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The Opioid Crisis Examined

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Abstract

The Opioid Crisis is a national crisis affecting public, social, and economic healthcare. Nearly 50,000 deaths were caused by opioid overdoses in 2017. Current treatments of opioid addictions include the use of methadone and buprenorphine. These medications have been known to reduce opioid dependency, lower tolerances, increase the opioid overdose threshold, and lower overdose mortality. An analysis was conducted on prominent research studies investigating the effectiveness, safety, side effects, and influence of Methadone and Buprenorphine. The meta-analysis confirmed that both drugs are effective opioid agonists that contribute to decreased opioid dependence and increased opioid abstinence. Due to a series of factors including, overdose risk, patient satisfaction, efficiency, ease of use, and availability, buprenorphine is more effective than methadone.

Introduction

The Opioid Crisis is a national crisis affecting public, social, and economic healthcare. Based on the CDC statistics, Opioids caused 47,600 overdose deaths in 2017. Nearly 70% of all drug overdoses are due to Opioids. Approximately 30% of patients that were prescribed opioids misuse them (CDC, 2018). Research has revealed that approximately 80 percent of heroin users initially abused prescribed opioids

(Muhuri, 2013). Based on the National Institute on Drug abuse, hydrocodone (Vicodin®), oxycodone (OxyContin®, Percocet®), oxymorphone (Opana®) morphine, codeine and fentanyl are the most commonly prescribed opioids. There are two main types of opioids, synthetic and natural. Natural opioids are derived from the plant Papaver somniferum, also known as the opium poppy plant. The opium poppy plant can be processed in a series of mechanical and chemical steps to produce morphine and codeine. Synthetic opioids are lab made and include methadone and fentanyl. Other opioids are classified as semi - synthetic, such as Oxycodone (Arfken, 2017).

Pathophysiology of opioid receptors

Opioids function in the body by activating nerve cell receptors that belong to a class of proteins called G protein-coupled receptors (GPCR). There are three main GPCR's called the Mu, Delta, and Kappa receptors that can be stimulated by opioid peptides (Scherrer, 2006). The Mu receptor has been discovered to play a substantial role in stimulation and addictive behaviors. The European College of Neuropsychopharmacology found that the lack of Mu receptors or the inhibition of the Mu receptors eliminated the analgesic effects of opioids, specifically morphine. Inhibited Mu receptors also led to a decrease in physical dependence to opioids. Opioid receptors are located in descending pain modulating pathways. G protein-coupled receptors activated in the midbrain; limbic, cortical structures inhibit neurons that transmit pain transmission (Al-Hasani, 2011).

Opioid side effects fall into the subdivision of peripheral effects and central effects. Peripheral effects may include bronchospasm, hives, constipation, and urine retention. Central side effects include nausea, respiratory depression, sedation, hypotension, miosis, and cough suppression. Side effects from central and peripheral subdivisions affect the quality of life in patients with opioid dependency. (Ahlbeck K, 2011) Opioid tolerance inevitably leads to higher doses consumed to maintain the same analgesic effects. Increased tolerance exacerbates peripheral and central side effects. One of the greatest challenges of the opioid crisis is insufficient analgesia due to long term tolerance. The opioid crisis can be described

as a collection of events that occurred based on the time period they occurred in. There are three main waves.

Waves of the opioid crisis

1991 marked the first wave where opioid involved deaths sharply rose due to the increase and over-prescription of opioid medications for pain management. The over-prescription of opioids can be partially attributed to reassurance given to prescribers by pharmaceutical industries that opioid prescription addiction risks were low. Pharmaceutical companies also promoted the use of opioids in acute and non-cancer pain. In 1999, approximately 86% of patients that were prescribed opioids were originally prescribed opioids for non-cancer pain (Liu, 2019).

The second wave of the opioid epidemic occurred around 2010 and was marked by an increase of heroin abuse related deaths. Heroin use increased in both sexes, social, and economic groups. This era also signified the first and early efforts to decrease opioid prescriptions. The CDC stated that "Deaths due to heroin-related overdose increased by 286% from 2002 to 2013, and approximately 80% of heroin users admitted to misusing prescription opioids before turning to heroin (CDC).

