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Methadone In Chronic Non-Oncological Pain: From Disassuefaction Of Painkillers Abuse To The Primary Management Of Opioid Hyperalgesia

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Abstract

Background and Aims

Methadone is a well-known drug for the treatment of heroinopathy but its role as an analgesic is often forgotten, especially in primary and non-specialist medicine settings. In this article we want to describe its characteristics in this application not only for the cessation of painkillers but above all for the management of neuropathic pain and hyperalgesia induced by opioid therapy in the long term.

Methods

The article was written by referring both to the technical data sheets of the drug and by associating research in paper and online books on databases such as Scopus, PubMed, Cochrane Library and Embase.

Discussion and conclusions

Methadone remains a mysterious but at the same time fascinating drug, both for the aura of mystery around its name, frowned upon by both patients and prescribers, but at the same time unparalleled in terms of efficacy for analgesia in cancer pain and not, especially in patients who have lost sensitivity to other opioids even more potent than methadone such as fentanyl. In other words, the efficacy in the cessation of abusers of painkillers both for recreational purposes and secondary to background pain now no longer controlled makes this drug unique as a maintenance therapy.

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Background and Aims

The current International Association for the Study of Pain (IASP) definition of pain as “An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” was recommended by the Subcommittee on Taxonomy and adopted by the IASP Council in 1979.[1] Chronic pain has been recognized by the World Health Organization as one of the world's major public health problems in general, as it affects all age groups with a higher prevalence in women. In Italy it affects one in 5 people, 21.7 % of the population, and one in 4 people suffer from it on average for 7 years.[2] The disease has disabling consequences from a physical, psychic and socio-relational point of view. 90 % of cases are treatable and treatable, yet as many as 40 percent of people with chronic pain are still unaware of the treatments available today. In addition, about two years elapse between the onset and the first medical visit and the times to receive a correct diagnosis are more than five years. Unfortunately, in fact, despite more than 10 years have passed since the approval of Law 38 which recognized chronic pain as a pathology that needs its own specific network of assistance and care to which citizens have the right to access, assistance for people with chronic pain turn out to be approximate and unsatisfactory: 21 percent of affected people do not know where to turn and 33 percent, before reaching a specialized center undergo inadequate therapies, unnecessarily consulting from three to seven specialists, with waste of time and resources.[3] On average, the social and economic costs per capita exceed 4,000 euros per year, weighing on the National Health Service with about 1,400 euros a year and more than 3,000 euros directly on people: 1 to 5 people suffer from it in Italy. In the context of pharmacological treatment of pain, opioids still play an important role, even in non-malignant pain. In this article we want to focus in particular on methadone regarding some of its characteristics that make it useful in the management of serious but frequent situations like the abuse of painkillers for recreational purposes, common among young people especially in America, where it acts as a maintenance therapy for psycho-physical cessation, and the management of opioid hyperalgesia in patients with chronic underlying pain, especially neuropathic and no longer controlled by other less potent opioids but taken for a long time which have led not only to physical dependence but above all to paradoxical worsening of the underlying pain and relative absence of other effective treatment techniques.[4]

Methods

The article was written by referring both to the technical data sheets of the drug and by associating research in paper and online books on databases such as Scopus, PubMed, Cochrane Library and Embase. We concentrated on research on articles that dealt mainly with the neurobiological correlates of methadone and its use in chronic non-malignant pain, without neglecting aspects relating to pharmaceutical chemistry and pharmacology. The keywords selected for the computer searches were "methadone - pharmacology, chronic pain - opioid hyperalgesia, NMDA system, methadone - role in, abuse painkillers".

