REVIEW ARTICLE

Drugs Aging 2009; 26 Suppl. 1: 63-73
1170-229X/09/0001-0063/$49.95/0

Opioids for the Treatment of Chronic Non-Cancer Pain in Older People

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Abstract

Chronic pain occurs in 45–85% of the geriatric population and the need to treat chronic pain is growing substantially. Unfortunately, treatment for chronic pain is not always correctly targeted, which leads to a reduced quality of life, with decreased socialization, depression, sleep disturbances, cognitive impairment, disability and malnutrition. Considering these consequences, healthcare professionals should aim at improving the diagnosis and treatment of chronic pain in older persons. One of the most important limitations in achieving successful pain management is that older people are not aware that pain management options exist or medications for pain, such as opioids, have associated benefits and adverse effects. Importantly, opioids do not induce any organ failure and if adequately used at the right dosage may only present some predictable and preventable adverse effects. Treating and controlling chronic pain is essential in elderly patients in order to maintain a good quality of life and an active role in both the family and society. To date there are only a few randomized clinical trials testing opioid therapy in elderly patients, and the aim of the present review is to highlight the efficacy and tolerability of opioid use through a literature search strategy in elderly people with chronic non-cancer pain.

Chronic pain is one of most prevalent conditions found in older people. Approximately 45–85% of the geriatric population have reported chronic pain in various settings. In epidemiological studies, chronic pain is often associated with depression and disability.[1-6] However, there is a lack of concordance concerning the definition of chronic pain. Chronic pain has been defined as the persistence of pain symptoms for more than 6 months.[7] Most recent studies agree to identify chronic pain with symptoms persistence for more than 12 weeks.[8]

According to the American Academy of Pain Medicine and the American Pain Society, pain is often undertreated despite the large availability of medical approaches.[8] It has been estimated that less than half of patients who have chronic pain are adequately treated by their general practitioner. This same finding is also seen in Europe, where approximately 40% of patients with chronic pain are undertreated.

Breivik et al.[9] showed that 50% of elderly patients are self-treated with non-prescribed drugs

(paracetamol – non-steroidal anti-inflammatory drugs; NSAIDs) and that 40% of them do not receive any benefit from treatment. Only 2% of interviewed patients are treated for chronic pain by a specialist. An Italian study[10] showed that more than 40% of elderly patients living in the community experienced daily pain and only one quarter of these individuals received an analgesic of any kind. Patients 85 years or older were even less likely to receive analgesics than the younger elderly population. Individuals with cognitive impairment were also at greater risk of receiving no analgesics than those with normal cognitive function.

Older patients with cognitive impairment may not obtain suitable analgesia partly as a result of an underestimation by physicians or by the inability of patients to describe their pain adequately. Indeed, it is known that underreporting of pain is frequent, especially in older people, and as a consequence, physicians tend to undertreat pain in this group. Pain especially from non-malignant causes such as osteoarthritis and joint pain, as well as cancer-related pain, is often under-recognized and undertreated.[11] Studies suggest that there are some age-related differences in the perception of, and response to, pain. The response to mild pain is reduced in many individuals, but older persons may be more sensitive to severe pain. The increase in pain threshold could lead to delays in diagnosis and poor recovery, whereas a decreased tolerance to severe pain presents management problems. In addition, the underprescription of opioids in elderly persons contributes to poor pain management. The reasons for these age-related changes in pain remain unclear.[12]

Even though there is a significant amount of pain literature on epidemiological evidence, as described above, there continues to be a lack of treatment guidelines for older persons. The only available international recommendation for the management of chronic pain in the elderly is described by the American Geriatric Society,[7] which suggests: (i) to use the least invasive route for medication; (ii) to choose, when possible, sustained release formulations; (iii) to introduce one agent at a time, at a low dose, followed by slow dose titration; (iv) to allow a sufficiently large interval between introducing drugs to allow an assessment of the effect; (v) to monitor treatment constantly and if necessary to adjust in order to improve efficacy and limit adverse events.

