An overview of the disease model for drug addiction and interventions used to address the current opioid epidemic

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AN OVERVIEW OF THE DISEASE MODEL FOR DRUG ADDICTION AND INTERVENTIONS USED TO ADDRESS THE CURRENT OPIOID EPIDEMIC

by

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KITAE CHANG

ABSTRACT

America is engulfed in an opioid epidemic. Whether this is depicted through the tens of thousands of lives claimed by the number of drug overdoses each year, the unprecedentedly high and increasing rates of opiate abuse, or the broadening demographic profile of the addict, it is clear that the current issue is one that requires serious attention. As informed by the negative attitudes toward drug addiction that have prevailed since the War on Drugs was declared, it is hypothesized that much of the contemporary predicament is a result of this misinformation that did not resolve, but exacerbated the drug crisis. Despite the concurrent emergence of evidence asserting that addiction is a disease, instead, the idea that drug addiction is a failure prevails.

As with many brain diseases, drug addiction displays both pathological alterations in the transmission of signals within the neural circuitries and the morphological defects associated with non-random regions of the brain. The alteration that is observed during opioid tolerance is the desensitization of mu opioid receptors to dopamine, resulting in the need of increased dosage of opiates to achieve the same high. During opioid dependence, key changes that are seen in the locus ceruleus and the mesolimbic reward system increase both the likelihood of an overdose event and withdrawal when an
exogenous opioid is present or absent, respectively. There are two models that describe additional changes that occur during the transition from frequent abuse to addiction: (1) the “Changed Set Point Model” and (2) the “Cognitive Deficits Model.” All three variants of the “Changed Set Point Model” portray a shift in the physiological set points of dopamine and glutamate levels in the reward system and regions that control it. The “Cognitive Deficits Model” theorizes that the modifications localized to the prefrontal cortex are responsible for the ultimate transition.

Once the abuser is thrust into the addiction cycle, additional changes in the neural networks are observed. These changes are seen in each of the three phases: (1) Binge and Intoxication, (2) Withdrawal and Negative Affect, and (3) Preoccupation and Anticipation. In the first phase, a process called drug-induced neuroplasticity occurs, resulting in the amplification of signals originating from dopaminergic neurons. Next, during Withdrawal and Negative Affect phase, among other changes, the amygdala is shown to be re-wired in such a way that the addict is more sensitive to stress. And finally in the last phase, the changes that occur, secondary to processes similar to drug-induced, are indicated in the prefrontal cortex.

The current FDA-approved medication-assisted therapies include methadone, buprenorphine, and naltrexone. The single outstanding abstinence-based treatment is the 12-step program. In the evaluation of medical and non-medical interventions the relative efficacies were measured using the metrics: (1) rates of abstinence achievement, (2) rates of opioid use, and (3) retention in treatment. Individually, all therapies show moderate success when measured against each metric, which further validates the brain disease
model for addiction, and also indicates that the future direction of addressing the opioid epidemic should point at combination therapies. What is most imperative now is for there to be more widespread recognition of the brain disease model for addiction.
TABLE OF CONTENTS

TITLE ............................................................................................................................ i
COPYRIGHT PAGE .................................................................................................... ii
READER’S APPROVAL PAGE ................................................................................. iii
ACKNOWLEDGMENTS ............................................................................................... iv
ABSTRACT ................................................................................................................... v
TABLE OF CONTENTS ............................................................................................... viii
LIST OF TABLES ........................................................................................................ x
LIST OF FIGURES ...................................................................................................... xi
ABBREVIATIONS ....................................................................................................... xiii
INTRODUCTION .......................................................................................................... 1
  The Current Scene ................................................................................................... 2
  The War on Drugs: Saying No to a Brain Disease Model for Addiction ............ 9
  Brain Disease Model for Addiction ....................................................................... 12
SPECIFIC AIMS .......................................................................................................... 30
INTERVENTIONS TO CURB THE OPIOID EPIDEMIC ........................................ 31
EVALUATION OF THE INTERVENTIONS .............................................................. 45
  Evaluation of Medication Assisted Therapy as Treatment for Drug Addiction46

viii
## LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Number and Age-adjusted Rates of Drug Poisoning Deaths Involving Analgesics and Heroin: United States, 2000-2014.</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>Definitions of Key Terms</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>Definitions</td>
<td>27</td>
</tr>
<tr>
<td>4</td>
<td>Processes Associated with the PFC that are Disrupted in Addiction</td>
<td>32</td>
</tr>
<tr>
<td>5</td>
<td>Characteristics of Medications for Opioid-Addiction Treatment</td>
<td>36</td>
</tr>
<tr>
<td>6</td>
<td>Total and Specific $[^{18}\text{F}]\text{cyclofox}$ Binding in Different Brain Regions</td>
<td>39</td>
</tr>
<tr>
<td>7</td>
<td>12 Concepts for Narcotics Anonymous Service</td>
<td>47</td>
</tr>
<tr>
<td>8</td>
<td>Outcome Measures of LAAM, Buprenorphine, and Methadone Based Maintenance Programs</td>
<td>51</td>
</tr>
<tr>
<td>9</td>
<td>Clinical Outcomes of XR-NTX</td>
<td>54</td>
</tr>
<tr>
<td>10</td>
<td>Forest Plot of Comparison: Flexible Dose Buprenorphine vs. Flexible Dose Methadone; Retention in Treatment</td>
<td>61</td>
</tr>
<tr>
<td>11</td>
<td>Prediction of Abstinence at Eight Years</td>
<td>65</td>
</tr>
</tbody>
</table>
# LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Age-adjusted Rates of Death Related to Prescription Opioids and Heroin Drug Poisoning in the United States, 2000-2014</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>Past Month Nonmedical Use of Types of Psychotherapeutic Drugs among Persons Aged 12 or Older: 2002-2013</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>Past Month and Past Year Heroin Use among Persons Aged 12 or Older: 2002-2013</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>Deaths from Drug Overdose Across Different Ethnicities in the United States, 1999-2014</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>Prescription Painkiller Sales and Deaths in the United States, 1999 - 2013</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>Number of People in Federal Prison for Drug Offenses, 1980-2014</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>The Mesolimbic Reward System</td>
<td>14</td>
</tr>
<tr>
<td>8</td>
<td>The Neurological Basis of Dependence and Withdrawal at the Cellular Level</td>
<td>17</td>
</tr>
<tr>
<td>9</td>
<td>Stages of the Addiction Cycle</td>
<td>22</td>
</tr>
<tr>
<td>10</td>
<td>The Buffering Effect of Methadone on Heroin Use</td>
<td>33</td>
</tr>
</tbody>
</table>
11 Specific Binding of $[^{18}\text{F}]$cyclofoxy in Various Brain Regions of Patients that Did or Did Not Receive Methadone Treatment

12 The Ceiling Effect of Buprenorphine

13 Time Course of Plasma Levels of Buprenorphine and Naloxone after Administration of Sublingual Suboxone

14 Oral Naltrexone Refills, 2000-2002

15 States that Provides Medicaid Coverage for Methadone, Buprenorphine, and Naloxone

16 Time Course of Changes in Opiate Craving

17 Change in Craving During the Course of Treatment with Vivitrol vs. Placebo

18 Pooled Effects of Various Drug Conditions in Comparison with High Dose Methadone on Prevention of Illicit Opioid Use

19 Percentage of Urine Samples Negative for Opioids (With Cocaine + Benzodiazepines) Through the Duration of Treatment with Suboxone

20 Proportion of Opioid-Free Participants in XR-NTX Treatment vs. Placebo

21 Retention in Treatment by Study Week and Dose-Dependent Treatment Group
### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACA</td>
<td>Affordable Care Act</td>
</tr>
<tr>
<td>AMPA</td>
<td>α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid</td>
</tr>
<tr>
<td>BNST</td>
<td>Bed Nucleus Stria Terminalis</td>
</tr>
<tr>
<td>DA</td>
<td>Dopamine</td>
</tr>
<tr>
<td>DAWN</td>
<td>Drug Abuse Warning Network</td>
</tr>
<tr>
<td>DEA</td>
<td>Drug Enforcement Agency</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>GABA</td>
<td>Gamma-aminobutyric acid</td>
</tr>
<tr>
<td>LAAM</td>
<td>Levo-alpha-acetylmethadol</td>
</tr>
<tr>
<td>LC</td>
<td>Locus Ceruleus</td>
</tr>
<tr>
<td>MAT</td>
<td>Medication Assisted Therapies</td>
</tr>
<tr>
<td>MHPAEA</td>
<td>Mental Health Parity and Addiction Equity Act</td>
</tr>
<tr>
<td>NA</td>
<td>Noradrenaline</td>
</tr>
<tr>
<td>NAc</td>
<td>Nucleus Accumbens</td>
</tr>
<tr>
<td>NIDA</td>
<td>National Institute on Drug Abuse</td>
</tr>
<tr>
<td>NMDA</td>
<td>N-methyl-D-aspartate</td>
</tr>
<tr>
<td>NSDUH</td>
<td>National Survey on Drug Use and Health</td>
</tr>
<tr>
<td>ORL1</td>
<td>Opioid-like Receptor 1</td>
</tr>
<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
</tr>
<tr>
<td>PFC</td>
<td>Prefrontal Cortex</td>
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VTA .............................................................................................. Ventral Tegmental Area
XR-NTX ........................................................................................... Extended Release Naltrexone
INTRODUCTION

This thesis has been organized with a specific chronology in mind. While the bulk of the text is devoted to laying out the current understanding of drug addiction as a disease of the brain, a substantial portion of the following introduction will lay down the context, both in the current and past fabric, for drug addiction in the United States. This task will first require observing the statistics that govern the current times followed by delving briefly into the recent history of drugs in this country to highlight remarkable events that have shaped the present circumstances.

It is beyond the scope of this thesis to conduct a comprehensive review of the underlying causes of addictive behaviors since it would be impossible to do so without detracting from the larger goal of this thesis, which is to validate the brain disease model for addiction. Instead, the discussion portion will evaluate various interventions, which either do or do not treat addiction as a brain disease.

Also it is worth mentioning here that in the interest of bringing focus to the thesis, the all-encompassing general term, “drug addiction issue,” and phrases of equivalent meaning will henceforth exclusively be referring to opioids, unless otherwise stated. This adjustment is being made in recognition of the notable impact of the opioid class of drugs, including heroin, on the contemporary epidemic. And as will be alluded to shortly, pain analgesics and heroin are the main drivers of the modern surge in drug-related deaths.
The Current Scene

It is often regarded that obesity is this generation’s primary medical and public health challenge. Especially when one considers the magnitude of the problem by size, with more than one-third of American adults and roughly 17% of the youth population classified as obese, it is of no surprise to observe the vast efforts that have been put forth to control and thwart the epidemic (Ogden et al., 2014). However, the drug addiction crisis is deserving of just as much attention given its unprecedented prevalence in modern day America. In 2014, 47,055 lives, which translate to roughly 0.01% of the United States population, were lost due to drug overdoses (Rudd et al., 2016). While this number starkly pales in comparison to the obese population by sheer size, it belies the startling fact of how quickly the problem is growing; from 2000 to 2014, the overall rate of death due to drug overdoses increased by 137% (Rudd et al., 2016; Table 1). These rates already eclipse the number of people who die from automobile accidents (Wilson, 2013). A closer look at the numbers in Table 1, and the corresponding plot portrayed in Figure 1, reveals that among all drug overdoses, those related to opioids, namely heroin and pain analgesics, have driven the surge since 2000. From the period spanning from 1999 to 2014, the rates of death due to opioid analgesics and heroin increased by 469% and 539%, respectively. These measures of drug impact not only reflect the challenge in treating drug addiction patients, but also imply the obstacles of preventing drug overdose deaths. As will be discussed in later sections, there currently exist medical interventions that can reverse the effects of opioid overdose.
Table 1. Number and Age-adjusted Rates of Drug Poisoning Deaths Involving Analgesics and Heroin: United States, 1999-2014. Figure taken from CDC/NCHS, National Vital Statistics, Mortality File 2014.

