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Methadone Maintenance Therapy (MMT) and Alternatives in Opioid Use Disorder: Reviewing the latest advancements, outcomes, and challenges in substitutional therapy for opioid addiction - literature review

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Abstract

Introduction and Purpose: Opioid addiction is a serious challenge for public health worldwide, and methadone maintenance therapy (MMT) is a key therapeutic approach. This review intends to provide an up-to-date summary of the pathophysiology, clinical manifestation, diagnostic techniques, and treatment options for Opioid Use Disorder.

Materials and methods: The literature available in PubMed, Scopus, and Google Scholar databases was reviewed using the following keywords: "MMT," "methadone maintenance therapy", “maintenance therapy”, "opioid use disorder", "opioid addiction," "methadone”, ”naloxone” “naltrexone”, and “buprenorphine”.

State of Knowledge: This review examines current approaches in maintenance therapy for Opioid Use Disorder (OUD). In the study, we focus on treatments using methadone, buprenorphine, naloxone, and naltrexone. It focuses on recent advancements, comparing the effectiveness, safety, and patient outcomes of these therapies. Key challenges in treatment accessibility and implementation are also discussed, providing an updated overview of the field and identifying areas for future research in opioid addiction therapy.

Conclusion: There is a series of studies researching the psychological and behavioral problems associated with opioid addiction. This research has given medical practitioners valuable guidance on effective management techniques. According to the authors, compared to other alternative treatment methods, methadone maintenance therapy (MMT) is still considered the most effective pharmacotherapeutic method in the treatment of opioid addiction. Nevertheless, ongoing research is essential to improve diagnostic processes, develop innovative therapies, and enhance the overall quality of care for those affected by these challenges.

Keywords: opioid addiction; methadone; MMT; buprenorphine; opioid use disorder;

Introduction

Opioid Use Disorder (OUD) has emerged as a critical public health crisis, affecting millions globally. Characterized by a pattern of opioid use leading to significant impairment or distress, OUD encompasses a range of legal and illegal substances, including prescription pain relievers, heroin, and fentanyl. Around the world, drug use leads to about 500,000 deaths

annually. Of these, a significant majority, over 70%, are due to opioids, with upwards of 30% of these deaths being a direct result of overdosing. This statistic highlights the severe impact of opioid addiction and the urgent need for effective treatment strategies to address this global health crisis [1].

Epidemiology and Impact

In Poland and across Europe, opioid use presents significant trends and challenges. In 2021, approximately 0.33% of the EU population, or 1 million people, were estimated to have used opioids. Opioids were the main reason for drug treatment entry for 71,000 patients in Europe, with heroin as the predominant opioid. This trend indicates a decrease in individuals seeking treatment for heroin use, given an average of 13 years between initial heroin use and treatment [2].

Additionally, data from 23 EU Member States, including Poland, indicated that around 419,000 patients received opioid agonist treatment in 2021. Heroin was the third most reported drug in acute drug toxicity presentations in European hospitals in 2021, and opioids accounted for an estimated 74% of fatal overdoses in the EU [2].