The third wave occurred in 2013 and was characterized by synthetic opioid related deaths specifically due fentanyl. The largest increase in synthetic opioid deaths was in 2016 with over 20,000 deaths (Liu, 2019). As of August 27, 2019 , Purdue pharmaceuticals reached a settlement of 12 Billion dollars against 2000 opioid related lawsuits against Purdue's role in the exacerbation of the opioid crisis (Strickler, 2019).

Opioid treatment

Current treatments of opioid addictions include the use of methadone and buprenorphine. These medications have been established to reduce opioid dependency, lower tolerances, increase the opioid threshold to overdose, lower overdose mortality and increase the amount of time an addicted patient will

remain in opioid treatment. Methadone and buprenorphine lower the risks of transmitting infectious diseases such as HIV (National Institute on Drug Abuse. (2018, June).

Methadone is a medication that is commonly used to treat patients suffering from opioid addiction. Methadone was discovered in 1938 and was approved for medicinal use in the United States in 1947 and has been listed on the World Health Organization's List of Essential Medicines. Methadone treatment involves relieving cravings for opioids and blocking euphoria from opioids by binding to opioid receptors. Methadone is a full agonist. The receptors that Methadone binds to, are the same receptors that opioids such as heroin, morphine, and oxycontin bind to. When bound to those receptors in the brain, methadone does not release any euphoria and helps reduce opioid use urges. Methadone treatment may be used as a maintenance therapy for long term opioid management or as a detoxification treatment that is short term and oriented at managing opioid withdrawal symptoms. The duration a patient may be on a methadone treatment plan varies widely. Since opioid addiction and dependency is considered a chronic disorder that may lead to relapse, methadone treatment may be lifelong for some patients.

Buprenorphine was approved for medical use in the United States in 2002 by the U.S. Food and Drug Administration (FDA). Buprenorphine is commonly used to treat patients with an opioid addiction. Buprenorphine is a “partial opioid agonist” and attaches to opioid receptors to activate them. Buprenorphine does not activate the receptor as strong as an opioid narcotic would. Similar to methadone, buprenorphine reduces withdrawal symptoms in patients without producing opioid analgesic euphoria. Buprenorphine reduces cravings and is tolerated well by the body. Prolonged buprenorphine treatment is associated with psychological or physical dependence. Once a patient has developed a tolerance toward buprenorphine and is stabilized on the medication then there are three treatment routes. These three routes include: “continual use, switching to buprenorphine/naloxone, or medically supervised withdrawal (Samhsa, 2016) ”.

Usually reported side effects of methadone treatment include chronic sweats, constipation, and sexual dysfunction. Buprenorphine common dosage route is sublingual administration and shows poor gastrointestinal absorption. Due to poor absorption, buprenorphine has a decreased risk of an overdose if accidentally ingested by non-tolerant individuals (Bonhomme). Based on a study conducted by Al-Gommer, fewer patients reported loss of erection, sexual fantasy and premature ejaculations on buprenorphine compared to methadone (Al-Gommer, 2007). Buprenorphine abuse may lead to fatal respiratory depression. Buprenorphine shows difficulty in reversing respiratory depression due to antagonist effects (Megarbane, 2006). It was found that "0.8 mg of intravenous naloxone was ineffective in reversing buprenorphine-induced respiratory depression". Naloxone had to be increased to 2-4 mg over a time of 30 minutes to fully reverse respiratory depression (Dorp, 2007). Additional major differences collected between methadone and buprenorphine are summarized in Table 1 found in the appendix section (Bonhomme).

Discussion

A study conducted by Stone A.C (Methadone maintenance treatment among patients exposed to illicit fentanyl in Rhode Island: Safety, dose, retention, and relapse at 6 months) examined the effects of a 6-month methadone treatment on opioid dependent patients. The main purpose of this study was to determine the effectiveness of methadone on attaining abstinence from fentanyl. A retrospective review of fentanyl addicted patients that were undergoing MMTP therapy was conducted.