<table>
<thead>
<tr>
<th>Year</th>
<th>All Number</th>
<th>Deaths per 100,000</th>
<th>Opioid analgesics Number</th>
<th>Deaths per 100,000</th>
<th>Heroin Number</th>
<th>Deaths per 100,000</th>
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<td>1999</td>
<td>16,849</td>
<td>6.1</td>
<td>4,030</td>
<td>1.4</td>
<td>1,900</td>
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<tr>
<td>2000</td>
<td>17,415</td>
<td>6.2</td>
<td>4,400</td>
<td>1.5</td>
<td>1,842</td>
<td>0.7</td>
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<tr>
<td>2001</td>
<td>19,394</td>
<td>6.8</td>
<td>5,526</td>
<td>1.9</td>
<td>1,779</td>
<td>0.6</td>
</tr>
<tr>
<td>2002</td>
<td>23,518</td>
<td>8.2</td>
<td>7,456</td>
<td>2.6</td>
<td>2,089</td>
<td>0.7</td>
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<td>2003</td>
<td>25,735</td>
<td>8.9</td>
<td>8,517</td>
<td>2.9</td>
<td>2,680</td>
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<td>2004</td>
<td>27,424</td>
<td>9.4</td>
<td>9,857</td>
<td>3.4</td>
<td>1,878</td>
<td>0.6</td>
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<td>2005</td>
<td>28,913</td>
<td>10.1</td>
<td>10,528</td>
<td>3.7</td>
<td>2,609</td>
<td>0.7</td>
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<td>2006</td>
<td>34,425</td>
<td>11.5</td>
<td>13,723</td>
<td>4.6</td>
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<td>2007</td>
<td>36,010</td>
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<td>14,498</td>
<td>4.8</td>
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<td>2008</td>
<td>36,450</td>
<td>11.9</td>
<td>14,800</td>
<td>4.8</td>
<td>3,041</td>
<td>1.0</td>
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<td>2009</td>
<td>37,004</td>
<td>11.9</td>
<td>15,597</td>
<td>5.0</td>
<td>3,278</td>
<td>1.1</td>
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<td>2010</td>
<td>38,329</td>
<td>12.3</td>
<td>16,651</td>
<td>5.4</td>
<td>3,036</td>
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<td>2011</td>
<td>41,340</td>
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<td>16,817</td>
<td>5.4</td>
<td>4,297</td>
<td>1.4</td>
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<td>2012</td>
<td>41,502</td>
<td>13.1</td>
<td>16,087</td>
<td>5.1</td>
<td>5,925</td>
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<td>2013</td>
<td>43,982</td>
<td>13.8</td>
<td>16,236</td>
<td>5.1</td>
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<td>2014</td>
<td>47,005</td>
<td>14.7</td>
<td>18,693</td>
<td>5.9</td>
<td>10,574</td>
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Figure 1. Age-adjusted Rates of Death Related to Prescription Opioids and Heroin Drug Poisoning in the United States, 2000-2014. The data used to depict the trends for
Prescription Opioids have been adopted from the CDC/NCHS, National Vital Statistics, Mortality File 2014 (See Table 1). Figure taken from (Compton et al., 2016).

According to the 2013 National Survey on Drug Use and Health (NSDUH), the primary source of information regarding the use of illicit drugs, alcohol, and tobacco, the levels of non-medical use of pain relievers and heroin have remained more or less stable from 2002 to 2013 (Substance Abuse and Mental Health Services, 2014; Figure 2; Figure 3). It seems reasonable to think that if drug overdose related deaths were to remain at levels previously observed with no significant increase in the number of opioid drug abusers, a moderate response could significantly curtail the number of deaths. However, this seems unlikely when considering that other indications suggest otherwise. The opioid drug usage is also growing at unprecedentedly high rates. In the Drug Abuse Warning Network’s (DAWN) reports on drug-related emergency department visits, the data showed that the time span from 2004 to 2011 a 153% surge in emergency department visits related to misuse or abuse of prescription opioids. A more than quadrupling of the rate of hospital admissions due to prescription-opioid overdose was also reported between 2002 and 2012 (Substance Abuse and Mental Health Services Administration, 2013; Substance Abuse and Mental Health Services Administration, 2014). This discrepancy, while putting to question the severity of America’s drug problem, also inadvertently shows the nature of drug addiction. That is, drugs are most commonly abused in private. So much so that even the numbers of self-proclaimed abusers of opioids and overdosed patients who end up in ERs are most likely not commensurate with the actual severity of the drug epidemic. Many excluded from these
counts are those who time and time again narrowly escape their death. And these individuals - or “hungry ghosts”, as physician Dr. Gabor Maté refers to them - are found in all corners of society and blend with the rest of the populous (Maté, 2010). Whereas an untrained eye can spot the obese, even the trained eye cannot easily identify the addict.

**Figure 2. Past Month Nonmedical Use of Types of Psychotherapeutic Drugs among Persons Aged 12 or Older: 2002-2013.** The levels of self-reported abuse of pain relievers have remained steady for the last decade. Figure taken from 2013 National Survey on Drug Use and Health.
Figure 3. Past Month and Past Year Heroin Use among Persons Aged 12 or Older: 2002-2013. Figure taken from 2013 National Survey on Drug Use and Health. There has been a generally consistent increase in the reported usage of Heroin in the last decade.

While there are some parallels to be drawn between each epidemic, there are certainly some notable differences that stand in the way of juxtaposing these two crises. And if anything, such differences may provide more reasons for also bringing the drug addiction issue to the forefront of nationwide concerns.

For one, the drug epidemic has displayed its unique versatility over the last few decades, which has added to the overall complexity of containing its spread. Drugs are now crossing demographic boundaries (Kolata & Cohen, 2016). In the 1960s and 1970s, heroin abuse and addiction were issues that were confined to young men from minority groups living in urban areas (Dupont, 1971; Greene, 1974). By numbers, some studies have reported that among those who began using heroin in the 1960s, approximately 82.8% were males of minority groups, most commonly those of African American and Hispanic
descent (Cicero et al., 2014). Today, heroin use is itself most prevalent among Caucasians, including those of affluent status (Figure 4).

[Figure 4. Deaths from Drug Overdose Across Different Ethnicities in the United States, 1999-2014. Figure taken from (Kolata & Cohen, 2016).]

Interestingly, studies have traced this most recent change in the demographics of the heroin problem to the initiation through prescription opioid abuse (Unick et al., 2013; Lankenau et al., 2012). The main reason for this switch is cited to be due to costs and barriers to accessing prescription pain relievers (Cicero et al., 2014). Furthermore, some correlative reports have pinned the increase in opioid abuse to concomitant increases in prescribing of opioid analgesics, with opioid pain reliever sales quadrupling between 1999 and 2010 (Paulozzi et al., 2011; Figure 5). Put another way, it seems as though the healthcare system is partly responsible for the exacerbating the burgeoning issue; this is something unseen in the obesity problem.
Figure 5. Prescription Painkiller Sales and Deaths in the United States, 1999 - 2013. Figure taken from the CDC, National Vital Statistics System mortality data (2015).

However, despite all the distinguishing features between the two epidemics, the most outstanding difference is the status of the fight against each problem. Whereas no significant changes in obesity prevalence in youth or adults were observed from 2003-2004 to 2011-2012, in the same window of time, the number of deaths related to drug overdoses soared from 27,424 in the 2003-2004 period to 41,502 in the years 2011-2012, approximately a 51% increase (Ogden et al., 2014; Rudd et al., 2016; Table 1). Put into words, the great advances that have been made in combating obesity in recent years is seen to a lesser extent in the drug epidemic.
The War on Drugs: Saying No to a Brain Disease Model for Addiction

In the not so distant future, it may be difficult to imagine a time in which drug addiction was not viewed as a disease, but instead, a willful behavior driven by moral turpitude. Today, however, despite the emergence of overwhelming amounts of scientific evidence which depict the chronic disease-like symptoms displayed by drug addiction along with the pathological changes of the neural circuitries in the addict’s brain, there is still a paradigm that treats drug addiction as a form of moral failing or a criminal behavior. The origins of this view can be traced to the middle of the 20th century, when drug addiction was an issue that was most prevalently found in minority and low socioeconomic status communities. It was during a period of American history, at the peak of racial tensions that President Nixon declared the “War on Drugs” in June of 1971 (drugpolicy.org, n.d.). Prior to the declaration of the “war on drugs,” in fact a very small fraction of the American public, approximately two percent, saw drugs as an important issue facing the country (Beckett, 1997).

Notwithstanding this fact, President Nixon and successors were not deterred from engaging in the war (Alexander, 2012). From the early 1980’s to the 1990’s, funding for the FBI anti-drug initiative soared from $8 million dollars to $95 million dollars, just as allocations for the Department of Defense’s programs for anti-drug hunts were also increased by over three thousand percent from $33 million to $1.042 billion dollars (Beckett, 1997). Following suit, the Drug Enforcement Agency’s (DEA) spending grew from $86 million to $1.026 billion (Office of National Drug Policy, 1992). In contrast, funding for groups like the National Institute on Drug Abuse (NIDA) and the Department
of Education, agencies that worked to improve drug treatment, prevention and education were truncated by nearly the same proportions by which drug criminalizing agencies’ budgets were expanded (Beckett, 1997). During this time period, the primary means by which the nation addressed drug addiction was not through treatment, but rather through policing. Consequently, while the full-fledged “war on drugs” instead gave birth to mass incarceration (Figure 6).

![Figure 6](image.jpg)

**Figure 6. Number of People in Federal Prison for Drug Offenses, 1980-2014.** Figure taken from The Sentencing Project (2015). As evident, convictions for drug offenses are the main cause of the sudden explosion in the prison population in recent history.

At a time when the earliest identifications of pathological morphologies of addicted brains were being made, the push to jail drug offenders gave rise to a sentiment that equated drug usage with criminal activity. Seminal studies in medicine and public health that went against the grain of dominating views by drawing ties between drug abuse, poverty, and failed school systems were ignored (Provine, 2007). Instead, the
major media outlets echoed and reinforced the criminalization of drug addicts (Alexander, 2012). As the movement gained traction, the government passed legislations that have made it more difficult for addicts to obtain treatment or help of any kind. The Anti-Drug Abuse Act of 1986 along with its amended version in 1988 included the elimination of several federal benefits – including healthcare – for drug-related criminals (Wright, 1987).

Despite its intent to curb the early surge in drug addiction, the “war on drugs” has had detrimental effects on society. As suggested by the current situation, the issue has grown in size since the drug epidemic no longer just plagues the inner city streets of urban, under-resourced areas, but nearly all factions of society. It has also shifted from being an issue primarily belonging to minorities to one that is colorblind (Figure 3). Further, as with all wars, the “war on drugs” was not without casualties: those who still remain behind bars and those who have died from having been barred from treatment and support. As society has opted to see drug addiction as a crime as opposed to a disease, what remains to be true is the fact there are thousands upon millions of addicts who are not receiving the care and treatment they require. While the 21st century has hinted at shifts in the attitude toward drug addiction, with the sprouting of treatment centers and the granting of presidential clemency for 46 mild-drug offenders, much remains to be done (Nelson & Tau, 2015).

Although a growing portion of American society no longer views drug addiction as previously understood, there is a good reason why residues of the former ideas still exists in the current fabric. As described by Longo et al. (2016):
“The concept of addiction as a disease of the brain challenges deeply ingrained values about self-determination and personal responsibility that frame drug use as a voluntary, hedonistic act. In this view, addiction results from the repetition of voluntary behaviors. How, then, can it be the result of a disease process? (p. 364)

Furthermore, those skeptical of the disease model have also argued that such thinking can act to excuse the addict and addict-potential from possessing any responsibility for actions and also lay grounds for justifying continuation and initiation of illicit drug use.

While these are reasonable counterarguments, the upcoming review of scientific literature will show that great advances have been made in elucidating the interruptions in the emotional balance and decision-making ability of addicts that have bolstered the brain disease model for addiction.