At present, there are no European guidelines on the use of long-acting analgesics in the treatment of chronic pain in elderly patients, although some recent reviews propose the use of long-acting analgesics and opioids as the mainstay for the treatment of chronic pain as a result of their stable pharmacokinetic and pharmacodynamic features, as well as for their overall therapeutic compliance. However, there still remains no scientific basis that supports the use of long-acting analgesics over short-acting analgesics in the elderly. Patients should also be prescribed short-acting analgesics for the treatment of breakthrough pain.[8,11,13-17]

Opioids belong to a class of drugs with a known efficacy in chronic pain, in both young and elderly populations.[18,19] More recently, the American Geriatric Society developed new guidelines for chronic pain in the elderly in which they favour the use of opioids over NSAIDs. This is the first recommendation regarding the use of opioids in elderly patients with chronic non-cancer pain. This class of drugs has a very well known risk profile with relatively benign or preventable adverse effects (constipation, nausea) and few serious adverse effects, such as organ failure, when dosed appropriately. This last feature, which is of crucial importance, is never sufficiently highlighted.[19]

The aim of the present paper is to review literature data concerning the use of opioids in the elderly with chronic non-cancer pain, highlighting their long-term efficacy and tolerability.

1. Literature Search Strategy

A Pubmed Medline search has been performed (2000–2009), using key words such as: 'pain', 'chronic pain', 'non-cancer pain', 'opioids' and 'elderly' (table I). All abstracts written in the English language were considered and full texts were selected according to the following criteria:

Table I. Studies resulted on PubMed search

Author	Year	Study	No. of patients	Age	Drug
Likar et al.[20]	2008	Comparative study	30 27 + 25	>65 years >64 years	Buprenorphine transdermal
Griessinger et al.[21]	2005	Clinical open study, not randomized, observational	13 179	68 ± 14	Buprenorphine transdermal
Rigler et al.[22]	2007	Retrospective analysis	2875	>60 years	Morphine oral, oxycodone CR oral, fentanyl transdermal
Roth et al.[23]	2000	RCT	133	62 years	Oxycodone CR

RCT = randomized clinical trial.

1. Systematic reviews concerning clinical efficacy or adverse events of opioids in elderly patients with chronic pain;
2. Randomized trials comparing the efficacy of different opioids or other non-opioid drugs in elderly patients with chronic pain;
3. Randomized and observational studies concerning the adverse effects of opioids;
4. Long-term studies were considered only after excluding those with the description of a single drug administration.

The same search strategy was also performed within the Cochrane database (table II).

Even if the impact of pain in the elderly is recognized as very important, many studies included only a small number of elderly subjects, while the literature testing the use of opioids in the older population was extremely small. Therefore, the results of the literature search and review are presented in the following section.

2. Use of Opioids in the Older Population

The above-described search strategy on Pubmed using the keywords 'chronic pain' and 'elderly', performed between 2000 and 2009, resulted in 12 696 articles of which 760 were reviews. The term 'opioids' was added as a supplementary keyword, thus generating 794 articles, 79 of which were reviews. To restrict the search further, the keyword 'non-cancer' was then included. This last search resulted in 125 articles, of which 14 were reviews. Among them, only 10 were performed in an elderly population. Four articles about efficacy and tolerability were retrieved,[20-23] whereas the other six were epidemiological studies concerning the evaluation of quality of life in the patient affected by chronic pain.[30-35] The four articles took into consideration different pharmacological approaches and specifically investigated the use of morphine and other long-acting opioids orally and transdermally administered, along with their efficacy and safety in elderly patient populations compared with control groups aged less than 65 years.[20-23] They concluded that in both groups efficacy, tolerability and safety were overlapping. These data have been further confirmed by a study investigating the tolerability of transdermally administered buprenorphine published by Griessinger et al. in 2005.[21] A study by Rigler et al.[22] compared the use of long-acting opioids administered by mouth versus transdermally in an elderly patient population (aged >65 years). They specifically investigated the efficacy of an oral administration of morphine and oxycodone compared with that of transdermally administered fentanyl. Unfortunately, no conclusive results emerged from the study. The only randomized study we were able to find was that by Roth et al.,[23] which investigated the use of orally administered oxycodone in the treatment of osteoarthritic chronic pain. This study was performed on 133 patients (median age 62 years) and was based on the high frequency of osteoarthritis in the elderly population, as well as on the need for adequate treatment for pain symptoms. These findings demonstrate that oxycodone administered by mouth is well tolerated and ameliorated symptoms with an improvement in the quality of life.

