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Methadone: from Chronic Non-Oncological pain and primary Management Of Opioid Hyperalgesia to Disassuefaction Of Painkillers Abuse

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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 and results

We conducted searches in PUBMED and MEDLINE for clinical trials and reviews done on the efficacy and safety of methadone used for analgesia in chronic pain and in the disassuefation from painkillers abuse. Clinical trials and the works found have overall shown that this drug has positive effects on the control of pain especially neuropathic and mixed and on some associated aspects such as the quality of life.

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

For the current International Association for the Study of Pain (IASP), “pain” can be defined as “An unpleasant sensory and emotional experience, associated with an actual or potential tissue damage, or described in terms of such damage” and 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 about one in 5 people, and one in 4 people suffer from it on average for 7 years.[2] The disease has disabling consequences from a physical and socio-relational point of view; ninety percent of cases are 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 don't 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. 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 aims to be a review of literature data, integrated with pharmacological technical aspects detected by the summary of the product characteristics of the drug and by pharmacological literature. We conducted searches in MEDLINE and PUBMED) for clinical trials and reviews on the efficacy and safety of these drugs for that use, selecting as keywords "methadone - pharmacology, chronic pain - opioid hyperalgesia, NMDA system, methadone - role in, abuse of painkillers ". No time limit has been set for the search. We focused on research on articles that mainly dealt with the neurobiological correlates of methadone and its use in chronic non-malignant pain, without neglecting aspects related to pharmaceutical chemistry and pharmacology.

Discussion

Methadone (MTD, image 1) is a synthetic opioid, synthesized in Germany in 1937 as an analgesic. Chemically it differs markedly from morphine and heroin, being a phenylpropylamine, obtained by eliminating the piperidine ring from the morphine 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]

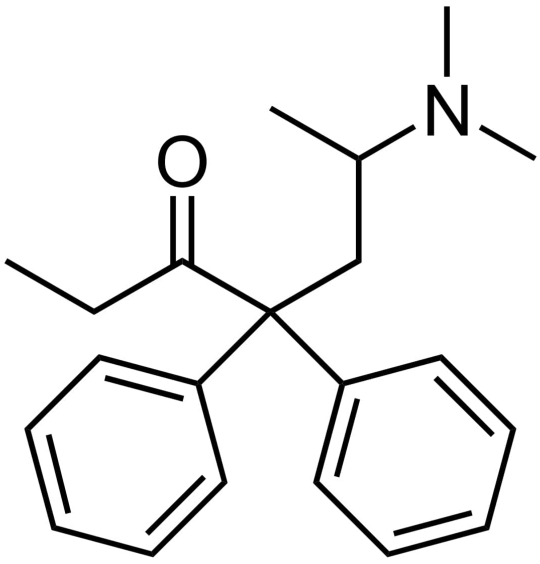

Image 1. *Chemical structure of methadone*

It's sold as an oral solution, in the form of a syrup in two formulations, normal (1 mg / ml) and concentrated (5 mg / ml) and also 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] The use of methadone is part of a context, not new, relating to the consumption of opioids which in the USA, in recent years, has reached worrying proportions. 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]