**Brain Disease Model for Addiction**

In an effort to organize the discussion on the disease model for addiction, this section will be laid out by looking at the phases of the addiction cycle: Binge and Intoxication, Withdrawal and Negative Affect, and Preoccupation and Anticipation. Using the different phases as a backbone, the correlative disruptions in the neural circuitries will be explored. However, before looking at the pathological implications of drug addiction on the brain, it is of interest to understand the actions of opiates on the brain and the steps stages that generally precede addiction – opioid tolerance, dependence, and withdrawal. For referencing purposes, a glossary of terms related to
opioid neurobiology, adapted from Kosten and George’s study (2002), has been included below (Table 2):

**Table 2. Definitions of Key Terms.** Adapted from (Kosten & George, 2002).

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine (DA)</td>
<td>A neurotransmitter present in brain regions that regulate movement, emotion, motivation, and the feeling of pleasure.</td>
</tr>
<tr>
<td>Gamma-aminobutyric acid (GABA)</td>
<td>A neurotransmitter in the brain whose primary function is to inhibit the firing of neurons.</td>
</tr>
<tr>
<td>Locus ceruleus (LC)</td>
<td>A region of the brain that receives and processes sensory signals from all areas of the body; involved in arousal and vigilance.</td>
</tr>
<tr>
<td>Noradrenaline (NA)</td>
<td>A neurotransmitter produced in the brain and peripheral nervous system; involved in arousal and regulation of blood pressure, sleep, and mood; also called norepinephrine.</td>
</tr>
<tr>
<td>Nucleus accumbens (NAc)</td>
<td>A structure in the forebrain that plays an important part in dopamine release and stimulant action; one of the brain’s key pleasure centers.</td>
</tr>
<tr>
<td>Prefrontal cortex (PFC)</td>
<td>The front-most part of the brain; involved in higher cognitive functions, including foresight and planning.</td>
</tr>
<tr>
<td>Ventral tegmental area (VTA)</td>
<td>The group of dopamine-containing neurons that make up a key part of the brain reward system; key targets of these neurons include the nucleus accumbens and the prefrontal cortex.</td>
</tr>
</tbody>
</table>

**Neurobiology of Opioid Use**

The euphoric episodes or the feelings of pleasure that are commonly associated with opioids are result of an opiate entering the brain through the bloodstream and binding to mu opioid receptors in the brain. The key neuro-circuitry involved in this process is called the mesolimbic reward system that is localized to the midbrain region (Figure 7). Specifically within the reward system is a region called the ventral tegmental area (VTA), in which the signals for the release of the neurotransmitter dopamine (DA),
into another compartment of the brain called the nucleus accumbens (NAc), originates (Kosten & George, 2002). It is the release of DA into the NAc that is actually responsible for the feelings of pleasure.

Figure 7. The Mesolimbic Reward System. VTA – Ventral Tegmental Area; NAc – Nucleus Accumbens; LC – Locus Cerelus: plays an important role in drug dependence; PFC – Prefrontal Cortex: feeds back to the VTA to control pleasure seeking that may be deleterious; Figure taken from (Kosten & George, 2002).

Even prior to developing an addiction, the early stages of opioid abuse, is marked by a drive for repeated use due to the stimulation of mesolimbic reward system and the subsequent sensations caused by dopamine release. However, gradually a compulsivity to seek opioid use – which transcends just a craving for the pleasure – develops, and a greater dosage of opioid is required to satiate the compulsion (Sinatra et al., 2011). This
phenomenon of needing greater doses of an opioid to reach the elated state is referred to as opioid tolerance. It occurs due to the mu receptors losing their responsiveness to the opiate ligand. The compensatory means by which the same level of dopamine release in the NAc can be achieved is by saturating the receptors with even higher concentrations of the opioid (Dean et al., 2009).

Opioid dependence, which is a state in which the body is physically reliant upon a hit of opioids to maintain baseline conditions, occurs due to alterations that are located in a region of the brain called the locus ceruleus (LC) (Strain & Stitzer, 2006; Figure 7; Figure 8). While other changes have been recorded to take place even in the mesolimbic reward system due to the reduced secretions of DA following opioid tolerance, such as the inability to experience pleasures from previously enjoyable activities, the primary site of modifications that lead to the onset of withdrawal symptoms is known to be localized to the LC. In the absence of opioids, a neurotransmitter called noradrenaline (NA) is produced by neurons of the LC. NA is a versatile compound that is active in various compartments of the brain and its downstream actions include, but are not limited to, stimulation of attentiveness, increasing respiration, and raising of the blood pressure (Kosten & George, 2002). However, in the presence of opioids, the mu receptors of the LC are bound, and consequently, NA is unreleased causing respiratory depression, tiredness, and a lowering of blood pressure. Interestingly, as occurs during the early phase of abuse, when the frequency of dosage of opioid use increases, the LC concordantly adapts by shifting to a more hyperactive gear; more NA is pumped. This adjustment allows for the brain to continue streaming NA in the face of opioid presence,
in effect, offsetting the suppressive effects which would ultimately be detrimental to the user. Therefore, a physical dependence is established; if opioids are not used, then the LC produces a surplus of NA that causes overstimulated responses including passing of looser stool, feelings of anxiety, and cramping of muscles, which are the commonly identified symptoms of opioid withdrawal (Wikler, 1980). Importantly, this means that for most drug users, the transition of opioid use into addiction is impelled by a need to mitigate undesirable withdrawal symptoms. While the impulse to use is not as strong earlier on, as dependence grows, the imminent addicted stage is framed by longer-lasting changes in the brain that shifts impulsive use of opioids to one that is driven from compulsion (Table 2). Currently, there exist two models that account for the neural changes that fuel the transition into addiction: (1) the “Changed Set Point Model” and (2) the “Cognitive Deficits Model.”
A. Prior to exposure to opioid drugs, baseline levels of NA are maintained through endogenous opioid compounds like endorphins. When such chemicals bind to the mu receptor, they cause a cascade which leads to the formation of a signaling compound called cyclic adenosine triphosphate (cAMP) that causes NA to be released. These normal levels of DA maintain important functions such as respiration and muscle tone.

B. When an exogenous opioid binds to the mu receptor, the enzyme that produces cAMP is inhibited, and consequently, NA levels decrease. Overdose-like symptoms arise.

C. As the frequency of opioid abuse increases, the neuron raises the amount of enzyme and ATP molecules, thereby generating more cAMP to compensate for the increased inhibition conferred by higher levels of exogenous opiates. This way the neuron can maintain roughly the same level of NA.

D. When the exogenous supply is stopped, the inhibition is lost and therefore even higher levels of NA are produced since the neuron had made offsetting adjustments. The effect of this is the onset of withdrawal symptoms.
The Changed Set Point Model for Transition into Addiction

There are three closely related variations of the “Changed Set Point” model, but all have in common the theme that prolonged opioid use shifts physiological set points in the brain, namely in the neurons of the mesolimbic reward system and the LC.

The first version is premised on the assumption that VTA neurons are innately preset to secrete an adequate amount of dopamine into the NAc in the face of regularly experienced pleasures, such as eating (Koob & LeMoal, 2001). Given the previously described effects of opioids in the VTA and the LC, repeated usage of these drugs is asserted to induce cycles of natural set point alterations in each region that in effect thwart the normal flux of DA in response to rewarding stimuli and excessively promote the release of NA. These inversely directed neuronal changes offer explanations for the phases of drug craving (negative reinforcement) and withdrawal seen in drug addiction.

The second variant, offered by the studies of Grace (2002), contends that the transition into addiction is driven largely by a set point change that occurs exclusively in the mesolimbic reward pathway. Specifically, the neurons of the VTA that release DA are rendered incapable of releasing normal amounts of DA under baseline conditions. Although there are several factors that regulate the concentration of DA secreted, as it pertains to this model, the two antagonistic components that go awry are the glutamate-releasing neurons – also known as the cortical excitatory neurons – which stimulate VTA neurons to secrete DA, and the autoreceptors that feedback inhibits the VTA neurons when there is an overabundance of DA in the NAc (Grace, 2002). In the same way that the LC adjusts to higher levels of opioids, as occurs during frequent opioid usage, the
study showed that autoreceptors purportedly become constitutively hyperactive upon incessant exposure to heroin and commonly used pain analgesics. As consequences of this new state of autoreceptor activity, in the absence of opioids, the new baseline levels of DA release by VTA neurons were recorded to be much lower and withdrawal symptoms ensued (Grace, 2002). In response, the addict compulsively takes more opioids to subdue or escape from withdrawal. And once more, when the pleasurable feelings whittle, the cycle re-begins.

Even in the absence of opioids, unlike the scenarios described in the previous two models, the mere craving for opioids can lead to changes in the biological set points. The third hypothesized model puts emphasis on the fact the brain is wired to recall the euphoric pleasantries associated with an opioid, and thus just the wanting or hunger for the drug can correspond to the surge of glutamate levels, which subsequently raises the baseline concentrations of DA in the NAc (Robinson & Berridge, 2000). This induces a vicious cycle because the usage of the drug, as explained earlier, also raises glutamate levels, which in effect also raises the activity of DA secreting neurons and thereby causes the craving feelings to recur even despite having already satiated the original hunger (Breiter et al., 1997). Thus, in this last version of the “Changed Set Point Model,” the frequent user of opioids is thrust into the addiction cycle through intrinsic changes that occur primarily in the elements that responds to anticipations and cravings, namely, the cortical excitatory neurons.
The Cognitive Deficits Model for Transition into Addiction

Unlike the “Changed Set Point Model,” the “Cognitive Deficits Model” points to derangements in a completely different region of the brain: the prefrontal cortex (PFC) (Figure 8). As is described in Table 2, the PFC has the overarching role of executive command. That is, the PFC controls humans’ abilities to judge and plan, which are cognitive abilities crucial for selecting choices that have long-term rewards in lieu of impulses for instant gratification, such as adverse drug use (Fuster, 2009). At the biological level, this occurs via inhibitory signals that are forwarded by the PFC to the neurons of the VTA, resulting in the attenuation of DA release (Kosten & George, 2002). In the transition from overuse of opioids to addiction, the PFC-mesolimbic reward system communication becomes distorted in such a way that the controls for judgment and decisions to forgo the impulses for drug usage are lost. This alteration has been verified even in the context of alcohol addiction, in which the levels of gamma-amino butyric acid (GABA) are pathologically low (Behar et al., 1999). GABA is a neurotransmitter that is secreted by the PFC to decrease secretion of DA in the VTA. Furthermore, studies have shown that in disorders associated strictly with PFC abnormalities, such as antisocial personality disorder, there is a higher propensity for developing opioid addiction (Raine et al., 2000).

Most likely, the gradual transition into addiction is caused by a combination of all of the aforementioned models and variants. In the shift from opioid abuse to opioid addiction, several changes involving multiple regions of the brain have been observed. And on top of these adjustments, during the addiction cycle even more components of
brain become defunct. Without proper intervention, what begins as transient changes will gradually transform into ones that become increasingly difficult to reverse.

The Addiction Cycle

It is generally understood that addiction is composed of three phases, namely the Binge and Intoxication Phase, the Withdrawal and Negative Affect Phase, and the Preoccupation and Anticipation Phase. Each part of the cycle is associated with the activation of a region of the brain as shown below with corresponding colors (Figure 9). Just as in the previous subsection, a list of terms and their definitions have been appropriately defined in Table 3 to fit the context of the following discussion.
Figure 9. Stages of the Addiction Cycle. Binge and intoxication phase (blue): when drug use occurs, the correspondingly colored regions – the reward systems – of the brain are activated. Preoccupation and anticipation (green): there is decreased inhibition by the PFC, which triggers the compulsive motivation for drug use; relapse occurs and the cycle is reinitiated. As can be seen above, there is a strong interplay between this region and the components shaded in green, which represent the areas that are areas that become sensitized to conditioned cues. Withdrawal and negative affect (red): when withdrawal occurs due to increased levels of NA, the regions in red are activated and negative mood and increased sensitivity to stress result. Figure taken from (Longo et al., 2016).
Table 3. Definitions. Adapted from (Koob & Volkow, 2010).

