Evolution of the Opioid Epidemic

February 5, 2018
2:30 PM-4:00 PM EST

Richard C. Dart, MD, PhD
Director, Rocky Mountain Poison and Drug Center, Denver Health
Professor, University of Colorado Health Sciences Center
Competing Interest Statement

History
- 2002, launched by Purdue Pharma L.P.
- 2006, independent ownership by Denver Health and Hospital Authority
  - Denver Public Hospital for 150 years
  - State sanctioned independent authority

Conflict of Interest Statement
- Many manufacturers of prescription opioids or stimulants as well as federal agencies subscribe to RADARS System.
- RADARS System is the property of Denver Health and Hospital Authority, a political subdivision of the State of Colorado.
- Subscribers receive information, but do not participate in developing the System, data collection, or analysis of the data. They do not have access to the raw data.
- Employees are prohibited from personal financial relationships with any company.
Mosaic Surveillance of Prescription Drug Abuse

- **Acute Health Events**
- **Poison Center Program**
- **Entering Treatment**
- **Survey of Key Informants’ Patients**
- **Opioid Treatment Program**
- **Advanced Users/Targeted Investigations**
- **Researcher & Patients Interacting Directly (RAPID)**

**Programs:***
- **Non-Medical Use**
  - Survey of Non-Medical Use of Prescription Drugs (NMURx)
- **Drug Transactions**
  - Drug Diversion Program
- **Illicit Market Price**
  - StreetRx Program
- **Internet Chatter**
  - Web Monitoring Program
Prescription opioid abuse is at record highs and increasing
Prescription opioid abuse is at record highs and increasing

Opioid addiction rates continue to skyrocket

By Nadia Kounang
Updated 10:35 PM ET, Thu June 29, 2017
Marked increases in prescription opioid and heroin overdose deaths in the USA 2000 to 2015.

USA 2015 overdose deaths:
- 52,404 any drug
- 33,091 any opioid

Marked *Increases in Prescription Opioid and Heroin Overdose Deaths* in the USA 2000 to 2015

Overdose Deaths Involving Opioids, United States, 2000-2015

One Problem?


www.cdc.gov

Your Source for Credible Health Information
Marked **Increases in Prescription Opioid and Heroin Overdose Deaths** in the USA 2000 to 2015

Overdose Deaths Involving Opioids, United States, 2000-2015

One Problem?

- **Any Opioid**
- **Commonly Prescribed Opioids** (natural and semi-synthetic opioids and methadone)
- **Heroin**
- **Other Synthetic Opioids** (e.g. fentanyl, tramadol)

Quarterly Revenue

Source: Company Filings (Oct 2012)

Peak Rx Drug Abuse Deaths
The problem is Apple!
The problem is Apple!
Prescription Opioid Abuse Decreasing in US

Trends in Opioid Analgesic Abuse and Mortality in the United States.
Prescription Opioid Abuse by Active Pharmaceutical Ingredient

RADARS Poison Center Program
Intentional Abuse Exposures

Per 100,000 population

Oxycodone
Fentanyl
Hydrocodone
Hydromorphone
Morphine
Oxymorphone
Methadone
Buprenorphine
Tramadol
Tapentadol
Prescription Opioid Abuse by Active Pharmaceutical Ingredient

RADARS Poison Center Program
Intentional Abuse Exposures

Per 100,000 population

Methadone

- Oxycodone
- Fentanyl
- Hydrocodone
- Hydromorphone
- Morphine
- Oxymorphone
- Methadone
- Buprenorphine
- Tramadol
- Tapentadol
Prescription Opioid Abuse by Active Pharmaceutical Ingredient

RADARS Poison Center Program
Intentional Abuse Exposures

Per 100,000 population

- Oxycodone
- Fentanyl
- Hydrocodone
- Hydromorphone
- Morphine
- Oxymorphone
- Methadone
- Buprenorphine
- Tramadol
- Tapentadol
Petty died at 66 of "multisystem organ failure due to resuscitated cardiopulmonary arrest due to mixed drug toxicity: fentanyl, oxycodone, temazepam, alprazolam, citalopram, acetylfentanyl, and despropionyl fentanyl."
What is the Problem We Need to Solve?

