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The Impact of Opioid Drugs on Memory and Other Cognitive Functions: A Review

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Abstract

Background and Purpose: Opioids, used for centuries to alleviate pain, have become a double-edged sword. While effective, they come with a host of adverse effects, including memory and cognition impairment. This review delves into the impact of opioid drugs on cognitive functions, explores underlying mechanisms, and investigates their prevalence in both medical care and illicit drug use. The ultimate goal is to find ways to mitigate their potential harm and address the ongoing opioid crisis. **Methods:** We sourced data from PubMed and Google Scholar, employing search combinations like "opioids," "memory," "cognition," "amnesia," "cognitive function," "executive function," and "inhibition." Our focus was on English-language articles spanning from the inception of these databases up to the present. **Results:** The literature consistently reveals that opioid use, particularly at high doses, adversely affects memory and other cognitive functions. Longer deliberation times, impaired decision-making, impulsivity, and behavioral disorders are common consequences. Chronic high-dose opioid use is associated with conditions such as amnesiac syndrome (OAS), post-operative cognitive dysfunction (POCD), neonatal abstinence syndrome (NAS), depression, anxiety, sedation, and addiction. Alarming trends show increased opioid use over recent decades, amplifying the risk of these outcomes. **Conclusion:** Opioids cast a shadow over memory and cognitive function. These effects range from amnesiac effects, lessened cognitive function, depression, and more. Contributing factors include over-prescription, misuse, misinformation, and prohibition policies. Focusing on correct informational campaigns, removing punitive policies, and focusing on harm reduction strategies have been shown to lessen the abuse and use of opioids and thus helping to mitigate the adverse effects of these drugs. Further research into the impacts of opioids on cognitive abil-

ities is also needed as they are well demonstrated in the literature, but the mechanism is not often completely understood.

Keywords

Opioids, Memory, Cognition, Pain

1. Introduction

Humanity has a long and complicated relationship with opium, which was first extracted from the milky latex of poppy flowers and is one of the most effective analgesics available. Opiates, or naturally derived drugs made from poppies such as morphine, codeine, and heroin, have been impacting humanity for millennia, in ways both beneficial and detrimental [1]. With advances in science, it is possible to create even more potent opioids, which refer to all-natural, semisynthetic, and synthetic opioids.

While opioid drugs are ubiquitous in modern medicine, there is no denying that illicit opioids pervade our society. Opioids are effective in reducing pain levels but, like any medication, they are not without their share of adverse effects. Many of these detrimental side effects are well documented, such as constipation, nausea, respiratory depression, sedation, and more [2]. However, research has shown that opioid use can impact memory and impair executive function [3], but a full understanding of how opioid impacts these functions is not widely known.

Since the 1990's the United States has been in an "Opioid Crisis" [4]. This crisis has had three waves. The first wave began in the 1990s following marketing campaigns created by pharmaceutical companies that claimed opioids to be effective and non-addictive [5]. This first wave consisted mainly of prescription drug overdoses. In 2010 the second wave began due to efforts to curtail prescription opioids and left a demand for cheap available alternatives leading to increased use and overdose of heroin. The third wave began in 2013 with the advent of synthetic opioids like fentanyl, which is 100 times more potent than morphine and 50 times stronger than heroin [4].

With each wave, the death toll has increased. From 1999 to 2020, over 564,000 people have died from opioid-related overdoses with the yearly deaths increasing exponentially (**Figure 1** and **Figure 2**). In 1999 opioid overdose deaths were estimated at less than 10,000, In 2020 68,630 people died from opioid overdose and in 2021 over 80,000 people died from opioid overdose, about 219 deaths per day. This is about twice as many deaths as those that occur annually from car accidents or firearms [6], and over ten times the number of United States service members killed in post 9/11 wars [7]. Since 2015 the Opioid Epidemic has lowered the life expectancy of the average American [8]. On top of the loss of life, the annual financial toll in the United States from opioid misuse is estimated around $78 billion [7].

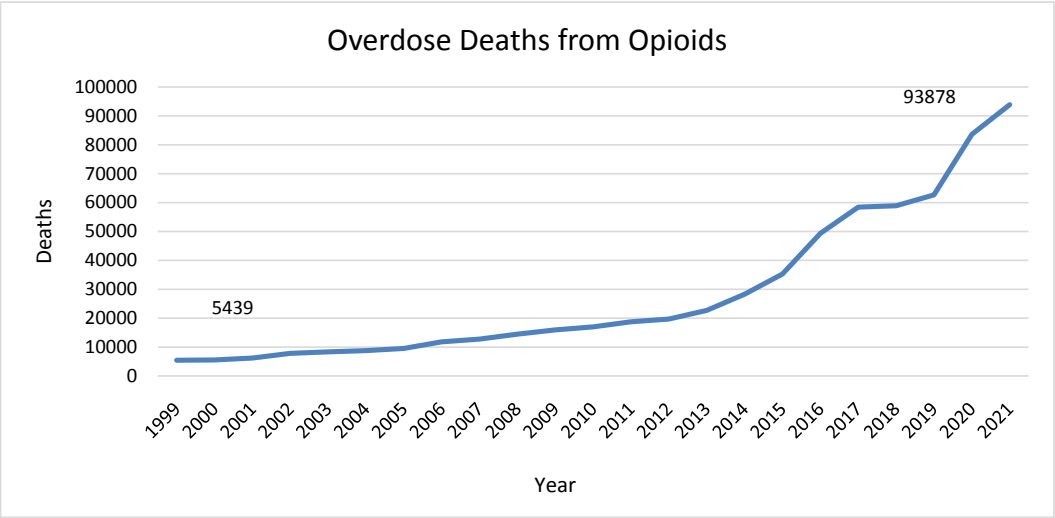

Figure 1. Overdose deaths from opioids from 1999 to 2021.