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addiction</td>
<td>Assumed to be identical to the syndrome of Substance Dependence (as currently defined by <em>Diagnostic and Statistical Manual of Mental Disorders</em>; American Psychiatric Association, 1994), and Substance Dependence on Alcohol is assumed to be identical to alcoholism. The term “addiction” is favored over dependence to avoid confusion with “physical dependence,” which refers to the physical adaptations that result in largely somatic withdrawal symptoms when drugs such as alcohol, heroin, and benzodiazepines are abruptly discontinued. The adaptations associated with physical drug withdrawal are distinct from the motivational changes of acute withdrawal and protracted abstinence.</td>
</tr>
<tr>
<td>Impulsivity</td>
<td>Defined behaviorally as ‘a predisposition toward rapid, unplanned reactions to internal and external stimuli without regard for the negative consequences of these reactions to themselves or others’ (Moeller et al., 2001). Impulsivity is often measured in two domains: the choice of a smaller, immediate reward over a larger, delayed reward (Rachlin &amp; Green, 1972) or the inability to inhibit behavior by changing the course of action or to stop a response once it is initiated (Logan et al., 1997). Impulsivity is a core deficit in substance abuse disorders (Allen et al., 1998).</td>
</tr>
<tr>
<td>Compulsivity</td>
<td>Defined as elements of behavior that result in perseveration in responding in the face of adverse consequences, perseveration in responding in the face of incorrect responses in choice situations, or persistent re-initiation of habitual acts (Everitt &amp; Robbins, 2005). The elements of compulsivity are represented in many of the symptoms outlined in the DSM-IV: continued substance use despite knowledge of having had a persistent or recurrent physical or psychological problem and a great deal of time spent in activities necessary to obtain the substance (American Psychiatric Association, 2000).</td>
</tr>
<tr>
<td>Positive Reinforcement</td>
<td>Defined as the process by which presentation of a stimulus, usually pleasant (e.g. the drug itself), increases the probability of a response.</td>
</tr>
<tr>
<td>Negative Reinforcement</td>
<td>Defined as the process by which removal of an aversive stimulus (e.g. the negative emotional state of drug withdrawal), increases the probability of a response (e.g. the dependence-induced drug intake).</td>
</tr>
<tr>
<td>Automaticity</td>
<td>Defined as behaviors that occur without conscious awareness of intentionality.</td>
</tr>
<tr>
<td>Motivation</td>
<td>Defined as a tendency of the whole animal to produce organized activity.</td>
</tr>
</tbody>
</table>
Binge and Intoxication

The Binge and Intoxication phase of addiction is marked by sharp increases in the release of dopamine in the reward regions of the brain upon usage of addictive drugs (Di Chiara, 2002; Wise, 2008). The increases in dopamine levels cause a reward signal which subsequently leads to what is called associative conditioning. Associative learning is when the mind makes linkages between the stimuli – drug usage in this context – and the reward experiences. Interestingly, it has been observed that with repeated exposures to an identical reward, dopamine cells become more responsive to anticipations for the reward than the reward itself (Schultz, 2002). These anticipatory urges, which are best understood as the cravings one has for a drug, can be induced by environmental stimuli such as the setting in which a drug was taken, the people who were present at the time of drug usage, and even the psychological state of the person at the time of use (Koob & Volkow, 2002). Unlike the drug abuse stage, in the addicted state, drug cravings can be induced by these stimuli even long after drug use has ceased, which is indicative of the depth to which the conditioned responses are ingrained.

At the molecular level, the physiological changes are driven by the exogenous opioid-induced secretion of DA. These changes, which are broadly termed drug-induced neuroplasticity, greatly impact the way in which communication occurs at the synapses between neurons and the susceptible reward systems of the brain (Kourrich et al., 2015). Further, it has also been shown that drug-induced neuroplasticity also affects learning and memory, which is important, when considering that the linkage between experience-
based learning activities, such as opiate use, can be bolstered by increased signal transmission between appropriate circuitries.

As is true between all synaptic junctions, the strength of signaling can be controlled by the density of functional receptors present on the postsynaptic cell. Also, in some cases such as for cortical stimulatory neurons, which are involved in activating dopaminergic neurons, compositional changes in the subunit of receptors can affect signaling by varying the affinity between the neurotransmitter glutamate and its respective receptor binding sites (Kauer & Malenka, 2007). Consistent with these facts are two receptors – AMPA and NMDA – that are involved in raising levels of DA in the NAc. In the animal model studies of Wolf and Ferrario (2010), it was observed that in addicted rats, the AMPA receptor had included into its structure a subunit highly permeable to calcium called GluR2. The effect of this inclusion was an enhancement in the long-term potentiation between neurons. In other words, the modified AMPA receptor conferred the release of more copious amounts of DA even in the presence of normal amounts of GABA, and furthermore, when an exogenous opioid stimulus was introduced even higher levels of DA could be achieved. Expectedly, this change enhances the intoxication experienced by the user. In addition to changes in synaptic signaling, other studies identified structural changes in neurons of addicted mice, specifically, remodeling in dendritic spines and shapes of postsynaptic neurons (De Roo, et al., 2008).

The ultimate impact of these molecular level changes – which mostly act to increase the amounts of DA released – is that in the addicted state, a strong association is positively reinforced between drug use and the motivational attribute that compels the
addict to want to use again. This learned association becomes so strong that for the seasoned addict the craving for opioid is more rewarding than the opioid itself (Schultz, 2002).

Withdrawal and Negative Affect

Of course there are compensatory mechanisms, such as the feedback inhibition loop between autoreceptors and VTA dopamine neurons that act to counter intoxication, ultimately inducing withdrawal symptoms, but clear abnormalities in this region have yet to be outlined. Where there have been notable changes in the neural circuitry is in the amygdala, an element of the basal forebrain that is responsible for emotions and survival instincts. As is distinct for the Withdrawal and Negative Affect phase of the Addiction Cycle, it was shown using an addicted mouse model that there were circuit disturbances in the bed nucleus stria terminalis (BNST) – a part of the extended amygdala – and the GABAergic projections that innervate postsynaptic VTA neurons that resulted from frequent exposures to elevated levels of DA secondary to opioid use (Jennings et al., 2013). Correspondingly, the results of these changes were that such mice were more prone to normalizing the adverse behaviors that induced the negative affect. Also, the mice expressing these phenotypes had a propensity to exhibit negative emotions and be more sensitive to stress (Jennings et al., 2013). Interestingly, a closer look revealed that the drivers of these downstream effects were neurotransmitters that are normally active during responses to stress: corticotropin-releasing factor and dynorphin. Just as the reward circuitry is hyperactive in the addict’s brain, so too is the “anti-reward” system.
Consequently, when the opioids are cleared from the mu receptors, the addict is pushed into withdrawal.

Another fascinating revelation conveyed by studies using mouse models have shown that drug consumption triggers significantly smaller increases in dopamine in the presence of addiction than in its absence (Zhang et al., 2013). Although the specific reason for this attenuated response cannot be traced, it is interesting to note that this restricted dopamine release has shown to be impartial to the type of reward, in that the addict’s brain becomes less sensitive to broad stimulation as a whole. It is for this reason that states of lull and lethargy often accompany addiction, especially in the absence of use. Because these changes are not superficially ingrained, the mere stoppage of opioid use, should it occur, does not reverse them. When considering the synergistic effects of the conditioned desire for reward along with the wanting to escape the dysphoria that ensues from not replenishing the addicted brain with opioids, it is of no surprise why an impulse to use evolves into a compulsion. In psychiatry parlance, this is referred to as negative reinforcement.

Preoccupation and Anticipation

The modifications that have been linked to the Preoccupation and Anticipation phase of addiction occur in the prefrontal cortex. As is the case in the reward system, the PFC regions of the brain also experience a decrease in DA signaling. Consequently, executive processes are severely, but not necessarily irreversibly, impaired (Goldstein & Volkow, 2011; Table 4).
Table 4. Processes Associated with the PFC that are Disrupted in Addiction.
Adapted from (Goldstein & Volkow, 2011).

<table>
<thead>
<tr>
<th>Process</th>
<th>Possible disruption in addiction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-control and behavioural monitoring: response inhibition, behavioural coordination, conflict and error prediction, detection and resolution</td>
<td>Impulsivity, compulsivity, risk taking and impaired self-monitoring (habitual, automatic, stimulus-driven and inflexible behavioural patterns)</td>
</tr>
<tr>
<td>Emotion regulation: cognitive and affective suppression of emotion</td>
<td>Enhanced stress reactivity and inability to suppress emotional intensity (for example, anxiety and negative affect)</td>
</tr>
<tr>
<td>Motivation: drive, initiative, persistence and effort towards the pursuit of goals</td>
<td>Enhanced motivation to procure drugs but decreased motivation for other goals, and compromised purposefulness and effort</td>
</tr>
<tr>
<td>Awareness and interoception: feeling one’s own bodily and subjective state, insight</td>
<td>Reduced satiety, ‘denial’ of illness or need for treatment, and externally oriented thinking</td>
</tr>
<tr>
<td>Attention and flexibility: set formation and maintenance versus set-shifting, and task switching</td>
<td>Attention bias towards drug-related stimuli and away from other stimuli and reinforcers, and inflexibility in goals to procure the drug</td>
</tr>
<tr>
<td>Working memory: short-term memory enabling the construction of representations and guidance of action</td>
<td>Formation of memory that is biased towards drug-related stimuli and away from alternatives</td>
</tr>
<tr>
<td>Learning and memory: stimulus–response associative learning, reversal learning, extinction, reward devaluation, latent inhibition (suppression of information) and long-term memory</td>
<td>Drug conditioning and disrupted ability to update the reward value of non-drug reinforcers</td>
</tr>
<tr>
<td>Decision making: valuation (coding reinforcers) versus choice, expected outcome, probability estimation, planning and goal formation</td>
<td>Drug-related anticipation, choice of immediate reward over delayed gratification, discounting of future consequences, and inaccurate predictions or action planning</td>
</tr>
<tr>
<td>Salience attribution: affective value appraisal, incentive salience and subjective utility (alternative outcomes)</td>
<td>Drugs and drug cues have a sensitized value, non-drug reinforcers are devalued and gradients are not perceived, and negative prediction error (actual experience worse than expected)</td>
</tr>
</tbody>
</table>

These changes are thought to occur due to similar kinds of drug induced neuroplasticity that is observed to be complicit in the Binge and Intoxication phase. It has been observed through the study by Britt and Bonci (2013) that a rewiring of the neurocircuitry takes place primarily in the mesolimbic reward circuits as well as in the PFC. Specifically, the drug induced synaptic modifications have been observed in glutamate signaling (Britt & Bonci, 2013). The abnormal dopamine and glutamate signaling
pathways in the PFC have been traced to certain behaviors such as the failure to resist urges and also a seeming impossibility to remain abstinent. Even though the negative consequences are well understood, the addict is in the harrowing position of following through on compulsions with automaticity despite sincere desires to abstain from using the drugs. When the addict succumbs yet again to the cravings, she is once again at the start of the seemingly endless cycle.

Aside from the painstakingly clear indications of disease, what is deeply implied by this paradigm for addiction is that there exist great potential for treatment, and if not that, then ways mitigate the harm caused by opiates. In the following section, the various interventions that have been made available today will be explored, followed by an evaluation of the impacts select interventions have had on the opioid epidemic.
SPECIFIC AIMS

The Specific Aims of this work include:

1. Comprehensive review of literature to highlight the interventions – that treat or do not treat drug addiction as a disease – being employed to address the opioid epidemic.