Filling the Balloon

Person in Pain

Susceptible Person

Recreational Abuser

Abuse of Other Drugs

Intact → Chewed → Crushed

Outcomes

Addiction

Overdose

Death
Prescription Drug Abuse
Opioid and Other

- Opioids with abuse deterrent properties (ADOs / ADFs)
- Public Health and Heroin
- The Rise of other Rx drugs abuse
Potential Effects of Interventions

Emptying the Balloon

Susceptible Person
Person in Pain

Recreational Abuser
Abuse of Other Drugs

Intact  Chewed  Crushed

Outcomes
OUD  OD  Dth

Potential Effects of Interventions
Potential Effects of Interventions

Emptying the Balloon

- Intact
- Chewed
- Crushed

Outcomes:
- OUD
- OD
- Dth

Person in Pain
Guidelines
Susceptible Person
Enforcement
Recreational Abuser
Abuse of Other Drugs
Potential Effects of Interventions

Emptying the Balloon

Person in Pain
Guidelines
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Abuse of Other Drugs

Intact  Chewed  Crushed

AD F

Outcomes

OUD
OD
Dth
Emptying the Balloon

Potential Effects of Interventions

Person in Pain
Guidelines
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Outcomes
OUD
OD
Dth

Intact → Chewed → Crushed

ADF

Susceptible Person
Person in Pain
Guidelines
Enforcement
Recreational Abuser
Abuse of Other Drugs
Potential Effects of Interventions

Emptying the Balloon

Person in Pain

- Guidelines
- Susceptible Person
- Enforcement

Recreational Abuser

Abuse of Other Drugs

Intact → Chewed → Crushed

Outcomes

- OUD
- OD
- Dth

Susceptible Person

Guidelines

Enforcement

Recreational Abuser

Abuse of Other Drugs
Potential Effects of Interventions

Emptying the Balloon

- Intact
- Chewed
- Crushed

Outcomes
- OUD
- OD
- Dth

Person in Pain
Guidelines
Susceptible Person
Enforcement
Recreational Abuser
Abuse of Other Drugs
Heroin

Abuse of Other Drugs

OD
Dth

Enforcement

Guidelines

Susceptible Person

FDF
FDF
FDF

Abuse of Other Drugs

Heroin

Enforcement

Guidelines

Susceptible Person
Potential Effects of Interventions

Emptying the Balloon

Susceptible Person

Guidelines

Enforcement

Recreational Abuser

Abuse of Other Drugs

Person in Pain

Heroin

Treat

OD

OUD

Intact

Chewed

Crushed

Outcomes

Potential Effects of Interventions

Chewed

Intact

Abuse of Other Drugs

Abuse of Other Drugs

Enforcement

Guidelines

Susceptible Person

Person in Pain

Heroin

Treat

OD

OUD
10 FDA-approved ADFs:
All physical/chemical or agonist/antagonist

<table>
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<tr>
<th>Product</th>
<th>Drug Substance</th>
<th>Sponsor</th>
<th>Approval</th>
<th>Marketed</th>
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<tbody>
<tr>
<td>Oxycontin</td>
<td>oxycodone</td>
<td>Purdue</td>
<td>4/4/2010</td>
<td>YES</td>
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<tr>
<td>Targiniq ER</td>
<td>oxycodone + naloxone</td>
<td>Purdue</td>
<td>7/23/2014</td>
<td>NO</td>
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<tr>
<td>Embeda</td>
<td>morphine + naltrexone</td>
<td>Pfizer</td>
<td>10/17/2014</td>
<td>YES</td>
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<tr>
<td>Hysingla ER</td>
<td>hydrocodone</td>
<td>Purdue</td>
<td>11/20/2014</td>
<td>YES</td>
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<tr>
<td>Morphabond</td>
<td>morphine</td>
<td>Inspirion</td>
<td>10/2/2015</td>
<td>NO</td>
</tr>
<tr>
<td>Xtampza ER</td>
<td>oxycodone</td>
<td>Collegium</td>
<td>11/6/2015</td>
<td>YES</td>
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<tr>
<td>Troxyca ER</td>
<td>oxycodone + naltrexone</td>
<td>Pfizer</td>
<td>8/22/2016</td>
<td>NO</td>
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<tr>
<td>Arymo ER</td>
<td>morphine</td>
<td>Egalet</td>
<td>1/9/2017</td>
<td>Limited</td>
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<tr>
<td>Vantrela ER</td>
<td>hydrocodone</td>
<td>Teva</td>
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<tr>
<td>RoxyBond</td>
<td>oxycodone</td>
<td>Inspirion</td>
<td>4/26/2017</td>
<td>NO</td>
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</table>
Systematic Review of Abuse Deterrent (Tamper Resistant) Formulations

