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Treatment of chronic pain in Italy: therapeutic appropriacy of opioids and fear of addiction: the situation in Italy vs. USA

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Introduction

Chronic pain is considered to be one of the most debilitating and expensive pathologies in Europe, North America and Australia. In Europe, 19% of adults suffer from moderate to severe chronic pain. Chronic pain has great impact on daily activities, work and social life, and represents an important problem for public health. That being said, most patients are not treated by a pain therapy specialist, and 40% are not provided adequate pain management (1).

In terms of the prevalence of chronic pain, Italy ranks third in Europe; it is estimated that about 26% of the population has had to resort to drugs to treat chronic pain at least once in their lifetime (2). In 2010, Law 38/2010, aimed at ensuring adequate treatment of patients suffering from cancer-related pain or chronic non-cancer pain through an integrated network of services, was approved in Italy (3). There is widespread consensus and international approval for the use of opioids in the management of pain associated with advanced-stage cancer (4). In such cases, the benefit of pain relief obtained via opioids fully justifies the risks of long-term therapy with this class of drugs. From a clinical standpoint, opioid use rarely interferes negatively with the overall management of these patients. However, the use of opioids in chronic non-cancer pain is still controversial today (5). Indeed, when the prescription of opioids is aimed at the treatment of chronic non-cancer and/or neuropathic pain, there is evidence of poor efficacy and the onset of serious complications (6). A recent meta-analysis of randomized clinical trials has shown that there are no significant differences in efficacy between opioids and other pharmacological and non-pharmacological treatments in the treatment of chronic non-cancer pain, and has concluded that there is

no evidence to support the use of opioids in the treatment of this type of chronic pain (7).

The most impactful consequences of long-term opioid treatment are the development of tolerance, physical and mental addiction and the potential risk of incurring a substance use disorder (SUD), according to the latest DSM V definition (8-10). In the United States of America, there is a real epidemic linked to overdoses and the misuse of opioid drugs prescribed for the control of non-cancer pain (11). The phenomenon affects almost all age groups, and the highest mortality rate, in both sexes, is seen in the 45–54-year age range. Currently, more than 3% of the adult population in the United States receives chronic opioid therapy (12).

In 1995, a prolonged-release formulation of oxycodone was introduced onto the American market. Its ready availability (prescribed for non-cancer pain even by general practitioners) coincided with an increase in the frequency of onset of misuse, addiction and diversion, to the point that in 2004 it became the most abused drug in the United States (13). In an attempt to counter this trend, an abuse-deterrent formulation was introduced onto the American market in 2010; these tablets were designed to be tamper-proof, preventing misuse of the active substance. However, the deterrent effect expected from the new formulation was still the subject of debate in 2015 (14). In fact, deaths from prescription opioid overdoses are steadily increasing in the United States, alongside a concomitant increase in heroin abuse (15).

In order to better understand this phenomenon, a central problem that remains to be clarified is how much abuse, misuse and diversion, and therefore addiction and overdose deaths, involve patients with properly diagnosed chronic pain, as opposed to a group of individuals who have exploited the easy prescription and dispensing of opioids for recreational, i.e. not medical, purposes. In this regard, it is worth remembering that in 2014 more than 10 million Americans reported having made illegal use of prescription opioids (16). It is also interesting to note that even though the number of individuals who switch from prescription opioids to heroin annually is low, 80% of 125,000 regular heroin users declare that they use prescription opioids (17). It is therefore probable that the epidemic of overdose deaths and the phenomena of addiction and abuse are mainly related to the non-medical use of opioids, while the real risk in the patient with chronic pain is yet to be clearly defined. A recent report entitled Pain Management and the Opioid Epidemic, prepared by a Commission from the National Academies of Sciences, Engineering, and Medicine, recommends taking a balanced attitude to combat the non-medical use of prescription opioids, while ensuring controlled access to all patients with chronic pain that may benefit from these drugs (18). In July 2010, the American Food and Drugs Administration (FDA) began a programme aimed at risk assessment, the 'Risk Evaluation and Mitigation Strategy' (REMS), which highlights the need for mandatory training for any doctor who prescribes opioids on prescription appropriacy and abuse prevention. Despite various awareness campaigns, the FDA is still attempting to outline a shared regulatory strategy aimed at promoting containment of the phenomenon of prescription opioid misuse (19). To this end, monitoring of this condition in the USA by the NIH is very important, and through the scientific articles analysing the most relevant aspects of the issue it is becoming increasingly apparent that the opioid crisis in the United States began with the misuse of prescribed opioids, which opened the door to a huge increase in heroin use (20-21).