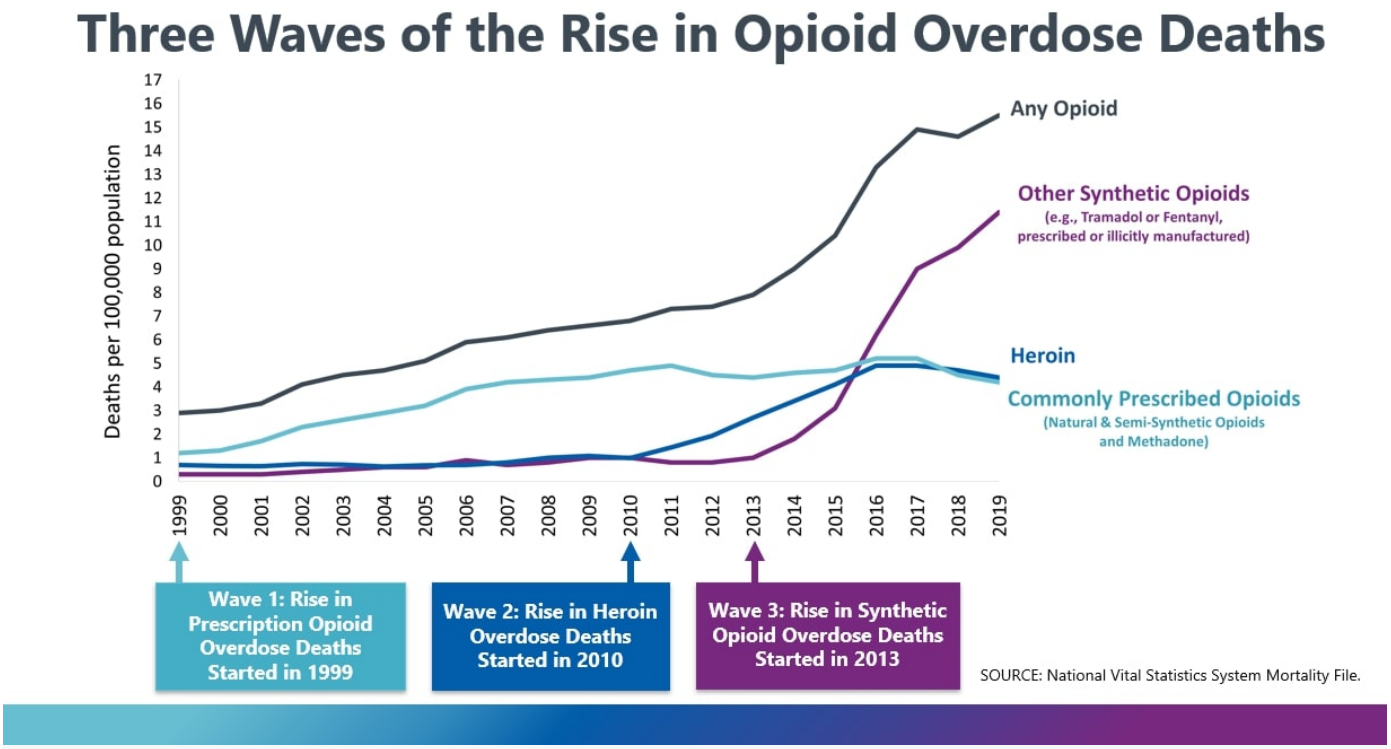

Image 2a. Total o*pioid overdose deaths in the USA from 1999 to 2019*

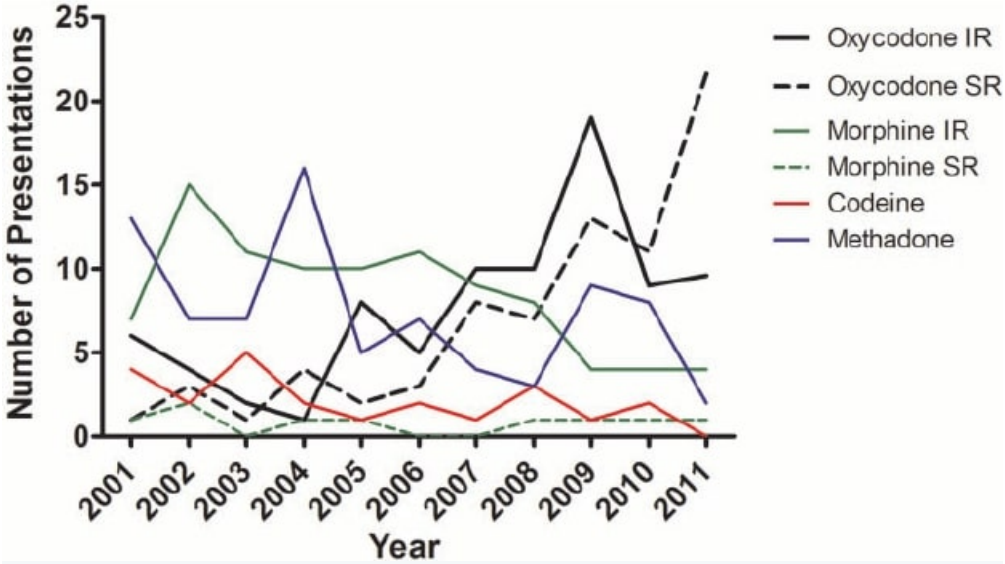

Image 2b. ***Painkillers most frequently involved in acute opioid poisoning in the US from 2001 to 2011***

However, studies in this regard have shown that the phenomenon of painkillers abuse is very different depending on whether it is the primary therapeutic context of patients (with chronic pain or primary abusers for euphoric purposes). We can distinguish two types of painkiller abusers:

