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ADDICTION AND MISUSE OF PRESCRIBED OPIOIDS: THERAPEUTIC MANAGEMENT (BUPRENORPHINE VERSUS METHADONE)

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SUMMARY

The misuse and addiction to prescribed opioids pose a serious public health risk. If you use prescribed opioids for an extended period, you run the risk of developing an addiction to them. Patients who have lost control of their painkiller consumption and fit the diagnostic criteria for addiction are increasingly being seen by physicians and addictologists working in a range of specialised facilities. This research was conducted with the goals of providing an overview of the facts on opioid misuse and addiction, as well as suggesting a synthesis of the therapeutic and pharmacological ideas that underlie the treatment of opioid substitution. Because they alleviate the discomfort associated with opioid withdrawal, the medicines methadone and buprenorphine have shown promise as potential opioid substitution treatments. The "ideal" drug would have to fulfil a desire, be free of any inherent toxicity, have a long half-life, have a low tolerance phenomenon, produce minimal euphoric and negative effects, cause as few overdoses as possible, and be safe to use.

KEYWORDS: Buprenorphine Methadone Substitution Treatment.

INTRODUCTION

Misuse and dependency are the two primary addictological issues that may arise from the chronic use of medications that act on the central nervous system. Opioid abuse and addiction have been more common since the turn of the century, notably in the United States and many other nations. Opioids are the subject of worldwide study, and their addiction is a major public health problem.[1,2] The word "misuse" refers to the subject's improper use of the substance,[3] which exposes him to possible social, psychological, or bodily effects.[4] In contrast, "addiction" refers to the processes of tolerance, i.e., the habituation of the brain and the rest of the body to the drug, resulting in a gradual loss of effect where increasing the dosages to retain the same effects is necessary, with a subsequent withdrawal episode in the case of abruptly quitting or lowering the substance.[5,6] Physicians and addictologists at several specialised North American institutions are increasingly faced with patients who have lost control of their analgesic usage, as diagnosed by diagnostic criteria.[7] Opioids are the principal medicines responsible for both of these secondary consequences of addiction.[4] It is typically impossible, even in a medical setting, to immediately wean these drug users due to the intensity of the phenomena of tolerance and dependency and the social issues connected with this addiction.[8] Opioid replacement therapy, such as methadone or high-dose buprenorphine, is used to treat addiction and ease the patient back into society by preventing withdrawal symptoms. These replacement programmes have resulted in a significant reduction in fatal "overdoses" and a noticeable decrease in hazardous behavior.[8]

The purpose of this study is to provide an overview of the evidence on opioid abuse and addiction and to provide a synthesis of the therapeutic and pharmacological concepts behind the treatment of opioid substitution.

The Different Categories of Opioid Substances

The term "opioid" refers to any drug, regardless of where it comes from, that has an impact that is comparable to that of morphine (natural, semi-synthetic, or synthetic). The World Health Organization classifies opioids as either moderately potent (level 2) or very powerful (level 3).[9] There is a significant problem with the misuse of these chemicals for recreational purposes throughout the world. Among these chemicals, some of the most notable examples are morphine, codeine, tramadol, fentanyl, hydromorphone, and oxycodone. Opium's principal alkaloid, morphine, serves as the molecular standard. Since ancient times, the cultivation of poppies to extract opium, which is used as a pain reliever, has been common. Morphine wasn't really "found" until the year 1804 when Friedrich Wilhelm Sertürner.[10] was able to get his hands on some of the substance. The other opioids common to all prescribers are increasingly

prescribed and classified based on their similar analgesic dose. The equivalence table compares the relative effectiveness of several drugs to that of morphine (Table 1).