Discussion

Methadone (MTD, image 1) is a synthetic opioid, synthesized in Germany in 1937 as an analgesic. It is produced entirely synthetically; Chemically it differs markedly from morphine and heroin, being a phenylpropylamine, obtained by eliminating the piperidine ring from the morphinic pharmacophore.[5][6] It comes in the form of colorless and odorless crystals or in the form of a white crystalline powder. Soluble in water, easily soluble in alcohol and in chloroform, practically insoluble in ether and in glycerol; is a chiral substance, therefore, it appears as a racemic mixture of two mirror molecules (enantiomers) in a mutual ratio of 1: 1, respectively the left-handed form of methadone (L) -methadone and the dextrorotatory (D)-methadone form (in clockwise). The dextrorotatory form possesses the powerful antitussive properties, but is almost entirely devoid of analgesic properties; it follows that levomethadone is about twice as effective as an analgesic, at the same dose, than the racemic form.[7][8]

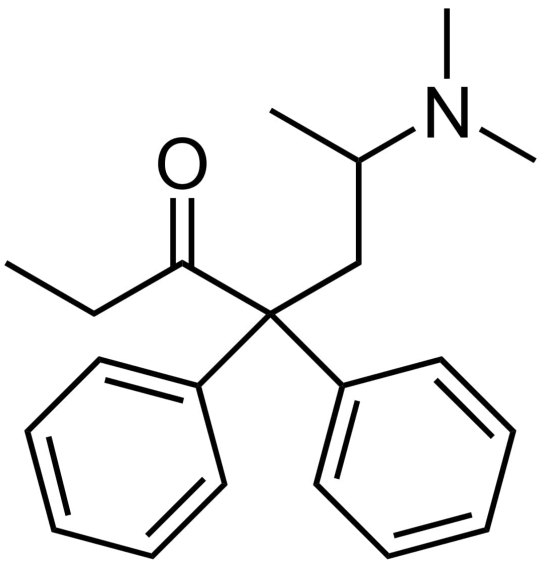

Image 1. *Chemical structure of methadone*

It is sold as an oral solution in the form of a syrup in two formulations, normal (1 mg / ml) and concentrated (5 mg / ml) or in injectable formulation (little used). The bottle is amber as the active ingredient is sensitive to light with possible photo-

induced decomposition. MTD recognizes two main therapeutic uses, which are the treatment of opiate addiction and pain.[9][10] How long concerns the latter has spread especially for the management of chronic pain, especially in intolerant patients or unresponsive to other opioid pain relief therapies. The increase in the use of MTD in recent years, especially as a painkiller, has determined, especially in the United States, an increase in overdose deaths. Just think that between 1999 and 2014 deaths attributed to MTD use increased by 390%, an effect due to the increase in its use, especially as a painkiller, and the phenomenon of diversion, that is, the use of the drug for non-therapeutic purposes (image 2).[11]

