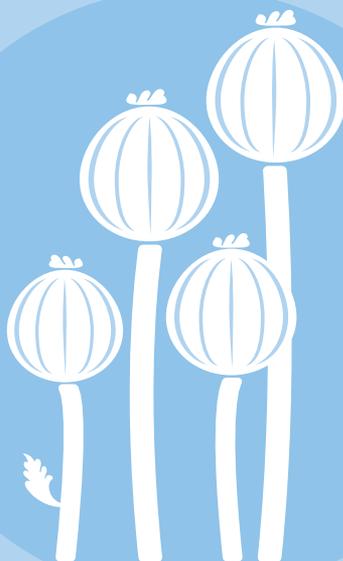




African Palliative Care Association  
**Using Opioids to Manage Pain:**  
A Pocket Guide for Health  
Professionals in Africa



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# Using Opioids to Manage Pain: A Pocket Guide for Health Professionals in Africa

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ISBN 978 9970 204 052

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The production of these guidelines was made possible by the support of the True Colours Trust, UK. The contents of this document are the sole responsibility of the African Palliative Care Association and do not necessarily reflect the views of the True Colours Trust.



## Table of Contents

FOREWORD .....	8
INTRODUCTION .....	9
Evaluation and assessment of pain .....	10
The Analgesic Ladder approach to pain management .....	11
THE IMPERATIVE FOR MEDICAL USE OF OPIOIDS .....	14
PRESCRIBING OPIOIDS .....	17
Who is permitted to prescribe strong opioids? .....	17
Prescription details required .....	17
OPIOIDS FOR MODERATE PAIN.....	19
Codeine phosphate .....	19
Tramadol .....	20
OPIOIDS FOR MODERATE-TO-SEVERE PAIN.....	22
Morphine .....	22
Oxycodone .....	26
Fentanyl.....	28
Methadone.....	32
Buprenorphine .....	36
CHANGING OPIOIDS OR ROUTES OF ADMINISTRATION .....	38
Opioid switching and rotation .....	40
DISCONTINUATION OF OPIOID THERAPY .....	41

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CO-ANALGESIC MEDICATIONS USED IN PAIN MANAGEMENT..... 42

- Anticonvulsants ..... 43
- Antidepressants ..... 44
- Corticosteroids..... 45
- N-methyl-D-aspartate receptor blockers ..... 46

MYTHS ABOUT USING OPIOIDS..... 48

NOTES..... 52



## Definitions

<b>Addiction (psychological dependence):</b>	A compulsive physiological and psychological need for a habit-forming substance. It is important to note that the World Health Organization (WHO) no longer uses the term; the preferred terminology is 'dependence syndrome'.
<b>Adjuvant analgesic drug:</b>	A drug that is not a primary analgesic but that research has shown to have independent or additive analgesic properties.
<b>Breakthrough pain:</b>	Transitory exacerbation of pain experienced by a patient who has relatively stable and adequately controlled baseline pain.
<b>Epidural:</b>	Situated within the spinal canal, on or outside the dura mater (the tough membrane surrounding the spinal cord); synonyms are 'extradural' and 'peridural'.
<b>Iatrogenic:</b>	Induced inadvertently by the medical treatment or procedures of a physician.
<b>Lancinating:</b>	Characterised by piercing or stabbing sensations.
<b>Neuropathic pain:</b>	A type of pain experienced where there is a disturbance of function or pathological change in a nerve, i.e. the pain pathway is not intact. In one nerve this is known as mononeuropathy; in several nerves, if diffuse and bilateral, it is known as polyneuropathy.
<b>Nociceptive pain:</b>	The process of pain transmission; usually relating to a receptive neuron for painful sensations. Nociceptive pain occurs in an intact pain pathway. It may be somatic, i.e. arising from musculoskeletal tissues, or visceral, i.e. from internal organs such as the intestines.

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<b>NSAID (non-steroidal anti-inflammatory drug):</b>	An aspirin-like drug that reduces inflammation (and hence pain) arising from injured tissue, e.g. ibuprofen, diclofenac.
<b>Opiate:</b>	A term used to describe a drug (natural or semi-synthetic) derived from the juice of the opium poppy plant.
<b>Opiate receptor:</b>	An opiate-binding site found throughout primary afferents and the neuraxis.
<b>Opioid:</b>	A general term that includes natural, semi-synthetic and synthetic drugs, such as morphine, which produce their effects by attaching to opioid receptors in the central nervous system.
<b>Opioid partial agonist:</b>	A compound that has an affinity for, and stimulates physiological activity at, the same cell receptors as opioid agonists, but that produces only a partial (i.e. sub-maximal) bodily response.
<b>Pain:</b>	A subjective, unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.
<b>Physical dependence:</b>	Physiological adaptation of the body to the presence of an opioid that is required to maintain the same level of analgesia.
<b>Suffering:</b>	A state of severe distress associated with events that threaten the intactness of the person.
<b>Tolerance:</b>	The state when a person's reaction to a drug decreases so that larger doses are required to achieve the same effect.



## Foreword

The medical need for opioids in Africa is enormous; indeed, about 90% of patients with advanced cancer experience severe pain. Unfortunately, a majority of patients' pain remains undertreated since treating cancer pain effectively poses a great challenge for clinicians as each patient's pain is unique.

Pain is also a common and debilitating symptom of HIV disease, present in more than 60% of HIV patients. Similar to the situation with cancer, a majority of patients with HIV-related pain do not receive any adequate pain treatment since in Africa many doctors either underestimate the pain or under-prescribe potent analgesics (or both). Consequently, the use of opioids for the treatment of pain across Africa remains very low.

The use of opioids in Africa is also affected by other factors that include: exaggerated fear of causing drug dependence syndrome (addiction); a lack of training in pain control using opioids among health professionals; a fear of legal consequences when found in possession of opioids; and a lack of guidelines on pain assessment and control. To address these challenges and to ensure effective pain control in life-threatening conditions, health professionals need to get the facts on using opioids.

In this guide, the African Palliative Care Association (APCA) has put together evidence-based information on the use of specific opioids commonly used in the management of moderate-to-severe pain to manage both cancer and non-cancer pain. APCA hopes that this guide will be a useful tool in aiding health professionals at all levels of healthcare delivery to assess and manage pain using opioids.

All opioids included in this guide are listed on the WHO model list of essential medicines but we remind readers that oral morphine is the standard opioid of choice for managing moderate-to-severe pain and we recommend that it should be made available at all times.