The search in the Cochrane library was first performed using a single keyword 'chronic pain',

Table II. Studies resulted on Cochrane library search

Author	Year	Study	No. of patients	Age	Treatment
Itoh et al.[24]	2006	RCT	26	>65 years	Acupuncture
Itoh et al.[25]	2007	RCT	35	>65 years	Acupuncture
Yang et al.[26]	2005	RCT	43	>65 years	Qi-therapy
Lee et al.[27]	2001	RCT	40	>65 years	Qi-therapy
Haas et al.[28]	2005	RCT	120	>60 years	Self-management
Ersek et al.[29]	2003	RCT	45	82 years	Self-management

RCT = randomized clinical trial.

with the limitation of age greater than 65 years and the period of publication between 2000 and 2009. This search resulted in 1083 Cochrane reviews, 250 other reviews, 2293 clinical trials, 30 methods studies, 122 technology assessments and 195 economic evaluations. The inclusion of 'elderly' as a keyword gave as a result of four Cochrane reviews and 13 clinical trials. The inclusion of 'opioids' as a further keyword showed a single paper, which was out of range because it was published before the year 2000.[36]

The analysis of articles obtained from the combination of 'chronic pain' and 'elderly' as keywords showed that the pharmacological approach was not included in any of the papers analyzed. Among 13 articles found, seven concerned chronic pain in elderly patients, six non-pharmacological approaches such as acupuncture,[24-29] whereas the last article concerned evaluation scales for the measurement of chronic pain.[37]

At present, an Italian investigation is in a preliminary and ongoing state. A recent survey of the Italian Society of Hospital Geriatricians[38] investigated the prevalence of chronic pain in 367 patients consecutively admitted to eight acute care wards of geriatric medicine. Patients' admission diagnosis, comorbidity, pain intensity, prescribed therapy, adverse effects, duration of pain and efficacy of therapy were monitored and recorded during two 15-day periods from 15 July to the end of August 2008, and from 1 October to 15 November 2008. Although findings from this study confirmed the high prevalence of pain, present in 67.3% of enrolled patients, only 49% of those with pain had any type of treatment. In addition, 74.5% of treated patients considered their therapy to be of low efficacy or not efficient. These data demonstrated the high presence of pain in elderly patients, which is either not treated or is treated inadequately. Controlling pain is essential in elderly patients in order to improve their quality of life significantly. Chronic pain is associated with psychological and physical deterioration and it interferes with normal daily activities, including social relations.

3. Pain-Related Issues and Management in the Older Population

Common aetiologies for non-cancer pain include herpes zoster, osteoarthritis and rheumatoid arthritis. In the United States, more than one million new cases of herpes zoster occur each year, with approximately 10–15% of those cases developing postherpetic neuralgia (PHN). The age distribution of people affected by PHN, however, includes a disproportionate number of elderly patients; the prevalence of PHN reaches approximately 65% among patients with herpes zoster aged 70–79 years.[39] PHN is usually refractory to simple analgesic therapies and treatment is most often pharmacological, including a wide variety of drugs and routes of delivery. The most commonly used analgesic agents are oral administrations. Currently, the standard treatment for PHN is with tricyclic antidepressants, pregabalin or duloxetine (according to European Federation of Neurological Societies guidelines) either as monotherapy or in combination with other medications, such as carbamazepine or opioids.[40] Unfortunately, only 50% of patients treated with tricyclic antidepressants for PHN in clinical trials experience pain relief in the absence of intolerable adverse effects.[41]

