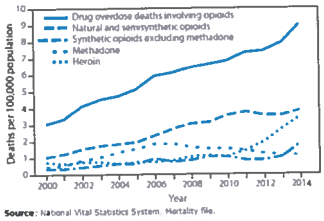


- Opioid prescribing is still high relative to historical levels
- Deaths from opioid overdose continue to rise; 15.5% increase 2014 to 2015.[10]

If meds in blood good.

No meds pills taken away.

Overdose Deaths



Source: National Vital Statistics System, Mortality file.

- Deaths from opioids continue to increase
- Deaths from heroin and fentanyl appear to be increasing at a faster rate[11]
  - Fentanyl deaths are likely 2° to illicitly manufactured fentanyl
- Since nearly 80% of heroin users report using prescription opioids prior to heroin, deaths from prescription and illicit opioids are inherently linked.[12]

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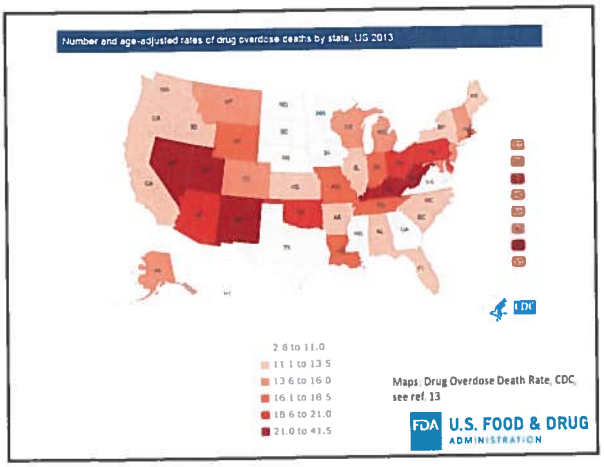

Maps: Drug Overdose Death Rate, CDC, see ref. 13

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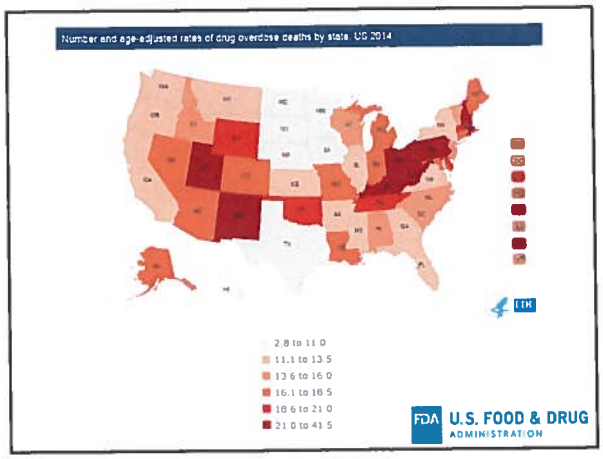

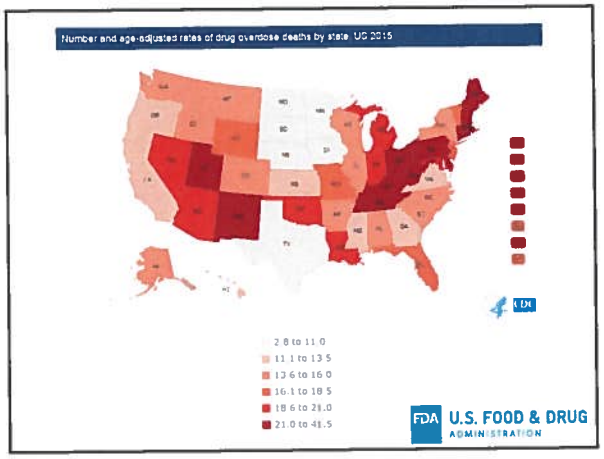

Opioid Epidemic in Maryland

- In 2015, 1259 overdose deaths state wide
- In 2016, 2089 overdose deaths
- , overdose deaths increased approximately 65%[14]

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County-level Impact

Photo, see ref. 15

- As of July 14, 2017, there were 48 deaths in 2017.[16]
- This projects to 89 deaths in 2017, a 65% increase over 2016.

