

# Management Beyond Methadone: Evaluating Heroin- Assisted Treatment for Opioid Use Disorder

University of the Incarnate Word Clinical Controversy Series

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## Learning Objectives

At the completion of this presentation, the participant will be able to:

- A. Summarize the current state of opioid misuse and abuse in the United States.
- B. Review current treatment options for opioid use disorder and identify limitations of these treatments.
- C. Examine the efficacy of supervised injectable heroin for the treatment of treatment-refractory opioid use disorder.
- D. Evaluate current and prospective heroin-assisted treatment programs in North America.

## Key Definitions

### Types of Opioids

1. Opioid: Natural or synthetic substances that act on the main opioid receptor systems; effects include analgesia, central nervous system depression, and euphoria.<sup>1</sup>
2. Prescribed Opioids: Opioid medications that are prescribed for pain relief. They include naturally occurring opiates (e.g. morphine and codeine), synthetic opioids (e.g. fentanyl and methadone), and semi-synthetic opioids (e.g. oxycodone and hydrocodone).<sup>1</sup>
3. Heroin: Derivative of morphine, with a chemical name of diacetylmorphine. Most common opioid to be abused via injection.<sup>1</sup>

### Types of Aberrant Drug-Related Behaviors

4. Misuse: Use of a medication for non-medical use, or for reasons other than prescribed.<sup>2</sup>
5. Abuse: Misuse with consequences. The use of a substance to modify or control mood or state of mind in a manner that is illegal or harmful to oneself or others.<sup>2</sup>
6. Opioid Use Disorder: A problematic pattern of opioid use leading to clinically significant impairment or distress, manifested by at least two of the following within a 12-month period:<sup>3</sup>
  - a. Opioids are often taken in larger amounts or over a longer period than was intended
  - b. There is a persistent desire or unsuccessful efforts to cut down or control opioid use
  - c. A great deal of time is spent obtaining/using the opioid, or recovering from its effects
  - d. Craving, or a strong desire or urge to use opioids
  - e. Recurrent opioid use resulting in a failure to fulfill role obligations at work, school, or home
  - f. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids
  - g. Important social, occupational, or recreational activities are reduced due to opioid use
  - h. Recurrent opioid use in situations in which it is physically hazardous
  - i. Continued opioid use despite knowledge of having a physical or psychological problem that is likely to have been cause or exacerbated by the substance
  - j. Tolerance to opioids
  - k. Opioid withdrawal syndrome

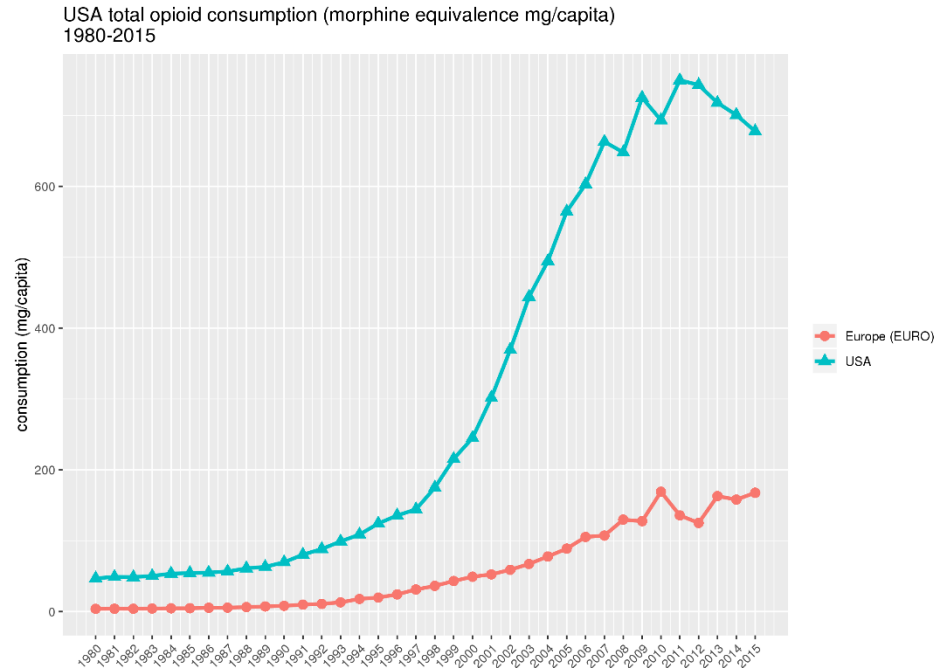
### Societal Effects of Opioids

7. Opioid Epidemic: Epidemiologic trend in the United States in which drug overdose mortality due to opioids has steadily increased despite widespread attention and public health initiatives.<sup>4</sup>

## Opioid Misuse and Abuse in the United States

### Trends in Opioid Use

- Large volumes of opioids are consumed in the United States compared to similarly developed nations<sup>5</sup>