Participants of Stones study were observed for time period of six months. Researchers focused on factors that included: patient retention in Methadone maintenance treatment therapy, fentanyl abstinence evidence, relapse, methadone dosage, and the amount of time to achieve opioid abstinence. Throughout the study, participants were randomly drug tested three times per month for a duration of six months. To prevent conflict of interest and bias, each drug test was administered and tested by an outside lab in a different state. There was no standard dosage of methadone. Each participant in the study had a

calculated dose of methadone that was specialized to their needs and was gradually increased throughout the length of the study.

Participants used in the study included, 147 patient's that tested positive for opioids at admission. The average age was 37 years old with a standard deviation of 11. 61% of the participants were male and 81% of them were Caucasian. Within the 6-month study, 49 patients stopped treatment early (Stone, 2018).

Results of this study found that MMTP therapy was safe, effective, and facilitated abstinence from opioids. Within the remaining population, 71% of the participants reached abstinence within 6-months (Stone, 2018). Additionally, the study concluded that methadone treatment had raised tolerance levels in the patients so when a patient had relapsed, they did not overdose. Researchers suggested that if their tolerance was not raised by the methadone, a relapse could have killed them from the same dose taken at relapse. Methadone treatment did not have any significant effects on the rate of relapse. Methadone helped prevent overdose related mortality. The author mentioned that "Continued fentanyl use and relapse appears to be a problem in this cohort of methadone patients" and that sustained abstinence had occurred in the majority of patients. No deaths had occurred during the 6-month study.

This study was the first of its kind to investigate the results of MMT therapy on fentanyl addicted patients and was published by Elsevier, a global information analytic that specializes in health and science. Elsevier publishes quality research and clinical studies that have been peer reviewed by an editorial board. The study uses many relevant and credible sources to help support its claims. One of the referenced studies was "Arfken, C.L., Suchanek, J., Greenwald, M.K., 2017. Characterizing fentanyl use in methadone-maintained clients. J. Subst. Abuse Treat. 75, 17–21". The study was approved by the Institutional Review Board at the Miriam Hospital in Providence, Rhode Island.

The following study conducted by Bruera, researched and compared methadone and morphine's side effects and effectiveness in patients with cancer pain. The name of the study is "Methadone versus

morphine as a first-line strong opioid for cancer pain: a randomized, double-blind study". The conducted study was a double blind, randomized, parallel trial that was conducted in 7 palliative care facilities.

A total of 103 patients were included in the study. The patients in this study were randomly placed into two experimental groups. The first experimental group investigated the effects of methadone. Patients in the methadone section were administered 7.5mg of oral methadone every 12 hours and 5mg every 4 hours as needed for breakthrough pain (Bruera, 2004). The second group utilized in this study was the morphine group. Patients in the morphine section were administered 15mg of morphine twice daily and 5mg morphine as needed for breakthrough pain. The experiment lasted for 4 weeks and the patients were checked on daily for the first 8 days then were assessed on days 8, 15, 22, and 29. Pain was assessed using the Edmonton system for cancer pain. Factors including pain, nausea, constipation, and sedation were measured on a scale of 1-10. Pearson correlation coefficients were used to correlate outcome measures". Nonparametric statistics were implemented to calculate the P values. In addition, the Wilcoxon rank sum test and Fisher's exact test were utilized (Bruera, 2004).

The two sections had comparable results for pain, sedation, nausea, confusion, and constipation. "Patients that received methadone had more opioid-related drop-outs (11 of 49; 22%) than those receiving morphine (three of 54; 6%; P =.019). The opioid escalation index at days 14 and 28 was similar between the two groups. More than three fourths of patients in each group reported a 20% or more reduction in pain intensity by day 8. The proportion of patients with a 20% or more improvement in pain at 4 weeks in the methadone group was 0.49 (95% CI, 0.34 to 0.64) and was similar in the morphine group (0.56; 95% CI, 0.41 to 0.70)" (Bruera, 2004). Opioid escalation was calculated using the formula in table 2 found in the appendix section. Results concluded that twice daily, 15 mg/day total methadone did not produce better cancer pain relief compared to 30 mg/day sustained-release morphine (Bruera, 2004). Table 3 displays the pain response from the patients in the appendix section.