Opiate & opioid analgesics

The term opioid, or opiate, analgesics refers to the natural opium alkaloids (morphine, codeine and thebaine) and their synthetic and semi-synthetic derivatives whose actions are blocked by the non-selective opioid antagonist naloxone.

Opiates have been used by humans for millennia — the opium poppy, from which opiates are obtained, was cultivated in Mesopotamia as early as 3400 BC.

The powerful analgesic effect of opioids depends on two factors: the strategic location of opioid receptors along the pain transmission and regulation pathways, and the intracellular events that result from the binding of opioids to these receptors. The opioid receptors μ, δ, and k are mainly associated with inhibitory G-proteins. The μ receptor, which can be considered the most relevant for clinical analgesia, is present at the presynaptic level on the nociceptive fibres A delta and C, and on the postsynaptic neurons in the spinal cord. When the opioid binds to this receptor, it activates a series of coordinated intracellular signals, adenylate cyclase inhibition and a decrease in cellular activity, as well as calcium channel blocking and potassium channel opening. Activation of

potassium channels leads to a hyperpolarization of the cells, which become less excitable, and blocking calcium channels diminishes the release of excitatory neurotransmitters such as substance P and glutamate, thereby greatly inhibiting the transmission of nociceptive stimuli. However, opioid receptors are also present in the brain, in the periaqueductal grey (PAG) and other areas, where they ultimately lead to activation of the descending pain suppression pathway, releasing opioid peptides, serotonin and norepinephrine at the spinal level. Therefore, the analgesic effect of opioids occurs both because they inhibit the transmission of nociceptive signals and because they enhance the descending modulatory systems. Furthermore, opioid receptors are also expressed on the free nerve endings of pain receptors, where they exert inhibitory control over the transduction of nociceptive stimuli into electrical activity. In addition to the antinociceptive effect, morphine also reduces the emotional component of pain, probably by acting on the limbic system.

Opioid receptors are also widely distributed in other areas of the central and peripheral nervous systems and peripheral tissues.

They therefore exert many pharmacological actions, some of which constitute the unwanted side effects that often arise during therapy with these drugs (22).

Psychological dependence on opioids

Opioids are known to induce psychological dependence, which can manifest independently of tolerance and physical addiction, two phenomena that must be distinguished from psychological dependence.

Psychological dependence is a chronically recurring disorder characterized by compulsive behaviour, i.e. a loss of control over the search for and intake of substances of misuse, regardless of the damage caused to oneself and others. The term “addiction” derives from the Latin addicere, to enslave, which well describes this pathological condition and indicates compulsive, uncontrolled behaviour in the search for a rewarding substance or situation.

The reinforcing effects of all substances of misuse are due to actions on the mesolimbic-mesocortical system, a circuit made up of neurons with a prevalently dopaminergic activity. Endogenous opioids and opiates facilitate the release of dopamine directly in the nucleus accumbens (NAc) by activating the μ and δ receptors, and indirectly activating the μ receptors on the GABAergic neurons of the VTA (ventral tegmental area); here, in fact, by inhibiting GABAergic neurotransmission, dopaminergic neuron firing increases. In contrast, the activation of κ receptors, induced by opioids and opiates, inhibits dopaminergic transmission in the mesolimbic and mesocortical pathways, where the κ receptors are located on the cell bodies of dopaminergic neurons in the VTA and nerve endings in the NAc (23). The brain areas linked to psychological dependence are in part different from the areas involved in the modulation of pain at the supraspinal level, in particular the PAG and the brain stem for the descending pain suppression pathway.

The release of dopamine in the NAc is associated with both the effects of the substance of misuse and the environmental context in which it is administered. Focus on these events is therefore enhanced and, upon their recurrence, it is easier to recognise the warning signs of the effects of the drug.

