

The Effect of Marijuana on the Outcome of Methadone Maintenance Treatment (MMT)

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Abstract: Opioid addiction and opioid dependence is a constantly growing problem in the US and about 33 million opioid users globally are affected. The illicit use of prescription opioids is a major factor for increased mortality and medical emergencies. The illicit use of opioids is associated with health problems, criminal actions, low socio-economic function and worst case, death. Methadone maintenance treatment is the most commonly researched treatment method for opioid use disorder. Methadone is a long-acting synthetic opioid that is used as harm reduction and prevent withdrawal symptoms, reduce cravings without induction of the euphoric effect that illicit opioids cause. About 245,000 people are enrolled in opioid treatment programs throughout the US. Poly substance use is very common among methadone maintenance patients and marijuana is the most frequently used drug. The percentage of patient's using marijuana while enrolled in MMT reported as high as 50%. The interpretation and consequence of the positive THC in the drug screen is left to the treating physician. Due to the high rate of positive THC in urine drug screens in the methadone patient population the detected THC has in many cases/treatment-centers no consequences for the patient. Very limited treatment guidelines are available how to respond to the patient population using marijuana. This article is a systematic review utilizing databases PUBMED, MEDLINE, Psych INFO, EMBASE. This article is designed to develop treatment guidelines for positive THC findings in urine drug screens of patients enrolled in MMT

Keywords: Alcohol consumption, gender difference, CVD mortality, Russia, 1956-2010.

1. INTRODUCTION

Opioid use disorder, defined by the DSM V criteria, has been an increasing problem over the last three decades.

The United States constitutes only 4.6% of the world population; however, it consumes 80% of

the world's opioid supply and 99% of the world's hydrocodone supply. Retail sales that use opioid medications, including methadone, oxycodone, fentanyl-based hydromorphone, hydrocodone, morphine, meperidine, and codeine, have increased from a total of 50.7 million grams in 1997 to 126.5 mg in 2007 (1).

SOURCE: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration, Treatment Episode Data Set (TEDS). Data received through 11.03.10.

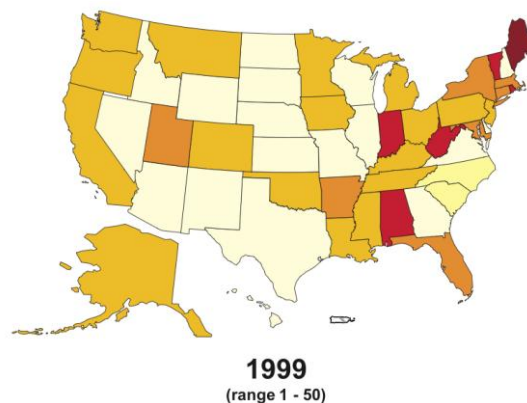


Figure 1. Primary non-heroin opiates/synthetics admission rates, by State (per 100,000 population aged 12 and over)

This is an overall increase of 149% with increases ranging from 222% for morphine, 280% for hydrocodone, 319% for hydromorphone, 525% for fentanyl-based, and 866% for hydrocodone to 1,029% for methadone. New surveys of opioid medications and mortality show a steadily rising rate of unintentional deaths due to prescription and therapeutic use of opioid medications (2).

In the US the number of opioid users has tripled since the 1990s and affects current about 33 million users globally. Particularly the illicit use of prescription opioid medications becoming more frequent compared to other opioids for example heroin leading to increasing numbers of emergency room visits and higher death rates (3, 4).

SOURCE: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration, Treatment Episode Data Set (TEDS). Data received through 11.03.10.

