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Risk Factors in Opioid Treatment of Chronic Non-Cancer Pain: A Multidisciplinary Assessment

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1. Introduction

When pain becomes chronic it assumes an almost absolute central role in the disease experience: it characterises and qualifies it, and constantly interferes with the daily life of the patient (Bonica, 1992). It could be said that chronic pain becomes a disease in itself in the patient's perception; daily activities, interpersonal relationships, feelings, are profoundly disturbed by living with pain (Loeser, 2000).

While modern medicine has made notable progress in understanding, diagnosing and treating chronic pain, it continues to be a very widespread problem that significantly compromises the professional, social and family life of the patient, and is often not adequately managed (Manchikanti et al., 2010).

The problem of inadequately managed pain is still a considerable one (Breivik et al., 2006), although the World Health Organization [WHO] (1990) has stated that to be pain free should be considered a right of every patient. The consequences of inadequately treated pain not only have an impact in terms of the physical and psychological suffering of the patient and his family, they also have an enormous economic impact on society as a whole (Brennan et al., 2007; van Leeuwen et al., 2006).

Options for the treatment of chronic pain include both pharmacological treatments (e.g. non steroidal anti-inflammatory drugs, opioids) and non-pharmacological treatments (e.g. physical therapies, acupuncture, cognitive-behavioural therapy, surgical procedures). Choice of treatment should be guided by a complex initial assessment of the patient, which includes the collection of historical information (e.g. pain history and treatments tried, surgical procedures, psychosocial and family history), a physical examination and appropriate diagnostic tests (Passik, 2009).

Opioids are considered one of the most efficacious groups of drugs in treating medium-severe pain (Portenoy, 2000), and their use can result in a significant improvement in the patient's quality of life (Dillie et al., 2008); while there is unanimous agreement on their use in acute and cancer pain, their long-term use for non-cancer chronic pain remains controversial (Dews & Mekhail, 2004; Manchikanti et al., 2010; Rosenblum et al., 2008). The discovery of the properties of these substances, and their use as analgesics, is lost in the mists of time: the Sumerians were starting to cultivate poppies as early as 3400 B.C. (Booth, 1986, as cited in Dews & Mekhail, 2004). In 1803, Friedrich Serturmer, a German pharmacist,

isolated an alkaloid from opium that he named morphine, and in 1853 Scottish physician Alexander Wood introduced the hypodermic needle and successfully used injections of morphine to treat neuralgia. As Way (1982, as cited in Dews & Mekhail, 2004) highlighted, morphine was the “mainstay” of medical treatment in the United States throughout the nineteenth century, used to treat pain, anxiety and respiratory problems as well as “consumption” and “women’s ailments”. Opium cultivation was legal in some states, and opium-based products could be bought over the counter (Dews & Mekhail, 2004). Between 1875 and 1877, German physician Eduard Levinstein published a series of articles calling attention to the problem of morphine dependence: his was one of the first studies on the risk of dependence on narcotics, which he estimated to be 75% (White et al., 2001a). In 1914 Kennedy Foster wrote, in *New York Medical Journal*, “...*morphinism is a disease, in the majority of cases, initiated, sustained and left uncured by members of the medical profession*” (White et al., 2001b); in the same year the US Congress approved the Harrison Anti-Narcotic Act, the first federal law to limit the sale of any drug. Opioids and cocaine were included in the list of drugs that could only be obtained from a physician or authorised pharmacist. Physicians were authorised to prescribe these substances, but not to patients with dependence problem; given the likelihood of arrest or prosecution, physicians became increasingly cautious in prescribing opioids even for chronic pain (Dews & Mekhail, 2004). In 1969, the WHO abandoned the belief that the medical use of morphine led inevitably to dependence; the WHO clarified that tolerance and physical dependence did not in itself constitute “drug dependence”, a diagnosis characterised by typical behaviours, including difficulty in controlling the assumption of drugs, compulsive use of the substance and inappropriate social behaviours (WHO, 1986). In 1970 the Harrison Anti-Narcotic Act and the other federal laws on drugs were replaced by the Comprehensive Drug Abuse and Control Act, which divided substances into six categories, according to their risk of addiction: category I includes heroin and marijuana, category II includes cocaine, opium and morphine, category III includes codeine, category IV includes diazepam and alprazolam, category V includes drugs with small quantities of codeine and category VI includes penicillin and ibuprofen (Dews & Mekhail, 2004). This law established that there were no impediments to prescribing drugs in categories II, III or IV provided there were indications for their use, including chronic non-cancer pain. There was a further development when the WHO Expert Committee on Essential Drugs recognised morphine, codeine and other opioids as “essential drugs,” defining them as: “*those that satisfy the health care needs of the majority of the population; they should therefore be available at all times in adequate amounts and in the appropriate dosage forms...*” (WHO, 1998). The WHO also introduced the “pain analgesia scale” (figure 1) which distinguishes between strong and weak opioids, and establishes their clear roles in pain relief. In Italy, which is one of the countries with the lowest morphine consumption in Europe, several measures have been developed to eliminate the bureaucratic obstacles to the use of opioid analgesics, starting with Law no. 12 of 2001. With Law no. 38 of 2010, opioids may finally be prescribed for pain relief in the same way as other prescription-only drugs.

As illustrated, the use of opioids has historically been subject to cycles of liberalisation and prohibition in clinical practice that account for their still-limited use today (WHO, 1998).

The potential barriers to treatment with opioids may be due to inadequate beliefs of both medical personnel and the patients themselves (Garcia & Altman, 1997).

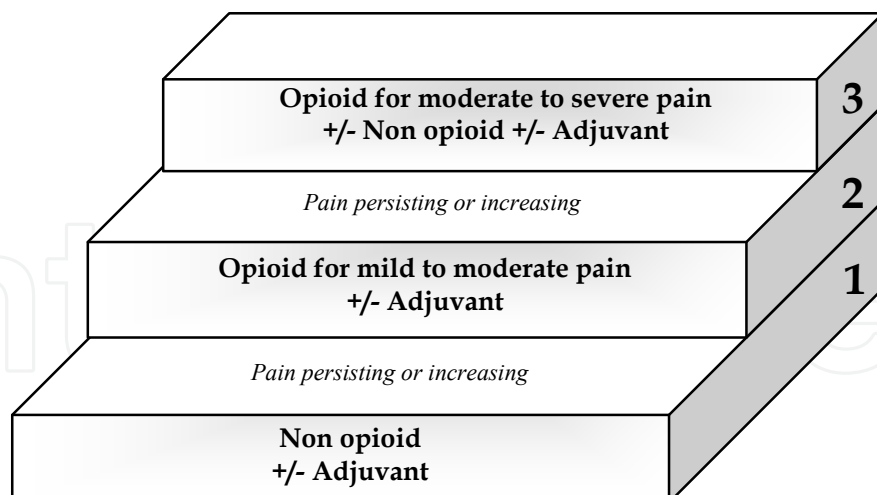


Fig. 1. The WHO pain analgesia scale

Physicians may not prescribe opioids at adequate doses because they do not know how to use them effectively, because they do not assess the pain or effects of treatment systematically, because of fear of sanctions by medical commissions. But some data lead one to believe that the overestimation of the risk of addiction is a significant problem (Dews & Mekhail, 2004); in this respect, the term *opiophobia* has been coined, to refer to the practice of under-prescription of opioid medication due to the fear of inducing addiction in patients (Collett, 1998). By interviewing over 248 US physicians, Bhamb et al. (2006) recently reported that just over half of those interviewed (55.9%), had specific clinical protocols for the prolonged use of opioids in patients with chronic non-cancer pain. 35.1% believed they prescribed opioids less frequently than their colleagues; while the most frequent concerns about starting treatment with opioids were the fear of abuse (84.2%) and addiction (74.9%). Concerns of patients should also be considered: they may not communicate their pain symptoms to their physicians, or may not take the drugs as instructed for fear of becoming dependent on “narcotics” (Dews & Mekhail, 2004). Furthermore, both physicians and patients may develop unjustified anxiety about the side effects of opioid use, believing that these drugs must therefore be reserved for cancer pain (Brennan et al., 2007). Finally, a further barrier to the use of these drugs may be due to overly restrictive national control laws and regulations. Because of this, the WHO has issued guidelines on legislative policies that enable Governments to check if their national laws ensure the availability of opioid analgesics to treat severe pain (WHO, 2002).

Given the importance of these drugs in pain management, as well as the concerns about their use, a series of investigations were carried out in the last twenty years to identify the risk factors that promote or exacerbate opioid misuse. In fact, for physicians, determining the patient’s risk of addiction to opioids is of fundamental importance, so that a series of measures can be taken to limit the negative consequences of this (such as constantly monitoring the patient during treatment, planning interdisciplinary treatment or scheduling regular urine toxicology screening).

The intention of this chapter is to examine the principal risk factors for opioid misuse in patients with chronic non-cancer pain. It will also describe the principal tools for selecting patients who are candidates for opioid treatment and for stratifying the risk of misuse. This will be followed by a presentation of the preliminary results of our experience using a

diagnostic protocol for patients undergoing long-term treatment with opioids in a multidisciplinary pain relief unit.

2. Risk factors in opioid treatment of patients with chronic pain: Theoretical and research aspects

Over the last twenty years, opioids have been used increasingly to treat chronic non-cancer pain (Ballantyne & Shin, 2008). A broad US investigation found that, between 1980 and 2000, prescriptions of opioids for musculoskeletal pain doubled from 8% to 16%. Over the same two decades, the use of more powerful opioids for chronic pain (hydrocodone, oxycodone, morphine) increased from 2% to 9% (Caudill-Slosberg et al., 2004). However, if some patients benefit from such treatment in terms of reduction of pain and improvement in quality of life (Dillie et al., 2008), others do not (Ballantyne, 2007; Trescot et al., 2008). Side effects, the absence of any improvement in physical function, the excessive use of opioids, abuse and addiction are common problems that may present during the administration of opioid analgesics (Manchikanti et al., 2010). So in recent years experts and researchers have sought to answer many questions regarding risk factor for opioid misuse, selection of patients, efficacy of treatment particularly over time, whether opioids are able to improve physical function and quality of life. The clear and urgent need to answer these questions is reflected in the considerable increase in studies on this topic in the last decade (Ballantyne & Shin, 2008). Moreover, many guidelines for the use of opioids in patients with chronic non-cancer pain have been produced, which recommend their use for those patients who have not benefited from other pharmacological and non-pharmacological treatments (Chou, 2009; Chou et al, 2009a; Chou et al, 2009b; Chou et al, 2009c; Kalso et al., 2003; Trescot et al., 2006; Trescot et al., 2008).

The following section will provide some notes on pain, on the recommendations contained in the guidelines for the prolonged use of opioids and on the terminology used. The intention is to offer adequate context for the subsequent discussion of the risk factors related to abuse of opioids and the tools that have been developed to select patients to treat with these drugs.

Finally, the preliminary data of our experience using two of these tools, the *Pain Medication Questionnaire* (PMQ; Adams et al., 2004) and the *Diagnosis Intractability Risk and Efficacy Score* (DIRE; Belgrade et al., 2006) in the Italian population are presented.

2.1 The definition and classification of pain

Pain is an extremely complex and subjective phenomenon, defined by the International Association for the Study of Pain [IASP] as “*an unpleasant sensory and emotional experience, associated with real or potential tissue damage or described in terms of such damage*” (Merskey, 1986a). Whether acute or chronic, pain is above all a subjective and multidimensional experience, influenced by biological, psychological and socio-environmental factors.

Pain may be distinguished as acute or chronic based on its duration in time and underlying pathology. Acute pain is produced by lesions to body tissues and the activation of the nociceptive transducers at the site of the tissue damage. It may be consequent on a trauma, a surgical procedure or an inflammatory process, and generally lasts for a relatively short period of time (hours, days or weeks) and stops when the underlying pathology is resolved. Chronic pain lasts for a long period of time (continuously or recurring at intervals of months or years), and is generally accompanied by a low level of underlying pathology which fully

explains neither the presence nor the intensity of the pain (Bonica, 1992). Disputes remain about the interval of time that needs to have elapsed since the trauma for pain to be defined as chronic; in clinical practice, a pain is generally described as chronic when it persists for more than 3-6 months (Bonica, 1991; Loeser & Melzack, 1999; Merskey, 1986b; Merskey & Bogduk, 1994).

From a pathogenic perspective, pain may be classified as nociceptive, neuropathic or mixed. Nociceptive pain (somatic or visceral pain) is determined by the activation of nociceptors located in the somatic and visceral structures. It may be further classified as superficial or deep, according to the structure involved, and is due to a tissue lesion that is often evident. Neuropathic pain is typically caused by a change or alteration in the transmission of impulses along the somato-sensorial pathways and is indicative of damage to the conduction systems or to the integration and transmission systems of the central or peripheral nervous system; often it is not accompanied by tissue damage. Finally, when these two types of pain (nociceptive and neuropathic) are both present, this is referred to as mixed pain (Mannion & Woolf, 2000).