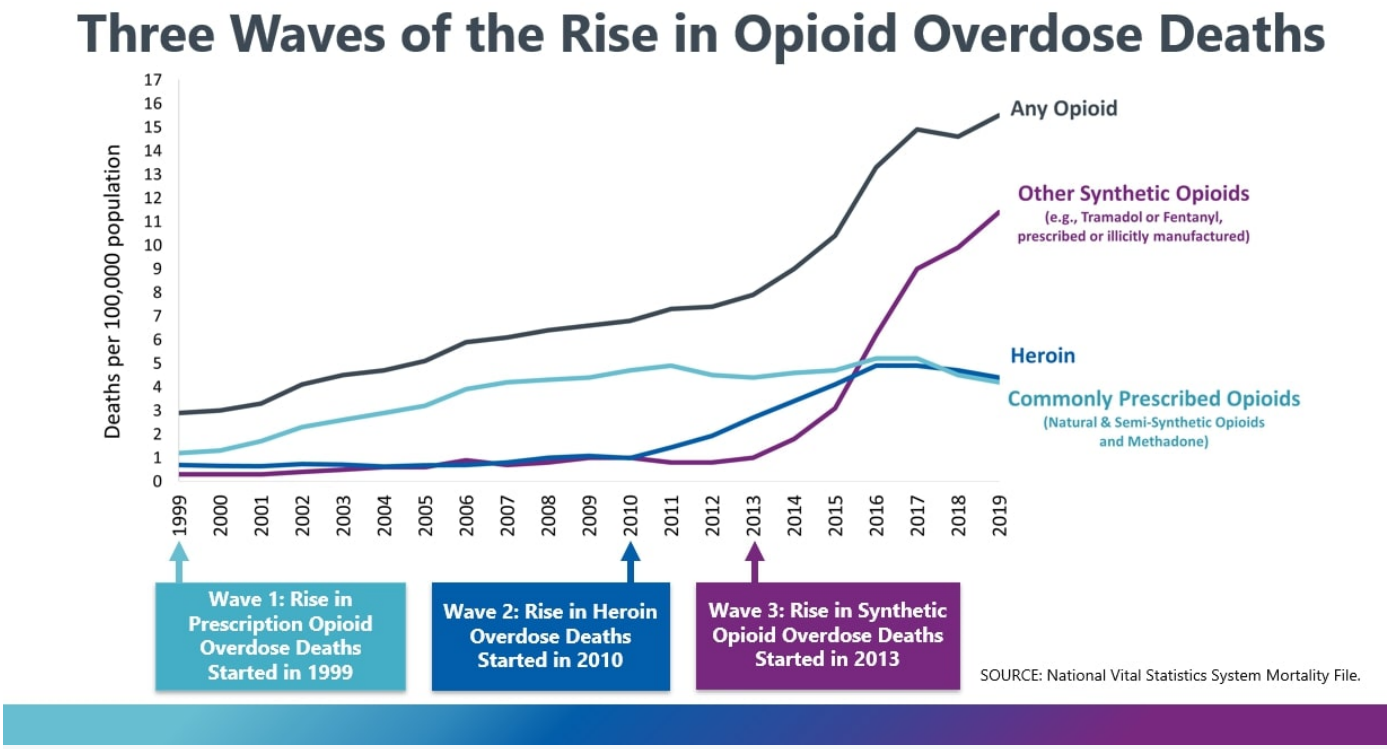

Image 2a. *Opioid overdose deaths in total in the US*

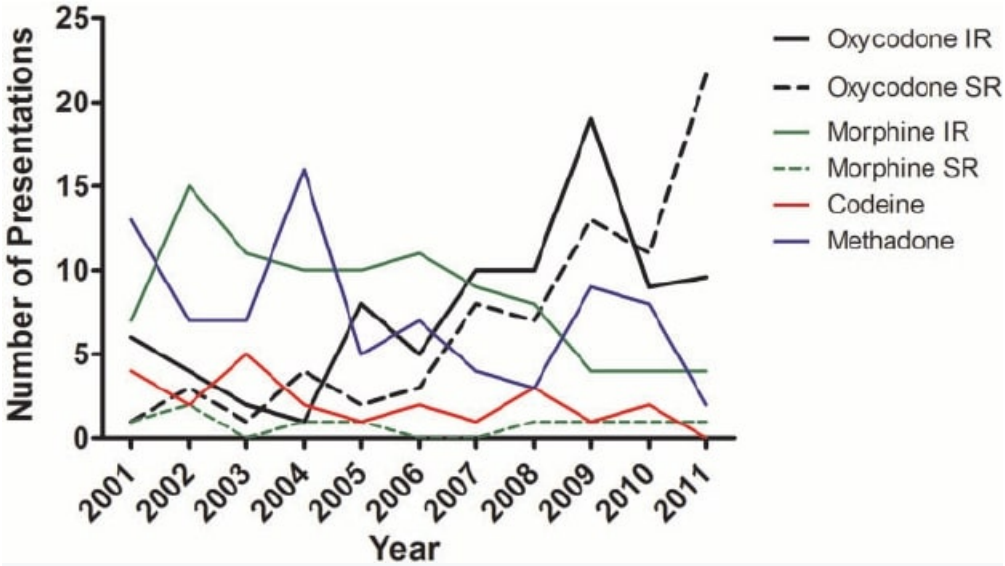

Image 2b. *Mainly involved painkillers*

However, studies in this regard have shown that the phenomenon of misuse in two therapeutic contexts is very different. In the case of the treatment of opioid addiction, the phenomenon of misuse involves above all young poly-consumers while in the case of the treatment of pain elderly subjects with serious pathologies and users of a polypharmacy.[12] On the other hand, the dosages used are completely different in the two clinical contexts, as well as the potential levels of toxicity. MTD is an opioid mu-receptor agonist with glutamate N-methyl-D-aspartate (NMDA) receptor antagonist and monoamine reuptake inhibitor properties; the plasma levels, following its oral administration, appears 30 minutes after its ingestion and presenting a bioavailability of about 70-90%. The plasma peaks of the drug appear, however, after 2-4 hours from its intake.[13] MTD is metabolized primarily by the liver to inactive metabolites by the action of P450 cytochromes, the main being CYP3A4, the same cytochrome which metabolizes many drugs used in the clinic for therapeutic purposes. Specifically, it was observed that MTD is a weak inhibitor of CYP3A4 and other substrates such as CPY2C89, CYP2C19 and CYP2D610. Since there also exist wide individual differences in CYP3A4 and CYP2D6 activities (which may have different polymorphisms), MTD may exhibit subjective variability both in therapeutic and side effects.[14] In this sense the MTD, in subjects particularly vulnerable, it can develop severe toxicity, especially if taken with drugs capable of causing prolongation of the QTc interval of the electrocardiogram. The half-life of the MTD is long, ranging from 5 to 59 hours, and in slow metabolizers, the MTD can be accumulated in the body by increasing vulnerability to the risk of respiratory depression and death.MTD has proved to be a relatively safe and manageable drug in clinical practice.[15] In any case, the greatest danger of the MTD is due to the risk of intoxication and overdose, in how much the drug has a long half-life, a high bioavailability and a tendency to accumulate due to its slow elimination from the body. In particular, the evidence shows how the risk of intoxication and death due to use of MTD are related to its long half-life, its high bioavailability, the tendency to accumulate and its slow elimination.