APCA is grateful to all the contributors, and especially the contributing editor Liz Gwyther, for sharing their clinical experience and expertise, and it is our sincere hope that readers will find this guide useful. We are optimistic that this book will enable health professionals to approach pain management with greater knowledge and confidence, hence improving patient care.

**Dr. Faith Mwangi-Powell**

Executive Director, APCA

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## Introduction

Pain is one of the most common and important symptoms in cancer, with incidence among cancer patients ranging between 14% and 100%.

### **Factors why use of opioids for pain control remains low**

- Exaggerated fear of causing addiction
- Lack of training in pain control using opioids among health workers
- An attitude amongst health workers that patients exaggerate the intensity of their pain
- Excessively restrictive laws and regulations regarding the use of opioids
- Fear of legal consequences – in case found in possession of opioids, etc.
- Insufficient amount of opioids within the country
- Cost of opioids
- Inadequate healthcare resources, including the number of health workers licensed to prescribe opioids
- Lack of national guidelines regarding the handling of opioids
- Lack of guidelines on pain assessment and control.

Figure 1: Factors why use of opioids remains low

Pain in cancer is highly prevalent; it is estimated that each year cancer-related pain affects approximately 9 million people, 75% of whom will suffer in the advanced and terminal stages.<sup>1</sup>

Chronic non-cancer pain – defined as pain that persists beyond the usual course of an acute disease or a reasonable time for any injury to heal that is associated with chronic pathological processes that cause continuous pain or pain at intervals for months or years – is also common, with a prevalence of 2% to 40%.<sup>2</sup>

1 Goudas L, Carr DB, Bloch R, Balk E. 'Management of cancer pain'. Evidence report/technology assessment no. 35. AHRQ publication no. 02±E002. Rockville, MD: Agency for Healthcare Research and Quality; 2001.

2 Boswell MV, Shah RV, Everett CR, Sehgal N, et al. 'Interventional techniques in the management of chronic spinal pain: Evidence-based practice guidelines'. *Pain Physician* 2005; 8:1–48.



World Health Organization (WHO) guidelines<sup>3</sup> for pain relief, based on the three-step ladder and the paradigm ‘by the mouth’ and ‘by the clock’, remain the mainstay of pharmacological pain management.

Pain is also a common and debilitating symptom of HIV disease, present in 62% of HIV inpatients. Pain severity decreases the quality of life of persons living with HIV/AIDS; unfortunately more than 50% of HIV/AIDS patients with significant pain do not receive any analgesic treatment as a result of many doctors both underestimating the pain and/or under-prescribing potent analgesics.

There are a number of factors why the use of opioids for pain control remains low, especially in sub-Saharan Africa (see Figure 1).

## Evaluation and assessment of pain

All patients should be evaluated for the presence of pain at every visit – supporting the claim that pain should be considered a fifth vital sign. Pain severity is best assessed by the patient self-reporting and may be aided by visual analogue scales, numerical rating scales and verbal rating scales.

Cancer and/or HIV/AIDS pain management is based upon the underlying pain mechanisms.<sup>4</sup> The extent of diagnostic investigation must be appropriate to the patient’s general status and the goals of care. Pain should be managed during the diagnostic evaluation.

Most patients with life-threatening illnesses can attain satisfactory relief of pain through an approach that incorporates:<sup>5</sup>

- Primary disease-modifying treatments (e.g. anti-tumour therapy, anti-retroviral therapy, etc.)
- Systemic analgesics, and
- Other non-invasive techniques e.g. psychological or rehabilitative interventions.

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3 World Health Organization. *Cancer Pain Relief*. 2nd edn. Geneva: WHO; 1996.

4 Caraceni A. ‘Evaluation and assessment of cancer pain and cancer pain treatment’. *Acta Anaesthesiol Scand* 2001; 45:1067–1075.

5 ‘Management of cancer pain: ESMO clinical recommendations’. *Annals of Oncology* 18 (Supplement 2): ii92–ii94, 2007.

Step-wise escalation of analgesic therapy should follow the WHO analgesic ladder (see Figure 2).

Good pain management uses a multi-disciplinary team approach that matches therapy to the individual patient. It needs interdisciplinary co-operation among healthcare professionals – doctors, nurses, social workers, pharmacists, occupational therapists and others. Pharmacological therapies should therefore be seen as part of an integrated plan to improve physical and social functions and support a rehabilitative approach.

### The Analgesic Ladder approach to pain management

The WHO analgesic ladder (see Figure 2) is based on the premise that most patients throughout the world should have adequate pain relief if healthcare providers learn how to use a few effective and relatively inexpensive medicines well and administer them by mouth, on a regular basis, and according to the individual needs of each patient.<sup>6</sup>

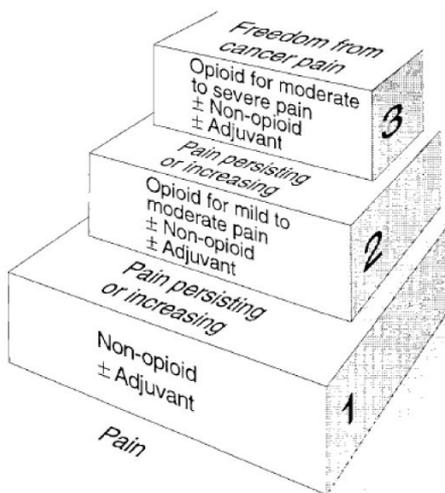


Figure 2: WHO analgesic ladder

6 World Health Organization. *Cancer Pain Relief*. Geneva: WHO; 1986



### **WHO Step 1 analgesics – treatment of mild pain**

Mild pain is treated with non-opioid analgesics – paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, diclofenac, aspirin, indomethacin, etc.

The main indication of NSAIDs is pain of inflammatory origin, especially bone metastases. There is no concrete evidence that NSAIDs selective for cyclo-oxygenase-2 (COX-2) isoenzyme, e.g. celecoxib or rofecoxib, are advantageous in treating cancer pain. However, such classes can be recommended in high-risk patients with gastro-intestinal or bleeding complications.<sup>7</sup>

### **WHO Step 2 analgesics – treatment of moderate pain**

Moderate pain should be treated with Step 2 analgesics, i.e. weak opioids. The prototype here is *codeine phosphate* and others include tramadol, dihydrocodeine, hydrocodone, etc. Traditionally, patients with moderate pain have been treated with a combination product containing paracetamol or an NSAID plus codeine, dihydrocodeine, etc. There is evidence of synergistic and opioid dose-sparing effects from co-administration of an NSAID, but no consistent reduction in side effects. There are currently on the market new opioid formulations including controlled-release formulations of codeine, dihydrocodeine, tramadol, etc. in doses appropriate for moderate pain.