Pain is physiological, i.e. it is a vital sign, and a defence system when it constitutes an alarm signal for tissue damage. It becomes pathological when it maintains itself, losing its initial meaning and becoming an illness in itself (pain syndrome) (Mannion & Woolf, 2000).

In biopsychosocial terms, the experience of pain and its impact on the individual are due to the complex interaction of somatic inputs (nociception), psychological processes (e.g. thoughts, coping strategies and emotions) and social contingencies (e.g. social context, significant others, roles and expectations) (Turk & Okifuji, 2002). In persistent pain syndromes, the weight of these three factors can change at different moments of the illness, and none alone can explain the pain situation as a whole. The biological factors can origin, maintain and modulate the physical disorder, the psychological factors influence perception and evaluation of body signals and the social factors give form to the patients' behavioural responses and their perception of their physical condition. Given this complexity, an adequate approach to chronic pain requires multidisciplinary intervention; the treatment aims in these patients are not only pharmacological treatment but also reduction of affective/emotional discomfort, functional recovery, return to work and improvement in family and social relationships.

2.1.1 The prevalence of chronic pain and its socio-economic impact

Chronic pain is a common and persistent problem in society, with a relatively high incidence and a low remission rate (Elliott et al., 2002). Verhaak et al. (1998), after reviewing 15 epidemiological studies on chronic pain in the adult population, concluded that its prevalence varied from 2% to 40%, with a mean value of 15%. Back pain is one of the most frequent forms of chronic pain, with a prevalence rate of approximately 48% (Gureje et al., 1998). Based on interviews of 2305 subjects aged between 35 and 45, Linton et al. (1998) showed that the prevalence of back pain is 66% with slightly higher incidence in women; in particular, 56% of the subjects complained of low back pain, 44% complained of neck pain, and 15% complained of pain in the thoracic spine.

A recent epidemiological study about the prevalence of chronic pain in European countries involving 46,394 subjects found that approximately 19% of adults suffer continuous pain of medium-high intensity that seriously compromises quality of their emotional, social and working life. The prevalence of chronic pain varies from 12% to 20%, and is highest in Norway, Poland and Spain. In Italy, people who suffer from chronic pain syndromes

account for approximately 27% of the population. It also emerged that: 59% of those interviewed had been experiencing pain for at least 2-15 years, 21% had been diagnosed with depression consequent on pain, 61% reported great difficulty or incapacity in working outside home, 19% had lost their job and 13% had been forced to change jobs because of the pain. Just 2% of patients reported they were being treated by pain specialists, and about half of these were receiving inadequate treatment (Breivik et al., 2006).

Therefore chronic pain has serious negative effects on the quality of life of the millions of people who experience it, and on the quality of life of their families. In the absence of adequate treatments, patients with chronic pain are often unable to work or even to carry out their normal daily activities.

As well as causing unspeakable suffering to millions of people all over the world, chronic pain has high social cost too. Analysing data from the 1997 Medical Expenditures Panel Survey, which involved 14,147 families, Yelin et al.(2004) found that expenditure by patients with rheumatic disorders was US \$ 4,865 per head, for a total of US \$ 186.9 million. In 1998, US healthcare expenditure on lower back pain was US \$ 90.7 billions (Luo et. al., 2004). A similar investigation found that in 2003 overall spending in the US on care for arthritis and other rheumatic disorders was approximately US \$ 128 billion, equivalent to 1.2% of the US gross domestic product in 2003 (Centers for Disease Control and Prevention, 2007).

So far as Europe is concerned, a study of the socio-economic costs of pain syndromes in the United Kingdom estimated that the cost of direct healthcare was £ 1.6 billion in 1998. But this direct cost is insignificant compared to the indirect costs (e.g. days of work lost and loss of productivity) associated with back pain, totalling 10.7 billion (Maniadakis & Gray, 2000). Winkelmann et al. (2011) estimated the annual costs per fibromyalgia patient for 2008 as € 7,900 in France (of which €960 direct costs, €6,990 indirect costs), and € 7,256 in Germany (€ 1,756 direct costs, € 5,491 indirect costs).

2.2 Opioid treatment of chronic non-cancer pain

In recent years, many guidelines for the use of opioids in patients with chronic non-cancer pain have been drawn up. In general the objectives of such documents are: to bring consistency in opioid prescribing to the many diverse groups involved; to provide analysis of evidence to treat a chronic pain patient with opioids, thus, maintaining reasonable patient access while reducing the risk of drug diversion; to provide practical prescribing guidelines for physicians to reduce the risk of legal and regulatory sanctions; and to emphasize the need for systematic evaluation and ongoing care of patients with chronic or persistent pain (Trescot et al., 2006). The perceived benefits of these guidelines include: increased physician awareness about the current issues involving opioids and non-cancer pain; improved patient access; reduced level of opioid abuse; improved ability to manage patient expectations; reduced diversion; improved understanding by law enforcement about proper prescribing patterns; improved cooperation among patients, providers, and regulatory agencies; improved understanding by patients regarding their rights as well as their responsibilities when taking opioid medications (Trescot et al., 2008). These guidelines should be applied flexibly: every physician must establish a treatment plan that takes account of the specific medical conditions of the patient and his personal preferences and needs, and of the physician's own professional experience (Trescot et al., 2006; 2008). Based on a systematic review of the efficacy of treatment with opioids in chronic non-cancer pain by a multidisciplinary group of experts, the American Academy of Pain Medicine formulated a series of recommendations for: patient selection and the stratification of risk of

abuse, informed consent to treatment with opioids, initiation and titration of chronic opioid therapy, the use of methadone, patient monitoring, the use of opioids in high risk patients, the assessment of the effectiveness of the drug and the aberrant drug-related behaviours, dose escalation and high dose therapy, opioid rotation, indications for discontinuation of therapy, prevention and management of opioid-related side effects and issues about driving and work safety during treatment with such drugs (Chou, 2009; Chou et al, 2009a; Chou et al, 2009b; Chou et al, 2009c). The recommendations of the American Pain Society and the American Academy of Pain Medicine are shown in table 1.

TOPIC AREA	RECOMENDATIONS
Patient selection and risk stratification	Prior to initiating chronic opioid therapy, clinicians should conduct a history, physical examination and appropriate testing, including an assessment of risk of substance abuse, misuse, or addiction (strong recommendation, low-quality evidence).
	Clinicians may consider a trial of chronic opioid therapy as an option if chronic non-cancer pain is moderate or severe, pain is having an adverse impact on function or quality of life, and potential therapeutic benefits outweigh or are likely to outweigh potential harms (strong recommendation, low-quality evidence).
	A benefit-to-harm evaluation including a history, physical examination, and appropriate diagnostic testing, should be performed and documented prior to and on an ongoing basis during chronic opioid therapy (strong recommendation, low-quality evidence).
Informed consent and opioid management plans	When starting chronic opioid therapy, informed consent should be obtained. A continuing discussion with the patient regarding chronic opioid therapy should include goals, expectations, potential risks, and alternatives to chronic opioid therapy (strong recommendation, low-quality evidence).
	Clinicians may consider using a written chronic opioid therapy management plan to document patient and clinician responsibilities and expectations and assist in patient education (weak recommendation, low-quality evidence).
Initiation and titration of chronic opioid therapy	Clinicians and patients should regard initial treatment with opioids as a therapeutic trial to determine whether chronic opioid therapy is appropriate (strong recommendation, low-quality evidence).
	Opioid selection, initial dosing, and titration should be individualized according to the patient's health status, previous exposure to opioids, attainment of therapeutic goals, and predicted or observed harms (strong recommendation, low-quality evidence). There is insufficient evidence to recommend short-acting versus long-acting opioids, or as-needed versus around-the-clock dosing of opioids.
Methadone	Methadone is characterized by complicated and variable pharmacokinetics and pharmacodynamics and should be initiated and titrated cautiously, by clinicians familiar with its use and risks (strong recommendation, moderate-quality evidence).
Monitoring	Clinicians should reassess patients on chronic opioid therapy periodically and as warranted by changing circumstances. Monitoring should include documentation of pain intensity and level of functioning, assessments of progress towards achieving therapeutic goals, presence of adverse events, and adherence to prescribed therapies (strong recommendation, low-quality evidence).
	In patients on chronic opioid therapy who are at high risk or who have engaged in aberrant drug-related behaviours, clinicians should periodically obtain urine drug screens or other information to confirm adherence to the chronic opioid therapy plan of care (strong recommendation, low-quality evidence).
	In patients on chronic opioid therapy not at high risk and not known to have engaged in aberrant drug-related behaviors, clinicians should consider periodically obtaining urine drug screens or other information to confirm adherence to the chronic opioid therapy plan of care (weak recommendation, low-quality evidence).

TOPIC AREA	RECOMENDATIONS
High-risk patients	Clinicians may consider chronic opioid therapy for patients with chronic non-cancer pain and history of drug abuse, psychiatric issues, or serious aberrant drug-related behaviours only if they are able to implement more frequent and stringent monitoring parameters. In such situations, clinicians should strongly consider consultation with a mental health or addiction specialist (strong recommendation, low-quality evidence).
Aberrant drug-related behaviours	Clinicians should evaluate patients engaging in aberrant drug-related behaviours for appropriateness of chronic opioid therapy or need for restructuring of therapy, referral for assistance in management, or discontinuation of chronic opioid therapy (strong recommendation, low-quality evidence).
Dose escalations and high-dose therapy	When repeated dose escalations occur in patients on chronic opioid therapy, clinicians should evaluate potential causes and re-assess benefits relative to harms (strong recommendation, low-quality evidence).
	In patients who require relatively high doses of chronic opioid therapy clinicians should evaluate for unique opioid-related adverse effects, changes in health status, and adherence to the chronic opioid therapy treatment plan on an ongoing basis, and consider more frequent follow-up visits (strong recommendation, low-quality evidence).
Opioid rotation	Clinicians should consider opioid rotation when patients on chronic opioid therapy experience intolerable adverse effects or inadequate benefit despite dose increases (weak recommendation, low-quality evidence).
Indications for discontinuation of therapy	Clinicians should taper or wean patients off of chronic opioid therapy who engage in repeated aberrant drug-related behaviours or drug abuse/diversion, experience no progress towards meeting therapeutic goals, or experience intolerable adverse effects (strong recommendation, low-quality evidence).
Opioid-related adverse effects	Clinicians should anticipate, identify, and treat common opioid-associated adverse effects (strong recommendation, moderate-quality evidence).
Use of psychotherapeutic co-interventions	As chronic noncancer pain is often a complex biopsychosocial condition, clinicians who prescribe chronic opioid therapy should routinely integrate psychotherapeutic interventions, functional restoration, interdisciplinary therapy, and other adjunctive non-opioid therapies (strong recommendation, moderate-quality evidence).
Driving and work safety	Clinicians should counsel patients on chronic opioid therapy about transient or lasting cognitive impairment that may affect driving and work safety. Patients should be counselled not to drive or engage in potentially dangerous activities when impaired or if they describe or demonstrate signs of impairment (strong recommendation, low-quality evidence).
Identifying a medical home and when to obtain consultation	Patients on chronic opioid therapy should identify a clinician who accepts primary responsibility for their overall medical care. This clinician may or may not prescribe chronic opioid therapy, but should coordinate consultation and communication among all clinicians involved in the patient's care (strong recommendation, low-quality evidence).
	Clinicians should pursue consultation, including interdisciplinary pain management, when patients with chronic non-cancer pain may benefit from additional skills or resources that they cannot provide (strong recommendation, moderate-quality evidence).
Breakthrough pain	In patients on around-the-clock chronic opioid therapy with breakthrough pain, clinicians may consider as-needed opioids based upon an initial and ongoing analysis of therapeutic benefit versus risk (weak recommendation, low-quality evidence).

Table 1. Guidelines recommended by the American Pain Society and the American Academy of Pain Medicine for the long-term treatment with opioids of patients with chronic non-cancer pain (adapted from Chou, 2009).

Trescot et al. (2006, 2008) confirmed the importance of an overall patient assessment (physical and psychological) before initiating long-term opioid therapy; this assessment must include an appropriate assessment of treatment efficacy at regular intervals (in terms of both pain reduction and recovery of physical function), the identification and treatment of side effects and the monitoring of any abuse or misuse of the drug. The authors proposed a ten step algorithm that physicians could use for this purpose during treatment with opioids.

2.2.1 Terminology of opioid abuse: Dependence, tolerance, addiction

To ensure effective communication between physicians, researchers and legislators, a clear common terminology is needed. Many drugs, including opioids, play an important role in the treatment of pain. However, as shown earlier, the use of opioids is often limited by concerns about abuse, dependence and their possible use for non-medical reasons. Addiction, tolerance and physical dependence are distinct and different phenomena that are often used in a confused way. Since their clinical implications and management are clearly different, it is important to establish uniform definitions based on current scientific and clinical knowledge, to improve the care of patients with chronic pain and encourage appropriate policies for the regulation and control of drugs. For this purpose, the American Academy of Pain Medicine, the American Pain Society and the American Society of Addiction Medicine (American Society of Addiction Medicine, 2001) have recognised the following definitions, and recommend their use:

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviours that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.

