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Opioid risk addiction in the management of chronic pain in primary care: the addition risk questionnaire

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Abstract. – OBJECTIVE: Chronic pain is one of the most common complaints for people seeking medical care, with a series of potential detrimental effects on the individual and his social texture. Despite the heavy impact of chronic pain on patients' quality of life, epidemiological data suggest that chronic pain is often untreated or undertreated. An accurate diagnostic flow and appropriate treatment should be considered as key factors for optimal management of patients with chronic pain. Opioids are recommended for treatment of chronic cancer pain (CCP) and chronic non-cancer pain (CNCP) in guidelines and can safely and effectively relieve pain in a number of patients with chronic pain. Conversely, fears of addiction and adverse events could result in ineffective pain management. Recent epidemiological and clinical data demonstrate that only low percentages of patients treated with opioids for chronic pain have a risk to develop addiction, with a prevalence rate similar to that observed in the general population.

METHODS: Despite the iatrogenic risk can be considered as low, validated tools for the early identification of patients at higher risk of addiction can help health professionals in the overall management of chronic pain.

CONCLUSIONS: Due to the increasing relevance of primary care physicians in chronic pain management, we propose a 28-item questionnaire to validate specifically conceived for GPs' and aimed at the preliminary evaluation of the risk of addiction in patients with chronic pain.

Key Words:
Pain management, Opioid, Quality of life.

Introduction

Chronic pain (CP) is a widespread pathological condition and a public health issue, with physical, emotional and cognitive repercussions. Beyond the traditional duration-based definitions, CP has been recently defined as pain persistent beyond the time necessary for the healing of tissues, arbitrarily established from at least 3 months and/or supported by an identifiable pathology whose gravity is not sufficient to justify the presence and or/pain intensity. However, according to the bio psychosocial model, CP should be considered an ongoing multifactorial process, influenced by physical, psychological and social factors[1]. Despite the detrimental impact of CP on patients' quality of life, epidemiological data suggest that CP is often untreated or undertreated[2].

Furthermore, CP is also the most common complaint for people seeking medical care, and pain under treated is one of the most common conditions reported by patients[3].

Opioids have demonstrated their usefulness in the multimodal treatment aimed at a fast reintroduction of the subject with CP in the social texture, to enhance rehabilitation and improve sleep and overall quality of life[4].

Physicians involved in the management of CP treat a lot of patients with opioids, whose effective analgesic effect improves overall functioning. Clinical experience and epidemiological research have demonstrated that opioids can safely and effectively relieve pain in a number of patients with CP, while fears of addiction and adverse events could result in ineffective pain management. However, considerable clinical experience and a series of evidences suggest that in appropriately selected patients, opioids have low morbidity, low addiction potential and can promote reduction in suffering, enhance functionality and improve quality of life[5].

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Recent epidemiological and clinical data demonstrate that only low percentages of patients treated with opioids for CP have a risk to develop addiction, with a prevalence rate similar to that observed in the general population[6]. Despite the iatrogenic risk can be considered as low, validated tools for the early identification of patients at higher risk will help health professionals in the overall management of CP. Here we propose the Addiction Risk Questionnaire, a 28-item questionnaire specifically conceived for general practitioners. However, in some specific EU countries like Italy, general practitioners (GPs) are now considered as key actors in the long-term management of patients with CP.

Pathophysiology of Chronic Pain

Chronic pain is associated with a broad spectrum of clinical conditions, including cancer, rheumatoid arthritis, fibromyalgia, osteoarthritis, low back pain (LBP), HIV/AIDS and spinal stenosis. The traditional broad classification distinguishes between chronic cancer pain (CCP) and chronic non-cancer pain (CNCP). CCP can derive from different pathological conditions, including the invasion of tissues or bone by the cancer, nerve infiltration, obstruction of hollow organs, pain mediators and hormones secretion by the cancer itself. Table I summarizes different types of CP by nature (nociceptive, neuropathic, mixed)[1].

Chronic pain is the result of the complex interaction of nociceptive, neuropathic or mixed pathogenic mechanisms. Nociceptive pain derives from the activation of primary afferent nociceptors in the peripheral nervous systems in response to mechanical, noxious or chemical stimuli. The transmission to the central nervous system (CNS) (brain stem, thalamus and cortex) via second order neurons of the dorsal horn of the spinal cord, allows the conscious recognition of a potential biological damage. A series of endogenous opiates and other neurotransmitters (i.e. serotonin, noradrenaline) are involved in the pain perception process, that is the result of the complex balance between stimulation and inhibition and is also dependent on emotional and behavioral factors[1].