Although under physiological conditions reward stimuli often activate the release of dopamine from this neuronal circuit, it does not seem that this neurotransmitter in itself produces gratifying or pleasant effects, as previously thought, but rather attaches relevance (salience) and facilitates the experiential learning associated with its release.

An involvement of the opioid system in the molecular mechanisms underlying the effects of numerous substances of abuse, including cocaine, amphetamines and alcohol, has also been suggested, as well as its close interaction with other neurotransmitter systems that participate in these dynamics, such as the cannabinoid system. In recent years, the hypothesis has emerged that there are at least three different types of factors, namely those related to the effects of the substance, genetic factors and environmental factors, that contribute to the susceptibility to developing drug dependence (22). Genetic and pharmacogenetic research, which led to the identification of polymorphisms in the genes coding for opioid system proteins, have shed new light on the phenomenon of psychological dependence; it has been proposed that genetic factors, i.e. gene polymorphisms, for example for the opioid receptor μ, account for 25% to 60% of the factors that determine the susceptibility to psychological dependence. However, a determining role

has also been attributed to environmental conditioning factors. It has been proposed that the onset of psychological dependence and susceptibility to relapse after deprivation are the result of neuroadaptive CNS processes that oppose the reinforcing action of drugs of abuse.

Adequate therapeutic use of opiates for the treatment of chronic pain has thus far been compromised by the erroneous belief that their use inevitably leads to psychological dependence. It has been suggested that the therapeutic use of the opioids is not associated with the environmental conditioning stimuli that are so important in determining the positive reinforcement that leads to compulsive use. The condition in which the drug is taken, and especially the underlying painful pathology, is not thought to provide the substrate and the context in which the person tends to seek the substance out; in this regard, recent clinical evidence in the field of pain therapy in Europe and Italy suggest that the phenomenon of abuse occurs fairly rarely (24). From a scientific point of view, in fact, there is experimental data to indicate that desensitization of the μ receptors in the ventral tegmental area and microglial dysregulation occur in conditions of chronic pain, with consequent reduction in the release of dopamine in the nucleus accumbens, thus providing a rational basis for the reduced opioid gratification observed in clinical settings (25).

Terminology & definitions related to non-therapeutic use of opioids

The current and growing attention paid to the use of opioids in pain therapy raises the issue of the need for discussion on the definitions associated with their use not in accordance with the therapeutic indications. Some authors propose specific terminology that can be used uniformly in healthcare, and promote its use in the context of drug treatment with opioids, underlining the importance of using the correct terminology and a detailed description of the patient's activities, the context in which they occur, and the severity of any associated harm (26).

The experience of adverse effects associated with taking a drug, including the poor efficacy of therapy in the control of chronic pain, can drive a patient to use the prescribed drugs in a way other than that indicated by a clinician. In this way, the patient can become non-adherent to the therapy. Some non-compliant practices can result in the aberrant behaviours indicative of SUD, as shown in the attached chart; the behaviours listed are indicative of risk of opioid misuse and addiction (27).

Hazardous and harmful use: risky use of a substance or drug in such a way as to increase the risk of negative health consequences. Malicious use, on the other hand, is a method of consumption that certainly increases the negative physical, psychological and/or social consequences, regardless of whether or not addiction is diagnosed (28).

Misuse: any use of the drug not according to the prescription; the patient may have medical reasons for taking the drug, but, for example, demand and use higher doses of a specific active ingredient, above the maximum indicated dose. Non-adherence to the doctor's instructions may be due to a lack of therapeutic efficacy, not necessarily an aberrant behaviour aimed at seeking the active ingredient for harmful use or due to physical dependence on opioids (29).

Diversion: the unapproved supply of a drug through illicit exchange, sharing, transfer or sale, putting it into circulation for the purpose of fuelling the illegal drug market. In this case, the person who uses the drug does not have a prescription for opioids, but purchases, shares, exchanges or receives the drug from a person who has a prescription but diverts the drug from its intended use. This can happen voluntarily (intentional supply to another person) or involuntarily (involuntary supply such as missing doses, theft and/or threats). This definition also includes the failure to store medicines in a safe place (for example, in places and containers accessible to young children) (30).