[16] The differences individual in the pharmacokinetics of the drug, in association with too rapid titration (fractionation) of the daily dose during the induction phase, are the main factors that can favor the development of intoxication and respiratory depression.because 30 mg of MTD can cause fatal respiratory depression in non-tolerant subjects, in the induction phases the MTD in the first day should not exceed 30 mg / die. In any case, the dosage increase may take place in the following days (up to 3-5 consecutive), with variable dosages between 10-20 mg, as long as the craving does not will be controlled and the euphoric effects of the substances will be under control.[17] Clinical evidence has now amply demonstrated that the greater number of deaths from overdose occur in the induction phases due to drug accumulation, even in subjects receiving MTD for pain treatment, especially if these are elderly and suffer from severe liver and kidney disease or take drugs capable of interfering with the metabolism of the MTD. Also, to increase its safety, the drug should not be used in subjects who have a prolongation of the QTc tract of the electrocardiogram greater than 500ms or with severe cardiopulmonary pathologies. The MTD should also be used cautiously in subjects suffering from syncope and convulsions and taking drugs that can interfere with CYP3A4 metabolism. THE patients who are being treated with MTD should not be treated with highs dosages of benzodiazepines, as this could lead to a potential respiratory depression. The induction phase is also used for the treatment of pain must be cautious: the initial dose should not exceed 15-30 mg / day for the first 3 days and a distribution of the drug every 8-12 hours is recommended, according to a fractionation of the

dosage between 2.5-10 mg, based on to the patient's ability to control the pain and to tolerate the drug.[18][19]

How to prescribe methadone

The MTD is found in the table of narcotic medicines, section A and therefore requires the ministerial prescription in tracing (RMR) in triplicate. However, in order to facilitate access to pain therapies, following Law 38 of 2010, simplifications were created for the prescription of certain drugs for this specific use.[20]20 Therefore MET for the cessation of addiction to illicit opioids remains prescribable only as RMR while for the treatment of chronic pain it can also be prescribed with a red prescription (SSN) by general practitioners, with the initials TDL01 in the "regional provisions" field. It must be said that drug prescriptions are always valid for 30 days from the date of issue and can only be delivered to adults and without obvious serious psychic alterations.[21]