Moderate to severe non-cancer pain arises from skeletal muscle disease, peripheral vascular disease and other conditions, such as diabetes, stroke and back pain. As curative treatment is often impossible, the management goal is usually palliative. There is still no consensus as to the pain mechanisms in skeletal muscle disease, but microfractures in osteoarthritic joints could produce an increase in prostaglandins, giving rise to an inflammatory component. Different therapeutic options do exist for these elderly patients, such as NSAIDs and cyclo-oxygenase 2 inhibitors, but common side-effects including gastrointestinal or cardiovascular toxicity play a major role in the criteria for analgesic selection. Therefore, the use of low-dose opioids as first-line therapy is becoming more rational. Besides some level Ib or IIb studies of evidence, the literature on opioid therapy for non-cancer pain consists of 'surveys' or uncontrolled case series. Despite this finding, the available data suggest that patients with non-cancer pain can achieve satisfactory analgesia by using a constant dose of an opioid, either by an oral slow-release preparation or a transdermal patch. Opioids are effective, but need careful individual dose titration in order to avoid their common side-effects.

The use of opioids is limited by patients' fears of addiction and sedation/confusion, as well as possible negative effects on balance and motor function. Indeed, there is a growing body of literature on the association between opioid use and falls in older persons.

The therapeutic options for non-cancer pain are increasing and there is now a number of oral sustained release and patch preparations. The desired advantage of sustained release or steady-state administration compared with intermittent dosing of an opioid (or any drug) is maintaining a steady plasma level of the drug within a therapeutic range to avoid peaks and troughs that might lead to either excess adverse effects or inadequate pain relief. If adequate compliance can be achieved with intermittent dosing, an equivalent therapeutic outcome would be expected and is reported. However, poor compliance, particularly with opioids, is not uncommon in the elderly for a variety of reasons. Among them is the concern that steady-state exposure of opioid receptors to agonists might lead to greater tolerance and dependence. However, studies of transdermal patches suggest that this is not an issue in treating older patients with opioids.[11]

For the evaluation of pain, the main efficacy measure used includes the intensity of pain, its duration and functionality. To date, no standard evaluation scales are available for this purpose. Several studies utilize the visual analogue scale and/or the numeric rating scale.[42-44] The best approach would be to use both scales in order to evaluate the intensity of pain, as well as to control for the resolution of symptoms. Functional aspects are commonly assessed by the Medical Outcomes Study Short Form 36, Short Form 12 or other questionnaires.[30] The evaluation of adverse events such as drug abuse, respiratory distress, nausea, vomiting, constipation and mental confusion is also very important.

4. Safety of the Use of Opioids in the Older Population

The tolerability of opioids is extremely important in older persons compared with younger adults, because adverse events such as drowsiness, dizziness and motor imbalance have more serious consequences in older frail patients already at a greater risk of falls. The most common adverse reactions with the use of opioids in older persons involve alterations in the following systems: gastrointestinal, central nervous, hepatic, renal, respiratory and immune.

The most common gastrointestinal problems observed with opioid use include constipation, nausea and vomiting. Such events may be explained by the fact that elderly patients often have increased gastric pH, reduced gastric and intestinal motility, decreased enzyme activity and absorption. These changes manifest themselves as prolonged colon transit times, frequent constipation and gastrointestinal distress. Constipation is one of the most frequent adverse events observed with opioid analgesics, and becomes exacerbated in those patients with reduced gastrointestinal function. Although constipation can be managed with bowel treatment regimens, it may be necessary to

Table III. Clinical outcomes of the use of opioids in elderly patients with impaired renal function