Physical dependence is a state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.

Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.

Pseudoaddiction is a term that has been used to describe behaviour that can occur when the pain is undertreated. Patients with inadequately managed pain may in fact become excessively focused on obtaining drugs. In their intent to obtain relief, patients may also resort to trickery and the use of unlawful substances. Pseudoaddiction may be distinguished from true addiction by the fact that the behaviour disappears when the pain is treated efficaciously.

Misuse is defined as the use of any psychoactive substance in a way other than that for which it has been indicated or prescribed (Wasan et al., 2007). In practical terms, opioid misuse means: inadequate pain management, ineffective treatment, excessive focus on the drug and its effects which does not allow the patient to use other strategies efficaciously to cope with the pain, and finally, worsening of quality of life and altered social, working and psychological functioning.

The term *aberrant drug-related behaviours* has been used to indicate the broad array of problematic nonadherence behaviours (Passik et al., 2006), the nature of which is uncertain until a diagnosis can be developed based on astute clinical assessment (Rosenblum et al., 2008). Portenoy (1996; 2004) has listed a series of behaviours that should engender suspicion of addiction in patients with pain being treated with opioids (table 2). Moreover, Savage

(1993), suggested that the following aspects should also be considered: frequent cancellation of appointments; asking for medicines at the end of every appointment; a history of non-responsiveness to treatment, apart from opioids; a history of negative relationships with many physicians; many “drug allergies” that limit treatment options; finally, a degree of disability that is disproportionate to the basic disorder.

As described above, the use of opioids has raised many concerns; in fact, the use of analgesics without medical prescription, or just to test their effects (“non medical use”) represents the second most frequent form of illicit substance use in the United States, after marijuana use (Office of Applied Studies, Substance Abuse and Mental Health Services Administration [SAMHSA], 2008). The National Survey on Drug Use and Health (Office of Applied Studies, SAMHSA, 2009) report on the use of opioids for non-medical purposes in the United States from 2002 to 2007 showed that: in 2007 approximately 5.2 million people of 12 years of age or more had used prescription-only analgesics for non-medical purposes in the previous month; from 2002 to 2007 the use of opioids for non-therapeutic purposes decreased among young people between 12 and 17 years of age (from 3.2% to 2.7%) , while it increased in young adults between 18 and 25 years of age (4.1% to 4.6%) and in adults over 26 (from 1.3% to 1.6%).

Behaviours probably more predictive of addiction

Selling prescriptions drugs

Prescription forgery

Stealing or “borrowing” drugs from others

Injection oral formulations

Obtaining prescription drugs from non-medical sources

Concurrent abuse of alcohol or illicit drugs

Multiple dose escalation or other non-compliance with therapy despite warnings

Multiple episodes of prescription “loss”

Repeatedly seeking prescription from other clinicians or from emergency rooms without informing prescriber or after warning to desist

Evidence of deterioration in the ability to function in work, in the family, or socially that appear to be related to the drug use

Repeated resistance to changes in therapy despite clear evidence of adverse physical or psychological effect from the drug

Behaviours probably less predictive of addiction

Aggressive complaining about the need for more drug

Drug hoarding during periods of reduced symptoms

Requesting specific drugs

Openly acquiring similar drugs from other medical sources

Unsanctioned dose escalation or other non-compliance with therapy on one or two occasions

Reporting psychic effects not intended by the clinician

Resistance to change in therapy associated with “tolerable” adverse effects with expression of anxiety related to the return of severe symptoms

Table 2. Behaviours predictive of addiction (adapted from Portenoy 1996, 2004).

Many studies have been carried out about the prevalence of opioid addiction in patients with chronic pain, but one of the limitations in interpreting their results is the fact that the researchers have used different criteria to establish problematic opioid use; some studies are based on behavioural observations, others on the results of urine toxicology screening, others again on the criteria Diagnostic and Statistical Manual of mental disorders – III or IV [DSM-III-IV] and yet other studies are based on definitions established by the authors themselves.

Based on an extensive literature review, Højsted & Sjøgren (2007) estimated that the prevalence of addiction in the population with chronic non-cancer pain varies from 0% to 50%. In particular, in the studies based on urine toxicology screening the prevalence varies from 17.2% to 39%; in the studies using the DSM-III or DSM-IV criteria it varied from 1.9% to 37%; and, finally, in the studies based on the various behavioural indicators, the prevalence varied from 0% to 50%. In a study of 100 patients with chronic pain in treatment with opioids, Manchikanti et al. (2001) found a prevalence of drug abuse, defined as the occurrence of obtaining a prescription of a controlled substance at least once a month from another physician without approval of the pain physician signing the controlled substance contract, of 24%. Fleming et al. (2007), considering 801 patients with non-cancer pain in chronic treatment with opioids, reported that 9.7% of the sample met the DSM-IV diagnostic criteria for opioid use disorder; the prevalence found by the authors was four times the prevalence in the general population.

Finally, a recent review of the prolonged use of opioids in patients with non-cancer pain estimated the prevalence of addiction indicators as 0.27% of the total number of patients examined (Noble et al., 2010); the authors also observed that minor unwanted effects (e.g. nausea, headache) are frequent during treatment with opioids, but more serious adverse events, such as addiction, are rare.

The hypothesis that short acting drugs such as hydrocodone may make patients more liable to ineffective pain management and misuse or abuse of the drugs than long acting drugs such as methadone was investigated by Manchikanti et al. (2005), who analysed 200 patients with chronic pain, half being treated with hydrocodone and the remainder with methadone. The study found no significant differences in the use of illegal substances and/or opioid abuse in patients treated with short- or long-acting drugs.

So addiction is a well documented problem in pain patients, although it is difficult to estimate its exact prevalence. It is therefore important that clinicians consider the risk of opioid addiction without this prejudicing their use where indicated. In fact, those who use opioids constitute a heterogeneous category that includes extreme cases of patients who abuse medical and non-medical substances, and patients who adhere to treatment (Passik, 2009). For adequate management and treatment of pain, physicians must balance the costs and benefits of opioid treatment; to maximise the benefits they can use different strategies, such as risk assessment and stratification, using specific tools, constant monitoring of treatment and any aberrant drug behaviours, regular urine screening and the possible involvement of another specialist (e.g. psychotherapist, addiction expert).

2.3 Risk factors for opioid abuse

Risk factors for opioid abuse and addiction may be divided into three categories: psychosocial factors, substance-related factors and genetic factors (figure 2). The risk of addiction is highest when the various categories of risk factor are combined. Pain patients without a genetic predisposition, without psychiatric comorbidity who take a stable dose of

opioids for the treatment of severe pain in a controlled clinical setting are most unlikely to develop addiction. In contrast, patients with a personal or family history of substance abuse, and with one or more psychosocial issues are at greater risk of developing addiction, especially if the treatment is not carefully structured (Ballantyne, 2007).

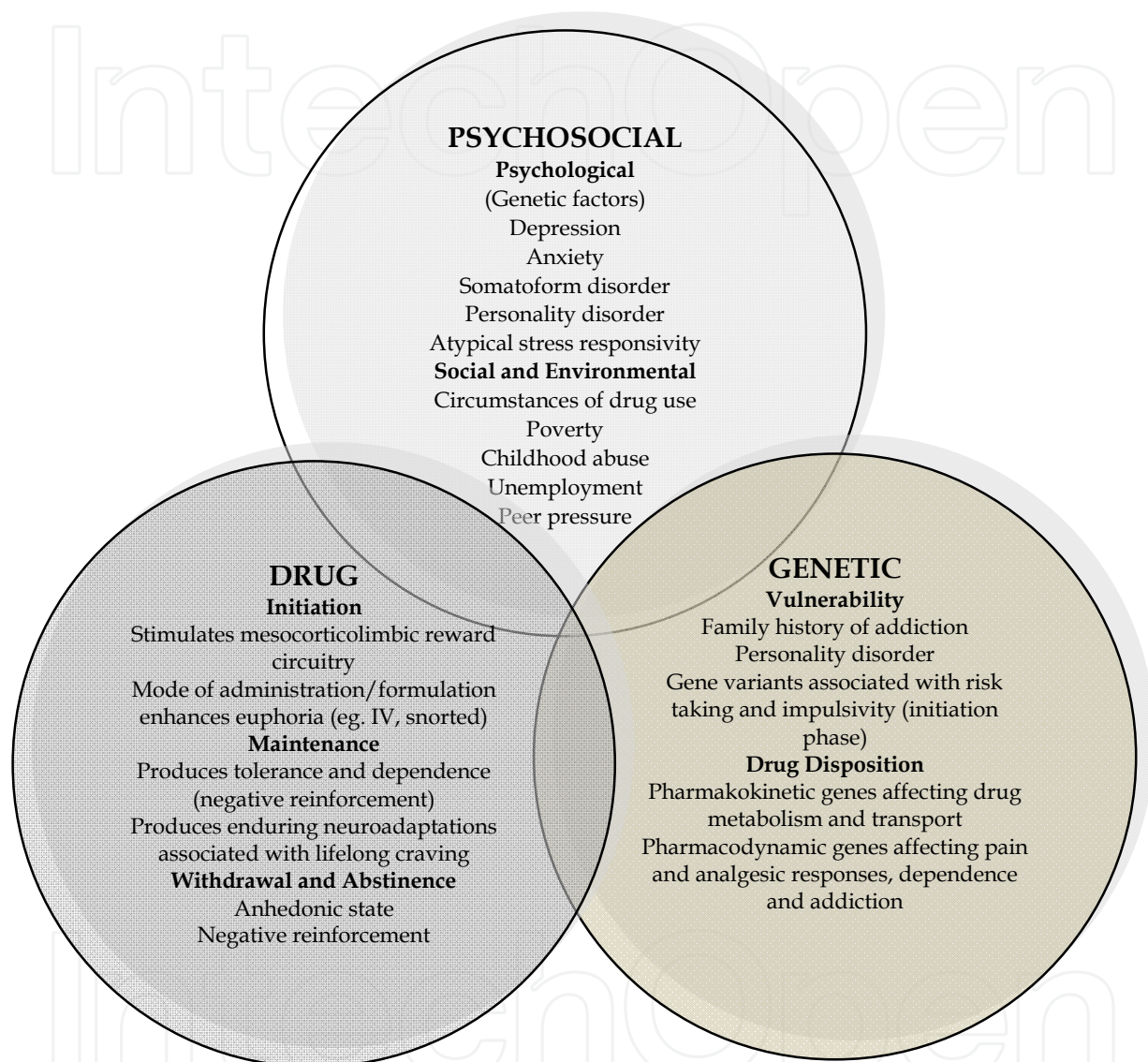


Fig. 2. Genetic, psychosocial and drug-related factors associated with the development of addiction. Adapted from Ballantyne (2007).

The psychosocial factors considered to be most predictive of opioid abuse are the presence of psychiatric disorders (Compton et al., 1998; Sullivan et al., 2006) and a personal and/or family history of substance abuse or drug abuse (Dunbar & Katz, 1996; Schieffer et al., 2005). A significant correlation has been found between chronic pain, mood disorders and aberrant drug use: patients with chronic pain report higher levels of anxiety and depression than patients with other medical conditions, and the incidence of mood disorders has been shown to be higher in patients at high risk of opioid misuse or dependence (Bair et al., 2003; Dersh et al., 2002; Fishbain, 1999).

Using logistic regression, the authors showed that panic attacks, high trait anxiety and the presence of a personality disorder are able to explain the 38% variance in potential abuse of prescribed opioids. To investigate the role of psychological adjustment and psychiatric symptoms in aberrant drug behaviours in pain patients, Wasan et al. (2007) divided the 228 patients enrolled into high-psychiatric and low-psychiatric morbidity, based on the responses to the psychiatric subscale of the Prescription Drug Use Questionnaire (PDUQ; Compton et al., 2008; see § 2.4.). Patients with high psychiatric comorbidity were significantly younger, with a longer mean opioid assumption time ($p < 0.05$); altered urine toxicology screening results were also more frequent among these patients ($p < 0.01$), and they often displayed aberrant drug-related behaviours.