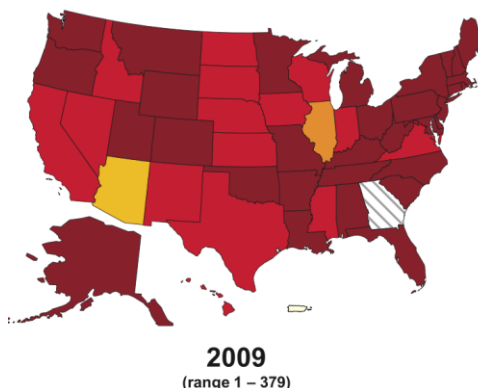


Figure 2. Primary non-heroin opiates/synthetics admission rates, by State (per 100,000 population aged 12 and over)

2. OPIOID ADDICTION/OPIOID USE DISORDER

The core essential features of addictive behavior due to drugs is involuntary and reflects a loss of control over opioid use:

1. Taking the opioid in larger amounts and for longer than intended
2. Wanting to cut down or quit but not being able to do it
3. Spending a lot of time obtaining the opioid
4. Craving or a strong desire to use opioids
5. Repeatedly unable to carry out major obligations at work, school, or home due to opioid use
6. Continued use despite persistent or recurring social or interpersonal problems caused or made worse by opioid use
7. Stopping or reducing important social, occupational, or recreational activities due to opioid use
8. Recurrent use of opioids in physically hazardous situations
9. Consistent use of opioids despite acknowledgment of persistent or recurrent physical or psychological difficulties from using opioids
10. Tolerance as defined by either a need for markedly increased amounts to achieve intoxication or desired effect or markedly diminished effect with continued use of the same amount. (Does not apply for diminished effect when used appropriately under medical supervision)
11. Withdrawal manifesting as either characteristic syndrome or the substance is used to avoid withdrawal.

3. METHADONE MAINTENANCE TREATMENT (MMT)

The treatment of opioid use disorder is the most researched therapy form for maintenance management in persons suffering opioid addiction (4, 5). Methadone is as a long-acting synthetic opioid is most widely researched pharmacological treatment for maintenance therapy for opioid addiction and dependence. Methadone does not induce the euphoric feeling that illicit opioids cause but is used to reduce cravings and withdrawal symptoms (6, 7).

Chart 1. DMV Criteria for Opioid Use Disorder (4)

A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

Studies have shown a significant decrease in criminal activity as well as reducing mortality rates among patients with opioid use disorder (6, 7).

The treatment with methadone is a federally regulated process that requires a slow and careful titration of the medication to avoid the risk of overdose. The phases in order to reach maintenance phase include initiation, induction and stabilization. In the early course of treatment, the patient is especially vulnerable to illicit drug use due to the gradual process to

establish the therapeutic blocking dose of their opioid receptors (8). The gradual introduction to methadone treatment takes several weeks and requires patience which is not easy to understand from the perspective of an addict. “The Here-and-Now-Thinking” will get addressed in counseling sessions and new goals and approaches will be illustrated and taught (9).

Importantly, behavioral changes and identification of triggers are addressed during the therapy session: People, Situations and Places. Therapy sessions are an important factor in the success for the MMT (10). Therapy and counseling is an important factor in the success of MMT. Polysubstance use is addressed and strategies to have shown to decrease illicit drug use in MMT patients are take-home doses, dose changes, time of dosing as well as rewards in form of money, goods and services (11).

Although MMT is overall and efficacious treatment for reducing illicit opioid use, it has high drop-out rates and often times is turning out to be in a longer time frame than initially intended, the relapse rates and mortality rates after 1 month 1 year and 5 years are much more successful than the abstinence-based treatment (10,12,13). One very important factor for the success for MMT is the identification of causes for relapses or factors that predict relapses. Lapses are crucial to study because they offer an opportunity to intervene early in the relapse process (14, 15). Some opponents of the MMT criticize such programs because MMT patients take an opioid medication to “substitute” for their major drug of abuse. They may be less likely than patient’s in abstinence-oriented treatment to hold rigorous abstinence goals, and abstinence goals might be less predictive of abstinence while addicts deciding to enroll in abstinence-based programs might present more “determined” to stop using (16).

