UW Opioid Use in the time of an Opioid Epidemic

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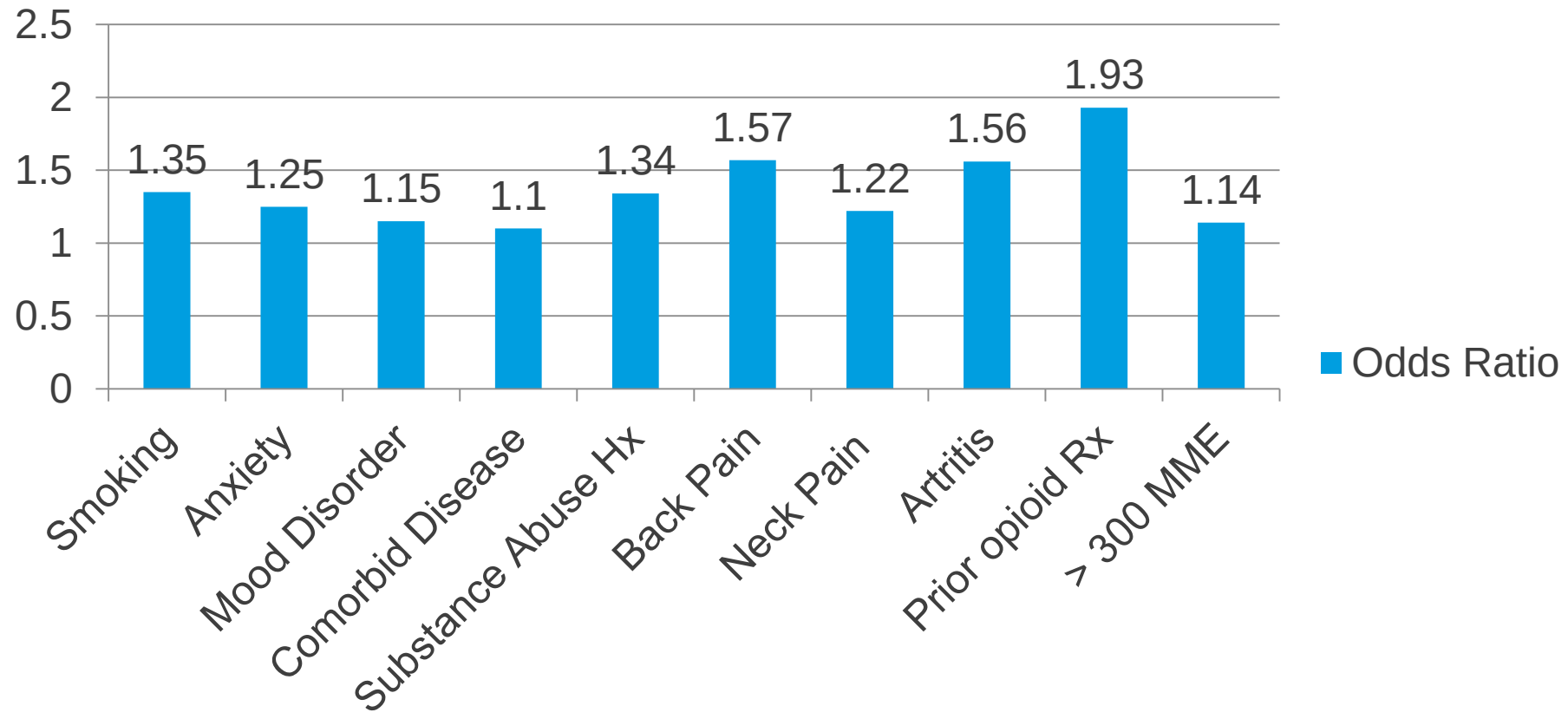
Pain & The Opioid Epidemic

- > 70 million people undergo surgeries in the US annually (2011 Study)
  - 80% experience post-operative pain and are most likely to receive opioids
  - 1 in 15 patients will go on to develop long-term use/abuse
- Canadian study showed more than 10% of patients prescribed opioids after low-risk surgery still receive these prescription opioids 1 year after the surgery
  - Recommendation is no more than 3 days prescription for acute pain
- Many reasons for continued prolonged use of opioids following surgery
  - Pain intensity not the principal driver behind prolonged use
  - High levels of psychological distress and previous problematic substance use best predict treatment with opioids rather than non-opioid analgesics
- Pre-operative prescribed opioids and co-morbid depressive symptoms are independent predictors of prolonged opioid use after surgery

Risk Factors for New Persistnt Opioid Use after Surgery

Odds ratio by factor



Brummett CM, JAMA Surg, 2017; 152:e170504..

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Pain & The Opioid Epidemic

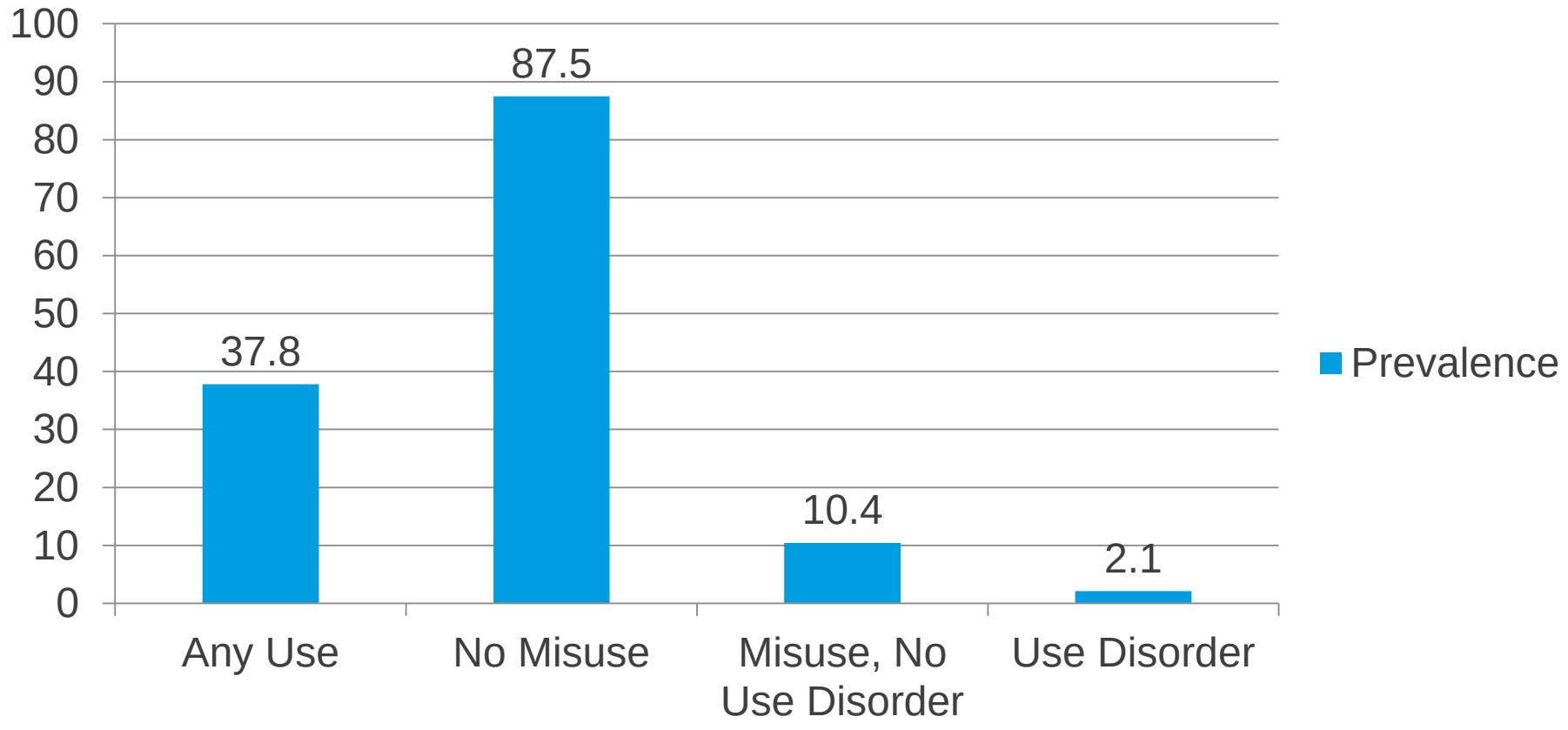
- Rapid increase of opioid use emanating from the acute care setting
- Overall amount of opioids prescribed is less than the peak in 2010
  - 782 morphine equivalent mg (MME) per capita to 640 MME in 2015
  - However still 3x as high as in 1999
- 94% of post operative patients get an opioid prescription
  - 75% of prior non-users get almost double the recommended dose (200 MME)
- US study (2012) estimates 1.1 million new users annually of prolonged opioid use following surgery according to data from 1999-2005
  - Risk is about the same for major or minor surgery (6.5% vs 5.9%) in a recent study

