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Early Intervention: Addressing Opioid Use Disorder with Emergency Department Initiated Buprenorphine Therapy

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by

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Abstract

The subsequent review evaluates opioid use disorder (OUD) as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnostic criteria, including the use of buprenorphine in the process of induction, its efficacy for the management of OUD, and barriers to its initiation. The outcomes of the initiation of office-based buprenorphine treatment are compared to emergency department-initiated buprenorphine treatment for the management of OUD. This project is a review of current meta-analysis, systematic reviews, cross-sectional, longitudinal, and survey methodologies were analyzed. The medical research databases PubMed, Embase, Cochrane Review, CINAHL Complete, and PsychINFO, have been utilized in obtaining peer-reviewed literature resources. The sources eliminated include those published before 2007, lacked a formal research format, or did not provide valid statistical information. A total of 20 sources were selected for this literature review. The research revealed that buprenorphine is effective in treating OUD when appropriate induction and maintenance doses are implemented. However, there continue to be barriers in prescribing buprenorphine resulting in limited access to the medication. Office-based buprenorphine treatment of OUD shows decreased engagement in treatment within the first 30 days. Emergency department-initiated buprenorphine treatment reveals increased participation in treatment within the first 30 and 60 days, a decrease in opioid use, and a decrease in adverse opioid-related events. The treatment outcome engagement data reveals that at the 6- and 12-month time frames, retention in buprenorphine therapy is essentially the same when comparing both treatment modalities.

Keywords: Opioid use disorder, buprenorphine, office-based therapy, emergency department initiated, adverse opioid-related event

Introduction

The abuse and misuse of opioids have sparked a crisis of epidemic proportions in the United States. Opioids are deemed the deadliest drug in American history as opioid deaths are currently the leading cause of mortality in Americans under the age of 50 (Katz, 2017). According to the Centers for Disease Control (2018), during the years of 1999 through 2017, more than 700,000 deaths were the result of a drug overdose, and of those, two-thirds were the result of an opioid overdose. In a 2018 report from The National Institute on Drug Abuse (NIDA), there were more than 70,200 drug overdose deaths in the United States in 2017, more than four times the rate of death from overdose since 1999. The sharpest increase in fatalities was related to fentanyl and fentanyl analogs (NIDA, 2019). "Overdoses killed more Americans in 2017 than guns (37,400), car accidents (38,000), or breast cancer (40,000)" (Salmond & Allread, 2019). These increases in mortality have led to the present opioid epidemic. They have left the healthcare system searching for viable solutions to address a problem that is becoming deadlier than ever.

Opioid addiction has been described as a three-stage cycle that becomes worse as time progresses. A 2018 article written by Gary Peltz and Thomas Südhof for *The Journal of the American Medical Association* (JAMA) elaborates on these stages and the course of addiction:

> The first stage involves opiate-induced reward sensations in the brain. The second stage is characterized by an elevation in the threshold for experiencing the reward sensation after drug use and a withdrawal state develops when the drug cannot be obtained. The third stage is characterized by chronic relapse in drug use, often triggered by environmental and emotional cues.

Opioid addicted individuals are often caught in this cycle leaving them susceptible to overdose and, as highlighted in the aforementioned statistics, death.

Historically, the use of opioid agonist medications, which include methadone and buprenorphine, have been the mainstays of treatment for opioid abuse. These opioid agonist medications are typically initiated and managed in an outpatient treatment setting. The goal of providing these medications is to curb cravings for opioids and decreases withdrawal symptoms, ultimately leading to sustained sobriety.

Statement of the Problem

Opioid use disorder (OUD) places patients at a higher risk for acute adverse events, including but not limited to overdose, and frequently involves acute interventions delivered in an emergency room setting. These acute interventions often prompt a referral to an outpatient facility to assess the need for addiction treatment. The time frame between an adverse event and the initiation of treatment leaves the patient vulnerable to their addiction with possible re-current opioid-related adverse events. A recent study published in the *Annals of Emergency Medicine* (2019) evaluated the short-term and 1-year mortality of patients treated in the emergency department for non-fatal overdose. The study concluded, “The short-term and 1-year mortality of patients treated in the ED for nonfatal opioid overdose is high. The first month, and particularly the first 2 days after overdose, is the highest-risk period” (Weiner, Baker, Bernson, Schuur, 2019).

There is an opportunity to intervene and bridge this gap in treatment. In the context of addressing opioid addiction in the emergency department, the manifestation of the disease is often evident and providing a chance for emergency room clinicians to intervene. Ideally,

intervention should include the initiation of traditional outpatient opioid agonist medications such as buprenorphine.

Research Question

In patients with opioid use disorder with acute adverse health events, does the initiation of buprenorphine treatment from the emergency department compared to the initiation of buprenorphine treatment from an outpatient setting decrease the incidence of acute adverse health events and long-term opioid use/misuse?

Methodology

Through a thorough literature review, this project will investigate the use of buprenorphine in addressing OUD by comparing the use of buprenorphine in the outpatient setting to its use in the emergency department. The review of current meta-analysis, systematic reviews, cross-sectional, longitudinal, and survey methodologies will be analyzed. The medical research databases PubMed, Embase, Cochrane Review, CINAHL Complete, and PsychINFO will be utilized in obtaining peer-reviewed literature resources. The patient population focuses on individuals who have had or those who are at increased risk for an adverse event such as opioid overdose. The subsequent review evaluates OUD as defined by the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnostic criteria, including the use of buprenorphine in the process of induction, its efficacy for the management of OUD, and barriers to its initiation. The outcomes of office-based initiated buprenorphine treatment will be compared to emergency department-initiated buprenorphine treatment for the management of OUD.

Defining the Diagnosis and Addressing the Problem: Opioid Use Disorder

The American Psychiatric Association (APA) defines opioid use disorder (OUD) in the DSM-5 as, "A problematic pattern of opioid use leading to clinically significant impairment or distress" (American Psychiatric Association, 2013). The diagnostic criteria are broken down into categories of impaired control, social impairment, and risky use behavior with specific defining criteria that fit into each category. The diagnosis of OUD is based off on an individual manifesting at least two of the criteria within 12 months (American Psychiatric Association, 2013). Diagnostic features, as described by the APA (2013), include the following:

> Opioid use disorder includes signs and symptoms that reflect compulsive, prolonged self-administration of opioid substances that are used for no legitimate medical purpose or if another medical condition is present that requires opioid treatment, that are used in doses greatly in excess of the amount needed for that medical condition.

It is important to note that the diagnosis of OUD is not limited to illegal procurement and the use of opioids, but it also includes individuals who are prescribed opioids and meet the diagnostic criteria as defined by the DSM-5.

Han et al. published the results of a 2015 National Survey on Drug Use and Health (NSDUH) to estimate the prevalence of prescription opioid use among adults. The objective of the survey included prescription opioid use, abuse, and use disorders as well as the motivations for misuse among adults in the United States. The methods of the NSDUH included a face-to-face household interview survey using a multistage area probability sample of noninstitutionalized adults. This method was a quantifiable design to provide a stratified representation of the nation as a whole. Data was collected confidentially through an interview in personal visits using audio computer-assisted self-interviewing. A total of 72,600 eligible

participants aged 18 years or older were selected for the NSDUH survey, and 51,200 completed the survey interview. The measure of the primary outcomes of the review inquired about lifetime and the past 12 months' use and misuse of prescription opioids. Opioid misuse was defined in the Han et al. study (2017) as:

> In any way that a doctor did not direct you to use them, including 1) use without a prescription or your own; 2) use in greater amounts, more often, or longer than you were told to take them; or 3) use in any other way a doctor did not direct you to use them.

The sources of obtained prescription opioids included from a friend or relative for free, prescribed by a physician, stolen from a friend or relative, brought from a drug dealer or stranger, or stolen from a clinic or pharmacy. The analysis of the statistical data estimated the national 12-month prevalence of prescription opioid use as well as use according to sociodemographic, health, and behavioral health characteristics.

The results based on the 51,200 respondents were compared to the United States population of noninstitutionalized adults to provide national prevalence estimations. According to the stratified data in 2015, 91.8 million people used prescription opioids in the previous year, 11.5 million people misused them, and 1.9 million people had a use disorder. The 12-month prevalence of misuse was 12.5%, and in adults with prescription opioid abuse, the 12-month prevalence of prescription opioid use disorders was 16.7%. Among the adults reporting misuse of prescription opioids, 59.9% used them without a prescription, 22.2% used them in higher amounts than directed, 14.6% used them more often than directed, and 13.1% used them for longer than directed (Han et al., 2015). Additionally, adults with prescription opioid use, misuse with and without use disorders were reported in those with lower reported family income or uninsured. Furthermore, it is interesting to note that in adults with prescription opioid use, those

with fair to poor health or three or more emergency room visits within that year had an increased incidence of use disorders. The stratified data reveals that more than one-third of the United States population used prescription opioids, 11.5 million adults misused them, and 1.9 million had use disorders in 2015. The data also exposes the perils of prescription opioids in OUD and the current opioid epidemic.