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Opioid Effects on the Brain

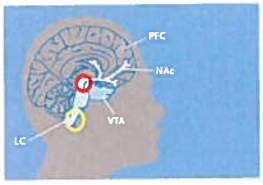
Early effect

- Opioids cause increased dopamine release in the midbrain, leading to feelings of pleasure.[17]

Opioid Effects on the Brain

Later effects

- Changes in activity in the lower brain stem are involved in withdrawal symptoms
- Tolerance – needing more drug to achieve same effect
  - Brain cells with opioid receptors become less responsive over time when exposed to opioids
- Dependence – susceptibility to withdrawal symptoms



The Brain Changes with Continued Opioid Use

- Lower brain stem is involved in basic life sustaining functions. Nerve activity stimulates alertness, breathing, and blood pressure.
- Opioids decrease activity in this part of the brain, causing drowsiness, decreased blood pressure, and slower breathing.

Photo: www.cdc.gov/sleep/index.html

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Dependence

- Over time, the brain responds by increasing activity, even when opioids are present, to maintain normal breathing and blood pressure.
- Thus, the brain adjusts, so that activity is more or less normal when opioids are present.

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Withdrawal

- Then, if opioids are no longer taken, activity increases even further, leading to more than usual activity.
- The result is jitteriness, yawning, sweating, anxiety, muscle cramps, and diarrhea

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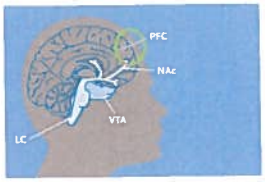
Opioid Effects on the Brain

- Frontal lobe may also be damaged.[17]
- Frontal lobe is involved in judgement, planning, and other "executive functions."
- Thus, opioid use may lead to impaired decision making and poor impulse control.



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What is FDA doing about Opioids?

- FDA has taken numerous actions to address risks associated with opioid use, misuse, and abuse.
- Actions include labeling changes, warning letters regarding misleading ads, scientific workshops, public hearings, advisory committee meetings, approval of abuse-deterrent formulations, and requiring postmarket safety studies.
- Opioid safety is not a new area for FDA – FDA's actions regarding opioid risks date back at least 15 years.[18]

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FDA Action Plan (February 4, 2016)

- In response to the opioid abuse epidemic, FDA leadership called for a far-reaching action plan to reassess the agency's approach to opioid medications. The plan focused on policies aimed at reversing the epidemic, while still providing patients in pain access to effective relief.[19]

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FDA Opioids Action Plan

To reverse the epidemic while still providing patients with access to effective relief

- Advisory Committees
- IR Labeling
- Post-market
- REMS
- Abuse Deterrent
- Supporting Treatment
- Risk-Benefit

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Expand use of Advisory Committees

"Advisory committees (ACs) provide FDA with independent advice from outside experts..."[20]

- FDA will convene an AC before approving any new opioid without abuse-deterrent properties
- Pediatric AC will make recommendations regarding pediatric labeling before any new labeling is approved
- FDA will consult an AC for abuse-deterrent formulations which raise novel issues.[19]

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Immediate Release Labeling

- In the Action Plan, FDA proposed to develop warnings for the immediate release (IR) opioids similar to the labeling for extended release/long-acting opioids (ER/LA).
- On March 22, 2016, FDA required the addition of a new boxed warning about the serious risks of misuse, abuse, addiction, overdose, and death.
- Indication was clarified to specify that opioids should be used only when alternative treatment options are inadequate or not tolerated.[21]

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Strengthen Postmarket Requirements

- Evidence to guide opioid use, particularly long term use, is substantially lacking.
- FDA is strengthening the requirements for drug companies to generate postmarket data on the long-term impact of ER/LA opioids.[19]

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Update the Risk Evaluation and Mitigation Strategy (REMS) Program

- REMS program: requires drug companies to fund continuing education programs on the use of these products.
- FDA has released a draft of revised topics to be included in the prescriber education program [22,23]
  - Principles of acute and chronic pain management
  - Non-pharmacologic treatments for pain
  - Opioid and non-opioid pharmacologic treatments for pain
- FDA held a public meeting regarding prescriber education on May 9 – 10, 2017[24]

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Abuse Deterrent Formulations (ADF)

- Abuse-deterrence targets the known or expected routes of abuse, such as crushing in order to snort and dissolving in order to inject
- Abuse-deterrent is **not** *abuse proof*
- FDA supports efforts to better understand the impact of ADFs in real-world settings.[25]
- FDA has issued guidance on generic ADFs, as less costly products should increase prescribers' uptake of ADFs.

