Medical-Assisted Treatments for Opioid Use Disorder: Methadone, Naltrexone, and Buprenorphine

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ABSTRACT

The Opioid Crisis has resulted in the death of over 650,000 people in the U.S. since it began in the 1990s. These deaths are mostly due to overdose, which is the result of Opioid Use Disorder (OUD), characterized by the increased desire for opioids, tolerance, and withdrawal symptoms. Medication-assisted treatment (MAT) is a popular therapy against OUD. The implementation of MAT is done with three FDA approved drugs for OUD: methadone (full agonist), naltrexone (full antagonist), and buprenorphine (partial agonist). This review discusses the effectiveness, dependency risks, and other limitations of the three drugs, along with future directions for improvement with MAT and other promising approaches for therapy. Methadone was found to be highly effective but had the highest abuse potential and stricter regulations. Naltrexone was found to be the least addictive and was highly effective for relapse prevention but requires complete detoxification before treatment. Buprenorphine was found to be the happy medium between the two due to its partial agonist properties but is less effective with those that have high opioid tolerance. Some limitations to MAT include challenges with meeting the starting requirements, adherence, and accessibility barriers. Although MAT is the gold standard for OUD treatment, OUD still affected 2.7 million people in the U.S in 2020, so more effective treatments are needed. These include novel treatment targets, enhancing accessibilities, and de-stigmatizing OUD and MAT. Collaborative efforts across research, healthcare, and policy regulations will be important for implementing a widespread solution to fight the ongoing Opioid Epidemic.

Three Waves of Opioid Overdose Deaths

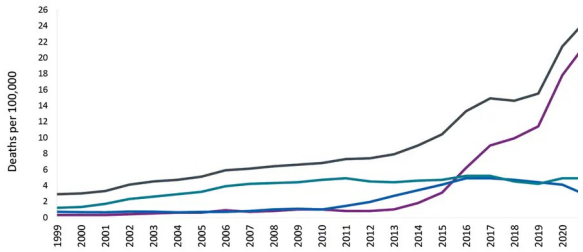

Figure 1. This graph shows the opioid overdose deaths per 100,000 due to prescription opioids **(green)**, heroin **(blue)**, and synthetic opioids **(purple)** from 1999 to 2020 (CDC, 2023).

- The first wave occurred in the 1990s. This was when opioids had their debut in the U.S., where doctors started prescribing opioids like OxyContin®.
- The second wave occurred in 2010, when heroin made its way to the streets.
- The third wave occurred in 2013, fentanyl being the main driver of these synthetic opioid deaths. It is 20x stronger than heroin and 50x stronger than morphine.

MOTIVE

- The motivation for this research was created during time in a local pharmacy and observing the prevalence of OUD and its treatments in the community.

METHOD

- The research conducted a thorough analysis of the literature regarding current Medical-assisted treatment evaluated by UW-Tacoma's TBIOMD 495 course. Sources included primary, secondary, news articles, treatment centers, and governmental sources. 35 sources have been investigated when writing the paper.

AKNOWLEDGEMENTS

- I would like to thank Dr. Baughman for all the mentorship and support throughout this whole process. `

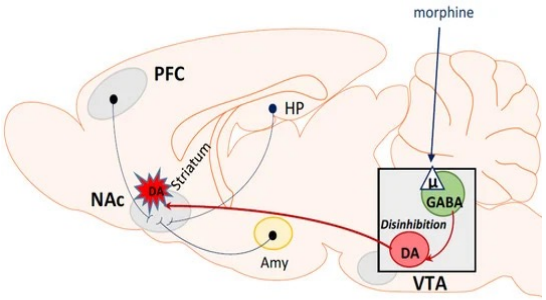

Figure 2. Simplified illustration on the pathway for morphine in the brain (Listos, 2019).

- This neurochemical activity involves the VTA and NaC (Ventral tegmental area and Nucleus Accumbens), regions of the brain that are responsible for motivation and key players for the reward pathway (mechanisms of addiction) (Kosten & George, 2002)
- Opioids activate μ-opioid receptors, leading to dopamine release and feelings of pleasure (Kosten & George, 2002).
- Creates associations with memories and good feelings, reinforcing drug us (Kalso et al, 2008).
- (Development of Tolerance)Receptors become less responsive over time, requiring higher doses for the same effect (Kosten & George, 2002).
- Increased dosage leads to higher risk of overdose (Kosten & George, 2002).
- Withdrawal symptoms occur when the body becomes reliant on opioids for homeostasis (Kosten & George, 2002).