The accessibility and abuse of prescription opioids reveals only a part of the picture in the predicament of opioid use in the United States. A comprehensive literature review conducted by Stoicea et al. (2019) designed to evaluate the current perspectives on the opioid crisis within the United States healthcare system elaborates on the responsible entities contributing to the ongoing opioid crisis. The review also provides insight into the possible relationships between demographics, opioid accessibility, abuse, and overdose. The methods utilized included an extensive literature review using the search engines Google Scholar and PubMed databases evaluating relevant material published between December 7, 1999, through January 9, 2018, using the Preferred Reporting Items for Systematic Reviews and meta-Analysis (PRISMA) guidelines. A total of 7,160 articles were initially identified, and after the removal of duplicates as well as abstract screening, a final 70 articles were selected as reliable full texts.

The results of the comprehensive review included a discussion that identified numerous associated factors that are either directly or indirectly related to the current opioid crisis in the United States. The first of these factors was related to the demographics and the United States regional distribution. In the year 2016, opioids were responsible for 66.4% of total overdoses affecting virtually all population demographics. Non-Hispanic whites aged between 45-54 experienced the highest rates of mortality, according to the National Center for Health Statistics (Stoicea et al., 2019). It is also important to note that there were a significant number of

schizophrenic and bipolar patients abusing opioids compared to the general population. The unintentional injury of opioid overdose contributed to a high financial burden on the healthcare systems. From 2001 to 2012, there were more than 660,000 hospitalizations related to opioid overdose with an accrued cost of more than $700 million healthcare dollars annually. The region with the highest rate of hospitalizations from the use of prescription opioids was in the South, and the highest rate of opioid-related hospitalizations from the use of heroin was in the Northeast and Midwest regions. Hospitalizations due to heroin use were highest in urban areas (5.5 per 100,000) compared to rural areas (2.1 per 100,000) (Stoicea et al., 2019). Hospitalizations due to prescription opioid overdose were 30% higher in rural areas compared to urban populations. The review also highlights that opioid prescriptions were reduced by 13.1% from 2012 to 2015 due to an increase in physician awareness. However, the US continues to have the highest rate of opioid prescriptions, with nearly 50,000 prescriptions per 1 million inhabitants. Synthetic opioid overdose accounted for 19,000 deaths in 2016, which was more than any other class of opioid drugs. The limitations of available prescription opioids through physician awareness and newly implemented policies have led to an increased rate of heroin abuse from former prescription opioid abusers (Stoicea et al., 2019).

Initiation and the Efficacy of Buprenorphine in the Treatment of Opioid Use Disorder

Attempts to develop viable and systematic programs are being made by healthcare facilities with assistance from the Drug Enforcement Agency (DEA) using opioid agonist medications to combat the opioid epidemic. Buprenorphine has been indicated for the use in the treatment of opioid dependence in the United States since 2002. Physicians are able to prescribe buprenorphine under the Drug Addiction Treatment Act (DATA 2000) for 30 patients following a series of training activities and competency testing. The completion of these training activities

and competency tests enables the provider to obtain X-Waiver and can prescribe buprenorphine through the DEA (Toce, Chai, Burns, & Boyer, 2018). A 2015 report conducted by Stein et al., published in *The Journal of Substance Abuse Treatment*, indicated that 43% of counties in the US still have no providers who can prescribe buprenorphine and only 25% of patients with OUD can access a provider who can prescribe buprenorphine (Stein et al., 2015). These limitations of accessibility to buprenorphine providers are thought to be the main factor in the diversion of buprenorphine in the informal treatment OUD (Toce et al., 2018).

Buprenorphine therapy can be administered in a variety of settings eliminating the need for daily clinic visits, as seen in methadone treatment. The initiation of treatment for OUD requires the individual to abstain from opioids for 12-48 hours or exhibit moderate symptoms of opioid withdrawal. The Clinical Opiate Withdrawal Scale (COWS) is utilized to reference the level of opioid withdrawal with scores of 5-12 indicating mild withdrawal, 13-24 moderate withdrawal, 25-36 moderately severe withdrawal, and >36 severe withdrawal (Toce et al., 2018). The initial dose is 4 to 8 mg with the titration of doses depending on the individual's needs.

Buprenorphine is a partial mu receptor agonist with a half-life of 37 hours with an affinity for the mu receptor of more than 1,000 times that of morphine. Buprenorphine also binds to the kappa and delta-opioid receptor with a lower affinity (Toce et al., 2018). Buprenorphine also binds to the opioid-like receptor known as NOP, and in occupying this receptor, buprenorphine blocks the rewarding and antinociceptive actions of morphine (Toce et al., 2018). Formulations of buprenorphine with naloxone, a mu receptor antagonist, deters the IV use of buprenorphine and if it is injected the naloxone will induce opioid withdrawal. The pharmacologic properties of buprenorphine precipitate opioid withdrawal in patients actively

using opioids. Therefore, it is vital to assess levels of withdrawal using COWS scoring before the initiation of buprenorphine therapy.

The use of buprenorphine has increased from 3,161 prescriptions in 2006 to 30,135 prescriptions in 2010 (Toce et al., 2018). Buprenorphine use associated with diversion is generally used to manage withdrawal symptoms rather than the seeking of its use for euphoric effects. According to the 2015 Annual Report of the American Association of Poison Control Centers' National Poison Data System, there were no reported deaths involving buprenorphine.

Gowing, Ali, White, & Mwebe (2017) completed an interventional review to evaluate the effects of buprenorphine compared to other medications commonly used in managing withdrawal symptoms in patients dependent on opioid drugs. The medications in comparison included tapered doses of methadone, alpha2-adrenergic agonists, symptomatic medications, or placebos. The evaluation of the efficacy of the various medications included the intensity of withdrawal symptoms, duration, and completion of treatment, and adverse effects.

The methods utilized a search of the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, PsycINFO, and the Web of Science. Randomized control trials involving the interventional use of buprenorphine in managing withdrawal symptoms in opioid-dependent patients were evaluated. The interventional study included 27 studies with 3,048 participants. The main comparators to buprenorphine being clonidine or lofexidine (14 studies), buprenorphine to methadone (6 studies), and buprenorphine dose reduction (7 studies). The standard methodological procedures expected by Cochrane were utilized, and the evidence was current to December 2016 (Gowing et al., 2017).

The results following the evaluation of meta-analysis data concluded that there was no difference between buprenorphine and methadone in terms of the average time of treatment with

a mean difference of 1.3 days (95% CI, -8.11 to 10.72; N=82, two studies; low quality). There was also no difference in treatment completion rates (95% CI, 0.91 to 1.20; N=457, five studies; moderate quality). Patients receiving buprenorphine had higher treatment retention compared to clonidine or lofexidine (95% CI 0.57 to 1.27; N=558; five studies; moderate quality). They were also more likely to complete withdrawal treatment (95% CI, 1.23 to 2.06; N=1264; 12 studies; moderate quality) (Gowing et al., 2017).

Conclusions of the interventional review suggest that buprenorphine and methadone appear to be equally effective There is a possibility that the pattern of withdrawal experienced by the patient may differ and that these withdrawal symptoms may resolve more quickly with the use of buprenorphine (Gowing et al., 2017). It can also be determined, with moderate evidence, that buprenorphine is more effective than clonidine or lofexidine for managing opioid withdrawal and treatment completion (Gowing et al., 2017).

The process of opioid agonist induction and engagement in treatment is important to evaluate. Jacobs et al. (2015) conducted a secondary analysis study with randomized adult patients who have met the DSM-IV criteria for opioid dependence and met the eligibility requirement for methadone and buprenorphine treatment. The National Drug Abuse Treatment Clinical Trials Network provided a multi-site trial “Starting Treatment with Agonist Replacement Therapies” (START) where the buprenorphine induction practices of eight different community treatment providers in differing geographical locales where examined.