Opioid Use for Pain Management

- Traditional WHO analgesic ladder that once advised a basic stepwise approach starting with non-opioid agents and eventually reaching for potent narcotics
- Replaced by neural blockade with local anesthetics followed in order by high dose opioid, epidural opioids, patient-controlled opioid therapy and only then NSAIDS
- 46 Americans die of a prescription overdose every day

2015 National Survey on Drug Use and Health (NSDUH)

12 month prevalence among US adults



Han B, Ann Intern Med, 2017; 167:293-301.

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Opioid Use for Pain Management - What Changed?

- Clinical US guidelines for the management of chronic pain changed in 1997
  - American Society of Anesthesiologists
  - American Academy of Pain Medicine
- Both guidelines encouraged expanded use of opioid pain medication
- Federation of State Medical Boards has also advocated adoption of model policies to promote more compassionate pain management
- With it has come a marked increase in opioid associated overdoses and deaths

Does Chronic Pain Itself Lead to Mortality?

- Chronic pain is defined as pain lasting longer than 3 months or past the time for tissue healing
- Studies have shown some mixed but generally negative results
- One study showed a relative risk of 1.49 for all-cause mortality
  - Problem - study was not fully adjusted for confounding factors
- Other studies have shown associations with all-cause, circulatory and cancer mortality
  - However, these relationships became non-significant when adjusted for comorbid conditions
  - Especially smoking, physical activity, psychiatric and medical conditions
- Bottom Line – chronic pain itself does not lead to a significant increase in all-cause or cause-specific mortality
  - Applies to joint, regional and widespread pain (fibromyalgia) conditions

Chronic Pain is Associated with Suicide Ideation and Attempts

- Chronic pain is associated with increased risk of suicidal ideation
  - Odds ratio 1.4 -1.46 after controlled for comorbid conditions
  - Lifetime prevalence is about 20%
- Chronic pain is associated with and increased risk of suicide attempts
  - Odds ratio of 1.94 in one study
  - Lifetime risk 5%-14%
- Risk of completed suicide is at least doubled
  - Drug overdose is the most commonly reported plan for committing suicide

Risk Factors for Suicide with Chronic Pain

- Family history of suicide
- Previous suicide attempt
- Female sex
- Presence of comorbid depression
- Type of pain (migraine with aura, abdominal pain)
- High pain intensity
- Long duration of pain
- Presence of insomnia
- Helplessness and hopelessness about pain

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Most Deaths with Chronic Pain Occur Secondary to Accidental Drug Overdose

Most often with Opioid Medications

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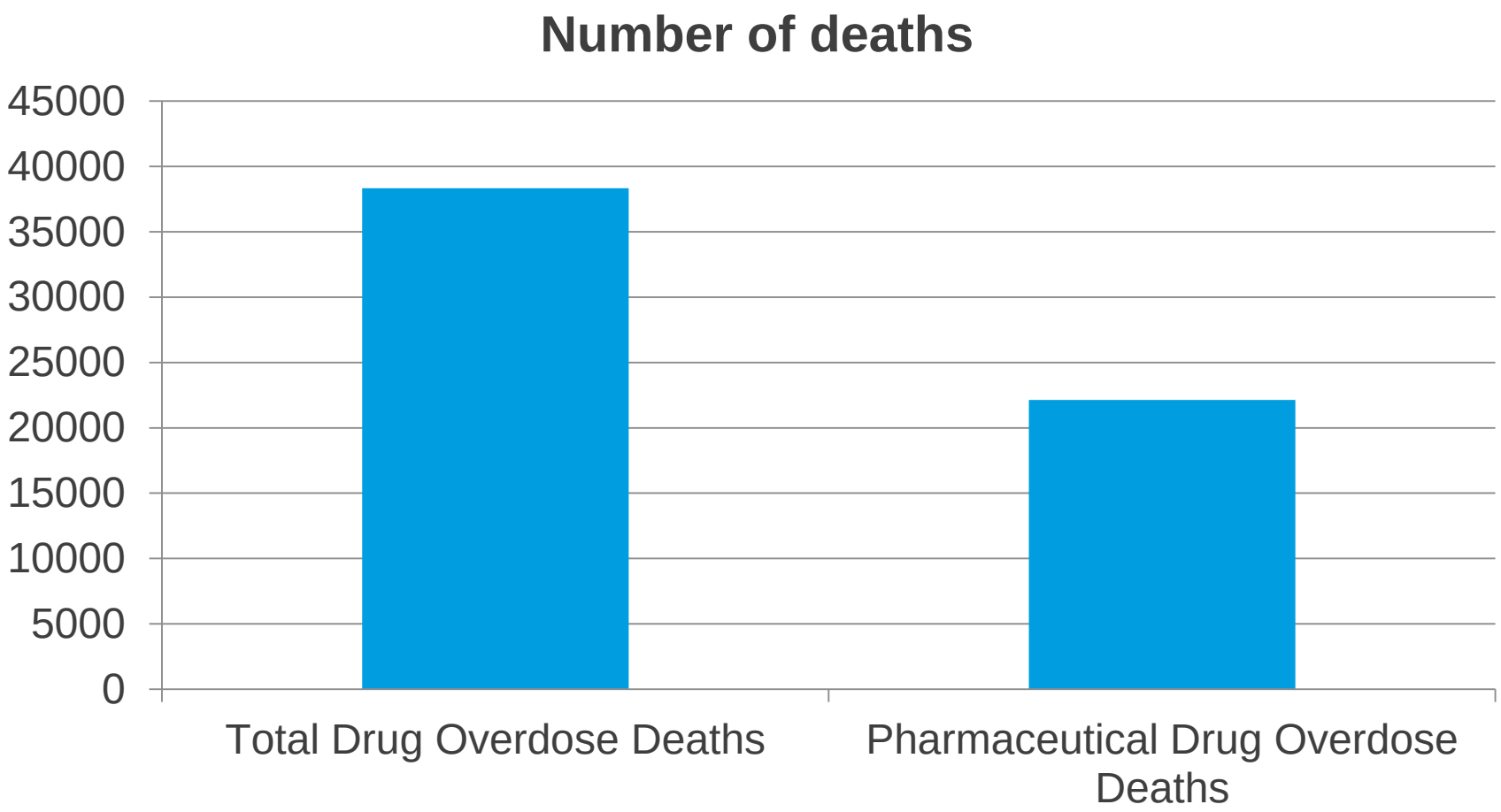
Snapshot of Drug Overdose Deaths 2010 (USA)



