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PROCEEDINGS

Pharmacotherapy of Opioid Addiction: "Putting a Real Face on a False Demon"

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Abstract Methadone maintenance therapy (MMT), a pharmacological treatment for opioid use disorder for the past 50 years, continues to remain controversial. Despite consistent and overwhelming evidence confirming the effectiveness and safety of MMT, misconceptions and myths persist regarding its legitimacy as a treatment for opioid addiction. This often results in the underutilization and limited availability of this treatment modality. Despite successful outcomes, the controversial nature of MMT, and the stigma experienced by the patients on methadone, has been a particularly difficult obstacle to overcome. We present the history of MMT, review the evidence for its efficacy in the treatment of opioid dependence, and explore the origins of the stigma and misconceptions related to MMT.

Keywords Methadone · Addiction · Medication assisted treatment · Drug dependence · Opioid addiction

Introduction

Prior to 1965, only non-pharmacologic abstinence-based treatments were available for the treatment of opioid use disorder. The federally operated "Narcotic Farms" were thought to be the most effective treatments of the time. These were an early form of therapeutic community, located in Lexington, KY, and Fort Worth, TX, and they provided detoxification with morphine, after which individuals spent 6 months working on the farm [1]. Despite prolonged abstinence, the vast majority of individuals relapsed when they returned to their home cities. The 1960s also saw a pronounced increase in heroin-related overdose fatalities, focused in New York City and other urban areas in the northeast. There was no effective durable treatment available. It was in this setting that the concept of opioid agonist therapy was developed. Based on a hypothesis that a long-acting opioid agonist would occupy the opioid receptor providing relief from opioid withdrawal and "narcotic hunger," researchers chose methadone based on its favorable pharmacokinetic profile.

Methadone History and the Early Pioneers

Methadone maintenance began in 1965, with the first clinic established as part of the Rockefeller University Addictions Research program. Federally regulated opioid treatment programs are unevenly distributed across the country. Several states have no clinics; in others, there are only one or two clinics, requiring patients to drive 100–200 miles each day to obtain their methadone. By state legislation, Montana, Wyoming, and the Dakotas do not allow methadone clinics to be established. Overall, physicians are not allowed to write a prescription for methadone for the treatment of opioid dependence, whether for maintenance or for detoxification, outside of an Opioid Treatment Program. When opioid addicted patients are hospitalized for various medical conditions, methadone can be dispensed to treat opioid withdrawal and to

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continue maintenance after dosage has been verified with the Opioid Treatment Program (OTP) [2, 3].

In the 1950s and 1960s, there was a heroin epidemic in New York City. Heroin overdose was the number one cause of death between the ages of 15–35, hepatitis transmission was increasing, and criminality associated with addiction rising [4]. At the time, Dr. Nyswander (an addiction psychiatrist) was treating patients in New York with heroin addiction, but they inevitably relapsed. She collaborated with Dr. Dole, a metabolism researcher at Rockefeller University, as he established a research laboratory to investigate the feasibility of opioid maintenance therapy. Drs. Dole and Nyswander hypothesized that the heroin addicts were relapsing because the heroin was providing something that their brains lacked; the heroin was making up for a shortage or imbalance in the addicted brain [4]. Their work occurred years before endogenous opioids or endorphins were discovered and chemically elucidated.

Methadone was introduced in the USA in 1947 by Eli Lilly and Company as an opioid analgesic under the trade name Dolophine™ [5]. The Rockefeller team began using methadone as a replacement for heroin in their research on feasibility of opioid maintenance therapy, under the hypothesis that methadone occupied a receptor and satisfied the craving in heroin addiction. The first 22 patients had excellent results [6]. They stopped having what he called "narcotic hunger"; their craving was satisfied with methadone. In 1965, Dole and Nyswander published their first paper, "A Medical Treatment for Diacetylmorphine (Heroin) Addiction—A Clinical Trial with Methadone Hydrochloride." This work demonstrated that methadone, accompanied by a comprehensive program of rehabilitation, was an effective treatment for heroin addiction [6]. The Dole/Nyswander treatment paradigm involved comprehensive treatment techniques, with the goal of reintegration into society. Methadone was a means to an end—the end being establishment of adequate hedonic tone and a purposeful, satisfying life.

The Dole/Nyswander hypothesis was that opioid addiction represented a dysfunction in the endogenous opioid system of the brain and that a long-acting opioid occupying the receptor would stabilize and normalize the brain. The opioid receptors may be genetically or environmentally dysfunctional, from years of use of heroin or other short-acting opioids, which produce an "on-off" phenomenon, and result in dysfunction [7].