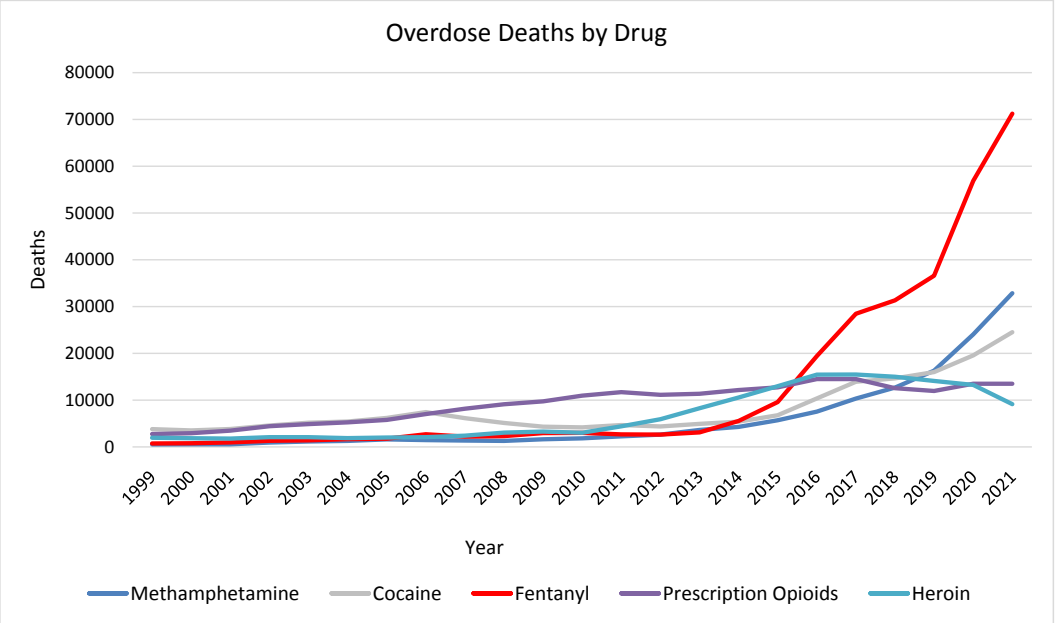

Figure 2. Overdose deaths separated by drug type from 1999 to 2021.

Opioids used to be only a drug for palliative care and cancer pain, but at the start of the opioid epidemic they began to be marketed as a first-line treatment for any non-cancer pain [9]. Some studies concede the benefit of opioids in acute cancer or palliative pain, but note the lack of evidence for the use of opioids in non-cancer pain [10] [11] [12] [13]. A proper knowledge of how opioids affect brain function is needed to ascertain their proper usage and safety. Therefore, the purpose of this study is to analyze the impact of opioid drugs on memory and other cognitive functions through a comprehensive review of the existing literature and find ways to mitigate the possible damages of opioids from mishandled opioid prescriptions, misinformation, and illicit use and avoid opioid crisis.

Keynotes

- Patients on opioid therapy for chronic pain have both short-term and long-term memory impairments.
- Fentanyl (a synthetic opioid) overdose can lead to Opioid-associated Amnesiac Syndrome (OAS).
- High doses of fentanyl damage the subiculum, amygdala, and hippocampus possibly due to excitotoxic effects causing hyper metabolism in conjunctions with ischemia.
- Patients on opioid therapy for chronic pain take longer for processing information and exhibit increased impulsivity.
- Infants with Neonatal abstinence syndrome (intrauterine exposure to opioids during pregnancy) more likely to have educational disabilities.
- Even subclinical exposure of opioids to infants increases the risk for behavioral or developmental disorders.

2. Methods

Our data is sourced from PubMed and Google Scholar using searches that included combinations of the following keywords: "opioids," "memory," "cognition,", "amnesia" "cognitive function," "cognitive performance," "executive function," and "inhibition." Studies were included if they met the following eligibility criteria.

1) Investigated the effects of memory and/or cognition.

2) Employed empirical methods, including experimental studies, observational studies, clinical trials, or literature reviews.

3) Study language available in English.

4) Data on children, adults, and older adults were included.

5) Studies with very small samples were excluded with the exception of some case reports documenting previously undefined conditions like OAS.

Sources were excluded for the reasons listed below.

1) While it is hard to exclude other illicit drugs in overdose cases thus, we allowed some studies looking at opioids mixed with substances such as cocaine, if there was too much contamination in the possible offending agent the source was excluded.