Jones CM et al. Pharmaceutical overdose deaths, United States, 2010, JAMA, 2013, v:309;i:7;p:657-9

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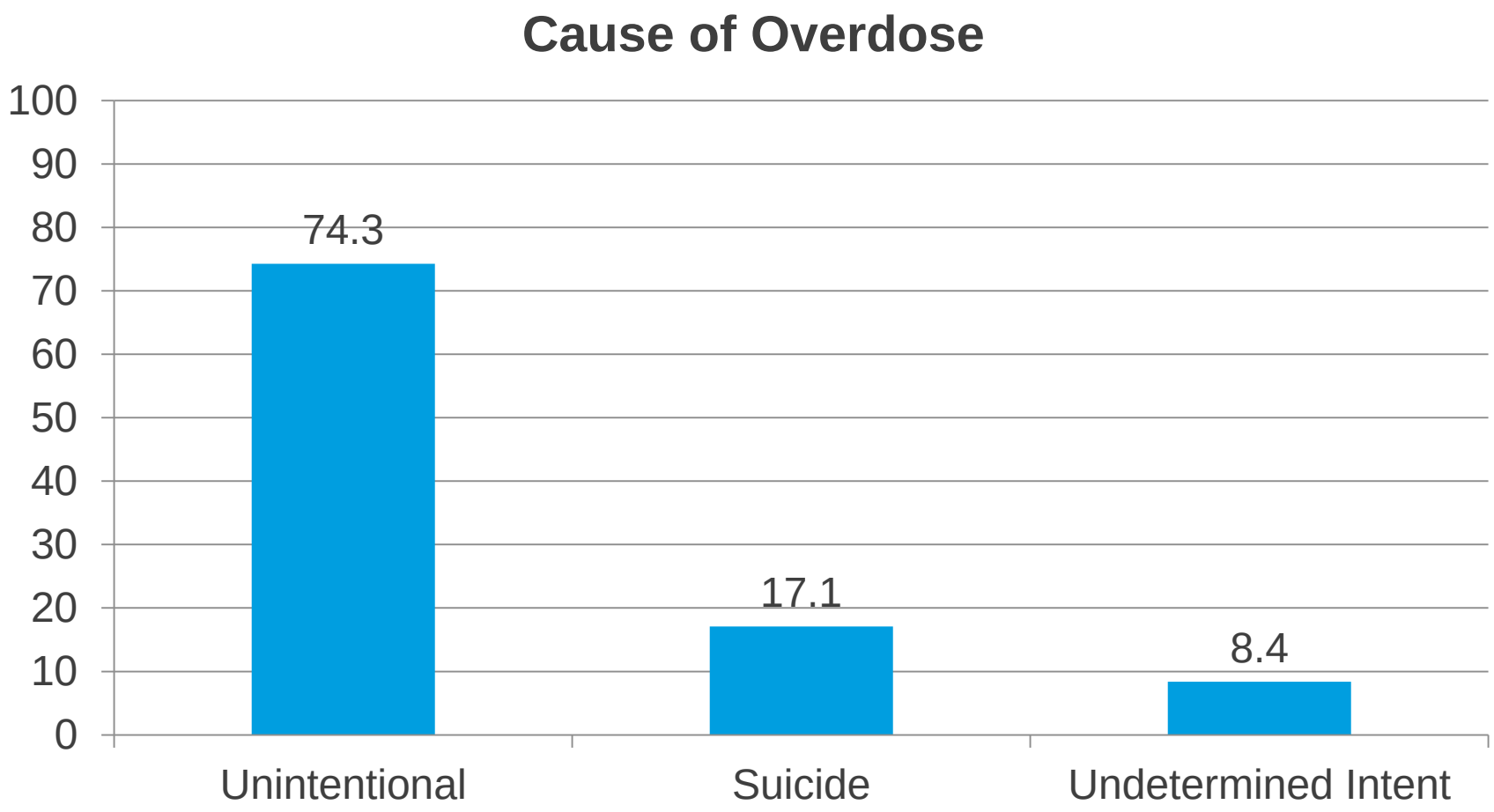
Snapshot of Pharmaceutical Overdose Deaths 2010 (USA)



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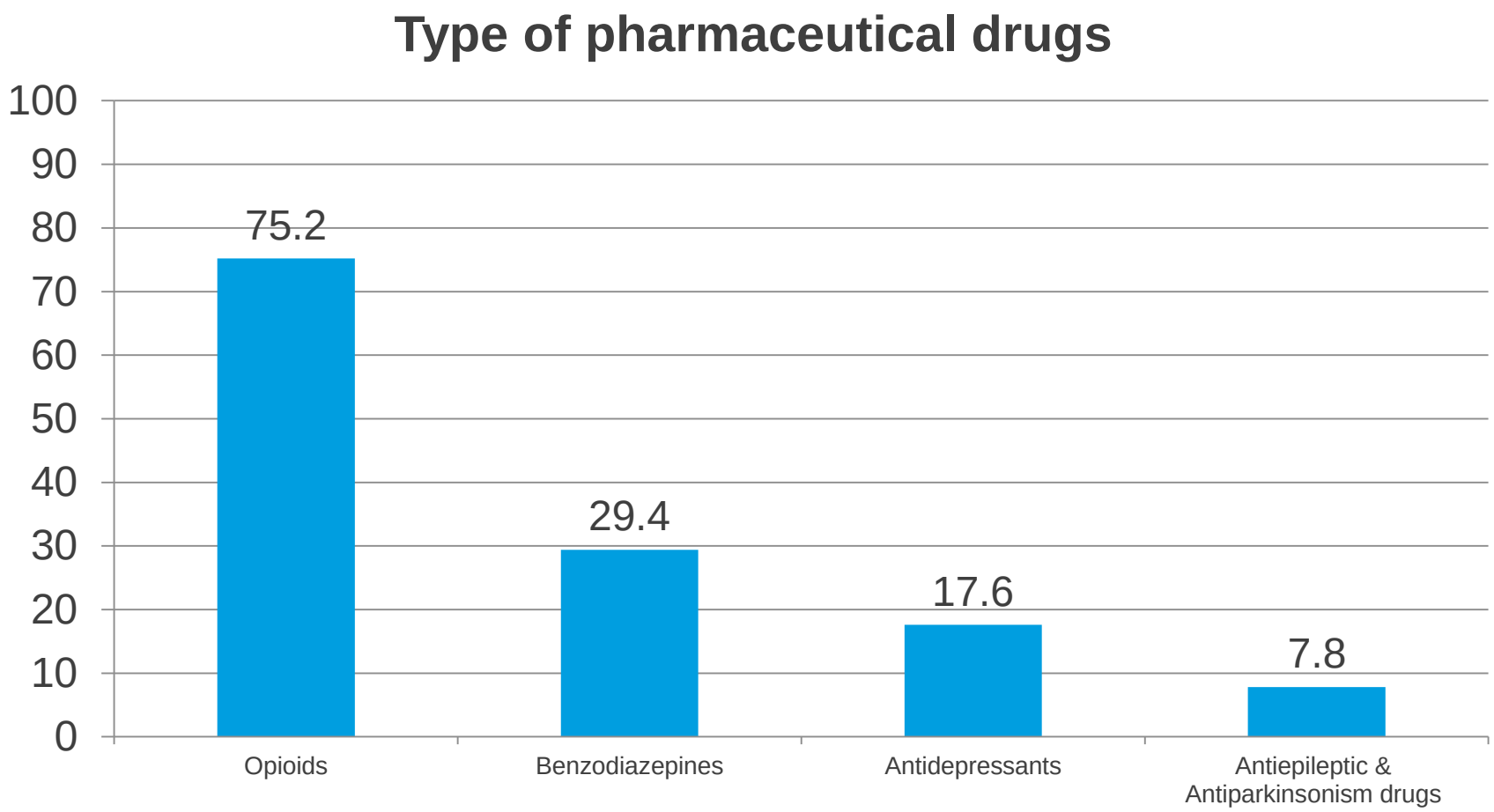
Commonest Drugs involved in Pharmaceutical Overdose Deaths