The Brain and the Biochemistry of Addiction

Three cohorts were evaluated in a small study using phosphorous MR spectroscopy. One group had been on methadone for an average of 137 weeks, while the other cohort had been on methadone for 39 weeks. A control group had no history of addiction. The study measured phosphocreatine, a measure of brain bioenergetic status related to ATP and cyclic AMP production, as well as phosphomonoester and phosphodiester, which relate to brain cell membrane integrity. After a cerebrovascular accident the levels of phosphomono and diesters rise, while the levels of phosphocreatine decrease. The control group of non-drug users had normal biomarker profiles. The group that had been in methadone treatment for 137 weeks had nearly normal biomarkers, more closely resembling controls while the 39-week cohorts were more abnormal. The conclusion was that polydrug abusers have abnormal brain metabolism and that with prolonged methadone use, these polydrug abusers may have a return to non-addicted brain neurochemistry [8].

Methadone concentrations rise soon after dose administration. If the methadone concentration is measured right before morning dosing, the concentration is a trough level. Patients typically present to the clinic at the trough level, before getting their methadone doses. When exposed to heroin-related videos to elicit craving during their trough, these patients show significant activation in their limbic system when measured on fMRI. Three hours later, at their peak serum methadone levels, activation is significantly less [9]. This study indicates that patients that have been on methadone for a long time are still vulnerable to cues and triggers and vulnerable to relapse. Mitigation of cue-induced craving is one of the effects of methadone.

Another study looked at methadone maintenance for 14 months versus methadone treatment transitioned to abstinence. The abstinence arm received methadone for 4 months, which was then tapered over 2 months in conjunction with psychosocial support. The other cohort continued on a stable dose for 14 months. In this study, when the methadone dose started to be tapered, retention decreased and illicit opioid use increased in the methadone to abstinence group only [10]. This study demonstrates the importance of longer-term methadone treatment, in terms of relapse prevention to illicit opioids. There are few studies of long-term outcome in the treatment of opioid dependence, and the optimal duration of opioid agonist therapy has not been clearly defined. Individualization of therapy is required, taking into consideration the lowest effective dose that keeps symptoms under control while minimizing adverse effects and maximizing quality of life. This goal of methadone maintenance therapy is essentially the same as the goal of pharmacotherapy instituted for any chronic disease state.

Methadone Pharmacokinetics

Methadone and buprenorphine, the only opioids available for maintenance therapy in the USA, have an initial onset of

action of approximately 30 minutes compared to nearly instantaneous effects of intranasal or intravenous heroin.

Methadone has several significant drug-drug interactions, primarily occurring through the CYP 450 system. Several different P450 iso-enzymes including 3A4, 2D6, and 2B6 are involved in methadone metabolism. Although drug-drug interactions are common, methadone metabolites are inactive. Methadone metabolites and unchanged methadone are both excreted in the bile and in the urine [11]. Hemodialysis with methadone is safe and well tolerated. There is no withdrawal produced with dialysis being performed in methadone-dependent individuals [12, 13].

At least 4 to 5 days are required to achieve a steady state serum level of methadone. A common error (seen both in clinics and analgesic use) is that methadone doses are increased too quickly [14]. The initial maximum dose of methadone in OTPs is 30 mg, according to federal regulations. An additional 10 mg can be given on day 1 after a period of observation. There are similar dosage guidelines in other countries as well because overdose is most common during the induction phase.

Methadone is also prescribed for pain management, perhaps because it is the least expensive long-acting opioid available [15]. The American Pain Society published a white paper which states that methadone should never be the first opioid used in the treatment of pain [16, 17]. Methadone has a high overdose death rate relative to other opioids [15]. Although methadone is an effective medication for the treatment of both addiction and pain, caution must be exercised in prescribing and additional training is warranted due to its unique pharmacokinetic profile [14, 16]. Patients may be rapid metabolizers of methadone. During pregnancy, this phenomenon is common, and splitting doses is recommended. Methadone blood levels are not helpful in guiding dosage, except for the diagnosis of rapid metabolism.

Methadone exists as a racemic mixture of the R (l) enantiomer, which is the mu receptor agonist, and an S (d) enantiomer, which has an NMDA receptor antagonist effect. The NMDA antagonist effect involves modulation of the glutamatergic system, which is thought to mediate the development of tolerance [11].