1) patients with primary abuse of painkillers (PK): we are talking about people who, for various reasons, have started taking opioid analgesics, from codeine to fentanyl, and who have developed tolerance and sometimes physical or psychological dependence over time (craving). These are both subjects who take painKiller with a primary euphoric purpose and exclusively for creatives (often in social contexts and together with other substances, generally taking them intranasally, by injection or by ingesting tablets with possible overdose effects, even fatal, especially in "naive "subjects) and patients who, after an initial opioid prescription (generally for post-operative pain or short-term pain), is followed by a phase of continuity in the intake of the drug for the management of other problems, for example minor pains , with generation of an abusive conduct [4]. It must be said that these cases mainly depend on factors relating to the aforementioned compounds (placing on the market of increasingly potent drugs and in rapid-release, buccal or liquid formulations or liable to misuse such as the shredding and pulverization of slow-release oxycodone tablets with release rapidity of large doses of the active ingredient). In particular compounds such as codeine, tramadol and oxycodone are, in Italy, the most prescribed for various types of pain (in the USA other compounds such as hydromorphone, hydrocodone etc ... have far exceeded hospital accesses for overdose compared to the same heroin). For that patients methadone can be used as in heroin stabilization therapy, by exploiting its physical anti-abstinence and anti-craving action [5]. In fact, in this type of patient, the mayor problem is the craving for the drug of abuse and therefore it is important to provide a maintenance phase that is aimed at extinguishing the craving, followed by a phase of progressive escalation of the methadone dose

2) patients with uncontrolled chronic pain with strong and / or high-dose opioid drugs for the development of opioid tolerance and hyperalgesia [6]. In this case we have subjects with chronic underlying pain, often resistant to normal

analgesic therapies, with a central spinal hyperexcitability who over time have developed a progressive tolerance to the analgesic effects, spinal and supraspinal spinal effects, of other opioids and above all hyperalgesia which , as known, is NMDA-mediated. The problem to be managed in these patients is not the primary craving for the overused opioid but the management of tolerance and hyperalgesia, in addition to that of underlying pain. Also in this cases, methadone offers advantages linked to its properties and the relative ease of use, with an induction phase with progressive increase in daily doses and followed by a maintenance [8].

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] 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]

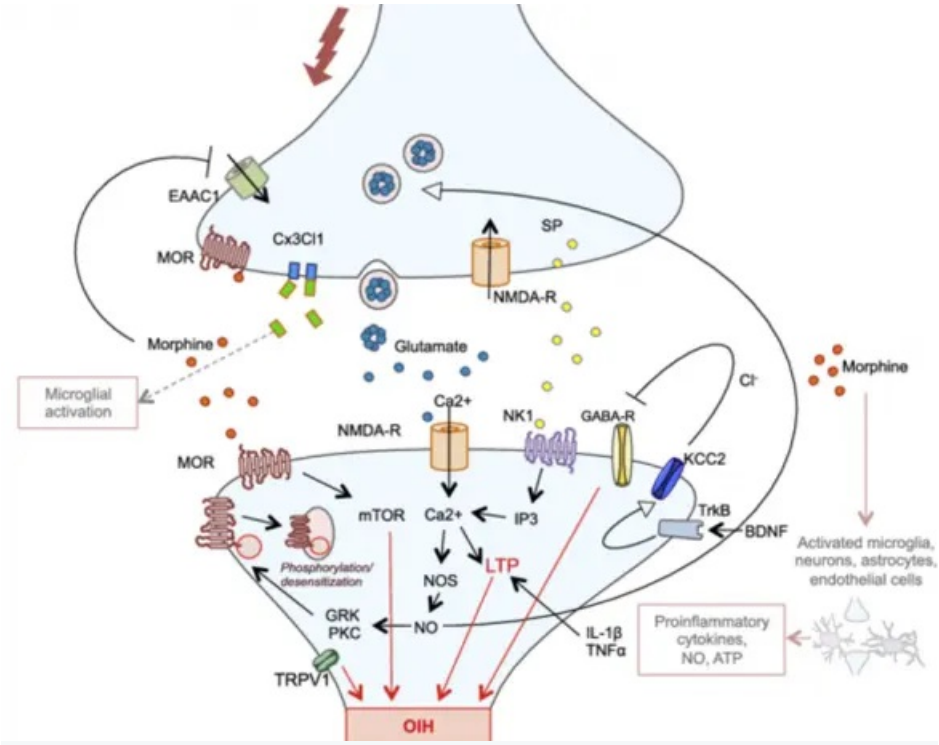

Image 3. *Molecular mechanisms of opioids- induced hyperalgesia*

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]

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