2. Evaluate the interventions by looking at patient-based clinical trials and meta-analyses.

3. Conclusion on the validity of brain disease model for addiction
INTERVENTIONS TO CURB THE OPIOID EPIDEMIC

Certain implications about the attitudes that rule society’s contemporary view of addiction can be inferred by the mere task of this thesis to validate the brain disease model for addiction. Even in the face of overwhelming amounts of knowledge that have been gained over the last few decades through research that has medicalized addiction, there still lacks a general consensus about how to treat the issue. Consequently, the drug issue has been addressed with a broad range of solutions, each based on its own theory about addiction, and each with its own degree of success. Although it would be of great interest to inspect and juxtapose all the interventions put forth to address the opioid epidemic, only a select few have been chosen based on the availability of data that can be used to gauge its impact. For heuristic purposes, the discussion will begin by looking at interventions that treat drug addiction as a disease followed by one that does not. After this review, the next section will aim at assessing the aspects of each initiative that have been successful at curbing the current epidemic by evaluating their impact.

Medication-Assisted Therapies for Opioid Addiction

Medication Assisted Therapies (MATs) is a collective term used to refer to the three pharmacotherapies currently approved by the Food and Drug Administration (FDA) (Table 5). The medications included in this list are: (1) methadone, (2) buprenorphine, and (3) naltrexone. Generally speaking, these drugs are utilized to either mitigate the effects induced by opioids or simply prevent them. What all three therapies have in common is their mode of action: through the binding of mu opioid receptors, to which the
opioids themselves attach. However, what causes the different responses to their binding is the way in which each compound stimulates the receptor. As will be shown in the following sections, these nuanced differences are what confer MATs their effectiveness in treating the eclectic symptoms of opioid addiction.

Table 5. Characteristics of Medications for Opioid-Addiction Treatment. Taken from (Volkow et al., 2014).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Methadone</th>
<th>Buprenorphine</th>
<th>Naltrexone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brand names</td>
<td>Dolphine, Methadone</td>
<td>Subutex, Suboxone, Zubsol</td>
<td>Depade, ReVia, Vivitol</td>
</tr>
<tr>
<td>Class</td>
<td>Agonist (fully activates opioid receptors)</td>
<td>Partial agonist (activates opioid receptors but produces a diminished response even with full occupancy)</td>
<td>Antagonist (blocks the opioid receptors and interferes with the rewarding and analgesic effects of opioids)</td>
</tr>
<tr>
<td>Use and effects</td>
<td>Taken once per day orally to reduce opioid cravings and withdrawal symptoms</td>
<td>Taken orally or sublingually (usually once a day) to relieve opioid cravings and withdrawal symptoms</td>
<td>Taken orally or by injection to diminish the reinforcing effects of opioids (potentially extinguishing the association between conditioned stimuli and opioid use)</td>
</tr>
<tr>
<td>Advantages</td>
<td>High strength and efficacy as long as oral dosing (which slows brain uptake and reduces euphoria) is adhered to; excellent option for patients who have no response to other medications</td>
<td>Eligible to be prescribed by certified physicians, which eliminates the need to visit specialized treatment clinics and thus widens availability</td>
<td>Not addictive or sedating and does not result in physical dependence; a recently approved depot injection formulation, Vivitol, eliminates need for daily dosing</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Mostly available through approved outpatient treatment programs, which patients must visit daily</td>
<td>Subutex has measurable abuse liability; Suboxone diminishes this risk by including naltrexone, an antagonist that induces withdrawal if the drug is injected</td>
<td>Poor patient compliance (but Vivitol should improve compliance); initiation requires attaining prolonged (e.g., 7-day) abstinence, during which withdrawal, relapse, and early dropout may occur</td>
</tr>
</tbody>
</table>

**Methadone**

Of the three approved treatments for opioid addiction, methadone has been utilized for the longest period of time. When it was first synthesized by German chemists in the late 1930s, it was described to induce the same subjective effects as morphine, including its ability to induce euphoria like most opioids (Freedman & Senay, 1973). This is because the active form of methadone is an opioid. However, unlike most
addictive opiates like heroin or pain analgesics such as oxycodone, it is long-acting. What this means is that, whereas commonly abused opiates are active for up to several hours, methadone lingers in the body for up to days (Kosten & George, 2012). Thus, methadone has great potential for being highly effective in lowering relapse rates for addicts since it can remain on the mu opioid receptor for longer periods of time. The increased duration of binding to the mu receptor also decreases the likeliness that drug craves and compulsive uses occur. Further, as observed in the seminal studies of Dole et al. (1966), it was shown that methadone also acted much like a buffer, such that even when heroin was used after the administration of methadone, the user did not experience the high normally associated with its use (Figure 10).

Figure 10. The Buffering Effect of Methadone on Heroin Use. When a patient was administered regularly occurring doses of methadone, the addict was stabilized in the zone of “normal function.” Even with the concomitant use of heroin – indicated by the H on the plot above – methadone imposed a buffer-like effect on the user’s functional state Figure taken from (Dole et al., 1966).
In brain imaging studies that looked at the effect of methadone on opioid receptor binding, it was seen that regional variations were observed in a few areas of the brain like the amygdala (Kling et al., 2000). These changes were observed with positron emission tomography (PET) by looking at the ability of $[^{18}\text{F}]$cyclofoxy, an opioid antagonist for the mu opioid receptor, to link to the receptors in various regions of the brain. The results of this experiment are shown in Table 6 and Figure 11. As a whole, what is indicated by the data is that the specific binding of $[^{18}\text{F}]$cyclofoxy was approximately 19 to 32% lower for methadone-treat patients than those who were not (Kling et al., 2000). Specifically, in select regions that are often altered in opioid addiction, such as the amygdala, the difference was more pronounced. The lower binding of $[^{18}\text{F}]$cyclofoxy in treated patients reflects the steady state binding nature of methadone. This explains then why methadone is observed to reverse the hormone-related modifications opioids make by binding to mu receptors that are involved in stress circuits. In fact, it was subsequently shown in a study reported by Schluger et al. (2001) that methadone could be modulating the cortisol-driven stress response.
Table 6. Total and Specific [18F]cyclofox Binding in Different Brain Regions. Table taken from (Kling et al., 2000).

<table>
<thead>
<tr>
<th></th>
<th>Total [18F]cyclofox Bindinga</th>
<th>Specific [18F]cyclofox Bindinga</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ml plasma / ml tissue</td>
<td>ml plasma / ml tissue</td>
</tr>
<tr>
<td>Normal Volunteers</td>
<td>Methadone-Treated Patients</td>
<td></td>
</tr>
<tr>
<td>Thalamus</td>
<td>20.7 ± 2.5</td>
<td>15.7 ± 2.0</td>
</tr>
<tr>
<td>Amygdala</td>
<td>17.8 ± 3.6</td>
<td>14.6 ± 3.5</td>
</tr>
<tr>
<td>Caudate</td>
<td>17.1 ± 2.7</td>
<td>14.1 ± 2.4</td>
</tr>
<tr>
<td>Insula</td>
<td>16.4 ± 2.1</td>
<td>12.9 ± 2.5</td>
</tr>
<tr>
<td>Anterior cingulate cortex</td>
<td>16.3 ± 1.9</td>
<td>13.0 ± 2.2</td>
</tr>
<tr>
<td>Putamen</td>
<td>16.2 ± 2.5</td>
<td>13.9 ± 2.5</td>
</tr>
<tr>
<td>Middle temporal cortex</td>
<td>14.4 ± 1.7</td>
<td>11.5 ± 1.7</td>
</tr>
<tr>
<td>Middle frontal cortex</td>
<td>13.7 ± 1.5</td>
<td>11.0 ± 1.7</td>
</tr>
<tr>
<td>Prefrontal cortex</td>
<td>12.6 ± 1.5</td>
<td>10.4 ± 1.7</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>11.5 ± 1.4</td>
<td>9.7 ± 1.1</td>
</tr>
<tr>
<td>Inferior temporal cortex</td>
<td>11.5 ± 1.8</td>
<td>9.6 ± 1.5</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>10.9 ± 1.7</td>
<td>9.1 ± 1.5</td>
</tr>
<tr>
<td>White matter</td>
<td>7.3 ± 0.7</td>
<td>6.4 ± 1.0a</td>
</tr>
<tr>
<td>Occipital cortex</td>
<td>6.4 ± 0.6</td>
<td>6.1 ± 0.7</td>
</tr>
</tbody>
</table>

a Values are mean ± S.D.

b n = 13.

Figure 11. Specific Binding of [18F]cyclofox in Various Brain Regions of Patients that Did or Did Not Receive Methadone Treatment. Figure taken from (Kling et al. 2000).
Given that methadone is itself an opioid, it can also cause dependence. As such, it is currently labeled as a schedule II controlled substance, and can only be administered in controlled clinical settings by specially licensed physicians. Further, as states have control over which clinics can offer methadone, there exist geographical barriers to its access (Figure 15). These regulations, while necessary, have served as impediments to opioid-dependent addicts requiring the drug for treatment and also the healthcare personnel providing the treatment. Because it is not the case that all addicted patients have the means by which to regularly visit clinics to receive treatment, the out-patient compliance rate in rural areas has been unimpressive (Fudala et al., 1990). In response to these barriers to access, a modified, longer-acting version of methadone called levo-alpha-acetylmethadol (LAAM) was introduced at the end of the 1990’s. However, it was quickly discontinued in 2003 when its usage resulted in heart problems, such as ventricular rhythm disorders (Johnson et al., 2000).

Buprenorphine

Buprenorphine, unlike methadone, is not a full agonist of the mu opioid receptor. Instead, it is what is called a partial agonist: a ligand that binds and activates a receptor, but only elicits are diminished response even at full occupancy. Interestingly, however, this property yields buprenorphine a duality of functions that manifest at varying doses. When present at low concentrations, the drug acts like methadone, and when present at high concentrations it can act like an antagonist (Kosten & George, 2012). This
phenomenon is called the “ceiling effect” and it is hypothesized to occur due to the presence of another sub-type of receptors called opioid-like receptors, also known as ORL1 (Ducharme et al., 2012; Walsh et al., 1994; Figure 12). Whereas buprenorphine can bind mu opioid receptors as an agonist, its actions by attaching to the ORL1 receptor are thought to be antagonistic. This latter behavior is especially evident through its mitigating effects when the drug is concomitantly administered with other opioids like morphine (Ducharme et al., 2012).

![Figure 12. The Ceiling Effect of Buprenorphine](image)

Although buprenorphine is characterized by low activity, due to its high specificity and binding affinity for mu opioid receptors, it is more effective than
methadone at causing withdrawal in addicts that are dependent on opioids. It has been reported in the study by Schuh et al. (1999) that the active form of the partial agonist, norbuprenorphine, can remain bound to mu receptors up to five days. Furthermore, the low intrinsic activity of the medication confers a normalizing, as opposed to an intoxicating, effect on opioid addict patients who are administered the drug during the withdrawal phase (Blom et al., 1987). Still, however, there are some side effects that accompany buprenorphine; these include: nausea, constipation and sedation. Despite these unfavorable reactions, when weighed against other therapies that possess greater intrinsic activity, buprenorphine is considered to be safer since it does not induce respiratory depression, even at high doses. In fact, a population cross-sectional study that juxtaposed the safeties of buprenorphine and methadone use reported that mortality was more greatly associated with the latter than the former (Connock et al., 2007).

Notwithstanding this fact, buprenorphine can still be abused. When users of buprenorphine, especially those with non-medical intentions, are misinformed about the drug, the drug is taken at very high doses along with other opioids that may provide the euphoria generally expected from taking opiates. When taken with benzodiazepines or alcohol, buprenorphine is capable of causing respiratory depression followed by inducing states of sedation, comatose, and even death (Mégrbane et al., 2006). Further, intravenous misuse – which is possible since buprenorphine used to be provided as a tablet – is reported to also take place. Although there was no implicit danger from this kind of misuse given the drug’s milder effects, the needle delivery method imposed the risks of
transmitting various infectious diseases like hepatitis C and HIV (Whelan & Remski, 2012).