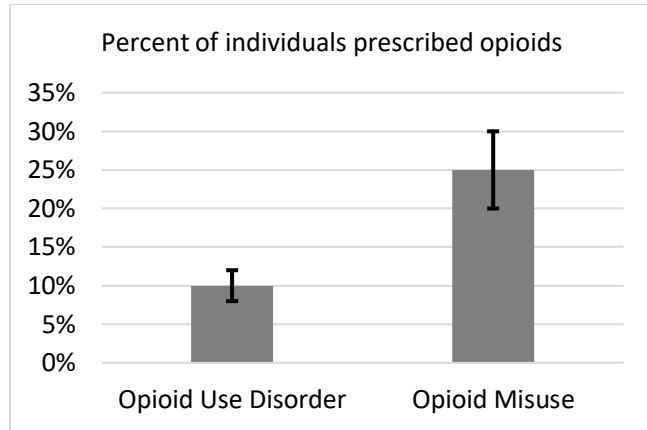


\*Graph courtesy of National Institute on Drug Abuse

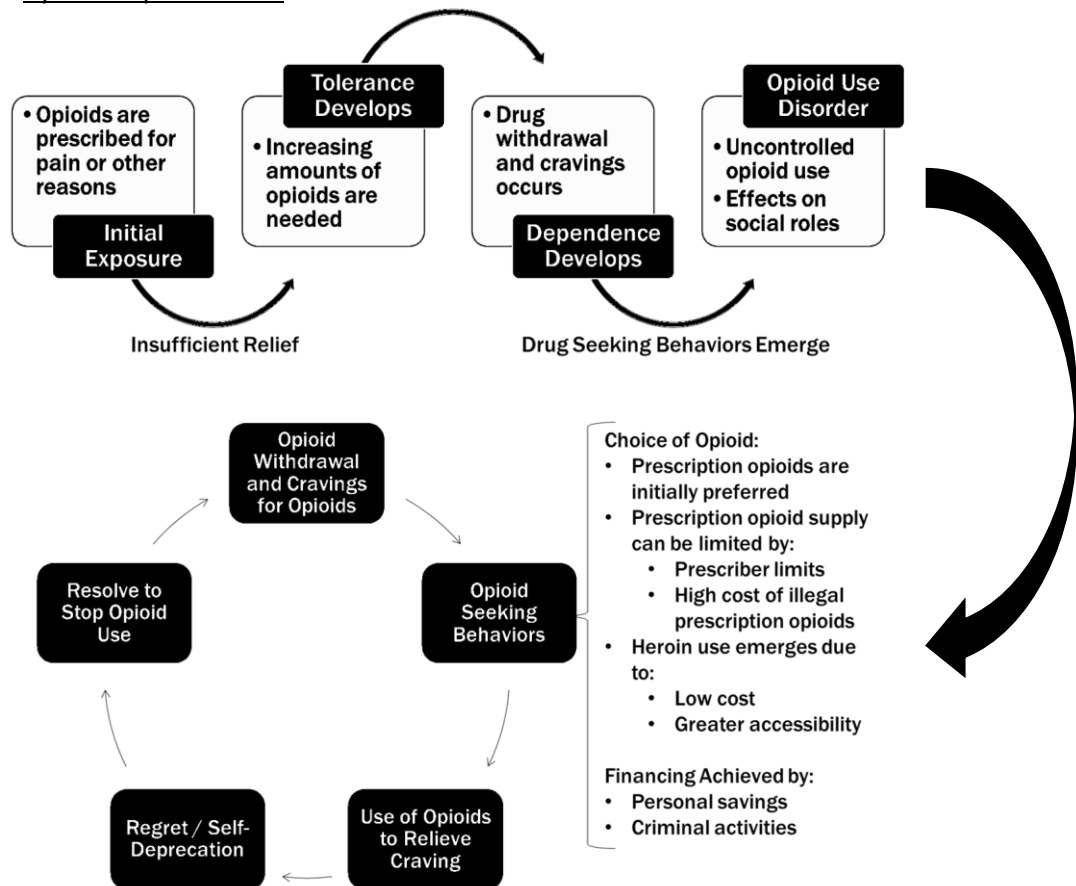
- Reasons for high volume of opioid prescriptions in the United States:
  1. Changes in Opioid Prescribing Patterns
    - Physicians went from being *opioid averse* to *liberal prescribers* in the 1990s.<sup>6</sup> This shift was driven by:<sup>7</sup>
      - Marketing techniques by drug manufacturers
      - Physician ignorance regarding abuse potential of opioids
      - Reassurance from various authorities that abuse, addiction, and diversion were not issues with opioid therapy
      - Availability of newer, long-acting opioid formulations
  2. Chronic Pain Management with Opioids
    - Chronic pain conditions (lasting 3 months or longer) affect approximately half of American adults<sup>8</sup>
    - Opioids are inappropriately used to treat chronic non-cancer pain despite lack of data supporting their efficacy for this indication<sup>6,9</sup>
      - 17% of Americans had at least one opioid prescription in 2017
      - 58 opioid prescriptions were written for every 100 Americans in 2017<sup>10</sup>

**Effects of Widespread Opioid Use**

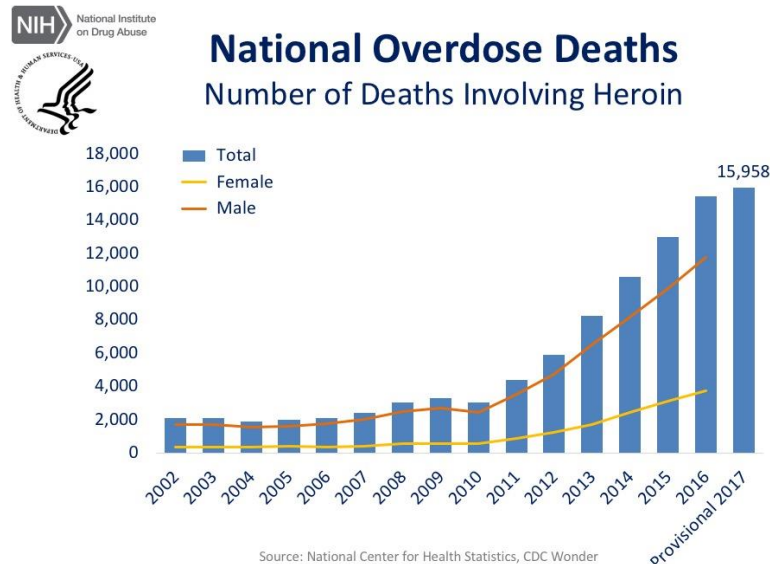
- Increased risk of misuse and abuse
  - Although most people use opioids appropriately, there is a high risk of opioid misuse and opioid use disorder in people prescribed opioids.<sup>6,9</sup>



