

Opioids: how to improve compliance and adherence

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Introduction

The treatment of chronic pain is a major worldwide public health issue [1]. The prevalence of chronic pain in several developed countries was the subject of a recent systematic review [2]. In 4 studies that used the International Association for the Study of Pain (IASP) definition for chronic pain, the prevalence of pain > 3 months duration ranged from 11.5% to 55.2% [2]. Nearly 50% of individuals with chronic severe pain do not have their pain under control [3]. A recent study of the general population in 15 European countries and Israel estimated that the point prevalence of chronic non-malignant pain ranged from 11% to 30%; 40% of patients with chronic pain were not satisfied with the treatment they received [4].

The World Health Organization (WHO) pain ladder is commonly used when selecting medication to treat chronic pain, regardless of the underlying cause [5]. The pain ladder recommends using a step-wise approach of non-opioids (step 1), then mild opioids (step 2), then strong opioids (step 3); pain therapy is given alone or combined with adjuvant therapies (anti-convulsants, anti-depressants, corticosteroids, and anti-histamines and α_2 blockers) [5].

Although the benefits of many pain treatments have been demonstrated clinically, not all treatment aims have achieved their goals in practice owing to various factors including patient expectation and the complexity of treatment regimens [6, 7]. It has been observed that “increasing the effectiveness of adherence interventions might have a far greater impact on the health of the population than any improvement in specific medical treatments” [8].

Effective pain management with opioids should be an achievable goal in many patients with pain [1, 9]. In this review we will describe the factors that interfere with the optimal use of strong opioids for chronic pain, and propose strategies to overcome them.

Methods

This was a review of the available literature on compliance, adherence, and analgesic pain management.

Relevant references were obtained by manual searches using PubMed and the internet search engine Google™. English language articles were identified using the search terms compliance, adherence, chronic cancer pain, chronic non-cancer pain, analgesic pain management, and opioids (once-daily, controlled-release, slow-release, and extended-release) separately or in combination; the year of publication was not limited in the search. A single reviewer evaluated the abstracts for identified references and decided which papers were relevant; reviews and references describing studies of patient compliance and adherence to medication for chronic conditions, particularly chronic pain, were considered to be relevant. As this was not a systematic review, there were no pre-specified selection criteria. All types of study could be included, without consideration of quality. Full-text copies of these references were then obtained. Any relevant references that came up during manual searching of these papers may have also been included in the review. In addition, authors suggested relevant references.

This was not a systematic review and no formal statistical analysis was done.

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Adherence with therapeutic regimens for chronic illnesses other than chronic pain

According to a WHO report, adherence to long-term therapy for chronic illnesses in developed countries averages 50%, and the rates are even lower in developing countries [5]. A systematic review of 76 studies that measured compliance in patients with a range of acute or chronic medical disorders using electronic monitoring found that the mean overall rate of compliance with prescribed medication regimens was 71% ± 17% (mean ± standard deviation; range 34%–97%) [10].

Factors affecting adherence

According to the WHO, factors that affect adherence are related to the patient, condition, therapy, health-care team and system, and social and economic factors [5]. Factors modulating adherence are summarized in Table 1. Positive influences for improving adherence include a basic knowledge of the disease, good motivation with respect to treatment, the patient's faith in his/her ability to self-manage the therapeutic regimen, and solid expectations in terms of treatment efficacy [5, 6, 7]. Depression is one of the most powerful factors for non-adherence to therapy and interruption of treatment [7]. Other negative factors reducing adherence include lack of faith in the doctor and/or health service, anxiety, high levels of emotional and psychosocial stress, financial problems, fear of adverse events, cultural or religious beliefs, and failure to perceive a personal benefit or greater physical or psychological well-being in comparison with not taking the medicine.