### **WHO Step 3 analgesics – treatment of severe pain**

Morphine is the most commonly used analgesic for severe pain and is still the absolute standard, but more for reasons of familiarity, availability and cost than superiority. Oral administration is the preferred route for both adults and children. If given parenterally, the equivalent dose is one-third of the oral medication. Other strong opioids include hydromorphone, oxycodone, fentanyl and methadone. Strong opioids may be combined with ongoing use of Step I analgesics.

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7 Mercadante S. 'The use of anti-inflammatory drugs in cancer pain'. *Cancer Treatment Rev* 2001; 27:51–61.

### **Principles of Pain Management**

- Assess and treat each cause of pain
- Primary management involves establishing and reversing the cause of pain (where possible)
- Remove or reduce exacerbating factors
- Explore the meaning of the pain to the patient (does it mean disease progression? etc.)
- Modify social/physical environment where relevant
- Treat mood disorders – depression and/or anxiety
- Principles of pain control – ‘by the mouth’, ‘by the clock’, ‘by the ladder’ and ‘for the individual’ are inexpensive and effective
- Use regular oral analgesics, and co-analgesics if appropriate
- Physical therapies provide advantages – safety and self-efficacy
- Psychological strategies – an important aspect of chronic pain control
- Needs of patient and family must be defined
- Multi-disciplinary teams should integrate generalist and specialist expertise
- Care must occur in the most appropriate setting for the patient and the procedure

Figure 3: Summary of pain management principles

### **General Rule:**

*The combined effect of a non-opioid (NSAID) and a strong opioid should be explored before introducing adjuvant analgesics.*



## The imperative for medical use of opioids

‘Opiates’ are naturally occurring alkaloids from the poppy, namely *Papaver somniferum*, and include morphine, papaverine and codeine. ‘Opioids’ refers to all agonists with morphine-like pharmacological activity that can be antagonised by opioid receptor antagonists – e.g. naloxolone.

Opioids have been used for medicinal purposes for several thousands of years. They have become the mainstay of effective cancer pain management and are increasingly used in the management of other persistent pains.

The UN Single Convention on Narcotic Drugs (1961), as amended by the 1972 Protocol, recognised that ‘*the medical use of narcotic drugs continues to be indispensable for the relief of pain and suffering ... and that adequate provision must be made to ensure the availability of narcotic drugs for such purposes*’. The Single Convention also establishes a *dual drug control obligation* i.e. to ensure adequate availability of narcotic drugs, including opiates, for medical and scientific purposes, while at the same time *preventing illicit production of, trafficking in and use of such drugs*.<sup>8</sup>

The Economic and Social Council (ECOSOC) resolution 2005/25 and the World Health Assembly (WHA) resolution WHA58.22 invited the International Narcotics Control Board (INCB) and the World Health Organization to examine the feasibility of a possible assistance mechanism that would facilitate the adequate treatment of pain using opioid analgesics.

Access to narcotic drugs such as morphine and codeine, both on the WHO Model List of Essential Medicines, is considered by the WHO to be a human right as defined by the International Covenant on Economic, Social and Cultural Rights (UN General Assembly resolution 2200 A (XXI), annex).

Globally, there is a great concern about the low consumption of morphine, with as many as 86 million patients annually suffering from untreated moderate-to-severe pain. Although the WHO considers access to controlled medicines, including morphine and codeine, to be a human right, these essential medications are not generally available in more than 150 countries.

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8 [www.incb.org/pdf/e/ar/1995/suppl1en.pdf](http://www.incb.org/pdf/e/ar/1995/suppl1en.pdf)

Despite the existence of plentiful supplies of opiate raw materials to meet global needs, many governments do not ensure the wider availability of the essential medicines that derive from them.

A survey of governments, carried out by the INCB in 2007, identified several reasons for this under-utilisation, which included:

- Concerns over addiction
- Insufficient training of healthcare professionals
- The existence of overly restrictive laws.

The INCB has therefore called on governments to establish policies to make these substances available for medical purposes and to support the WHO Access to Controlled Medications Programme.<sup>9</sup>

Indeed, in its report for 2008,<sup>10</sup> the INCB continued to emphasise that *'the primary objective of the 1961 and 1971 Conventions is to ensure the availability of controlled drugs for medical and scientific purposes and to prevent the non-medical use of those drugs'*.

The INCB noted that the discrepancies in consumption levels of narcotic drugs and psychotropic substances continue to be very significant in different regions. Some of those differences can be explained by cultural differences in medical treatment and by varieties in prescription patterns – for example:

- In many countries, medical schools provide little or no training in palliative medicine.
- Tight restrictions and excessive paperwork deter doctors from prescribing opioids.
- Fears persist among patients and clinical staff with regard to the addictive potential of opioids – fears that are largely without foundation when administered under medical supervision in the treatment of moderate-to-severe pain.

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<sup>9</sup> [www.incb.org/documents/President\\_statements\\_09/2009\\_ECOSOC\\_Substantive\\_Session\\_published.pdf](http://www.incb.org/documents/President_statements_09/2009_ECOSOC_Substantive_Session_published.pdf)

<sup>10</sup> [www.incb.org/incb/annual-report-2008.html](http://www.incb.org/incb/annual-report-2008.html)



The INCB recommendations to governments are thus:

To regularly examine trends in the consumption of internationally controlled substances in their countries and to take appropriate action if necessary

To promote the rational use of controlled substances, in accordance with the pertinent recommendations of the World Health Organisation

To identify the impediments in their country to adequate use of opioids for the treatment of pain, and to take steps to improve the availability of those narcotic drugs for medical purposes

- To cooperate with the WHO in the implementation of the Access to Controlled Medications Programme and to provide resources to the WHO to enable the programme to be implemented without undue delay.

The *Political Declaration*, adopted at the High Level Segment of the 52nd Session of the UN Commission on Narcotic Drugs, 2009, called for continued cooperation between member states, the INCB and the WHO to ensure the adequate availability of narcotic drugs and psychotropic substances under international control, including opiates, for medical and scientific purposes, while concurrently preventing their diversion into illicit channels, pursuant to the international drug control conventions.