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Support Better Treatment

- FDA is reviewing options to make naloxone more accessible to treat opioid overdose.[19]
  - This could include over-the-counter availability
    - Naloxone is currently available without a prescription or by standing prescription in many states
  - FDA sponsored a competition to design an app to increase the likelihood that an opioid user will receive naloxone in the event of an overdose[26]
    - A low-cost, scalable, crowd-sourced mobile phone application
    - "OD Help" is in development

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Support Better Treatment

- FDA "actively supports the Centers for Disease Control and Prevention guidelines for prescribing opioids for the treatment of pain and will facilitate the development of evidence and improved treatments."[19]
- Guideline can be found at https://www.cdc.gov/drugoverdose/prescribing/providers.html

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Reassess the Risk-Benefit Approval Framework

- FDA is assessing "how to take into account our evolving understanding of the risks of opioids, not only to the patient but also the risks of misuse by other persons who obtain them."[19]
- Thus, the broader public impact of opioid abuse will be formally incorporated into approval decisions.

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CDC Guideline

- Intended to help providers make informed decisions about pain treatment for patients in primary care settings.[27]
- Best practices include use of non-opioid therapies for pain management, "start low and go slow," follow-up with regular assessments
- https://www.cdc.gov/drugoverdose/pdf/guidelines_at-a-glance-a.pdf
- CDC now has an app to assist with opioid prescribing.[28]

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Solutions will need to come from many Sources

- FDA is one of many Federal agencies addressing issues involving opioids (n = 1)
- Many Federal Agencies share information via the Federal Interagency Working Group on Opioids
- Each state has programs to address opioids (n = 50)
- Guidelines and educational programs are available from specialty societies
- Healthcare institutions
- Advocacy groups
- Individual providers (n = 809,845)[29]
- Patients (n = millions)

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Solutions can take many Forms

See ref. 30

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States and their Interventions

States with Education Initiatives for Various Stakeholders on the Risks of Opioids[31]

Target audience	Number of States
General Public	48
Prescribers	31
Patients and Families	24
Pharmacists	22

States indicating no educational programs on opioids: Alaska, Kansas, and Wyoming.

Other Inventions of Note

- Increased funding for medication-assisted treatment: 29 states
- Expanded availability of naloxone: 28
- Guidelines for safe opioid prescribing: 23
- Enacted legislation to regulate pain clinics: 14

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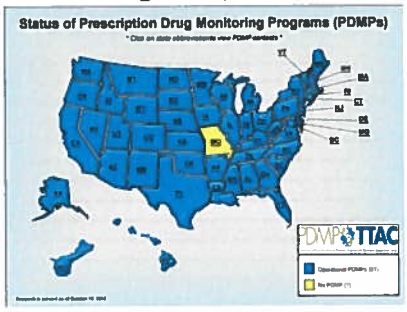
States and Prescription Drug Monitoring Programs (PDMPs)



Map, see ref. 32

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PDMPs

- Collect data on the prescribing of drugs with the potential for abuse
- Allow providers and pharmacists to access data to evaluate
  - Specific drugs, doses, amount, and dates of recent prescriptions
  - If > 1 provider has prescribed for a patient
- Goal is to increase patient safety and decrease practices such as "doctor shopping."

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State examples - Ohio

The Problem

- Ohio has one of the highest rates of drug overdose deaths (24.6/100,000).[33]
- Unintentional drug overdose is the leading cause of injury related death in Ohio.

Interventions

- 3 Guidelines developed
- Prescribers required to check state PDMP (2014)
- Strengthened "pill mill" laws
  - Ohio revoked licenses of 61 doctors and 15 pharmacists between 2011 – 14.
- Drug take back program
- Increased access to naloxone without a prescription
- Education programs on naloxone administration

Ohio – Results of Interventions

- Doses dispensed decreased 10.4% from 2011 to 2015.
- Proportion of unintentional drug overdose deaths involving a prescription opioid has decreased: 45% to 22% (2011 compared to 2015)
- Instances of "doctor shopping" decreased from 2205 (2011) to 720 (2015)
- **Deaths from unintentional overdose continue to increase: 3050 in 2015 compared to 1722 in 2011**[34]

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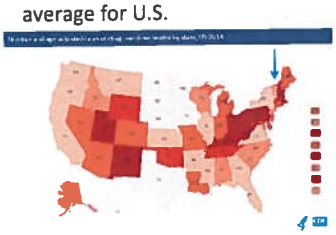
Vermont

- Vermont is often listed as a state that has taken many actions toward addressing opioid use
- Drug poisoning deaths 14.7/100,000 (2014) about average for U.S.