Bruera's study was published by the journal of Clinical oncology, an American society of clinical oncology journals. The journal of Clinical oncology specializes in publishing quality research articles. The majority of the articles published relate to patients with cancer and are peer reviewed. The author, Bruera E has published many other quality articles including, "Symptom distress in advanced cancer patients with anxiety and depression in the palliative care setting." and "Prescribing patterns and purchasing costs of long-acting opioids over nine years at an academic oncology hospital." This research also referenced 37 studies that relate to cancer analgesia.

The following study, "Dose-response effects of methadone in the treatment of opioid dependence" was conducted in 1993 by Strain EC. 247 participants with an average age of 34 years old participated. 70% of the participants were male and 50% were African American. For a participant to be eligible for this study they had to be within 1850 years old, have a history of opioid dependent and have no chronic physical or mental illness.

Intervention included methadone treatment of a steady dose of methadone for the first 5 weeks and then a various steady dose (50mg, 20mg, or 0mg) for the following 15 weeks. Participants were originally started on 25mg of methadone for the first week of the study and then were randomized into different dosage groups for the remainder of the study. Methadone tapering was conducted in weeks 21-26. Group and individual counseling was provided on a weekly basis. Opioid levels of all the patients in the study were monitored by urine testing.

Results confirmed that methadone is an effective treatment plan for assisting opioid addicted patients achieve abstinence and recovery. The study measured results based on patient retention to treatment and their illicit drug use. The 20th treatment week showed a 52% treatment retention rate for the 50mg group, 41.5% for the 20mg group, and 21% for the 0mg group. Only the 50mg group had the rate of illicit drug use decrease (56.4% for 50mg, 67.6% for the 20mg group, and 73.6% for the 0mg groups). The main results indicated that methadone treatment improves retention but is inadequate in

significantly suppressing illicit drug use. Major results of this study are presented in table 4 in the appendix section.

Furthermore, a study conducted in 2008 by Gruber investigated the effects of methadone detoxification compared to methadone maintenance with minimal counseling and methadone maintenance standard counseling. The study investigated and compared three treatments to each other. Treatments investigated in this study included six months of methadone maintenance with standard or minimal counseling compared to a 21 day methadone detoxification. The study conducted was a randomized, double-blind, prospective trial.

Methadone detoxification programs are common for patients that have partial access to methadone maintenance treatment programs. Limitations to methadone maintenance treatment programs are due to a lack of insurance coverage, methadone prescribers, and distance. Patients used in the study originated from a public hospital's 21 day methadone detoxification program. A statistician randomly sorted 111 patients into three treatment groups. Patients received a sealed envelope with the group they would be participating in. The staff were unaware of which group the patients were in. Urine drug tests and self reported tests were collected at 1, 6, and 8 month intervals.

Results of this study concluded that compared to a 21 day detoxification treatment, a six month methadone maintenance program resulted in fewer opiate positive drug tests. In both six month maintenance groups, self reported alcohol and heroin use was lower. Standard vs minimal counseling did not result in statistically significant differences in outcomes. In months 1-6, participants in the detoxification group resulted in 78%-96% opioid positive drug test results. This group of patient's also reported an average use of heroin of 15.5–18.4 days in each follow up. The six month methadone maintenance program showed a greater decrease of opioid positive drug tests (65%–85%). Self-reported heroin and alcohol also decreased to an average of 5.8–8.1 days in each month. The study concluded that six months of methadone maintenance reduced heroin and alcohol use as well as lowered opioid positive

drugs treats more effectively than 21-day methadone detoxification. Another study conducted in 2005 by Amato et al concluded similar results. The study found that Methadone detoxification is not an effective treatment for opioid dependence (Amato et al., 2005b).

Results did not show significant differences between standard and minimal counseling over the six month periods. In contrast to these results, in 1993 McLellan et al found that in long term methadone maintenance programs standard counseling resulted in fewer opioid positive urine results when compared to minimal counseling (McLellan et al., 1993).

An additional study conducted by sabzghabaee investigated the effects of both intranasal and intravenous administration of naloxone in overdosed patients.