Abuse: sporadic or persistent excessive and intentional use of a drug, which is accompanied by potentially harmful physical and psychological effects.

Overdose: taking an excessive amount of the drug at once, or several, times, exceeding the maximum dose indicated on the official drug information sheet included in the packaging (available from the AIFA database)

Dependence: diagnosed substance use disorder characterized by maladaptive behaviours such as loss of control over use, non-therapeutic use, abuse, craving or persistent use of a substance or drug despite evidence of danger and the resulting harm. There are variations in the definitions used for the problematic uses of prescription and "street" opioids (heroin) in both the International Classifications of Diseases 10 (ICD-10 and the imminent ICD-11) and in the Diagnostic and Statistical

Manuals of Mental Disorders (DSM-IV and DSM-V) (31).
ICD-10: defines opioid addiction by a set of symptoms that typically include craving, difficulty in controlling use, persistent use despite negative consequences, tolerance and withdrawal (32).
ICD-11 draft (still under development): no longer speaks of addiction, but rather a substance use disorder arising from the repeated or continuous use of opioids. The main characteristic of the disorder is the subject's strong desire to use opioids, which manifests itself as: reduced ability to control use; priority given to the use of opioids over other activities; persistence of use despite harm and negative consequences; and development of symptoms of tolerance and withdrawal syndrome.
The constellation of behaviours that suggest addiction is evident for a period of at least 12 months if the use is episodic, or for a period of at least a month if the use is continuous (daily or almost daily).
DSM-IV: the definitions for abuse and dependence are very similar to those in the ICD-10.
DSM-V: combines the criteria for abuse and dependence within a single disorder indicated as a substance use disorder, or SUD, with different degrees of clinical severity, (divided into mild, moderate and severe based on the number of symptoms) and contains 11 criteria with a minimum of two necessary for a diagnosis (33-34). In addition, addiction and withdrawal are no longer considered pathological if they derive from prescription opioids, and this is the biggest difference.

Main prescription opioids worldwide

"Essential, adequately available and not unjustifiably limited"; these were the words used at the United Nations Convention on Narcotic Drugs to underline the importance of making controlled substances available for therapeutic purposes, as reported by the International Narcotics Control Board (INCB) in 1961.
Opioid analgesics are essential for the treatment of pain caused by cancer, AIDS, cardiovascular and chronic respiratory diseases, diabetes, childbirth, surgery, damage or trauma, and other conditions or situations. However, currently available data indicate that 75% of the world's population has limited or no access to appropriate drug treatment for pain. An unacceptable inequality and therefore social injustice between the different areas of the world is represented by the average availability of morphine equivalents (ME) in milligrams: from 0.014 milligrams ME per capita in sub-Saharan countries to more than 800 mg ME per capita in North America. The lack of availability of internationally controlled drugs, in particular pain medications, has been attributed to a series of obstacles; among the major barriers listed by the various countries are concerns about the risks of psychological dependence, reluctance to prescribe or supply drugs, and also inadequate and insufficient training of professionals.
Unjustified restrictive laws and strenuous regulations are commonly perceived as a way of playing a highly significant role in limiting the availability of opioid drugs. A reduced number of governments have also reported that difficulties with distribution and restocking, as well as the high cost of opiates, have been the largest obstacles to making these drugs adequately available.
The International Narcotics Control Board (INCB) and UNODC (UN Office on Drugs and Crime) suggest laws and regulations be reviewed or revised to improve access to controlled substances at the international level; they also encourage improvement of formation and training, as well as raising awareness among health professionals and, above all, politicians.

