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Recommendations for using opioids in chronic non-cancer pain

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Abstract

1. The management of chronic pain should be directed by the underlying cause of the pain. Whatever the cause, the primary goal of patient care should be symptom control.
2. Opioid treatment should be considered for both continuous neuropathic and nociceptive pain if other reasonable therapies fail to provide adequate analgesia within a reasonable timeframe.
3. The aim of opioid treatment is to relieve pain and improve the patient's quality of life. Both of these should be assessed during a trial period.
4. The prescribing physician should be familiar with the patient's psychosocial status.
5. The use of sustained-release opioids administered at regular intervals is recommended.
6. Treatment should be monitored.
7. A contract setting out the patient's rights and responsibilities may help to emphasize the importance of patient involvement.
8. Opioid treatment should not be considered a lifelong treatment.

Keywords: Opioids; Opiates; Noncancer pain; Guideline

1. Introduction

Many doctors will be faced with patients who have chronic pain. Opioids such as morphine and fentanyl (which are full opioid agonists and classified as being on Step III of the World Health Organization analgesic ladder, World Health Organization, 1996), are now an established part of the care of patients with cancer and in palliative care settings, but they are still relatively new and unfamiliar in many areas for the treatment of chronic non-cancer pain. In most countries, the use of such opioids is controlled (e.g., a special prescription form is required and their storage and dispensing is regulated). Guidance is therefore needed about their use. This document aims to provide a framework for the development of national or local guidelines (American Academy of Pain Medicine, 1996; Kalso et al., 1999; National Agency for Medicines Sweden, 2002; Perrot et al., 1999) but not to provide detailed advice about doses or formulations. It is designed to be a starting point for discussion and to be sufficiently flexible to gain practical acceptance in different regions. It aims to assist prescribers (whether in primary care or specialist

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settings) in the appropriate use of opioids in pain management.

One of the aims of the recommendations is to discuss the well-documented problems of undertreatment and avoidance of strong opioids, as well as to address possible problems of overuse or inappropriate use (Large and Schug, 1995; Melzack, 1990; Zenz and Willweber-Strumpf, 1993).

The decision to initiate or terminate long-term opioid therapy should, ideally, involve a multidisciplinary pain clinic with experience in this field. However, in many cases this is not practical, since there are insufficient pain clinics to be able to evaluate every patient. In such circumstances, referral to a pain clinic would result in patients waiting unacceptably long periods for treatment. These recommendations, while emphasizing the central role of specialist teams, therefore recognise the fact that, in many cases, treatment decisions will have to be made by other doctors without the support of a specialist team. However, prescribing clinicians are encouraged to contact pain clinics, multidisciplinary teams or other colleagues if they are unsure about any aspects.

Patients with severe, continuous pain are not a homogenous group and management will be more complex and problematic for some patients than others. Clinicians need to assess not only the likelihood of benefit from strong opioids, but also the potential for their misuse in each case. Other guidelines have recommended different approaches for patients considered at low or high risk of inappropriate use. However, we have not adopted this approach, but, rather, recommend similar assessment, initiation and termination procedures for opioid therapy in both straightforward and problematic patients. Despite this common framework, treatment should be individualized for each patient and patients should be involved in treatment decisions.

> 1. The management of chronic pain should be directed by the underlying cause of the pain. Whatever the cause, the primary goal of patient care should be symptom control.

Treatment of pain should be directed by the underlying cause. A clear-cut diagnosis of the cause of the pain seems to improve treatment outcome with opioids. A precise diagnosis of the cause of pain is the gold standard but this is often not attainable. Use of opioids without a clear diagnosis of the cause of pain is appropriate if the pain is severe and continuous, and is responsive to opioids.

Care should be individualized, and patients should be involved in treatment decisions. The consent process is useful for clarifying patient expectations and defining limitations of therapy. It can also be used to set out the consequences if compliance with medication is poor and to agree on the circumstances that will lead to treatment being stopped.

> 2. Opioid treatment should be considered for both continuous neuropathic and nociceptive pain if other reasonable therapies fail to provide adequate analgesia within a reasonable timeframe.

Division of pain into nociceptive and neuropathic may be out-dated (Woolf et al., 1998), but is probably still helpful. Opioids are considered to be effective in nociceptive pain (Allan et al., 2001; Caldwell et al., 1999, 2002; Moulin et al., 1996; Roth et al., 2000). The efficacy of opioids in certain neuropathic pains has also been shown (Attal et al., 2002; Dellemijn and Vanneste, 1997; Harke et al., 2001; Huse et al., 2001; Rowbotham et al., 1991; Watson and Babul, 1998). However, the benefit of opioids in terms of quality of life in long-term use is still a matter for debate. With the current state of knowledge, opioids should not be prescribed for chronic pain syndrome (idiopathic pain).