Overdosed Patients administered to Noor and Ali Asghar Hospital were immediately randomly placed into one of two treatment groups. The first group received naloxone administration through IV and the second group received intranasal administered naloxone. A total of 100 patients participated in this study. The ages of the participants ranged from 15-50. The study was approved by the Ethics Committee of Isfahan University and registered with clinicalTrials.gov. After Naloxone administration, blood pressure, heart rate, respiratory rate, and level of consciousness were measured. Researchers measured additional factors including: time to response, arterial blood oxygen saturation, agitation, and duration of hospital stay. The primary factor measured was consciousness measured by the Glasgow Coma Scale (GCS). Table 5 displays the level of consciousness before and after naloxone administration split by the intranasal and intravenous group.

Patients who had been administered intranasal naloxone demonstrated significantly higher levels of consciousness than those in the intravenous group using both descriptive and GCS scales ($p < 0.001$). There was a significant difference in the heart rate between intranasal and intravenous groups ($p = 0.003$). However, blood pressure, respiratory rate and arterial O2 saturation were not significantly different

between the two groups after naloxone administration ($p = 0.18$, $p = 0.17$, $p = 0.32$). There was also no significant difference in the length of hospital stay between the two groups ($p = 0.14$).

This study was published by the journal, Archives of Medical Science (AMS). AMS publishes quality medical papers globally and all of them are peer reviewed by an international editorial board. The main authors in this study come from various high level medical backgrounds including, toxicology and anesthesiology. The study were randomized and conducted by the Department of Poisoning Emergencies at Noor and Ali Asghar Hospital in Iran. The author used many other prominent research articles to support his results and the author formed a sound and logical rationale for the study.

The study conducted by Marteau D assessed the mortality rates of methadone and buprenorphine within the population of England and Wales. The researchers first determined the total quantities of methadone and buprenorphine dispensed in England and Wales from 2007 to 2012. Data was collected from the National Health Service in England, and the National Health Service in Wales. "Mortality data were drawn from the Office for National Statistics 'Deaths Related to Drug Poisoning in England and Wales'" (Marteau, 2015). The sample included 2,366 methadone-related deaths and 17,333,163 methadone prescriptions as well as 52 buprenorphine related deaths and 2,602,374 buprenorphine prescriptions. Table 6 displays the total methadone and buprenorphine related death rate per 1000 issued prescriptions. Results concluded that buprenorphine was six times safer than methadone. Directly from the study, "Among the whole population of England and Wales, there were 0.137 methadone-related deaths per 1,000 prescriptions of methadone and 0.022 buprenorphine-related deaths per 1,000 prescriptions of buprenorphine-based drugs for the substitution treatment of opioid dependence"

Limitations

The study Conducted by Stone, AC had elements of randomization and blindness although the study itself was not double blind. Patients were randomly selected for the study and had randomized drug tests. The author also stated that "The patient population at the MMTP that participated in this study may not be

representative of methadone patients in other regions". The results and findings of this study were limited by the short length and the small population size of the study. The size originally was small at 113 patients, but the number quickly shrank as participants withdrew from the study. At the end of the 4 months, 47 patients withdrew from the study. The results were drawn from the results of only 66 patients. Methadone treatment varies based on location, the amount of tolerance a patient has, the type and the combination of drugs a patient has in their system. The researchers also acknowledged that the conversion of doses from methadone to morphine may have been off and the methadone dose was higher than it should have been. The higher than needed dose could have explained the toxicity in the methadone group. Overall the limitations were significant and could have influenced the results of the study.

In the study comparing intranasal naloxone to intravenous naloxone, level of consciousness was measured using descriptive scales (lethargic, conscious, obtundation, stupor, and coma) and the Glasgow Coma Scale (GCS). There could have been some limitations or bias in the level of consciousness test. The main bias in the study was unknown patient history. Many of the participants were heavy drug abusers that had incomplete or nonexistent medical histories. Limitations are addressed by the author in the study. One of the limitations included the small and not necessarily "representative of all" population used in the study. Participants were not screened and randomly selected for the study. This leads us to the next observed limitation which is the substance that the patient had overdosed on. Some participants did not regain complete consciousness after being administered Naloxone, indicating that the drugs in the body were not opioids. The major source of bias that could have occurred is the researches not knowing what substance the patient had overdosed on.

Marteau's study was one of the first studies conducted regarding overdose mortality rates being compared between methadone and buprenorphine. Suggestions were made to have additional studies in different areas of the world to compare results. The major limitations of this study included unidentified differences in drug dependence between patients. Additionally, the number of buprenorphine prescriptions was calculated based on mean doses.