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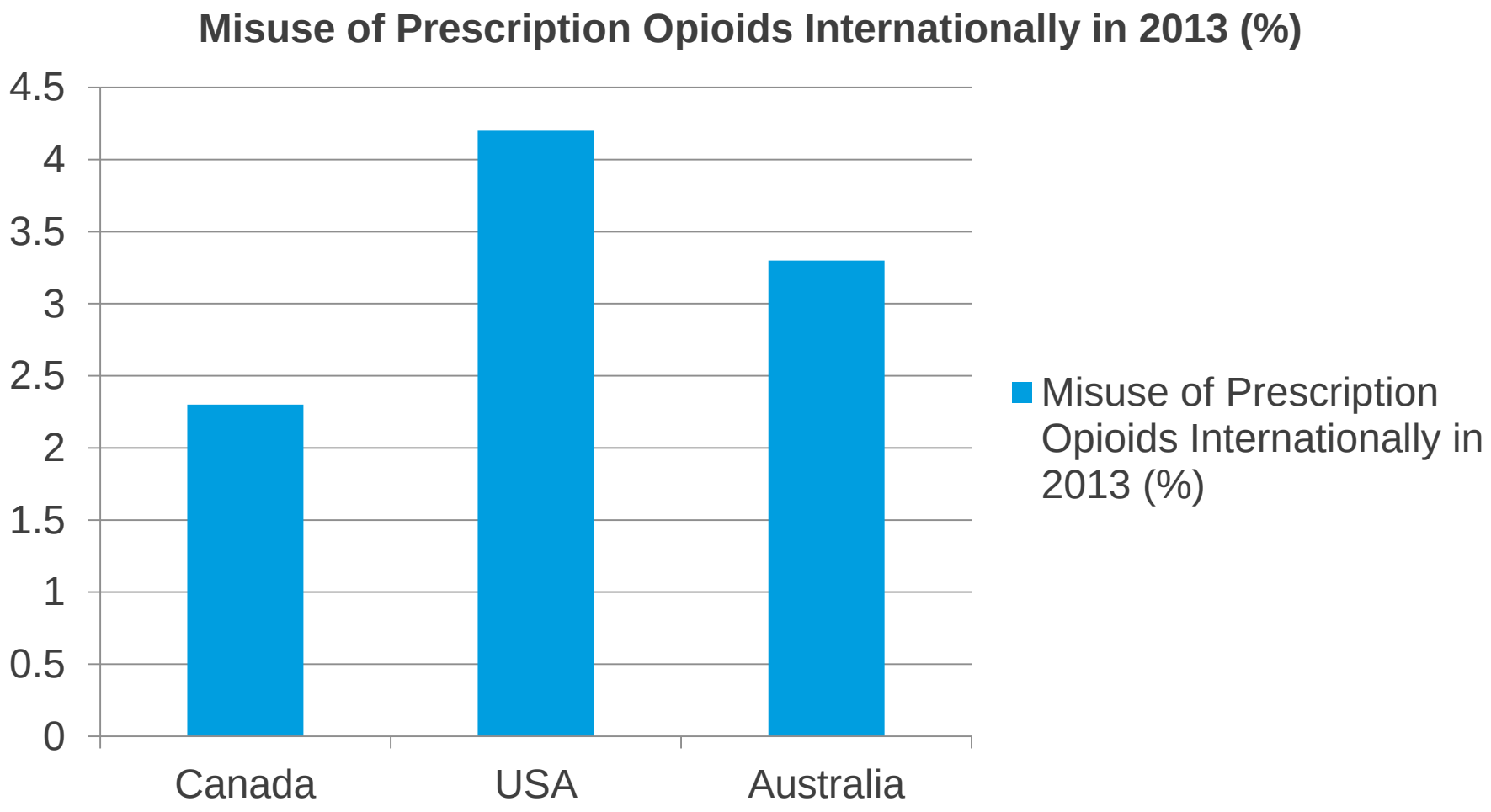
Accidental Drug Overdose

- Accidental death rates in the US were at their lowest level in 1992
- Rates have steadily increased since then driven by increased drug overdose death rates
- Death rates from drug poisoning passed those of motor vehicle accidents in 2009
- Most drug overdoses are now due to prescription medications
- Opioids and sedative/hypnotics, especially benzodiazepines are the principle drivers of this trend
- *If you are going to worry about MVA related mortality you should be worried about prescription medication overdoses*

Opioid prescribing

- USA & Canada and Australia have highest per capita consumption of opioids in the world and highest overdose rates.