Methods utilized in this study included 740 randomized patients who were instructed to abstain from opioids for at least 12 hours and present to the clinic in mild to moderate withdrawal (Jacobs et al., 2015). The Clinical Opioid Withdrawal Score (COWS) was utilized to objectify the level of withdrawal. The induction dose was variable based on the clinicians’

judgment of the level of withdrawal the patient was experiencing, and the first buprenorphine doses ranged from 2 mg to 8 mg. Following induction doses, the participants were observed for two hours, and if the COWS scores remained elevated, doses were titrated to a maximum of 16 mg on the first day. The maximum buprenorphine dose on days two or three was 32 mg. Outcome measures included the number of days of opioid use while taking buprenorphine, retention in buprenorphine therapy, and the number of adverse events related to buprenorphine therapy. The outcome measures were evaluated in three different periods: the first seven days of early induction, the first 28 days of stabilization, and the last 28 days of the 6-month treatment to signify the end of treatment (Jacobs et al., 2015). Three hypotheses were proposed within the outcome measures framework. Hypothesis one suggested that a higher induction dose on days one and three will have better outcomes and have fewer days of opioid use and higher retention. The first three days of treatment were identified as the most crucial in the treatment of opioid use disorder. Hypothesis two proposed that participants given greater than 16 mg of buprenorphine on day 28 will have better outcomes compared to participants given less than 16 mg of buprenorphine in the same time frame. Participants should be stabilized by day 28, and 16 mg is considered the minimally effective dose to suppress opioid cravings. Hypothesis three proposed that participants who reach their buprenorphine maintenance dose more quickly will have better outcomes than those who reach their buprenorphine dose more slowly (Jacobs et al., 2015).

Results revealed a higher dropout rate in those participants who started on a low dose and remained on a low dose of buprenorphine. Participants who started on a higher buprenorphine dose and remained on the higher dose had fewer opioid using days. Also, participants who received greater than 16 mg per day dose of buprenorphine on day 28 were less likely to drop out in the first 28 days. Additional results revealed that the mean number of days it took to reach the

maintenance dose was 23.22 days (sd=8.54); the median was 24 days (Jacobs et al., 2015). It is also important to note that across all trajectories and hypothesis groups, the days of opioid use did not differ with the use of buprenorphine during the first seven and 28 days of the study. The study also revealed that participants who had a higher initial COWS score and had their buprenorphine dose-adjusted more quickly were less likely to drop out in the first seven days compared to those whose doses were adjusted slower (Jacobs et al., 2015).

The efficacy of buprenorphine was expounded on further in a Meinhofer, Williams, Johnson, & Shackman (2019) study that investigated the buprenorphine treatment retention in association with days supplied as well as the daily dosage of the initial supply of the medication. The sample size contained 17,158 individuals who initiated treatment for opioid use disorder (OUD), who were 18-64-year-old. Meinhofer et al. (2019) used NDCs provided by the Centers for Disease Control and Prevention to compile data of buprenorphine prescriptions for OUD in pharmacy claims. The daily dosage was indicated as low with a prescription of <4 mg and was defined as high with a daily dosage >4 mg. The days of supply were split into categories of <7 days, 8-15 days, 16-27 days, >28 days based on the prescribing quantities. “Adverse events were defined as having at least one emergency, or inpatient admission with a first or secondary diagnosis of opioid poisoning, dependence or abuse in the 360 days following treatment initiation” (Meinhofer et al., 2019). The estimate of adjusted odds ratios (AORs) of treatment discontinuation that was associated with the daily dosage and days of the initial prescription was analyzed.

The results of the study based on the 17,158 individuals included a population of mostly males (64%) and individuals mainly in the age group of 18 and 34 (52%). Of the participants, those who were diagnosed with a drug use condition (37%), a mental health condition (42%),

and chronic pain (55%) were identified (Meinhofer et al., 2019). As far as retention, 55% of individuals in this sample stopped using buprenorphine within 180 days and 18% discontinued use within the first 30 days of the initial prescription. Adverse opioid-related events within 360 days of treatment totaled 13%, and 68% of the adverse events occurred after the discontinuation of treatment (Meinhofer et al., 2019). A daily dosage of <4 mg was associated with an AOR of 1.79 of the discontinuation of treatment ($p < 0.01$) and receiving an initial prescription of 15 days or less was associated with increased odds of discontinuation. A combination of a dose <4 mg and supply of <7 days was associated with an AOR of 3.2 of having at least one adverse opioid-related event ($p<0.01$) (Meinhofer et al., 2019).

Barriers in The Use of Buprenorphine Therapy

It is important to review the efficacy of buprenorphine, and it is equally vital to review the potential barriers in prescribing the medication because this is ultimately how the medication is utilized. These barriers may be present within a healthcare provider's practice without clear rationale as to why they may be reluctant to prescribe buprenorphine. The subsequent text elaborates on these impediments that could possibly limit buprenorphine's use.

Barry et al. (2008) conducted a qualitative study using both individual and group semi-structured interviews. The main objective of the study was to identify barriers to the potential or the actual implementation of buprenorphine by office-based providers. The interview process was conducted face-to-face with 23 participants between October 2002 and June 2005. The results of the study revealed three main themes, identified by the respondents, that serve as barriers to the potential or actual implementation of buprenorphine therapy. These three themes include physician factors, patient factors, and logistical factors (Barry et al, 2008). Physician factors include the competing clinical activities that impede on introducing buprenorphine into

their practice. Also, there was a perceived lack of expertise regarding the implementation of buprenorphine therapy because of their lack of experience in treating addiction. This perception stems from no formal training in medical school education and the advancement of their practices (Barry et al., 2008). Some physicians responded with little interest in treating addiction, which was also based around the difficulty of the patient population and the challenge in implementing treatment. Other respondents felt that they had a lack of expertise surrounding the management of co-existing psychiatric and medical disorders that frequently occur in conjunction with opioid use disorder (Barry et al., 2008). There were also positive responses, as several providers regarded buprenorphine therapy as a viable alternative to methadone in the treatment of opioid use disorder. Patient factors include satisfaction in receiving buprenorphine treatment in an office-based setting rather than in a methadone clinic. The respondents identified potential patient barriers in opioid-dependent patients to be motivated enough to start treatment and the possibility of diversion of the buprenorphine (Barry et al., 2008). Logistical factors included a perceived lack of opioid prevalence in their patient populations, thus not needing buprenorphine treatment.

The potential barriers to buprenorphine therapy were also evaluated by Andraka-Christous & Capote (2018) where they conducted individual semi-structured and in-depth interviews of 20 licensed physicians in the United States. The aim was to compare reported barriers in the prescribing of buprenorphine and extended-release naltrexone in U.S. office-based practices and to identify potential future policies to minimize these barriers. The methods of this study involved the recruitment of 20 U.S.-licensed physicians through sampling using both physician-based referrals and networking. Physicians included in the study were from various

geographic locations and specialties, and either had or had no experience prescribing sublingual buprenorphine or extended-release naltrexone.

The results of the study included the identification of general barriers to treating addiction, including “difficult patients” and the prevailing stigmas surrounding addiction rather than barriers to specific medications. Providers with experience prescribing medication-assisted treatment (MAT) described both general obstacles and barriers to specific medications. Seventy-five percent agreed that a lack of education in medical school and residency was the most commonly described barrier to OUD treatment (Andraka-Christous & Capote, 2018). There was also a perception that patients with addiction are viewed as “difficult,” as this was described as the second most common barrier (60%). Time and staff limitations are also a barrier to OUD treatment because conversations about addiction take more time and are more difficult to approach. The stigma of addiction also limits providers in the treatment of disease, and at times providers do not want to be seen as the addiction treatment provider in the community. Misconceptions about MAT also serve as a prescribing barrier, especially when providers view the use of buprenorphine or naltrexone as “just another drug”. Regulatory restrictions also play a role in the lack of prescribing in the federal education requirements for buprenorphine prescribing and the concern that the enrollment in such programs may invite greater federal government oversight of the provider’s practice (Andraka-Christous & Capote, 2018).

Also related to the potential barriers to buprenorphine treatment, DeFlavio, Roland, Nordstrom, & Kazal (2015) completed research in analyzing the barriers in providing buprenorphine therapy in the family practice setting. The information was obtained by an anonymous survey of family physicians who were practicing in the rural areas of Vermont and New Hampshire. The methods of the study included the development of an anonymous online

survey designed to capture both quantitative and qualitative questions. Data was analyzed with descriptive statistics regarding the respondent's quantitative responses.

The results of the study included (n=108) completed surveys from the family physicians with 10% (n=11) of the respondents being buprenorphine prescribers and (n=97) a majority were buprenorphine non-prescribers. Over 80% of the family physicians reported that they regularly saw patients who were addicted to opioids. The majority (94%) that treating the opioid using and the addicted population was difficult, and nearly three quarters (73%) reported that they felt a responsibility to address opioid addiction (DeFlavio et al., 2015). Buprenorphine prescribers were 100% confident in their ability to prescribe buprenorphine, and 91% were confident in its efficacy. Non-buprenorphine prescribers were 16% confident in prescribing buprenorphine, and nearly 50% were confident in its efficacy (DeFlavio et al., 2015). The cost of buprenorphine therapy as a concern to patients was also inquired about; both the prescribing and non-prescribing group saw this as a concern (7/11) and (89/97) (DeFlavio et al., 2015). Although the potential limitations to this review are that this was a small sample size and consists of a family physician from a similar region, which makes it difficult for the study to be generalized nationally.