- Definitions of opioid use disorder and opioid misuse are provided on page Key Definitions1
- Opioid use disorder now affects ~1.5% of the US adult population, due to:<sup>11,12</sup>
  - Prescription opioids: 2.1 million adults (2013)
  - Heroin: 1.0 million adults (2013)
- Cycle of Opioid Abuse<sup>9,10</sup>



- Increased risk of opioid overdose
  - Despite recent attention from the media, government, and health-care professionals, drug overdose deaths continue to increase in the United States<sup>13,14</sup>
  - Drug overdose mortality (any drug) increased 12.5% from 2016 to 2017 (72,000 deaths in 2017)
  - Opioids make up a disproportionate share of drug overdose deaths
    - Opioid overdose mortality increased 16% from 2016 to 2017<sup>13</sup> (49,000 deaths in 2017)
    - Overall rate of opioid overdoses is likely underreported by as much as 20% due to incomplete death certificates which fail to specify the agent of harm<sup>15</sup>
  - Deaths from heroin have increased 8-fold since 2010<sup>13</sup>
    - Approximately 80% of people who use heroin report that their opioid use disorder began with prescription opioids.<sup>9,10</sup>
    - The convergence of a) poorly managed pain, and b) restrictions on prescription opioids have resulted in an increase in heroin use as cheaper, more available alternative to prescription opioids.<sup>9</sup>



\*Graph courtesy of National Institute on Drug Abuse

### Strategies for Curbing Opioid Epidemic

- Centers for Disease Control and Prevention (CDC) recommend pursuing four primary objectives to address the current opioid epidemic:<sup>16</sup>
  1. Improve opioid prescribing practices
  2. Prevent opioid use disorder
  3. **Treat opioid use disorder**
  4. **Increase access to effective overdose treatment**

## Treatment Options for Opioid Use Disorder

### Historical Perspectives: Medical Disease versus Moral Weakness

- Treatment of opioid use disorder is complicated by diverging views on whether opioid use disorder is a moral problem or a medication condition<sup>17,18</sup>

|                       | Moral Problem  | Medical Problem  |
|-----------------------|--|--|
| Key Belief:           | Opioid use disorder is a result of moral weakness and a lack of self-control   | Opioid use disorder is a medical disease, the result of physical and chemical brain changes that reduce an person's ability to exert self-control over drug use    |
| Goal:                 | "Cure" of opioid use disorder, defined as complete abstinence from opioids   | Management of opioid use disorder as a chronic disease state, with goals of reducing illicit opioid use, reducing harmful behaviors, and improving quality of life |
| Advocated Treatments: | <ul style="list-style-type: none"> <li>• Abstinence pledges</li> <li>• "Cold turkey" withdrawal</li> <li>• Residential treatment programs</li> </ul> | <ul style="list-style-type: none"> <li>• Maintenance treatment with medications</li> <li>• Psychosocial support</li> </ul>   |

- Presence of these competing worldviews is still evident in the United States, as evidenced by the following paradoxes:
  - Opioid use disorder is a disease, yet misuse of opioids by those with opioid use disorder is a criminal offense.
  - Access to opioid maintenance therapy, the most effective treatment for opioid use disorder, is highly restricted, regulated, and stigmatized, contributing to utilization rates of only 14%.<sup>11,12,18,19</sup>
  - People with opioid use disorder are highly stigmatized by community members and health care workers due to the perceived controllability of the disease. However, diseases such as diabetes and hypertension, which have similar chronicity, relapse rates, and controllability (i.e. diet, physical activity, obesity, and other controllable factors) are generally accepted as medical conditions that occur without fault or control of the patient.<sup>20,21</sup>

### Treatments for Opioid Use Disorder

- Types of available treatment can be divided into the following categories:
  - Emergency (overdose reversal)
  - Detoxification (achieving drug free condition in a short period of time)
  - **Maintenance (reduce illicit drug use, improve health and social behavior)**
  - Rehabilitation (achieve reintegration into society)

## Review of Maintenance Treatments for Opioid Use Disorder

- Long-term treatment is generally required to prevent relapse in patients who have achieved abstinence from opioids of abuse
- Psychosocial Treatment<sup>17,22</sup>
  - Broad term encompassing multiple programs and therapies
  - Aims to assist patients in maintaining abstinence and to reintegrate into society
  - Provided with medication maintenance as part of a comprehensive care program
- Medication Assisted Treatment: Opioid Agonist Therapy (i.e. methadone or buprenorphine)
  - How it Works:<sup>23</sup>
    - Patients are transitioned from opioid of abuse to an alternative opioid agonist (such as methadone or buprenorphine)
    - Although patients are physically dependent on the medications, they typically do not have the pattern and severity of problematic behaviors associated with addiction to heroin or pharmaceutical opioids
    - Patients may remain on agonist maintenance therapy indefinitely, or may be tapered off if they have no illicit drug use, as well as psychosocial stability and supports
  - Goals of Care:
    - Suppress opioid craving and withdrawal symptoms
    - Block acute effects of other opioids
    - Allow patients to return to productive lifestyle, engage in pro-social behaviors, and reintegrate into society
- Medication Assisted Treatment: Opioid Antagonist Therapy (i.e. naltrexone)
  - How it Works:<sup>17,23</sup>
    - Patients are transitioned from their opioid of abuse to an alternative opioid agonist, and then are tapered off opioid agonists entirely
    - An opioid antagonist is then prescribed by a clinician to reinforce abstinence and prevent relapse by keeping the patient from experiencing opioid intoxication or physiologic dependence on opioids
  - Goals of Care:
    - Block acute effects of other opioids
    - Maintain abstinence from opioids
    - Allow treatment of patients who are in occupations that do not permit agonist treatment, such as public safety, transportation, and healthcare