Edlund et al. (2007) conducted a broad prospective study of the risk factors for opioid abuse and addiction using the South Central Veterans Affairs Health Care Network databank. The sample included 15,160 chronic users of opioids in 2002; 45.3% of the sample had a psychiatric diagnosis and 7.6% had a non-opioid substance abuse diagnosis. The results show that prior abuse of non-opioid substances is a strong predictor of abuse/addiction to opioid drugs, while mental disorders are moderately strong predictors. The authors also found that the risk of abuse decreases uniformly with age. Other risk factors for opioid abuse/addiction were male gender, being divorced/separated or single and, finally, being in treatment with opioids for longer. A broad retrospective cohort study that involved 704 patients with chronic pain being treated with opioids was carried out by Banta-Green et al. (2009a) to further comprehend the complex interaction between pain, mental health and addiction. The patients were initially assessed using a structured interview based on DSM-IV criteria for abuse and dependence on opioids, misuse of opioids, anxiety and depression. By regression analysis, the authors identified three distinct categories of patients which they called: a) Typical group (characterised by moderate pain symptoms and limited psychiatric problems); b) Addictive Behaviours group (high psychiatric symptoms, misuse of opioids and moderate pain symptoms); c) Pain Dysfunction group (high intensity and interference of pain, high psychiatric symptoms and consistent misuse of opioids). The patients in the last two groups took an average daily dose of opioids that was three times that of the typical group. The authors suggest that the use of high doses of drugs could constitute a simple indicator to identify those patients that might benefit from further medical or psychiatric assessment, or assessment of drug misuse behaviours.

To determine the incidence of opioid addiction, and the factors predictive for abuse, Ives et al. (2006) carried out a prospective cohort study of 196 patients with chronic pain being treated with opioids. Patients were monitored at regular intervals for an entire year. Opioid abuse was defined based on the presence of: negative urine toxicology screening for prescribed opioids; positive urine toxicology screening for non-prescribed drugs or opioids; supplies of opioids obtained from more than one provider; diversion of opioids, prescription forgery and positive urine toxicology screening for narcotics (cocaine or amphetamines). Opioid abuse was observed in 32% of patients; the most common form of misuse was the detection of cocaine or amphetamine in urine (40.3% of misusers). Abusers were found to be significantly younger ($p < 0.001$); male ($p = 0.023$); with a history of abuse of alcohol ($p = 0.004$) and cocaine ($p < 0.001$) than non-abusers. Ethnicity, income, education, levels of depression or disability and pain intensity were not found to be associated with drug misuse. Manchikanti et al. (2006) carried out a prospective longitudinal study of 500 patients with chronic pain to evaluate and correlate multiple variables with the abuse of opioids and illegal substances. Patients who obtained opioid

drugs from sources other than the physicians at the clinic where the study was carried out were considered abusers; use of narcotics was ascertained through urine toxicology screening. Opioid abuse was observed in 9% of patients, while the use of illegal substances (e.g. cocaine, marijuana, metamphetamines) was detected in 16% of the sample. Opioid abuse was found to be more frequent in patients with pain due to road traffic accidents, pain in more than one region of the body and subjects with prior substance abuse. The use of illegal substances was more frequent among women and in patients under 45 years of age. The onset of pain after a road traffic accident and the presence of pain in more than one part of the body were also risk factors for narcotic substance abuse. To investigate the effect of gender on aberrant drug-related behaviours, Back et al. (2009) carried out a study on 121 patients (49 male and 72 female), who had to complete a set of tests designed to collect personal and clinical information and data on aberrant drug behaviours (e.g. prescription fraud, using other drug administration routes) and the use of nicotine, alcohol, marijuana, cocaine and hallucinogens. The results show that men were taking the prescribed drug significantly more regularly than women (91.7% v 77.8%, $p < 0.05$), while women tend to keep unused drugs (67.6% v 47.7%; $p = 0.04$) and to use other drugs (e.g. sedatives) to enhance the efficacy of analgesics (38.8% v 20%; $p = 0.04$) more than men. Men tend to use other drug administration routes (e.g. crushing and snorting pills) than women, although this difference was not statistically significant. For men, there was an association between alcohol abuse, use of oxycodone or morphine and aberrant drug behaviours, while in women the aberrant drug behaviours were associated with the use of hydrocodone.

In conclusion, the presence of psychiatric disorders and a personal and/or family history of substance abuse seem to be the most predictive factors of risk of opioid misuse in patients with chronic pain. Other variables such as gender, age and marital status may influence the risk of abuse, although the relationship is less clear, and further investigation is required (Savage, 2002).

2.4 Tools to assess the risk of addiction and dependence

Guidelines suggest that the use of opioids in patients with chronic non-cancer pain must be preceded by an initial stratification of the risk of drug misuse; this evaluation should include even a psychological and psychiatric assessment (Chou, 2009; Chou et al, 2009a; Chou et al, 2009b; Chou et al, 2009c; Kalso et al., 2003; Trescot et al., 2006; Trescot et al., 2008). In recent years, many tools have been developed and examined for this purpose; most investigate the presence of a family and/or personal history of addiction and other factors correlated with opioid misuse, such as age, history of childhood sexual abuse and the presence of mental distress. Some of these tools, were created specifically for use in a population of patients with chronic pain, while others assess the addiction risk factors in general. Table 3 summarises the tools that will then be described in greater detail; however, it is important to bear in mind that none is able to produce an accurate diagnosis about the presence of addiction, abuse or dependence. Besides, many of these are self-assessment tools, and therefore potentially at risk of falsification by the respondent. It is therefore advisable to supplement the information obtained with such tools with data obtained from direct observation of the patient during medical appointments. Anyhow, for patients who are found to be at high risk of misuse of the drug from the initial assessment with one of these scales, it is advisable to provide for constant monitoring of treatment, with regular urine toxicology screening.

	Name	Abbreviated name	Authors	Year	Method of administration	Number of items
a	<i>CAGE- questions Adapted to Include Drugs</i>	CAGE-AID	Brown & Rounds	1995	Self-administered	4
b1	<i>Prescription Drug Use Questionnaire</i>	PDUQ	Compton et al.	1998	Interview	42
b2	<i>Prescription Drug Use Questionnaire – patient version</i>	PDUQp		2008	Self-administered	31
c	<i>Screening Tool for Addiction Risk</i>	STAR	Friedman et al.	2003	Self-administered	14
d	<i>Pain Medication Questionnaire</i>	PMQ	Adams et al.	2004	Self-administered	26
e1	<i>Screener and Opioid Assessment for Patients with Pain</i>	SOAPP	Butler et al.	2004	Self-administered	14
e2	<i>Screener and Opioid Assessment for Patients with Pain – Revised</i>	SOAPP-R		2008		24
f	<i>Opioid Risk Tool</i>	ORT	Webster et al.	2005	Self-administered	5
g	<i>Addiction Behaviour Checklist</i>	ABC	Wu et al.	2006	Interview	20
h	<i>Diagnosis Intractability Risk and Efficacy Score</i>	DIRE	Belgrade et al.	2006	Team assessment	7
i	<i>Drug Abuse Screening Test</i>	DAST	Yudko et al	2007	Self-administered	28

Table 3. Principal tools for the stratification of the risk of opioid addiction and abuse.

- a. The *CAGE questions Adapted to Include Drugs* (CAGE-AID; Brown & Rounds, 1995) is an adaptation of the CAGE questionnaire, used for a short screening for alcohol abuse, which also includes substance use. The name CAGE is derived from 4 key words: “cut”, “annoyed”, “guilty” and “eye-opener”. The questionnaire consists of the following 4 questions, to which the subject must reply “yes” or “no”: 1) Have you felt you ought to cut down your drinking or drug use?; 2) Have people annoyed you by criticizing your drinking or drug use?; 3) Have you felt bad or guilty about your drinking or drug use?; 4) Have you ever had a drink or used drugs first thing in the morning to steady your nerves or to get rid of a hangover (eye-opener)?. The addiction screening is positive with at least 2 affirmative responses. The CAGE-AID has been validated on a sample of 124 pain patients, demonstrating high values of sensitivity (0.70) and specificity (0.85).
- b1. *Prescription Drug Use Questionnaire* (PDUQ, Compton et al., 1998) is a tool, consisting of 42 items to be administered in the form of an interview, that assesses the degree of abuse / misuse of the drug in patients with chronic pain. Care staff trained in the use of the tool take about twenty minutes to complete the interview. The patient must answer yes/no to questions that investigate: pain condition (e.g. “Has the patient explored and/or tried non-opioid or non-pharmacological pain management techniques?”), the ways in which they use drugs (e.g. “Does the patient have more than one prescription

provider?"), social/family factors (e.g. "Have family members expressed concerns that the patient is addicted?"), family history of chronic pain and/or addiction (e.g. "Is there a positive history of chronic pain in the patient's mother, father, sibling or blood relative?"), personal history of substance abuse (e.g. "Has the patient ever been diagnosed with addiction to any drug or alcohol") and psychiatric history (e.g. "Has the patient ever been diagnosed with a psychiatric disorder?"). The tool has good internal consistency (Cronbach's $\alpha = 0.79$). To identify a cut-off, the 52 patients with chronic pain who participated in the pilot study to validate the PDUQ were initially classified as addicted or non-addicted based on criteria developed by the American Society of Addiction Medicine (see § 2.2.2.). Patients with scores of less than 11 did not meet the criteria for a substance abuse disorder, while patients with scores of 15 or more reflected the criteria for a substance abuse disorder. So those who achieved scores of less than 11 use the drug in a suitable way. Moreover, positive answers to 3 specific items of the tool (notably "patient believes he/she is addicted"; "increases analgesic dose/frequency"; "specific drug or route of administration preference") have been identified as more predictive of addiction, with a 92.9% of correct classification. Banta-Green et al. (2009b) carried out a study of 704 patients who had been prescribed long-term treatment with opioids, aimed to examine the factorial structure of the PDUQ. The results show that the items may be grouped into three distinct types of factor "addictive behaviours", "addiction concerns" and "pain treatment problems". The limits of the PDUQ concern the fact that it relies solely on the sincerity of the patient and is difficult to use in an overloaded clinical context.

- b2. The *Prescription Drug Use Questionnaire - patient version* (PDUQp) was created by Compton et al. (2008) to obviate the difficulty mentioned above. The PDUQp is a self-administered instrument which consists of 31 items and the total score can vary from 0 to 30. Analysis of the psychometric properties of the new self-administered version was carried out on 135 patients with chronic pain being treated with opioids, monitored for 12 months. The PDUQp proved to have good concurrent validity, calculated by comparing the scores obtained with the scores obtained with the PDUQ ($r = 0.64$). The tool also proved to have good test-retest reliability, assessed at 4, 8 and 12 months after its first administration ($r = 0.67$, $r = 0.61$ and $r = 0.40$ respectively). A cut-off of 10 is suggested as indicative of drug misuse.
- c. The *Screening Tool for Addiction Risk* (STAR, Friedman et al., 2003) consists of 14 questions with true/false responses that investigate potential risk factors for drug. The items were developed based on a literature review carried out by a team of specialists in pain and addiction. Validation of the questionnaire was carried out on 48 patients with chronic pain, 14 of whom had a diagnosis of addiction based on the DSM-IV criteria. The authors found a close correlation between addiction and prior treatment in a rehabilitation unit for alcohol or drug dependence, smoking, and intensity of nicotine craving. In particular, the item on prior experience of alcohol and/or substance detoxification was able to identify correctly 93% of the patients who met the addiction criteria.
- d. The *Pain Medication Questionnaire* (PMQ, Adams et al., 2004) is a self-administered questionnaire that describes a series of dysfunctional behaviours and characteristics that underlie the use of drugs for the treatment of pain. The tool consists of 26 items, for each of which the subject must indicate his degree of agreement or disagreement on a 5 point Likert scale, and a score is attributed to the selected response (disagree = 0, somewhat disagree = 1, neutral = 3, somewhat agree = 4, agree = 5). The sum of the

scores of the single items gives a total score, which can vary from a minimum of 0 to a maximum of 104. High scores are correlated with a high risk of opioid misuse. In particular, scores of 25 or more are indicative of opioid misuse, while scores of 30 or more suggest that the patient should be constantly monitored during treatment (Dowling et al., 2007). The validity of the tool was investigated by Adams et al. (2004) on 184 patients with chronic pain, comparing the results obtained with the PMQ with a series of assessment of substance abuse, degree of psychosocial distress, and some indicators of psychological and physical functioning; the test-retest reliability coefficient is 0.85 and the internal consistency is acceptable (Cronbach's $\alpha = 0.73$). A further study to examine the psychometric characteristics of the PMQ in greater depth was carried out by Buelow et al. (2009). One of the aims was to examine the accuracy of the short form of the PMQ (from which items 5, 10 and 23 had been eliminated, since they had the lowest correlation coefficients) in predicting opioid misuse. Examining 4.182 subjects, of whom 1.813 were involved in an interdisciplinary treatment programme (that included physical, pharmacological and psychological therapy) the authors confirmed the adequate internal consistency of the abbreviated form (Cronbach's $\alpha = 0.70$) and of test-retest reliability ($r = 0.77$). Significant differences also emerged in the mean PMQ score of patients with a history of substance abuse (mean = 24.39) and of patients without a history of abuse (mean = 21.95). Moreover, those patients who interrupted the treatment had mean scores that were significantly higher than those of patients who displayed good compliance. By logistic regression, the authors showed that early request of opioids is the only factor able to predict high or low questionnaire scores of those assessed (age, history of alcohol and/or substance abuse).