Main prescription opioids in Europe

Over the past decade, the use of opioids for chronic non-cancer pain has significantly increased in Europe (35-36). In Germany, for example, the incidence of opioid prescriptions for chronic non-cancer pain increased by 37% from 2000 to 2010 (6).
In Europe, the abuse of synthetic opioids represents a growing problem. While heroin remains the most frequently used opiate, synthetic opioids are increasingly becoming the object of misuse.
In 2014, 18 European countries reported that more than 10% of patients who turned to drug treatment services for problems related to opioid narcotics were taking opioids other than heroin; this figure had increased compared to 2013. The drugs most frequently involved include: methadone, buprenorphine, fentanyl, codeine, morphine, tramadol and oxycodone. In some European countries, it is not heroin but other opioids that are currently the most frequent form of drug use/abuse in patients attending addiction services. In Estonia, for example, the majority of new patients who come for

opioid-related problems take fentanyl, while in Finland and the Czech Republic the main drug of misuse is buprenorphine (37).

Main prescription opioids in Italy

The latest report available from the National Observatory on the Use of Medicines (OsMed), which describes the trends in drug prescription across Italy in the period January to December 2016, as compared to the same period in the previous year (2016 vs. 2015), details an increase in opioid prescriptions in terms of variation in the defined daily dose ratio (DDD) for opiate alkaloids, opioids derived from phenylpiperidine (such as fentanyl), and other opioids. Growth has also been observed in the use of drugs for the treatment of opioid substance use disorder, such as methadone and buprenorphine. The 2015 OsMed report, which assessed the period between 2007 and 2015, documented an almost four-fold increase in opioid prescriptions, potentially correlated to the reduction in the prescription of NSAIDs observed (from 25 DDD in 2007 to 20 DDD in 2015).

Among the most prescribed drugs were oxycodone in combination (for example oxycodone/naloxone) and tapentadol, although it should be noted that at the beginning Italian consumption figures for both were very low, close to zero. In fact, the increase in prescription of the major opioids in Italy seems to be modest compared to other European countries, like Germany (6).

As already mentioned, in recent years there has been heated debate in the USA, and consequently Europe, on the problems of non-therapeutic use, deviation and risk of abuse related to the treatment of chronic non-cancer pain with opioid analgesics, with the increase in opioid overdose deaths (38-40) and also involvement in the paediatric field (41).

Abuse-deterrent pharmaceutical formulations have been developed to prevent inappropriate use of these drugs. Although the use of opioid analgesics in Italy is far lower than in Northern Europe and the USA, great care must be taken to prevent the risk of abuse while guaranteeing all patients with pain the right to access to treatment, as required by law 38/2010.

US and Canadian Guidelines on the use of opiates have recently been released in order to counteract overdose deaths, which have taken on epidemic proportions in those countries (42). A book has just been published on this interesting topic, where the relationship between the benefits to patients with pain and the risk of abuse are discussed in depth (43).

Moreover, although there has been an increase in deaths in Europe, in Italy, in contrast, there has been a reduction in fatal events (Repubblica, 7th June 2017).

Strategies for controlling and preventing the problem of abuse

The role of pharmacovigilance

Beginning in 2012, with the application of the new 84 EU directives and Law 348/74 (dated 31st December 2010), the definition of adverse drug reaction (ADR) was extended to include "harmful and unwanted adverse effects as a consequence not only of the authorized use of a drug at normal doses, but also of therapeutic errors and uses that do not comply with the indications provided in the marketing authorization, including improper use and abuse of the drug". To ensure the identification of these new ADRs, it would be necessary to implement a new pharmacovigilance system. This was made possible by the activation of numerous pharmacovigilance projects, promoted by the Regional Pharmacovigilance Centres (CRFV) in collaboration with the Anti-Poison Centres (CAV), as privileged monitors of ADRs.

Among the various active pharmacovigilance projects, the FarViCAV (Pharmacovigilance of Therapeutic Errors and Adverse Reactions Based on the Cases Examined by Poison Control Centres) and MEREAFaPS (Epidemiological Monitoring of Reactions and Adverse Events from Drugs in First Aid), the latter ongoing, should be noted. While the FarViCAV project was active, the ADR reports collected by the Florence Careggi University Hospital Agency (AOUC) CAV in the period from July 2012 to July 2013 show that 45% of suspected ADRs were linked to analgesics, including opioids. This data is in line with that currently collected by pharmacovigilance operators who work in collaboration with AOUC toxicologists as part of the MEREAFaPS project.