Opioid prescribing

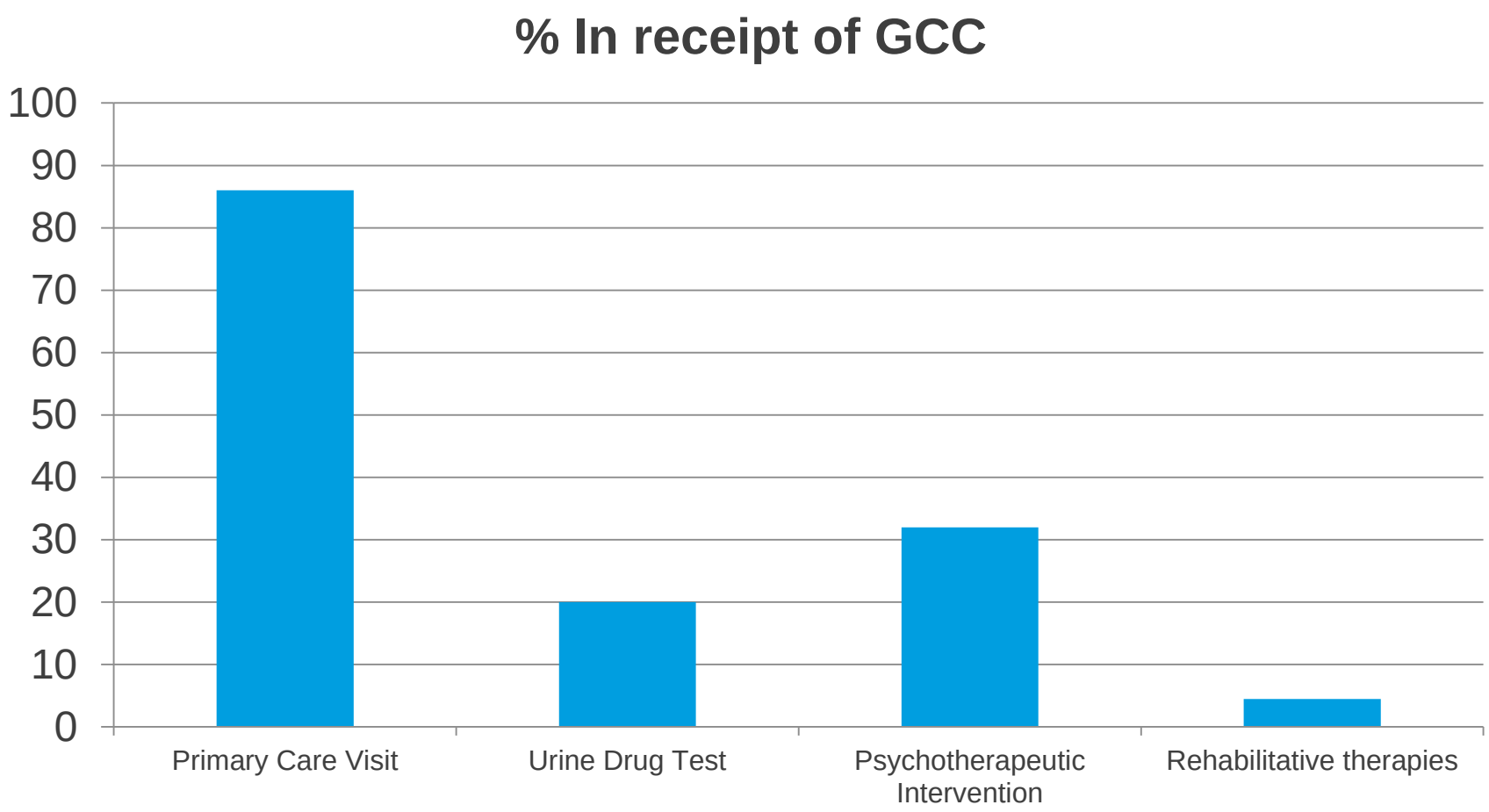


Canadian Centre on Substance Abuse. Canadian Drug Summary: Prescription Opioids. July 2015.www.ccsa. Accessed 04/25/2017

Long-term Opioid Therapy (LtOT)

- Rarely provided in accordance with clinical practice guidelines
- Majority of recommendations by leading medical societies supported by low-quality evidence
- None of the guidelines supported by high-quality evidence
- Lack of quality evidence – 37 key areas of patient care and LtOT where there are critical deficiencies in the medical literature
- No studies compare opioids to placebo for treatment of treatment of pain of more than 1-year duration

Receipt of Guideline-Concordant Care (GCC) for LtOT



Gaither J et al. The Association Between Receipt of Guideline-Concordant Long-Term Opioid Therapy and All-Cause Mortality. Journal of General Internal Medicine, 2016, v:31;i:5;p:492-501

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Guideline-concordant Care and All-Cause Mortality

Guideline-concordant Care Indicator	Hazard Ratio for All Cause Mortality
Primary care visit	1.12
Urine drug testing	0.96
Psychotherapeutic co-interventions	**0.62**
Rehabilitative therapies	0.81
Benzodiazepine co-prescribing	**1.39**
Substance use disorder treatment	**0.47**

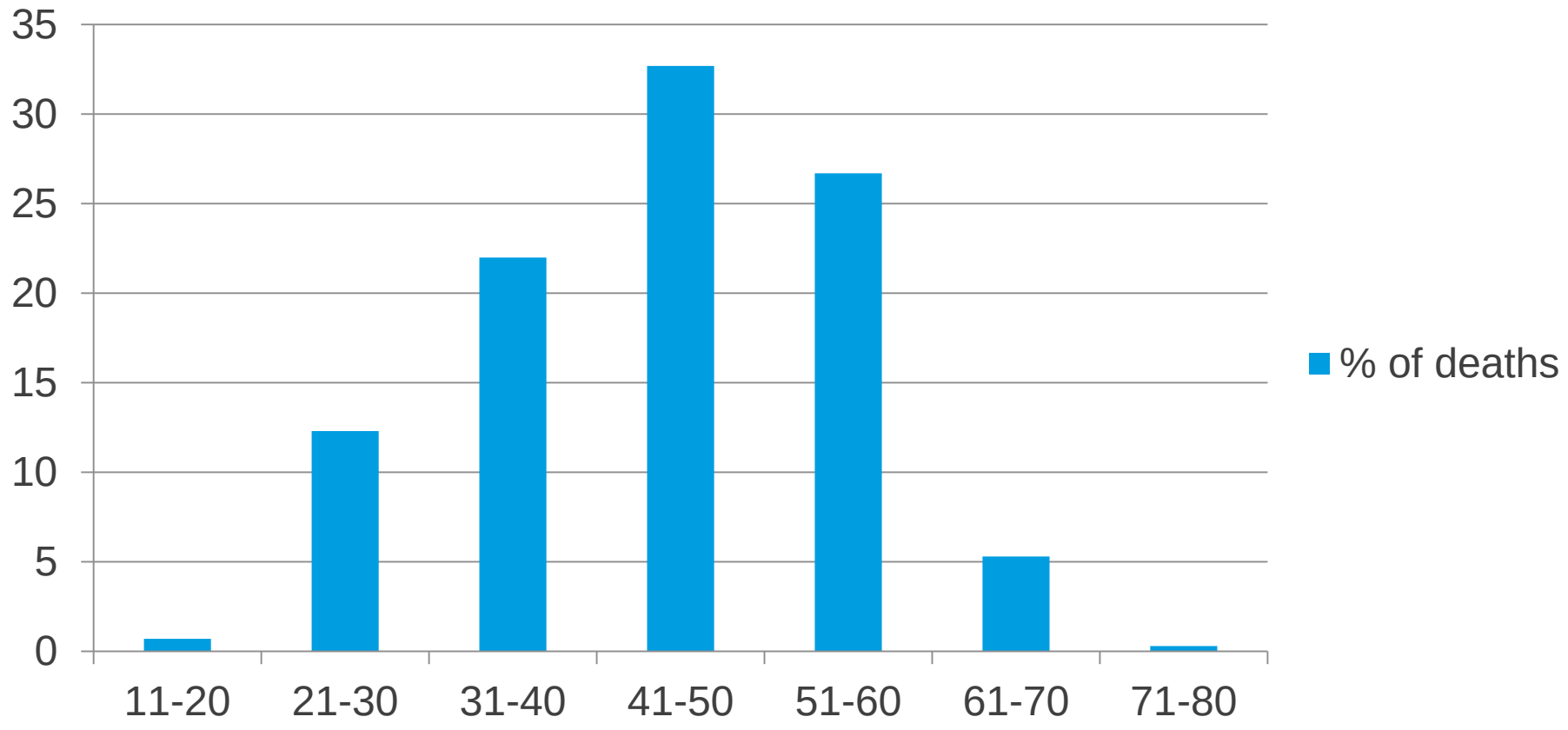
Gaither J et al. The Association Between Receipt of Guideline-Concordant Long-Term Opioid Therapy and All-Cause Mortality. Journal of General Internal Medicine, 2016, v:31;i:5;p:492-501