As pain is such a complex process, its control is multimodal. Chronic pain is likely to benefit from a combination of pharmacological and non-pharmacological therapies.

Strong opioids should not be used as monotherapy, but in the context of a rehabilitation programme setting goals of improved physical and social function. The need for other pharmacological treatments (e.g., antidepressants) and non-pharmacological treatments (e.g., cognitive behavioural therapy and physiotherapy) should be evaluated regularly. Careful assessment and optimization of other pain therapies will reduce the need for opioids (Maier et al., 2002).

> 3. The aim of opioid treatment is to relieve pain and improve the patient's quality of life. Both of these should be assessed during a trial period.

The patient's current pain level, quality of life and functional status should be assessed carefully at the start of treatment (baseline). Sustained-release strong opioids should be introduced in the context of a trial period of 3–4 months (Dellemijn et al., 1998; Roth et al., 2000), during which the dose is titrated. Long acting, sustained-release opioids are usually the most practical preparations for dose titration.

The maximum length of the trial period should be agreed by the physician and the patient. At the end of

the trial period, the patient's pain level, the intensity of adverse effects, quality of life and functional status should be assessed again and compared to the baseline levels. In some cases, a pain diary is helpful to assess pain intensity and relief before and after treatment.

The use of an intravenous opioid infusion test can help to predict whether opioids will be beneficial. The negative predictive power of such tests is generally good, but a positive result may not predict long-term treatment success. If the test is performed in a double-blind fashion with saline, the placebo response can also be assessed. The assumption that a particular pain is unresponsive to opioids implies that the opioid dose has been individually titrated to the appropriate maximum level and that the opioid has reached the opioid-receptor. Acute intravenous testing allows the opioid to be titrated to the level of dose-limiting adverse effects for each individual under safe and controlled circumstances. The potential analgesic effect of the particular opioid in a specific pain syndrome and for the individual patient can be assessed. However, intravenous testing is not able to determine the balance between analgesic effect and adverse effects in long-term opioid use. If the result of intravenous testing is positive (maximum pain relief with opioid minus placebo response is greater than 50%), the likelihood of long-term treatment being effective is about 50%. If the response to intravenous testing is negative, the odds for a positive treatment result are negligible (Dellemijn and Vanneste, 1997; Dellemijn et al., 1998). Intravenous opioid testing may save a bothersome opioid titration period of several weeks with initial gastrointestinal adverse effects for patients who are unlikely to benefit.

In most cases, however, opioid therapy is initiated without intravenous testing. A prolonged trial period with gradual dose increments of oral opioids and aggressive treatment of opioid-induced adverse effects has the advantage of achieving a balance between pain relief and adverse effects for the individual patient. The balance between pain relief and adverse effects must be acceptable to the patient. Unless unwanted effects such as nausea, vomiting and constipation are treated immediately, many patients will stop opioid treatment in the early phase and not give it a fair trial. Most patients receiving strong opioids will require continuous prophylaxis against constipation, while tolerance to other adverse effects is likely to develop with continued treatment (Dellemijn et al., 1998).

The aim of treatment is to improve quality of life by relieving pain and improving functional status. Assessing a global measure such as quality of life ensures that both the beneficial and unwanted effects of treatment are taken into account. Relief of pain would be expected to be reflected in an improvement in quality of life, while the occurrence of adverse effects might decrease quality of life. However, clinical trials have shown that significant pain relief does not necessarily imply an improvement in physical function (Moulin et al., 1996). The optimum treatment will balance pain relief and adverse effects. The patient's views about the overall benefits of the treatment (in terms of analgesia, effects on functional status and quality of life, and any unwanted effects) should be determined and respected. A useful series of questions for pain assessment and a list of factors that may predict the outcome of opioid treatment are shown in Box 1. If the outcome of the trial treatment is unclear, a multidisciplinary pain clinic should be consulted.

Box 1

Useful questions for assessing patients before opioid treatment

- Has a realistic attempt been made to diagnose the underlying cause of pain?
- Have other reasonable treatments been properly tested and exhausted?
- Does the patient have a history of mental illness, or substance or alcohol abuse?
- What is the patient's current functional status?
- What improvement in functional status is desired, and how will this be measured?
- Has the patient kept a pain diary?
- Does the patient understand and accept the goals of treatment?
- What is the patient's physical and psychosocial status?