Evaluation of The Outcomes: Office-Based Treatment of Opioid Use Disorder with Buprenorphine

The treatment of OUD requires access to providers and patient care environments where effective, evidence-based medication-assisted treatment (MAT) can be offered. Office-based treatment has been one of the mainstays in the treatment of OUD, providing opportunities to initiate treatment, monitor the effectiveness of therapy, and adjusting medication doses as needed to decreased opioid abuse and encourage retention in buprenorphine therapy. The recognition of

the opioid crisis has increased the diagnosis of OUD and has subsequently increased the need for options to treat the disorder itself effectively.

Rhee and Rosenheck (2019) conducted a cross-sectional survey with data collected from 2006 through 2015 National Ambulatory Medical Care Surveys (NAMCS) to evaluate the diagnosis of opioid use disorder (OUD) and buprenorphine prescribing. The methods of the study included data from 2006-2015, obtained from the NAMCS surveys. The specific population of patients evaluated in this study included the use of ICD-9-CM diagnostic codes of those diagnosed with OUD and other opioid-type dependence disorders from 2006-2015 with a total study population of 1,034 (n=1034) (Rhee & Rosencheck, 2019). The measures of the study pertained to buprenorphine prescribing, demographic covariates, and clinical covariates. Demographic information included patients age 18-44, 45-64, or >65 years of age, gender, race, the region of residence, and insurance coverage. Clinical covariates included physician specialty, psychiatric disorders, and pain conditions (Rhee & Rosencheck, 2019).

The stratified results revealed a three-fold increase from 0.14% of all office visits in 2006-10 to 0.38% in 2011-15 with a specific increase in diagnosis in primary care and specialty care clinics for OUD. The prescribing of buprenorphine increased from 56.1% of those diagnosed with OUD in 2006-10 to 73.6% in 2011-15 (p=0.124) (Rhee & Rosencheck, 2019). The results of the Rhee and Rosencheck study (2019) revealed a weighted estimate of the diagnosis of OUD was more than 2 million physician visits, and buprenorphine was prescribed at approximately 1.4 million visits. The diagnosis of OUD was highest in younger adults aged 18-44 (72.7%) and males (61.7%). The prescribing of buprenorphine was also highest among younger adults (78%) compared to those who were not prescribed buprenorphine (60.9%). The majority of visits were among non-Hispanic whites (84.0%), and they were more likely to be

prescribed buprenorphine (Rhee & Rosencheck, 2019). Covariate results revealed that patients who were prescribed buprenorphine were also less likely to have a comorbid psychiatric disorder or have a diagnosis of a separate substance use disorder. Hispanics were least likely to receive a buprenorphine prescription (AOR=0.26). Adults with OUD and Medicaid (AOR=0.27), any psychiatric disorder (AOR=0.45), or any other substance use disorder (AOR=0.19) were least likely to receive a buprenorphine prescription (Rhee & Rosencheck, 2019). The information provided by the Rhee and Rosencheck (2019) study represents a large sample size covering differing demographics across the United States, enabling national weighted estimates. The data also suggests that the trends of buprenorphine prescribing are tailored towards younger, lower-risk populations without psychiatric comorbidities.

Simon et al. (2017) conducted a study evaluating factors and predictors that cause patients with opioid use disorder (OUD) not to reach the induction of buprenorphine. The study is one of the first to investigate factors that contribute to OUD patients being lost in the engagement process of buprenorphine treatment and ultimately not reaching the induction period of therapy. The population sample included 100 consecutive patients seeking treatment in 2016 at a buprenorphine treatment program in an urban, academic primary care clinic. The methods of the study involved data collected from an embedded primary care clinic that follows the Massachusetts Model for office-based buprenorphine treatment. There are four patient contact periods, including telephone screening, nursing intake visit, initial physician visit, and observed induction (Simon et al., 2017). Data was obtained from the electronic medical record with clinical and social characteristics being extracted from the intake questionnaire completed with the initial contact. The primary outcome of the study was reaching induction with buprenorphine within 90 days of the initial contact with the program. Descriptive analysis included the

percentage of patients completing each of the four steps and the average time to induction (Simon et al., 2017).

The results of the study found the sample population to have a mean age of 39, predominately male, and non-Hispanic white. The rates of unemployment, psychiatric comorbidity, and incarceration history all exceeded 70%. Approximately 33% of the population was homeless. Patients were all referred to treatment with a referral from a physician (64%) with the next largest groups being referred by county needle exchange (21%) and the next being from a family or friend (6%). Overall, 60% of the sample failed to reach the induction period within 90 days, with 32% dropping out after the initial step of the telephone interview (Simon et al., 2017). The median time frame between intake and the first dose of buprenorphine was 18 days, with the longest time between steps occurring between the screening telephone intake and nurse visit. Recent polysubstance abuse and any previous substance use treatment were all associated with failure to reach the induction step (Simon et al., 2017). Also, homelessness and being in a partnered relationship were predictors of failure to reach induction.

Cunningham, Roose, Starrels, Giovanniello, & Sohler (2013) evaluated the prior experience of buprenorphine to the outcomes of office-based buprenorphine treatment. The study examined whether previous experience with the use of buprenorphine was associated with higher treatment retention and opioid use. It is also important to note that this study explored if the prior buprenorphine exposure was from previous prescriptions or through illicit use. The methods of the study involved an analysis of a longitudinal cohort study of opioid-dependent who initiated buprenorphine treatment. The original study aimed to identify the factors that predict positive outcomes in participants receiving buprenorphine therapy. The participants were followed for six months, and the data was collected from interviews and medical record extractions. The

participants of the study were at least 18 years old and insured by an insurance plan that was willing to pay for buprenorphine therapy, the mean age was 43.5 years, and most were males. Participants were interviewed at one, three, and six months. Dependent variables involved two primary outcomes: buprenorphine treatment retention and opioid use (Cunningham et al., 2013). Treatment retention was evaluated at one, three, and six months following of induction of buprenorphine therapy. The primary independent variable included previous buprenorphine experience. The past experience was defined as have ever taken buprenorphine before the initiation of treatment. The prior exposure to buprenorphine was further broken down into those participants with previous prescriptions for buprenorphine and those who used buprenorphine illicitly (Cunningham et al., 2013).

The results of the study included a total of 87 eligible participants (n=87), 75 (86.2%) interviews were conducted at one month, 79 (90.8%) at three months, and 73 (83.9%) at six months. Of the participants, 57.4% reported prior exposure to buprenorphine, and of this number, 40.0% reported using prescribed buprenorphine, and 60.0% reported using illicit buprenorphine (Cunningham et al., 2013). Treatment retention at one month was 92%, at three months 69%, and at six months 54%. A multivariate analysis compared those who were buprenorphine-naïve to those with prior buprenorphine exposure. Those with previous buprenorphine exposure were more likely to be retained at six months (adjusted odds ratio [AOR]=2.65, 95% CI= 1.05-6.07, $p<0.05$) (Cunningham et al., 2013). Among all participants, opioid use did decrease over time form 89.7% at baseline to 41.9% at one month, 32.9% at three months, and 27.4% at six months (Cunningham et al., 2013).

The successes and failures of outpatient buprenorphine therapy were identified in a Marcovitz, Volpe, Votaw, & Connery (2016) retrospective chart review from two separate

outpatient buprenorphine treatment clinics. The study had the objective of evaluating the predictors of early drop out from outpatient treatment of opioid use disorder utilizing MAT with the use of buprenorphine. The methods of the study involved a retrospective chart review for patients from a private, academic psychiatric hospital and a federally qualified health center with community mental health services. The care the patients received was offered in an outpatient setting. Participants totaled 84 patients (n=84) from the academic who were initially hospitalized for OUD between 2006 and 2013 and were discharged to outpatient buprenorphine treatment (Marcovitz et al., 2016). The treatment of the participants totaled 118 participants (n=118) between 2008 and 2014. A combination of both populations revealed that 79.7% had opioid use disorder and one co-occurring psychiatric disorder (Marcovitz et al., 2016). The stabilization period was one and three-months with weekly, supervised toxicology with quantitative results of an expanded narcotic panel in both facilities. Weekly buprenorphine prescriptions were provided in the initial three-month stabilization period, and then prescriptions were supplied on a monthly (Marcovitz et al., 2016). The dosage of buprenorphine was flexible, with a majority of patients receiving 16-24 mg daily dosage to control withdrawal symptoms and cravings. Early dropout was determined as the dependent variable in the study (Marcovitz et al., 2016).