According to the aggregate data provided by the National Pharmacovigilance Network from 2001 to today, the drugs belonging to the "opiates and other drugs for the treatment of pain" class most frequently reported in connection with suspected ADRs in Italy

have been the non-opioid analgesic paracetamol, followed by tramadol, paracetamol in combination with opioids, fentanyl, codeine, oxycodone, tapentadol, buprenorphine and morphine.
Recently, with a view to enhancing data collection on drug safety (including opioids), the Italian Medicines Agency (AIFA) has created a web-based platform, Vigifarmaco (www.vigifarmaco.it), available to healthcare professionals and citizens, who can use it to register and report any suspected ADR online, both spontaneously and as part of the active surveillance promoted by the CAVs.
In this complex scenario, the recent close collaboration between CRFV and CAV, through pharmacovigilance and pharmacoepidemiology, may represent an excellent tool for better risk assessment of prescription appropriacy and prevention of prescription opioid abuse in patients with chronic pain.

Abuse-deterrent formulations

Among the many strategies that are being adopted to decrease the risk of abuse, misuse and diversion of prescription opioids, new formulations with "abuse-deterrent" properties have been developed. Some of these are already on the market, whereas others are undergoing registration or preclinical trials.
The simplest approach is to create physical and chemical barriers which prevent the possibility of chewing, breaking, cutting, scraping or grinding down the drug or dissolving it in water, alcohol or other solvents in order to obtain all the active ingredient contained within the slow-release formulations at once. These anti-tamper preparations therefore prevent the use of the opioid through routes of administration other than the oral (e.g., intravenously or intranasally). Many formulations of this type are now commercially available.

In agonist-antagonist combinations, an opioid antagonist such as naloxone or naltrexone is added to the formulation in order to block the euphoric effects of the opioids sought by the would-be abuser. Indeed, naloxone is known to have a very low oral bioavailability, but its bioavailability increases after intranasal administration or injection. Naltrexone, on the other hand, which has good oral bioavailability, must be sequestered within the formulation to minimize its absorption from the gastrointestinal tract during normal use. If the formulation is manipulated, naltrexone is released and blocks the opioid's effects. At least three formulations of this type containing oxycodone or morphine have been approved by the FDA.
Combinations of opioids with aversive substances have also been formulated; if tampered with, they produce an unpleasant effect, such as nausea, a laxative effect or itching, to deter potential abusers. At present, only one formulation of oxycodone plus an irritant has been approved by the FDA.
Prodrugs which activate the opioid action only upon contact with the gastrointestinal system are still in the research stage.
Although it has been suggested that the development of abuse-deterrent formulations is actually a method of extending patents on opioid molecules, the first data coming from the USA on anti-tamper preparations of oxycodone seem to indicate the presence of a decreasing trend in abuse.

Risk assessment

The practice of prescription does not always conform to what current guidelines recommend. Although opioid analgesics may be prescribed for valid medical reasons, they tend to be used in a manner that does not comply with medical advice unless accompanied by adequate counselling on the risks associated with their abuse and the development of a substance use disorder, making them a serious public health problem. We need to learn from what has happened in the United States, where phenomena related to the abuse of prescription opioids (especially oxycodone) are now considered a real medical emergency (11).
The efficacy and tolerability of opioids may differ significantly from patient to patient for reasons related to pharmacogenetics, opioid receptor polymorphism, pharmacokinetic differences and the presence of other pathologies (44-45).
In a randomized clinical trial (RCT) conducted on 135 patients in 2011 by Naliboff et al., whose aim was to compare the effectiveness of a conservative prescription strategy with fixed doses with one characterized by progressively increasing doses, opioid abuse issues occurred even among the carefully selected patients. Furthermore, as many as 27% of patients dropped out due to abuse, or misuse, and no between-group differences emerged in the rate of opioid misuse (46).
A small RCT from 2010 can be considered a pilot study in terms of identifying an effective strategy for preventing the therapeutic non-compliance that has been widely observed in the past 20 years. The purpose of the

study was to evaluate the effectiveness of close monitoring and counselling in the prevention of misuse, as assessed by means of a score, the Drug Misuse Index (DMI). Surprisingly, the results obtained in this small but important RCT have demonstrated that the preventative intervention effectively reduces the DMI, and therefore reveals how a cognitive-behavioural approach can significantly reduce the potential for abuse of drugs such as opioids (47).