Neuropathic pain occurs when an injury to tissues sustains a primary lesion or dysfunction in the central nervous system. It can be mediated centrally or peripherally with differences in syndromes mainly depending on the types of fibers involved. It is usually described as burning or shooting/stabbing pain, while physical examination can reveal numbness and/or coolness in the pain territory and sensitivity to a non-noxious stimulus. A further distinction should be made between stimulus-evoked and spontaneous (stimulus-independent) pain, likely sustained from different underlying mechanisms. Chronic neuropathic pain is quite common in clinical practice and greatly impairs patients' quality of life[7].

Nociceptive and neuropathic components can coexist in CP[8]. In particular, untreated nociceptive pain can acquire a neuropathic component, thus sustaining a mixed pain syndrome[9]. The impact of CP with predominant neuropathic component has been underestimated for a long time due to the lack of specific epidemiological researches. The prevalence of pain of predominantly neuropathic origin (POPNO) was 8% in a random sample of 6000 adults in UK, when specifically investigated[10]. Thus, this type of mixed pain appears to be more common than previously suggested.

Table I. Different types of chronic pain by nature[1].

Primary nociceptive pain	Primary neuropathic pain	Mixed type pain
Osteoarthritis	Postherpetic neuralgia	Oncologic pain, with nerve infiltration
Visceral pain	Trigeminal neuralgia	Complex regional pain syndrome I, without nerve injury
Headache	Pain from HIV/AIDS	Chronic back pain (nerve lesion or dysfunction with nociceptive activation from ligaments, joints, muscles, tendons)
Ischaemic pain	Complex regional pain syndrome II	
Oncologic pain without nerve damage	Phantom pain	
Back pain without nerve damage	Post-stroke pain, pain from multiple sclerosis, spinal cord injury pain	

Epidemiology of Chronic Pain

Epidemiological and clinical data show that chronic non-cancer patients are not a homogeneous group and may present a wide range of biological, psychological and social symptoms, often complicated by depression, anxiety, somatoform disorders and substance abuse disorders[11-14].

It is quite difficult to state an accurate estimate of CP prevalence in the general population due to disagreement on definition and to methodological issues. Recent data suggest that 10-55% of all adults have a form of CP. In the Pain Europe Study CP was defined as pain experienced for at least 6 months, reported in the last month and at least twice a week. The prevalence rate in 15 EU countries varied from 12% (Spain) to 30% (Norway), with variability likely due to differences in age stratification of studied populations, therapeutic approaches, lifestyle and cultural approach. Since CP is more common in the elderly, the proportion of subjects over 65 years in a specific population will inevitably match a higher prevalence of CP in the respective country. As an example, in Italy and Spain, with two of the oldest populations at global level, the elderly subjects/children ratio is expected to reach four to one by the end of the first half of this century.

In the European Pain in Cancer study, up to 56% of 5084 patients with cancer reported moderate to severe chronic cancer pain at least monthly[15]. The same study revealed that treatment of cancer pain was often suboptimal and the assessment of its severity frequently poor.

Non cancer-pain is sustained from highly prevalent medical conditions, including osteoarthritis, back pain, diabetic neuropathy and migraine headaches. Prevalence rates vary from 5% to 33% according to different source populations. CNCP has an important economic impact, mainly due to patient discomfort, poor quality of life and increased use of health services[16]. In Europe, osteoarthritis represents the most common cause of CP (42% of patients), followed by trauma or surgery (15%) and nerve damage or whiplash (4% each). Musculoskeletal pain, or non-specific pain, is another highly prevalent condition associated with CP. CNCP is common in primary care settings and often associated with distress and functional impairment[1].