Results included a mean age of 41 years (SD 12.4), with 17% of the population sample under the age of 25 years. The mean duration of OUD was 18.7 years (SD 12.0). There was a total dropout rate of 56 out of 202 participants (27.7%) with 23 dropouts before the end of month two and 33 dropouts before month three (Marcovitz et al., 2016). The early dropouts were more likely to test positive for both opioids and other drugs in month one and opioids in month two. The variables associated with early dropout included younger age, unemployment, the absence of chronic pain, the absence of prior suicide attempts, the first time receiving opioid agonist

treatment, and opioid use in one month (Marcovitz et al., 2016). Additional multivariable analysis data indicated that age under 25 and opioid use in the first month were associated with early dropout. Those with a history of suicide attempts were significantly less likely to drop out ($p<0.05$). The lack of initial treatment response with opioid use in the first month was strongly associated with early dropout, and participants who used opioids in the first month were 4.5 times more likely to drop out of treatment (Marcovitz, 2016).

Weinstein et al. (2016) conducted a retrospective cohort study to examine the prevalence and patient characteristics of long-term treatment of greater than one year in office-based treatment with buprenorphine (OBOT). The methods of the research involved a retrospective cohort study (Disenrollment and Re-engagement in an OBOT Program) titled DROP. The study examined patients treated with buprenorphine at Boston Medical Center's OBOT from January 2002 to February 2014, intending to describe patient characteristics associated with OBOT treatment retention for at least one year. The study population included all men and women who entered a buprenorphine program, completed induction, and were retained for at least one year. Data, including basic patient demographics, medical diagnoses, and laboratory tests, were obtained from the electronic medical record. The primary outcome was at least one year of continuous OBOT with buprenorphine. Patients periods of at least one year of therapy were designated as "OBOT veterans" (Weinstein et al., 2016).

Results of the 12-year study period totaled a patient population of 1237 ($n=1237$) who entered the OBOT program. The demographic specifics revealed that a majority were male (61.4%), of the white race (68.2%), unemployed (64.2%), and had completed high school (64.3%). The medical characteristics included those with a psychiatric diagnosis (66.0%) and Hepatitis C antibody (58.7%) (Weinstein et al., 2016). The mean daily dosage of buprenorphine

was 16 mg, the first reported opioid abuse was at a mean age of 22, and the fist OBOT enrollment mean age was 38 years of age. (Weinstein et al., 2016). Of the population, 45.7% resulted in treatment retention greater than one year. Older age, female gender, and psychiatric diagnosis were associated with higher odds of greater than one-year retention. Black and Hispanic compared to white, unemployment, HCV positive were associated with lower odds of retention of greater than one year. Relapse was the reason for disengagement among all treatment periods (32.6%), and relapse was less common among treatment periods greater than one year compared to those less than one year (23.3% vs. 40.1%, $p<0.0001$) (Weinstein et al., 2016)

Evaluation of Outcomes: Emergency Department Initiated Treatment of Opioid Use Disorder with Buprenorphine

The emergency department (ED) provides a unique environment for the initiation of buprenorphine therapy in the treatment of patients with OUD. The ED is unique in that it allows for an opportunity to engage patients with OUD in treatment with buprenorphine rather than referral to outpatient treatment where this patient population may be lost to follow-up.

Edwards et al. (2019) conducted a prospective study to assess the feasibility of using a community hospital emergency department as an immediate resource for MAT for patients in opioid withdrawal. The methods of this study included an observational cohort study in an ED with 41,000 visits per year in rural New York state. The population were patients older than 16, no medical issues requiring hospitalization, mild or greater opioid withdrawal based on COWS of 5 or greater, no use of heroin or fentanyl within the past 12 hours, no use of hydrocodone or oxycodone within the past 24 hours, no use of methadone within the past five days, and no clinical indications of intoxication (Edwards et al., 2019). Patients who met eligibility criteria

were administered buprenorphine and were assessed by the same provider at 30 minutes and 60 minutes after administration. If the patient's subjective reports of withdrawal symptoms improved, they were discharged, and an appointment was set-up at the affiliated treatment facility. The subjects of this study presented to the ED and requested enrollment under this program from March 2018 to March 2019. This program did not implement an active screening process for potential candidates, and all enrolled were voluntary. The initial dose of buprenorphine was 4 mg, and additional doses could be administered if withdrawal symptoms had not been resolved within 30 minutes. If care was established in the outpatient facility, there was an evaluation of whether they were engaged in MAT and 30 and 90 days.

The outcomes measured by this study were rates of compliance with initial follow-up appointments, treatment engagement at 30 and 90 days, and the presence or absence of adverse medication side-effects. Results included a total of 62 eligible patients over the 12-month time frame who were enrolled in the program. Out of the 62 patients, 53 met the criteria of buprenorphine induction in the ED. Of the 62 patients, the follow-up rate was 81% (95% CI 71% to 91%). The patients who received buprenorphine in the ED had a higher likelihood of keeping their follow-up appointments, 86.7% (Edwards et al., 2019). The patients who were not eligible for ED induction had a follow-up rate of 44%. A total of 50 patients completed their follow-up visit [81% (95% CI 71%-91%)]. Of this population, 43 were still engaged in treatment at 30 days [86% (95% CI 76% to 96%)] and 33 were still engaged at 90 days [66% (95% CI 53% to 79%)] (Edwards et al., 2019).

A retrospective analysis conducted by Kaucher et al. (2019) had the objective to describe a logical approach to buprenorphine induction, referral to outpatient treatment, and assess follow-up rates of patients who underwent buprenorphine induction in the ED. The method of

this study was a single-center, retrospective analysis of emergency department patients undergoing buprenorphine induction and referral to outpatient MAT. Data was obtained from May 2017 to October of 2018 of the ED-based buprenorphine induction program with referral to a MAT facility for outpatient follow-up.

The primary outcomes evaluated include follow-up or intake at the MAT facility after ED induction, retention rates at 30-days after induction, buprenorphine dosing for induction, ED length of stay (LOS), and demographic information to describe the population. The study was conducted at Denver Health Medical Center (DHMC), annually there are 110,000 patients seen per year, and the MAT outpatient treatment is located on the same campus. Buprenorphine doses were based on a buprenorphine induction algorithm based on the Substance Abuse and Mental Health Services Administration's (SAMHSA's) Center for Substance Abuse Treatment guidelines. A total of 219 patients were included. A majority of the population were male, white, and previous or current IV opioid users (75%). MAT intake and retention at 30 days following ED induction were 74% and 49.3%, respectively (Kaucher et al, 2019). The mean buprenorphine dose used for induction was two to three doses of 2 to 6 mg of buprenorphine. The last recorded COWS score at discharge was 3.6, revealing that most patients did not have complete resolution of withdrawal symptoms. The 30-day dose of buprenorphine was significantly higher than the induction dose (Kaucher et al., 2019).

An additional retrospective review was conducted by Dunkley et al. (2019) evaluating a new approach of buprenorphine administration implemented in an Emergency Department's Clinical Decision Unit (ED-CDU). The hospital where this study was based out of is a large tertiary-care public hospital with an on-call medical toxicology fellow who is involved in the care of patients with identified OUD. The method of this study is a retrospective cohort study of

patients who were seen in the ED-CDU with identified OUD in 2017 through 2018. “Criteria for inclusion were as follows: all patients with OUD who received a medical toxicology consultation and were placed in the ED-CDU during the study period” (Dunkley et al., 2019). The diagnosis of OUD was based on the presence or absence of specific diagnostic items in the DSM-V criteria for OUD. The severity of illness was determined by the total number of criteria met from the DSM-V criteria with mild (two-three criteria), moderate (four-five criteria), and severe (six or more of the criteria) (Dunkley et al., 2019).

The results of the study identified 18 different patients in the specified timeframe who were evaluated with the methods mentioned above. The median age was 36 years, and 32% were older than 50 years old. The population was also predominately males, 74%, 16% were employed, and 47% were homeless. The most common substance used was heroin (84%), and the primary method of use was intravenous (56%). Upon presentation to the ED, 26% presented with an acute opioid overdose, and 58% presented to the emergency department seeking treatment. The mean COWS at the time of induction was 10, and the median dose of buprenorphine was 8 mg. Sixty-three percent (12/19) of the patients kept their initial follow-up appointment, and thirty days 9/19 (47%) were active in the clinic, and 4/19 (21%) were active at six months (Dunkley et al., 2019).

D’Onofrio et al. (2015) conducted a randomized clinical trial study designed to test the efficacy of interventions for the treatment of opioid dependence in the ED. The original study was conducted in 2015 and was the first to evaluate outcomes of ED initiated buprenorphine therapy with randomized clinical trial data. Three interventions were implemented and evaluated in the study: 1) Referral to treatment 2) Screening, brief intervention, and facilitated referral to

treatment 3) Screening, brief intervention, ED-initiated buprenorphine treatment, and referral to primary-care buprenorphine treatment (D'Onofrio et al., 2015).