**Medication Assisted Treatments: Comparison Chart**<sup>16,18,23,24</sup>

|                        | <b>Methadone</b>   | <b>Buprenorphine</b>   | <b>Naltrexone</b>  |
|------------------------|--|--|--|
| <b>Brand Names</b>     | <ul style="list-style-type: none"> <li>• Dolophine</li> <li>• Methadose</li> </ul>   | <ul style="list-style-type: none"> <li>• Subutex</li> <li>• Suboxone</li> <li>• Zubsolv</li> </ul>   | <ul style="list-style-type: none"> <li>• Depade</li> <li>• ReVia</li> <li>• Vivitrol</li> </ul>  |
| <b>Mechanism</b>       | Mu-opioid receptor agonist: <ul style="list-style-type: none"> <li>• Prevents withdrawal</li> <li>• Reduce cravings</li> <li>• Maintains high levels of opioid tolerance in order to temper the effects of opioids</li> </ul>                                | Mu-opioid partial agonist: <ul style="list-style-type: none"> <li>• High affinity to binding site to displace illicit opioids and temper their effects</li> <li>• Low binding efficacy with a ceiling effect</li> </ul>  | Mu-opioid antagonist: <ul style="list-style-type: none"> <li>• Binds strongly to mu-opioid receptor to displace opioids and prevent receptor activation</li> </ul>   |
| <b>Effectiveness</b>   | Retention Rates: ~60%<br>Reduces illicit opioid use, criminal activity, and risk of infectious activity  | Retention Rates: ~50%<br>Reduces illicit opioid use and criminal activity  | Retention Rates: < 30%<br>Reduces opioid use   |
| <b>Adverse Effects</b> | Constipation, drowsiness, sweating, edema, reduced libido, QTc prolongation, respiratory depression  | Headache, nausea, constipation, insomnia, sedation, respiratory depression   | Nausea, headache, dizziness, fatigue, liver injury   |
| <b>Regulation</b>      | <ul style="list-style-type: none"> <li>• DEA Schedule II</li> <li>• Use for opioid use disorder is limited to licensed opioid treatment programs</li> </ul>  | <ul style="list-style-type: none"> <li>• DEA Schedule III</li> <li>• Use is limited to clinicians who have registered with CSAT and the DEA</li> </ul>   | <ul style="list-style-type: none"> <li>• No special regulatory status</li> </ul>   |
| <b>Administration</b>  | <ul style="list-style-type: none"> <li>• Oral               <ul style="list-style-type: none"> <li>○ Typically administered as single daily dose</li> <li>○ Patients must receive dose from treatment center (cannot take doses home)</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>• Sublingual or Buccal               <ul style="list-style-type: none"> <li>○ Home doses allowed</li> </ul> </li> <li>• Implant               <ul style="list-style-type: none"> <li>○ Lasts for 6 months</li> </ul> </li> <li>• Depot Injection               <ul style="list-style-type: none"> <li>○ Lasts for either 1 week or 1 month</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>• Oral               <ul style="list-style-type: none"> <li>○ Home doses allowed</li> </ul> </li> <li>• Depot Injection               <ul style="list-style-type: none"> <li>○ Lasts for 4 weeks</li> </ul> </li> </ul> |
| <b>Advantages</b>      | <ul style="list-style-type: none"> <li>• Highly effective at reducing opioid cravings and withdrawal symptoms</li> <li>• Highest retention rate</li> </ul>   | <ul style="list-style-type: none"> <li>• Lower risk of respiratory depression due to ceiling effect</li> <li>• Easier for patients to take (no daily clinic visits)</li> </ul>   | <ul style="list-style-type: none"> <li>• Non-sedating, and no physical dependence</li> <li>• Enables treatment in settings where opioid agonists cannot be used</li> </ul>   |
| <b>Limitations</b>     | <ul style="list-style-type: none"> <li>• Patients must attend clinic daily to receive methadone dose</li> <li>• Highly regulated</li> <li>• Provider and Patient Stigma</li> </ul>   | <ul style="list-style-type: none"> <li>• Can precipitate withdrawal</li> <li>• Highly regulated and limited provider availability</li> </ul>   | <ul style="list-style-type: none"> <li>• Retention is poor</li> <li>• Can precipitate withdrawal</li> <li>• Reduces opioid tolerance, increasing future overdose risk</li> </ul>   |

Definitions: DEA: Drug Enforcement Administration; CSAT: United States Center for Substance Abuse Treatment; PK/PD: Pharmacokinetics/Pharmacodynamics; Hrs: hours;



## Efficacy of Heroin for Treatment-refractory Opioid Use Disorder

### Need for New Approaches to Treat Opioid Use Disorder

- **Need to improve enrollment in treatment:** Despite the increasing prevalence of opioid use disorder, there has not been a corresponding increase in the number of opioid treatment programs.<sup>19,25</sup> Only 14% of the estimated 3.1 million people with opioid use disorder were receiving treatment in 2015.<sup>11,12,18,19</sup>
  - Uptake is low for a variety of reasons:<sup>16,18</sup>
    - Policy barriers which limit the availability of opioid use disorder treatments
    - Health insurance utilization-management techniques which may hinder access to maintenance treatments, such as limits on dosages prescribed, annual or lifetime medication limits, prior authorizations, and “fail first” criteria
    - Negative attitudes and beliefs about treatments held by the public, providers, and patients
- **Need to improve efficacy of treatment, especially for people who use heroin:** For people who receive treatment, 40-70% fail current first-line medication therapies, including methadone.<sup>18,23,24</sup> Despite rising numbers of people who use heroin, there are no effective treatment options for this population after they have failed methadone therapy.<sup>9</sup>