2) Sources where research was performed by "pain groups" that are largely funded by pharmaceutical companies that profit off the sale of opioids and pain medications, such as the American Pain Foundation, the American Pain Society, the U.S. Pain Foundation and The American Academy of Pain Medicine, were excluded.

3. Results

Based on chemical structure, opioids have been classified into three subtypes: 4,5 epoxymorphinans, diphenylheptylamines, and the phenylpiperidines [14]. They all exert their effects by binding to the G-protein coupled receptors located on target cell membrane. The original three receptors that were discovered were named mu, delta, and kappa, but may also be called MOP, DOP, and KOP respectively. In 1994 a fourth receptor was discovered and named the nociceptin receptor or NOP [15] [16]. Commonly prescribed opioids, and classification and affinity to their receptors [16] [17] are shown in **Table 1**.

Table 1. Commonly prescribed opioids. Number of "+" symbols in the table indicates potency.

Opioids	Natural or Synthetic	Chemical Structure Class	Receptor Binding
Morphine	Natural	4,5-epoxy morphinan ring	μ +++ κ +
Codeine	Natural	4,5-epoxy morphinan ring	μ +
Hydromorphone	Semi-synthetic	4,5-epoxy morphinan ring	μ +++
Oxycodone	Semi-synthetic	4,5-epoxy morphinan ring	μ + κ ++
Tramadol	Synthetic	phenylpiperidine	μ +
Tapentadol	Synthetic	phenylpiperidine	μ +++
Fentanyl	Synthetic	phenylpiperidine	μ +++
Methadone	Synthetic	diphenylheptylamine	μ +++

Despite their differences, all groups primarily target the mu (μ) opioid receptor. The classic analgesic effect of opioid drugs is caused by agonism or partial-agonism of MORs. Also, opioids exert effects on the other G-Protein coupled opioid receptors like DORs, KORs, and NORs which also produce effects beyond pain relief such as stress, temperature, respiration, gastric motility, memory, mood, and more [18]. It is these accessory actions that lead to the myriad of side effects that occur from opioid use [15].

Among many things, this table indicates the potency of different opioid drugs. Classically fentanyl is known as one of the strongest opioids, 100 times stronger than morphine as mentioned earlier [4] but opioids vary in potency and are measured against morphine in morphine equivalent dosages (MED). In this paper high dosage and overdoses are mentioned. Due to tolerability and physiological differences between people, it is difficult to pinpoint the exact dosage when the effects of opioids will be seen. The literature doesn't list consistent dosages between studies. Therefore, with high doses mentioned in this paper, it refer to the upper limits of MED recommended by medical practice. Additionally, overdoses are those that exceed daily MED levels and are more likely with higher potency opioids.

The association between different opioids and cognitive dysfunction is summarized in **Table 2**.

4. Discussion

4.1. Opioid's Relation to Depression and Anxiety

Depression and anxiety are seen in 30% - 40% of patients chronically taking opioids [19]. While there are a lot of outside factors that may affect this number, such as living with the limitations of a chronic injury or chronic pain, there have been several studies looking at the causal relationship between opioids and depression and suggest there may be a genetic predisposition in some to be at higher risk for depression with opioid use [20]. The exact relationship between

opioids and depression, as well as the possible mechanism of action are still not fully understood and warrant further research.

Table 2. Association between different opioids and cognitive dysfunction.

Cognitive Effects	Strong Association	Moderate Association	Weak Association
Memory Loss/Amnesia	Fentanyl overdose (Barash *et al.*, 2020)	Fentanyl (Barash & Kofke, 2018)	
Episodic Memory	Methadone at 100% daily dose (Curran *et al.*, 2001)	Methadone (Mintzer *et al.*, 2005))	10 mg morphine or 5 mg oxycodone (Friswell *et al.*, 2008)
Dementia			Heavy opioid exposure (Dublin, 2015) Patients with dementia also had higher opioid use (Jensen-Dahm *et al.*, 2014)
Memory Consolidation	Methadone and buprenorphine therapy in pregnancy (Konijnenberg & Melinder, 2022)	Morphine with sustained-release opioid (Kamboj *et al.*, 2005)	
Inhibition Dysfunction/ Compulsive Behaviors	Heroin addiction leads to compulsive decision making (Fishbein *et al.*, 2007) Heroin users found to have increased impulsiveness (Kirby *et al.*, 1999) Long-term opioid users (Tolomeo *et al.*, 2019)	Medication for Opioid Use Disorder (Mistler *et al.*, 2022)	
Longer Deliberation Times	Long term opioid use (Schiltenwolf *et al.*, 2014)	Heroin (Fishbein 2007), Medication for Opioid Use Disorder (Mistler *et al.*, 2022)	
Working Memory	Long term opioid use (Schiltenwolf *et al.*, 2014) Chronic opioid use (Sjøgren *et al.*, 2000; Sjøgren *et al.*, 2005)	Neonatal Abstinence Syndrome (Nygaard *et al.*, 2015)	
Visiospatial Memory	Long term opioid use (Schiltenwolf *et al.*, 2014) Methadone and buprenorphine treatment (Tolomeo *et al.*, 2019) Heroin (Baldacchino *et al.*, 2018)		
Cognitive Function	Neonatal Abstience Syndrome (Nygaard *et al.*, 2015)	Methadone maintenance therapy (Mintzer *et al.*, 2005) Strong opioids for non-cancer pain (Schulte *et al.*, 2021), Fentanyl and heroin use in HIV patients (Tamargo *et al.*, 2020)	
Behavioral and Emotional Disorders	Neonatal Abstinence Syndrome (Fill *et al.*, 2018)		Infants with subclinical intrauterine opioid exposure (Hall *et al.*, 2019)
Educational Disabilities	Neonatal Abstinence Syndrome (Fill *et al.*, 2018; Nygaard *et al.*, 2015)		
POCD		Oral Morphine Equivalent (Awada *et al.*, 2019)	High dose fentanyl (50 μg/kg) (Hou *et al.*, 2018)