Diagnosis and Treatment of Chronic Pain

The diagnosis of CP primarily requires the identification of the nature of pain and the knowledge of underlying pathophysiology. Due to the multifactorial nature of CP and the possible overlapping of its components, a complex diagnostic work-up is often required for an adequate clinical assessment. A general history and physical examination are necessary in all patients referring to physician for CP, while specific diagnostic tests include radiography, computed tomography (CT) or magnetic resonance imaging (MRI) scan[1,17]. In the "patient-centered" approach, a clear picture of the multiple factors involved in the CP syndrome should be obtained at this stage. A complete evaluation include medical and pain history, previous treatment, age, sex, and social, cultural and psychological factors. Assessment of pain should always be performed using validated tools to obtain successful pain management; nevertheless, well-designed surveys show the relative low tendency to the routinary use[15,18]. Compared to one-dimensional scales (i.e. visual analogue scales, verbal-rated scales and numerical-rated scales), multidimensional scales such as the Brief Pain Inventory, McGill Pain Questionnaire and the Western Ontario and McMaster University Osteoarthritis Index, are able to measure both pain intensity and the detrimental effects of pain on life activity and emotional functioning. Since pain is a purely subjective experience, pain intensity can be only compared *intra-individually*[19].

Based on recent epidemiological evidence, the neuropathic component should always be investigated in CP. Nociceptive pain can acquire a neuropathic component if not treated promptly[9]. A diagnosis of POPNO is generally associated with worse prognosis, greater pain intensity and increased complexity of the treatment. In this view, it is highly recommended to screen CP patients for risk factors associated with the neuropathic component. The assessment should also include routine screening for psychosocial comorbidities, just as depression and substance abuse.

The goals of CP treatment should include improving of individual functionality and developing self-management skills that focus on fitness and a healthy lifestyle. Opioids are considered the *gold standard* for the treatment of moderate to severe pain in CCP and, concomitantly, have been found effective for the treatment of moderate CNCP. Opioids have demonstrated their effectiveness in a polimodal treatment of cancer pain, aimed at rapid reintegration of the subject in his own social context besides the overall improvement of quality of life. Their effectiveness in the control of CCP has been reported in 70-

90% of patients. Concomitantly, their use has been associated with improvement in terms of morbidity and psychosocial distress. A series of issues, epidemiological and clinical evidences suggest that, in appropriately selected patients, opioids-based treatment for CP is characterized by a relative low addition potential and can significantly enhance functional activity level of patients, finally improving their quality of life[5].

The WHO analgesic ladder proposes to start the treatment of pain with non-opioid medication; if pain is not adequately controlled, physicians should then introduce a weak opioid (step II). If also weak opioids are insufficient to treat pain, a strong opioid should be selected (step III). Several proposals for modification have addressed the diagram of the analgesic ladder, but despite controversies, its educational value and a series of benefits deriving from its worldwide diffusion are uncontested[20]. While some authors focus on the need to enlarge the diagram with the IV step (including nerve block, PCA pump, neurolytic block therapy, spinal stimulators and epidural injection) several others proposed the abolition of the second step, thus starting with low dose of strong opioids earlier. This approach is supported by different clinical studies, which show that the efficacy of the second step is limited over time (30-40 days) and the migration to strong opioids is primarily due to insufficient analgesia rather than adverse events. Accordingly, the WHO has recently revised the Principles for the pharmacological management of pain in children with medical illnesses. In particular, the former three-step ladder has been abandoned in favor of a two-step approach, excluding the use of intermediate potency opioids (previous second step). However, according to the WHO Guidelines Development group, the benefits of using an effective strong opioid outweigh the benefits of intermediate potency opioids, and although recognized, the risks associated with strong opioids are acceptable when compared with the uncertainty associated with the response to codeine and tramadol in children[21].

Addiction, Tolerance and Pseudoaddiction

Addiction is defined as a chronic, relapsing brain disease, characterized by compulsive drug seeking and use despite harmful consequences. The development of drug addiction can be considered the result of a complex interaction between biological and environmental factors. The drug intake is the final step of compulsive dynamics with low or no ability of the subject to control over it. The strong and overwhelming wish to obtain the drug (craving) can't be overcome if people, places or objects previously associated with addiction development are present. The "*brain-reward*" model explains the behavioral patterns as drug intake produces *rewarding* effects due the euphoric perception following the assumption, and *reinforcing* effects which are redundant due to the supporting (reinforcing) effect on a series of associated behaviors.

While the concept of addiction may include the symptoms of physical dependence and tolerance, physical dependence and/or tolerance alone does not equate with addiction[22]. Tolerance should only be considered an adaptive consequence of drug exposure, so that increasing doses are necessary to obtain adequate pain control[22].