In response to potential abuse, today, buprenorphine is co-administered with another substance called naloxone. Naloxone is an opioid receptor antagonist that prevents the binding of opioids to mu receptors. The two drugs have been combined – four parts buprenorphine to one part naloxone – to form a pill that is referred to as suboxone. Suboxone is designed for sublingual delivery, but given naloxone’s poor bioavailability in the oral tract due to its higher hydrophilicity, the effects of buprenorphine shadow those of naloxone (Chiang & Hawks, 2003; Figure 13).

![Figure 13. Time Course of Plasma Levels of Buprenorphine and Naloxone after Administration of Sublingual Suboxone. Figure taken from (Chiang & Hawks, 2003).](image-url)
Still, suboxone has proven to be quite effective, if not more effective than buprenorphine alone given its even lower abuse potential. Even when suboxone was subjected to diversion, via intravenous or subcutaneous uses, the major event that ensued was withdrawal among opioid dependent addicts (Whelan & Remski, 2012). Unlike methadone, buprenorphine can be prescribed by physicians to addicts. Thus, there are less restrictions to access that may stand in the way of adherence.

Naltrexone

Whereas both methadone and buprenorphine are utilized as maintenance therapies for opioid dependent addicts, naltrexone is usually administered at the conclusion of the detoxification therapy in the absence of therapies including those mentioned above. While its specific mode of action, like those of methadone and buprenorphine, is to bind mu receptors, it does not propagate the signals for reward upon linkage. This is because naltrexone is singularly an antagonist for the mu opioid receptor. In other words, the action of this compound is to block and prevent the firing of the dopaminergic reward systems that occurs when opioid receptor agonists bind. When administered, naltrexone is a powerful drug for thwarting relapse because it is capable of clinging onto mu receptors with approximately more than 100 times the affinity of most addictive opioids (Kosten & Kleber, 1984). Along with its impressive pharmacokinetics comes a list of potent side effects such as abdominal pain and severe dysphoria (Crowley et al., 1985).

In spite of these unpleasant side effects, Petrakis et al. (2007) reported that patients who have successfully completed 12-week naloxone treatment courses indicated
improved depressive symptoms. Although these results have the implications that naltrexone, like methadone, may also be activating receptors in the amygdala, neither biochemical pathways nor modes of actions have yet been elucidated.

The greatest challenge associated with naltrexone administration, especially in the oral form, is compliance (Sullivan et al., 2006; Figure 14). Approximately one-third of patients enrolled in naltrexone treatment regimen stop taking the drug after a mere two weeks, and the dropout rate at the eight month mark lingers around 90% (Judd et al., 1980). Because this medication does not provide the “high” addicts seek, there is little incentive for poorly motivated addicts to continue its usage. The consequence of this is a very high likelihood of opioid-overdose mortality due to a relapse accompanied by high dosed abuse.

![Figure 14. Oral Naltrexone Refills, 2000-2002.](image)

In response to this predicament, an extended-release intramuscular version of naltrexone called Vivitrol or XR-NTX was released in 2010. Compared to the daily intake required by the previous tablet version of naltrexone, the longer-acting injectable
drug only needs to be administered once every four weeks at a dosage of 380 mg (Harrison et al., 2006).

**Abstinence-Based Treatment for Opioid Addiction**

If there could exist an antagonist to the aforementioned therapies, it would be the concept of abstinence-based therapy for drug addiction, a model for treatment that does not condone the use of medication, but instead a following of a strict sets of rules. Although many versions of abstinence-based treatments have sprung up since the idea was first conceived – and largely endorsed as the standard for addiction recovery – in the 1930s, they all have been adaptations of what have famously become known as the “12 Step Recovery Program” (Flanagin, 2014). For reference, the 12 Steps from Narcotics Anonymous have been listed in Table 7 below.

**Table 7. 12 Concepts for Narcotics Anonymous Service.** Adapted from (Narcotics Anonymous, 1991).

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>To fulfill our fellowship’s primary purpose, the Narcotics Anonymous groups have joined together to create a structure which develops, coordinates, and maintains services on behalf of Narcotics Anonymous as a whole.</td>
</tr>
<tr>
<td>2.</td>
<td>The final responsibility and authority for Narcotics Anonymous services rests with the Narcotics Anonymous groups.</td>
</tr>
<tr>
<td>3.</td>
<td>The Narcotics Anonymous groups delegate to the service structure the authority necessary to fulfill the responsibilities assigned to it.</td>
</tr>
<tr>
<td>4.</td>
<td>Effective leadership is highly valued in Narcotics Anonymous. Leadership qualities should be carefully considered when selecting trusted servants.</td>
</tr>
<tr>
<td>5.</td>
<td>For each responsibility assigned to the service structure, a single point of decision and accountability should be clearly defined.</td>
</tr>
<tr>
<td>6.</td>
<td>Group conscience is the spiritual means by which we invite a loving God to influence our decisions.</td>
</tr>
<tr>
<td>7.</td>
<td>All members of a service body bear substantial responsibility for that body’s</td>
</tr>
</tbody>
</table>
decisions and should be allowed to fully participate in its decision-making processes.

8. Our service structure depends on the integrity and effectiveness of our communications.

9. All elements of our service structure have the responsibility to carefully consider all viewpoints in their decision-making processes.

10. Any member of a service body can petition that body for the redress of a personal grievance, without fear of reprisal.

11. Narcotics Anonymous funds are to be used to further our primary purpose, and must be managed responsibly.

12. In keeping with the spiritual nature Narcotics Anonymous, our structure should always be one of service, never of government.

12 Step Recovery Program

Today, the twelve step program is one of the cornerstones of addiction recovery. Widely integrated into the curricula of various self-help groups, such as Alcoholics Anonymous and Narcotics Anonymous, it has been reported that approximately 9% of American adult population have participated in such therapies (Moos & Timko, 2008). In the course of attending such programs, members participate in activities that include service work, readings of twelve-steps-embODYing texts, practice of integrating the steps into daily life, the partnering up with sponsors, and the training to become a sponsor. While there are variations in the day-to-day occurrences within treatment centers, the central means by which sobriety is attained is through the application of the 12 rules and partaking in personal conversations with other members who have also suffered with addiction. It is hoped that through this sort of connection with other sufferers and mentoring from sponsors that recovery, or complete abstinence, is achieved. In this
approach, what is implied is that it is the addict who ultimately possesses the will to step away from addiction.
EVALUATION OF THE INTERVENTIONS

If there was a litmus test to measure the degree of support for abstinence-based programs in the United States, it would look like a map that is singly colored. The test would be redundant given the overabundance of such programs today; there were 57,905 registered groups in 2011 (Magura et al., 2013). However, the same test to get a sense of the states’ position on medication assisted treatment, and by extension the brain disease model for addiction, would be far more colorful, as indicated by Figure 15.

Figure 15. States that Provides Medicaid Coverage for Methadone, Buprenorphine, and Naloxone. Figure taken from (Rinaldo & Rinaldo, 2013).
In this section the efficacies of the various interventions reviewed in the previous section will be gauged by presenting the results of studies that evaluated the on addicted patients. Because each intervention is not aimed at the same specific issues within the larger problem, there is no single metric that will be used to establish causal relationships between interventions and the status of the current epidemic.

**Evaluation of Medication Assisted Therapy as Treatment for Drug Addiction**

On the whole, there is a plethora of scientific evidence that suggests that MATs have been immensely successful in treating opioid addiction. For the purpose of evaluating their success the different MATs will be assessed using the following metrics: (1) degree by which abstinence of drug was achieved, (2) efficacy in reducing opioid use, and (3) efficacy in retaining addicts in treatment.

*Rates of Abstinence Achievement*

Whether by means of maintenance therapy using methadone or buprenorphine or relapse-prevention with extended-release naltrexone, addicts who are enrolled in such regimen are shown to double their likelihood of achieving abstinence (Fudala et al., 2003; Kruptisky et al., 2011).

*Methadone*

For methadone, it is often noted in clinical studies that the efficacies for achieving abstinence is the highest among all agonist based maintenance treatments (Connery,
2015). It is for this reason that it still serves as the gold standard against which new therapies are held. In the seminal 11-year study that assessed the impact of methadone maintenance therapy on abstinence rates, it was reported that of the 161 patients enrolled in the treatment regimen, 51 former addicts – about 23% - were completely abstinent at the third year post-treatment (Cushman, 1978). More contemporary measurements of abstinence, using surrogate quantifications through opioid positive urine analysis, show that levels of abstinence levels have remained at similar levels (Johnson et al., 2000; Table 8).

Table 8. Outcome Measures of LAAM, Buprenorphine, and Methadone Based Maintenance Programs. Taken from (Johnson et al., 2000).

<table>
<thead>
<tr>
<th>MEASURE*</th>
<th>LEVOMETHADYL ACETATE (N=55)</th>
<th>BUPRENORPHINE (N=55)</th>
<th>HIGH-DOSE METHADONE (N=55)</th>
<th>LOW-DOSE METHADONE (N=55)</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Study retention (days)</td>
<td>Mean ±SE</td>
<td>89±6</td>
<td>96±4</td>
<td>105±4</td>
<td>70±4</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>78–100</td>
<td>88–105</td>
<td>98–112</td>
<td>62–79</td>
</tr>
<tr>
<td></td>
<td>Mean ±SE †</td>
<td>52±4</td>
<td>62±4</td>
<td>62±4</td>
<td>79±5</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>44–60</td>
<td>55–70</td>
<td>54–69</td>
<td>70–88</td>
</tr>
<tr>
<td></td>
<td>Self-reported opioid use (no. of times/wk)</td>
<td>Mean ±SE ‡</td>
<td>4±1</td>
<td>4±1</td>
<td>4±1</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>3–6</td>
<td>3–5</td>
<td>3–6</td>
<td>4–8</td>
</tr>
<tr>
<td></td>
<td>≥12 Consecutive opioid-negative urinalyses (% of patients)</td>
<td>Mean ±SE †</td>
<td>35±4</td>
<td>34±4</td>
<td>38±4</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>28–43</td>
<td>27–42</td>
<td>20–45</td>
<td>45–60</td>
</tr>
<tr>
<td></td>
<td>Patient’s rating of severity of drug problem</td>
<td>Mean ±SE ‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary outcome</td>
<td>≥12 Consecutive cocaine-negative urinalyses (% of patients)</td>
<td>Mean ±SE †</td>
<td>36</td>
<td>30</td>
<td>38</td>
</tr>
</tbody>
</table>

In the study it was shown that lower dose methadone treatments exhibited higher levels of opioid-positive urinalysis, 79% (p=0.005; 95% CI), than high-dosage
methadone, 62% (p=0.005; 95%), suggesting a concentration-dependent efficacy of methadone in thwarting relapse (Johnson et al., 2000). A more telling indicator of efficacy is portrayed by the primary and secondary outcome measures; high-dose methadone and buprenorphine display an increasing trend in continuous abstinence, increases of 28% to 38% and 26% to 30% of the patient pools, respectively. Although the levels of abstinence conferred by methadone treatments seem fairly low, it is important to consider that even 30% abstinent rates is correlated to prevent expenditures of billions of dollars and spare tens of thousands of lives (Jackson et al., 2015).

**Buprenorphine**

Because there are few prospective cohort studies that have been conducted to directly measure rates of abstinence following treatment, another metric used to gauge the degree of abstinence, which generally correlates well with abstinence rates is the change in craving for drugs over the course of treatment (Figure 17; Table 9). In the double-blind trials conducted by Fudala et al. (2003), in which 323 participants were given either subutex (just buprenorphine) or suboxone (buprenorphine and naloxone), it was shown that both treatment regimen produced earlier and more pronounced decreases in the craving when compared to placebo (Figure 16).
Interestingly, the data indicated that significant group-by-week interactions (p<0.001), which indicate that the impact of treatment varied with time, were present. Given the trend in drug craving over the course of four weeks, this means that the effect of the partial agonists was greatest at the start of treatment and gradually waned. Despite the tapering effect, the decrease in opioid craving remained non-negligible until the completion of the trial. This finding in combination with the urinalysis results for buprenorphine shown in Table 8 suggest that it may be this decaying effectiveness of suboxone and subutex which lead to a more moderate increasing trend in abstinence when compared to methadone.
Naltrexone

Extended-release naltrexone, also known as vivitrol or XR-NTX, yields similar results. In a 24-week double-blind, placebo-controlled, multicenter randomized trial involving 250 patients who had histories of opiate addiction, it was shown that XR-NTX administration had a significant impact on abstinence rates (Krupitsky et al., 2011; Table 9). Abstinence was indicated in two ways: (1) through a self-reported timeline follow-back (TLFB) survey and (2) and through the collection of negative urine drug tests. Abstinence was also implicated, as was done for buprenorphine studies, through changes in reported cravings for opiates during the course of the treatment period (Figure 17).