4. POLY SUBSTANCE USE AMONG MMT PATIENTS

Poly substance use is fairly common among MMT patients (3, 4, 17). Marijuana is seen as the most frequently used “gateway drug” that introduces the users to the use of illicit substances. This is also mostly due to the perception that marijuana is seen as “natural” or “harmless”. Cannabis use disorder is a classified DSM V diagnosis as well (5). About one in ten persons is to be estimated to become dependent upon cannabis. Studies have shown an increased

risk for Marijuana users for other illicit substance use disorders as well as alcohol use disorder (17, 18, 19)

An increasing number of states are currently in the process of legalizing the use of marijuana and making the drug even easier available and more socially acceptable (20). Marijuana is classified by Drug Enforcement Agency (DEA) in the US as a Schedule I drug which, like heroin, contains substances with a high potential for abuse, with no current accepted medical use and a lack of accepted safety for medical use (21). Marijuana induces the release of endorphins in the brain from the nucleus accumbens and the orbito-frontal cortex, which produce the feeling of pleasure and reward. Endorphins are hormones that are naturally produced in the brain that have an opioid- like effect. In addition, Marijuana acts as a dopamine agonist in the brain, stimulating reinforcement regions in the meso-telencephalic dopamine system. (22, 23). Research with marijuana due to its federal regulation is very limited. Studies mostly focus on the interaction of cannabinoids with opiates in terms of signaling and eventual synergistic effects.

The use of marijuana causes higher drop-out rates in school and lower academic performance and causes overall decreased life satisfaction which might be a “trigger” for consecutive drug use. As with published reports on social security disability associated with prescription opioid medications, it is likely that marijuana use leads to high rates of disability that is caused by the marijuana (24, 25, 26). As with opioid addiction and induced disability, disability due to marijuana renders the user unable to perform social, occupational, and avoid legal consequences at government expense. Prescribed opioid use in relation to disability, which has been more extensively studied, can serve as a comparison to marijuana addiction affecting disability claims. In a study of disabled Medicare beneficiaries under age 65 years, there was a significant overall rise in prescription opioid consumption. This increase was not driven by overall use in more people using opioids but rather the proportion of those using opioids chronically and addictively, at least 6 and on average 13 prescriptions per year. The authors state that the effectiveness of such a sustained and high dose is supported by scant evidence in this study (24).

Specifically, for marijuana and disability, a study looked at the level of drug abuse among

individuals enrolled in the Supplemental Security Income and Social Security Disability programs. Among these individuals, 23% had a lifetime dependency on marijuana, consistent with the various populations of federal aid recipients. This finding illustrates that almost one quarter of individuals receiving federal aid were using marijuana regularly. This percentage will undeniably increase as the marijuana is more easily accessible through legal means as with opioids and marijuana addiction will lead to disability (24). The study also illustrated that the individuals that had the most difficulty obtaining work were the group with the most psychiatrically impairments. Marijuana use increases psychiatric symptoms and is associated with psychiatric disorders at alarmingly high rates. Therefore, marijuana use and addiction lead to increased unemployment and disability rates resulting in extremely high costs not only to the individual but also to the public. As in the case of prescribed opiate use, marijuana is not a permanent and medically necessary disability under Social Security Disability and/or other forms of disability. Marijuana associated disability is reversible and improves or resolves with cessation of marijuana use (24-29).

5. RISKS OF MARIJUANA USE

Marijuana is derived from the plant *cannabis sativa* and most commonly smoked in its natural form. Other possible routes are eatables, oils and lotions or even suppositories (30,31). Marijuana consists of more than 421 components and 60 pharmacologically active cannabinoids. The two best-described cannabinoids are THC and cannabidiol (CBD). Most of the other compounds are not yet understood and their mental and physical effect are unknown (32). Marijuana has a high addiction potential, impairing the user's judgment and leading to hazardous situations when used despite the negative consequences in user's personal life, occupation and lastly health (30,31). Marijuana is known to cause severe toxic effects on the user including physical as well as psychological effects:

1. **Cognition:** Marijuana causes an impairment in cognition and judgement. A study with airline pilots showed that even if their judgement was subjectively not impaired, they showed impairment in cognitive tests. The reduced cognitive function might also be the causing factor for increased criminal activity and higher rate of motor vehicle

accidents (30-33).