In the last decades a series of concerns about the safety, efficacy and appropriateness of opioids in the treatment of chronic patients (CPPs) have been reported. The main point of weakness of opioids as a drug-class was identified in their long-term safety profile, tolerance, interferences with physical and/or psychosocial functioning and addiction. The risk to develop addiction should be reasonably considered in opioids naïve patients without a previous history of addiction. Nevertheless, available data are quite reassuring, suggesting that the incidence rate is similar to that observed in the general population[23-29].

The Boston Collaborative Surveillance Program involved 11.882 subjects treated with opioids for a wide range of indications. Excluding those subjects with a positive history of substance abuse, only four cases of addiction were reported[30]. Similarly, a national survey involving over 10.000 patients in long-term treatment with opioids did not find any case of addiction. These data support the assumption that the fear to induce addiction is completely unfounded, despite being one of the most common barrier for opioids prescription[28].

Severe CCP can hide pain of different nature and of lower intensity that can overcome when treatment with opioids reduces CCP intensity. A possible mistake is to consider the consequent request of more effective drugs an addictive behavior.

With the term "Pseudoaddiction" some authors describe a reversible condition observed in patients with undertreated CP, characterized by erratic behavior and resolved when pain control is achieved. The patient focuses on obtaining

medications and thus induces the physician to suspect an addictive behavior. Pseudoaddiction is generally consequent to low, ineffective dosages of opioids and does not represent a risk factor for the development of addiction. Nevertheless, if undertreatment is incorrectly prolonged, the risk of addiction increases as the subject may start to take opioids by himself in the attempt to gain an effective dose for pain control[31].

Many physicians remain reluctant to prescribe opioids for CP, mainly because of the fear of iatrogenic addiction, a frequently reported situation in clinical practice. Opioids are theoretically able to activate the reward system in the CNS of all individuals. These central effects can be interpreted and experienced in different manners among subjects: in some cases they are elaborated as not important and do not induce any variation of the individual psychological and behavioral pattern. In other cases, these effects can represent the basis for the onset of drug misuse and of a progressive instauration of addiction. Despite all opioids are able to induce iatrogenic additive behavior due to their pharmacodinamic properties, this should not be considered as a pathological condition by itself, but a physiological and reactive process associated to tolerance development. Thus, the presence of addiction during opioid-based therapy should not be intended as a medical illness neither its anticipation. Similarly, pseudoaddiction should not be considered as predictive of addiction, except in the case it is wrongly maintained over time. However, recent experimental studies in neurobiology show how in neuropathic pain models, prolonged treatment with opioids is not associated with increased dopamine release in the CNS and, thus, unable to activate the reward circuitry[32]. A series of genetic, psychosocial and drug-related factors able to influence the perception of additive effects of opioids should, therefore, be identified and considered for evaluation of iatrogenic risk.

GPs', Chronic Pain and Opioid Addiction Risk

The management of CP involves a number of difficulties. These include the onset of treatment, its monitoring over time, the customization based on individual needs, the treatment of severe pain in the frail elderly, the switch from a drug to another on the basis of efficacy and safety and the evaluation of risk of drug addiction.

The role of GPs in the management of patients with moderate to severe CP is crucially based on their ability to recognize the different levels of intervention for each selected patient/case. The GP can early select those cases requiring the activation of the specialists' network from those that can be managed in primary care. Recent data show how GPs' intervention can lead up to a significant reduction of pain level, especially when informatics technologies are adequate to share a common and always updated strategy with specialists. Furthermore, a close information exchange and a shared report form have been found to produce macroeconomic benefits.

The key role of the GP in the management of patients with CP has been recently stated in the Italian law (law n. 38, May 2010) regarding pain treatment and palliative care. It defines a new example of "home-based" management of CP. However, due to the great amount of information about social, psychological and familiar status of patients, GPs can easily detect cases requiring further or critical attention in terms of prevention and treatment. Beyond the ability of GPs to select patients requiring different levels of intervention, their capability to monitor patients over time is another key factor supporting the strength of the new Italian normative asset. GPs are able to detect a series of conditions occurring during the treatment period, including drug-drug interactions, tolerance, addiction and safety concerns. These evaluations can be easily shared with specialists before dose adjustments and/or other interventions. In the view of iatrogenic risk, despite the very low frequency of drug addiction observed among patients treated with opioids, a validated tool able to identify subjects with higher levels of vulnerability will be useful for GPs, especially in countries as Italy where new normative provide for their central role in the management of CP[33].