4.2. Neuropsychologic Effects of Opioids

Opioids produce several neuropsychologic effects. About 15% of patients may experience sedation due to opioid's inhibition of nociceptive pathways [19]. Nociceptive pathways regulate and transmit pain signals, but they also help with arousal, thus their inhibition will lessen arousal [21]. Paradoxically, around 25% of patients taking opioids long-term may have disruption of their sleep [19]. This is likely due to opioids acting on MORs and KORs in the pontine reticular formation and the substantia innominata within the basal forebrain, lowering endogenous adenosine levels, increasing arousal, and disrupting sleep [22] [23].

4.3. Opioid Addiction

Addiction is a common problem with opioid use. Substance abuse problems occur in 15% - 23% of patients with chronic pain who use opioid therapy [24]. Addiction may occur when opioids activate MORs which are part of the Mesolimbic Reward System in the brain, stimulating dopamine production in the ventral tegmental area which is then sent to the nucleus accumbens. This biochemical brain process is responsible for feelings of pleasure [25]. Over time the brain acclimates to the high levels of opioids and develops a tolerance, thus needing high amounts of opioids to reach the same level of pleasure. Unfortunately, when patients have chronically high levels of opioids in their systems, many of the previously discussed side effects or even death may occur.

4.4. Opioids and Cognitive Dysfunctions

Use of opioids has been associated with a plethora of different cognitive issues. A review of the literature shows a common thread of problems with working memory, decision making, impulsivity, and other cognitive impairments [26].

Just 30 mg of methadone delivered as a single dose daily, has impacts on episodic memory or "memory of personally experienced events". The hypothesized mechanism is that the memory problem comes from opioid's inhibitory effect on the release of acetylcholine [27]. Methadone maintenance for Opioid Use Disorder (OUD) patients compared against currently abstinent opioid users found that the methadone maintenance group had more impairments in a recognition memory test [28]. As little as 10 mg of morphine or 5 mg oxycodone can cause episodic memory problems and subtle memory impairments [29]. This is concerning since the rate and dose of opioid prescriptions is consistently increasing [30] [31]. Although, some studies show that even small doses may cause problems [32]. However, most of the problems with opioids occur with large or potent doses [33].

A Russian study of heroin users found they needed longer times deliberating decisions and had problems with visual memory [34]. Patients in long-term opioid treatment scored lower on tests measuring attention, working memory, and psychomotor speed or the ability to maintain and manipulate information over a short interval of time [35] [36]. The impacts of opioid use on short-term

memory and quick-thinking tasks, such as Reitan's Trails, shows that those taking morphine performed worse than controls ($p = 0.03$) [37]. This further strengthens the link between opioid use and memory. In a retrospective cross-sectional analysis of 300 patients receiving opioids for non-cancer pain, 23% reported difficulty with mental activities and 17% reported poor memory to the point that 46% of these patients were discussing cessation of the opioid treatment [38]. Tamargo *et al.* found HIV patients using heroin or fentanyl were at higher risk for cognitive impairment [39].

Comparing those receiving opioid treatment for chronic non-malignant pain against healthy controls found that chronic nonmalignant pain patients receiving long-term opioid therapy had significant impairments in vigilance/attention, psychomotor speed, and working memory. There was a statistically significant difference ($p = 0.004$) between the chronic pain group receiving no treatment and the chronic pain group receiving long-term opioid treatment in a Paced Auditory Serial Addition Task (PASAT), which is a 10 to15 minutes exam that measures auditory information processing speed and flexibility [40] [41]. This demonstrates that opioid use can cause problems with working memory and cognition.

Chronic pain patients have longer times processing information compared to a healthy control group. Chronic pain patients receiving opioid treatment had "significantly reduced spatial memory capacity, flexibility for concept change, and also impaired performance in working memory assessment". While chronic pain can also cause memory and cognitive difficulties, the addition of long-term opioid treatment can add further dysfunctions [36], especially with more potent opioids like heroin instead of methadone [42]. It is apparent in the research that opioid use can cause various problems with memory. This is something physicians and patients need to be aware of when deciding on a treatment plan.