Table 9. Clinical Outcomes of XR-NTX. The primary endpoint was marked to be the end of the 24 weeks of treatment. Taken from (Krupitsky et al., 2011).
According to responses of TLFB surveys, there was a clearly larger proportion of participants in the extended-release naltrexone group who remained abstinent, 99.2% (p=0.0004), than in those in the placebo group. Although urine analysis findings digress slightly from the purported self-reported abstinence levels, nonetheless, at the conclusion of 24 weeks of treatment, the percent of weeks that were remained abstinent was measured at 90.0% (p=0.0002). In comparison to the placebo group, this indicates that XR-NTX treatment had a 55% improvement factor in terms of abstinence (Krupitsky et al, 2011). In accordance to expected correlations between abstinence and cravings, statistically significant (p=0.0004) reductions in cravings were observed. In a double-
blind study conducted by Comer et al. (2008), similar results correlating Vivitrol use to improved rates of abstinence were recorded.

Oral naltrexone, an earlier version of Vivitrol that is required to be taken once a day given its shorter lasting effects, does not convey similar trends of abstinence. This is purported to be because of the difficulty in achieving high levels of adherence to regimens based on this drug. The reason for this low compliance, as explained in the previous section, is due to it being an antagonist that does not satiate pleasure seeking motivation.

Rates of Opioid Use

Methadone

In the meta-analysis of several clinical trials conducted by Farré et al. (2002), the efficacy of methadone maintenance treatments on the rates of opioid use – the dependent variable – was quantified by looking at the odd ratios using a logistic regression. The analyses were computed for various comparisons including methadone versus placebo and methadone versus buprenorphine. For the former, even the effect of methadone dosage was assessed; the results are presented in forest plot below (Figure 18).
The results depicted in Figure 18 indicate that high doses of methadone, which was defined by the study as greater than or equal to 50 mg/day, were far more efficacious than lower doses in lowering opioid use: odds ratio – 1.72 (95% CI; p=0.0007). Further, compared to placebo, the higher dosages also proved to be better at decreasing abuse rates: odds ratio – 2.44 (95% CI; p=0.0033). Consistent, with most other comparisons between methadone and buprenorphine, it was also concluded that maintenance treatments involving the former were far more successful in this regard than those utilizing the latter.
**Buprenorphine**

In order to detect reduction in the use of opioid while being administered buprenorphine, Fudala et al. (2013) conducted a longer open-label study after the double-blind trials previously discussed. While all the original participants were summoned and randomly assigned to subutex and suboxone treatment groups, as was done in the double-blind studies, this time, treatment courses were extended to between eight weeks to one year. Concurrent opioid use was measured through random urine sampling that occurred twice a month (Fudula et al., 2013). As depicted in **Figure 19**, the overall rate of opioid use decreased over the course of a year for those on suboxone. Although corresponding data for subutex was absent in the report, it is stated that similar trends were observed. Further, compared to drug-in-urine analyses that were conducted during the double-blind experiments – which were not included in this report – the rate of opioid use in the open-label studies was significantly lower.
As might be expected, there seems to be time-dependent factor in predicting success of buprenorphine-based maintenance treatments: the longer patients are administered suboxone or subutex, the higher the likelihood they will cease concomitant usage of other opioids. Another outstanding finding is conveyed by the data presented in Figure 18. Just as was true for methadone, there seems to be also be an inverted correlation between concentration of buprenorphine and opioid abuse probability, as indicated by the odds ratio from the comparison of high buprenorphine and high methadone: odds ratio – 1.08 (95% CI; p=0.68) (Farré et al., 2002).
**Naltrexone**

At the conclusion of 24-weeks of extended-release naltrexone treatment, it was indicated through urinalysis that number of opioid-free weeks was substantially higher in the XR-NTX groups than those receiving either placebo or no treatment (p=0.0002) (Krupitsky et al., 2011; **Table 9**). Of 126 patients in the XR-NTX group, 119 participants, or approximately 94%, were determined to be opioid free at end conclusion of two weeks. At the same time point, the placebo group showed that 96 members out of 124, or 77%, were drug free. This gap between the two groups was more or less consistent through the remainder of the trial (Krupitsky et al., **Figure 20**). A waning effect, similar to the one associated with abstinence achieve rates, of the MATs ability to thwart opioid is visible. Nonetheless, it appears that relative effective of MATs to reduce opioid use is greater.

![Figure 20. Proportion of Opioid-Free Participants in XR-NTX Treatment vs. Placebo. Figure taken from (Krupitsky et al., 2011).](image-url)
Retention in Treatment

While the absolute time of retention varies from study to study, and thus may be of little value, when the values are juxtaposed to retention rates as they relate to placebo and other treatments much can be gleaned about the effectiveness of the therapies.

Methadone

It was shown that when compared to buprenorphine maintenance treatment, methadone based treatments generally enjoyed greater periods of retention, lasting approximately 271 days on average, or roughly 231 more days than buprenorphine based regimens (Bell et al., 2009). In the meta-analysis conducted by Mattick, et al. (2014), it was shown that this trend held even for different dose combinations of methadone and buprenorphine (Table 10).
Table 10. Forest Plot of Comparison: Flexible Dose Buprenorphine vs. Flexible Dose Methadone; Retention in Treatment. MMT = methadone maintenance treatment; BMT = buprenorphine maintenance treatment. Taken from (Mattick et al., 2014).

Furthermore, the results in the table above also indicate that in both double blind and open label studies, the same trend was observed: the rates of retention was found to be lower with relative risk values of 0.83 (95% CI) and 0.80 (95% CI), respectively. The reason for retention, which correlates well with the data for these drugs in reducing rates of opioid use, may be conferred by the greater intrinsic activity associated with methadone. In other words, since methadone is a far more potent agonist that provides the similar states of euphoria addicts crave, compliance to regimen tends to be higher.
**Buprenorphine**

Although the Fudala et al. report (2003) on the efficacies of buprenorphine did not intend to gauge retention in their treatment regimen, in both open-label and double-blind trial studies it was shown that retention was greater than 82% and 74%, respectively. Surprisingly, these figures even reflect patients whose participation was suspended due to adverse reactions to prolonged suboxone and subutex treatment. A systematic review of 55 studies of buprenorphine-naloxone therapies that occurred between 2010 and 2014 has also reached conclusions that echo the findings of previous studies: compared to placebo, suboxone-based treatments yielded substantially higher retention rates at time points ranging from three months to up to 12 months (Timko et al., 2016).

**Naltrexone**

In regards to retention rates for extended-release naltrexone, the double-blind studies by Krupitsky et al. (2011) reported that the median measure of retention equated to 168 days for XR-NTX group and 96 days for the placebo group (p = 0.0042). The improvement factor attributed by XR-NTX is roughly doubled. Similarly, the works of Comer et al. (2008) corroborate the results of these observations by showing robust increases in retention rates for patients put on vivitrol-based regimen as opposed to non-medication based therapies. Interestingly, it was determined that there exists a dose dependent correlation between patients retained in the treatment and adherence as measured by time (Comer et al., 2008; **Figure 21**). This has important implications for determining proper dosages to administer for maximal benefits.
Evaluation of Abstinence-based Therapy for Drug Addiction

To date, there are not a lot of studies that have been conducted to assess the impact of abstinence-based therapies such as the 12-step program, and even less so for those that specifically deal with opioid abuse. Of the ones that have been published in reputable sources, an overwhelming majority deal with alcohol addiction. Although alcohol addiction and opiate addiction are by no means the same disease, they have been cited to trace similar courses (Degenhardt et al., 2002). Hence, by heeding the recommendation from the works of Moos & Timko (2008), the following evaluation will explore studies that have challenged the efficacies of abstinence-based treatment in the
context of alcoholism. To make for apt comparisons with the medication-based
treatments, the 12 Step Programs will also be assessed using the following metrics: (1)
degree by which abstinence of drug was achieved, (2) efficacy in reducing opioid use,
and (3) efficacy in retaining addicts in treatment.

*Rates of Abstinence Achieved*

Despite the dearth of studies that appear in scientific literature, it is often
purported that addicts who partake in twelve-step-based therapies for long durations
enjoy better drug use outcomes than those who opt out (Moos & Timko, 2008). A meta-
analysis conducted by Humphreys et al. (1997) asserts that long-lasting positive
outcomes from the participation in Alcoholics Anonymous groups were consistently
found. Specifically, participants that frequented meetings more in the first three years of
the evaluation period displayed a higher propensity to remain abstinent at eight years
(Table 11).
Table 11. Prediction of Abstinence at Eight Years. Table taken from (Humphreys et al., 1997).

<table>
<thead>
<tr>
<th>Baseline demographics</th>
<th>Remitted (0 = no, 1 = yes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.14 ± 0.013</td>
</tr>
<tr>
<td>Sex (0 = male, 1 = female)</td>
<td>0.491 ± 0.248*</td>
</tr>
<tr>
<td>Married (0 = no, 1 = yes)</td>
<td>0.435 ± 0.309</td>
</tr>
<tr>
<td>Employed (0 = no, 1 = yes)</td>
<td>0.270 ± 0.256</td>
</tr>
<tr>
<td>Family income (U.S.$)</td>
<td>-0.004 ± 0.008</td>
</tr>
<tr>
<td>Baseline problems</td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>0.020 ± 0.012</td>
</tr>
<tr>
<td>Alcohol dependence</td>
<td>0.024 ± 0.018</td>
</tr>
<tr>
<td>Depression</td>
<td>0.001 ± 0.016</td>
</tr>
<tr>
<td>Treatment, first 3 years</td>
<td></td>
</tr>
<tr>
<td>Outpatient sessions</td>
<td>0.011 ± 0.004*</td>
</tr>
<tr>
<td>Inpatient days</td>
<td>0.001 ± 0.002</td>
</tr>
<tr>
<td>Community Resources</td>
<td></td>
</tr>
<tr>
<td>AA meetings, 0-3 years</td>
<td>-0.007 ± 0.002*</td>
</tr>
<tr>
<td>Relig. serv., 0-3 years</td>
<td>-0.002 ± 0.002</td>
</tr>
<tr>
<td>Baseline friend quality</td>
<td>-0.066 ± 0.028*</td>
</tr>
<tr>
<td>Baseline family quality</td>
<td>0.85 ± 0.042*</td>
</tr>
</tbody>
</table>

Note: 69.7% of the individuals were correctly classified by the model.
*p < .05  \( b < .0001 \)

For the data presented above, abstinence – or remission as it is referred to the table – was gauged by using a regression. According to the exponentiated \( b \) weights, \( \text{Exp}(B) \), for Alcoholics Anonymous meetings, it can be seen that participants who were involved in such programs were 1.007 times more likely to be abstinent at the eight year mark. Not shown in the data is the trend that depicted a correlation between the intensity of participation, quantified by the frequency of attendance, and remission rates (Humphreys et al., 1997). In studies conducted by Tonigan et al. (2003), it was similarly shown that addicts whose frequency of attendance was higher experienced correspondingly increased rates of abstinence in a three-month period.
Although these phenomena may be partially driven by selection bias, according to subsequent analyses using two-stage sample selection models, it has been concluded that the purported bias caused by self-selection actually pales in comparison to actually efficacy of Alcoholics Anonymous (Humphreys et al., 1997).