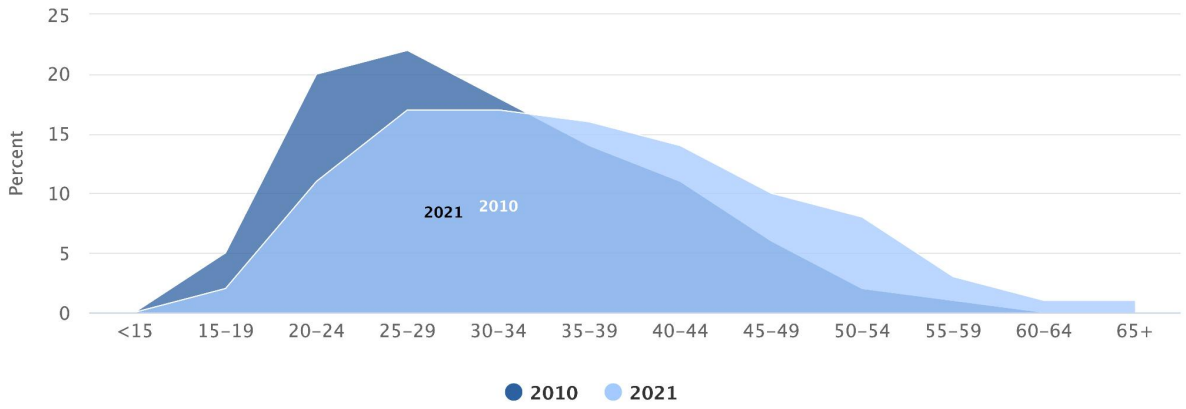

Figure 1. Age distribution of never previously treated patients entering treatment with heroin as their primary drug, 2010 and 2021.

Source: European Monitoring Centre for Drugs and Drug Addiction. (2023). Heroin and other opioids – The current situation in Europe.

As indicated in *Figure 1* there is a significant shift in the age distribution of patients entering treatment with heroin for the first time. In 2021 the distribution is highly more skewed

towards younger segments than in 2010. Nevertheless, the most numerous segment remains unchanged (patients between 25 and 29 years old).

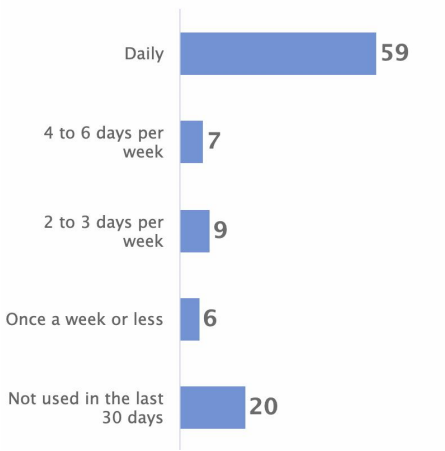

Figure 2. Frequency of use in the last month (%): all treatment entrants [heroin treatment]

Source: European Monitoring Centre for Drugs and Drug Addiction. (2023). Heroin and other opioids – The current situation in Europe.

The distribution of addiction severity across Europe is highlighted in *Figure 2* where 59% of treatment entrants declared that they used heroin daily. The mean use per week reaches 4.7 days with only 20% claiming that they have not used heroin in the last 30 days.

The extent of the opioid issue is highlighted by the 9.5 tonnes of heroin seizures in the EU in 2021, evidencing a significant presence of heroin in the region [2]. These statistics emphasize the ongoing challenge of opioid use in Poland and Europe, necessitating sustained efforts in treatment, harm reduction, and law enforcement.

Social Problem	Very Important	Important	Moderately Important	Of Little Importance	Unimportant	Difficult to Say
Economic Crime	27.7	44.7	18.7	5.8	1.5	1.6
Common Crime	28.8	44.3	18.8	5.1	1.1	1.9
Drug Addiction	33.6	41.6	17.4	5.4	1.3	0.7
Environmental Pollution	37.5	41.9	14.9	4.2	0.9	0.6
Alcoholism	35.7	42.7	15.9	4.1	1	0.5
Moral Crisis	18.4	38	27.1	9.8	2.6	4.1
Poor State of Health of Society	28.5	43.8	19.7	5.6	1	1.3
Decrease in Standard of Living	25.6	42.4	23.1	5.5	1.3	2
Housing Situation	26.7	46.3	19.1	5.9	1	1
Domestic Violence	37.5	40.9	15.3	4.3	1.2	0.9
Violence and Aggression on Streets	32.9	43.9	16.2	5.2	1.3	0.6
Youth Alcohol Consumption	35.4	41.4	16.8	4.5	1.2	0.6
Unemployment	30.1	40.9	18.4	7.3	1.9	1.3
AIDS	23.3	34.9	21.7	11.6	3	5.4

Table 1. Assessment of the importance of various social problems at the country level (percentage of respondents) 2018/2019 (%) [Poland]

Source: Own elaboration based on Krajowe Biuro ds. Przeciwdziałania Narkomanii. (2020). Raport o stanie narkomanii w Polsce 2020.(National Bureau for Drug Prevention. (2020). Report on the State of Drug Addiction in Poland 2020.)