### Pharmacological Properties of Heroin

- Heroin is a crude preparation of diacetylmorphine (diamorphine).
  - Diacetylmorphine is a semisynthetic product obtained by acetylation of morphine, which is a natural product in opium.<sup>26</sup>
  - First synthesized in 1874, heroin was marketed by Bayer Pharmaceuticals as a non-habit forming cough suppressant and cure for morphine addiction; however, by 1910 heroin was the most commonly used illicit drug in the United States.<sup>17</sup>
  - Modern street preparations range in purity (generally 14-43% diacetylmorphine), with the remainder consisting of preparation byproducts.<sup>26</sup>
- Compared to morphine, heroin...<sup>26</sup>
  - Is 3-times more potent
  - Has a shorter half-life (~3 minutes)
  - Produces greater euphoria due to high penetration into the brain

### Supervised Injectable Heroin, a type of Heroin Assisted Treatment

- Characteristics of Supervised Injectable Heroin:<sup>27</sup>
  - Maintenance treatment option for people dependent on heroin who have failed other treatments
  - Patients receive injectable heroin in a clinic setting under medical supervision
    - Supervision of patients occurs prior to injection (to assess for intoxication) as well as 30 minutes following injection (to assess for adverse events)
    - Should a patient overdose, they are revived with naloxone by the medical staff
  - Clinic site is available for multiple sessions per day, every day of the year
  - Patients are provided with psychosocial support services and referrals for treatment

## Supervised Injectable Heroin: Randomized Controlled Trials

|  | Switzerland (1998) <sup>28</sup>   | Netherlands (2003) <sup>29,30</sup>  | Spain (2006) - PEPSA <sup>31,32</sup>   |
|--|--|--|---|
| Setting                                | <ul style="list-style-type: none"> <li>Outpatient clinic, Geneva, Switzerland</li> </ul>   | <ul style="list-style-type: none"> <li>Methadone maintenance programs in six cities in the Netherlands</li> </ul>  | <ul style="list-style-type: none"> <li>Hospital in Andalusia, Spain</li> </ul>  |
| Population                             | <ul style="list-style-type: none"> <li>Primarily men, early 30s</li> <li>Av. 12 yrs heroin use</li> <li>Av. 8 previous drug tx</li> </ul>  | <ul style="list-style-type: none"> <li>Primarily men, late 30s</li> <li>Enrolled in methadone program for 6 months and continued to use heroin</li> </ul>  | <ul style="list-style-type: none"> <li>Primarily men, middle 30s</li> <li>Av. 19 yrs heroin use</li> <li>Av. 3 previous drug tx</li> </ul>  |
| Intervention                           | <ul style="list-style-type: none"> <li>Intravenous heroin and health/psychosocial services (n=27)</li> </ul>   | <ul style="list-style-type: none"> <li>Injectable heroin plus methadone, with psychosocial services (n=98)</li> </ul>  | <ul style="list-style-type: none"> <li>Intravenous diacetylmorphine BID, oral methadone once daily, and health/psychosocial services (n=31)</li> </ul>  |
| Control                                | <ul style="list-style-type: none"> <li>Conventional drug tx, generally methadone maintenance (n=24)</li> </ul>   | <ul style="list-style-type: none"> <li>Methadone alone, with psychosocial services (n=76)</li> </ul>   | <ul style="list-style-type: none"> <li>Oral methadone once daily, and health/psychosocial services (n=31)</li> </ul>  |
| Outcomes (intervention versus control) | <ul style="list-style-type: none"> <li>Duration: 6 months</li> <li>Retention: 93% vs 92%</li> <li>Daily Heroin Use: 4% vs 48%**</li> <li>Benzo Use: 0% vs 33%*</li> </ul>  | <ul style="list-style-type: none"> <li>Duration: 12 months</li> <li>Retention: 85% vs 72%*</li> <li>40% improvement in physical, mental, or social domains: 56% vs 31%*</li> <li>SAEs: 12% vs 7%</li> <li>4 yr retention: 55.7%</li> </ul> | <ul style="list-style-type: none"> <li>Duration: 9 months</li> <li>Retention: 74% vs 62%</li> <li>Ave. days heroin use in last month: 8 vs 17 days*</li> <li>SAEs: 19% vs 23%</li> <li>2 yr retention: 57%</li> </ul>   |
| Limitations                            | <ul style="list-style-type: none"> <li>Self-reported outcomes</li> <li>Small sample size</li> <li>Not blinded</li> <li>Control group w/ multi tx</li> <li>Control group retention augmented by heroin-arm enrollment option</li> </ul> | <ul style="list-style-type: none"> <li>Self-reported outcomes</li> <li>Not blinded</li> <li>Unstandardized psychosocial txs</li> <li>Control group retention augmented by heroin-arm enrollment option</li> </ul>                          | <ul style="list-style-type: none"> <li>Small sample size</li> <li>Not blinded</li> <li>Poor follow-up of patients who dropped out</li> <li>Control group retention augmented by heroin-arm enrollment option</li> </ul> |
| Contribution to Literature             | <ul style="list-style-type: none"> <li>First RCT of supervised injectable HAT</li> <li>Established feasibility and safety of trial design</li> </ul>   | <ul style="list-style-type: none"> <li>Methadone was used in both groups, isolating effect of heroin</li> <li>Study design and results guided design of subsequent trials</li> </ul>   | <ul style="list-style-type: none"> <li>Utilized optimal doses of methadone, strengthening confidence in the study findings</li> </ul>   |