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## Prescribing opioids

### Who is permitted to prescribe strong opioids?

Article 30 (b)(i) of the UN Single Convention does not specify who may or may not prescribe controlled medicines (opioids), other than to say that a *‘medical prescription’* is required for the supply and dispensation of opioids to individuals. Those permitted to prescribe opioid medicines are defined in the national laws or regulations governing medicines in each respective country. Usually, the following cadres are allowed to prescribe opioids:

- Registered medical and dental practitioners – doctors /dentists
- Registered veterinary surgeons/doctors
- In some countries where the doctor to population ratio is poor, the need for pain relief overwhelming due to burden of disease, and where palliative care needs to reach out to the remotest village, there is a case for widening the prescriber area. Specially trained Clinical Palliative Care Nurses and Clinical Officers can be given special authorisation to prescribe – as in Uganda since 2004. This would mean that such cadres of health workers would be allowed to prescribe opioids.

### Prescription details required

Some governments require that prescriptions for opioid medicines be made in duplicate.

The prescriptions need to be written in amounts and for a period long enough to allow patients who need to travel long distances ample time to make the necessary arrangements or long enough to last the patient until the next appointment.

A prescription for opioid medicines should contain at least the following details (see Figure 4):

- Name, age and address of patient
- Date of issue
- Medicine name, dosage strength and form
- Directions for use (e.g. take 5 (five) mL every four hours and 10 (ten) mL at bedtime)
- The total quantity of medicine to be dispensed, written in both figures and words
- The duration (e.g. one week, one month)
- Prescriber’s name and business address
- Prescriber’s signature



Ministry of Health				
Medical Prescription Form				
Date	Name:	Sex:	Age:	Patient No.
31/10/10	Mr. Kauka Oale Mugabo	Male	34	0000123
	Rx			
	1. Morphine Solution 5mg/5mL. To take 5 (five) mL 4 hourly during the day and 10 (ten) mL at bedtime. Please supply <b>250</b> (two hundred and fifty) mL only.			
	2. Senna Tablets. Dosage 2–4 tablets PO at night (to prevent constipation). Please supply <b>40</b> (forty) tablets.			
	<b>H Mathinge</b> Dr Henry Mathinge 0772-123456			

Figure 4: Example of a prescription for opioids

## Opioids for moderate pain

Opioids used for moderate pain (Step 2 of the WHO analgesic ladder) include *codeine* and *tramadol*. Their use is restricted to moderate pain because of dose-limiting adverse effects or because they are combined with non-opioids.

Lower doses of a strong opioid, e.g. morphine, may be useful for moderate pain instead of Step 2 analgesics.

### Codeine phosphate

#### Codeine phosphate

**Class:** Opioid analgesic (opioid agonist)

**Indication:** Mild-to-moderate pain, cough, diarrhoea

**Contra-indications:** Hypersensitivity to drug; respiratory depression; paralytic ileus

Codeine is an opium alkaloid and is the prototype of the weak opioid analgesics with weak affinity to the *mu*-opioid receptor.

It is about one-tenth as potent as morphine. It is practically used as an oral dose of 30mg four-hourly. It is generally given in combination with a non-opioid.

The main metabolite is codeine-6-glucuronide, which binds weakly to *mu*-opioid receptors, together with small amounts of norcodeine, morphine, morphine-3-glucuronide and morphine-6-glucuronide. Codeine is mainly a pro-drug of morphine.

Codeine phosphate is commonly given as a compound preparation with a non-opioid but can also be given as a single agent. When used alone, the dose is generally 30–60mg every four hours; higher doses are not recommended. Many compound medications have a low dose of codeine that is not effective for analgesia.

Bioavailability is 40% on average (12–84%) following oral administration, and the onset of action for analgesia is 30–60 minutes. Time to peak plasma concentration is 1–2 hours, with a plasma half-life of 2.5–3.5 hours. Duration of action is 4–6 hours.

Like morphine, codeine is antitussive and also slows gastro-intestinal motility.



## Tramadol

### Tramadol

**Class:** Opioid analgesic

**Indications:** Moderate-to-severe pain

**Contra-indications:** *None, if titrated carefully against a patient's pain*

**Caution:** Use with care in patients predisposed to epileptic activity (e.g. those with brain tumours)

Tramadol is a synthetic centrally acting analgesic with both opioid and non-opioid properties.

In addition to binding to the *mu*-opioid receptor, it stimulates neuronal serotonin release and inhibits the pre-synaptic re-uptake of serotonin and norepinephrine (mono-aminergic effect) similar to tricyclic antidepressants.

Tramadol is metabolised in the liver to O-desmethyltramadol (M1), an active substance 2-4 times more potent than tramadol.

Tramadol may be safely combined with non-opioids, especially with paracetamol, with an improvement in analgesia but no increasing toxicity.

A dose of 50–100mg of tramadol is usually effective in treating moderate pain. The daily total dose of tramadol should not, however, exceed 400mg because, like tricyclic antidepressants, it lowers the seizure threshold.

Seizures can occur with the use of tramadol and the risk may be higher in those who have had a seizure disorder, epilepsy, a head injury or a metabolic disorder. It is therefore prudent to avoid tramadol in patients predisposed to epileptic activity, such as those with brain tumours.

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Tramadol is less likely to cause respiratory depression and constipation than equi-analgesic doses of pure opioids, but it might cause dizziness, nausea, vomiting, fatigue, dry mouth, sedation, and orthostatic hypotension; another side effect is impaired thinking and reaction time. However, all of these side effects resolve after stopping treatment.

Patients who suddenly stop taking tramadol can experience withdrawal symptoms that include anxiety, nausea, sweating, chills, tremors, diarrhoea, hallucinations, trouble sleeping and breathing problems.

Tramadol and neuropathic pain

There is evidence that tramadol 100–400mg per day is an effective symptomatic treatment for peripheral neuropathic pain.<sup>11</sup>

*In summary, tramadol should probably be used only for patients with mild-to-moderate pain who do not tolerate typical opioids, both because of its potential to cause seizures at high doses, and its higher cost.*

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<sup>11</sup> Duehmke RM, Hollingshead J, Cornblath DR. 'Tramadol for neuropathic pain'. *Cochrane Database of Systematic Reviews* 2006, Issue 3. Art. No.: CD003726. DOI: 10.1002/14651858.CD003726.pub3.



## Opioids for moderate-to-severe pain

Opioids of high potency are recommended for moderate-to-severe pain or pain that is not controlled by WHO ladder Steps 1 or 2. In the management of severe pain, pure opioids are generally used as they are associated with less withdrawal reactions and do not have a ceiling effect. Such opioids include morphine, oxycodone, fentanyl and methadone.

### Morphine

#### **Morphine**

**Class:** Opioid analgesic

**Indications:** Moderate-to-severe pain, diarrhoea, cough, dyspnoea

**Contra-indications:** *None, if titrated carefully against a patient's pain*

Morphine is the principal derivative of opium, which is the juice in the unripe seedpods of the opium poppy, *Papaver somniferum*.