Table 1 displays the results of a nationwide survey conducted in Poland. Respondents perceived drug addiction as one of the most significant and urgent social problems with 33.6% considering it as "Very Important," and 41.6% as "Important".

Opioids

Opioids as agonists stimulate opioid receptors. Opioids include opiates - plant alkaloids, endogenous opioids (endorphins, enkephalins, dynorphins), semi-synthetic opioids like heroin and oxycodone, as well as synthetic opioids (pethidine, fentanyl, methadone, diphenoxylate, loperamide). Plant alkaloids are components of opium and include substances such as codeine, morphine, and papaverine. Due to their potent euphoria-inducing effects, these substances frequently result in addiction development. In modern times, the significance of opioids initially used for pain therapy is increasing compared to their non-medical uses [3].

Opioid Use Disorder

Opioid Use Disorder is characterized by the need for temporary or continuous opioid intake, often at the expense of other activities, regardless of the resulting consequences that impact health and quality of life. This behavior underscores the compulsive nature of the addiction, where obtaining and using opioids becomes a priority, often leading to the neglect of personal, professional, and social responsibilities [4].

DSM-5 Criteria for Diagnosis of Opioid Use Disorder:

- Opioids are often taken in larger amounts or over a longer period than was intended
- Persistent desire or unsuccessful efforts to cut down or control opioid use.
- A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
- Craving, or a strong desire or urge to use opioids.
- Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.
- Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
- Important social, occupational, or recreational activities are given up or reduced because of opioid use.
- Recurrent opioid use in situations in which it is physically hazardous.
- Opioid use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
- Tolerance, as defined by either of the following: a need for markedly increased amounts of opioids to achieve intoxication or desired effect, or a markedly diminished effect with continued use of the same amount of the substance.
- Withdrawal, as manifested by either of the following: the characteristic opioid withdrawal syndrome or opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms [4].

Severity: Mild: 2-3 symptoms. Moderate: 4-5 symptoms. Severe: 6 or more symptoms [4].

Pathophysiology

Opioid addiction is characterized by its impact on systems responsible for motivational processes and reward system. The dysregulation of these systems is accompanied by cognitive function impairment and an elevated level of stress. Gradually, tolerance to the opioid's effects develops, along with repeated episodes of bodily intoxication. Following this, an addiction forms, characterized by habitual misuse, an intense desire and active pursuit of the substance, along with an overwhelming urge to consume and distress experienced when the opioid is not available (often described as "craving") [5,6].

The reward system consists of neurons located in the ventral tegmental area (VTA) and their target projection areas, such as the nucleus accumbens (NAS), the ventral-anterior part of the caudate nucleus, the amygdala, the extended amygdala, and the prefrontal cortex. Other brain structures significantly involved in emotional behaviors include the limbic system and the prefrontal cortex, which is engaged in working memory (controlling the "craving" for opioids). Additional structures are the cingulate cortex, the hippocampus, and the amygdaloid complex. In addition, the increased activity in the amygdaloid complex is responsible for levels of anxiety and aggression. As a result of adaptive processes influenced by addiction, the activity of reward structures weakens, leading to reduced dopamine release, as well as a decrease in the number of D2 dopamine receptors. This is accompanied by the development of tolerance, with decreased sensitivity to opioids, including natural ones. There is also a reduced sensitivity to natural stimuli of the reward system, such as those provided by sex or food [6].

A significant body of research suggests that genetics are important in the onset of addiction [7]. Genetic mutations, including those in genes encoding opioid receptors, can have a profound effect on addiction development. Specific modifications in DNA, believed to be linked to addiction predispositions, have been identified. Research in this field points to the role of genes involved in opioid metabolism in opioid addiction, shedding light on the disease's origins, the individual variation, and the risk of addiction. The OPRM1 variant of one of the genes is used in individual methadone dosing recommendations. This approach reflects personalized medicine strategies, where genetic information is employed to adjust treatment plans to an individual's specific genetic composition, potentially improving treatment effectiveness and reducing the risk of adverse effects [6,7].