Accidental Drug Overdose

- 50%-80% of individuals with a prescription opioid overdose have a history of chronic pain
- Fatal overdoses are highest in middle age for both unintentional events and suicides
- Prescription drug overdose deaths are more likely in Caucasians
- Risk for prescription overdose is higher in small towns, suburban and rural areas
  - Illicit drug overdose is more common in urban areas

Fatal Opioid Overdose by Age – New Mexico Study

Percentage of Deaths with Prescription Drug Overdose by Age



Paulozzi LJ, Pain Med, 2012; 13:87-95.

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Addiction Concepts

- Gamut of terminology around substance use
  - Often not well understand, can be confusing

- DSM 5 attempted to address the confusion by replacing terms substance abuse and substance dependence with one diagnostic term → Substance Use Disorder

Addiction Concepts

- Current state of addiction terminology:

  - **Unhealthy Drug Use** - umbrella term for spectrum of drug use
  - **Risky Use** is defined by the **consumption amount** likely to cause health problems
  - **Problem Use** is defined as use that has resulted in **consequences (health or other) but not yet diagnosable disorder**
  - **Substance Use Disorder** incorporates **diagnosable substance disorders** and range from **mild (previously called substance abuse) to moderate/severe (aka substance dependence)**

Addiction Concepts

DSM 5: Substance Use Disorder

- DSM-5 diagnostic criteria — DSM-5 diagnostic criteria for SUD are described below

A problematic pattern of use leading to clinically significant impairment or distress is manifested by two or more of the following within a 12-month period:

1. Often taken in larger amounts or over a longer period than was intended.
2. A persistent desire or unsuccessful efforts to cut down or control use.
3. A great deal of time is spent in activities necessary to obtain, use, or recover from the substance's effects.
4. Craving or a strong desire or urge to use the substance.
5. Recurrent use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by its effects.
7. Important social, occupational, or recreational activities are given up or reduced because of use.
8. Recurrent use in situations in which it is physically hazardous.
9. Continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10. Tolerance.
11. Withdrawal.

Addiction Concepts

DSM 5: Substance Use Disorder

- DSM-5 severity specifiers mild, moderate, and severe are based on the number of diagnostic criteria met by the patient at the time of diagnosis:
  - Mild – Two to three criteria
  - Moderate – Four to five criteria
  - Severe – Six or more criteria
- Substance abuse – Mild subtype of SUD
- Substance dependence – Moderate to severe subtype of SUD

Addiction Concepts

- Tolerance
  - Exposure to a drug over time leads to diminution of its physiologic effects
  - Result is that higher doses are needed to produce the same effects over time
- Withdrawal
  - Physical dependence on the drug
  - Physical symptoms develop if the drug is reduced or withdrawn
  - Symptoms from **opioid withdrawal** can be severe but **never fatal** and include:
    - Diarrhea
    - Sweating
    - Fatigue
    - Anxiety/irritability
    - Shaking
    - Pain, cramps
    - Insomnia

Addiction Concepts

- Physical dependence does *NOT* mean addiction
- Addiction is characterized by the 4 C's
  - Control – impaired re drug usage
  - Compulsive use
  - Continued use despite harm
  - Craving
- Pain relief versus addictive behavior
  - Individuals seeking pain relief focus on the pain
    - Willing to try other treatments
  - Addicts focus on the drug
- Terminology not in DSM 5

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Do Not Need to Be Dependent or Addicted to Misuse Opioids

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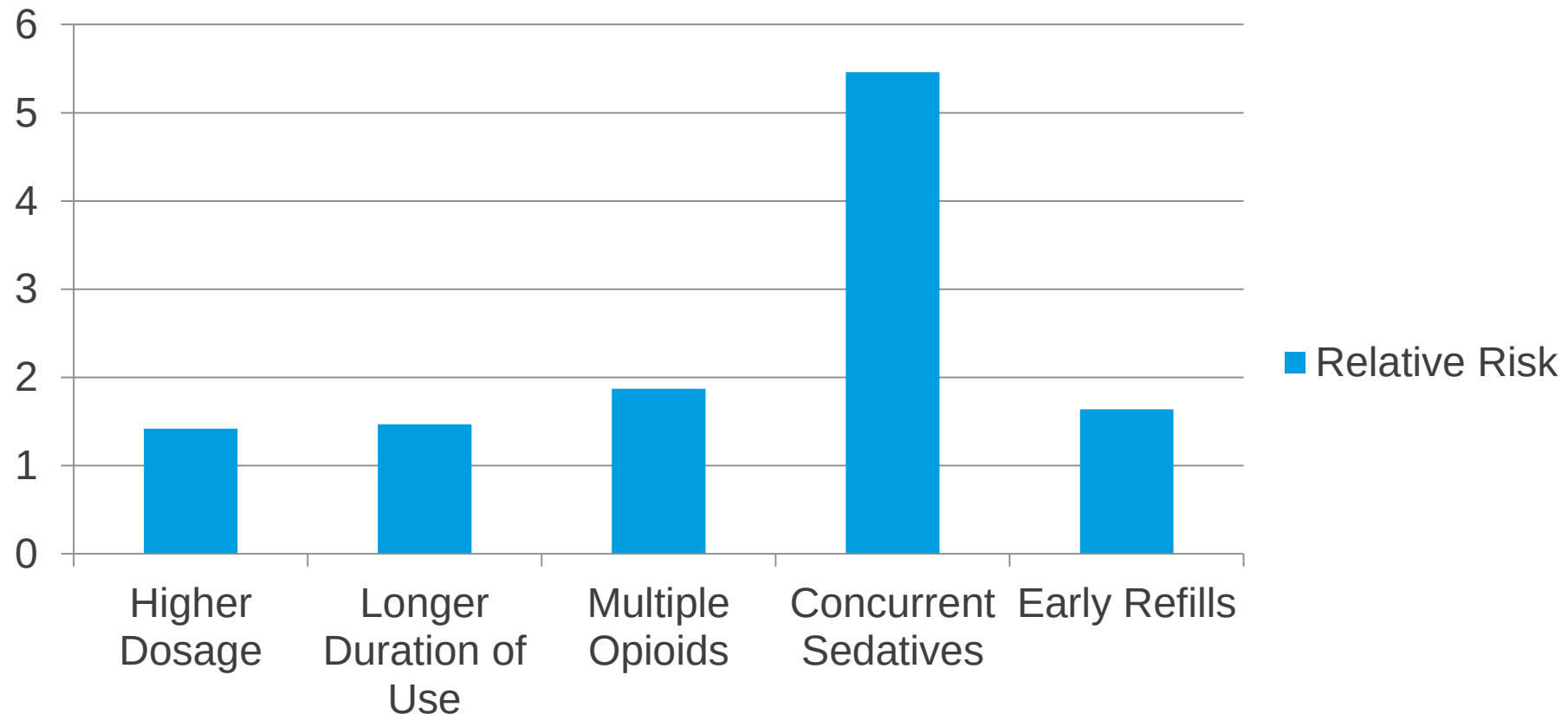
Problem Use of Opioids in Individuals with PTSD

PTSD With or Without Another Mental Health Diagnosis



Seal KH, JAMA, 2012; 307:940-947.