• Question: What is the evidence that opioid analgesics with abuse deterrent labeling improve outcomes (abuse, misuse, overdose, death)?
• 45 reports on opioids with abuse deterrent labeling
  o Hydrocodone (n=7)
  o Morphine (n=5)
  o Oxycodone (n=32)*
• Hill Criteria
• Also assessed confounding factors and bias

RADARS: Change in Abuse after OxyContin Reformulation

(a) PC

(b) OTP

(c) SKIP

(d) DD

Timeline of Interventions vs. Oxycodone ER

Rate adjusted for population

Percent of Population Covered by PDMP


Oxycodone ER
PDMP
Other Opioids

All Other Opioids (per 100,000 population) Oxycodone ER (per 10,000 population) PDMP Coverage
Timeline of Interventions vs. Oxycodone ER

Rate adjusted for population

Oxycodone ER

PDMP

Other Opioids

Percent of Population Covered by PDMP

Oxycodone ER Reformulation
Timeline of Interventions vs. Oxycodone ER

Rate adjusted for population

Oxycodone ER

PDMP

Other Opioids

WA Rx Guidelines

National Drug Take Back

Oxycodone ER Reformulation

Percent of Population Covered by PDMP

0 10 20 30 40 50 60 70 80 90 100


- All Other Opioids (per 100,000 population)
- Oxycodone ER (per 10,000 population)
- PDMP Coverage
Timeline of Interventions vs. Oxycodone ER

Oxycodone ER

PDMP

Other Opioids

WA Rx Guidelines

National Drug Take Back

Oxycodone ER Reformulation

FL

Percent of Population Covered by PDMP

Rate adjusted for population

0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8


All Other Opioids (per 100,000 population) Oxycodone ER (per 10,000 population) PDMP Coverage
Timeline of Interventions vs. Oxycodone ER

Rate adjusted for population

Percent of Population Covered by PDMP


Oxycodone ER

PDMP

Other Opioids

WA Rx Guidelines
National Drug Take Back
Oxycodone ER Reformulation
FL
TIRF REMS
ER/LA REMS

All Other Opioids (per 100,000 population)
Oxycodone ER (per 10,000 population)
PDMP Coverage
Problems with a Reactionary Agenda
Problems with a Reactionary Agenda

• “OxyContin is the Problem”
Problems with a Reactionary Agenda

• “OxyContin is the Problem”
• “Drug manufacturers are the Problem”
Problems with a Reactionary Agenda

• “OxyContin is the Problem”
• “Drug manufacturers are the Problem”
• “Addicts / Drug dealers are the Problem”
Problems with a Reactionary Agenda

• “OxyContin is the Problem”
• “Drug manufacturers are the Problem”
• “Addicts / Drug dealers are the Problem”
• The core problem is human frailty and susceptibility to opioids (or perhaps to mind altering substances in general?)
Problems with a Reactionary Agenda

- “OxyContin is the Problem”
- “Drug manufacturers are the Problem”
- “Addicts / Drug dealers are the Problem”
- The core problem is human frailty and susceptibility to opioids (or perhaps to mind altering substances in general?)
- When we are looking back at the past…
Heroin - Push? Or Pull?

Alcohol
↓
Marijuana
↓
Polysubstance Abuse
↓
Opioid Abuser

Heroin (Fentanyl)

• Availability
• Cost
• Setting

Other Drugs

IR Rx
Opioid
ER Rx
Opioid
Heroin - Push? Or Pull?

Alcohol
↓
Marijuana
↓
Polysubstance Abuse
↓
Opioid Abuser

Heroin (Fentanyl)

• Availability
• Cost
• Setting

Other Drugs

Rape
Physical Abuse

Family Dysfunction
Trauma
Isolation

IR Rx Opioid
ER Rx Opioid
Heroin - Push? Or Pull?

- Alcohol
  - Marijuana
  - Polysubstance Abuse
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    - Heroin (Fentanyl)
      - Availability
      - Cost
      - Setting
  - Other Drugs
  - IR Rx
  - Opioid
  - ER Rx
  - Opioid

- Rape
- Physical Abuse
- Family Dysfunction
- Trauma
- Isolation
How Else Might Someone Cope?