Table 1: Basic/IV Dosage Equivalence Table: intravenous, SC: subcutaneous, PO: peros, TD: transdermal.[11]

ICD	Ratio	Oral morphine dose equivalence
Morphine intravenous (IV)	3	1 mg IV morphine = 3 mg oral morphine
Morphine subcutaneous (SC)	2	1 mg SC morphine = 2 mg oral morphine
Tramadol (PO)	1/5 à 1/6	50 to 60 mg of tramadol = 10 mg of oral morphine
Codeine (PO)	1/6	60 mg codeine = 10 mg oral morphine
Opium powder (PO)	1/10	25 mg of opium powder = 2.5 mg of morphine
Oxycodone (PO)	2	5 mg of oxycodone = 10 mg of oral morphine
Oxycodone in mg/d (IV, SC)	3	10 mg of oxycodone = 30 mg of oral morphine
Hydromorphone (PO)	7,5	4 mg of hydromorphone = 30 mg of oral morphine
Nalbuphine (SC)	2	5 mg nalbuphine = 10 mg oral morphine
Fentanyl (DT) in µg/h	variable	25 mg/h of FTD = 60 mg/d of morphine

Clinical Manifestations

Morphinomimetics generate central pharmacological analgesic effects, euphoria (which explains why they might create dependency and tolerance), and then a condition known as "descent," which is characterised by respiratory and pituitary depression. Morphine is often the principal metabolite as well as the energetic component of a substantial number of other opiates. Morphine has a variety of effects, and these effects shift depending on the kind of receptors that are activated (table 2).[12,13]

- Mu receptors: as a consequence of this, the individual will experience central analgesia, euphoria, hallucination, respiratory depression, miosis, and bradycardia.
- Kappa receptors result in spinal analgesia, sedation, and miosis as its consequences.
- Delta receptors are suspected to have a role in spinal analgesia, behavioural changes, and effects on the cardiovascular system.

Table 2: Summary of the main effects of opioids.[14]

Targets	Effects
Central nervous system (CNS)	Desired effects: opioid intoxication (euphoria, even dose-dependent dysphoria, well-being, drowsiness, forgetfulness of worries; analgesic effects) Undesirable effects: convulsions, panics, tremors, delirium
Cardiovascular system	Hypotension, bradycardia, syncope, increased heart rate
Digestive system	Vomiting, constipation
Others	Severe miosis (mydriasis signs a state of withdrawal), respiratory depression, inhibition of cough
Pregnancy	Non-teratogenic; passes through the placenta and into breast milk

Incidences of Prescription Opioid Use

Opioids were traditionally reserved for treating acute pain and the pain associated with cancer; but, in the early 1990s, the World Health Organization (WHO), academic communities, and state authorities pushed physicians to administer long-term opioids to patients suffering from chronic pain that was not caused by cancer.[15] In the United States, the number of morphinomimetics prescribed to patients increased by a factor of ten between 1990 and 2010.[16] Unfortunately, abuse and misuse, which has been a major cause of overdose deaths and is the root of a global health crisis, have followed this expansion of therapeutic indications.[17] The mortality rate associated with an overdose of opioids for analgesic purposes more than doubled between 2003 and 2011 in England and Wales.[18] This finding is similar to what was found in the United States, where there is a parallel evolution between the number of prescriptions and the mortality rate. Between the years 2000 and 2010, the total number of patients in Germany who were treated with morphinomimetics increased to 3.71 million from a total of 2.72 million.[19] The United Kingdom has also experienced a similar pattern of change, with the percentage of patients using potent opioids skyrocketing by 466% in just the past ten years.[20] Except for Sweden, all of the other Scandinavian nations saw a rise in their usage of morphinomimetics between the years 2002 and 2006. According to the findings of a study that tracked a group of 13,127 Danes from 2000 to 2011, it was discovered that more than 4% of the population uses opioids and that the risk of mortality is increased by a factor of 1.7 in patients who are treated for a longer period of time.[21]

Opioid Misuse

Misuse is defined as any use that is not following the recommendations of the summary of the characteristics of the therapeutic product concerned and is therefore outside the scope of the MA. This includes any use that is done for reasons other than medically necessary, such

as recreational use, injection, or sniffing, and is therefore the responsibility of the patient and/or the prescribing physician.[22]

Opioid Addiction

The presence of a withdrawal syndrome after abrupt cessation of drug use is usually accepted as a diagnostic indicator of addiction. It has been connected to prolonged exposure of some kind, as well as an adaptation of the organism to these foreign compounds.[22]