Factors predicting outcome with opioid treatment

Adverse (negative) predictors:

Non-opioid responsive pain type
Evoked pain, paroxysmal pain or pain on weight bearing
History of drug or alcohol abuse
History of psychotic illness
Patient without a clear idea or desire for functional improvement

Positive predictors:

Continuous pain with high pain intensity
Clear-cut pain diagnosis
Spontaneous pain
Limited treatment period
Positive outcome of intravenous opioid testing
Younger age (fewer adverse effects)
Patient accepts treatment goals
Patient has kept a pain diary
Patient makes attempts to maintain physical fitness
Patient has good psychosocial status

4. The prescribing physician should be familiar with the patient's psychosocial status.

Full assessment of psychosocial status and history is an important part of the assessment before treatment is initiated. It may be helpful to involve a psychologist or psychiatrist. If the patient has a history of psychiatric illness, a full psychiatric analysis should precede initiation of opioid therapy. Patients with a history of drug or alcohol abuse should be referred to a multidisciplinary pain clinic.

Alcohol or drug abuse is a relative (not an absolute) contraindication for opioid therapy. Such patients can develop pain that is suitable for treatment with opioids. It is important for pain to be treated promptly and controlled in such patients, otherwise it can reactivate the addictive behaviour. The complex nature of these cases is probably best handled by a multidisciplinary team, ideally including an addiction specialist. If a multidisciplinary team considers that a patient's compliance would be inadequate, then the patient should not receive opioid therapy.

5. The use of sustained-release opioids administered at regular intervals is recommended.

The efficacy of sustained-release opioids in the management of chronic pain has been demonstrated in randomized controlled studies (Allan et al., 2001; Caldwell et al., 1999, 2002; Dellemijn et al., 1998; Milligan et al., 2001; Moulin et al., 1996; Peat et al., 1999; Roth et al., 2000). Such preparations should be taken regularly (by the clock) rather than as needed.

Breakthrough pain may occur on movement in patients with spinal or vascular pain. The use of short-acting opioids (acting on the same receptor as the main therapy, i.e., pure μ-agonists) should be considered carefully in such cases. As a rule, short-acting opioids should be avoided.

Opioid treatment is initiated at a low dose, and this dose is increased gradually if the patient reports unsatisfactory pain relief with acceptable or no adverse effects. The maximum dose is reached when the patient reports satisfactory pain relief or if unacceptable adverse effects persist despite symptomatic treatment. The optimum dose is essentially determined by the patient, who is the best judge of the balance between pain relief and adverse effects.

6. Treatment should be monitored.

Thorough monitoring of treatment includes measuring not only pain relief and adverse effects, but also the patient's functional status and quality of life. Quality of life may be perceived as difficult to measure, but published rating scales or simple tools such as visual analogue scales can overcome this. Absolute measures of quality of life or comparisons between patients are not the aim of such assessment. Rather, the aim is to use measures that compare the situation before and during opioid treatment for an individual patient.

Functional status, such as the ability to return to work, is an important goal of pain relief. However, functional goals must be individualized, and will depend on the patient. For example, return to work might be the most important outcome for a young woman with low back pain, but ability to sit comfortably might be an equally valid goal for an elderly man with hip pain (Follett, 1999; Rowland and Torgerson, 1998). In some countries reimbursement is dependent on measurement of functional status.

Ideally, a single physician or members of one team should be responsible for the prescription of opioids and should monitor the outcome of treatment. Changes in treatment/dosage are best handled by this physician/team who should also have information about the use of other drugs. Treatment by an individual physician ensures continuity of care and a good understanding of the patient's psychosocial background, but arrangements must be in place to ensure that patients are not left without pain control if access to specific physicians is not possible (e.g., during vacations or sickness).

For patients with a history of non-compliance or abusive behaviour, access should be restricted to one prescribing physician or team and one dispensing pharmacy. Such patients should not have the opportunity to 'shop around' different doctors for different drugs or to provide false information to obtain extra opioids (American Academy of Pain Medicine, 2001). The prescribing physician should monitor the patient's use of other drugs, such as recreational (illicit/lifestyle) drugs and alcohol, other analgesics and co-medications. These should all be checked and recorded prior to starting opioid therapy.

In many areas, access to multidisciplinary teams/pain clinics is limited and waiting lists for consultations may be long. This may mean that primary care physicians have to take responsibility for patient care and analgesic prescribing while they await referral. Box 2 suggests measures that should be taken with problem patients.