The methods of the study include a screening of all patients 18 years and older with a 20-item health questionnaire with embedded questions on prescription opioid and heroin use. The Mini-International Neuropsychiatric Interview (MINI) was also utilized, and the diagnosis of opioid dependence was made using the Diagnostic and Statistical Manual of Mental Disorders-fourth edition (DSM-4). The study included 329 participants, and it took place at a large urban teaching hospital from 2009 to 2013. The referral group was provided a handout providing names, locations, and phone numbers of addiction treatment programs in the area that were covered under the patient's current insurance plan. The provided addiction services included a varying range of treatment options and access to buprenorphine providers. The brief intervention group received a modified Brief Negotiation Interview (BNI) that contained four components: Raise the Subject, Provide Feedback, Enhance Motivation, and Negotiate, and Advise (D'Onofrio et al., 2015). Following the interview, a research assistant discussed a variety of treatment options based on the patient's insurance eligibility and preferences. The patient was then directly linked with the referral. The buprenorphine group received a BNI and began ED-initiated buprenorphine if they exhibited moderate to severe withdrawal. Following induction, adequate doses of buprenorphine were given for take-home use until the scheduled appointment time within 72 hours of presentation to the ED. Doses included 8 mg to be taken on day 1 and 16 mg doses that were to be taken on days two and three. The patients then entered primary-care based buprenorphine treatment and continued for ten weeks. Following the completion of the ten weeks, all these patients were referred to the opioid agonist treatment program in a community-based program (D'Onofrio et al., 2015).

The primary outcome was the engagement in treatment with enrollment and receiving formal addiction treatment within 30 days. Secondary outcomes evaluated at 30 days included a self-reported number of days of illicit opioid use in the past seven days (D'Onofrio et al., 2015). The patient population was randomized with 114 patients in the buprenorphine group, 102 patients in the referral group, and 111 patients in the brief intervention group.

Results of the study revealed that overall, 34% of the participants were seeking treatment for opioid dependence, 8.8% presented to the ED with an overdose. The remainder of the patients were identified through screening, with 25% reported using only prescription opioids and 53% of the total sample using opioids intravenously. Following the 30th day of randomization 89/114 patients (78%; 95% CI, 70%-85%) in the buprenorphine group were engaged in treatment, 38/102 patients (37%; 95% CI, 28%-47%) in the referral group, and 50/111 patients (45%; 95% CI, 36%-54%) in the brief intervention group (p=<0.001) (D'Onofrio, 2015). Secondary outcomes revealed that the buprenorphine group showed a greater reduction in the mean number of days of illicit opioid use per weeks from 5.4 days (95% CI, 5.1-5.7) to 0.9 days (95% CI, 0.5-1.3) compared to the referral group, which showed a decreased form 5.4 days (95% CI, 5.1-5.7) to 2.3 days (95% CI, 1.7-3.0) and the brief intervention group, which decreased from 5.6 days (95% CI, 5.3-5.9) to 2.4 (95% CI, 1.8-3.0) (D'Onofrio et al., 2015). Patients in the referral and brief intervention groups were enrolled in inpatient treatment services at a higher rate than the patients in the buprenorphine group 37% in the referral group, 35% in the brief intervention group, and 11% in the buprenorphine group (D'Onofrio et al, 2015).

The follow-up to the D'Onofrio et. al (2015) study is a D'Onofrio et al. (2017) study that evaluates the long-term outcomes of emergency department (ED)-initiated buprenorphine

therapy with the continuation of treatment in a primary care setting. The long-term outcomes were assessed at two, six, and 12 months following the emergency department initiation of buprenorphine. The study is an extended investigation into a previously published article (2015) regarding the 30-day outcomes of ED-initiated buprenorphine. Methods and randomization of the patient population were elaborated on in a review of the 2015 D'Onofrio et al. in the previous text. The cohort of patients was established in the 2015 study, and follow-up assessments at 2, 6, 12 months were evaluated in this study. The primary outcome of the study involves the engagement of addiction treatment at 2, 6, and 12-month assessments. Secondary outcomes collected in 2, 6, and 12-month time frames included the number of illicit opioid use in the past seven days and HIV risk (D'Onofrio et al., 2017).

The results of the study include important clinical characteristics, 32% were seeking treatment for opioid dependence, 9% presented with an overdose, and 58% were identified through the screening process. Patients also reported the abuse of other substances and prevalent mental health problems, with 23% requiring an acute psychiatric evaluation. Outcome data revealed that patients in the buprenorphine group were receiving addiction treatment at a higher rate (74% 95% CI 65-83) compared to those in the referral (53%, 95% CI 42-64) or brief intervention groups (47% 95% CI 36-58; $p<0.001$). However, the differences were not present at 6 months (53% 95% CI 43-64);(60% 95% CI 48-72); (51% 95% CI 40-63) or at 12 months (49% 95% CI 38-60); (49% 95% CI 38-61); (63% 95% CI 52-74); $p=0.546$ and $p=0.136$ (D'Onofrio et al., 2017). Outcome data also revealed that at two months the buprenorphine group reported less illicit opioid use with 1.1 (95% CI 0.7-1.5) days of use in the past 7 days, compared to 1.8 (95% CI 1.2-2.4) in the referral group and 2.0 (95% CI 1.4-2.6) in the brief intervention group ($p=0.546$) (D'Onofrio et al., 2017). There was a significant trend in the reduction of opioid use in

all groups at the 12-month time interval eliminating group differences. The difference between the groups did not persist at the six-month time interval. Illicit opioid-negative urine toxicology tests were not significantly different at two months 52/83 (67%) in the buprenorphine group, 42/71 (59.2%) in the referral group, and 42/71 (58.6%) in the brief intervention group. There was also no significant difference in urine results at six months 47/74 (63.5%) in the buprenorphine group, 33/59 (55.9%) in the referral group, and 332/61 (52.5%) in the brief intervention group (D'Onofrio et al., 2017).

Discussion

There has been much discussion regarding the current opioid crisis within the media and within the realm of healthcare. The present quantitative data of 91.8 million American adults using a prescription opioid in the year, 11.5 million adults misusing opioid medications, and nearly two million American adults with a diagnosed opioid use disorder warrants the current rhetoric surrounding this crisis (Han et al., 2017). The effect of opioid use and abuse is far-reaching within the United States, virtually affecting all demographics of people within the population. Those affected the greatest are non-white Hispanic males and individuals with mental health disorders such as schizophrenia and/or bipolar disorder. The range of ages who are most frequently diagnosed with OUD are 18-34-year-old males (Mienhofer et al, 2019) and the age ranges shown to have the highest rates of mortality are 45-54-year-old males (Stoicea et al., 2019). The burden to the healthcare system includes is also staggering with a reported 660,000 hospitalizations totaling nearly $700,000 million healthcare dollars annually from 2001 to 2012 (Stoicea et al., 2019). It is interesting to note that the types of opioids used differed among rural and urban areas with the abuse of heroin highest within urban areas and the abuse of prescription opioids greatest among rural areas. Synthetic opioid abuse is also noteworthy due to its

associated increase in mortality rates since 2016 (Stoicea et al, 2019). The use of potent synthetic opioids in combination with heroin has not only increased mortality among users, but it has also become increasingly challenging to treat acutely with conventional opioid antagonist medications.

Buprenorphine has been indicated in the treatment of opioid dependence in the United States since 2002. When compared to other medications used to manage withdrawal symptoms in opioid-dependent patients, buprenorphine is found to be more effective in the treatment of opioid withdrawal and the completion of treatment compared to clonidine or lofexidine with a moderate level of evidence (Gowing et al, 2017). It is important to compare buprenorphine to one of the other mainstays in the treatment of OUD, methadone. Literature has shown that there is no difference in the duration of treatment (low quality of evidence) and treatment completion rates (moderate quality of evidence) when comparing the two medications (Gowing et al., 2017). The use of buprenorphine in treating OUD is on the rise with its use with nearly a ten-fold increase in prescriptions from 2006 to 2010 (Toce et. al., 2018). Dosing of buprenorphine based off of COWS scoring criteria is important because induction dosing in an opioid-dependent patient who is not in withdrawal will precipitate withdrawal symptoms following the administration of buprenorphine. The proper dosing of buprenorphine in the induction and maintenance of OUD also requires keen attention. Patients treated with greater than 16 mg of buprenorphine per day were more likely to be retained in treatment and it will take 24 days to get to the maintenance dose of treatment (Jacobs et al., 2015). It is also important to note that across all trajectories and hypothesis groups in the Jacobs et al. (2015) study, the days of opioid use did not decrease in the first 28 days while using buprenorphine. The Meinhofer et al. study (2019) provides more recent data with a large study population to support the findings of the Jacobs et

al. study (2015). AOR of treatment discontinuation was associated with the daily dosage and days of the initial prescription. A daily dosage of <4 mg was associated with an AOR of 1.79 of the discontinuation of treatment ($p < 0.01$) and receiving an initial prescription of 15 days or less was associated with increased odds of discontinuation. A combination of a dose <4 mg and a supply of <7 days was associated with an AOR of 3.2 of having at least one adverse opioid-related event ($p<0.01$) (Meinhofer et al., 2019). However, the acute adverse events associated with opioid use were decreased due to buprenorphine's antagonistic opioid receptor effects keeping patients from an opioid overdose. Adverse opioid-related events, as defined in the Mienhofer et al. study (2019), were patients having at least one emergency or inpatient admission with a primary or secondary diagnosis of opioid poisoning, dependence, or abuse within the first 360 days of buprenorphine initiation. The study revealed that adverse opioid-related events were significantly lower while receiving treatment with buprenorphine, and nearly 70% of the adverse events from this study population occurred following the discontinuation treatment. The efficacy of buprenorphine in the treatment of OUD mirrors that of methadone. However, buprenorphine provides dosing alternatives for home administration, eliminating the need for daily clinic appointments, and the option of flexible dosage titrations to manage withdrawal symptoms may make it more appealing in seeking treatment. Nevertheless, it is important for the clinician to assess the patient's level of withdrawal throughout the induction phase and increase the buprenorphine dose to levels that encourage retention in treatment.