Abbreviations: Av: average; Tx: treatment; yrs: years; multi: multiple; RCT: randomized controlled trial; BID: twice daily; HAT: heroin assisted treatment; SAE: serious adverse event; benzo: benzodiazepine; \*p<0.05; \*\*p<0.01; \*\*\*p<0.001

## Supervised Injectable Heroin: Randomized Controlled Trials

|                            | Germany( 2007) <sup>33-35</sup>   | Canada (2009) - NAOMI <sup>36</sup>   | England (2010) - RIOTT <sup>37</sup>   |
|----------------------------|---|---|--|
| Setting                    | <ul style="list-style-type: none"> <li>Seven treatment centers throughout Germany</li> </ul>  | <ul style="list-style-type: none"> <li>Montreal, Quebec and Vancouver, British Columbia in Canada</li> </ul>  | <ul style="list-style-type: none"> <li>Outpatient clinics throughout England</li> </ul>  |
| Population                 | <ul style="list-style-type: none"> <li>Primarily men in mid-30s who failed tx or have not received recent tx</li> <li>Av. 14 yrs heroin use</li> <li>Failed prev. tx: 85%</li> </ul>  | <ul style="list-style-type: none"> <li>Slightly more men to women (3:2 ratio) in mid-30s to mid-40s</li> <li>Av. 16 yrs heroin use</li> <li>Av. 11 prev. drug tx</li> </ul>   | <ul style="list-style-type: none"> <li>Primarily men in late-30s</li> <li>Enrolled in methadone program for 6 months and continued to use heroin</li> <li>Av. 14 yrs opioid use</li> </ul>   |
| Intervention               | <ul style="list-style-type: none"> <li>Injectable heroin up to 3x/day and counseling, with optional nighttime methadone for withdrawal (n=515)</li> </ul>   | <ul style="list-style-type: none"> <li>Injectable diacetylmorphine, self-administered up to 3x/day (n=115)</li> </ul>   | <ul style="list-style-type: none"> <li>A) Supervised injectable heroin (n=43)</li> <li>B) Supervised injectable methadone (n=42)</li> </ul>  |
| Control                    | <ul style="list-style-type: none"> <li>Methadone and counseling (n=500)</li> </ul>  | <ul style="list-style-type: none"> <li>Oral methadone (n=111)</li> </ul>  | <ul style="list-style-type: none"> <li>C) Optimized oral methadone (n=42)</li> </ul>   |
| Outcomes                   | <ul style="list-style-type: none"> <li>Duration: 12 months</li> <li>Retention: 67% vs 40%*</li> <li>≥40% Reduction in illicit drug use: 69% vs 55%***</li> <li>Improvement in physical/mental health: 80% vs 74%*</li> <li>SAEs: 24% vs 18%</li> <li>2 yr retention: 81%</li> </ul> | <ul style="list-style-type: none"> <li>Duration: 12 months</li> <li>Retention: 88% vs 54%***</li> <li>Reduction in illicit drug use or illegal activities: 67% vs 48%**</li> <li>Ave. days heroin use in last month: 5 vs 12 days***</li> <li>SAEs: 44% vs 16%</li> </ul> | <ul style="list-style-type: none"> <li>Duration: 6 months</li> <li>Retention: 88%(A) vs 81%(B) vs 69%(C)</li> <li>≥50% Reduction in illicit heroin use: 72%(A) vs 39%(B) vs 27%(C)***</li> <li>SAEs: 16%(A), 10%(B), 21%(C)</li> </ul> |
| Limitations                | <ul style="list-style-type: none"> <li>Methadone dropout rate possibly due to patient disappointment in not being in heroin group</li> <li>Not blinded</li> </ul>   | <ul style="list-style-type: none"> <li>Methadone dropout rate possibly due to patient disappointment in not being in heroin group</li> <li>Not blinded</li> </ul>   | <ul style="list-style-type: none"> <li>Small sample size</li> <li>Open-label study design may have affected patient expectations and behaviors</li> </ul>  |
| Contribution to Literature | <ul style="list-style-type: none"> <li>Largest RCT of injectable HAT to date</li> <li>First trial to use laboratory tests to assess illicit heroin use</li> </ul>   | <ul style="list-style-type: none"> <li>First RCT of injectable HAT outside of Europe</li> <li>Small hydromorphone arm (n=25) had similar retention (88%) and response (64%) rates as diacetylmorphine arm</li> </ul>  | <ul style="list-style-type: none"> <li>Demonstrated efficacy of injectable heroin when compared to injectable methadone</li> </ul>   |

Abbreviations: Av: average; Tx: treatment; yrs: years; multi: multiple; RCT: randomized controlled trial; BID: twice daily; HAT: heroin assisted treatment; SAE: serious adverse event; benzo: benzodiazepine; \*p<0.05; \*\*p<0.01; \*\*\*p<0.001

**Takeaways from Randomized Controlled Trials:**

- Overall, retention was higher in patients treated with heroin compared to patients treated with methadone
  - A meta-analysis of the Swiss, German, Canadian, and English trials identified a Relative Risk of 1.37 [95% CI 1.03-1.83, heterogeneity ( $p < 0.00001$ ),  $I^2 = 91\%$ ]<sup>27</sup>
  - A Cochrane review of the Spanish, German, Canadian, and English trials showed a Relative Risk of 1.44 [95% CI 1.19-1.75, heterogeneity ( $p = 0.03$ ),  $I^2 = 67\%$ ]<sup>38</sup>
- The Swiss, Spanish, German, Canadian, and English trials each reported a positive effect of supervised injectable heroin on illicit heroin use
  - Each study used different criteria to define “reduction in illicit heroin use”, precluding a meta-analysis of this outcome<sup>27</sup>
- The risk of serious adverse events was higher in patients treated with heroin compared to patients treated with methadone
  - A meta-analysis of the Dutch, Spanish, German, Canadian, and English trials identified a relative risk of 4.99 [95% CI 1.66-14.99, heterogeneity ( $p = 0.25$ ),  $I^2 = 26\%$ ]<sup>27</sup>
  - Sudden-onset respiratory depression in people receiving heroin occurs at a rate of 1 in every 6000 injections<sup>27,36,37</sup>