Box 2
Problem patients may require:

- referral to a multidisciplinary team (including a psychologist and an addiction specialist)
- a contract/agreement
- a trial period of opioid therapy (e.g., 3 months)
  - with a predetermined, acceptable endpoint
  - with structured follow-up (e.g., efficacy, adverse effects, quality of life, drugs prescribed/consumed)
- one doctor/team/pharmacy.

7. A contract setting out the patient's rights and responsibilities may help to emphasize the importance of patient involvement.

Patients have the right to be fully informed about the nature of their treatment and its possible benefits and harmful effects. Obtaining agreement from the patient about the conditions for stopping opioid therapy is as important as obtaining consent for the initiation of therapy. Agreeing a contract also shows that the patient is committed to the aims of treatment and understands that receiving opioid therapy entails certain responsibilities. Topics that should be covered in a contract are shown in Box 3, and sample contracts and consent forms are available from other organisations (American Academy of Pain Medicine, 2001, 2002; National Agency for Medicines Sweden, 2002; Fishman et al., 1999; Gitlin, 1999).

Box 3

Topics that should be included in a patient contract (adapted from guidelines issued by the National Academy of Medicine, Sweden (National Agency for Medicines Sweden, 2002))

1. An explanation of the nature of the treatment and its possible beneficial and adverse effects.
2. Patients' should inform the doctor/team if they take any other analgesic or medication for a psychiatric condition, or if they take alcohol or recreational (illicit/lifestyle) drugs.
3. Patients should not request prescriptions for analgesics from another doctor.
4. The medication should be taken only as prescribed, and never passed on to anybody else.
5. The medication should be kept in a safe place (out of the reach of children) and the police should be informed if it is stolen.
6. Patients need a written document from the doctor when travelling abroad and may be limited in the amount of opioid they can carry for their personal use (e.g., under the Schengen agreement).

8. Opioid treatment should not be considered a lifelong treatment.

Treatment may be stopped, or the dose reduced, if the patient experiences a significant improvement in the painful condition (such as improvement of the underlying disease), or a poor outcome of treatment (e.g., intolerable adverse effects). Treatment should be stopped in cases of poor compliance. Compliance problems might include uncontrolled dose increases or decreases, uncontrolled co-medication, or abandonment of non-pharmacological therapies.

2. Discussion/conclusions

Guidelines should be based on available evidence and this was the ambitious goal of this expert group. However, we soon realised that most of the key issues had to be discussed without evidence (Jadad and Browman, 1995). Several randomised controlled clinical trials have been performed with opioids in some chronic pain conditions. However, the opioid responsiveness of many chronic pain conditions has not been assessed in controlled settings and we know very little about the long-term (months to years) efficacy and adverse effects of opioids.

Our understanding of many basic factors such as the mechanisms of pain and their relevance to the responsiveness to opioids and true differences between opioids is still meagre. So is our understanding of pharmacogenetics and differences between individuals in pain perception and risk for addictive behaviour. Some specialists report successful treatment with methadone when other opioids have failed (Gardner-Nix, 1996). However, no clinical studies have been performed in this area. Another "phenomenon" that is much discussed but about which there is hardly any evidence is "opioid rotation" (Do Quang-Cantagrel et al., 2000; Thomsen et al., 1999). Another field for future research is the possibility of co-administering drugs that will increase the effectiveness of opioids or reduce their adverse effects including the development of tolerance.

In these guidelines the patient is considered the "key participant" in the management of his/her pain. The patient, together with the responsible physician, must take control of the pain. Pharmacists, pharmaceutical companies and society also have necessary and important contributions. The main object of guidelines such as these is to encourage the positive participation of all stakeholders in order to provide the maximum benefit to the patient.

3. Declaration of interests

Eija Kalso, Laurie Allan, Leon Plaghki and Michael Zenz have participated in clinical studies on opioids sponsored by Janssen-Cilag and Purdue Pharma (Napp Laboratories). They have also lectured at meetings organised by these two pharmaceutical companies. Michael Zenz has also worked with Mundipharma, Braun and Astra. Paul Dellemijn has participated in clinical studies sponsored by Janssen-Cilag and has lectured at meetings organised by Janssen-Cilag and Pfizer. Troels

S. Jensen has done consultancy for various medical companies including: GSK, Pfizer, Janssen-Cilag, Astra, Novartis, Pharmacia, and Schwartz. Clara C. Faura has lectured at a meeting organised by Janssen-Cilag. Wilfried Ilias has no financial interest in companies that market opioid analgesics.

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