Provider perspectives into the barriers for the implementation of buprenorphine in the treatment of OUD are as equally as critical as the evaluation of the medication's efficacy. The medical provider's perceived lack of expertise regarding the implementation of buprenorphine therapy related to their lack of experience in treating addiction. The etiology of this perception

stems from reports of no or limited formal training in medical school education, as addressed in both the Barry et al. (2008) and Andraka-Christous & Capote (2018) studies. In addition, the stigma of addiction, the view that this patient population is viewed as "difficult", and the perception that buprenorphine is "just another drug" to replace the patient's addiction were also identified in the literature. When considering other common chronic medical conditions, the implementation of medication to manage symptoms and decrease the progression of the disease is foundational in treatment. The treatment of addiction, in particular OUD, should be no different, and barriers to treatment should not be limited by a medical provider's presuppositions. There are effective medications and treatments available to the opioid-addicted population, but the interventions are only effective when they are accessible and implemented.

The recognition of the current opioid crisis has led to an increase in the diagnosis of OUD and treatment of the diagnosis in the office-based setting. The Rhee and Rosencheck (2019) study revealed that there had been a three-fold increase in the diagnosis in office visits from 2011-2015. Prescriptions for the use of buprenorphine in treating OUD in office-based settings has led to a 17.5% increase in prescriptions from 2006-2015. Slightly over 75% of prescriptions were given to younger adults, and of these patients receiving prescriptions, they were less likely to have a comorbid psychiatric condition or a separate substance abuse disorder. These statistics are important to keep in mind because the perceived successes in office-based buprenorphine treatment, may be dependent on the prescribing trends towards younger, lower-risk populations without psychiatric comorbidities. When patients were referred to office-based treatment the Simon et al. (2017) study showed that 60% of referred patients failed to reach the induction of buprenorphine within 90 days. These patients were lost to follow-up in that time frame and did not receive treatment for OUD. The Markovitz et al. (2016) study evaluated the predictors of

early dropout from outpatient buprenorphine treatment and yielded results that suggest the lack of initial treatment response and illicit opioid use within the first month were 4.5 times more likely to drop out of treatment. The various studies show reassuring retention rates beyond the 30-day period when the inductions phase of treatment has been completed with appropriate stabilization and maintenance dose, as mentioned previously. It is interesting to note that patients who have previous exposure to buprenorphine either through failed treatment or through illicit use have higher rates of retention at the six-month time frame (Cunningham et al., 2013). Retention rates in office-based treatment show a steady decline following the first 30 days of treatment, and relapsing opioid use was the leading cause of cessation of treatment. In the various studies that evaluated the retention rate at six months was close to 50% of the original buprenorphine treatment populations. However, retention rates at 12 months and beyond continued to reflect the 50% retention indicating that successes in office-based buprenorphine treatment may stabilize following the six-month period.

The initiation of buprenorphine therapy from the ED provides a unique platform to treat OUD. Patients with OUD are likely to utilize emergency services throughout the course of their disease and providing opportunities for treatment similar to that of other chronic diseases is sensible. It was found that patients who received buprenorphine in the ED had an increased likelihood of keeping their intake appointments to continue treatment (86.7%), at 30 days (86%), and at 90 days (66%) (Edwards et al., 2019). The Kaucher et al. (2019) study yielded results of significantly lower retention rates at 30 days, with 74% of the patient population completing treatment intake and 49.3% retention at 30 days. It is important to note that buprenorphine doses in the Edwards et al. (2019) study was titrated in 4 mg increments up to 16 mg until resolution of withdrawal symptoms was established by COWS scoring. The Kaucher et al. (2019) study had

lower induction doses of 2 to 6 mg, and withdrawal symptoms were not resolved according to the revaluation of COWS scoring at discharge. This reiterates the previous discussion in regard to adequate induction doses to resolve withdrawal symptoms to encourage retention in treatment. The original randomized clinical trial completed by D'Onofrio et al. (2015) provides foundational data in the evaluation of interventions to treat OUD from the ED. Engagement in treatment at 30 days was 78% compared to 37% engagement with referral to outpatient treatment, and 45% engagement with brief intervention in the emergency department. When compared to other studies evaluating the 30-day engagement in outpatient treatment, this data provides a nearly 18% increase with buprenorphine induction from the ED. The evidence also suggests that ED initiated buprenorphine provides treatment within the 30 days when patients with OUD may be lost to follow-up with referral-based treatment models. In addition, secondary outcome data revealed that patients receiving buprenorphine had decreased illicit opioid use, minimizing the risk for adverse opioid related events within 30 days of the initial ED encounter. The assessment of outcomes beyond 30 days to a 2, 6, and 12-month time frame was evaluated in an additional D'Onofrio et al. (2017) study using the original study population. Retention rates at two months continued to be higher within the group of patients who received buprenorphine in the ED. However, the retention rates among the referral and brief intervention groups were all nearly the same at six months, with approximately 50% engagement currently. It is interesting to note that the results also mimic the trends of office-based therapy at six months, with retention rates also at around 50%. The data at 12 months also reveals nearly 50% retention, again, mirroring the data trends seen in outpatient treatment for opioid use disorder.

In summation, the initiation of buprenorphine in the ED is effective in treating OUD in the first 30 days and is successful in engaging patients in outpatient treatment. It also provides an

opportunity to decrease adverse opioid-related events within the first 30 days and decreases illicit opioid use. ED initiated buprenorphine therapy also bridges the gap to outpatient treatment where patients may be lost to follow-up. However, the differences were eliminated at the 6- and 12-month period where data among all treatment modalities all approached 50% engagement. Long-term outcome data from randomized clinical trials and multiple healthcare facilities throughout the United States is limited due to the recent utilization of buprenorphine in the emergency department for OUD. There is ongoing research involving protocols in implementing emergency department-initiated buprenorphine and long-term outcome data with the largest being Project ED HEALTH. The results of this study will be published following the analysis stage in late 2021 and will provide additional evidenced-based research supporting the treatment of OUD from the emergency department setting.

Applicability to Clinical Practice

The treatment of the addicted population, including patients with OUD, will be a continued challenge to medical providers. There are various logistical, professional, and personal impediments within the realm of healthcare that are difficult to overcome. However, the experience of witnessing the triumphs of treatment in a patient who has battled the torment of addiction may provide a respite from some of the aforementioned difficulties. OUD is a diagnosable medical condition, and with the current opioid crisis, it is a diagnosis that necessary to make. Where there are limited psychiatric and addiction services, the diagnosis of OUD may take place within the clinic or ED setting with the presentation of these patients. Therefore, the implementation of a COWS scoring protocol to assess a patient's level of withdrawal and response to treatment may also prove to be beneficial. The use of buprenorphine is a viable alternative with similar efficacy to methadone in treating OUD. The completion of DATA 2000

training and obtaining X-Waivered licensing through the DEA enables providers to prescribe buprenorphine, increasing the access to opioid addiction treatment. The ability of the practitioner to prescribe dosing for extended timeframes and titratable doses adds to buprenorphine's appeal (Gowing et al., 2017). The literature does show that adequate dosing to alleviate withdrawal symptoms and convenient dosing time frames encourage retention in treatment (Markovitz et al., 2016).