Opioid	T1/2	T1/2 Metabolites	Clinical outcomes of decreased renal function	Recommendations
Morphine	↑	↑ ↑	Increased active metabolities M3G and M6G may lead to long-lasting respiratory depression	Dosage ↓
Oxycodone	↑	↑	Clearly reduced renal clearance of parent compound and metabolites	Dosage ↓
Hydromorphone	↑	↑ ↑	Accumulation of metabolites described	Dosage ↓
Fentanyl TD	↑	↑	Decreased renal clearance	Dosage ↓
Buprenorphine TD	=	=	No clinically relevant changes	Adjust ±
Methadone	↑	↑	Not extensively evaluated in patients with renal impairment – use with caution	Dosage ↓

T½ = half life; **M3G** = morphine-3-glucuronide; **M6G** = morphine-6-glucuronide.

change opioids. Buprenorphine and potentially transdermal fentanyl produce less constipation than morphine and oxymorphone, and may be preferable to other opioids when constipation cannot be easily managed.[11]

Opioid neurotoxicity is a significant issue in the elderly, and is presented clinically as sedation, confusion, as well as hallucinations and loss of cognition. Most opioids have the risk of such effects especially at high doses for long periods of time and/or when patients present with severe renal failure. Therefore, the risk of falls and fractures become particularly high. Indeed, a Danish nationwide register-based study has shown that the use of morphine and other opioids, including fentanyl and oxycodone, increased the risk of fractures.[45] Those authors speculated that the use of such drugs increased the risk of falls because of effects on the central nervous system (CNS) due to an altered state of consciousness. Increased fracture risk was lowest in those patients taking buprenorphine.

Recent data from an Italian survey show a lack of CNS complications both with the use of low-dose transdermal buprenorphine and a low dose of oxycodone administered by mouth.[38]

Older persons often have existing renal and/or hepatic impairment, which complicates the use of opioids due to an increase in drug half-life and thus difficulties in dose recommendations (tables III and IV). Further complicating this complex scenario is the high prevalence of concealed renal dysfunction in older patients, which can predispose to an increased risk of adverse reactions to water-soluble drugs.[46,47]

It is important to recall that existing opioids differ in terms of their pharmacokinetics in hepatic and renal impairment. Morphine is metabolized in the liver mostly into the analgesically inactive metabolite morphine-3-glucoronide (M3G) and morphine-6-glucoronide (M6G), which is a potent analgesic.[48] Both metabolites are completely eliminated by the kidneys and secreted through the urine. The elimination of metabolites is reduced in the case of renal impairment, with metabolite accumulation. An accumulation causes increased plasma concentrations of M3G and M6G, whereas higher levels of M6G and M3G levels result in intoxication. Oxycodone has many active metabolites that may accumulate during renal dysfunction. Hydromorphone has only one glucuronide, which is neuroexcitatory and accumulates during renal dysfunction. Fentanyl is metabolized by the liver into the active norfentanyl along with several other unspecified inactive metabolites. Nearly 10% of the active substance is not metabolized, with less than 10% of the inactive metabolite, norfentanyl, eliminated by the biliary system and excreted in the faeces. Approximately 75% of metabolites are eliminated in the urine. Therefore, during renal impairment, the clearance of fentanyl is reduced and its half-life is prolonged. To date, the kinetics of fentanyl in geriatric patients has not been extensively studied. Indeed, older patients taking fentanyl, as analgesic therapy, need to be monitored very closely. However, due to the lack of data investigating the use of fentanyl in older persons, especially with hepatic or renal impairment, specific recommendations cannot be

formulated. With regard to the use of buprenorphine, approximately only a third is metabolized by the liver into three major metabolites: norbuprenorphine, buprenorphine-3-glucuronide and norbuprenorphine glucuronide. Approximately two-thirds of the parent drug is eliminated by the biliary system by way of the faeces. The metabolites are eliminated mainly by the biliary system and in a small quantity of buprenorphine by the renal system. Even though the half-life of the drug is prolonged during hepatic impairment, the low activity of the metabolites does not cause significant clinical relevance. However, careful monitoring of patients with hepatic impairment is recommended. During renal impairment, there is no clinically important accumulation of metabolites, thus dose reduction is not necessary. In elderly patients with impaired hepatic and renal function, the accumulation of metabolites from specific opioids, such as morphine, is important to recognize. In general practice, it is important to avoid such accumulation through the use of drugs such as hydromorphone and buprenorphine.[11]

