CHAPTER 5

OPIOIDS AND NON-CANCER PAIN

Background 78
Side-effects of opioids 78
Tolerance, physical dependence and addiction 79
Opioid-induced pain 79
Practical issues 80
Many patients are prescribed weak opioid preparations, often combined with paracetamol as part of their analgesic regimen. The role of strong opioid medication (such as morphine, oxycodone, fentanyl and buprenorphine) in the management of persisting pain has been unclear and is the subject of continuing debate. There has been a traditionally held belief, promulgated in the late 1980s, that opioids to not provide effective relief of many persistent pains, particularly those with a neuropathic component. This assumption has been questioned more recently. A number of randomized controlled trials have shown that opioids may be useful for a number of conditions, including back pain, neuropathic pain and central pain. Not all patients are helped and tolerability of these drugs limits use in many of these trials. Long-term open-label studies suggest that patients who derive relief of pain do so over long periods without the need for dose escalation and with little evidence of cognitive impairment. Although these drugs provide effective analgesia, improvements in other outcomes, such as physical functioning and mood, are disappointing and there is debate as to whether pain relief alone (without functional improvement) is sufficient justification for use of this class of drugs in patients with non-cancer-related pain.

These are well described in Chapter 4. When used for persisting pain, tolerance to side-effects, particularly nausea and sedation, usually occurs quickly. Constipation and pruritus almost always persist. Constipation should be managed actively, with attention to diet and appropriate laxatives.

Respiratory depression, an important side-effect in the acute setting, is rarely an important concern in the prescription of these drugs for chronic pain.

There is evidence that a small percentage of patients taking long-term opioids may develop subfertility, weight gain or symptoms of adrenal insufficiency, and appropriate consent should be obtained from patients, particularly those of child-bearing age, when starting these drugs.
Concerns remain regarding the widespread prescription of opioids, particularly in regard to physical dependence (which should be distinguished from addiction), tolerance and abuse potential. Terminology in this regard is often confused and is summarized in the box. There are considerable retrospective survey data that suggest that addiction is rare following opioid prescription for chronic pain. Tolerance to analgesic effects of opioids has been demonstrated in animals and humans but is rarely a problem in clinical practice, and patients can be maintained for many years on stable drug doses. The use of sustained-release preparations at fixed dose intervals may reduce the likelihood of tolerance and is recommended practice for the management of non-cancer pain. Worsening pain in a patient on a stable dose of opioid may be a result of worsening of the underlying disease process.

**TOLERANCE, PHYSICAL DEPENDENCE AND ADDICTION**

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**American Society of Addiction Medicine Definitions**

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

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

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

**Pseudoaddiction** describes patient behaviours that may occur when pain is undertreated.

**OPIOID-INDUCED PAIN**

A further concern is the potential for development of a hyperalgesic syndrome following effective opioid administration. The emergence of increasing pain following opioid therapy has usually been assumed to be a phenomenon of pharmacological tolerance. However, there are
both preclinical and clinical data to support the development of a state of abnormal pain sensitivity following opioid administration. This may be mediated by:

- central glutamatergic mechanisms
- increase in the synthesis of excitatory neuropeptides such as dynorphin
- descending facilitatory mechanisms arising in the medulla.

The relative contributions of these mechanisms may vary between drugs and routes of administration. It is not clear to what extent these phenomena are important in routine clinical practice but there are important therapeutic implications. An opioid-induced pronociceptive state will be worsened by increasing opioid dose, whereas a patient who has increased pain as a result of tolerance would be expected to improve with further opioid administration.

**PRACTICAL ISSUES**

Use of strong opioid medication may be considered when:

- pain is interfering with function
- pain is not controlled by other drugs
- side-effects limit the use of other drugs.

**Starting opioid therapy**

- Assess the patient.
- Discuss the treatment, including side-effects.
- Agree short- and long-term outcomes.
- Start therapy and actively manage side-effects.
- If side-effects persist, consider changing opioid.
- Monitor therapy for efficacy and tolerability.
- Keep under regular review.

*Dose titration and stabilization should be carried out by one practitioner and prescriptions should be provided from a single source.*
Requests for repeat prescriptions at decreasing intervals, repeated loss of prescriptions, requests for dose escalation following the titration phase, and frequent missed appointments are causes for concern and should prompt urgent review of therapy.