Symptoms

The use of opioids usually produces the following symptoms: experiencing euphoria, reduced hunger, pain and sexual needs, restlessness or psychomotor retardation, and drowsiness. Users of opioids may exhibit either excessive physical activity or, conversely, significant slowing of actions and a tendency to fall asleep. They often feel an internal warmth despite having a normal or lowered body temperature, a result of dilated blood vessels. This can also lead to decreased blood pressure. Other symptoms include nausea, sometimes vomiting, dry mucous membranes, pupil constriction, poor light response, and reduced cough reflex, increasing the risk of aspiration. Ingesting large doses, especially in non-addicted individuals, can lead to life-threatening respiratory depression. This risk is heightened when opioids are combined with other substances that similarly affect the respiratory center [8].

Substitution therapy

Although we have effective treatments for detoxification and reducing the symptoms caused by opioid use, we still lack effective medications to cure addiction. Addiction leads to morphological and chemical restructuring of the brain, which often results in frequent relapses into the addiction. Options for addressing opioid addiction are constrained, requiring an integrated treatment strategy that combines drug therapy and psychological counseling. Gaining insights into the neurobiological foundations of opioid dependence is essential for enhancing our understanding and improving the treatment of this ailment.

For the majority of individuals addicted to opioids, substitution therapy is considered the treatment of choice. International and local organizations, along with institutions from countries with an advanced medical culture, emphasize the importance of expanding access to substitution treatment. This approach is particularly recommended for those suffering from opioid addiction who are willing to engage in this form of treatment. Substitution therapy involves replacing more harmful substances like heroin or homemade opiate concoctions with medications like methadone and buprenorphine, which have similar effects but are pharmaceutically safer and more beneficial for the patient. This therapy allows for precise control of dosage, chemical purity, duration of action, and safer administration methods, avoiding dangerous equipment like contaminated needles. The compounds used in substitution therapy have a less euphoric effect, practically no need for dose escalation, and a weaker depressive effect on the respiratory center.

The switch from illegal opioids to substitution medications allows for the creation of space to treat and control other somatic diseases that affect patients addicted to opioids, including AIDS, liver diseases, tuberculosis, infectious diseases, and mental illnesses. Extracting patients from situations often associated with the illegal acquisition of substances opens the door to systematic psychotherapeutic and re-adaptation interventions, as well as to receiving community assistance.

Substitution therapy significantly reduces or limits the use of opioids and other psychoactive substances. This results in a decrease in risky behaviors related to blood-transmitted diseases improves both the somatic and mental health of patients, contributes to better social functioning, and enhances the quality of life for those affected by addiction.

In Poland, orally administered methadone and buprenorphine are primarily used, while other countries also permit alternatives like injectable methadone, codeine, oral extended-release morphine, and pharmaceutical heroin. In 2020, substitution therapy was provided to 3170 patients in Poland. During that year, there were 25 programs conducted by healthcare facilities, as well as those performed in prisons [9]. In Poland, unlike in Western countries, the development of substitution therapy is not as advanced. Instead, therapy in specialized, residential rehabilitation centers is predominant, with a focus on achieving total and long-term abstinence. These centers are often located outside major urban agglomerations. Within these programs, psychotherapeutic approaches based on various theoretical premises are mainly used, but most often they are grounded in the principles of therapeutic communities. Patients who leave rehabilitation centers often continue to face environmental issues such as homelessness, which can be a trigger for relapse into addiction.