Finally, it is widely known that for all opioids except buprenorphine, the half-life of the active drug and metabolites is increased in the elderly and in patients with renal dysfunction. It is recommended that doses should be reduced, a longer time interval should be used between doses and creatinine clearance should be monitored.[11] Oxycodone, hydromorphone and buprenorphine appear to be a safe choice for opioid treatment in the elderly.[49]

Another possible adverse effect with the high-dose use of opioids is respiratory depression, which is mediated by the μ-opioid receptor. Agonists, such as morphine and fentanyl, create a clear dose-dependent effect, which, at high doses or combined with other CNS system depressants, may progress to respiratory depression.[50,51] Respiratory depression is rare in opioid-naive patients with low starting doses and proper titration. However, the use of opioids in elderly patients with underlying pulmonary conditions such as chronic bronchitis, multiple sclerosis, chronic obstructive pulmonary disease, etc. or who receive other CNS drugs that affect ventilation are of great concern. Morphine, oxycodone, hydromorphone, fentanyl and methadone cause a dose-dependent decrease in respiration, with apnoea at high doses. Buprenorphine has a well-defined ceiling effect for respiratory depression due to an instrinic analgesic activity of the receptor.[52] Respiratory depression with buprenorphine can be reversed with opioid antagonists, such as naloxone,[50] CNS depressants, such as benzodiazepines, barbiturates, antidepressants, phenothiazine derivatives, and alcohol increases the risk of respiratory depression if taken with any opioid analgesic.[50] Fortunately, not all opioids show equal effects on respiratory depression; indeed buprenorphine is the only opioid that demonstrated a ceiling effect for respiratory depression. The different features of opioids regarding respiratory effects need to be taken into consideration when treating older patients at risk of respiratory problems.

It is also important to highlight the immunomodulating effects of opioids. Indeed, aging is associated with a gradual decline in the responsiveness of the immune system, known as immunosenescence.[53] Such a decline leads to increased susceptibility to infectious diseases, cancer and an increased inflammatory state.

Table IV. Effect of reduced hepatic function on pharmacokinetics of opioids

Opioid	T1/2	Plasma concentration of metabolites	Finding	Recommendations
Morphine	↑	↓	M6G ↓	Dosage ↓
Oxycodone	↑	↑		Dosage ↓
Hydromorphone	?	?	No data available	Dosage ↓
Fentanyl TD	↑	?		Dosage ↓
Buprenorphine TD	↑	↓	Low activity metabolites	Dosage ↓
Methadone	↑	?	No data available	No dosage change

T½ = half life; **M6G** = morphine-6-glucuronide.