2. **Mental Health:** Marijuana use causes earlier onsets of Bipolar disorder in predisposed persons. It also can cause manic episodes in already existing bipolar disorder. In addition, marijuana causes psychotic symptoms and paranoia that can be severe and lead to hospitalizations. Marijuana use also increases anxiety and depression (34, 35, 36).
3. **Cardiovascular system:** The effects of Marijuana on the cardio-vascular system range from tachycardia and increased cardiac labor to ischemia in organs due to higher levels of carboxyhemoglobin (37, 38).
4. **COPD:** Marijuana causes similar to nicotine symptoms of COPD and users wheeze and frequently cough (34, 37).
5. **Immune system:** Marijuana use suppresses the immune system in the user which causes especially in HIV patients a higher risk and rate of opportunistic infections (37, 38).
6. **Reproductive System:** THC suppresses the adrenal cortical hormones prolactin, thyroid hormones and growth hormones (34, 38).
7. **Cancer:** Increased risk and incidence of certain cancers: Gliomas, prostate and cervical cancers (37, 38).
8. **Pregnancy:** THC alters the neurological development in the embryo in utero. Marijuana is getting transferred through the breast milk (36, 38).

In addition, Marijuana causes dependence, tolerance and addiction. Tolerance to cannabis occurs in relation to mood, psychomotor performance, sleep, arterial pressure, body temperature and antiemetic properties (25, 38). The attempt to discontinue its use causes withdrawal symptoms consisting of: anxiety, depression, decreased appetite, headaches, insomnia, irritability, muscle tension, nausea, nightmares and unpleasant vivid dreams (28,38). Marijuana has a long half-life and, due to its lipophilic quality, persists in the body for a long time following its last exposure and makes its effects dangerous to predict in terms of its toxicity. This pharmacological quality differentiates marijuana from other drugs for example opioids and alcohol, which are cleared out of the user's system in a shorter, specific time window and do not accumulate and have more predictable effects (38, 39).

Marijuana acts as a dopamine agonist in the brain, stimulating reinforcement regions in the meso- telencephalic dopamine (DA) system (34, 38, 39). Further, marijuana is not FDA approved and classified as a Schedule I medication with no proven medical benefit (40).

6. EFFECTS OF MARIJUANA METHADONE MAINTENANCE TREATMENT

The rate of patient's using Marijuana while enrolled in MMT is on average as high as 50% but reported to range from 40-95%. The high percentage of patients using marijuana as a co-occurring substance is a big challenge for the treating physician in MMT programs (41, 42). There is no clear clinical guideline for the interpretation and consequences of the positive THC finding in the routine UDS obtained in MMT programs. The current opioid dependence treatment philosophies in the U.S. range from mandated drug-free policy, meaning the patient must commit to abstinence to all substances to remain in treatment to maintenance-only approach where methadone treatment is provided and all other substance use is tolerated.

Since marijuana is legal in certain States in the U.S. and patients in MMT are able to obtain a "Medical Marijuana Card" physicians are more frequently accepting the positive THC without any negative consequences for the patient in terms of the patient's progress in the treatment program. Positive THC with legal marijuana status is seen equal to a written prescription medication by the physician. Studies on the association of marijuana use and MMT outcomes have shown conflicting results, but the majority of studies have shown adverse outcomes. Also, there appears to be a difference of the effect of cannabis depending on the stages of agonist therapy. The initiation phase is the most vulnerable phase and shows the most negative impact on the outcome (43,44).

However, cannabinoids are known to impact opioid signaling in the brain when administered concurrently (43-49). The maintenance phase is on the other hand less vulnerable and patients are more stable and progressed in therapy and behavioral changes. Poly substance use has been associated with poorer treatment outcome for patients in MMT compared to patients that only use opiates. This has been confirmed in studies back from 1970, 1971 (5, 50, 51, 52).

Early reports from 1989 by *DuPont and Saylor* already raised the concern that Cannabis use in Methadone-maintained patients can interfere

with their treatment goals. The group tested 300 patients per urine drug screen from two different clinics but in their analysis had difficulties distinguishing from other co-occurring substance use (42). *Weiss et al* showed no adverse outcome in a group of adolescents with cannabis use while in Opioid maintenance treatment. The study included 152 patients 15-21 years who were followed for 12 weeks. The patients enrolled in this study were mild users and used cannabis only 3 days per month (52, 53).