The GP has the opportunity to establish a lasting partnership with the patient[34]. With this partnership, the GP provides counseling, continuity of care, and prevention of forms against misuse of drugs. The doctor-patient partnership has a pivotal role in prevention management and patient care.

GPs are early able to identify different "types" of patients. In fact, GP has knowledge of his patient, his attitudes, personal and family, the degree of intensity of pain and disease that generates it, the co-existing medical conditions and related therapies, can identify the person with personality at risk. In the case of a patient with personality at risk, but who may need treatment with

opioid analgesic, it is appropriate to administer the lowest effective dose, preferably at normal release frequent monitoring of the clinical response (Table II). The involvement of GPs in the course of treatment of the patient with pain, as suggested by a recent expert opinion[35], allows you to monitor and prevent cases against misuse and to avoid under treatment of patients with unnecessary pain.

Questionnaire for the Detection of Opioid Addiction Vulnerability

Despite recent data have demonstrated the low potential of opioids to induce addiction when used for the treatment of CP, several psychological and social factors can affect the interplay of subjects with the rewarding effects of the drug, thus increasing their vulnerability to opioid addiction. GPs should be able to select those cases requiring strategies or interventions to minimize the risk of drug abuse/misuse. Some authors focused on the need of specific validated tools to evaluate iatrogenic risk, mainly depending from the high rate of drug misuse observed in last decades in countries like US[34]. Notably, in countries with more strict prescribing procedures (i.e. Italy) the iatrogenic risk has quite always been lower. Several tools have been made available in order to identify potential opioids abusers in the context of CP management (*Screener and Opioid*

Table II. The validation process includes a score for each question and an overall score to identify patients at risk. This questionnaire, until its validation, shows a list of information that the doctor can obtain from the medical history of the patient.

N.	Questionnaire	Yes	No
1	I'm / I smoked in my life for more than six months continuously		
2	I take an alcoholic drink every day before meals or a digestive after meals		
3	I use / I have used drugs to treat anxiety and depression		
4	My parents, brothers or sisters have had the need to take drugs for the treatment of anxiety and depression		
5	I use / have used drugs in my life for more than six months continuously		
6	In my family there were problems with drugs or alcohol		

		Totally agree	Quite agree	Neither agree nor disagree	Quite disagree	Strongly disagree
7	I spend more time than I should every day in front of the PC, smartphone or console not for work					
8	I always run the risk of taking penalties / fines in my life					
9	Because of my behavior I changed school several times					
10	I often try the luck					
11	The drugs can not help me heal my pain					
12	I've always been considered a troubled student by teachers					
13	I can always control my anger					
14	Everybody hates me					
15	I often like to look for exciting experiences					
16	I always want to exceed the limit					
17	When I wake up, I immediately desire to smoke					
18	I have been criticized for the way I drink					
19	I have a satisfying sex life					
20	After all sexual relations, although satisfactory, I feel the need to have others in a short time					
21	I have a lot of trust into myself					
22	During this time I have problems at work					
23	During this time I have problems in the family					
24	I sleep soundly					
25	I feel depressed					
26	I feel I have the resources to deal with the difficulties of life					
27	When I feel the desire for something, I do everything to achieve it					
28	I follow closely the requirements of the doctor					

Addiction risk questionnaire. Rapid Indicators of Suspected Vulnerability to Addiction in patients with chronic pain (RISVA), by Claudio Leonardi, MD.

Table III. Strategies to manage the opioid treatment, modified from[35].