- e1. The Screener and Opioid Assessment for Patients with Pain (SOAPP, Butler et al., 2004) is a self-administered tool with 14 items that investigate potential risk factors for opioid misuse (e.g. "How often do you take more medications than you are supposed to?"; "How often have others expressed concerns over your use of medication?"). These items were proposed and voted on by a team of experts; the patient must indicate the frequency of each behaviour on a 5 point Likert scale (0 = "never"; 4 = "very often"). The tool was administered to 175 patients with chronic pain and readministered 6 months later to 95 of these patients, to test its reliability over time. The SOAPP proved to have adequate internal consistency (Cronbach's $\alpha = 0.74$) and good test-retest reliability six months after its first administration ($r = 0.71$). Scores of 8 or more are indicative of high risk of abuse (sensitivity: 0.91; specificity: 0.69). In a study investigating the psychometric characteristics and clinical utility of the SOAPP in 397 patients, Akbik et al. (2006) found patients classified at high risk were significantly younger, with altered urine screening results ($p < 0.05$) than low risk patients. The factor analysis also revealed the presence of 5 factors, called: 1) History of substance abuse; 2) Legal problems; 3) Craving medications; 4) Heavy smoking and 5) Mood swings. Moore et al. (2009), in a study to examine the efficacy of the SOAPP and other tools in predicting the risk of opioid misuse, found good sensitivity for the tool (0.72); combining the data from the SOAPP with those from a semi-structured clinical interview designed to investigate prior treatments used, the presence of emotional distress and prior substance abuse, the sensitivity increased to 0.90.
- e2. *The Screener and Opioid Assessment for Patients with Pain – Revised* (SOAPP-R) is a 24-item version developed by Butler et al. (2008) in order to overcome some limitations of the original SOAPP. The new version, tested on a sample of 283 patients, proved to have

- good internal consistency (Cronbach's $\alpha = 0.88$); the cut-off of 18 shows adequate sensitivity (0.81) and specificity (0.68). Patients with low SOAPP-R scores appear to be at less risk of developing a substance abuse disorder.
- f. The *Opioid Risk Tool* (ORT, Webster et al., 2005) is a self-administered tool developed to estimate the probability that the patient displays aberrant drug behaviours during long-term opioid treatment. The ORT consists of 5 items which investigate the following risk factors: family history of substance abuse (alcohol, drugs or prescribed medicines); personal history of substance abuse (alcohol, drugs or prescribed medicines); age (if between 16 and 45 years); history of childhood sexual abuse; presence of psychological distress (attention deficit disorder, obsessive-compulsive disorder, bipolar disorder, schizophrenia and depression). Each factor has a different weight in determining the potential risk of drug misuse, and so a specific numerical value is assigned to each, which also varies according to the sex of the respondent. There are three risk levels: scores from 0 to 3 are indicative of low risk; scores from 4 to 7 determine moderate risk; finally, scores of 8 or more are indicative of a high risk of misuse. This questionnaire was validated on 108 women and 77 men with chronic pain, followed for a period of 12 months from the initial appointment. 94% of the patients classified as low risk based on the total ORT score did not display aberrant drug behaviours in the year in which they were monitored, while 90.9% of the patients with scores of the cut-off value of 8 or more displayed aberrant drug behaviours.
- g. The *Addiction Behaviour Checklist* (ABC, Wu et al., 2006) consists of 20 items to be administered in the form of an interview. The items are grouped in two principal categories: 1) addicted behaviours noted during visit (e.g. "patient running out of medications early"; "receiving narcotics from other providers"); 2) addictive behaviours observed within the visit (e.g. "patient appearing sedated"; "patient expressing concern about the future availability of narcotics"). Finally, there is a further question that can be used if family members of the patient are present during the medical appointment ("significant others express concern over patient's use of analgesic"). The answer system is binary (yes/no): each affirmative answer is assigned a point and the total score can vary from 0 to 20. To investigate its psychometric characteristics, the ABC was administered to 136 patients with chronic pain prescribed long-term opioid treatment. The tool proved to have high inter-rater validity (0.94 - 0.95) and significant concurrent validity: a significant correlation ($r=0.40$; $p < .01$) was found between the ABC score and the Prescription Drug Use Questionnaire (PDUQ, Compton et al., 1998) score. A cut-off value of 3 on this tool is able to provide a good estimate of appropriate/inappropriate use that the patient will make of the drug. For scores of 3 or more, the authors suggest that the patient should be monitored frequently, including more frequent urine toxicology screening.
- h. The *Diagnosis Intractability Risk and Efficacy Score* (DIRE, Belgrade et al., 2006) is a tool that is compiled by a multidisciplinary team of physicians and psychologists. It consists of 4 scales: Diagnosis, Intractability, Risk (4 subcategories) Efficacy. Each class requires assessment on a 3 point scale, where a score of 1 corresponds to characteristics and behaviours that are indicative of a negative prognosis, and a score of 3 is indicative of suitability for treatment with opioids. The Diagnosis factor requires the clinician to determine the extent to which the patient's diagnosis is sufficiently compelling or advanced to warrant an aggressive pharmacological approach. The Intractability factor requires a determination of how many appropriate treatments the patient has undergone

and how he or she is involved in the treatment, i.e. if they play a passive or an active role in managing their pain. The Risk factor was created to estimate the extent to which the patient would adhere to the instructions of the clinician during treatment. As stated above, it comprises four categories: Psychological health assesses the psychiatric and psychological status of the patient; Chemical health assesses the patient's relationship with substances with potential risk of abuse; Reliability assesses compliance with treatment in the past, whether or not the patient attends appointments and following the physician's recommendations fully; Social support assesses the patient's support network and his or her ability to function in life roles, such as work, school, parenting, etc. Efficacy assesses the analgesic effectiveness of opioids, based on physical functionality and patient's pain self-report. When efficacy cannot be assessed because the patient has not yet started to take opioids, or takes them in quantities that are too low (less than the equivalent of 30 mg/day of morphine) a score of 2 is attributed. All the scales and subscales of the Risk factor are firstly assessed individually and then added together to obtain the DIRE score. The total score can vary from a minimum of 7 to a maximum of 21; scores between 14 and 21 are indicative of a greater degree of patient compliance and, in general, greater treatment efficacy. The psychometric analyses of the original version, carried out on a group of 61 patients with chronic pain, shown an internal consistency alpha coefficient of 0.80 and an inter-rater validity of 0.95.

- i. The Drug Abuse Screening Test (DAST, Yudko et al., 2007) is a self-administered questionnaire consisting of 28 items with binary (yes/no) answers. Scores of 6 or more indicate the presence of substance dependence or abuse. In addition to the complete version of the questionnaire, which can be too time-consuming in some clinical contexts, there are various short versions of the DAST, based on 10 items instead of 28. The 28-item DAST has proved to have high test-retest reliability ($r = 0.85$) and good internal consistency (Cronbach's α 0.92-0.94). The tool has shown good sensitivity, between 81% and 96%, and good specificity (from 71% to 94%). One limitation of the tool is the fact that it is susceptible to falsification and may therefore not identify those people who, while abusing the drug, intentionally give false answers. Moreover, the tool is predictive of substance abuse but does not specifically examine the aberrant drug behaviours.

2.4.1 Ways of monitoring treatment

A number of different tools have been created for clinicians to monitor opioid treatment and as checklists for the systemic observation of aberrant drug behaviours. The tools most widely mentioned in the literature are described briefly below.

The *Prescription Opioid Therapy Questionnaire* (POTQ; Michna et al., 2004) is a tool with 11 items to which the clinician must answer yes or no to assess opioid misuse. The items reflect the behaviours suggested by Chabal et al. (1997) as indicative of substance abuse. These behaviours include multiple unauthorised dosage increases, episodes of lost or stolen prescriptions, frequent unplanned visits to the clinic or emergency room, excessive telephone calls and inflexibility about treatment options. Patients who were positively rated on two or more of the items met criteria for prescription opioid misuse.

The *Pain Assessment and Documentation Tool* (PADT; Passik et al., 2004; Passik et al., 2005) is a brief (takes between 10 to 20 minutes to complete) clinician-directed interview. The clinician asks the patients questions that are organized in four primary areas called the "Four A's" and are notably: Analgesia - focuses on pain intensity (numeric rating scales) and pain relief; Activities of Daily Living - focuses on whether the patient's functioning since the last

assessment is better, same, or worse; Adverse Events - identifies whether the patient is experiencing side effects from current pain relievers, and if so, what they are; potentially Aberrant Drug-Related Behaviours - assesses 17 aberrant behaviours. The availability of this checklist is likely to improve the ability of clinicians to capture problematic behaviours and implement appropriate actions in response. In addition, there is a fifth section on "Assessment" which identifies a specific analgesic plan.

The *Current Opioid Misuse Measure* (COMM, Bultler et al., 2007) is a tool with 17 items, asking the patient how he or she currently uses pain medication. For each behaviour listed (e.g. "how often have you needed to take pain medications belonging to someone else?"), the patient must indicate the frequency of each behaviour on a 5 point Likert scale (0 = "never"; 4 = "very often"). The current 17-item version of COMM was created from the 40-item version produced from the concept mapping work carried out by 26 pain and addiction professionals. Validation of the tool was carried out on 227 patients with chronic pain. Scores of 9 or more (sensitivity=0.77; specificity=0.68) are considered to be indicative of high risk of drug abuse. The tool has excellent internal consistency (Cronbach's α = 0.86) and very good test-retest reliability one week after its first administration (r = 0.86).

As well as the tools mentioned above, urine drug screens and other laboratory tests can help the clinician to understand if the patient is using illegal substances or non-prescribed drugs. It is important to supplement the observation-based tools with laboratory tests. In fact, Katz et al. (2003) showed that even if a clinician has been very careful to detect aberrant drug behaviours, some signals may be missed: approximately 20% of patients considered compliant with the treatment prescribed by expert clinicians actually tested positive in urine toxicology screening. Urine screening is an economical and non-invasive monitoring strategy that enables most drugs to be identified between 1 and 3 days after they were taken (Heit & Gourley, 2004). In addition, urine screening may be very useful in preventing opioid abuse, detecting the presence of illegal substances, identifying those patients who are not taking the prescribed drugs, or those who are using non-prescribed opioids (Atluri & Sudarshan, 2003). However, the results of urine toxicology screening must be interpreted with caution, since they may not always be correct, and in some cases can produce false positives and false negatives. Moreover, some substances are not detected by standard urine screening, and so clinicians must resort to more specific or costly urine tests (or to blood or hair analysis). For this reason the results of urine drug screen should be considered a further piece of the puzzle in assessing patients with problematic opioid use behaviours (Ballantyne, 2009).

2.5 The research

This section describes the preliminary results of a prospective longitudinal study to identify some procedures that allow the risk of opioid misuse to be determined in patients with chronic non-cancer pain. Specifically, the study examines the efficacy and clinical utility of the Pain Medication Questionnaire - PMQ (Adams et al. 2004) and the Diagnosis, Intractability, Risk and Efficacy - DIRE (Belgrade et al. 2006). The PMQ was selected because it is a self-administered scale that can easily be integrated into clinical-care routine, and the DIRE because it is an assessment tool used in a multidisciplinary setting that requires a medical and psychological assessment of the patient. In addition, both tools have been shown to possess characteristics that make them suitable for use in clinical practice: good psychometric properties in their original version, easy to complete, and sufficiently short to administer and score.

The specific aim of the study is to identify and examine the efficacy of a clinical protocol for the systematic assessment of patients who are candidates for starting opioid treatment. As a

preliminary step, the predictive validity of the Italian versions of the PMQ and the DIRE was investigated: until now the Italian versions of these instrument are not available. Besides, the capacity of the two tools to predict opioid misuse was compared to the subjective estimate made by the physician based on his or her clinical experience. Furthermore, the presence of possible relationships between aberrant drug behaviours and the presence of risk factors for treatment compliance was examined, as was any use of illegal substances established by urine drug tests. Finally, the efficacy of the treatment was analysed the patient's perceived quality of life and pain experience after 2 and 4 months after the start of treatment.

2.5.1 Subjects

The preliminary data presented below refer to 25 patients treated in the Pain Relief and Palliative Care Unit. The inclusion criteria were: age between 18 and 70 years; presence of non-cancer pain for at least 6 months; pain intensity assessed on an 11 point Numerical Rating Scale of at least 4 in the last month; good knowledge/understanding of Italian; absence of cognitive deficit; use of fixed regime weak opioids insufficiently efficacious; other pharmacological and non-pharmacological treatments used for at least 3 months not sufficiently efficacious; no significant decrease in life expectancy; informed consent to participation in the study obtained.