Conclusion

Methadone and buprenorphine are both useful in helping patients struggling with opioid addiction. Methadone has been one of the most prominent and oldest treatment options for opioid addiction. The availability of methadone is disadvantageous when compared to buprenorphine. Methadone is only prescribed and distributed in specialized clinics while buprenorphine prescriptions may be picked up and taken home by patients. Buprenorphine is also easier to be prescribed by physicians and allows more patients to be monitored by one physician. Buprenorphine is only a partial agonist while methadone is a full opioid agonist. Buprenorphine is generally safer to use than methadone partially due to its "ceiling effect". Because of the ceiling effect, buprenorphine's effects do not increase after a certain point, even with increases in dosage. This helps reduce the risk of overdose and respiratory depression from occurring. Additionally, buprenorphine has shown a decrease of overdose risk due to its sublingual administration. Due to poor absorption, buprenorphine has a decreased risk of an overdose if accidentally ingested by non-tolerant individuals (Bonhomme). Further confirmation of buprenorphine's safety can be drawn from Marteau D study. "Among the whole population of England and Wales, there were 0.137 methadone-related deaths per 1,000 prescriptions of methadone and 0.022 buprenorphine-related deaths per 1,000 prescriptions of buprenorphine-based drugs for the substitution treatment of opioid dependence". A comparison of side effects indicated that buprenorphine causes less withdrawal symptoms when abruptly stopped compared to methadone (Schottenfeld RS, 1997). Fewer patients reported loss of erection, sexual fantasy and premature ejaculations on buprenorphine compared to methadone (Al-Gommer). When facing an over-dose from any opioid, Sabzghabaee study concluded that intranasal naloxone is an effective and life saving medication that is easy to administer in emergency situations to reverse opioid overdose.

Both methadone and buprenorphine are effective drugs at helping patients manage opioid addiction. Due to a series of factors including, overdose risk, patient use, efficiency, and ease of use and availability, buprenorphine is more effective than methadone.

Appendix

Table 1

Buprenorphine	Methadone
Less risk of sexual dysfunction	Greater risk of sexual dysfunction
Less risk of respiratory depression but more difficult to reverse if present	Greater risk of respiratory depression, more readily reversible if present
Deaths during induction phase very rare	Higher risk of death during induction phase
May raise liver function tests	Proven safe in chronic liver disease
If more analgesia required, may block other opiate analgesics in pain treatment	Highly effective in pain treatment
pain treatment	
Partial antagonist to other opiates	Pure opiate agonist
Lower risk of neonatal abstinence syndrome	Higher risk of neonatal abstinence syndrome
Less κ effect, lower risk of dysphoria	More κ effect, higher risk of dysphoria
Poor oral absorption, less overdose risk in diversion	Well absorbed orally, higher overdose risk in diversion
Lower risk of dependence	Higher risk of dependence
Lower risk of death with benzodiazepines	Higher risk of drug interaction fatalities with benzodiazepines

Table 2

$$\text{Day 14 opioid escalation index} = \frac{\text{total dose on day 14} - \text{total dose on day 1}}{\text{total dose on day 1}} \times 100$$

$$\text{Day 28 opioid escalation index} = \frac{\text{total dose on day 28} - \text{total dose on day 1}}{\text{total dose on day 1}} \times 100$$

Table 3

Parameter	No. of Responders	% of Responders	95% CI (%)	P
Pain response of 20% or greater				
Methadone	24	49	34 to 64	.50
Morphine	30	56	41 to 70	
Composite toxicity worse by 20% or more				
Methadone	33	67	53 to 82	.94
Morphine	36	67	53 to 80	
Pain response with stable composite opioid toxicity (obvious benefit)				
Methadone	12	24	11 to 38	.56
Morphine	16	30	16 to 43	
Patient-reported global benefit (at least moderate)				
Methadone	26	53	38 to 68	.41
Morphine	33	61	47 to 75	

Table 4

Table 1. Demographic Characteristics for Patients (n = 247) Assigned to Different Methadone Doses*