Appropriate use of opioids to manage pain in patient at risk
Multimodal therapies (aiming at opioid-sparing)
Opioid titration
Long-acting formulations only for persistent pain
Prefer abuse-deterrent formulation and child-proof packaging
Frequent assessment of patient
Prefer centralized prescription of opioids
Periodic monitoring of drug consumption
Continuous counseling
Screening patients at potential risk
Sharing of patient at risk with other specialists

Assessment for Patients with Pain-Revised, SOAPP-R; Current Opioid Misuse Measure, COMM, Opioid Risk Tool, ORT et al[36], but no one has been conceived for primary care professionals. Here, we propose the validated Addiction Risk Questionnaire, a 28-item questionnaire specifically developed for general practitioners (Table III)[35]. An ongoing prospective clinical study has been specifically designed to evaluate its predictive role. The detection of patients with high level of vulnerability to drug addiction should not exclude them from the appropriate treatment of CP but should represent the signal for specific and adequate monitoring. An initial questionnaire was designed and subsequently it has been revised, both in terms of linguistic and psychological, in order to ensure understanding by the patient. Each question in the questionnaire has a relative weight that contributes to give an overall score to identify patients at risk. The validation of the questionnaire will be useful to understand if it is able to identify patients at risk, in which it is necessary to put a special care with the use of analgesics, compared to the rest of the population treated.

Conclusions

Effective CP treatment is a clinical and ethical imperative. Opioids have been found effective in the polimodal treatment of cancer pain, aimed at rapid reintegration of patients in their own social texture, and thus improving their overall quality of life. Recent epidemiological and clinical data demonstrate that only low percentages of patients treated with opioids for CP have a risk to develop addiction, with an incidence rate similar to that observed in the general population.

The combined intervention between the specialist and the general practitioner (a successful model recently introduced in the Italian law), the application of tools for prevention, the active monitoring, the conscious participation of the patient, and the case-oriented management are the key factors for an adequate CP management and iatrogenic risk reduction.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Vellucci R. Heterogeneity of chronic pain. Clin Drug Investig 2012; 32 Suppl 1: 3-10.
2) Torrance N, Ferguson JA, Afolabi E, Bennett MI, Serpell MG, Dunn KM, Smith BH. Neuropathic pain in the community: more under-treated than refractory? Pain 2013; 154: 690-699.
3) Heit HA. Addiction, Physical Dependence, and tolerance precise definitions to help clinicians to evaluate and treat chronic pain patients. J Pain Palliat Care Pharmacother 2003; 17: 15-29.
4) AMDG agency medical directors' group. Interagency Guideline on Prescribing Opioids for Pain. 2015. www.agencymeddirectors.wa.gov
5) Aronoff GM. Opioids in chronic pain management: is there a significant risk of addiction? Curr Rev Pain 2000; 4: 112-121.
6) Fishbain DA, Cole B, Lewis J, Rosomoff HL, Rosomoff RS. What percentage of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy develop abuse/addiction and/or aberrant drug-related behaviors? A structured evidence-based review. Pain Med 2006; 9: 444-459.
7) Dworkin RH, Backonja M, Rowbotham MC, Allen RR, Argoff CR, Bennett GJ, Bushnell MC, Farrar JT, Galer BS, Haythornthwaite JA, Hewitt DJ, Loeser JD, Max MB, Saltarelli M, Schmader KE, Stein C, Thompson D, Turk DC, Wallace MS, Watkins LR, Weinstein SM. Advances in neuropathic pain: diagnosis, mechanisms and treatment recommendations. Arch Neurol 2003; 60: 1524-1534.

8) Freynhagen R, Baron R, Toile T, Stemmler E, Gockel U, Stevens M, Maier C. Screening of neuropathic pain components in patients with chronic back pain associated with nerve root compression: a prospective observational pilot study (MIPORT). Curr Med Res Opin 2006; 22: 529-537.

9) Cruccu G, Anand P, Attal N, Garcia-Larrea L, Haanpaa M, Jorum E, Serra J, Jensen TS. EFNS guidelines on neuropathic pain assessment. Eur J Neurol 2004; 11: 153-162.

10) Torrance N, Smith BH, Bennett MI, Lee AJ. The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population survey. J Pain 2006; 7: 281-289.

11) Dworkin SF, Von Korff M, LeResche L. Multiple pains and psychiatric disturbance:an epidemiologic investigation. Arch Gen Psychiatry 1990; 47: 239-244.

12) Schofferman J. Long-term use of opioid analgesics for the treatment of chronic pain of nonmalignant origin. J Pain Symptom Manage 1993; 8: 279-288.

13) Becker N, Thomsen AB, Olsen AK, Sjogren P, Bech P, Eiriksen J. Pain epidemiology and health related quality of life in chronic non-malignant pain patients referred to a Danish multidisciplinary pain center. Pain 1997; 73: 393-400.