	Descriptives (mean SD or % frequency)
Age	56.2 (10.6)
Sex	
- Women	17 (68.0%)
- Men	8 (32.0%)
Education (years)	
- 5	5 (20.0%)
- 8	10 (41%)
- 9-13	9 (35%)
- >13	1 (4%)
Marital status	
- Never married	2 (8%)
- Married	13 (52%)
- Divorced	3 (11%)
- Widowed	7 (27%)
Occupation	
- Employed	6 (24%)
- Housewife	7 (28%)
- Unemployed	1 (4%)
- Retired	11 (44%)
Type of pain	
- Nociceptive	10 (40%)
- Neuropathic	5 (20%)
- Mixed	10 (40%)
Duration of pain (months)	88.2 (57.7)

Table 4. Socio-demographic characteristics.

The socio-demographic and clinical characteristics of the group of subjects are represented in table 4. The mean age is 56.2 years (± 10.6) and 68% are women. Most subjects were not working at the time of the study due to their pain condition. Regarding the characteristics of their pain symptoms, the most prevalent types were nociceptive (40%) or mixed (40%); the average duration of the pain condition was 88.2 months (± 57.7). There were no statistically significant differences between men and women in any of the descriptive variables considered.

2.5.2 Instruments

The *Checklist for medical selection* is a tool constructed ad hoc that enabled physicians to collect information needed to check the suitability of the patient for inclusion in the study. It includes the collection of personal data (age, sex, nationality), clinical data (disorder causing the pain, characteristics of the pain, prior pharmacological and non-pharmacological treatments) and the assessment of pain intensity (in the last month) using the *11-point Numerical Rating Scale* (NRS-11). The doctor must also indicate the drug administration route (oral or transdermal) and the initial dosage.

The *11-point Numerical Rating Scale* (NRS-11) is a pain assessment scale in which the patient is asked to report the intensity of the pain, over a specific time interval, with a number from 0 to 10, where 0 indicates no pain and 10 the worst possible pain.

The risk opioid misuse was assessed using the Pain Medication Questionnaire- PMQ (Adams et al., 2004) and the Diagnosis Intractability Risk and Efficacy Score - DIRE; Belgrade et al. 2006): see § 2.4 for a detailed description of these tools. The Italian version of the tools elaborated for this study was authorised and approved by the original Authors.

The *Medical risk prediction* requires the physician to provide an estimate, based on his or her clinical experience, of the risk of opioid misuse, answering 3 questions on an 11 point numerical scale: compliance with medical treatment (0=no compliance; 10=maximum compliance), risk of abuse and/or underuse of the drug (0=no risk, 10=maximum risk) and expected efficacy of treatment (0=no efficacy, 10=maximum efficacy).

The *Medical control form* was designed to collect clinical information about the progress of the treatment, any side effects, and the intention to continue or suspend treatment. It contains also a list of aberrant drug behaviours, based on the reference literature; the physician must tick those behaviours displayed by the patient (e.g. The patient uses other opioids in addition to those prescribed, The patient displays little interest in managing himself and his rehabilitation).

Urine toxicology screening was performed with fast immunodosages that could be read visually, allowing the qualitative determination of the pharmacological substances and their metabolites present in the urine. For opiates, marijuana and buprenorphin, QuikStrip™ OneStep immunodosages were used; QuikPac II™ OneStep were used to detect the presence of amphetamines, metamphetamines and cocaine.

Regarding the psychological assessment the following tools were used.

The *Initial pain interview* is a semi-structured interview designed to reconstruct the clinical history of the pain, and its progress over time. The interview is used to gather a wide range of personal information (e.g. marital status, level of education, employment status, etc.) and other information about the pain and its interference in daily activities. The habits and behaviours that, based on the literature, are considered risk factors for aberrant opioid use were also investigated (smoking, alcohol consumption patterns, use of drugs, family history of alcohol and/or drug abuse, sexual abuse).

The *Visual Analogue Scale* (VAS) consists of a 10 cm long horizontal line, the start and end points of which are labelled “no pain” and “worst possible pain”. The patient is asked to mark the precise points corresponding to his or her maximum, minimum and habitual pain in the last month.

The *Minnesota Multiphasic Personality Inventory II* (MMPI-2; Hataway e McKinley, 1989; Italian adaptation by Pancheri et al., 1996) is a self-administered questionnaire used to assess personality characteristics. It consists of 567 items to be answered “true” or “false”. Scores are obtained referred to three control scales and ten clinical scales (Hypochondria, Depression, Hysteria, Psychopathic Deviate, Masculinity - Femininity, Paranoia, Psychasthenia, Schizophrenia, Hypomania and Social Introversion).

The *Beck Depression Inventory II* (BDI-II; Beck et al., 1996; Italian adaptation by Ghisi et al., 2006) is a 21-item self-administered questionnaire commonly used among chronic pain patients to determine their depressive reaction, assessing both the cognitive component (e.g. sadness, pessimism) and the somatic component (e.g. loss of appetite, sleep disorders).

The *State Trait Anxiety Inventory-Y* (STAI-Y, Spielberger, 1983; Italian adaptation by Pedrabissi and Santinello, 1989) is a 40-item questionnaire that assesses the level of patient anxiety. Two scores can be obtained, referring to two subscales that assess state anxiety (i.e. the anxiety experienced by the patient at the time they complete the questionnaire) and trait anxiety (i.e. the anxiety that the patient habitually experiences).

The *Pain Related Self-Statement Scale* (PRSS; Flor and Turk, 1988; Italian adaptation by Ferrari et al., 2004) is a self-administered scale developed to assess the cognitions specifically triggered in the pain situation that might inhibit or promote coping responses. The tool consists of 18 items, from which two total scores can be obtained for the subscales called Catastrophizing and Coping.

The *Nottingham Health Profile* (NPH, Hunt et al., 1985; Italian adaptation by Bertin et al, 1992) was used to assess quality of life. It consists of 38 items covering 6 content areas: physical mobility, energy, sleep, pain, social isolation, emotional reactions. The scores are expressed on percentage scales and correspond to the level of compromise perceived by the subject in the quality of life area considered.

The *Multidimensional Pain Inventory* (MPI, Kerns et al., 1985; Italian adaptation by Ferrari et al., 2000) is a 61-item self-administered questionnaire that allow a multidimensional assessment of the pain experience. The tool is divided into 3 parts: the first focuses on assessing the intensity of the pain, its interference in the life of the patient, the patient’s perceived control of the pain and of events in his or her life (it consists of the following subscales: pain severity, interference, life-control, affective distress and support). The second part investigates the patient’s perception of the responses of his or her significant others to his or her pain communications (negative/sollicitous and distracting responses). The third part examines the frequency with which the patient carries out common daily activities (household chores, outdoor work, distant activities, social activities and general activity).

Finally, the *McGill Pain Questionnaire* (MPQ, Melzack, 1983; Italian adaptation by Maiani and Sanavio, 1985) is a tool consisting of a list of 78 adjectives related to pain grouped into 20 subclasses of homogeneous content; within each subgroup the descriptors are arranged in order of increasing intensity. The subject is invited to choose the adjective that best describes his or her pain in each category. The tool allows the pain to be assessed as an experience with three major dimensions: sensory-discriminative, motivational-affective and cognitive-evaluative.

2.5.3 Procedure

The study is observational prospective and longitudinal; patient selection, data collection and the subsequent follow-ups took place from December 2009 to March 2011 in the Pain Relief and Palliative Care Unit of Vicenza hospital. The study consisted of the following assessment phases: patient selection, collection of pre-treatment data, 2 and 4 month follow-ups (figure 3).

The specialist physician selected patients according to the personal and clinical criteria indicated above, as well as by using the numerical scale to assess pain intensity. Patients who were candidates for opioid treatment were asked to undergo psycho-clinical assessment in accordance with the multidisciplinary care diagnostic protocol, for patients with chronic non-cancer pain referred for opioid treatment at our Centre.

Pre-treatment data were collected in the two week period following selection. It consisted of the compilation of the questionnaire to determine the risk of opioid misuse (PMQ) by the patient, and the compilation of the DIRE by the team of pain specialists. Questionnaires to assess the intensity and experience of pain (VAS, MPI, MPQ, PRSS) and affective/emotional state (STAI-Y, BDI-II), quality of life (NHP) and personality characteristics (MMPI-2) were also administered. Medical and psychological follow-ups were scheduled 2 and 4 months after the start of treatment. At 2 months, medical data such as the presence of any side effects, changes in dosage, presence of aberrant drug behaviours and any intention to stop treatment were collected for treatment monitoring. The PMQ was administered again, to assess its reliability over time, and the questionnaires assessing quality of life and pain experience (VAS, MPI and NHP) were also administered. The same medical and psychological data were collected at 4 months, apart from the PMQ. At both follow-up appointment urine drug test was proposed. The study protocol was approved by the competent Ethics Committee.

PATIENT SELECTION	PRE-TREATMENT	2 MONTH FOLLOW-UP	4 MONTH FOLLOW-UP
<ul style="list-style-type: none"> Checklist for medical selection Intensity of pain in the last month $\geq 4/10$ (NRS) 	<p><i>Medical assessment</i></p> <ul style="list-style-type: none"> Medical risk prediction <p><i>Psychological assessment</i></p> <ul style="list-style-type: none"> Risk of opioid misuse (PMQ) Initial pain interview Pain intensity (VAS) Personality characteristics (MMPI-II) Affective-emotional state (STAI-Y, BDI-2) Pain experience and coping strategies (MPI, MPQ, PRSS) Quality of life (NHP) <p><i>Team assessment</i></p> <ul style="list-style-type: none"> Risk of opioid misuse (DIRE) 	<p><i>Medical assessment</i></p> <ul style="list-style-type: none"> Medical control form Urine drug tests 	<p><i>Medical assessment</i></p> <ul style="list-style-type: none"> Medical control form Urine drug tests <p><i>Psychological assessment</i></p> <ul style="list-style-type: none"> Pain intensity (VAS) Experience of pain (MPI) Quality of life (NHP)

Fig. 3. Study procedures

2.5.4 Statistical analysis

Continuous variables are expressed with mean, standard deviation, minimum and maximum and centiles into which the variables fall, when possible. Discrete and nominal variables are reported in frequency tables with the related percentages. To examine the differences between continuous variables, Student's parametric t test was used, with Chi squared for the comparison of frequency distributions.

The reliability of the PMQ was assessed using test-retest, and Cronbach's α , while the internal consistency of the DIRE was determined from Cronbach's α .

Correspondence Analysis was used to examine the relationship between the PMQ and DIRE scores obtained by the patients in the pre-treatment phase and the number of aberrant drug behaviours detected in the patients at the medical follow-ups recorded in the "Medical control form", the duration of treatment and the presence of the drug in the urine. Analysis of variance and correlational analysis with Spearman's non-parametric coefficient were used to analyse the relationship between the PMQ scores and the DIRE and the clinical variables related to pain, psychological function and quality of life.

2.5.5 Results

All the patients reported continuous pain; table 5 shows the mean values for pain intensity (assessed using the VAS) and the data on pharmacological treatment in the three assessment phases. No significant gender differences were found in maximum, minimum or habitual pain intensity. However, there was a statistically significant reduction in maximum and minimum pain intensity from the pre-treatment to the 2 month follow-up ($F_{1,24} = 4.64$; $F_{1,24} = 6.75$ respectively; both for $p < 0.05$); from pre-treatment to the 4 month follow-up the only difference was in maximum VAS ($F_{1,24} = 8.21$; $p < 0.01$). This variation was not influenced by the active substance administration route.

Analysing the type of pharmacological treatment, it may be noted that at both the start of the pharmacological treatment and at the subsequent follow-ups, the most frequently administered active substance was oxycodone. The administration route during the data collection phases remained primarily oral. The drug dosages were transformed into equivalent mg of morphine, and classified as mild/average/high based on the indications supplied by Bruera et al. (1995). Regarding the dosage, it showed a tendency to increase at the 4 month follow-up.

Approximately half (46%) of the patients reported the presence of at least one side effect at the follow-ups; the most frequently reported side effects were sleepiness (29%), constipation (29%) and nausea (21%). The drug administration route did not appear to have any effect on the number and type of side effects reported by the patients.

With respect to the psychological indicators investigated in the pre-treatment assessment, it was found that, based on the personality profile obtained with the MMPI-2, 56.2% of women and 33.3% of men had clinically significant scores in at least one of the clinical scales with psychopathological content (Paranoia, Schizophrenia, Hypomania). As for the affective-emotional variables, the mean total score at BDI-II in the initial treatment phase was 24.6 (SD= 13.40) in women and 18.2 (SD= 9.94) in men; the level of depression was clinically significant (scores higher than 95th percentile) in 61% of women and 50% of men. Considering trait anxiety, the mean score was 52.7 (SD= 11.97) in women and 46.2 (SD= 7.22) in men, with 27.7% clinically significant levels of anxiety only in women (scores higher than 95th percentile). Regarding PRSS, the subjects reported a mean score of 3.20 (range 0-5, SD= 1.15) on the Catastrophizing scale and 2.76 on the Coping scale (range 0-5, SD= 0.88).