Characteristic	Randomized Dose Assignment		
	0 mg (n = 81)	20 mg (n = 82)	50 mg (n = 84)
Male, %	72	67	70
Black, %	47	52	51
Unmarried, %	75	83	92
Unemployed, %	56	60	69
On parole or probation, %	28	29	27
Mean education, *y (SD)*	11.4 (1.5)	11.0 (1.7)	11.4 (2.3)
Mean age, *y (SD)*	33.4 (5.6)	33.1 (5.7)	34.6 (6.4)
Previous drug treatment episodes, *mean n (SD)*	2.0 (2.3)	1.8 (1.9)	1.6 (1.7)
Other drug use†, %			
Cocaine	43	55	45
Alcohol	25	22	23
Other opioid	15	16	11
Marijuana	5	4	7
Sedatives-hypnotics	9	10	13

Data Analysis

Retention to week 20, days in treatment, percentage of days attended, and amount of counseling contact time were analyzed with a one-way analysis of variance with methadone dose as the grouping factor and the Tukey Honestly Significant Difference (HSD) test was used for post hoc analyses. Comparisons for which the critical difference value corresponding to $P < 0.05$ are reported as significant for this and all subsequently described analyses. Treatment survival curves were compared using the Lee-Desu statistic, with pairwise comparisons between each of the three treatment groups.

The percentages of urine positive for opioids, cocaine, benzodiazepines, and any other drugs were calculated for each patient through the end of the stable dosing period. A one-factor analysis of variance with methadone dose as the grouping factor was used for each of these analyses.

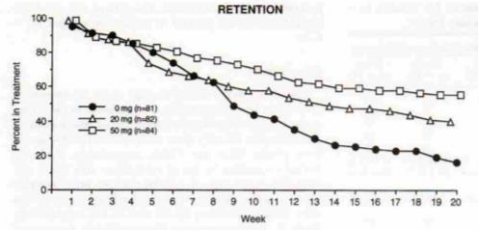

Table 5

Level of consciousness	Before naloxone	After naloxone
Intranasal administration, *n* (%)		
Coma	12 (24)	0
Stupor	24 (48)	0
Obtundation	14 (28)	0
Lethargic	0	28 (56)
Conscious	0	22 (44)
Intravenous administration, *n* (%):		
Coma	10 (20)	0
Stupor	28 (56)	0
Obtundation	12 (24)	20 (40)
Lethargic	0	18 (36)
Conscious	0	12 (24)

Table 6

	Buprenorphine		Methadone			
Year	Deaths	per 1000 ℞	Deaths	per 1000 ℞	Relative risk	CI (95%)
2007	8	0.022	325	0.129	5.77	2.86 to 11.64
2008	9	0.023	378	0.136	5.85	3.02 to 11.33
2009	9	0.021	408	0.135	6.55	3.38 to 12.68
2010	7	0.015	355	0.113	7.28	3.44 to 15.38
2011	14	0.030	486	0.161	5.35	3.15 to 9.11
2012	10	0.020	414	0.146	7.32	3.91 to 13.71
Total	**57**	**0.022**	**2366**	**0.137**	**6.23**	**4.79** to **8.10**

Works cited

1)

Stone A.C., Carroll J.J., Rich J.D., Green T.C. (2018) Methadone maintenance treatment among patients exposed to illicit fentanyl in Rhode Island: Safety, dose, retention, and relapse at 6 months. Drug and Alcohol Dependence, 192 ,94-97.

2)

Sabzghabaee AM, Eizadi-Mood N, Yaraghi A, Zandifar S. (2014). Naloxone therapy in opioid overdose patients: intranasal or intravenous? A randomized clinical trial. Arch Med Sci.10(2):309–314. doi:10.5114/aoms.2014.42584

3)

Bruera E, Palmer JL, Bosnjak S, Rico MA, Moyano J, Sweeney C, … Fisch MJ. (2004). Methadone versus morphine as a first-line strong opioid for cancer pain: A randomized, double-blind study. Journal of Clinical Oncology, 22(1), 185–192.

4)

Marteau D, McDonald R, Patel K. The relative risk of fatal poisoning by methadone or buprenorphine within the wider population of England and Wales. BMJ Open 2015;5:e007629. doi: 10.1136/bmjopen- 2015-007629

5)

Bruchas, Michael R., Ph.D. (2011/12/01/). Molecular Mechanisms of Opioid Receptor-dependent Signaling and Behavior. Anesthesiology: The Journal of the American Society of Anesthesiologists, 115, 1363-1381.