It is known that the administration of opiate drugs is able to induce the phenomenon of tolerance, which consists in the decreased response to a certain drug or substance. Tolerance, from a clinical point of view, can be demonstrated by the decrease in effect following the administration of a date dose or the need to increase the dose, to have the same effect, detected with previously lower doses.[22] Tolerance is a mechanism that finds one base in precise alterations of the bond of the substance with its own receptor and of specific alterations of the signal transduction processes. The different opioids that are capable of inducing the development of tolerance in a different way because there are different mechanisms of signal transduction that they can evoke. The chronic administration of morphine is, for example, capable of determining a strong tolerance for receptor desentization. More generally, in the case the system plays a decisive role in the tolerance induced by opiates of glutamate.[23] Numerous studies have, in fact, shown how the activation of NMDA receptors of glutamate is capable of inducing greater "resistance" to the effects of opioids. In other words, the glutamate NMDA receptors are able to regulate the expression of the mu opioid receptors and represent the pharmacological basis for the development of tolerance.[24] From the point of Clinically, opioid tolerance is also capable of producing the so-called cross-tolerance, i.e. a condition of cross tolerance also towards other opiates that is also used for therapeutic purposes (as occurs in the case of the use of the MTD to block heroin withdrawal). After all, the basis of safety there is also induced tolerance of chronic opioid administration on respiratory depression. In general, opiates are capable of promoting tolerance through a receptor desentization, while the MTD is able to determine a reduced tolerance through a process of internalization mu opioid receptors and an antagonistic action on NMDA receptors of glutamate, provided that it is used with doses capable of controlling the craving and pain (i.e. used with a so-called blocking dose).[25] For all for the aforementioned reasons, MTD appears to be the most effective opioid drug in control craving and pain, with minimal effects on developmental mechanisms of tolerance. Opioid-induced hyperalgesia (HIO, image 3) is considered a complication of opioid therapy and improves if the opioid is reduced or eliminated. In other words, HIO represents a kind of pain sensitization that MTD seems to be able to reduce. The molecular basis of HIO are probably linked to the mechanisms of tolerance, through an activation of NMDA receptors of glutamate and an altered sensitivity of the mu opioid receptors.[26]