It is also interesting to note that a harm-reduction strategy based solely on pharmacokinetic factors, such as the introduction of prolonged-release opioids, offers no advantage over short-acting opioids, in either pain reduction or harm resulting from improper use of the drug. In addition, the number of opioid overdose deaths, around 16,000 a year, is still on the rise, according to 2017 data from the National Institute of Drug Abuse (NIDA).

The goal of good clinical practice for treating chronic pain is essentially based on appropriate prescription and careful counselling before and during therapy. Therefore, the doctor-patient communication that must accompany all phases of the therapeutic process appears to be of fundamental importance, contributing to reducing the risk of diversion, misuse and abuse. The prescriber is obliged to inform the patient about the therapeutic and side effects of the treatment, trying to engage and empower them.

It could also be very useful to get professional nurses involved as counsellors. It is also fundamental to inform the patient and his or her general practitioner, or any other specialists involved in the treatment process, of the treatment plan.

Conclusions

The Italian Pharmacology Society believes that, although the use of opioid analgesics in Italy is far lower than seen in Northern Europe and the USA, great attention should be paid to preventing the risk of abuse, while ensuring all patients with pain the right to access to treatment, as required by Law 38/2010.

To this end, it will certainly be useful to identify tools such as the Opioid Risk Tool (ORT), the questionnaire proposed by the National Institute of Drug Abuse (NIDA) and available on the website: https://www.drugabuse.gov/sites/default/files/files/OpioidRiskTool.pdf or other questionnaires available on the Italian network.

These tools consist of questionnaires that evaluate patients' pathologies and personality, the presence of anxiety, depression or personality disorders, as well as the existence of any psychological stress, sex or gambling addiction, pathological hyperactivity, and the ability of the patient to adhere to the prescribed treatment (48). Indeed, the early identification of high-risk patients enables them to be carefully monitored through a more intense monitoring programme, and therefore more effectively managed through motivational counselling and/or diversion-prevention strategies.

This would ensure greater safety in the treatment of chronic pain without undermining the therapeutic alliance or patient compliance, thereby improving their adherence to the treatment plan.

Key points

When initiating opioid therapy for the treatment of chronic pain (especially non-cancer pain) it would be appropriate to (42, 49):

1. evaluate the possibility of resorting to multi modal therapy with diversified pharmacological treatments that have different mechanisms of action, potentially integrated with complementary medicine and the use of physiotherapeutic devices;
2. re-assess the results of unsatisfactory drug therapy with the patient and propose either i) rotation of the opioids and administration route, ii) the integration of other non-opioid drugs, iii) abuse-deterrent/transdermal formulations, or iv) the adequate use of drugs indicated for chronic neuropathic pain (gabapentinoids, SNRI and SSRI antidepressants, antiepileptics, local anaesthetics and cannabinoids);
3. monitor the risk of compulsive use (addiction) with validated tests such as the Opioid Risk Tool;
4. to allow stratification of patients into groups with high, medium and low risk of abuse/addiction, and to channel the various resources to those who need it most. ORT:https://www.drugabuse.gov/sites/default/files/files/OpioidRiskTool.pdf amended in Ref. 42.
5. carefully evaluate opioid therapy in patients with a past history of substance use disorder (SUD), including alcohol abuse, or active mental illness.

Opioid therapy in cases of previous SUD should not be criminalized or avoided a priori, but instead decided upon jointly with drug-addiction service experts in order to evaluate the best opioid dosage, route of administration (preferring transdermal) and abuse-deterrent formulations, so as to treat pain without inducing withdrawal symptoms. In cases of active SUD and methadone replacement therapy, the dosage should be adjusted to allow proper pain control;

6. start with doses lower than 90 morphine milligram equivalents (MME) per day in naive patients (whenever possible start with dosages lower than 50 mg MME) (42,49,50);

7. undertake gradual dose reduction (tapering) in patients who receive high-dose opioid therapy (≥ 90 mg ME) and have satisfactory pain control, offering them multidisciplinary support until they discontinue treatment if possible, with adequate pain control.

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