	Initial treatment	2 month follow-up	4 month follow-up
	Mean (SD)	Mean (SD)	Mean (SD)
Pain intensity	Mean (SD)	Mean (SD)	Mean (SD)
- maximum VAS	90.2 (12.9)	80.6 (16.4)	78.7 (28.3)
- minimum VAS	33.1 (22.4)	24.0 (18.7)	31.8 (19.6)
- habitual VAS	55.5 (20.6)	52.6 (13.8)	56.1 (24.5)
	Frequency (%)	Frequency (%)	Frequency (%)
Drug active substance			
- Oxycodone	12 (48%)	12 (48%)	15 (60%)
- Fentanyl	10 (40%)	6 (24%)	5 (20%)
- Hydromorphone	3 (12%)	4 (16%)	5 (20%)
- Buprenorphine	-	3 (12%)	-
Route of administration			
- Oral	15 (60%)	16 (64%)	20 (80%)
- Transdermal	10 (40%)	9 (36%)	5 (20%)
Dosage (mg morphine)	Frequency (%)	Frequency (%)	Frequency (%)
- Mild (<60 mg)	24 (96%)	11 (44%)	6 (24%)
- Average (60-300mg)	1 (4%)	14 (56%)	11 (44%)
- High (>300 mg)	-	-	8 (32%)

Table 5. Pain intensity, active medication taken, administration route and dosage in initial treatment and in subsequent follow-ups.

In the description of the pain characteristics at the MPQ, higher scores emerged in the evaluative and affective -evaluative dimensions (means 0.87 and 0.73, respectively), while the lower scores referred to the affective and mixed-sensory dimensions (means 0.4 and 0.52, respectively).

In the MPI the subjects reported high mean on "Pain severity" (mean: 4.6; SD= 0.9), "Interference" (mean: 4.3; SD= 1.1) and "Affective distress" (mean: 3.6; SD= 1.1) in the pre-treatment assessment. Quality of life, measured using the NHP, appears more compromised in the following areas: "Emotional reactions" (mean: 80; SD= 56), "Pain" (mean: 77; SD= 26.2) and "Energy" (mean: 64; SD= 40). There were no statistically significant variations in the mean scores at the start of treatment and at the subsequent follow-ups for either the MPI or the NHP.

As for the tools to assess the risk of opioid misuse, the mean score at the PMQ was 24.59 (SD=9.43); there were no significant gender differences in the PMQ scores. Figure 4 shows the three different levels of the PMQ scores that, according to the cut-offs established by Dowling et al. (2007), identify a low/moderate or high risk of drug misuse. Overall, 36% of the subjects were found to be at high risk of misuse, 20% at moderate risk, and the remaining 44% at low risk. The distribution in the three risk levels between men and women was comparable.

The group was subsequently divided into patients with high PMQ scores (H-PMQ; n=9) and patients with low PMQ scores (L-PMQ; n=11) in order to analyse the presence of any significant differences in the psychological variables considered in the study. The patients with H-PMQ had a mean score of 3.78 on the Catastrophizing scale of the PRSS, statistically higher than that of the L-PMQ patients (mean 2.61) ($t=-3.16$; $p<0.01$); while on the Coping scale the H-PMQ subjects had mean scores that were significantly lower than those of the L-PMQ group ($t=-2.18$; $p<0.05$). Further statistical differences were found for the "HS" scale

(Hypochondria) of the MMPI-2, in which the H-PMQ subjects had scores that were significantly higher than the L-PMQ subjects (means 21 and 16.5 respectively, $t=23.60$; $p<0.05$) and for the total depression score in the BDI-II (H-PMQ mean =27.36; L-PMQ mean =17.88; $t=26.18$, $p<0.05$).

As for the predictive validity of the tool, a highly significant correlation was found between the total PMQ score (high risk of opioid misuse) and the number of aberrant drug-related behaviours noted by the physician at the 4 month follow-up ($r=0.95$; $p<0.01$). Significant correlations were also found between the PMQ score and the "HS" (Hypochondria) scale of the MMPI-2 ($r=0.49$; $p<0.01$), the total score in the BDI-II ($r=0.43$; $p<0.05$), the trait anxiety score of the STAI-Y ($r=0.38$; $p<0.05$) and the "emotional reaction" scale of the NHP ($r=0.39$; $p<0.05$).

The mean time required by the patient to complete the tool was 12'02" (SD=6.35; range: 4-30). Finally, analysis of internal consistency produced an alpha coefficient of 0.82, indicating that the tool has excellent internal coherence; the test-retest reliability at 2 months was very high ($r=0.76$; $p<0.001$).

In the DIRE, the mean score assigned by the multidisciplinary team was 15.35; in this case too there were no significant differences in the mean scores of men and women. Figure 5 shows the percentage of patients suitable or not suitable for treatment based on DIRE total Score according to the cut-offs established by Belgrade et al. (2006). Most women (81.2%) and men (87.5%) were found suitable to start chronic opioid treatment according to the DIRE score.

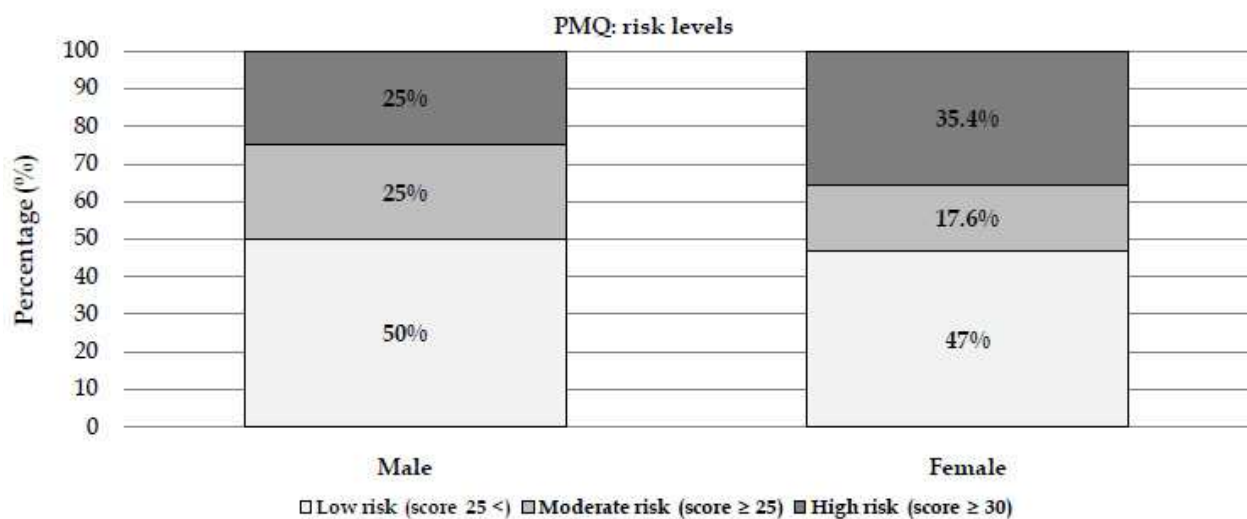


Fig. 4. Percentage of patients with low/moderate/high risk level for opioid misuse, based on PMQ scores.

The total DIRE score was not found to be significantly correlated with the number of aberrant drug behaviours recorded by the physician at 2 and 4 months; however, a significant negative correlation ($r=0.83$; $p<0.05$) was found between the scores in the "Risk" category of the DIRE (psychological risk, chemical health, reliability, social support) and the number of aberrant drug behaviours recorded by the physician at the 4 month follow-up.

The total DIRE score correlates negatively with the total BDI-II score ($r=0.46$, $p<0.01$) and with many of the MMPI-2 scales, and specifically: "PD" (Psychopathic Deviate) ($r=0.44$; $p<0.05$), "PA" (Paranoia) ($r=0.40$; $p<0.05$), "D" (Depression) ($r=0.39$; $p<0.05$), "FAM" (Family Problems) ($r=0.44$; $p<0.05$), "WRK" (Work Interference) ($r=0.40$; $p<0.05$) and "TRT" (Negative Treatment Indicators) ($r=0.39$; $p<0.05$).

The mean time required by the multidisciplinary team to complete the tool was 7'23" (SD=3.38; range: 1-16). The internal consistency of the Italian version of the tool was 0.48, which is very low; the item that contributed least to the internal consistency of the DIRE was Diagnosis (α if item deleted=0.51).

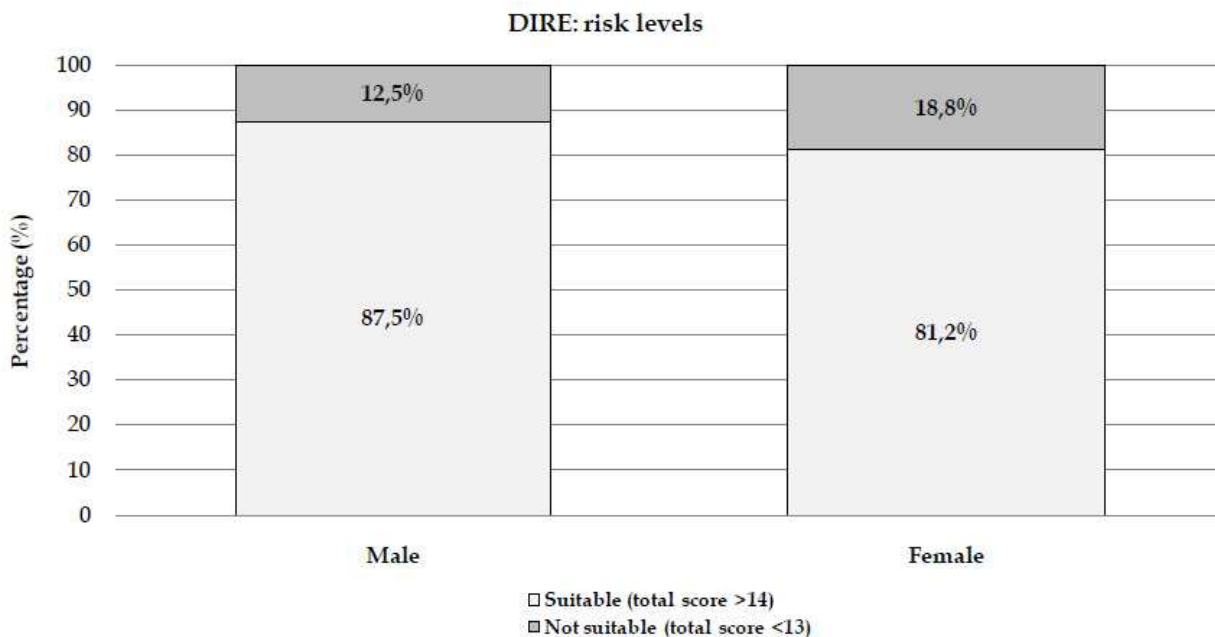


Fig. 5. Percentage of patients suitable or not suitable for treatment based on DIRE total Score.

As for the concurrent validity of the two tools, there were no significant correlations between the total scores of the PMQ and the DIRE. However, there was a moderate negative correlation ($r=0.36$; $p<0.05$) between high total PMQ scores (high risk of opioid misuse) and low scores in the Risk category of the DIRE.

Both the PMQ and the DIRE proved to be more effective than the Medical risk prediction in estimating the risk of drug misuse: the subjective estimate of the physician based on his or her clinical experience does not in fact correlate with the aberrant drug behaviours displayed by the patient at 2 and 4 months.

In the urine toxicology screening, only one patient tested negative for the active principle at the two month follow-up, while all the patients were positive for the drug used at the four month follow-up. None of the patients tested positive for illegal substances.

In relation to aberrant drug behaviours, most of the subjects (71%) displayed no aberrant drug behaviour at the two month follow-up; there was a potential misuse indicator in 19%, and the remaining 10% displayed three or more. At the 4 month follow-up, 22% of the patients displayed three or more aberrant drug behaviours while no indicators of misuse were found in 56% of the subjects.

Regarding other factors that according to the literature might be predictive for improper use of opioids, none of the patients reported that they abused alcohol or narcotic substances at assessment; 4.9% reported a personal history of alcohol abuse and 5.4% stated that they had abused illegal substances in the past. 7.3% of the subjects had a family history of alcohol abuse and 2.4% had a family history of the use of narcotic substances. None of the patients reported that they had suffered sexual abuse in childhood or adolescence, 17.1% of the patients had a prior psychiatric diagnosis and 9.8% of the subjects were being treated by a psychiatrist at the time of the evaluation.

2.5.6 Discussion

The main purpose of this study was to identify clinical procedures that allow to estimate the risk of opioid misuse in patients with chronic non-cancer pain treated as outpatients in a pain relief centre. With this aim, two tools were selected and adapted in Italian – the Pain Medication Questionnaire (PMQ) and the Diagnosis, Intractability, Risk and Efficacy Score (DIRE). These tools examine the perspectives of the patient and the multispecialist team, respectively.