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Opioid Prescriptions and Substance Use Disorders

- Untreated Substance Use Disorder (SUD) with concurrent LtOT had mortality rate of 2.6 times that of current SUD engaged in treatment

Opioid Dosage

- Different opioids have different potency
- Assessing the daily exposure may be difficult when different drugs are used
  - Especially if multiple drugs are used
- Solution – Morphine Equivalent Dose
- Different drugs are compared with morphine as the standard measure
- Morphine is given the potency of 1
  - Heroin also has a relative potency of 1
- Other drugs are given a potency value relative to this standard
- The total daily dose of opioids can then be expressed as a morphine equivalent dose

Morphine Equivalent Conversion Factors

Generic Name	Brand Name	Morphine Eqiv Conversion
Morphine	Avinza, Kadian, MS Contin, Oramorph SR	**1**
Propoxyphene	Darvon, Darvon-N, Darvocet, Balacet	**0.23**
Tramadol	Ultram, Rybix, Ryzolt, Syapryn, Tramalgin	**0.10**
Codeine	Tylenol with codeine	**0.15**
Oxycodone	Oxycontin, Oxyir, Percodan, Percocet, Roxicet, Tylox, Combunox	**1.5**
Hydrocodone	Lortab, Maxidone, Norco, Vicodin, Xodol, Zydone, Ibudone	**1**
Hydromorphone	Dilaudid, Dilaudid HP	**4**
Meperidine	Demerol	**0.10**
Fentanyl transmucosal	Fentora, Onsolis	**0.13**
Fentanyl transdermal	Duragesic	**2.4**
Oxymorphone	Opana, Opana ER	**3**
Levorphanol	Levo-Dromoran	**11.0**
Methadone	Methadose, Dolophine	**3**

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There is No Universally Accepted Definition of "High Dose" by Morphine Equivalent Standards

Tolerance is an Issue

Opioid tolerance is defined as: Patients already taking at least morphine **60 mg** orally daily

Differential Effects Depending on Duration of Treatment

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Studies analyzing outcomes associated with different opioid doses have grouped patients as:

- Low dose ≡ Morphine Equivalent Dose of 5 – 20 mg
- Moderate dose ≡ Morphine Equivalent Dose of 20.1 – 50 mg
- Higher dose ≡ Morphine Equivalent Dose of 50.1 – 120 mg

Bender K. Patients Report Worse Outcomes with Higher Opioid Doses. Pain Medicine News, April 10 , 2017

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What are the factors that predict who gets an increase in their prescription opioid dose?

- Pain related factors
- Mental health factors (Depression and Anxiety)

Study emphasized that higher doses don't necessarily give better pain relief

- Treating patients with high distress and high pain levels becomes very difficult

Bender K. Patients Report Worse Outcomes with Higher Opioid Doses. Pain Medicine News, April 10 , 2017

Signs of Abuse

- Obtaining prescriptions from multiple physicians
  - “Doctor shopping”
- Obtaining prescriptions from multiple pharmacies
  - Even more concerning
- Filling prescriptions early
- Reluctance to use other means to control pain
- Bullying or abusing the medical staff
- Presence of a psychiatric condition
  - PTSD is especially problematic

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Risk of Overdose and Death Increases with the Opioid Dosage

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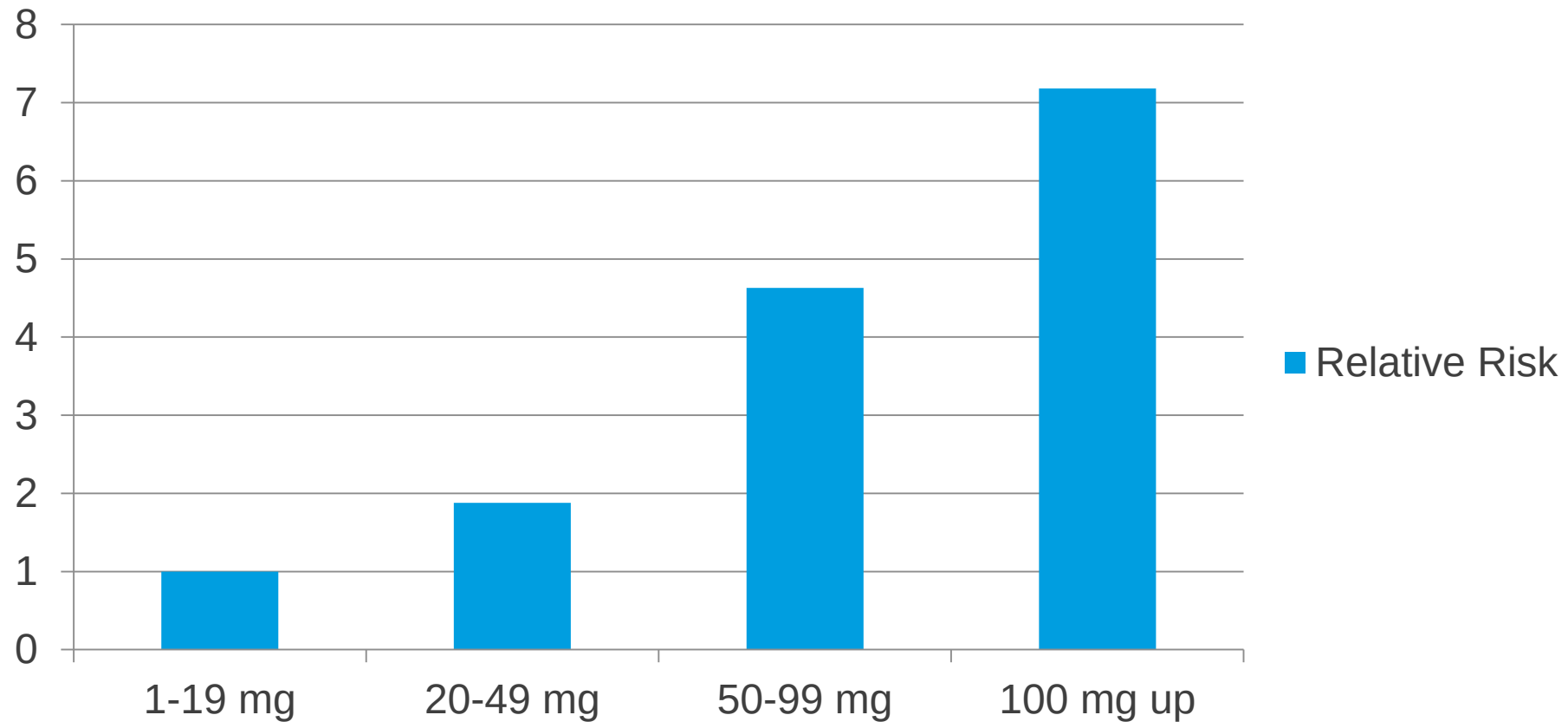
Risk of Fatal Prescription Opioid Overdose by Dosage

Opioid Dosage in Morphine Equivalents



Bohnert AS, JAMA, 2011; 305:1315-1321.