Dosing frequency and adherence

Numerous studies and meta-analyses have shown that the more complex the treatment regimen, the worse the adherence [11–15]. The error rate in therapy adherence (missed doses) is 15% for single daily doses, 25% for twice- or thrice-daily doses, and 35% for even higher numbers of daily doses [11]. In a prospective, open study in 2001, 821 clients of New York pharmacies reported on adherence to their dispensed medication; the reasons given by patients for their non-adherence were extremely varied, but many of them (55%) say they simply forgot to take the medicine [16]. Therefore, administration frequency can have a decisive effect on adherence to the therapy.

Ways to improve adherence

A sense of participation in the therapeutic choice alongside the doctor improves adherence to therapy [5, 6, 7], and treatment strategy should be based on the requirements and wishes of the patient [6]. Patients should feel able to openly discuss the proposed treatment and potential associated side effects with their physician; awareness of possible adverse effects will reduce the likelihood that patients will not take their medication because of them [7]. A high rate of non-adherence may arise if there are misunderstandings in communication between the doctor and the patient. The quality of the relationship between the doctor and patient is also important. Patients have been found to be more likely to take their medication if they perceive that the healthcare provider is interested in them first of all as a person, and with an empathic attitude, rather than from an exclusive, detached/distant/cold medical or scientific perspective [17].

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Adherence with pain therapy

In a recent multi-center cross-sectional study, adherence of patients to their medication for chronic non-malignant pain was examined; the study focused on factors related to all five WHO defined categories of determinants of medication non-adherence [18]. The study included 265 patients and the most commonly prescribed analgesics were opioids (80.4%). 38% of patients were fully adherent; 40% of patients underused their prescribed medication, 14% of patients overused their medication, and 8% of patients both under- and over-used their medication. Multivariate analyses showed that underuse was significantly associated with more prescribed analgesics (odds ratio [OR] = 2.303), self-medication (OR = 4.679), lower pain intensity (OR = 0.821), active coping strategies (OR = 1.132), and lack of information (OR = 0.268). Overuse of medication was associated with more prescribed analgesics (OR = 1.645) and current smoking (OR = 2.744).

Attitudes to pain medication may differ from attitudes to other medications. Patients with chronic pain associated with osteoarthritis (OA) were interviewed about their compliance with medications for their illness. They were found to intentionally take lower doses of their pain medication or to take their pain medication at less frequent intervals than prescribed, usually for fear of side effects or because on-going side effects were difficult to tolerate when a full daily dose of the prescribed medication was used. In contrast, adherence to their other medications was generally good [19]. Contextual factors such as the attitude of relatives or significant others towards pain and opioids may further modulate the overall acceptance of the drug and lead to ambivalence in following the prescribed regimen, with the consequences of inadequate adherence or dropout.

Satisfaction with pain therapy is associated with the perception of a specific improvement (i.e. reduced pain), increased well-being, and/or better impact on quality of life associated with an analgesic [7]. The patient's perceived physical and psychological benefit from therapy directly and indirectly boosts compliance, adherence, and persistence with the therapy [7]. Providing continuous pain relief is an important component of effective pain management [20], as irregular intake may lead to pain exacerbation resulting in worsened quality of life, a negative emotional impact with increased anxiety and depression, and emergency visits, with increased personal and familial distress and a frustrating sense of impotence in controlling pain [7]. Non-adherence to opioids is influenced by the real or feared side effects on the central nervous system and the gastrointestinal system. Opioid side effects in patients with chronic pain can reduce quality of life, increase morbidity, and may result in the patient discontinuing therapy [21]. Side effects should be treated pro-actively to foster adherence to treatment.

The requirement for multiple-daily doses of oral opioids may be associated with inconvenience for patients and result in reduced adherence and consequent diminished pain control [22, 23]. Some patients may decide to adapt the frequency of intake and the dosage of their prescribed medication if they experience inadequate pain control. Several studies [24–27] of long-acting opioid usage by sufferers of chronic non-cancer pain (CNCP) have found that a substantial number of patients exceeded the prescribed daily dose recommended by the manufacturer. Increasing analgesic tolerance with a shorter duration of pain relief may explain this behaviour: this might vary from one sustained release analgesic to another, and one patient to another. However, taking extra doses of analgesics because of insufficient pain relief from prescribed medication not only increases treatment costs but is also potentially dangerous. Health and economic consequences of non-adherence to prescribed treatment include excess hospitalizations and office visits, disease progression, complications, and premature disability and death [6, 7].