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Vermont - Interventions

- Interventions to address opioid misuse and abuse in Vermont include:
  - Mandatory prescriber education
  - PDMP
  - Increased naloxone access
  - Increased availability of opioid use disorder treatment[35]
    - Vermont has one of the highest rates of treatment capacity

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Vermont - Results

- Opioid prescriptions decreased by an estimated 7.9% from 2014 to 2015. This would be the first decrease since 2010.
- Non-medical use of prescription pain relievers has decreased across all age categories (from 2010/11 to 2013/14)
- Use of naloxone has increased
- **Opioid-related fatalities have continued to increase (41 to 106, 2010 to 2016)**[36]

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Tennessee

- Ranks 2nd in the U.S. in opioid pain relievers sold/10,000 persons[37]
- ED visits for opioid poisoning increased 51% from 2005 to 2011.
- Hospital costs related to opioids exceeded $29,000,000 in 2012
- Direct costs for medication-assisted treatment were almost $60,000,000 in 2013

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Tennessee - Interventions

- PDMP
  - Registration required 1/2013
  - Mandatory checking before prescribing 4/2013
- Drug take back initiative
- Educational symposia to educate prescribers
- Requirement to identify top 50 prescribers
  - Top 50 prescribers accounted for 15% of opioids dispensed[38]
  - Prescribers required to justify their prescribing practices within 15 days of being notified

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Tennessee – Results

- Decline in opioid MMEs to patients of 14.3% from 2012 to 2015.[39]
- Opioid prescriptions decreased 7.8% from 2012 to 2015.
- The amount of MMEs dispensed per County on a per capita basis decreased for every county during 2013 – 2015.
- A decrease of 50.1% of potential doctor shopping patients from 2011 to 2015*

*patients seeing providers out of TN would not be identified in this analysis

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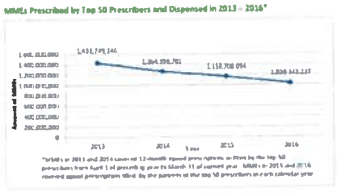
Tennessee - Results

- MMEs prescribed by top 50 prescribers have decreased 28% since 2013.



- **Drug Overdose deaths rose 14.5%, from 1263 to 1451 from 2015 to 2016.**[40]

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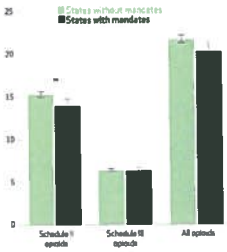
Do PDMPs Work?

- A PDMP with a mandate (registration or use) was associated with a 9 – 10% reduction in prescriptions for Schedule II opioids by Medicaid enrollees.[41]



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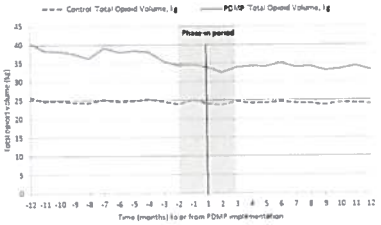
Do PDMPs Work?

- PDMP implementation was associated with a reduced opioid volume but no changes in MMEs or opioid prescriptions 12 months after implementation compared with non-PDMP states (Medicare beneficiaries, 2007 – 2012, in 10 states).[42]



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Issues that limit PDMPs

- Different PDMPs collect information on different groups of drugs.
- PDMPs do not all collect the same data
- It can be difficult to identify the correct individual.
  - People can have the same similar names, 1 person with >1 name
- Each PDMP has a unique mandate from the state
  - Changing a PDMP to allow a change in provider access or data sharing can require the passage of new legislation.