- Opioids
- Opioids that you didn’t think were opioids
- Non-opioids
Loperamide (Immodium)

- Antidiarrheal
- Prescription and OTC
- Intestinal mu agonist
- Poor systemic absorption due to p-glycoprotein
- Abused alone or in combination with opioids
Loperamide Abuse

National Poison Data System

Miller H et al. JAPHA 2017, 57(2): S45–S50
Loperamide Abuse Associated With Cardiac Dysrhythmia and Death

William Eggleston, PharmD*; Kenneth H. Clark, MD; Jeanna M. Marraffa, PharmD, DABAT

*Corresponding Author. E-mail: williamdeggleston@gmail.com, Twitter: @WillieDoesTox.

Loperamide is an over-the-counter antidiarrheal with μ-opioid agonist activity. Central nervous system opioid effects are not observed after therapeutic oral dosing because of poor bioavailability and minimal central nervous system penetration. However, central nervous system opioid effects do occur after supratherapeutic oral doses. Recently, oral loperamide abuse as an opioid substitute has been increasing among patients attempting to self-treat their opioid addiction. Ventricular dysrhythmias and prolongation of the QRS duration and QTc interval have been reported after oral loperamide abuse. We describe 2 fatalities in the setting of significantly elevated loperamide concentrations. [Ann Emerg Med. 2017;69:83-86.]
GABA Analogs

- Gabapentin, pregabalin
- 10-15% prescribed opioids also prescribed gabapentin
- Misuse common in opioid use disorders (15% - 28%)
- Increased mortality when combined with opioids
  - Likely synergistic respiratory depression
RADARS: Diversion of GABA Analogs

Rates of gabapentin diversion (per 100,000) by quarter, 2002-2015
Increasing Abuse of Gabapentin and Pregabalin as Reported to US Poison Centers 2006 through 2014

B Bucher Bartelson¹, G Bau¹, G Severtson¹, JL Green¹, RC Dart¹,²
¹Rocky Mountain Poison and Drug Center, Denver Health and Hospital Authority
²Department of Emergency Medicine, University of Colorado School of Medicine

Abstract

Increasing Abuse of Gabapentin and Pregabalin as Reported to US Poison Centers 2006 through 2014
B Bucher Bartelson¹, G Bau¹, G Severtson¹, JL Green¹, RC Dart¹,²
¹Rocky Mountain Poison and Drug Center, Denver Health and Hospital Authority
²Department of Emergency Medicine, University of Colorado School of Medicine

Methods: Data from the National Poison Data System from January 2006 to December 2014 were queried for gabapentin and pregabalin exposures and were utilized to determine if the category of intentional abuse cases were increasing in the US and if gabapentin and pregabalin abuse cases are changing at different rates. The total number of cases of intentional abuse where the exposure was to gabapentin or pregabalin was calculated and divided by the estimated population of the US and scaled per 100,000 population. A Poisson regression model was used to determine the percent change per quarter in the intentional abuse rates.

Results: Of the 8,111 intentional abuse cases exposed to gabapentin, 8,111 (14.0%) were male and the median age was 30 years (QR: 21-42). Of the 3,869 intentional abuse cases exposed to pregabalin, 3,869 (33.3%) were male and the median age was 26 years (QR: 14-40). Only 32% (30.1%) of the exposures involved a single substance. The rate of abuse per 100,000 population in first quarter 2006 was 0.0037 and in fourth quarter 2014 was 0.0241 for gabapentin. Using Poisson regression intentional abuse population rates increased at a rate of 3.7% (95% CI: 3.3-4.1%) per quarter for gabapentin and 18% (95% CI: 15.1-21.4%) per quarter for pregabalin (p < 0.0001). The medical outcomes were similar between gabapentin and pregabalin, with 14% and 20% death, 12% (9%) major effect, 82% (91%) minor effect, and 96% (94%) and 94% (92%) moderate effect, respectively.

Conclusions: Population-based rates of intentional abuse reported to US poison centers have increased since 2006, and abuse rates of gabapentin are increasing faster than pregabalin. Continued monitoring and increased awareness of these rates is warranted.

Results (continued)

• Only 1,328 (32.1%) of the intentional abuse exposures involved a single substance
• For gabapentin, the rate in first quarter 2006 was 0.0168 per 100,000 population while the rate for fourth quarter 2014 was 0.0571 per 100,000 population, a 3.4-fold increase
• For pregabalin, the rate in first quarter 2006 was 0.0037 per 100,000 population while the rate for fourth quarter 2014 was 0.0059 per 100,000 population, a 2.4-fold increase

Conclusions

• Population-based rates of gabapentin and pregabalin intentional abuse reported to US poison centers have increased since 2006, and

Graphs showing yearly gabapentin and pregabalin intentional abuse rates per 100,000 population.
Gabapentin and Mortality