The German pharmacist F. W. A. Sertürner, who named it after Morpheus, the god of dreams, first extracted morphine from opium in 1803.

Morphine, a *mu*-opioid receptor agonist, is said to be the most powerful pain reliever medicine has to offer today and sets the standard by which the potency of all other opiates is tested. It is recommended as the drug of choice for the management of moderate-to-severe pain.

There is a linear dose-response curve with no ceiling effect; however, sometimes side effects may preclude reaching optimum analgesia.

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## Pharmacology

- Morphine is the main pharmacologically active constituent of opium.
- Its effects are mediated by specific receptors (*mu*-opioid receptors), both within the central nervous system (CNS) and peripherally.
- Under normal circumstances, its main peripheral action is on smooth muscles.
- Liver is the principal site of morphine metabolism, albeit that it occurs in other organs.
- Metabolism is rarely impaired except in severe liver failure, and morphine is well tolerated in patients with mild-to-moderate hepatic impairment.
- Major morphine metabolites are morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). M6G is the active metabolite; it binds with a high affinity to *mu*-opioid receptors and contributes substantially to the analgesic and side effects of morphine.
- In renal failure the plasma half-life of M6G increases from 2.5h to 7.5h, resulting in cumulative toxicity. Thus patients with significant renal impairment need dose reduction to minimise the accumulation of glucuronide metabolites.
- When administered orally, morphine undergoes a high degree of first-pass metabolism, so oral bioavailability is only 20–30%.
- Peak effect: 30–60min IM; 5–90min SC.
- Time to peak plasma concentration: 15–60min following oral administration; 10–20min IM/SC.
- Plasma half life: 1.5–4.5h after oral administration; 1.5h after IV.
- Morphine's analgesic effects last for around 4 hours, probably as a result of low lipid solubility, slow uptake into the CNS, and slower elimination from the brain.



## Dose and usage

Morphine can generally be given together with a non-opioid.

Morphine, usually as the sulphate or hydrochloride salt, is available in four oral formulations:

- An elixir or solution of morphine in various concentrations
- An immediate-release tablet
- A number of different preparations of modified (slow) release tablets or capsules
- Modified-release suspensions.

Modified-release morphine (M/mr) products are effective for pain relief. Modified-release tablets are available in both 12-hour and 24-hour release patterns and should be swallowed whole.

The oral to SC potential of morphine is between 1:2 and 1:3.

Morphine is effective in a wide dose range when administered by mouth.

The normal starting dose of morphine, when converting a patient from a Step 2 analgesic, is 10–20mg of immediate-release morphine 4 hourly (or the equivalent dose of modified-release morphine, ie 30–60mg M/mr 12hourly).

Patients who are HIV-positive often respond well to lower doses of morphine and can be started on 5–10mg of immediate-release morphine.

The simplest method of dose titration is with a dose of normal (immediate) release morphine given every 4 hours and the same dose given for breakthrough pain (a European Association for Palliative Care (EAPC) Recommendation). The EAPC guidelines support the use of a double dose of normal-release morphine at night.

When adjusting the dose of morphine, generally increase by 25%, 75% or 100%. Instructions must be clear: any extra breakthrough dose of morphine does not imply the next regular dose should be omitted. In addition, *the breakthrough dose must be increased whenever the regular dose is increased.*

A laxative should be prescribed routinely unless there is a strong reason for not doing so, because constipation may be more difficult to manage than the pain.

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### **Use in the elderly**

When starting treatment in elderly patients, morphine should be prescribed at low doses and titrated to the patient's response and adverse effects. Use of a short-acting oral form is recommended when initiating treatment, to allow for more rapid adjustments.

Once the patient's morphine requirements have been established, switching to a long-acting formulation is recommended so as to help improve compliance, avoid peaks and troughs in drug concentrations, and maintain a constant level of drug in the body to both prevent and treat pain.

Elderly patients must be monitored closely for adverse effects and treatment should be adjusted as necessary. Furthermore, older patients need to be re-evaluated on a regular basis to ensure ongoing effectiveness and safety.

### **Morphine-related side effects**

As with any medicine, morphine can cause side effects. However, not everyone who takes the medication will have problems – in fact, some people tolerate it quite well.

If side effects occur, in many cases they are minor and either require no treatment or are easily treated by a healthcare provider.

The most common side effects of morphine are thought to include nausea and vomiting, light-headedness, dizziness, sweating, headaches, constipation and somnolence.



## Oxycodone

### **Oxycodone**

**Class:** Opioid analgesic

**Indications:** Moderate-to-severe pain; an alternative in cases of intolerance to other strong opioids

**Contra-indications:** *None, if titrated carefully against a patient's pain*

Oxycodone is a semi-synthetic strong opioid with similar properties to morphine.

It is more expensive and therefore its use should be reserved for patients who cannot tolerate morphine.

Oxycodone is a pure *mu*-opioid receptor agonist whose principal therapeutic action is analgesia. The *mu*-opioid receptor binding affinity of oxycodone is, however, less than that of morphine or methadone.

There is no defined maximum dose for oxycodone – increasing dose results in increasing analgesia and the ceiling to analgesic effectiveness is imposed only by side effects, such as somnolence and respiratory depression.

Oxycodone is well absorbed when orally administered, and it has a higher oral bioavailability (60–87%) than morphine.

Onset of action is 20–30 minutes following oral administration. It has a plasma half-life of 3.5 hours and a duration of action of 4–6 hours (12 hours for modified release – OxyContin®).

Oxycodone is partly metabolised to *oxymorphone* (which by injection is about 10 times more potent than morphine) and *noroxycodone*, its major metabolite. It is eliminated primarily in the urine as both conjugated and unconjugated metabolites.

The parenteral potency of oxycodone is approximately three-quarters that of parenteral morphine. Oral oxycodone is approximately twice as potent as oral morphine, with an equianalgesic ratio of oxycodone to morphine ranging from 1:1 to 1:2.3.

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Patients with acute hepatic dysfunction may require downward titration of previously established effective analgesic doses to avoid excessive sedation, but there is no evidence for the accumulation of active metabolites, making oxycodone a good choice for patients with organ failure.

Side effects of oxycodone are similar to those of morphine, except for fewer oxycodone-induced hallucinations and less itching. The most common side effects are nausea, constipation, dizziness, pruritis and somnolence.