In the same way, as addictive behaviours might reflect an emotional or mental disorder, these behaviours are the consequence of a combination of individual elements (biological and psychological vulnerabilities) and contextual factors (availability and trivialization of the toxic in the environment).[23] The doctor has to empathise with his or her patient's powerlessness in the face of the uncontrollable desire to consume (known as "craving") and recommend a therapy that may include chemicals (such as substitution treatment) and psychotherapy. At this time, it is considered that all drugs that have the potential to cause addiction operate on dopamine neurons, particularly those that are located in the cortico-limbic region of the nucleus accumbens of the brain, to produce a feeling of pleasure. A "reward circuit" is activated as a consequence of the inhibition of dopamine absorption in the synaptic cleft, which causes a transient increase in the concentration of this neurotransmitter. When the amount of dopamine in the brain recovers to its usual level, a new cycle of drug use will "impose itself."

Opioid Substitution Therapy

The majority of patients who are addicted to opioids are treated with substitution medicines. These medications work by reducing withdrawal symptoms by acting as a substitute for the opioid that was consumed. After the treatment has been brought into balance, doctors will be in a better position to address comorbidities in the areas of education, socialisation, psychological health, and physical health. Non-drug treatments that provide a substantial amount of follow-up, especially those that focus on psychosocial and socio-educational aspects, play an important part in the prevention of recurrence or relapse.[24]

Because they do not cause plasma peaks or a "flash" of pleasure, opioid substitution drugs that are taken orally do not have an impact that is similar to that of a reinforcing drug. Because pharmaceutical opioid substitution treatment does not imitate the effect of opioids, it cannot be considered a "true" substitute. Oral administration, on the other hand, reduces the desire to use without matching the effect of an injection.[25] They do this by decreasing the patient's compulsive craving for opiates, which in turn frees the patient from the consumption constraints that are characteristic of addiction.

Opioid substitution is a strategy that may be used to maintain a patient's participation in a treatment programme. Craving is the clinical indication that determines whether or not a dosage adjustment is appropriate. The pharmacological and therapeutic approaches that are used to treat opioid addiction include methadone and high-dose buprenorphine (HDB). A person who is taking methadone or (HDB) but who continues to use opioids has to have a reevaluation done to see whether or not they have the motivation and ability to adhere to the programme.[23]

1. Methadone

Methadone maintenance therapy (MMT) was the first treatment that was used as a substitute (or replacement) in the United States of America, Australia, and Europe. Therefore, in 1964, Dole, Nyswander, and Kreek began developing methadone as a therapeutic for a specific addiction disease.[26]

Methadone is often given in increasing doses until the patient reaches an effective dosage of 60 to 80 mg per day or more. A titration procedure carried out for two weeks is used to establish this dosage. Except for periods of relapse, this dose is maintained for the whole of therapy and does not result in addiction. Due to the possibility of a fatal overdose in the event of improper administration, however, strict regulations (licenced healthcare institutions, secure prescriptions) limit its use.[27]

Methadone is metabolised in the liver and has a usual half-life of 22 hours after it has been taken orally. The absorption rate of methadone after oral administration is typically 75%. These pharmacokinetic features make it possible to administer the drug once every day. Interindividual variability in methadone metabolism results in large changes in pharmacokinetic parameters. This variability, which may be the source of withdrawal symptoms or overdose, may also be the reason for methadone metabolism. The pharmacological interactions that result from them may contribute to the therapy's failure, which may be the result of an inadequate or excessive dose. In addition to pharmaco-therapeutic monitoring of residual plasma concentrations, the doctor has to be aware of all of these different features for his replacement therapy approach to be effective.[28]

2. High dose buprenorphine

Buprenorphine is often suggested in doses ranging from 8 to 16 mg per day, and there is no risk of death associated with using these levels. The ease with which it may be obtained, on the other hand, has contributed to a rise in instances of its misuse and diversion. The combination of HDB and naloxone, which is available but not used to its full potential, inhibits the impact of buprenorphine injection that is intended to be its "injection".[29]

HDB is both a partial agonist for the mu-opioid receptor and an antagonist for the kappa opioid receptor.[30]

Its action in opioid substitution treatment is because it binds to mu receptors in a slowly reversible way. This allows for its daily administration. It is thought that its sublingual bioavailability ranges between 15% and 30%, and its elimination half-life ranges between 2 and 5 hours on average. The majority of its metabolism occurs in the liver through CYP3A4, and biliary excretion is the primary route by which it is excreted. In contrast to methadone, the prescription structure is not nearly as rigorous, and outpatient dispensing does not require patients to meet any criteria. When it comes to opioids, on the other hand, the prescription may only be granted for a maximum of 28 days using a system called secure prescription.