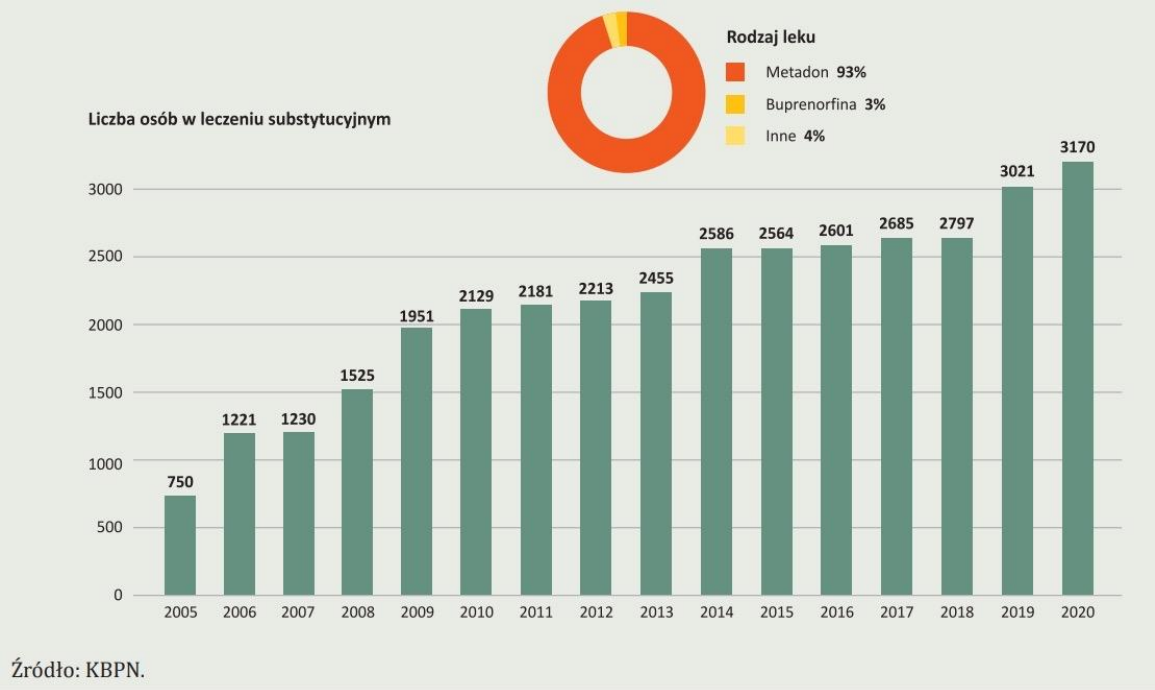

Figure 3. Change in the number of people in substitution treatment in Poland

Source: Krajowe Biuro ds. Przeciwdziałania Narkomanii. (2020). Raport o stanie narkomanii w Polsce 2020. (National Bureau for Drug Prevention. (2020). Report on the State of Drug Addiction in Poland 2020.)

Methadone Maintenance Therapy

Methadone Maintenance Therapy (MMT) is a cornerstone in the treatment of OUD. Introduced in the 1960s, MMT involves the long-term prescription of methadone, a synthetic opioid, to individuals addicted to opioids. The primary goal of MMT is to stabilize patients, reduce the harms associated with illicit opioid use, and provide a platform for recovery and rehabilitation. Methadone, a full agonist at the mu-opioid receptor, helps alleviate withdrawal symptoms and cravings associated with opioid dependency. Methadone has a typical oral bioavailability of approximately 80% and a range of 41–95% [10]. The initial effects occur within 30 minutes; however, after ingestion, the peak effects and peak plasma levels are attained on average at approximately 4 hours (range, 1–6 hours) [11]. Methadone has an average terminal half-life of 22 hours (range, 5–130 hours) [12,13]. The catalyst of methadone metabolism is the liver enzyme CYP 450 3A4. It is possible that other enzymes such as CYP2B6, CYP2D6, CYP1A2, CYP2C9, and CYP2C19 also contribute to methadone metabolism. Each patient's body processes methadone uniquely due to genetic factors, making

it necessary to adapt the dosage to the individual. For most patients, a stable dose ranges from 80–120 mg per day. Its long half-life allows for once-daily dosing, making it a practical and effective option for maintenance treatment [13].