The preliminary results reported above show that the PMQ has a good capacity to predict the risk of drug misuse by the patient. A strong correlation was found between high PMQ scores and the number of aberrant drug behaviours reported by the physician 4 months after the start of the study.

From the PMQ scores, 36% of the subjects were found to be at high risk of misuse, 20% at moderate risk, and the remaining 44% at low risk. High PMQ scores (high risk of misuse) were found to be associated with higher levels of anxiety, depression and persistent body-related worries. Furthermore, those patients classified as high risk of misuse, based on the cut-offs suggested by Dowling et al. (2007), were found to be significantly more depressed, and with a greater tendency to somatise their emotional distress than those classified as low risk. High risk patients were also found to be less active in managing their pain condition, and to have a greater propensity to produce pessimistic and catastrophic thoughts about their pain symptoms. The association that emerged, between high PMQ scores and the presence of symptoms of depression, appears to be in line with the findings of Holmes et al. (2006) in their work assessing the long-term utility of the PMQ in 271 subjects. In this study the low risk patients had mean BDI scores that were significantly lower than those of the high risk of misuse group.

Furthermore, based on the initial results, the PMQ has demonstrated adequate internal consistency and good reliability over time. This suggests that the items composing it measure a single construct, and that the tool provides a reliable estimate of the risk of medication misuse. In addition, completing the PMQ requires just over ten minutes of the patient's time, and this makes it easy to incorporate into clinical practice.

To summarise, the tool seems to possess a good predictive capacity in relation to the use that the patient will make of the drug, and his or her compliance with treatment. The total score on the questionnaire, and the stratification of risk based on the cut-offs suggested by the authors therefore appear to be reliable indicators that the clinician can use to plan regular treatment monitoring. The strong association between high PMQ scores and the presence of symptoms of depression, tendency to somatisation and catastrophization, suggest that pharmacological treatment with opioids needs to be combined with psychological treatment to reduce the affective and emotional distress and modify the patient's dysfunctional convictions and behaviours in relation to use of the drug.

As for the Italian version DIRE, the preliminary results show that the total score for risk of drug misuse is a poor predictor with limited psychometric quality. The Risk category, which specifically assesses psychosocial aspects such as psychological adaptation, substance abuse, reliability in complying with previous treatments and perceived social support in life context, is an exception to this. The tool in fact has low internal consistency, which improves slightly when the Diagnosis factor is removed. This means that the items of which the tool is composed are very heterogeneous, and that the tool probably has a multifactorial structure. Our finding does not agree with the results reported by Belgrade et al. (2006) in the original validation study, in which the DIRE displayed a very high internal consistency. The total

score of the DIRE - Italian version - is not at present predictive of the number of aberrant drug behaviours detected by the physician at the follow-ups. This seems to be in line with the work of Moore et al. (2007), who found that the DIRE had low sensitivity (0.17) in predicting aberrant drug behaviours. The authors suggest that the DIRE is more than simply an addiction risk tool and some of its items may not to be appropriate to predict drug misuse. However, as mentioned above, the score of the Risk category was found to be predictive of the number of aberrant drug behaviours at 4- months follow-up. This result is coherent with the findings of many studies on opioid abuse risk factors, which found that the factors considered to be most predictive of opioid abuse are the presence of psychiatric disorders (Compton et al., 1998; Sullivan et al., 2006) and a personal and/or family history of substance abuse or drug abuse (Dunbar & Katz, 1996; Schieffer et al., 2005). Our data indicate that a low score (not suitable for opioid treatment) is associated with depressive symptoms, the presence of paranoid personality traits and family and work difficulties. Completing the DIRE requires a few minutes of the team's time, but this must be preceded by an in-depth psychological assessment of the patient to determine if psychiatric disorders and past abuse, or current alcohol or substance abuse, are present.

The two tools selected do not appear to be correlated; instead, it is clear that there is an association between high PMQ scores (high risk of misuse) and low scores in the DIRE Risk category.

The prediction made by the physician based on his or her clinical experience was not found to be valid in estimating the risk of opioid misuse. This result highlights the need to use tools specifically created to assess the risk of opioid addiction in the chronic pain patient; clinical experience can be used to understand and contextualize the results obtained from these scales, but seems to be insufficient on its own.

So far as the experience of pain and the indicators of psychophysical function are concerned, the use of opioid drugs proved efficacious in reducing the maximum and minimum intensity of the perceived pain 2 months after the start of the treatment. A parallel improvement in the quality of life of the patients was not recorded by the questionnaire used in this study. This result seems to be in line with the data in the literature: despite ongoing research and the growing use of opioids in clinical practice, the effect of this treatment on the quality of life of the patient remains a subject of debate (Dillie et al., 2008). The reduction in pain, unaccompanied by an improvement in physical function and quality of life, indicates that these patients need psychological support, to examine their life habits, coping strategies and any secondary gain that might interfere with recovery of a state of psychophysical well-being. Quality of life is in fact a wide ranging concept, influenced by perception of one's health in a biopsychosocial sense, level of independence, social relationships and interaction with one's own specific environmental context in a complex way (Apolone et al., 1997).

As for the psychological variables considered in the study, half of the men and 60% of the women reported clinically significant levels of depression; and almost 30% of the women displayed high levels of anxiety. These data are in line with the findings of many authors, that clinically significant levels of depression and anxiety are very frequent in patients with chronic pain (Banks & Kerns, 1996; Boersma & Linton, 2006; Dersh et al., 2006; Gatchel, 2005; Vlayen & Linton, 2000). In addition, there was a high incidence of alterations in patients' personality profiles: over half of the women and approximately one third of the men reported high scores in at least one of the clinical content scales of the MMPI-2. This result too seems coherent with the reports in the literature, that the presence of psychiatric and

personality disorders is more frequent in these patients (Banta-Green et al., 2009a; Haller & Acosta; 2010), and therefore it is advisable to involve a psychotherapist or psychiatrist in the treatment process (Chou, 2009; Chou et al, 2009a; Chou et al, 2009b; Chou et al, 2009c; Trescot et al., 2006; Trescot et al., 2008).

The analyses carried out to date have shown that only one patient in twenty five did not test positive to the prescribed drug; and no patients tested positive for illegal substances in the urine toxicology screening. These data seem very different to those of other studies, which found the prevalence of abuse of illegal substances in patients being treated with opioid to be 16% (Machikanti et al., 2006), 20% (Heit & Gourlay, 2004) or 40.3% (Ives et al., 2006). The preliminary results seem to suggest that in our context the more frequent problem may be the underuse of opioid analgesics rather than their compulsive use and abuse: this interpretation is supported by the difficulty, frequently expressed by our patient, in accepting these drugs for fear of dependence, loss of mental lucidity or being socially stigmatised as drug addicted. A further important objective of the management of patients who are candidates for opioid treatment in a multidisciplinary setting is thus to assess their convictions about the use of these drugs and their expectations of treatment, so as to be able to modify any dysfunctional beliefs and unrealistic hopes for the outcome of treatment.

The limitations of this study are primarily the small number of subjects examined and the differing distribution of men and women. In addition, the limited number of patients did not allow us to examine the effect of other variables that, based on the reference literature, can constitute risk factors for opioid addiction, such as a personal or family history of alcohol and/or substance abuse, or episodes of sexual abuse in childhood or adolescence.

Despite these limits, the high degree of correlation between risk of misuse and the psychological aspects supports the view that an in-depth assessment of the affective-emotional, cognitive and behavioural variables of the patient is crucial. So future research may be focused on understanding which psychological variables are most connected to the risk of opioid misuse (e.g. personality traits, anxiety, depression, etc.) so as to be able to develop tailored psychological interventions that maximise treatment efficacy, with positive outcomes for quality of life and overall well-being, as well.

Overall the results that have emerged so far highlight the need for a multidisciplinary assessment of patients who are candidates for opioid treatment so as to improve compliance and treatment benefits. The use of tools specifically designed to determine the risk of inappropriate use of the drug has proved to be more efficacious than the opinion expressed by the clinician based on his or her experience. The strong association between psychosocial distress and high risk of opioid misuse also suggests that pharmacological treatment should be combined with psychological interventions that can reduce the anxiety-depression symptoms and correct any irrational ideas about the use of these drugs. Furthermore, systemic monitoring of treatment and regular urine drug screen can contribute to improve adherence to treatment.

3. Conclusions

Chronic non-cancer pain remains a condition that affects a large number of people throughout the world, and is associated with significantly compromised quality of life. Although many pharmacological and non-pharmacological treatments have been proposed to manage chronic pain, the results have proved disappointing for a significant proportion of patients.

Opioid drugs seem promising for the management of chronic pain of medium-severe intensity, but many uncertainties remain about the long-term use of these drugs and the risk of dependence and abuse. In this respect, many guidelines and protocols with recommendations have been developed in recent years precisely to allow safer and more targeted use of opioid drugs in chronic non-cancer pain syndromes; these recommendations highlight, primarily, the importance of carrying out stratification of risk in the patient who is a candidate for pharmacological treatment with opioids. A number of standardised tools have been developed with the aim of identifying and objectively measuring the risk of abuse, dependence and aberrant drug behaviours.

This chapter has presented the preliminary results of a study that aims to analyse the clinical utility of the Italian adaptation of two tools for stratification of the risk: a self-administered patient questionnaire, the Pain Medication Questionnaire, and a team assessment tool, the Diagnosis Intractability Risk and Efficacy Score.

These tools have been used as part of a multidisciplinary medical and psychological assessment and treatment protocol; the data in the literature, confirmed in our study, clearly indicates that there is a frequent association between high risk of opioid misuse and the presence of psychological distress (Banta-Green et al., 2009a; Haller & Acosta; 2010). This emphasizes the importance of a physical, psychological and social assessment before starting treatment with opioids. In this respect, based on literature data and the preliminary results of the study described, we believe that an effective psychological assessment must consist of an initial clinical interview, specific tools to assess the risk of drug misuse, and questionnaires that investigate the patient's subjective experience of pain, perceived quality of life and personality characteristics. The interview, which may be more or less structured, is essential to understand the individual's experience of pain and its interference in the patient's family, professional, social and emotional life; it also allows the clinician to investigate behaviour habits related to opioid misuse (e.g. prior abuse of alcohol or illegal substances) and the presence of traumatic experiences such as sexual abuse in childhood or adolescence. During the interview the clinician may also identify any fears and worries about taking these drugs, the patient's expectations of the treatment and their reliability in following the indications of the therapist. Further areas of investigation concern the strategies that the patient uses to deal with the pain, and the possible presence of secondary gain that could compromise the efficacy of the treatment. Our results show that the indications provided by the specifically designed tools are more reliable than the clinical experience of the specialist physician in estimated aberrant drug behaviours. Investigation of the emotional-affective state of the patient, and his or her personality characteristics, always an important aspect of the multidimensional assessment of chronic pain, appears indispensable when long-term opioid therapy is initiated, since the presence of depression, anxiety or personality disorders has been found to be correlated with a greater risk of addiction. Pain coping strategies and any tendency to "catastrophize" must also be investigated using suitable questionnaires. Based on our experience, patients at greater risk of opioid misuse in fact seem to display a passive attitude to the management of their pain condition, and to have exaggeratedly pessimistic expectations of the progress of their symptoms. Finally, it is important to systematically assess the quality of life of these patients, as effective pain relief should always be accompanied by functional improvements in their physical, psychological and social area. The preliminary results of our study show that reduction in pain intensity of pain due to opioids does not seem to be accompanied by an improvement in physical and psychological functionality. This indicates that the patient

needs to be monitored not only in medical term, but also from a psychological perspective, to be able to make cognitive, emotional and behavioural changes that can enhance and consolidate the efficacy of the treatment.

From our experience in the Italian context, the prevalence of addiction or misuse in patients with chronic pain in treatment with opioids appears to be low. The systematic assessment of risk using the tools created in recent years allows the clinician to overcome some biases, such as the overestimation of the risk of addiction, and hence avoid considering the entire population of chronic pain patients to be at risk of abuse.

The treatment of pain is a public health problem that is of such critical importance as to constitute an international imperative, as well as a fundamental human right (Brennan et al., 2007); opioid drugs appear as a potential resource to manage chronic pain efficaciously. However, their targeted use must be preceded by a suitable assessment of the patient by a multidisciplinary team that clarifies not only the causes of the pain, but also any risk factors or dysfunctional psychological aspects related to use of the drug, so as to increase the benefits of treatment and reduce the costs.

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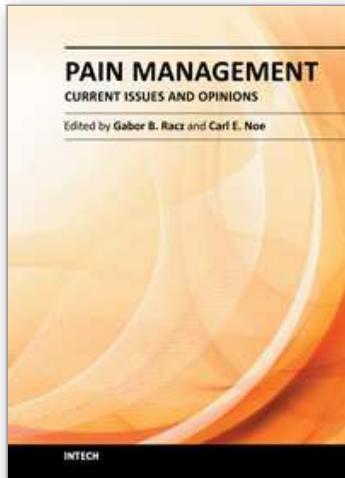
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