Even though total T-lymphocyte count production is reduced, memory T cells increase and B-cell production in the bone marrow is diminished. The decrease in neutrophils and granulocytes leads to fewer reactive oxygen species.[54] Macrophage production of reactive oxygen species is also reduced, whereas cytokine and prostaglandin production is increased, leading to a pro-inflammatory environment. This general change in immune responses may lead to immunosuppression, especially in the presence of immunomodulating drugs. Moreover, it is well known that pain itself is an exquisite stressor as it has both psychological and physiological components. The linked responses of the CNS and the hypothalamic–pituitary adrenal axis to a perceived stress involve a complex network of signals, including catecholamines, peptides (endorphins) and corticosteroids (cortisol). All of these above factors may lead to immunosuppression. Therefore, pain relief is beneficial for immune function; however, several opioids possess intrinsic immunosuppressive activities. For example, morphine is the most immunosuppressive of the opioids and activates the μ-opioid receptor.[55,56] These receptors are found on all immune cells and are activated directly by morphine. There are also indirect effects via the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system, the former generating the release of glucocorticoids, and the latter norepinephrine, which binds to leucocytes, modulating the immune function.[57] The immunopharmacological profile of the potent opioid, fentanyl, does not seem to differ from that of morphine. In experimental animal models, fentanyl induced a clear dose-related immunosuppression.[58] The immunosuppressive properties of fentanyl have also been observed in a small number of studies investigating acute fentanyl treatment in humans.[59,60] Those studies underlined fentanyl's ability to affect cellular immune responses while immune modulation seemed to be dose related. It is not clear why other opioids, buprenorphine, hydromorphone and oxycodone, which also bind to the μ-receptor, do not depress the immune system and have been reported to be less immunosuppressive than morphine.[58] It is speculated that non-immunosuppressive opioids, such as buprenorphine, hydromorphone and oxycodone have little or no neuroendocrine effect, or that κ-opioid receptor antagonism may be involved. Either way, there is little evidence available to estimate the immunosuppressive effects of other opioids, especially in the elderly. Considering that the long-term clinical impact of opioid-induced immunomodulation is lacking, further studies are needed, in order to determine adequate pain control with immunosuppressive or non-immunosuppressive opioid drugs.

Drug interactions represent another important safety issue. Some opioids are metabolized by CYP P450 isoenzymes with a variability that is largely determined by genetic polymorphisms. CYP polymorphisms may account for high rates of side-effects or minor efficacy in affected patients. This applies to oxycodone and tramadol, which are metabolized by CYP 2D6, and to buprenorphine, which is metabolized by CYP 3A4. CYP is among the principal pathways of drug metabolism for several drugs, and this could represent a relevant problem in older patients treated with complex polypharmacological regimens.[11] In addition, an age-related reduction in the metabolism of CYP 2D6 substrates by approximately 20% has been observed,[61,62] whereas such a finding has not been confirmed for the CYP 3A subfamily.[63-65] Finally, protein binding could represent another important site of interaction. Buprenorphine binds to alpha and beta globulins, unlike the majority of drugs, which bind to albumin. As a result, the likelihood of drug–drug interactions related to protein binding for this drug is small.[11]

5. Conclusions

To date the literature does not hold sufficient data to draw conclusive evidence regarding the use of opioids in older people with non-cancer chronic pain. There is thus a need to encourage further studies, both observational and comparative, concerning the use of major opioids, as well as to target clinical trials investigating the safety profile of this class of drugs in elderly populations.

Special care should be taken in the evaluation of opioid adverse effects, such us gastrointestinal and effects on the CNS. In particular, our unpublished data suggest that cognitive impairment is not modified by low doses of opioids (transdermally administered buprenorphine and orally administered oxycodone), and on the other hand a significant positive effect on depressive status and an improvement in quality of life evaluated by the Short Form 12 was described.

A recommendation can also be made to dissuade patients from using NSAIDs for more than 10 days and suggest the use of major opioids at a low dosage for chronic conditions.

Last year,[66] the Italian health regulatory body introduced new rules that facilitate the prescription of oxycodone in patients with chronic pain. Therefore, an expected increase in the number of prescriptions for oxycodone will improve the use of this class of drug, which in turn has the advantage of being safe at the right dosage and less expensive than other drugs (€11.56 for one month of treatment with oxycodone vs €34.25 for one month of treatment with cyclo-oxygenase 2 selective inhibitors). More recently this facilitation has been extended to all opioids[67] administered at low dosages, while excluding the formulations for systemic use, and these new prescription rules will allow for a more appropriate approach to chronic non-cancer pain in the increasing number of elderly Italians.

Acknowledgements

No sources of funding were used to assist in the preparation of this review. The authors have no conflicts of interest that are directly relevant to the content of this review.

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