Alternative Substances

Buprenorphine/naloxone

Buprenorphine is a partial agonist of the μ-opioid receptor, and it functions as an antagonist at the κ-opioid receptor, demonstrating a lower addiction potential. Additionally, it dissociates from the receptor more slowly. Administered orally, it reduces drug cravings and is also used sublingually in combination with naloxone. Buprenorphine has a lower treatment retention rate compared to methadone. It is better at reducing extra-medical opioid use, cocaine use, cravings, anxiety, and cardiac dysfunction. Currently marketed buprenorphine for treating opioid use disorder comes in three sublingual formulations: buprenorphine sublingual tablets; buprenorphine/naloxone sublingual tablets; and buprenorphine/naloxone sublingual film. The buprenorphine-only tablets are supplied as 2-mg tablets and 8-mg tablets. The buprenorphine/naloxone tablets are supplied as 2 mg buprenorphine/0.5 mg naloxone and 8 mg buprenorphine/2 mg naloxone. The buprenorphine/naloxone film has two additional dosage forms: 4 mg buprenorphine/1 mg naloxone and 12 mg buprenorphine/2.5 mg naloxone. Subdermal implant, a new form of buprenorphine is currently under investigation. It is designed to release the medication steadily over six months. Buprenorphine is quickly absorbed when taken sublingually, though its bioavailability varies significantly between individuals, typically around 35% for the tablet form. The drug starts to take effect within 30 minutes, with peak levels and effects generally reached about 1 hour after intake. Its average terminal half-life is roughly 32 hours, but this can vary widely. Buprenorphine is metabolized through glucuronidation and N-dealkylation, the latter primarily by the liver enzyme CYP 450 3A4. This process produces norbuprenorphine, an active metabolite of buprenorphine. Final stabilization doses of buprenorphine range from 2–32 mg per day. Current data suggest monitoring liver enzymes with buprenorphine/naloxone for improved liver outcomes [13,14].

Naltrexone

There is also the possibility of treating patients with oral naltrexone. The action of naltrexone involves binding to opioid receptors, thereby preventing their activation by administered opioids, such as heroin. Naltrexone causes the absence of positive feelings associated with the intake of the substance and simultaneously protects against overdose, as it is an antidote, a first-line substance in case of opioid overdose. From a pharmacological perspective, naltrexone seems to have several advantages, but unfortunately, patients often independently leave the program and stop taking naltrexone [6].

The U.S. Food and Drug Administration (FDA) has authorized the market release of a muscle-injected drug (Vivitrol) designed to aid in the treatment of addicted patients. This drug is an extended-release formulation of naltrexone, administered intramuscularly once a month. Naltrexone was previously approved in the United States in 2006 for the treatment of alcohol addiction. The medication administered by a physician, is injected using special needles included in the package. Like many other medications, the treatment also has side effects, including nausea, fatigue, headaches, vomiting, decreased appetite, and muscle pains and cramps. Due to the risk of patients attempting to overcome the antagonistic effects on opioid receptors, which can lead to respiratory failure, the use of this medication in opioid therapy is not recommended according to the Physician’s Desk Reference. This concern arises from the possibility that patients might try to counteract the drug's action by consuming large amounts of opioids, potentially leading to dangerous health consequences [6,15].

Naltrexone is primarily used in young individuals who are motivated for treatment, have a short history of drug addiction, possess a stable work and family situation, and are surrounded by a supportive environment. It is also an option for those who, for various reasons, do not want or cannot use other forms of treatment. This often applies to healthcare workers.

Methadone or buprenorphine

In a study evaluating the efficacy of opioid agonist drugs using buprenorphine, 40 patients were divided into two groups: one receiving buprenorphine at a dose of 16 mg per day for a year, and the other having their dose gradually reduced to a placebo. In the buprenorphine group, 75% remained in therapy, no deaths occurred, and 75% of urine samples were negative for illegal drugs. In contrast, none in the placebo group stayed in therapy for a year, and there were four deaths. These results suggest buprenorphine is effective in retaining patients in treatment and reducing illegal drug use. Similarly, in a study with methadone, the treated group had 0% mortality compared to 11.8% in the control group receiving only psychosocial support [16].