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Medication treatment options for severe chronic pain

In patients with severe chronic pain, treatment with strong opioids is often a critical and effective part of treatment [17, 28–37]. Modern dosage forms may improve adherence to treatment with medications by reducing side effects and simplifying dosing regimens. Guidelines on the use of opioids for chronic pain have recommended the use of controlled release formulations and scheduled regimens [38–41]. Strong opioids that are currently available as oral once-daily or twice-daily dosing formulations include morphine, hydromorphone, oxycodone, and oxycodone (see Table 2; these trademarks are only available in a limited number of countries). Fentanyl and buprenorphine are available as transdermal patches [42]. Long-acting formulations aim to maintain sustained opioid plasma concentrations with minimal fluctuations between doses. Improved adherence can provide both clinical and economic value by improving treatment outcomes thus diminishing pain-related physical and emotional distress, and reducing the use of medical services [6, 7]. Key recommendations to improve adherence with opioid therapy for chronic pain are summarized in Table 3. Analgesic therapy should involve sharing with the patient the reasons for the choice, the achievable objectives, the time needed to achieve them, and analysis of the main difficulties that the patient perceives in adhering to the proposed treatment [5, 6, 7]. Opioid therapy should be carefully planned, and progress towards therapeutic goals regularly assessed by documenting pain intensity and level of functioning [43]. Tools involving prognosis, such as the Diagnosis, Intractability, Risk, and Efficacy (DIRE) score, can be used to facilitate the decision to initiate, or withdraw, long-term treatment with opioid analgesics [44]. Successful opioid therapy is achieved when sufficient pain relief is achieved with tolerable treatment-related adverse events [45]. Opioid side effects should be anticipated and treated as appropriate, giving consideration to the expected duration of therapy, the severity and nature of the side effects that may be expected, and the potential influence of co-morbidities and concurrent medications [45]. Patients should be informed that side-effects such as nausea, vomiting, sedation, and somnolence often diminish over time [46]. Constipation is a common and persistent side effect of opioid therapy [20]. Questions regarding the patient's bowel habits should be asked routinely before deciding to prescribe opioids, and the effective management of opioid-induced constipation requires both prophylaxis and symptomatic treatment. The management of opioid-induced constipation in palliative care patients or elderly patients may be particularly challenging [47, 48].

The doctor has a key role in identifying the link between mood and perception of pain, and should support and/or refer the patient for help accordingly [5, 6, 7]. Depression is a very strong cause of non-adherence to analgesic therapies, and anti-depressant management is essential for improving adherence and reducing the perception of pain [5, 6, 7]. Patient support, such as good doctor-patient communication and regular appointments to check treatment comprehension and adherence, is important to ensure adherence [5, 6, 7]; a low-literacy opioid contract between the treating physician and the patient may also be useful [49, 50]. Involvement of other family members or volunteers, especially in long-term regimens or with elderly or depressed patients, is also beneficial [5, 6, 7]. Daily or weekly pill-organized receptacles, prepared by a relative, nurse, or pharmacist, may assist the patient in checking his/her regular intake and improve compliance and adherence. Education and training programmes on pain management for patients and carers may help to alleviate fears of dependence, oversedation, and respiratory depression [51].