**Patient Perceptions of Supervised Injectable Heroin:**

- Follow-up of NAOMI trial found that patient satisfaction was higher in the injectable heroin group, and that patient satisfaction at 3 months increased odds of treatment retention at 12 months<sup>39</sup>
- Qualitative interviews with patients in the Spain PEPSA study revealed that...<sup>40</sup>
  - Providing heroin within a clinic changed people’s perception of the substance: instead of taking an “illegal poison” they were now being prescribed a “legal medicine.” This effectively changed the ‘meaning’ of heroin use, as patients and family members were now more likely to see people who use heroin as “chronically ill” instead of as “addicts.”
  - Providing heroin within a clinic setting helped patients to move out of the cycle of drug seeking behavior that previously defined their lives. Patients reported that they spent less time and money acquiring doses of heroin in response to cravings, and as a result they were better able to focus on employment, personal relationships, and health.

**Countries with Supervised Injectable Heroin:**

- Europe: Switzerland, Germany, the Netherlands, Denmark, Spain, United Kingdom
- North America: Canada

**Summary of Supervised Injectable Heroin:**

- Advantages over current treatment options:
  - More effective than methadone at retaining patients in treatment
  - More effective than methadone at decreasing illicit heroin use
  - Positive patient perceptions after receiving treatment
- Disadvantages over current treatment options:
  - Higher risk for severe respiratory depression compared to methadone (must be given under medical supervision)
  - Currently not feasible in the United States due to legal and regulatory status
- Similarities to current treatment options:
  - Chronic, maintenance treatment option for people with opioid use disorder
  - Psychosocial and health services are provided as an integral part of therapy
  - Similar barriers to access as methadone (insurance utilization-management techniques, general lack of willing providers, need for daily clinic visits)

## Heroin Assisted Treatment Programs in North America

### Supervised Injection Facilities versus Supervised Injectable Heroin

- Supervised injectable heroin, described in the previous section, is a patient-specific intervention to treat opioid use disorder in people who use heroin and have failed other treatment options.
- Supervised injection facilities are an alternative form of heroin assisted treatment in which patients bring their own drugs to a facility to inject under medical supervision, with the goal of reducing overdoses and referring people to treatment for opioid use disorder. Supervised injection facilities are a public health initiative, not a patient-specific intervention.
  - In areas where supervised injectable heroin is legally prohibited, supervised injection facilities offer another route to reduce harm and improve health for people who use heroin.

### INSITE: A Model Supervised Injection Facility

- INSITE is a supervised injection facility in Vancouver, Canada which opened in 2003
- Facility Objectives:<sup>41</sup>
  - Increase access to healthcare and addiction care
  - Reduce overdose fatalities
  - Reduce infections related to injectable drug use, such as HIV, Hepatitis C, and skin abscesses
  - Improve public order
- Core Services:<sup>41,42</sup>
  - Provides supervision of patients as they inject their own drugs
    - Provides clean injection equipment (i.e. syringes, water, filters)
    - Intervenes to revive patient if overdose occurs
  - Provides wound care and immunization services
  - Refers patients to recovery and treatment programs, such as ONSITE
    - ONSITE: withdrawal management unit that is available on the premises, and enables connection to counselors, case managers, physicians, and transitional recovery housing to aid in recovery
- 2017 Statistics:<sup>43</sup>
  - 175,464 visits by 7,301 individuals
    - 537 visits/day for needle exchange service
    - 415 injection room visits/day
  - 2,151 overdose interventions
  - 443 clients referred to ONSITE

- Outcomes:
  - Mortality reduction of 35% within a 500 meter radius of the clinic site<sup>44</sup>
  - Increased access to routine primary care, including health and social services<sup>45</sup>
  - Increased referrals to and uptake of drug treatment and detoxification<sup>46</sup>
  - No increase in community drug-related crime, littering, or loitering<sup>41</sup>

### **Countries with Supervised Injection Facilities**

- Europe: Denmark, France, Germany, Luxembourg, the Netherlands, Norway, Spain, Switzerland
- Oceania: Australia
- North America: Canada

### **United States: Supervised Injection Facilities in Development**

- New York City, New York<sup>47-49</sup>
  - May 2018: Mayor Bill de Blasio declared intention to open four injection sites in the city
    - City report found that establishment of four supervised injection facilities could prevent 130 overdoses and save \$7 million in healthcare costs annually
  - October 2018: Approval from the Governor and the New York State Department of Health is pending
- Philadelphia, Pennsylvania<sup>50,51</sup>
  - January 2018: Mayor's Task Force to Combat the Opioid Epidemic recommended supervised injection facilities, and the city thereafter announced plans to support comprehensive engagement sites for people who use drugs
    - City report found that one supervised injection facility could prevent up to 18 HIV infections, 213 hepatitis C infections, and 76 deaths annually
  - October 2018: Development is currently in place
- San Francisco, California<sup>52,53</sup>
  - September 2017: Endorsed supervised injection as a public health intervention
    - City report found that one supervised injection facility could prevent 415 hospital stays, 3 HIV cases, 19 hepatitis C cases, and save \$3.5 million in healthcare costs annually
  - September 2018: A bill allowing a 3-year pilot program was passed by the California State Legislature. However, Governor Jerry Brown vetoed the legislation.
- Seattle, Washington<sup>54,55</sup>
  - January 2017: First city to declare its intention to open a safe injection site
  - June 2018: Seattle in process of creating a 'fixed mobile' unit (large mobile health van) to provide supervised injection services