Methadone and Adverse Effects

Higher doses of methadone may be associated with QT prolongation and subsequent Torsade de Pointes. One study associated doses >60 mg in 98 % of patients with QT prolongation [18]. The risk for QT prolongation and subsequent TdP during methadone maintenance is not simply a high-dose phenomenon. There are a complex array of variables that must be considered including family history, genetic risk, other medications, nutritional status, and disease states when considering this risk in any individual patient. When methadone maintenance patients develop prolonged QT intervals, clinicians can switch them to buprenorphine maintenance. When making the switch from methadone to buprenorphine, the methadone dose should be tapered as allowed, ideally to less than 40 mg/day. Before starting buprenorphine, at least 24 hours should elapse from the last dose of methadone in order to avoid a precipitated withdrawal syndrome. Buprenorphine does not prolong the QT interval in a clinically significant manner [19].

Once tolerance is achieved, side effects of methadone include sedation (minimal once the patient is stabilized), excessive sweating, and constipation. Complete tolerance does not develop to the constipating effects of methadone. Increased appetite and weight gain can also occur although this may be a result of leaving the hectic life style of opioid addiction. Methadone can also lower testosterone levels and decrease libido by inhibiting gonadotropin-releasing hormones. Some studies indicate methadone-maintained patients have lower testosterone than individuals do on buprenorphine [20, 21].

Goals of Pharmacotherapy

The goals of opioid agonist pharmacotherapy include prevention or reduction of withdrawal symptoms, prevention or reduction of drug craving, prevention of relapse to addictive drug use, and restoration toward normalcy of physiological function disrupted by drug abuse [22]. Opioid agonist therapy is effective in managing opioid withdrawal and in reducing craving; the primary issue is whether people can rehabilitate and return to a job, education, and a family. These medications cannot, by themselves, overcome the significant challenges of severe destitution.

Medication assisted treatment stabilizes the fluctuation from euphoria to withdrawal. With chronic use of short-acting opioids, euphoria diminishes, withdrawal and dysphoria increase, and continued opioid use is related to preventing withdrawal symptoms. Methadone occupies the mu opioid receptor and “blocks” the euphorigenic effects of short-acting opioids when adequate doses of methadone are used. This blockade can be overcome when higher than normal doses of short-acting agonists are used (e.g., when the treatment of acute pain with opioid agonists is required for patients on methadone maintenance). Higher doses of the opioid analgesic may need to be increased to achieve analgesia in methadone-maintained patients, and more potent opioids (such as hydromorphone or fentanyl) may be required [14].

Methadone Maintenance Effectiveness

Opioid agonist effectiveness can be defined in a variety of ways. Evidence accumulated over many years shows that

stable methadone maintenance patients who withdraw from methadone have relapse rates approaching 80–85 % within 1 year [23]. In methadone-maintained patients, there are demonstrated reductions in death rates [24], reductions in the rates of intravenous drug use [23], reductions in crime [5, 25, 26], and reductions in rates of HIV seroconversion [27, 28]. During 1983–84 the prevalence of HIV infection in untreated heroin addicts in New York City was 50–60 %, while only 9 % of methadone maintenance patients had the HIV-1 antibody [29]. In 1990, there was zero HIV antibody presence in another study involving an office-based pilot program of methadone maintenance [30]. In addition to harm reduction, there are also improvements in employment and in social functioning among methadone-maintained patients [5, 6, 26, 31].

One complicated and intangible variable is destitution; in methadone treatment programs, there is an overrepresentation of poverty and social ills. Even an ideal pharmacotherapeutic regimen can be hamstrung by accessibility, due to transportation, childcare, and employment issues. The OTPs must provide support while navigating these issues to foster successful treatment.

Methadone as a "Black Box"

Methadone clinics are a "black box" to health care providers and the public. Initially, patients must attend the clinic either 6 or 7 days a week, with observed dosing of methadone in the clinic. Methadone is dispensed in individual bottles for each daily dose, and the bottles are required to be returned to the clinic. The initial methadone dose during the induction period with methadone cannot exceed 30 or 40 mg total in the first day. With evidence of compliance and abstinence from illicit drug use over time, patients earn take home methadone doses and the required number of attendance days decreases. After 2 years, federal regulations allow 27 take home doses per month; however, state and local regulations may not allow this privilege. If a patient is trying to keep their involvement with a methadone program confidential, numerous concerns arise. Concerns regarding methadone doses, losing the doses, having someone find the bottles, and identify the patient are real daily issues for methadone patients, and they permeate a methadone maintenance patient's life. Traveling for work or vacations can be a challenge when one is in a methadone program. I (ES) was quoted in the New York Times in 1996 stating, "a methadone-maintained patient is monitored more closely than a paroled murderer." This is true, especially early in treatment.