Both methadone and buprenorphine can cause several side effects typical of opioid medications. These include drug-induced sedation, weight gain, nausea, constipation, swelling, decreased libido, and headaches. Methadone may also prolong the QT interval of the heart. Many of these adverse effects can be minimized or reduced by the dose of methadone or buprenorphine [17].

Few high-quality randomized controlled trials focus on the comparison of buprenorphine and methadone in the treatment of opioid use disorder. In the study "Starting Treatment with Agonist Exchange Therapies" conducted on a representative sample, the treatment of buprenorphine/naloxone was compared with methadone treatment, focusing primarily on liver condition and patient behavior such as the propensity for risky actions (e.g., risk of HIV infection), illegal use of psychoactive substances, and willingness to continue treatment. Participants were randomly assigned to either a buprenorphine/naloxone group (with an average maximum daily dose of 22.2 mg) or a methadone group (with an average maximum daily dose of 93.2 mg) for a period of 24 weeks. Both groups underwent the same regimen of laboratory and survey tests (liver tests, urine drug screening, and patient drug use reports). 74% of patients in the methadone group completed the full treatment cycle, compared to 46% in the buprenorphine/naloxone group. Additionally, for those receiving higher maximum daily doses of methadone (60 mg/day or more), the completion rate was 80%. Higher doses of buprenorphine/naloxone also showed better outcomes, with a virtually linear relationship. However, at the highest administered maximum daily dose of 30–32 mg, the completion rate

for buprenorphine/naloxone was 20 percentage points lower (i.e., 60% of participants) than in the comparable methadone group [13,18,19,20].

Transcranial Magnetic Stimulation

A promising approach to treat addiction involves using therapeutic techniques to bring about changes in the brain's neuroplasticity, specifically targeting the disrupted neural circuits. Repetitive transcranial magnetic stimulation (rTMS) has emerged as a non-invasive method for this purpose. The process entails creating a brief yet potent magnetic field by channeling a quick burst of electric current through a magnetic coil. This field can either stimulate or suppress a small region of the brain located directly under the coil [21,22,23].

It has been increasingly used over the last twenty years to stimulate brain areas on the surface, which in turn affects deeper brain structures, inducing neuroplastic changes. This technique helps to alleviate addiction-related symptoms, such as cravings, and can reduce the consumption of drugs. rTMS has shown effectiveness in other clinical disorders, but its application in treating substance abuse disorders is still developing. More research is necessary to fully understand how to use rTMS most effectively for addiction treatment, including determining the best practices for its application and identifying which groups of patients are most likely to benefit from it [24, 25, 26,27].

Challenges in MMT:

Despite its effectiveness, MMT faces significant challenges. Stigma continues to be a major barrier to treatment, affecting both societal perceptions and patient self-esteem. Regulatory hurdles can limit access to treatment and complicate the management of therapy. Certainly, one difficulty is the access to medication for patients from outside large cities, living far from helping centers. Managing the side effects of methadone and ensuring patient compliance are ongoing challenges, as is preventing the diversion of methadone for non-therapeutic use [28,29,30,31].

Conclusions

Substitution therapy seems to still be the best source of help for patients with opioid addiction. In our opinion, the advantages of Methadone Maintenance Therapy (MMT) over alternatives

include the fact that the substance is administered orally by qualified personnel in outpatient conditions, always in the appropriate dose. Methadone performs better in studies compared to buprenorphine with naloxone. However, it is important to remember that buprenorphine with naloxone also brings beneficial effects and is widely available. Thanks to therapy, we are in constant contact with the patient, the addicted person is in the system, and the oral form they take is not burdensome for them. Methadone therapy allows for the possibility of taking up work, continuing education, and keeping addicted individuals within the community from which they are often excluded. It is a chance to treat other co-occurring diseases and reduce risky or criminal behaviors. Substitution therapy is an opportunity to break free from addiction and repair family ties. It offers a chance for a dignified life and brings significantly better long-term effects than addiction therapies, although it should be supported by them.

Author Contributions

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