4.5. Opioid-Associated Amnesiac Syndrome (OAS)

Starting in 2012, right around the cusp of the third wave of the Opioid Crisis in USA, patients started to present with acute amnesia and MRI visualized bilateral damage to the hippocampus. Dr. Jed Barash noted this trend and collected a cluster of cases in hospitals around eastern Massachusetts who all presented with acute bilateral injury to the hippocampus visualized on MRI and sudden-onset amnesia. Barash suspected opioid overdose as a culprit [3] [43] [44]. After displaying cases of OAS with the 18 patients from Massachusetts, Barash also found 21 published articles containing 40 cases of possible OAS. A thorough review of these articles led to more conclusive evidence to support Barash's claims that this amnesiac syndrome is caused by opioids and substantiated OAS.

Another researcher, Dr. Andrew Kofke, used animal models from rats to non-human primates to show that fentanyl overdose causes damage to structures of the limbic system such as the subiculum, amygdala, and hippocampus [45] [46] [47]. In another study, Kofke used another animal model consisting of 40 rats and demonstrated forebrain ischemia with moderate to high doses of

fentanyl [47]. These cases in conjunction with Barash's formulated a theory that opioids play a key role in hippocampal damage and memory problems. In 2020 Barash proposed criteria for Opioid-associated amnestic syndrome (OAS): a patient must have new onset amnesia greater than 24 hours in duration and positive toxicology for opioids [48].

It is possible that this damage from opioids comes from a combination of hypermetabolism that occurs in conjunction with ischemic damage [47]. However, it seems likely that the conjunction of ischemia and hypermetabolism, along with the propensity for opioids to target the limbic system, maybe the root of the issue. However, it may be more complex as researchers speculate that opioids inhibit the effect of GABAnergic inhibitory neurons and may cause an excitotoxic effect in the damage [3]. Nevertheless, it is clear that high potency or high dose opioids can damage the hippocampus causing amnesiac symptoms. Further understanding of the mechanism and damage needs to be explored.

4.6. Impact of Opioids on Executive Function of Brain

Impulsivity is increased in those dependent on opioids, and this may be because cognitive processes controlled in the prefrontal cortex are weakened in those using opioids long-term [49]. The impairments in executive function and inhibition are thought to be a consequence of grey matter reduction in areas responsible for cravings, addiction, pain, and emotion such as the prefrontal cortex, anterior mid-cingulate cortex, and basal ganglia. Impulsivity and a desire for immediate gratification are more common in heroin users when monetary rewards are offered, even when a monetary reward now is less in value than a larger monetary reward available in 1 week to 6 months [50]. This may be because the long-term opioid use resulted in impaired motor inhibition which led to impulsive behavior and more mistakes. This also precipitates difficulties in making high-risk decisions and increases decision-making times [34] [51] showing that opioid use can increase risky behavior.

4.7. Post-Operative Cognitive Dysfunction

Use of opioid drugs has been linked to increased Postoperative Cognitive Dysfunction (POCD). Researchers have found decreased incidence or severity of POCD when non-opioid drugs are used instead of opioids [52]. In a study of 66 patients undergoing elective total knee replacement surgery, they looked at the use of high and low dose of fentanyl in their study. They found a significant difference ($p = 0.025$) between high and low dose revealing the low-dose fentanyl group had a shorter duration of POCD [53]. Many studies have shown that use of opioids increases the duration and severity of POCD while using non-opioid analgesics lessens the incidence of POCD [54].

The mechanism of this effect once again points at opioid neurotoxicity causing hypermetabolism and possible ischemia similar to what occurs in opioid overdose [46]. Having the patient intubated provides a protective factor. Anoth-

er hypothesis for the mechanism of injury is from the induction of amyloid β peptide (Aβ) oligomerization as some anesthetics promote their formation through caspase-3 activation and inhibition of phosphatase activity [32] [55]. Others hypothesize that it may have to do with calcium dysregulation from isoflurane, a non-opioid anesthetic [56]. Some studies also share a concern for an inflammatory stress response in the brain due to the trauma of surgery [57] and one speculated that high levels of opioids, like fentanyl, impact this stress response and exacerbate the problem [53].

However, the literature examines many possible causes for the development of POCD like the type of surgery, age of patient, patient's predisposition to dementia, length of surgery, etc. Due to this speculation of the exact mechanism, it is hard to point the finger at opioids as the sole cause of POCD. Thus, more investigation into the role opioids play in POCD is warranted.

4.8. Neonatal Abstinence Syndrome

Neonatal Abstinence Syndrome (NAS) is a condition where opioids taken by the mother have crossed the placenta and caused dependence in the fetus that continues in the neonate. In 2012 an infant was born with NAS in the United States every 25 minutes [58]. Classic symptoms of NAS are tremors, high-pitched crying, irritability, poor feeding, vomiting, diarrhea, and inability to regulate their temperature. However, NAS has also been shown to have lasting cognitive impacts on children.

Children with NAS are more likely than control groups to receive a disability evaluation, be diagnosed with a disability and need assistance in the classroom later in life. The divide was so severe that seventh-grade children previously diagnosed with NAS often scored worse than other children with no NAS diagnosis who were two years younger and in fifth grade [58]. Children with an NAS diagnosis were found to perform lower on verbal and non-verbal memory tasks [59]. These stark differences in cognitive abilities did not lessen over time, the children stayed behind their peers throughout childhood [60]. Infants remained at risk for neurodevelopmental problems, and surprisingly, lower height through childhood. Psychometric assessments taken at 18 months and three years found significantly lower scores except with the psychomotor development index of the Bayley Scales of Infant Development [61]. Infants with subclinical exposure to opioids were more likely than infants with no exposure to be diagnosed with behavioral or emotional disorders, developmental delay, speech problems, and even strabismus [62].