Office-based methadone maintenance, generally termed medical maintenance, has been piloted successfully in a number of research projects in the USA. The patients involved with these programs were transferred from traditional methadone clinics. In the future, this treatment paradigm could expand thereby eliminating some of the stigma and regulatory issues. Mount Sinai Beth Israel has had an office-based methadone maintenance program that has been ongoing since 1983. The top cause of death in the program of 347 enrolled patients is not opioid related; in fact, it is tobacco-related diseases [32].

There is no patient population or disease that has been as stigmatized as the opioid dependent patient treated in a methadone clinic. Nobody says, "We're going to close down all the hypertension or primary care treatment clinics," but a politician can say they are going to close down a methadone clinic and be cheered for doing so. Currently, the governor of Maine wants to eliminate all Medicaid funding for methadone [33].

On television, methadone is often used as a synonym for useless, futile, stupid, and hopeless. Often these insulting, erroneous, and derogatory depictions of methadone are done innocently. There is no political correctness involved with depictions of addiction in general, and methadone in particular, in the media.

Rockefeller University, where methadone maintenance originated, listed their top ten accomplishments in their first 100 years of existence. The University highlighted methadone treatment to manage heroin addiction, and yet health care providers sometimes state, "I never use methadone it's worse than heroin!"

The co-founder of Alcoholics Anonymous (AA) asked Dr. Dole, who was an AA board member, if he could please work on a "methadone" for alcoholism. Dole did research on such a treatment, but due to alcohol, lacking a specific receptor was unsuccessful. It is both ironic and unfortunate that some AA groups are opposed to effective addiction pharmacotherapy in 2015.

Methadone Verse Buprenorphine and Naltrexone

How does one choose between methadone and buprenorphine? Buprenorphine has a lower risk of overdose and overdose deaths and does not prolong the QT interval. Patients with chronic pain might choose methadone for its more effective analgesic action. Buprenorphine has less inhibition of gonadotropin-releasing hormones than methadone and therefore libido should be less affected [21, 34]. Hepatotoxicity does not occur with either agent. Elevated liver enzymes are common and likely due to chronic Hepatitis C infection or concomitant misuse of alcohol. Although pharmacological differences are important, the regulatory differences, the methadone clinic verse office-based treatment with buprenorphine often trumps the pharmacological differences. Naltrexone, an opioid antagonist, is approved for the treatment of opioid use disorder. Early studies using daily naltrexone tablets did not demonstrate good outcomes. This was secondary to medication adherence issues however. A newer intramuscular depot formulation taken once monthly is now

approved (Vivitrol™). Studies show good outcomes compared to placebo and decreased craving in the naltrexone-treated patients [35].

Conclusion

Methadone maintenance treatment for opioid use disorder has been in existence for 50 years in the USA. There is a robust evidence demonstrating its effectiveness and safety. Methadone maintenance treatment has resulted in lives saved and decreased prevalence of significant infections such as HIV and hepatitis. The World Health Organization lists methadone as an essential medication. Patients who have been maintained for long periods do not demonstrate any end organ damage. Once stabilized on a proper dose of methadone, a patient should be able to engage in any occupation they are otherwise eligible for, start or continue with their education, and be a fully functional member of their families and communities. Unfortunately, severe stigma has been part of the methadone "experience" from its inception. Detractors claim that methadone maintenance is simply substituting one addiction for another. Despite the strong evidence base, there has been a lack of acceptance of opioid agonist treatment in many quarters, including the addiction treatment community. Patients who are doing well on methadone remain invisible to the public. They try not to reveal their methadone treatment. A patient taking his/her dose of methadone daily, having negative urines for illicit and non-prescribed drugs, using their time productively, is not "addicted" to methadone, is "abstinent," and is in "recovery." Rehabilitated patients on methadone are able to perform in any occupation they are otherwise qualified for. Stable rehabilitated methadone patients are employed in many different occupations, some in safety sensitive positions, with employer knowledge. There are patients in methadone treatment for which full rehabilitation is a challenge. In these patients, methadone maintenance is a harm reduction modality—decreasing the amount of opioids used and maintaining contact with the clinic and its treatment options. Methadone has worked well for many patients over the past 50 years. Effectively integrated methadone maintenance programs remain a critical treatment option in the treatment of opioid dependence today.

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