Antipsychotic Medications

- Atypical antipsychotics commonly abused both alone and in combination with other drugs
- Especially popular in incarcerated population
- Quetiapine (Seroquel) often drug of choice
Antipsychotic Abuse

- 429 patients from detox and rehab units
- 73 (17%) abuse atypical antipsychotics with alcohol, opioids, cocaine/crack, methamphetamine, and/or cannabis
- Quetiapine most common (84.9%)
- Other antipsychotics - olanzapine (17.8%), risperidone (24.7%), aripiprazole (20.5%), ziprasidone (8.1%), and asenapine (2.9%)
- Goals: "getting mellow", "slowing down", or enhancing effects of other drugs
Quetiapine DAWN ED visits

Antidepressants

• Reports of abuse of all classes
• May have higher rates with SNRI
  o Stimulant effects due to norepinephrine reuptake inhibition
  o When used with opioids, pharmaceutical “speedball” effect
  o Adverse effects include seizures and dysrhythmias
Cyclobenzaprine

• National Poison Data System (NPDS)
• Few studies of misuse/abuse
• Anticholinergic effects
• Structural similarity to tricyclic antidepressants
• Anticipate synergistic CNS and respiratory depression with opioids
Other Anticonvulsants

• Nearly all have been reported both in single substance and polysubstance abuse cases
• Levitiracetam may be on the horizon
• Synergistic CNS depression with opioids
• Cardiac effects also possible
Medical Cannabis Use Leads To Decrease In Opioid Abuse

The opioid crisis is hitting large cities and small towns indiscriminately and included in this is prescription drugs

By Alexandra Hicks - August 21, 2017
U.S.

CAN LEGAL MARIJUANA SOLVE THE OPIOID CRISIS? MEDICAL POT STATES SEE DECREASE IN PAINKILLER ABUSE
Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States

**OBJECTIVE**
State medical cannabis laws related to opioid analgesic overdose mortality?

**DESIGN, SETTING, AND PARTICIPANTS**
Time-series analysis of medical cannabis laws and state-level death certificate data in the United States from 1999 to 2010; all 50 states were included.

Deaths from Opioid Analgesic

Deaths from Opioid Analgesic

Deaths from Opioid Analgesic

Deaths from Opioid Analgesic

Figure 2. Association Between Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in Each Year After Implementation of Laws in the United States, 1999-2010

Difference in Age-Adjusted Mortality Rate, %

Years After Law Implementation, No.
National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)

• Methods
  o Associations between cannabis use at wave 1 (2001–2002) and nonmedical prescription opioid use and prescription opioid use disorder at wave 2 (2004–2005) of NESARC.
  o Cannabis and prescription opioid use by structured interview.
  o Other covariates included age, sex, race/ethnicity, anxiety or mood disorders, family history of drug, alcohol, and behavioral problems, and nonmedical opioid use.

https://doi.org/10.1176/appi.ajp.2017.17040413
NESARC: Cannabis Use Associated with Increased Opioid Use

• Cannabis use at wave 1 associated with
  o Increased incident nonmedical prescription opioid use (odds ratio=5.78, 95% CI=4.23–7.90)
  o Increased opioid use disorder (odds ratio=7.76, 95% CI=4.95–12.16) at wave 2
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  o Increased opioid use disorder (odds ratio=7.76, 95% CI=4.95–12.16) at wave 2

• Associations remained significant after adjustment for background characteristics.

• Among adults with pain at wave 1, cannabis use was also associated
  o Increased incident nonmedical opioid use (adjusted odds ratio=2.99, 95% CI=1.63–5.47) at wave 2
Conclusions

• Abuse and death of analgesic opioids are decreasing
  o Heroin and illicit fentanyl deaths are increasing more
Conclusions

• Abuse and death of analgesic opioids are decreasing
  o Heroin and illicit fentanyl deaths are increasing more
• Dramatic changes in heroin distribution has rapidly changing the opioid abuse environment
  o Just call 1-800-Givememyfix
Conclusions

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• “Squeezing the Balloon” may also affect non-opioids
Conclusions

• Abuse and death of analgesic opioids are decreasing
  o Heroin and illicit fentanyl deaths are increasing more
• Dramatic changes in heroin distribution has rapidly changing the opioid abuse environment
  o Just call 1-800-Givememyfix
• “Squeezing the Balloon” may also affect non-opioids
• Cannabis may or may not affect opioid use
  o Studies intriguing, but stronger analytic designs needed
Questions?

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