In mouse models of perinatal morphine exposure, the prefrontal cortex and amygdala, which modulate executive function, are sensitive to opioids prenatally. Activation of microglia through opioid binding to toll-like receptor 4 impacts synaptic pruning. Male mice exposed to morphine perinatally had attention impairments and other executive function deficits [63]. The mechanism of action is thought to be from oxidative stress and inflammation in the hippocampus [59].

4.9. Reasons for Opioid Epidemic in the United States

4.9.1. Over-Prescription and Use of Opioids

The United States consumes far more opioids than the rest of the world. With only 4.4% of the world's population, the USA uses over 80% of the world's opioids. Broken down by type of opioid the US consumes 99% of the hydrocodone in the world, 85% of the oxycodone, and 65% of hydromorphone [64] [65] [66]. Compared to European countries, US doctors are more likely to write a prescriptions for opioids. One study saw that 98% of American orthopedic surgery patients received opioids on the first post-operation day compared to only 70% of comparable European patients. Paradoxically, European patients reported less pain and emotional distress [67].

4.9.2. Misinformation of Opioids

Misinformation of opioids is not uncommon. Researchers found the Drug Enforcement Administration (DEA) and other government agencies are at fault for misinformation by being, "slow to counter and remedy misleading statements, raising questions about objectivity and conflicts of interest." [68].

In fact, the US Drug Enforcement Administration has shared verifiably false information about fentanyl saying, "fentanyl can be absorbed through the skin or accidental inhalation of airborne powder can also occur…. Just touching fentanyl or accidentally inhaling the substance during enforcement activity or field testing the substance can result in absorption through the skin…. The onset of adverse health effects, such as disorientation, coughing, sedation, respiratory distress or cardiac arrest is very rapid and profound, usually occurring within minutes of exposure" [69]. It is hard to really solve the problem when the very agencies created to control it don't fully understand the issue. In 2019 a similar video and statement was released by the Center for Disease Control and Prevention [70] which has since been withdrawn.

The reliability of the sources (DEA and CDC) of these now retracted statements helped establish a lot of the misinformation claims. Additionally, people find a lot of credibility in their friends and acquaintances and therefore get their news from social media. Researchers looked at 551 news articles shared on Facebook from 2015-2019. Articles with misinformation received around 450,000 shares and had the potential to reach 70,000,000 people. Corrective information and articles only received 30,000 shares with the potential to hopefully educate only 4,600,000 Facebook users, this is 15 times less coverage than the misinformation so readily shared [68].

Fearmongering about opioids in the media leads people to believe that mere skin contact with a miniscule amount of fentanyl will lead to absorption and overdose. There is also the problem of police and other first responders giving large repeat doses of Narcan for symptoms such as heart palpitations, fainting, shortness of breath, feeling faint, and more, which resemble anxiety attacks, not opioid overdose [68] [71].

Another issue with this widespread misinformation is the fear it may cause in

a responder to delay intervention during an overdose, since they mistakenly assume mere contact with the drug may put the responder at risk for overdose themselves. This worry, with erroneous news articles showing minuscule amounts of fentanyl and claiming it can kill millions, will lead to panic that can foster "counterproductive policies" and "hyper-punitive responses" to the drug crisis [68]. It also leads to increased stress and burnout among paramedics and police officers [69].

4.9.3. War on Drugs and Prohibition

Opioids are not the only drug that has been abused in the United States. However, to understand how the Opioid Epidemic came about, some general background is needed. This is especially true in order to use these general failings to inform decisions on how to proceed and get out of the Opioid Epidemic. By alleviating the epidemic society can better avoid all of the negative effects of illicit and high-dose opioid use that this paper has already explored.

The United States has been waging a war on drugs since President Nixon [72]. Everything from excessively punitive policies to a police-run information campaign called Drug Abuse Resistance Education or D.A.R.E, which is still in effect despite evidence that it is ineffective [73] [74]. Analyses looking back on the past 40 years have found the "War on Drugs" to be a failure and led to unintended consequences.

The Drug Enforcement Administration (DEA) was created in 1972, yet in 1971 the CDC reported about one death per 100,000 people due to drug overdose in the United States. The creation of the DEA did not seem to slow down the almost 1500% growth of this statistic as, in 2014, there were 47,000 overdose deaths, around 14.7 deaths per 100,000 people. In the US, from 2000 to 2014 more people died of overdose than car crashes. The conclusion was that the war on drugs and strict prohibition, along with punitive punishments, was "not only ineffective but counterproductive, at achieving the goals of policymakers" [72].

An unintended consequence came from the illegality of drugs in the War on Drugs. In their study, Conye says "Making markets illegal fails to reduce, much less eliminate, the market for drugs. Instead, these mandates mainly push the market for drugs into underground black markets." [72]. This should have been foreseen as the United States has a history of ineffective prohibition policies, as seen in the alcohol prohibition from 1920-1933 as alcohol prohibition led to increased homicide rates, flourishing organized crime, and gangsters like Al Capone [75] [76]. One sociologist studying the alcohol prohibition of the early 1900's said, "A major wave of crime appears to have begun as early as the mid-1920s and increased continually until 1933…when it mysteriously reversed itself." [77]. These line up with the years of the prohibition when illegal sale of alcohol was rampant.