### **Dose and usage**

In palliative care settings, oxycodone may be administered as: a pure immediate-release preparation in liquid, pills or capsules; compounded with paracetamol or ibuprofen; or in various delivery systems intended to create a sustained release into serum with the goal of attaining steadier serum levels for around-the-clock analgesia.

Oral use of immediate-release oxycodone is as with morphine but given 6-hourly (not 4-hourly). When oxycodone is administered rectally, start with approximately one-half of the previous oral morphine dose.

#### ***Morphine or oxycodone?***

Both morphine and oxycodone provide effective analgesia in acute and chronic pain.

Oxycodone has a more favourable pharmacokinetic profile, with a significantly higher oral bioavailability.

Parenterally, oxycodone is about as potent as morphine.

Both drugs cause typical opioid-related adverse effects; oxycodone causes fewer hallucinations and less itching.

Oxycodone is not particularly effective when administered epidurally, whereas morphine has a powerful spinal analgesic effect.

Oxycodone is far more expensive than morphine.



## Fentanyl

### Fentanyl

**Class:** Opioid analgesic

**Indications:** Severe chronic pain; morphine intolerance

**Contra-indications:** *The need for rapid titration of strong opioid medication for severe pain*

**Side Effects:** Respiratory depression, apnoea, muscular rigidity, myoclonic movements and bradycardia.

Fentanyl is a synthetic strong *mu*-opioid receptor agonist that is highly lipophilic.

It is approximately 100 times more potent than morphine, 1000 times more lipophilic and has a lower molecular weight.

The oral (enteral) bioavailability of fentanyl is poor and hence the usual routes of administration are intravenous, subcutaneous, spinal, transdermal and transmucosal.

Fentanyl is used in the management of chronic severe pain, particularly in patients with cancer.

It is highly lipophilic and gets sequestered in body fats including the white matter of the brain. Given by any route, it acts supraspinally, mainly in the thalamus (white matter). The highly lipophilic nature of fentanyl accounts for its reduced tendency to cause constipation.

Fentanyl is traditionally used as an *intravenous* preparation for perioperative anaesthesia and analgesia. When given intravenously, systemic clearance occurs in two phases: the first is related to rapid redistribution of the drug into body tissues; and the second is due to hepatic and renal drug elimination.

Intravenously administered fentanyl has a very short duration of action of 0.5–1 hour. The usual duration of the analgesic effect is 30–60 minutes after a single IV dose of up to 100mcg for a 60kg adult (1–2mcg/kg would be the guiding dosage).

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In general, we would avoid using the IV administration of analgesics in the palliative-care setting and would preferentially use the oral route – or, if a patient is not able to take medication orally, the rectal or subcutaneous route. Fentanyl has the added advantage of being available transdermally.

### **Transdermal (TD) fentanyl**

Transdermal (TD) fentanyl is available via a self-adhesive skin patch with a rate-limiting membrane, which allows a standardised amount of fentanyl to pass each hour from the patch to the skin.

Peak concentrations are achieved between 8 and 16 hours after application, with a steady state being reached within 24 hours. In most cases, serum levels can be maintained long enough to provide constant analgesia for 72 hours. The half-life after removal of the patch is between 13 and 25 hours.

The transdermal route:

- Can achieve constant plasma concentrations comparable with continuous infusion
- Can be used in patients who cannot take oral medication because of vomiting, dysphagia or poor absorption
- Unlike parenteral opioids, is non-invasive and does not require infusion equipment.

TD fentanyl is less constipating than morphine. Healthcare workers need to halve the laxative dose when converting from morphine to fentanyl.

TD fentanyl can be continued until the death of a patient, and the dose adjusted accordingly. It is, however, contra-indicated in patients who need rapid titration for their pain; thus, rescue (breakthrough) doses of an alternative strong opioid should be given, usually immediate-release morphine such as morphine elixir. The alternative is to give transmucosal fentanyl.



TD fentanyl may offer particular advantages for patients in the following situations:

1. Patients with difficulty swallowing, where the transdermal (TD) formulation may be a particular advantage
2. Those with itching or urticaria, in response to opioids, since fentanyl has a relatively low tendency to cause histamine release
3. Those with renal insufficiency, since fentanyl has a lack of active metabolites
4. Where intolerable undesired effects are experienced with morphine, such as nausea, vomiting, constipation or hallucinations.

**Caution:** *the rate of absorption of fentanyl from a patch may be increased in febrile patients, resulting into unexpected toxicity.*

## Dose and usage

The conversion ratio of oral morphine to transdermal fentanyl is 100:1 as a reasonable starting dose.<sup>12</sup> Thus, using this ratio, a 60mg/day dose of oral morphine is equianalgesic to 25 mcg/hr of transdermal fentanyl.

An approximate ratio of 1mcg fentanyl per 2mg of morphine is used when determining the starting dose of fentanyl. It is advisable to refer to the manufacturer's recommendations of equivalence.

TD fentanyl patches are available in four strengths: 25, 50, 75 and 100 microgram/hour for 3 days and need to be prescribed as required by the regulations. Thus:

### TD fentanyl: the bottom line

Patients who have not been using opioids should not be started on a fentanyl patch.

When rotating to a fentanyl patch, it is important to start low and go slow, especially in elderly or debilitated patients.

The shortest titration period is 3 days because of the extended time required for the plasma concentrations of the drug to stabilise.

Fentanyl patches should not be used for end-of-life care, especially when there is uncontrolled pain.

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<sup>12</sup> Donner B, Zenz M, Tryba M, Strumpf M: 'Direct conversion from oral morphine to transdermal fentanyl: A multicenter study in patients with cancer pain'. *Pain* 1996; 64: 527-34.

- Patients with inadequate response from Step 2 analgesics (e.g. codeine) start on 25mcg/hour
- For patients on oral morphine, divide the 24-hour dose by 3 and choose the nearest patch strength.

The patch should be applied to dry, non-inflamed, non-irritated, hairless skin on the upper arm or abdomen.

Steady plasma concentrations of fentanyl are achieved after 36-48 hours. Patients should be given breakthrough doses of a strong opioid (e.g. morphine) in doses approximately half the fentanyl patch strength. If after 48 hours a patient continues to need two or more rescue doses of morphine a day, increase the patch strength by 25 mcg/hr.

Remove patches after 72 hours and change their position on the skin when another is applied. Used patches should be disposed of into a sharps container or dustbin. Any unused patches should be returned to the pharmacy.



## Side effects of fentanyl

The major side effect of fentanyl is respiratory depression (which is dose dependent) and this is usually only seen when administering intravenously. Other side effects include apnoea, muscular rigidity, myoclonic movements and bradycardia.