6)

Scherrer G, Tryoen-Toth P, Filliol D, Matifas A, Laustriat D, Cao YQ, Basbaum AI, Dierich A, Vonesh JL, Gaveriaux-Ruff C, Kiefer BL. Knockin mice expressing fluorescent delta-opioid receptors uncover G protein-coupled receptor dynamics in vivo. Proc Natl Acad Sci USA 2006;103(25):9691-6

7)

Bonhomme, J., Shim, R. S., Gooden, R., Tyus, D., & Rust, G. (2012). Opioid addiction and abuse in primary care practice: a comparison of methadone and buprenorphine as treatment options. Journal of the National Medical Association, 104(7-8), 342–350. doi:10.1016/s0027-9684(15)30175-9

8)

Strain EC, Stitzer ML, Liebson IA, et al. Dose-Response Effects of Methadone in the Treatment of Opioid Dependence. Ann Intern Med. 1993;119:23–27. doi: https://doi.org/10.7326/0003-4819-119-1-199307010-00004

9)

Strickler, L. (2019, August 28). Purdue Pharma offers $10-12 billion to settle opioid claims. Retrieved from https://www.nbcnews.com/news/us-news/purdue-pharma-offers-10-12-billion-settle-opioid-claims-n1046526.

10)

Valerie A. Gruber, Kevin L. Delucchi, Anousheh Kielstein, Steven L. Batki, A randomized trial of 6-month methadone maintenance with standard or minimal counseling versus 21-day methadone detoxification, Drug and Alcohol Dependence, Volume 94, Issues 1–3,

11)

McNicol E, Horowicz-Mehler N, Fisk RA, Bennett K, Gialeli-Goudas M, Chew PW, Lau J, Carr D. Management of opioid side effects in cancer-related and chronic noncancer pain: A systematic review. J Pain. 2003;4:231–256.

12)

CDC/NCHS, National Vital Statistics System, Mortality. CDC WONDER, Atlanta, GA: US Department of Health and Human Services, CDC; 2018. https://wonder.cdc.gov.

13)

Muhuri PK, Gfroerer JC, Davies MC. Associations of Nonmedical Pain Reliever Use and Initiation of Heroin Use in the United States. CBHSQ Data Rev. August 2013.

14)

National Institute on Drug Abuse. (n.d.). How effective are medications to treat opioid use disorder? Retrieved from https://www.drugabuse.gov/publications/research-reports/medications-to-treat-opioid-addiction/efficacy-medications-opioid-use-disorder.

15)

Arfken, C.L., Suchanek, J., Greenwald, M.K., 2017. Characterizing fentanyl use in methadone-maintained clients. J. Subst. Abuse Treat. 75, 17–21

16)

Ahlbeck K. Opioids: a two-faced Janus. (2011). Current Medical Research & Opinion, 27(2), 439–448. https://doi-org.ezproxylocal.library.nova.edu/10.1185/03007995.2010.545379

17)

Al-Gommer O, George S, Haque S, et al. Sexual dysfunctions in male opiate users: a comparative study of heroin, methadone, and buprenorphine. Addict Disord Treat. 2007;6(3):137.

18)

Megarbane B, Hreiche R, Pirnay S, et al. Does high-dose buprenorphine cause respiratory depression?: Possible mechanisms and therapeutic consequences. Toxicol Rev. 2006;25(2):79–85.

19)

Van Dorp E, Yassen A, Sarton E, et al. Naloxone reversal of buprenorphine-induced respiratory depression. Anesthesiology. 2006;105(1):51.

20)

National Institute on Drug Abuse. (2018, June). How effective are medications to treat opioid use disorder? Retrieved from https://www.drugabuse.gov/publications/research-reports/medications-to-treat-opioid-addiction/efficacy-medications-opioid-use-disorder.

21)

Liu, L. (2019, November 13). History of the Opioid Epidemic. Retrieved from https://www.poison.org/articles/opioid-epidemic-history-and-prescribing-patterns-182.