Adjustment of treatment

Causes for apparent dose escalation are many and can include one or more of: disease progression or new disease, mood disorders/changes (such as caused by interpersonal conflicts), increased physical activity, poor compliance, abuse,

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misuse, drug interactions, concomitant medical problems, and opioid tolerance: a neurobiological change in actual opioid effect mediated in part by N-methyl-D-aspartate (NMDA) receptor changes. Opioid tolerance, where repeated exposure to an opioid results in decreased therapeutic effect of the drug or need for a higher dose to maintain the same effect, may develop during long-term treatment [52, 53]. It is important to determine the contributing causes to the loss of effect and to formulate on-going treatment decisions based on the diagnosis/recognition of predisposing, precipitating, and maintaining factors. Opioid-induced tolerance or hyperalgesia occur in some patients, and tapering of the opioid dose may restore the analgesic effect in patients experiencing these troublesome complication [52, 54].

Risk of abuse: facts and fears

A neglected and yet important factor in poor adherence is the fear of addiction and/or opioid abuse, often shared by relatives or significant others. In a prospective, randomized study 11,352 patients with no current substance abuse problem were treated with analgesics for CNCP. The number of patients scoring positive for abuse at least once during the 12-month follow-up was 2.5% for non-steroidal anti-inflammatory drugs (included in the study as a negative control as they were considered to have almost no abuse liability), 2.7% for tramadol, and 4.9% for hydrocodone [55]. However, the risk of abuse and addiction amongst patients prescribed opioids for chronic pain has not been clearly established. A prospective cohort study in an academic primary care practice enrolled 196 opioid-treated patients with non-cancer pain of more than 3 months duration [56]. Enrolment of patients whose pain was considered difficult to manage and in whom opioid misuse was suspected was encouraged. In this study 32% of patients misused opioids. The key to safe opioid initiation and management for CNCP is developing an individual treatment algorithm that includes an initial patient assessment and abuse risk stratification, initiation of opioid therapy, and reassessment of opioid therapy [57, 58]. Patients with a personal and/or family history or other risk factors that indicates increased addiction risk must be managed more carefully [59]. The most vulnerable to abuse risk are those with a personal history of opioid or other psychoactive/recreational drug use, even years before. The clinical implication is that any past use of recreational drugs should be actively investigated in the clinical history to optimize the current opioid prescription and the follow-up. There should also be an assessment of what other interventions, particularly psychological, the patient may be offered [60]. Opioid therapy should always be considered a “trial” with clear goals established by mutual agreement between the patient and physician and with parameters for an exit strategy clearly delineated.

Conclusions

We have reviewed the factors that interfere with the optimal use of strong opioids for chronic pain and proposed strategies to overcome them. Proper adherence to pain treatment should contribute to a good treatment outcome. Therefore factors that influence treatment adherence—involving the patient in the therapeutic choice, maintaining a good doctor-patient relationship, lowering the dose frequency, and minimising treatment-related adverse effects—should be carefully observed.

The treatment of severe CNCP with prescription opioids is becoming more widely used and accepted. Less frequent daily dosing of opioids may enhance patient adherence and consistency of use, giving more effective pain relief and improved quality of life. However, more studies need to be done to investigate the benefits of once-daily dosing of opioids in patients with chronic pain.