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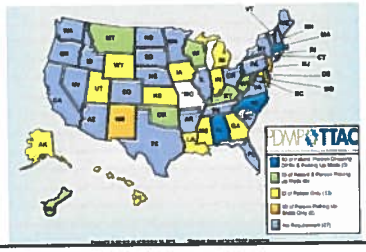
Issues that limit PDMPs

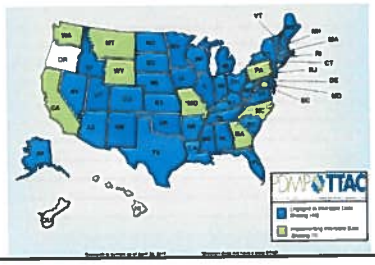
- Positive Identification: 27 states have no requirement regarding checking ID when dropping off or picking up a prescription.



See ref. 43

Issues that limit PDMPs

- Data sharing: as of 4/20/2017, 40 states are engaged in data sharing with at least one other state.



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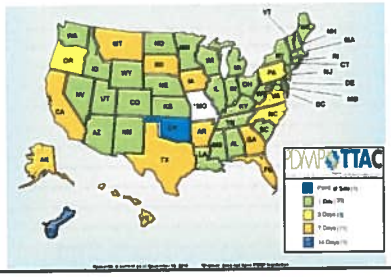
Issues that limit PDMPs

- 14 states allow > 1 day interval for a pharmacy to transmit information to the PDMP.



See ref. 43

Where are we now?

- Almost 2 million Americans abused or were dependent on prescription opioids in 2014.[1]
- An estimated 4.3 million people used prescription opioids for non-medical use in the past month.[2]
- There were 33,091 overdoes deaths in the U.S. in 2015 from opioids.[3]
  - For perspective, this is the average attendance of a NY Yankees game (33,027)[4]

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What has "Worked" to Date?

- There is some evidence that PDMPs can effect modest change.
- Overall, opioid prescribing is decreasing over the last several years.
- Deaths from opioids continue to rise.
- Finding new and additional ways to address opioid use, misuse, and abuse remains an urgent public health issue.

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What do the Experts Say?

- National Academies of Sciences, Engineering, and Medicine developed a report to:
  - inform FDA on the state of the science regarding opioid misuse and abuse
  - make recommendations on the options available to FDA to address the prescription opioid overdose epidemic.
  - Report released July 13, 2017[44]

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NASEM Recommendations

- Invest in research to better understand pain, opioid use disorder, and public health implications of opioids.
- Improve reporting of data on pain and opioid use disorder
- Improve the use of PDMP data
- Improve education for health care providers and evaluate the impact of patient and public education
- Reduce barriers to accessing non-opioid treatment options for pain

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NASEM Recommendations

- Reduce barriers to coverage of medications used to treat opioid use disorder
- Improve access to naloxone
- Incorporate public health considerations into opioid-related regulatory decisions
- Increase the transparency of regulatory decisions regarding opioids
- Strengthen the post-approval oversight of opioids
- Conduct a full review of currently marketed opioids

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No Quick Fix

- The opioid crisis did not develop overnight and it won't be fixed quickly, either.
- Any solution is going to require changes by multiple stakeholders.
- No solution is going to be "perfect."
- Any solution is going to require cultural change, which is difficult to achieve.

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Behavioral Change

"Previous experience is clear that to be effective, behavior change, including prescribing opioids, is extraordinarily difficult and requires technical assistance including mentoring, skills development, and most of all, systems redesign."

-Lessons Learned from Implementing Project Lazarus in North Carolina[45]

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My Guess about "What's Next?"

- Increased intensity of familiar interventions, resulting in modest reductions in prescribing
  - More mandatory prescriber education
  - PDMP technology and data sharing will improve.
  - More mandated use of PDMPs
  - Continued emphasis on identifying "pill mills."
- Larger decreases in prescribing and a subsequent reduction in overdose deaths are unlikely until prescribers alter their thinking about opioids and develop a higher threshold to prescribe.
  - -Perhaps this cultural shift is already underway but it is too early to see a reduction in fatalities.
- Fentanyl and its derivatives will be involved in a significant number of overdose deaths until we can decrease the number of opioid abusers, increase access to treatment, and/or decrease the supply of illicit fentanyl.

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What's Next for FDA?

"Unquestionably, our greatest immediate challenge is the problem of opioid abuse. This is a public health crisis of staggering human and economic proportion ... we have an important role to play in reducing the rate of new abuse and in giving healthcare providers the tools to reduce exposure to opioids to only clearly appropriate patients, so we can also help reduce the new cases of addiction."

- Scott Gottlieb, FDA Commissioner[46]
Address to FDA staff, May 15, 2017

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Questions???

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