Budney et al did not show a difference in treatment outcomes for MMT patients either in his study that had 107 patients enrolled. 60% of his patients were using marijuana upon intake and 94% of those continued to use while enrolled in MMT. The group did notice a higher incidence of marijuana users in MMT to not be married, have higher financial difficulties and be more frequently involved in drug dealing or engaging in sharing of needles (46). *Wasserman et al* discovered that marijuana use caused a significant increase in subsequent heroin use. The group followed 74 patients who had stopped using heroin within the last 3 weeks and analyzed particular factors for relapse. The group found a significant correlation between positive THC finding in urine drug screen and called cannabinoid-positive urine as a robust predictor of resumption of heroin use (14). Several studies did not notice any difference on the outcome in opioid agonist therapy depending on the use marijuana. (54,55). Few studies (42,43) found that patients using cannabis used less opioids while using marijuana and marijuana is even called successful substitute for heroin.

There have several studies showing a negative outcome on socio-economic functioning such as marriages or employment (56). *Epstein and Preston* showed in their study that cannabis use increased the outcomes for jail time and family conflict (45). An additional study by *Newville et al* tested for an interaction of substance use on HAART adherence among MMT patients. They showed an association between the non-adherence to HIV medication adherence with the use of cannabis while in opioid agonist therapy (18). Another study done by *Calsynin* 1998 looked at the change of MMT outcome and marijuana use after making a policy change in the methadone clinic. 120 patients were enrolled with the status of dosing on site twice per week and positive

THC in urine drug screens. The new policy required the patients to stop using marijuana in order to maintain their dosing status. Mean length of time in treatment was 105 months. The outcome was that 50% of the patients remained their dosing status of twice a week on site and negative drug screens. Those patients who lost their status suggested minimal negative impact from the policy change and mostly lost their status due to the use of other illicit substances. The patients reported productivity in the counseling sessions guided towards desire to quit since policy change. Criticism to this study are the small patient number and the selection of higher functioning patients (41).

7. DISCUSSION

Methadone maintenance programs have been shown to be a successful way to help patients with opioid use disorder. The overall the success of MMT depends on elimination of the use of the drug of choice but also on the co-occurring substance use. Evidence indicates that treatment retention is a major factor in success for the treatment. So, the focus in treatment should be on eliminating high risk behavior and co-occurring substance use, including the use of marijuana. There are no clear defined guidelines available for the physician in methadone clinics how to address and respond to positive THC findings. The current literature shows inconsistent data but overall the risks of marijuana outweighs its benefit.

Marijuana remains a Schedule I federally controlled substance but the ongoing legalization in many states bears an increasing risk for availability for the user. It also increases the difficulty how to justify the negative impact of marijuana with legal status and on the other hand associate the illicit use with negative consequences in treatment phase or take-out. Can marijuana be justified as a medication in MMT without any negative consequences? How does the legally consumed marijuana affect the patient's brain differently than the illicit one? To address these concerns will remain up to the treating physician but the clinic should have consistencies in policy of these positive THC and THCRx findings. "Medical Marijuana" is not prescribed by a physician and not filled in a pharmacy. In addition, the actual content of the marijuana and percentage of THC varies with each sample. Users utilize the marijuana at their own discretion without any guidance from a physician or medical follow-up. Patients need to be aware of the consequences regarding their

take-home status and proper psycho-education would be beneficial to the patient about the toxic effects of marijuana and the negative outcome on MMT.

The list of the toxic effects of marijuana is long and involves most organ systems and does affect cognition negatively as well as the judgment. Patients with impaired judgment are more likely to use, which decreases the barrier to use heroin or other opioids in addition to the methadone which is negative for the outcome of the maintenance treatment and also increases the risk of overdose or death. Current studies are difficult to interpret since most have a high rate of cross-addictions and small study populations with only a short follow up period. Also, there are significant differences noticeable in the comparison of most marijuana versus control populations mostly pointing to a lower socio-economic status to start with and a larger amount of risk factors and psychosocial instabilities. The use of marijuana has also shown to further progress the decline in psychosocial functioning. The loss of support from family through divorce or jail time in the course are the named risks in the available studies, certainly not supportive of gaining or remaining in sobriety.

In addition, there has been shown an association between poorer treatment follow-up with HIV medications and therefore negative consequences on that condition. Increasing health problems also have a negative impact on the outcome of MMT. The development of clinical guidelines for the physician to address the licit as well as illicit use of marijuana in methadone maintenance programs are needed to improve treatment outcomes for their patients.

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