	Methadone	Naltrexone	Buprenorphine
Mechanism of Action (μ-opioid receptor)	• Full agonist • Synthetic • High affinity • High intrinsic activity	• Antagonist • Semi-synthetic • High affinity • No intrinsic activity	• Partial agonist • Synthetic • High Affinity • Low intrinsic activity
Form of administration	• oral (liquid or tablet)	• oral tablet • ER injection	• sublingual tablet/film • ER injection • subdermal implant
Advantages	• detoxification period not needed • reduces cravings/withdrawal symptoms • long-lasting effects (24-36 hours)	• no dependency potential	• the safest, due to ceiling effect on respiratory depression • available in the most forms
Challenges	• risk of overdose • needs daily administration at specialized facility • abrupt discontinuation leads to severe withdrawal symptoms	• requires full detoxification prior to implementation • poor adherence due to strict requirement • liver toxicity with prolonged use	• withdrawal symptoms upon discontinuation • withdrawal symptoms upon abrupt discontinuation
Conclusions	• highest risk • long term use concerns (2-20 years). • higher overdose compared to other treatments	• high relapse rate during detoxification period • not suitable for severely opioid-dependent individuals • no abuse liability.	• easier detoxification period compared to naltrexone • lower dependency risk than methadone/ • small abuse of liability.

Table 1. A comparison chart for Methadone, Naltrexone, and Buprenorphine, the three FDA approved drugs for MAT.

Methadone

- Used in MAT since the 1970s. Two-week adjustment period with higher overdose risk. Risk decreases after two weeks.
- Randomized, double-blind, placebo-controlled study saw higher retention in 50mg group (52.4%) vs. control group (21%) by week 20 (Strain et al.)
- Another randomized trial saw heroin-positive urine test results drop from 63% to 29% in the treated group, while the control group remained almost unchanged. (Yancovitz et al.).

Naltrexone

- Double-blind, placebo-controlled trial by Krupitsky et al. (2011) saw that XR-NTX led to more opioid-free weeks and faster decrease in cravings and relapse.
- Long-acting injectable naltrexone had faster MAT initiation compared to buprenorphine tapers (Sullivan et al).
- Naltrexone increased the odds of being opioid–free by 1.63 times compared to control (Zangabadian, 2022) .

Buprenorphine

- Kalso et al (2008): lower abuse liability compared to heroin and morphine, with longer duration of action that reduces the need for frequent dosing.
- Effective on reducing dependance on higher-scheduled opioids (i.e. Heroin and oxycodone) (Kalso et al., 2008).
- Not primarily for analgesia. Other pain management options will be needed for pain.

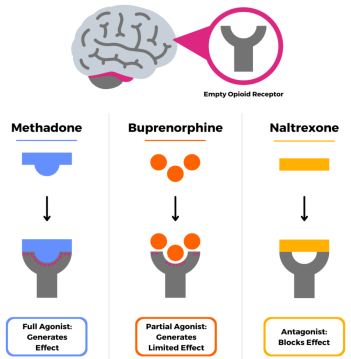

Figure 3. An illustration of the different mechanisms of action for Methadone, Naltrexone, and Buprenorphine.

CONCLUSIONS

- OUD is a challenge across healthcare, pharmaceuticals, and society.
- Methadone, buprenorphine, and naltrexone have all shown to reduce opioid cravings and dependence. It provides professional guidance, monitoring, and more safety for those seeking sobriety.

FUTURE DIRECTIONS

- Improve accessibility to MAT through digital tools (video calls, apps, websites)
- Expansion of telehealth programs to rural areas.
- Support networks: importance of support groups, counseling, and family In long-term odds of recovery.
- Advocating for policy changes to lower costs, expand insurance coverage for MAT, and increase funding for OUD research.
- Development of new treatments for OUD, focusing on mechanisms that inhibit the formation of addiction.
- Research on TLR4/STAT3 pathway. Promising results in inhibiting TLR4 and STAT3 in morphine addiction; do more research using other opioids like oxycodone, heroin, fentanyl, etc.
- Investigate BNDF's role in neuroplasticity and the dopaminergic reward system in human models to understand its role in addiction.

References **Literature Review**