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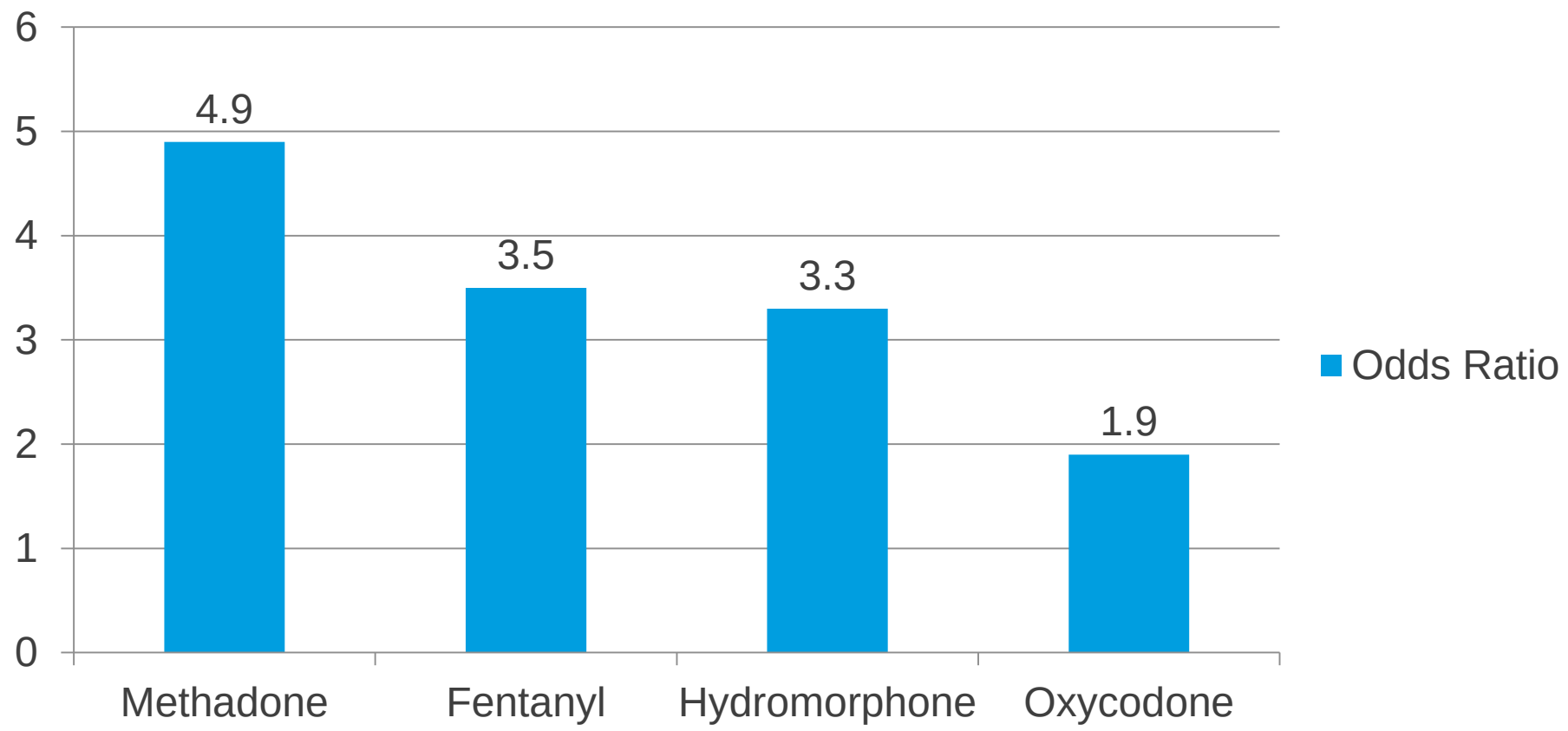
Red Flags for Opioid Overdose Mortality

- Male sex
- Smoking
- Middle age
- Caucasian
- Presence of a psychiatric condition
  - Especially ADHD, obsessive compulsive disorder, depression, PTSD
- Use of a sedative/hypnotic
  - Especially benzodiazepines
- Use of methadone
- Use of fentanyl
- Evidence to suggest alcohol abuse
  - Alcohol criticism
  - DWI, CDT, high HDL, clinical factors

Red Flags for Opioid Overdose Mortality

- Evidence of regular marijuana use
- More than one opioid prescription
- Obtaining prescriptions from multiple providers
- Obtaining prescriptions from multiple pharmacies
- Period of change in regimen – tolerance comes in to play
  - New onset of use
  - Restarting after a period of abstinence
  - Changing from one opioid to another
    - Especially with methadone

Risk of Overdose Death by Type of Opioid



Paulozzi LJ, Pain Med, 2012; 13:87-95.

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Methadone is Particularly Problematic in Terms of Overdose Death

CDC Weekly Update, 2012; 61:493-497.

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Methadone

- Advantages for pain relief
  - Long duration of action
  - Relatively low cost
  - Availability in a liquid formulation
- Disadvantages/risks
  - Increased potency
    - Morphine equivalent factor of at least 4
    - MME increases as the dose goes up (12 with a dose of 60 mg up)
  - Long and unpredictable half-life
    - Analgesic hal-life is shorter than its elimination half-life
    - Associated with accumulation and respiratory depression
    - Cannot be used like other opioids
  - Most patients and non-specialist physicians are unfamiliar with its idiosyncrasies
  - Multiple interactions with other drugs, especially benzodiazepines
  - Ability to cause cardiac rhythm disturbances

Methadone – Red Flags

- Never used for acute pain, breakthrough pain or on an “as needed” basis
- Not a drug of first choice
- Should never be used in someone naïve to opioids
- Special caution if an applicant is starting or being switched to methadone
- Combination of methadone and benzodiazepines is especially high risk
  - Potential for severe respiratory depression

Other Opioid Related Mortality and Morbidity Risks

- Study found increased risk of hip, humerus and wrist fractures in current prescribed opioid use compared to nonuse → OR of 1.27
- Two studies found an increased risk of myocardial infarction associated with prescribed opioid use (OR 1.28 in a good quality case-control study)
- One study showed increased risk of motor vehicle accidents at MED of at least 20mg/day (OR 1.21 to 1.42)

Chou R et al. The Effectiveness and Risks of Long-Term Therapy for Chronic Pain: A Systematic Review for a National Institutes of Health Pathways to Prevention Workshop. Annals of Internal Medicine Vol 162 No 4 17 Feb 2015

Good Case Factors

- Low dose of opioids
- Followed by a *reputable* pain specialist
- Stable dosage over time
- No evidence to suggest drug seeking behavior
- Willing to use alternative means of controlling pain / evidence of rehabilitative therapies
- No significant psychiatric comorbidity
- In presence of mild psychiatric comorbidity evidence of psychotherapeutic support
- No use of benzodiazepines
- Functional at home and work
- Good compliance with therapy
- Regular follow-up

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Final Pearl – 2/3 of Patients Saw a Physician in the Month Before Overdose Death

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Questions?

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