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Tables

Table 1 Factors modulating adherence

Positive	Negative
<ul style="list-style-type: none">• Basic knowledge of the disease and the nature of chronic non-cancer pain	<ul style="list-style-type: none">• Ignorance about the disease and/or the characteristics of chronic nociceptive and/or neuropathic pain
<ul style="list-style-type: none">• Clearly perceived analgesic benefits and improvement in well-being	<ul style="list-style-type: none">• No perceived, or only marginally perceived, personal benefit or greater physical or psychological well-being compared with not taking the medicine perceived
<ul style="list-style-type: none">• Realistic treatment expectations	<ul style="list-style-type: none">• Unrealistic expectations for pain relief
<ul style="list-style-type: none">• Patient’s faith in their ability to manage the therapeutic regimen	<ul style="list-style-type: none">• Patient’s lack of faith in their ability, or fear they will be unable to manage, the therapeutic regimen
<ul style="list-style-type: none">• Low dosing frequency	<ul style="list-style-type: none">• Frequent daily dosing
<ul style="list-style-type: none">• Good mood	<ul style="list-style-type: none">• Anxiety and/or depression
<ul style="list-style-type: none">• Low levels of emotional and psychosocial distress and/or positive active coping	<ul style="list-style-type: none">• High levels of emotional and psychosocial stress
<ul style="list-style-type: none">• Positive doctor–patient relationship and trust in the health services	<ul style="list-style-type: none">• Lack of faith in the doctor and/or health services
<ul style="list-style-type: none">• Solid economic background	<ul style="list-style-type: none">• Financial problems
<ul style="list-style-type: none">• Positive family and/or friend relationships	<ul style="list-style-type: none">• Loneliness, or confrontational and/or unsupportive relationships
<ul style="list-style-type: none">• Coping attitude towards side effects	<ul style="list-style-type: none">• Fear of adverse effects
<ul style="list-style-type: none">• Positive cultural or religious beliefs about the right to control pain	<ul style="list-style-type: none">• Negative cultural or religious beliefs about pain control

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Table 2 Once-daily and twice-daily oral dosing formulations of strong opioids¹

Formulation	Opioid	Dosing
Avinza [®] [61]	Morphine	Once-daily
Kadian [®] /Kapanol [®] [62]	Morphine	Once-daily, twice-daily
MST [®] CONTINUS [®] [63]	Morphine	Twice or three times daily
Jurnista [™] [64]	Hydromorphone	Once-daily
Hydromorph Contin [®] [65]	Hydromorphone	Twice-daily
Palladone [®] SR [66]	Hydromorphone	Twice-daily
OPANA [®] ER [67]	Oxymorphone	Twice-daily
OxyContin [®] [68]	Oxycodone	Twice or three times daily

¹This table contains examples of once-daily and twice-daily formulations; there are different availabilities in different markets

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Table 3 Recommendations to improve adherence with opioid therapy for chronic pain

<p>A good patient-doctor relationship</p> <p>The doctor should base the treatment strategy on the requirements and wishes of the patient, allowing the patient to participate in the therapeutic choice; a low-literacy opioid contract between the doctor and patient may be useful. An empathic attitude towards the intrusiveness of the pain and its meaning in the patient's life is key in improving the dialogue and ensuring that the patient feels fully understood and supported</p>
<p>Defined treatment objectives</p> <p>The doctor and patient should discuss the achievable objectives and the time needed to achieve them</p>
<p>Tools for disease prognosis</p> <p>Tools involving prognosis, such as the DIRE-score, can facilitate the decision to initiate, or withdraw, long-term treatment with opioid analgesics</p>
<p>Simple treatment regimens</p> <p>Treatment regimens that have a low dosing frequency of medication and fit into the daily routine should be used</p>
<p>Identification of patients at higher risk of side effects or drug abuse</p> <p>Detailed questioning on predisposing, precipitating, or maintaining factors for severe constipation and/or for drug abuse should be routinely included in the history taking and decision making process</p>
<p>Management of side effects</p> <p>Possible side effects should be fully explained to the patient and treated pro-actively</p>
<p>Monitoring treatment success</p> <p>Satisfaction with analgesics is associated with the perception of a specific improvement, i.e. a reduction in pain or an increase in well-being; increased perception of satisfaction of use may motivate the patient to continue therapy</p>
<p>Anti-depressant management</p> <p>Depression should be carefully monitored and treated appropriately</p>
<p>Support within the community</p> <p>Family members or friends can remind the patient to take their medication and/or assist with preparing dosage receptacles to enhance compliance</p>
<p>Educational program for patients and carers</p> <p>Improving the understanding of the benefits and side-effects of the treatment regimen may help to motivate patients to follow the therapy correctly. Educating relatives and/or caregivers in understanding chronic pain and being positive and proactive about analgesics and other pain management strategies will increase the overall adherence to achieve effective pain control</p>