- Burlington, Vermont<sup>56</sup>
  - July 2018: City council passed a resolution directing city official and community members to begin logistical planning for supervised injection facilities
- Other Cities Considering Supervised Injection Facilities
  - Denver, Colorado<sup>57</sup>
  - Madison, Wisconsin<sup>58</sup>
  - Washington, D.C.<sup>59</sup>
  - Boston, Massachusetts<sup>60</sup>

### **Federal Law Perspective**

- Heroin is a Schedule I controlled substance, making it illegal to produce, possess, prescribe, or dispense in the United States
- Anti-Drug Abuse Act of 1986 [21 U.S. Code § 856]:<sup>61</sup>
  - Makes it unlawful (felony) to “knowingly open, lease, rent, use, or maintain any place, whether permanently or temporarily, for the purpose of manufacturing, distributing, or using any controlled substance”
- Department of Justice:
  - Rod Rosenstein, deputy attorney general of the United States, recently promised “swift and aggressive action” against any city which opens a supervised injection facility<sup>62</sup>
- Federal law would have to be changed in order to implement heroin assisted treatment programs in the United States. Such changes would have to include:
  - Changes to the controlled substance designation of heroin as a schedule I substance
  - Changes to the Anti-Drug Abuse Act of 1986 to enable the provision of heroin assisted treatment facilities



## Common Misconceptions

*Provision of heroin assisted treatment makes it easier for people with opioid use disorder to continue abusing drugs.*

- Data from the RIOTT trial showed that 81% of patients wanted help reducing their drug use, and that 59% of patients achieved reduction in drug use.<sup>63</sup>
- Data from a supervised injection facility in Sydney, Australia showed that 16% of referrals led to patient engagement in opioid use disorder treatment services.<sup>64</sup>
- People who utilize INSITE are 30% more likely to engage in treatment for drug use<sup>41</sup>

*Heroin assisted treatment will attract people who use drugs to the area where treatment is provided, which will in turn increase public disorder.*

- Effects on public disorder:
  - Data from INSITE demonstrated that following the opening of the facility, there was a decline in vehicle break-ins/vehicle theft. Additionally, there were no increases seen with respect to drug trafficking or assaults/robbery in the surrounding neighborhood.<sup>65</sup>
  - Data from the Montreal and Vancouver Police departments reveals that the presence of NAOMI trial sites had no discernable effect on crime.<sup>66</sup> However, weather conditions (temperature and precipitation) were strongly correlated with crime rates.
  - A review of RIOTT trial sites showed similar null effects on crime rates.<sup>67</sup>
- Concerns about attracting people who use drugs:
  - Data from the New York City Injection Drug User Health Alliance Survey (2013-2015) as well as Canadian feasibility studies demonstrates that most people who use supervised injection facilities are not likely to travel more than 20 minutes to a given facility.<sup>47,68-70</sup>

*Supervised injection facilities will enable drug use among new people and cause relapse of people who have previously used drugs.*

- Data from INSITE shows that most people who use the facility have been injecting drugs for a median of 16 years (IQR 9-26 years). There was no evidence to suggest that the safer injecting facility resulted in higher rates of initiating into injection drug use in the community.<sup>71</sup>
- Data from an ongoing community survey of people who use drugs in Vancouver demonstrates that after opening INSITE, there was no change in the rate of relapse into injected drug use.<sup>72</sup>

*No-one in the community will support implementing a supervised injection facility.*

- Surveys have shown that using the term “overdose prevention site” in place of “safe consumption site” to describe a supervised injection facility improved support from 29% to 47% of respondents (62% relative increase).<sup>73</sup>
  - Use of positive messaging and communicating the benefits of supervised injection facilities only stands to increase public support.

## Conclusion

### Review of Evidence

- Clinical trials consistently demonstrate that compared to methadone maintenance therapy, supervised injectable heroin...
  - Improves retention in treatment
  - Decreases illicit drug use
  - Increases the risk of severe respiratory depression (reversed at clinic)
- Supervised injection facilities in various countries have been associated with:
  - Improvements in local opioid overdose mortality
  - Increased access to health and psychosocial services by people who inject drugs
  - No increase in deviant behaviors or public disorder

### My Recommendations

1. Supervised injectable heroin should be utilized as part of opioid use disorder treatment in the United States.
  - Patients with opioid use disorder should pursue traditional treatment options as first-line therapy.
  - It is reasonable to provide heroin injections as maintenance treatment for patients with treatment-refractory opioid use disorder.
  - Supervised injectable heroin should be integrated into comprehensive health programs with the goal of improving the physical and psychosocial health of patients
2. Supervised injection facilities should be implemented as a public health initiative to achieve harm reduction in communities with large numbers of people who inject drugs.
  - Eligible patients should be referred from supervised injection facilities into opioid use disorder treatment and recovery programs
3. Legal frameworks should be enacted to enable the provision of heroin assisted treatment in the United States.

## **Recommended Resources**

### **Government Agency Websites**

- SAMHSA (Substance Abuse and Mental Health Services Administration)
  - [www.samhsa.gov](http://www.samhsa.gov)
- National Institute on Drug Abuse
  - [www.drugabuse.gov](http://www.drugabuse.gov)
- CDC (Centers for Disease Control and Prevention)
  - [www.cdc.gov](http://www.cdc.gov)

### **Professional Societies**

- American Society of Addiction Medicine
  - <https://www.asam.org/>

### **Reports**

- National Academies of Sciences, Engineering, and Medicine. 2017. Pain management and the opioid epidemic: Balancing societal and individual benefits and risks of prescription opioid use. Washington, DC: The National Academies Press. doi: <https://doi.org/10.17226/24781>.

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