Less common side effects include hypotension (sometimes severe), dizziness, blurred vision, miosis, nausea, vomiting, laryngospasm, diaphoresis, itching, euphoria, seizures, spasm of the sphincter of Oddi, and anaphylaxis.

Care should be taken in severely cachectic patients because they have a smaller volume of distribution and altered end organ function.

## Methadone

### **Methadone**

**Class:** Opioid analgesic

**Indications:** *Moderate-to-severe pain, treatment of opioid (heroin) dependence*

**Contra-indications:** *Hypersensitivity to the drug*

**Caution:** *In cases of cardiac disease*

Methadone is a synthetic strong opioid. Its use in the treatment of pain is still limited to a few individuals working from specialist settings.

Methadone has a complex pharmacology and a wide range of pharmacological effects.

Methadone is a potent agonist at the *mu*-opioid receptor; an agonist at the *delta*-opioid receptor; an N-methyl-D-aspartate (NMDA) receptor antagonist; and it inhibits serotonin pre-synaptic re-uptake.

The high affinity of methadone for *mu*-receptors and delta-receptors is the reason why it is recommended for use as an analgesic in moderate-to-severe pain. A combination of NMDA receptor antagonism and opioid agonism might provide valuable analgesic effects with fewer side effects.

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Methadone exists in formulations for oral, rectal and parenteral administration. It is well absorbed by all routes. Oral administration is followed by rapid gastro-intestinal absorption.

Peak plasma levels after an oral dose occur at 4 hours and begin to decline 24 hours after dosing. Oral bioavailability of methadone is high – generally more than 85% (41–99%).

Methadone has unusual pharmacokinetic properties that contribute to unintentional toxicity. Its elimination half-life (8–130 hours) is longer than its duration of analgesic action (4–8 hours).

Special characteristics of methadone that result in its use in pain management include:<sup>13</sup>

- High oral bioavailability
- Rapid onset of analgesic effect
- Long half-life (resulting in infrequent dosing schedules)
- Lack of active metabolites
- Low rate of induction of tolerance
- Low cost.

The clinical scenarios where methadone is used are as follows:

- Moderate-to-severe cancer pain
- Nociceptive pain and neuropathic pain, especially if poorly opioid-responsive
- During opioid rotation, for relief of opioid toxicity
- Morphine allergy
- Renal failure
- When morphine doses need to escalate rapidly – suggesting tolerance
- Pain that fails to respond to other *mu*-opioid agonists.

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<sup>13</sup> Ripamonti C, Zecca E, Bruera E. 'An update on the clinical use of methadone for cancer pain'. *Pain* 1997. 70: 109–15.



## **Methadone dosage formats**

*Injection, solution: 10mg/mL (20mL)*

*Solution, oral: 5mg/mL, 10mg/mL*

*Solution, oral, as hydrochloride (concentrate): 10 mg/mL (Methadone Intensol™, Methadose®: 10 mg/mL)*

*Tablet: 5mg, 10mg (Dolophine®: 5mg, 10mg; Methadose®: 5mg, 10mg [DSC])*

*Tablet, dispersible: 40mg (Methadose®, Methadone Diskets®: 40mg)*

## **Dosing of methadone in adults**

### **Moderate-to-severe acute pain**

Opioid-naive: initial oral dose is 2.5–10 mg every 8–12 hours, but more frequent administration may be required during initiation to maintain adequate analgesia.

Dosage interval may range from 4 to 12 hours, since the duration of analgesia is relatively short during the first days of therapy but increases substantially with continued administration.

### **Chronic pain (opioid-tolerant)**

Conversion from oral morphine to oral methadone should be handled as set out below:

- Daily oral morphine dose <math>\leq 100</math> mg: estimated daily oral methadone dose is 20%–30% of total daily morphine dose
  - Daily oral morphine dose 100–300 mg: estimated daily oral methadone dose is 10%–20% of total daily morphine dose
  - Daily oral morphine dose 300–600 mg: estimated daily oral methadone dose is 8%–12% of total daily morphine dose
  - Daily oral morphine dose 600–1000 mg: estimated daily oral methadone dose is 5%–10% of total daily morphine dose
  - Daily oral morphine dose > 1000 mg: estimated daily oral methadone dose is <math>\leq 5</math>% of total daily morphine dose.
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The total daily methadone dose should then be divided to reflect the intended dosing schedule.

Initial IV dose is 2.5–10 mg every 8–12 hours in opioid-naïve patients; titrate slowly to effect. The dose may also be administered by subcutaneous or IM injection.

### **Conversion from oral to parenteral dose**

Initial dose: parenteral-to-oral ratio should be 1:2 (e.g., 5 mg parenteral methadone equals 10 mg oral methadone).

### **Methadone drawbacks**

Unfortunately, the use of methadone could be complicated by the long and unpredictable half-life, by large inter-individual variations in pharmacokinetics, and, above all, by a limited knowledge of the equianalgesic dose/ratio with other analgesic opioids when switching in tolerant patients.

These complications can result in significant systemic accumulation of methadone, leading to delayed toxicity.

### **Methadone as an alternative to morphine**

No evidence that methadone is superior to morphine as an analgesic

It is not easy to use and can be hazardous because of its complex pharmacology

Accumulation of methadone in tissues with chronic administration results in a potential for toxicity

Methadone is best initiated as an alternative opioid in a specialist inpatient setting by an experienced team

Methadone is, however, cheap and may be useful in particularly challenging pain syndromes.



A group of palliative-care experts produced consensus guidelines intended to inform the parenteral use of methadone among patients with cancer-related pain, HIV-related pain, sickle pain, and postoperative pain.<sup>14</sup> The guidelines specifically recommend:

- Use of a rate-controller patient-controlled analgesia (PCA) device with adequate rescue/breakthrough pain doses
- Very conservative dose calculation when switching from other opioids (dose reduction of 75%–90% of equivalents using standard charts), with slow upward titration over 24–48 hours
- ECG monitoring when possible, after counselling of patients/families about the small but real risk of QT<sub>c</sub> prolongation and even sudden cardiac arrest from Torsades des pointes
- Palliative-care physicians prescribing methadone to remain mindful of methadone's complex pharmacokinetics.

## Buprenorphine

### **Buprenorphine**

**Class:** Opioid analgesic

**Indications:** *Moderate-to-severe cancer pain, and severe non-malignant pain not responding to non-opioids*

**Contra-indications:** *Hypersensitivity to buprenorphine*

Buprenorphine is a mixed *mu*-opioid receptor partial agonist and *kappa*-opioid receptor antagonist.