Comparison Of Opioid Substitution Treatments

The "ideal" drug would have to fulfil a need, be safe, have no inherent toxicity, have a long half-life, a phenomenon of low tolerance, little euphoric and negative effects, and as few overdoses, as is practically possible. Additionally, it would need to have a lengthy half-life. (Table 3).[24,31,32]

1- Efficiency

Based on a study that compared methadone at a daily dose of approximately 70 mg to buprenorphine at a daily dose of approximately 13 mg per day, the findings of this analysis suggest that methadone was slightly more cost-effective in maintaining patients in a drug treatment programme, but that buprenorphine was superior in helping patients to stop using drugs.[33] This conclusion was reached as a result of a comparison between the two medications. A multicenter prospective research called.[34] was carried out on ninety pregnant women who were exposed to buprenorphine and forty-five pregnant women who were exposed to methadone. The purpose of this study was to examine the effects of exposure to buprenorphine and methadone during pregnancy. Buprenorphine appears to be just as safe for substitution as methadone, which is considered the standard treatment for pregnant women who are dependent on opiates. The authors of the study did not observe any malformations or withdrawal syndromes, and they concluded that buprenorphine was just as effective. It should also be brought to everyone's attention that the use of opioid substitutes during pregnancy is connected with an increase in preterm births, a drop in birth weight, and a rise in the incidence of neonatal diseases.

Table 3: Characteristics of opioid substitution drugs.[32]

Characteristics/objectives	High-dose buprenorphine	Methadone
Long half-life:	Short life (3-5 hours) but strong tissue binding Sufficient daily intake	Long life (25 hours) after impregnation Sufficient daily intake
No flash effect, non-injectable: Gradual appearance of the effects without feeling the effects of the lack	Cmax1 = 1 h 30 Possible diversions by injection	Cmax = 3 h Syrup and capsule Difficult to inject
Little tolerance: Avoid increasing doses	Long duration of effect	Long duration of effect
Use security : Avoid overdose	Ceiling effect Low risk of overdose in monotherapy	Linear dose-effect relationship Risk of major overdose
No side effects: Keeping the patient in the care pathway	Side effects but potentially correctable	
Pharmacodynamics	Mu agonist and kappa antagonist opioid	mu agonist opioid
Pharmacologic	Absence of withdrawal symptoms Reduction of craving Absence of euphoria	Analgesic Antitussive Mild euphoria Risk of dependency Absence of tolerance

2- Toxicity

In male Sprague-Dawley rats, Table 4 presents a comparison of the relative 50 lethal doses of morphine, methadone, and buprenorphine: The opioid with the least amount of potential for adverse effects was buprenorphine, whereas methadone was the most hazardous and morphine was in the middle.[35] For the last several years, researchers from a variety of nations have conducted an increasing number of studies on the role that methadone plays in mortality.[36,38] According to the findings of a study that connected toxicological data relevant to mortality with patient registrations conducted by Bernard et al.[39] 78% of the participants who passed away were not engaged in a care programme. There is less information available on the mortality risk that is related to the use of buprenorphine therapy,[40] even though some studies have shown that there is an increase in mortality risk after the termination of methadone treatment.

Table 4: Buprenorphine intravenous median lethal dosage determination in male Sprague-Dawley rats.[41]

Opioids	DL50 (mg/kg)
Buprenorphine	230,6 + 49,3
Methadone	23,8 + 5,2
Morphine	60,3 + 21,3

CONCLUSION

Opioid use disorder is a chronic condition that may relapse often. It has been shown that methadone and buprenorphine are useful for opioid substitution therapy because they decrease the discomfort associated with opiate withdrawal. Our comprehension of the relative effectiveness, safety, and acceptability of each style of care will be enhanced by this technique, which will yield much-needed data on alternative treatment alternatives. This data will be utilised to direct the healthcare system's approach to the current opioid crisis.

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