Because illegal groups supplying drugs do not have access to the legal system they resort to other methods to settle disputes, such as violence. Economist Jeffry Miron argues that eliminating drug prohibition could reduce homicides by 26%

- 75% in the United States [78].

Prohibition has had far-reaching impacts on the American prison system and may be used to perpetuate unfair policies and biases. Drug offenses are the leading cause of arrests in the United States. In 2017 the FBI reported that 1.63 million arrests were made for drug violations [79]. This equals an arrest every 20 - 25 seconds. Even though Black people make up 13% of the U.S. population, and they use and sell drugs at similar rates to White people, Black people make up 24% of those arrested [80]. In 2015 there were around 10.35 million people incarcerated worldwide, with 2.2 million or 21% in the U.S. despite the fact that the U.S. only makes up 4.25% of the world's total population [81] [82]. Instead of fixing the issues, all of this has led to a culture and environment where illicit drugs are abused, among those are opioids. The increased use of opioids and their high mortality rate compared to other illicit drugs (**Figure 2**) and has led to the Opioid Epidemic described in the introduction with all of the negative side effects on memory and cognition.

4.10. Strategies to Mitigate the Harm

4.10.1. Judicial Use of Opioids

Physicians who prescribe opioids need to fully understand the extent of what they are offering. Unfortunately, the view physicians have towards opioid users seems to be lacking in empathy and understanding. A 2006 survey found that 25% of physicians didn't know that naloxone could be prescribed as an opioid overdose intervention and had negative attitudes about drug users [83]. It was determined that educational training for medical students and residents is lacking and needs more exposure and information to help physicians in their practices [84].

Physicians also need to understand that opioid use can affect memory, thus a patient recovering from surgery, or needing to follow up with therapy, may not remember or do all the things they are asked. Thus, problems with follow-up care may not be due to "non-compliance" but may be the result of adverse memory and cognition consequences from the opioids that were prescribed. Doctors need to be aware of what signs to look for in an overdose, not just life-threatening ones, but quieter insidious memory problems as well.

Training doctors in alternative but effective methods of pain management could provide more therapeutic choices. Medical professionals need to understand that opioids can be helpful in controlling pain but may cause severely detrimental issues, thus they should seek a care plan that includes careful administration and, hopefully, eventually cessation of opioid use. As recommended by the European Pain Federation, "Opioid therapy should only be initiated by competent clinicians as part of a multi-faceted treatment programme in circumstances where more simple measures have failed" [85].

If opioids were just used for cancer-related or severe chronic pain then many adverse events from memory impairment to death, would be averted. The overuse of opioids for any analgesic therapy can be dangerous in its outcomes and is

also risky by providing a large number of opioids out where they can be used in black markets or illicitly. This also requires further research in pain management. There are some conditions where patients cannot manage their chronic pain without the help of these powerful drugs. The medical field needs to cease leaning on them as long-term answers and develop equally effective but safer methods to manage chronic pain.

4.10.2. Correct Information

As mentioned before, misinformation is common where opioids are concerned but distributing correct information will help reduce the weight of the drug crisis. Black box warnings on cigarettes reduce smoking in low-nicotine users and this kind of information could assist opioid users [86]. An informational campaign for teenagers and older children could enlighten a new generation of people about opioids. This would have to be done better than the D.A.R.E. program. Additionally, as demonstrated earlier, law enforcement is especially ill-informed about the truths concerning opioids and thus it would be better to have real addiction specialists, not police, run and teach these informational campaigns.

A program that trained patients seen in Emergency Departments, a place where frequent interventional care for opioid overdose occurs, on opioid education and naloxone distribution showed success in helping high-risk populations [87]. The distribution of naloxone did not increase opioid use or overdose but led to more people intervening when witnessing an overdose. Training patients and the public about dangers and ways to help and intervene can save lives and prevent many of the ill effects this paper has explained.

Patients are not exempt from the responsibility of knowledge. They need to be properly educated on the negative effects of opioids so that they may be good stewards of their own health. Patients need to be aware that it may affect their personal life, work life, and more. That way they can make informed decisions about what to accept for their health and be able to bring concerns or questions to their doctor.

Misinformation is rampant and within the public, police, media, and also large agencies meant to help the problem. People can't change something they don't understand. The need for proper information and education about the risks and dangers of opioid use was the impetus for this paper. It is dangerous how widespread misunderstanding is in lay people, policymakers, police, and healthcare professionals. Until there is understanding there cannot be change.

4.10.3. Change in Policy and Opioid Harm Reduction

Prohibition has not worked. The Global Commission on Drug Policy admitted that "the global war on drugs has failed, with devastating consequences for individuals and societies around the world" [88]. A review of policies and solutions looked at Australia's focus on law enforcement as a way to control the opioid crisis and harsh criminal sentences. Researchers found that there was little evi-

dence of law enforcement being effective in the "War on Drugs". However, they found ample evidence for harm reduction to be effective and cost-effective in reducing illicit drug use, which includes opioids [89].