The D'Onofrio et al. studies (2015,2017) do provide evidence that the ED initiated buprenorphine therapy does offer an opportunity to connect patients with OUD to treatment when compared to referral and brief intervention groups. In addition to engaging this population in treatment, the illicit use of opioids within the first 30 days of treatment also decreased, thus reducing the amount of adverse opioid-related events. The successes of this early intervention are not independent in treating OUD, but the linkage to ongoing outpatient treatment is essential. Identifying the vulnerable periods in treatment is vital and is addressed when considering the implementation of buprenorphine therapy in the ED. However, OUD treatment beyond the 6-month time frame requires keen attention due to data supporting decreased retention rates within this timeframe. The successes in the treatment of disease is oftentimes due to the progression of treatment options, increased access to medications, and continued evaluation of the efficacy of implemented treatments. The successful treatment of OUD should be approached in a similar fashion, with provider's presuppositions and stigmas aside, in order that lives may be restored from the throes of addiction.

References

American Psychiatric Association. (2013). Opioid use disorder. *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.) http://dx.doi.org/ezproxylr.med.und.edu/10.1176/appi.books.9780890425596.dsm16

Andraka-Christou, B., and Capone, M. (2018). A qualitative study comparing physician-reported barriers to treating addiction using buprenorphine and extended-release naltrexone in U.S. office-based practices. *The International Journal on Drug Policy,* 9–17. http://dx.doi.org/10.1016/j.drugpo.2017.11.021

Barry, D., Irwin, K., Jones, E., Becker, W., Tetrault, J., Sullivan, L.,… Fiellin, D. (2008). Integrating buprenorphine treatment into office-based practice: A qualitative study. *Journal of General Internal Medicine, 2,* 218–225. http://dx.doi.org/10.1007/s11606-008-0881-9

Centers of Disease Control and Prevention (2018). Opioid overdose: Understanding the epidemic. U.S. Department of Health and Human Services. Retrieved from https://www.cdc.gov/drugoverdose/epidemic/index.html

Cunningham, C., Roose, R., Starrels, J., Giovanniello, A., and Sohler, N. (2013). Prior buprenorphine experience is associated with office-based buprenorphine treatment outcomes. *Journal of Addiction Medicine, 4,* 287–293. http://dx.doi.org/10.1097/ADM.0b013e31829727b2

DeFlavio, J., Rolin, S., Nordstrom, B., and Kazal, L. (2015). Analysis of barriers to adoption of buprenorphine therapy by family physicians. *Rural and Remote Health,* 3019. http://dx.doi.org/10.1016/j.annemergmed.2018.04.007

D'Onofrio, G., Chawarski, M., O'Connor, P., Pantalon, M., Busch, S., Owens, P., … Fiellin, D. (2017). Emergency department-initiated buprenorphine for opioid dependence with continuation in primary care: Outcomes during and after intervention. *Journal of General Internal Medicine, 6,* 660–666. http://dx.doi.org/10.1007/s11606-017-3993-2

D'Onofrio, G., O'Connor, P., Pantalon, M., Chawarski, M., Busch, S., Owens, P., … Fiellin, D. (2015). Emergency department-initiated buprenorphine/naloxone treatment for opioid dependence: A randomized clinical trial. *JAMA, 16,* 1636–1644. http://dx.doi.org/10.1001/jama.2015.3474

Dunkley, C., Carpenter, J., Murray, B., Sizemore, E., Wheatley, M., Morgan, B., … Steck, A. (2019). Retrospective review of a novel approach to buprenorphine induction in the emergency department. *The Journal of Emergency Medicine, 2,* 181–186. http://dx.doi.org/10.1016/j.jemermed.2019.03.029

Edwards, F., Wicelinski, R., Gallagher, N., McKinzie, A., White, R., and Domingos, A. (2019). Treating opioid withdrawal with buprenorphine in a community hospital emergency department: An outreach program. *Annals of Emergency Medicine.* http://dx.doi.org/10.1016/j.annemergmed.2019.08.420

Han, B., Compton, W., Blanco, C., Crane, E., Lee, J., and Jones, C. (2017). Prescription opioid use, misuse, and use disorders in U.S. adults: 2015 national survey on drug use and health. *Annals of Internal Medicine, 5,* 293–301. http://dx.doi.org/10.7326/M17-0865

Gowing, L., Ali, R., White, J., and Mbewe, D. (2017). Buprenorphine for managing opioid withdrawal. *The Cochrane Database of Systematic Reviews,* CD002025. http://dx.doi.org/10.1002/14651858.CD002025.pub5

Jacobs, P., Ang, A., Hillhouse, M., Saxon, A., Nielsen, S., Wakim, P., … Blaine, J. (2015). Treatment outcomes in opioid dependent patients with different buprenorphine/naloxone induction dosing patterns and trajectories. *The American Journal on Addictions, 7,* 667–675. http://dx.doi.org/10.1111/ajad.12288

Katz J. (2017). Short answers to hard questions about the opioid crisis. The New York Times. Retrieved from https://www.nytimes.com/interactive/2017/08/03/upshot/opioid-drug-overdose-epidemic.html

Kaucher, K., Caruso, E., Sungar, G., Gawenus, L., Hurlbut, K., Sanchez, D., and Broderick, K. (2019). Evaluation of an emergency department buprenorphine induction and medication-assisted treatment referral program. *The American Journal of Emergency medicine,* 158373. http://dx.doi.org/10.1016/j.ajem.2019.158373

Magura, S., Lee, S., Salsitz, E., Kolodny, A., Whitley, S., Taubes, T., Seewald, R.,… Rosenblum, A. (2007) Outcomes of buprenorphine maintenance in office-based practice, *Journal of Addictive Diseases*, 26:2, 13-23. http://dx.doi.org/ 10.1300/J069v26n02_03

Marcovitz, D., McHugh, R., Volpe, J., Votaw, V., and Connery, H. (2016), Predictors of early dropout in outpatient buprenorphine/naloxone treatment. *Am J Addict*, 25: 472-477. http://dx.doi.org/10.1111/ajad.12414

Meinhofer, A., Williams, A., Johnson, P., Schackman, B., and Bao, Y. (2019). Prescribing decisions at buprenorphine treatment initiation: Do they matter for treatment discontinuation and adverse opioid-related events? *Journal of Substance Abuse Treatment,* 37–43. http://dx.doi.org/10.1016/j.jsat.2019.07.010

National Institute of Drug Abuse. (2018). Opioid overdose crisis. Retrieved from: https://www.drugabuse.gov/drugs-abuse/opioids/opioid-overdose-crisis. NIDA 2019

Peltz, G., and Südhof, T. (2018). The Neurobiology of opioid addiction and the potential for prevention strategies. *JAMA, 20,* 2071–2072. http://dx.doi.org/10.1001/jama.2018.3394

Rhee, T., and Rosenheck, R. (2019). Buprenorphine prescribing for opioid use disorder in medical practices: Can office-based out-patient care address the opiate crisis in the United States? *Addiction (Abingdon, England).* http://dx.doi.org/10.1111/add.14733

Salmond, S., and Allread, V. (2019). A population health approach to America's opioid epidemic. *Orthopedic nursing, 2,* 95–9108. http://dx.doi.org/ 10.1097/NOR.0000000000000521

Simon, C., Tsui, J., Merrill, J., Adwell, A., Tamru, E., and Klein, J. (2017). Linking patients with buprenorphine treatment in primary care: Predictors of engagement. *Drug and Alcohol Dependence,* 58–62. http://dx.doi.org/10.1016/j.drugalcdep.2017.09.017

Stein, D., Gordon, J., Dick, W., Burns, M., Pacula, L., Farmer, M., …Sorbero, M. (2014). Supply of buprenorphine waivered physicians: the influence of state policies. *Journal of Substance Abuse Treatment, 1,* 104–111. http://dx.doi.org/ 10.1016/j.jsat.2014.07.010

Stoicea, N., Costa, A., Periel, L., Uribe, A., Weaver, T., and Bergese, S. (2019). Current perspectives on the opioid crisis in the US healthcare system: A comprehensive literature review. *Medicine, 20,* e15425. http://dx.doi.org/10.1097/MD.0000000000015425

Toce, M., Chai, P., Burns, M., and Boyer, E. (2018). Pharmacologic treatment of opioid use disorder: A review of pharmacotherapy, adjuncts, and toxicity. *Journal of*

medical toxicology: Official Journal of the American College of Medical Toxicology, 4, 306–322. http://dx.doi.org/10.1007/s13181-018-0685-1

Weiner,S., Baker, O., Bernson, D., and Schuur, J. (2019). One-year mortality of patients after emergency department treatment for nonfatal opioid overdose. *Annals of emergency medicine, 1,* 13–17. http://dx.doi.org/10.1016/j.annemergmed.2019.04.020

Weinstein, Z., Kim, H., Cheng, D., Quinn, E., Hui, D., Labelle, C., Drainoni, M.,…Samet, J. (2016). Long-term retention in office based opioid treatment with buprenorphine. *Journal of substance abuse treatment, ,* 65–70. http://dx.doi.org/ 10.1016/j.jsat.2016.12.010