*Rates of Drug Usage*

Further, it was also shown using a longitudinal study that drug usage decreased for members who reported attended 12-step program meetings (Gossop et al., 2003). The general trend appears to be that longer and more consistent attendance correlates to less relapse. Among 150 alcohol-dependent participants in the study, the number of members who reported drinking “in the month prior” dropped from 148 (99%) at the start of the trial to 84 (70%) at the half-year point. Furthermore, it was recorded that approximately 51% of the cohort reported drinking on a less frequent basis, and that 70% had reduced their daily intake of alcohol. This decrease in substance abuse was also depicted by counting the number of times alcohol was consumed on a per monthly basis (*Table 12*). In the month prior to the start of abstinence based therapy, the participants were drinking on average 29 days a month. At the conclusion of six months, this number decreased to roughly 17 times per month.
Table 12. Changes in Alcohol Consumption Post-6 Months of Participation in Alcoholics Anonymous. Taken from (Gossop et al., 2003).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Intake</th>
<th>6 months</th>
<th>t (d.f.)</th>
<th>Significance (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of drinking*</td>
<td>28.9 ± 3.7</td>
<td>17.2 ± 13.6</td>
<td>9.1 (119)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Quantity (units/day)*</td>
<td>35.2 ± 16.7</td>
<td>19.5 ± 21.5</td>
<td>8.8 (117)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol problems (range 0–23)</td>
<td>12.6 ± 4.2</td>
<td>9.5 ± 5.5</td>
<td>6.1 (97)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Global severity index (range 0–4.0)</td>
<td>1.9 ± 0.7</td>
<td>1.6 ± 0.8</td>
<td>5.2 (118)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symptom total (range 0–53)</td>
<td>38.7 ± 11.2</td>
<td>34.6 ± 13.1</td>
<td>4.5 (116)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symptom distress (range 3–4.0)</td>
<td>2.5 ± 0.5</td>
<td>2.3 ± 0.5</td>
<td>4.3 (116)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Quality of life (range 20–120)</td>
<td>66.5 ± 12.3</td>
<td>69.8 ± 15.0</td>
<td>2.8 (116)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

*Frequency scores are shown for number of days drinking in past 30 days. *Units are shown for 1 unit = 8 g of ethanol; mean per day in past 30 days.

In regards to the frequency of participation in a 12-step program, it was noted that, in general, addicts who were actively attending – defined as at least once a week – displayed lower abuse rates of alcohol. This correlation was bolstered by controlling for confounding variables such as the duration of meetings (Fiorentine, 1999; Ouimette et al., 1998).

Retention in Treatment

It is immensely difficult to gauge retention to 12-step programs given the discrepancies reported by groups such as Alcoholics Anonymous and Narcotics Anonymous and those determined from case reports. For instance, in his study of long-term recovery from alcoholism, Chappel (1993) cites that the retention rate for the first three months of participation is approximately 50%. Comparably, the Alcoholics Anonymous organization also self-proclaims that year-long attendance amongst its most
avid members, a term that is undefined, runs as high as 75% (Orrok, 1976). While these levels of retention are remarkably high and quite promising, some doubt is cast by the recently measured rates of retention in both Alcoholics Anonymous and Narcotics Anonymous groups, in the study by Gossop et al. (2008) (Table 13).

Table 13. Retention Rate at One, Two, and Four-Five Years Follow Up. NA: Narcotics Anonymous; AA: Alcoholics Anonymous. Table taken from (Gossop et al., 2008).

<table>
<thead>
<tr>
<th>Self-help contact</th>
<th>1 year</th>
<th>2 years</th>
<th>4–5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Any self-help</td>
<td>25</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>% NA</td>
<td>21</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>% AA</td>
<td>17</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>% NA only</td>
<td>8</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>% AA only</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>% NA + AA</td>
<td>13</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Mean (SD) NA meetings*</td>
<td>26.3 (28.9)</td>
<td>14.2 (16.1)</td>
<td>18.5 (19.1)</td>
</tr>
<tr>
<td>Mean (SD) AA meetings*</td>
<td>12.0 (14.4)</td>
<td>11.8 (12.8)</td>
<td>9.1 (12.6)</td>
</tr>
<tr>
<td>Mean (SD) combined NA + AA meetings*</td>
<td>30.7 (31.5)</td>
<td>18.0 (20.7)</td>
<td>20.7 (22.7)</td>
</tr>
</tbody>
</table>

*Number of meetings shown for patients attending meetings during 90 days prior to each follow-up point.

Contrary to the findings of the earlier studies, only 17% of original attendees were retained in Alcoholics Anonymous meetings at the one year mark (Gossop et al., 2008). Subsequent measures that were conducted at two years and also at the four-five year points showed decreasing retention trends that were around 10%. The similar downward change in participation was also seen in the Narcotics Anonymous groups. The discrepancy which portrayed retention rates for the Narcotics Anonymous group to be generally higher than those of Alcoholics Anonymous cannot be explained, and is not thought to project an implication about the relative needs of one group over the other.
Results from a previous study conducted by Gossop et al. (2003) also corroborate these findings: only 15% of 150 participants reaped the benefits associated with Alcoholics Anonymous attendance. Given the wide discrepancy of retention rates, it is not apt to draw any meaningful conclusion about the success of abstinence-based programs in retaining their participants.
CONCLUSION - THE VALIDITY OF THE BRAIN DISEASE MODEL FOR DRUG ADDICTION

Government policies, which have a great clout over how healthcare is practiced, are great litmus tests for gauging the overarching attitudes toward drug addiction. The passage of the Data Addiction Treatment Act of 2000, which for the first time in almost 80 years allowed for the expansion of pharmacotherapies to be used for opioid addiction, is one of the great indicators of forward movement (Merrill, 2002). Also, the 2008 Mental Health Parity and Addiction Equity Act (MHPAEA) of the Affordable Care Act (ACA), which requires insurance companies to raise the standards of coverage for mental health or substance-use disorders to the same level as general medical care, is another step that drives positive change by appropriating the resources necessary to combat the addiction problem (Volkow et al., 2014). These sorts of policies have served as gateways into an era of innovation in which new methods corroborated by empirically measured success can be utilized to revolutionize drug addiction treatment. However, in order to continue pushing toward progress, access to the approved treatments must also be improved. As depicted in Figure 16, not all states have equal access to the MATs. When this data is overlapped with the drug overdose-related deaths in states, it is noted that the some of the states that do not offer coverage for all three FDA-approved MATs also have the highest rates of mortalities (Appendix 1). Conversely, many of the states that hold a more receptive position toward medicalized treatment enjoy lower rates of drug-related mortalities.
In the process of validating the brain disease model for addiction, it was not the goal to disenfranchise abstinence based therapies. Were that even the intention, such devaluation could not have occurred given that each individual treatment evaluated showed meager success under efficacy tests. That is, a single intervention alone would not substantially dent the current opioid epidemic. Hence, the soundest conclusion that can be drawn from the reviews is that it is immensely complex. Just as the drug addict can embody a person of any race or socioeconomic status, the addiction itself – even to the same drug – can exist in several forms with each one paired to its own remedy. To this end, the various therapies should not be thought of as competing treatments, but rather modalities of treatment that can coexist and supplement one another. As substantiated by numerous studies, therapies that combine psychosocial and agonist maintenance treatments are far more effective in treating opioid dependence (Amato et al., 2011; Amato et al., 2008).

Although research has validated the disease model for addiction, as evident by the limitations of current treatments, both medical and non-medical, and the current status in the fight against opioid epidemic, there is still ample room for improvement. Influenced by the broad push in cancer medicine for individualized treatment, an area of growing interest for many research clinicians is the concept of personalized addiction treatment (Oslin, 2011). Given the multidimensional nature of addiction, such a therapy would most certainly be even more efficacious than currently existing standardized protocols for treating drug dependence.
Table taken from (Rudd et al., 2016).
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CURRICULUM VITAE

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EDUCATION

Boston University School of Medicine - Boston, MA (September 2014 — May 2016)
Degree: M.S. in Medical Sciences

University of Michigan: School of Literature, Science & Arts - Ann Arbor, MI
(September 2007 — December 2011)
Degrees: Chemistry B.S.; Cellular and Molecular Biology B.S

HONORS

American Society of Hematology Trainee Research Award (2011)

RESEARCH EXPERIENCE

Department of Chemistry:
Organic chemistry research - Propargyl functional group transfers using metal catalysts
Research Advisor: Masato Koreeda, Ph.D.

Department of Pediatrics/Hematology:
Design of zinc fingers that target specific genes in the coagulation cascade. Knock-out
zebrafish screened chemically to identify modifier genes (2011).
Research Advisor: Jordan Shavit, M.D., Ph.D.

EMPLOYMENT

University of Michigan: Science Learning Center (January 2009 — May 2009)
  • Study Group Leader for CHEMISTRY 215 and CHEMISTRY 215HH
    o As a study group leader, I was required to design learning environments,
      in which, instead of teaching, I facilitated rich, scientific discourse
amongst students. The greatest value of this experience stems from all that came out of working alongside other students – learning to effectively assess and address needs.

**Life Science Institute** (January 2010 — December 2010)
- **Research Assistant**
  - I performed basic cloning techniques. I had my first hands on experience working with zebrafish and learned to breed them and properly handle them.

**VOLUNTEER EXPERIENCE**

**Ti Kay Haiti** (2014 - present)
- Clinical volunteer at the General Hospital (Port-au-Prince, Haiti Jan. – June 2014)
- Grant writing and fundraising (July 2014 - present)

**UMHS** (2009-2010)
- Through this experience I was able to work with diverse groups of patients at the C.S. Mott Children's Hospital as well as in the 6C pulmonary department. I was able to take part in rich interactions with patients as well as the hospital staff, which included nurses, residents, and doctors

**Uganda** (2009)
- I was able to partake in a wide range of activities spanning from helping to set up a computer lab, writing letters to President Museveni asking for more educational funds, to drawing blood from young children to check for malaria. Although I was able to gain clinical experience during the trip, the most valuable part was being introduced to poverty and the challenges it poses on health deliverance in resource-limited settings.

**EXTRACURRICULAR ACTIVITIES**

**Harvard-MIT Health Sciences & Technology – HST.936 Global Health Informatics Course** (2015-present)
- I enrolled in this free course offered by the Health Science and Technology division of the Harvard and MIT consortium to further my education of global health practices. Through the course of this term, I will have the opportunity to learn alongside students from various disciplines and contribute to ongoing global
health projects directed at driving quality improvement through the use of informatics and mobile technologies.

**Boston Student Health Activist Community** (2014-present)

- As a member of this organization, I have found opportunities to explore and learn about the various local issues that are of concern to students. The Boston Student Health Activist Conference, which was held on October 4th, 2014, was an excellent venue at which students from eclectic backgrounds gathered to discuss issues such as Massachusetts’s push for a single payer health care system and improving health care for incarcerated patients.

**DeveloMaps (2011-2014)**

- I co-founded an internet web tool that has facilitated the process. Develomaps is a website that I designed to help volunteers find projects and organizations connect and collaborate. Develomaps’ main feature is a map that pinpoints the locations of projects launched by organizations. In its functional form, the site served as a database from which users accessed up-to-date information about specific projects as well as a network in which users can connect.

**Dialogue for Development** (2011-2013)

- Following my trip to Uganda, I co-founded the organization, “Dialogue for Development.” The group’s mission is to create spaces in which students can enhance their understanding of the challenges of development. A major project I have led through my participation was organizing the “Good Development Conference.”

**LEADERSHIP**

- **Project Manager for Ti Kay Haiti** (2014-present)
- **Dialogue for Development** (2011-2013)
  - Organization co-founder; executive board
  - Good Development Conference Director (April 7, 2012)
- **Bursley Hall Council Co-advisor** (2010-2011)
- **Residential Advisor** (2010-2011)
  - Bursley Residential Hall
  - Leader for CHEMISTRY 215 & 215HH