Harm reduction is a collection of strategies that try to understand people with addictions to lead to safer managed use and abstinence. It realizes that the complete prohibition of drugs is unfeasible and harmful and thus seeks to mitigate the harm. The National Harm Reduction Coalition (NHRC) [90] state that harm reduction:

1) Accepts, for better or worse, that licit and illicit drug use is part of our world and chooses to work to minimize its harmful effects rather than simply ignore or condemn them.

2) Understands drug use as a complex, multi-faceted phenomenon that encompasses a continuum of behaviors from severe use to total abstinence, and acknowledges that some ways of using drugs are clearly safer than others.

3) Establishes quality of individual and community life and well-being, not necessarily cessation of all drug use, as the criteria for successful interventions and policies.

4) Calls for the non-judgmental, non-coercive provision of services and resources to people who use drugs and the communities in which they live in order to assist them in reducing attendant harm.

5) Ensures that people who use drugs and those with a history of drug use routinely have a real voice in the creation of programs and policies designed to serve them.

6) Affirms people who use drugs (PWUD) themselves as the primary agents of reducing the harms of their drug use and seeks to empower PWUD to share information and support each other in strategies which meet their actual conditions of use.

7) Recognizes that the realities of poverty, class, racism, social isolation, past trauma, sex-based discrimination, and other social inequalities affect both people's vulnerability to and capacity for effectively dealing with drug-related harm

8) Does not attempt to minimize or ignore the real and tragic harm and danger that can be associated with illicit drug use.

It is worth noting that harm reduction strategies can be applied to many different illicit drugs, however this paper will focus on opioid specific harm reduction policies.

Other countries have instituted opioid harm reduction approaches with different encouraging levels of success. For example, Canada created a comprehensive website where people can get reliable information on opioids and learn about Canada's efforts to help with the crisis at Canada.ca/Opioids. Other efforts explained on the website include substance use programs, restricting marketing of opioids to healthcare professionals, and more. These efforts have been effective at lessening opioid use. One of Canada's most effective measures to combat

its own opioid crisis was opening multiple supervised consumption locations where people who use drugs could do so in a supervised and safe location. As of 2017 they have fourteen such locations including two mobile sites [91]. Canada's first supervised consumption site saw that 23% of people stopped injecting and 57% entered addiction treatment [92].

This is consistent with Switzerland which implemented heroin-assisted treatment and legalized heroin in 1994. These efforts have influenced the number of new heroin users to decline by 80% and between 1991 and 2010 overdose deaths decreased by 50% [93]. Switzerland has adopted a "four pillar model" of prevention, treatment, harm reduction, and law enforcement. This model has been adopted in other places, for example, it is the policy of the city of Vancouver, Canada [94].

Portugal suffered a severe opioid pandemic in the 1990's and the city of Lisbon was given the moniker "Heroin Capital of Europe" (95). However, they instituted a policy of harm reduction and passed laws that decriminalized possession of up to 10 days' personal use of a narcotic while leaving dealing of the drugs illegal [72]. Those found in possession of a personal supply of the drug meet with a commission of three individuals who help with drug dissuasion. The commission usually consists of a lawyer, physician, and other healthcare or addiction specialists. This has cut the number of heroin drug users by 75% and given Portugal the lowest rate of drug related deaths in Europe [95].

A harm reduction approach could help reduce the damage cause by opioids. Seeing how the stance of strict prohibition has proven to be a failure after all these years it would be good to give new programs a try.

5. Limitations and Further Research

One of the greatest challenges in experimenting human with opioids is their dangerous and addictive nature and that is not ethical. This limitation is one reason why many studies use methadone. Methadone is an opioid but because of its long-acting property is used to treat OUD and get patients off more dangerous opioids. Many of these studies can observe the effects of methadone while also treating patients for OUD and keeping the risk of addiction or overdose low.

This is why, at times, this review has had to depend on methadone studies or large case reports of patients who themselves overdosed on more potent and dangerous opioids. Being able to observe these effects from less potent drugs or after an overdose in a non-controlled environment makes it more challenging to point to opioids as the sole cause of these problems. However, the literature still provides ample evidence to implicate opioids as a culprit in these deleterious memory and cognitive effects.

The study of the memory and cognitive effects of opioids is still relatively new. There is debate in the literature about the extent of these problems, the dosage or concentration of opioids that may cause them, and the exact mechanism of ac-

tion by which they occur. This is a burgeoning topic that needs more study to differentiate some of the factors and answer important questions.

6. Conclusion

This review shows a clear pattern that the use of opioids, the most potent and powerful analgesics, has an impact on several mental functions such as memory consolidation, precipitation of dementia-like symptoms, working memory, episodic memory, lessened inhibition, as well as behavioral and educational disorders. These problems occur most often with high dosages of opioids of any kind which are linked to potential damage of several structures of the limbic system like the subiculum, amygdala, and hippocampus. Focusing on correct informational campaigns, removing punitive policies, and focusing on harm reduction strategies along with its deliberate use have alleviated the abuse and use of opioids in many countries and can thus help mitigate all the negative effects of these drugs.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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