14) Eriksen J, Sjøgren P, Bruera E, Ekholm O, Rasmussen NK. Critical issues on opioids in chronic non-cancer pain: an epidemiological study. Pain 2006; 125:172-179.

15) Breivik H, Cherny N, Collett B, de Conno F, Filbet M, Foubert AJ, Cohen R, Dow L. Cancer-related pain: a pan-European survey of prevalence, treatment, and patient attitudes. Ann Oncol 2009; 20: 1420-1433.

16) Carrington Reid M, Engles-Horton L, Weber MAB, Kerns RD, Rogers EL, O'Connor PG. Use of opioids medications for chronic noncancer pain syndromes in primary care. J Gen Intern Med 2002; 17: 173-179.

17) ICSI Guidelines on Chronic Pain Assessment and Management. Available at: http://www.icsi.org/pain__chronic__assessment_and_management_of_14399/pain__chronic__assessment_and_management_of__guideline_.html

18) Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence , impact on daily life, and treatment. Eur J Pan 2006; 10: 287-333.

19) Fainsinger RL, Nekolaichuk CL. A "TNM" classification system for cancer pain: the Edmonton Classification System for Cancer Pain (ECS-CP). Support Care Cancer 2008; 16: 547-555.

20) Vargas Schaffer G. Is the WHO analgesic ladder still valid? Can Fam Phys 2010; 56: 514-517.

21) WHO Guidelines on the Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses. http://www.ncbi.nlm.nih.gov/pubmed/?term=who+guideline+persisting+pain+children+2012

22) Sees KL, Clark HW. Opioid use in the treatment of chronic pain: assessment of addiction Journal of pain and symptom management. J Pain Symptom Manage 1993; 8: 257-264.

23) Borgland SL, Connor M, Osborne PB, Furness JB, Christie MJ. Opioid agonists have different efficacy profiles for g protein activation, rapid desensitization, and endocytosis of mu-opioid receptors. J Biol Chem 2003; 278: 18776-18784.

24) Portenoy RK. Chronic opioid therapy for nonmalignant pain: from models to practice. APS Journal 1992; 1: 285-288.

25) Portenoy RK. Chronic opioid therapy in nonmalignant pain. J Pain Symptom Manage 1990; 5: 46-62.

26) Portenoy RK. Opioid therapy for chronic nonmalignant pain: a review of the critical issues. J Pain Symptom Manage 1996; 11: 203-217.

27) Portenoy RK. Opioid therapy for chronic nonmalignant pain: clinician's perspective. J Law Med Ethics 1996; 24: 296-309.

28) Porter J, Jick H. Addiction rare in patients treated with narcotics. N Engl J Med 1980; 302: 123.

29) Perry S, Heidrich G. Management of pain during debridement: a survey of U.S. burn units. Pain 1982; 13: 267-280.

30) Medina JL, Diamond S. Drug dependency in patients with chronic headache. Headache 1977; 17: 12-14.

31) Weismann DE, Haddox JD. Opioid pseudoaddiction--an iatrogenic syndrome. Pain 1989; 36: 363-366.

32) Niikura K, Narita M, Butelman ER, Kreek MJ, Suzuki T. Neuropathic and chronic pain stimuli downregulate central μ-opioid and dopaminergic transmission. Trends Pharmacol Sci 2010; 31: 299-305.

33) Mammucari M, Muscas F, Arpino G, Aronica A, Russo P, Visconti M. Role of intensive medical training on law 38 to improve pain management in primary care. Recenti Prog Med 2014; 105: 159-165.

34) Mammucari M, Lazzari M, Maggiori E, Gafforio P, Tufaro G, Baffni S, Maggiori S, Sabato AF. Role of the informed consent, from mesotherapy to opioid therapy. Eur Rev Med Pharmacol Sci 2014; 18: 566-574.

35) Maremmmani I, Gerra G, Ripamonti IC, Mugelli A, Allegri M, Vigano' R, Romualdi P, Pinto C, Raffaeli W, Coluzzi F, Gatti RC, Mammucari M, Fanelli G. The prevention of analgesic opioids abuse: expert opinion. Eur Rev Med Pharmacol Sci 2015; 19: 4203-4206.

36) Jamison RN, Serraillier J, Michna E. Assessment and treatment of abuse risk in opioid prescribing for chronic pain. Pain Res Treat 2011; 2011: 941808.