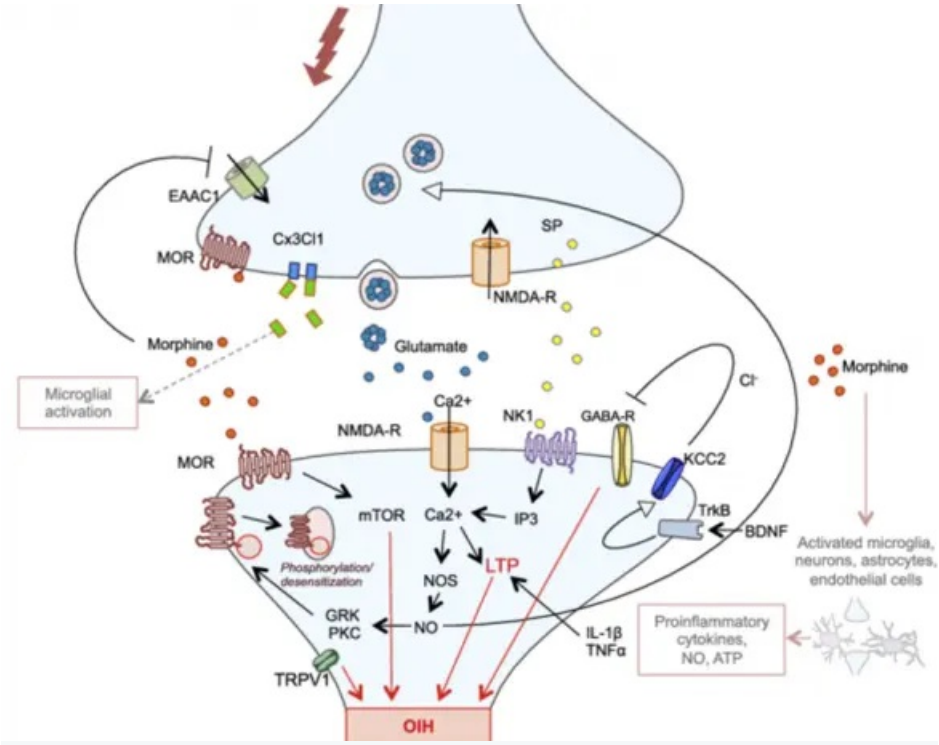

Image 3. *Molecular mechanisms of opioids- hyperalgesia*

The HIO- treatment consists in the reduction or elimination of the opiate, in the use of a glutamate NMDA receptor antagonist, or in the consider other pain relief solutions (such as the use of physical or neurosurgical techniques).[27] Interestingly, some anecdotal reports have shown how reducing the dosage of the opiate and administering a low dose of MTD can improve the HIO. In this sense, MTD, unlike other opiate drugs, appears to be, due to its pharmacokinetic properties, particularly effective also for treatment of the HIO. The use of opiates is continuously increasing around the world and therefore always is more patients with tolerance.[28] It is currently estimated that around 30% of the population in the United States suffer from chronic pain and that one high percentage of them use opiate drugs, such as MTD which, in fact, in patients with chronic pain, in addition to being effective, has been shown to be able to induce, only in rare cases, phenomena of severe dependence and tolerance, probably due to its ability to block glutamate NMDA receptors. MTD is also the most indicated opioid drug for the treatment of pain, especially chronic, in subjects who have a tolerance due to the use of substances.[29] Recent data suggests that around 20 millions of people in the United States have a disorder related to the use of substances and how about ⅓ of the entire aforementioned population consumes substances. After all, substance abuse is present in 25-40% of patients who are hospitalized and in 40-60% of those who experience trauma. Moreover, always in the United States, there has been an exponential increase in access to the emergency room for the abuse of opioid analgesics. In these patients the management pain, both acute and chronic, is very complex, and MTD would be the most suitable drug, at least for subjects who do not present a present or past history of opiate addiction. In any case, a survey conducted on more than 10,000 patients afferent to centers for the treatment of pain has proven, as well as in patients with a history of addiction, only rarely phenomena of iatrogenic dependence on MTD have developed. In the case of, instead, the control of acute pain should take place in the subjects undergoing therapy a maintenance with MTD, although pain sensitivity is impaired in them, the use of any

painkillers should follow the "normal" directions of prescription.[30] For the treatment of chronic pain, in subjects with tolerance, the opioid drug of choice is always the MTD, for at least two reasons that are: its long half-life and the drug's ability to block NMDA receptors of glutamate. Both factors are, in fact, capable of limiting the phenomenon of tolerance and the possible development of HIO. The greatest limits of use of the MTD in the treatment of pain, in the presence of tolerance, are however, the prolongation of the QTc interval of the electrocardiogram (which should be performed before the start of treatment), pharmacokinetic interactions with other drugs and the risk of overdose. In these cases, where tolerance is also present, it might be useful to apply the so-called "rotation" of opiates or increase their dosage.[31]

Focus on: L-methadone

A 5: 1 formulation of concentrated methadone has been available on the market for some time, marketed as ellepalmiron, consisting of the sole left-handed form of racemic methadone. This formulation, in Italy only for hospital distribution, is indicated only for the cessation of addiction to opioid abuse. The advantage is the relative greater cardiovascular safety without compromising its mu agonist properties. It must be said that it could represent an advantage in chronic pain precisely due to the lower risk of long QT but to date it has not yet received such approval and the use would therefore be off-label.[32]

Conclusions

Methadone is an atypical opioid, with pharmacological characteristics that make it very useful not only for detoxifying heroin addicts but also for treating patients with chronic pain and concomitant opioid hyperalgesia and the development of tolerance associated with a now intractable background pain.[33] In particular, the switch from the abused opioid (usually oxycodone or tramadol but also hydromorphone, morphine or fentanyl) to the exclusive use of methadone at adequate dosages, usually with 2 or 3 administrations per day, allows to interrupt the vicious circle of pain - overuse of the opioid - hyperalgesia and sensitization - aggravation of the pain itself, by decreasing the doses and, taking advantage of the equianalgesia, switching to an opioid capable of also treating the hyperalgesia itself by restoring the opioid tone. In the primary abusers of painkiller for euphoric purposes instead it assumes the same role as in heroin, stabilizing the patient from physical abstinence and reducing the craving until he is controlled. Unfortunately, it is still little known in Italy today and often a shadow only of SERDs or the bad reputation of "drug addicts".[34][35]

Conflict of Interest Statement: The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript
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