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<sup>14</sup> Shaiova L, Berger A, Blinderman CD, Bruera E, Davis MP, Derby S, Inturrisi C, Kalman J, Mehta D, Pappagallo M, Perlov E: 'Consensus guidelines on parenteral methadone use in pain and palliative care'. *Palliat Support Care* 2008. 6: 165–76.

Buprenorphine has a high affinity for the *mu*-opioid receptor;<sup>15</sup> but owing to a misunderstanding of the fundamental difference between intrinsic activity and efficacy, it was mistakenly extrapolated from these findings that buprenorphine is a partial agonist that should display a ceiling effect with respect to analgesia in humans. However, many new studies indicate that buprenorphine does not act as a partial agonist at the *mu*-opioid receptor.

Buprenorphine has poor oral bioavailability as a result of extensive first-pass hepatic metabolism but a better sublingual bioavailability.

It is metabolised in the liver by CYP3A4 to inactive norbuprenorphine.

Buprenorphine is highly lipid-soluble and is available as a sublingual (SL) tablet and as a transdermal patch.

The usual starting dose is 200–400 mcg SL eight-hourly. Transdermal (TD) buprenorphine is available in strengths of 800, 1200 and 1600 mcg/24h.

In the clinical situation, no dose adjustment is necessary in patients with renal impairment who are receiving transdermal buprenorphine up to the highest dose tested (70 mcg/h).

TD buprenorphine may be considered suitable for use in elderly patients, not only because of its ease of use and long duration of patch application, but primarily for its unaltered profile in this age group.

### **Buprenorphine drawbacks**

Adverse effects of buprenorphine are qualitatively similar to those of morphine and are dose-related. They include sedation, dizziness, vertigo, headache, confusion, euphoria, weakness, fatigue, nervousness, mental depression, slurred speech, paresthesia, dreaming, psychosis, malaise, hallucinations, depersonalisation, light-headedness, insomnia and disorientation.

Seizures, muscle twitching, lack of muscle coordination, ataxia, dysphoria and agitation have been reported rarely.

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15 Huang P, Kehner GB, Cowan A, Liu-Chen L-Y. Comparison of pharmacological activities of buprenorphine and norbuprenorphine: norbuprenorphine is a potent opioid agonist. *J Pharmacol Exp Ther.* 2001;297:688-695.



## Changing opioids or routes of administration

Dose-limiting side effects, loss of the previous route of administration, and rapidly developing tolerance are the usual reasons for changing opioids or their routes of administration.

When changing a long-acting opioid to another drug or route of administration, conversion is usually made with the assistance of a conversion chart (see Table 1 for an example). All opioid doses can be expressed in parenteral morphine equivalents. Typically, 10 mg of parenteral morphine is considered the unit dose, and doses of other drugs for oral or parenteral administration are listed in equianalgesic amounts.

**Table 1: Opioid equianalgesic conversion**

Product	Equianalgesic parenteral dose to 10 mg parenteral morphine (mg)	Equianalgesic oral dose to 10 mg oral morphine (mg)	Equianalgesic oral dose to parenteral dose (mg)
Morphine	10	10	10:3.3
Fentanyl	0.1	-	-
Pethidine	75	100	10:2.5
Hydromorphone	1.5	2.5	10:2
Methadone	2.0	6.7	10:1
	-	1	10:2.5
Codeine	120	66.7	10:6
Oxycodone	-	6.7	-

Conversion tables contain approximations based largely upon short-term use of smaller opioid doses.

Incomplete cross-tolerance between opioids may account for the apparent decrease in required dose and side effects when changing drugs. Thus, the calculated dose equivalents using a conversion table may not be accurate in patients tolerant to opioids, and an unanticipated effect may result from incomplete cross-tolerance.

The following general principles should be observed:

- When any change in opioid or route is made, frequent assessments are needed both to maintain adequate analgesia and to prevent excessive narcosis.
- When converting large opioid doses, caution dictates a 25–50% dose reduction to account for incomplete cross-tolerance. If, however, inadequate analgesia necessitates the conversion, the new drug may be started at or near an equianalgesic dose.
- An additional short-acting opioid should be made available while titrating the new drug to achieve stable analgesia.
- Converting from a drug with a short half-life to one with a long half-life requires gradual dose reduction over several days to allow for accumulation of the longer-acting agent.
- Increasing amounts of a short-half-life drug are needed to replace a long-half-life drug while the first drug is eliminated.
- Conversion from IV to transdermal fentanyl (or from transdermal to IV) can be safely accomplished using a 1:1 dose ratio.



## Opioid switching and rotation

Responses to opioids vary significantly among patients and even in an individual patient at different stages of treatment, leading to difficulties in accomplishing long-term analgesia with minimum side effects.<sup>16</sup>

‘Opioid switching’ (sometimes referred to as ‘opioid rotation’) is the term given to the clinical practice of substituting one strong opioid with another in an attempt to achieve a better balance between pain relief and side effects. This occurs when the opioid being substituted has failed to provide adequate analgesia at doses below those that produce adverse side effects.

There is no single mechanism that adequately explains the intra-individual or inter-individual variability observed with opioids. It is thought that several factors may contribute to the diminished analgesic efficacy of opioids given in chronic pain conditions, including pharmacological tolerance, possible development of opioid-induced hyperalgesia, and progression of the disease.<sup>17</sup> The recommended practice for opioid switching and rotation is to use an equianalgesic table to estimate the dosing equivalence for the new opioid relative to the previous opioid.

There is however, insufficient evidence to make recommendations about opioid switching as a strategy for managing intolerable opioid-related adverse effects or inadequate symptom relief.<sup>18</sup>

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16 Slatkin NE. ‘Opioid switching and rotation in primary care: implementation and clinical utility’. *Curr Med Res Opin* 2009. 25: 2133–50.

17 American Pain Society. *Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain*. Glenview: American Pain Society. 2008.

18 Quigley C. ‘Opioid switching to improve pain relief and drug tolerability’. *Cochrane Database Syst Rev*. 2004: CD004847.

## Discontinuation of opioid therapy

Successful opioid therapy requires that the benefits of analgesia outweigh treatment-related side effects. Sometimes opioid side effects can impair a patient's quality of life, increase morbidity, and may cause a patient to discontinue therapy. One systematic review found that 22% of patients with chronic non-cancer pain discontinue opioid therapy because of side effects.<sup>19</sup>

Most morphine side effects resolve within a short time with regular dosing as the patient develops tolerance to the side effect. Nausea, confusion and somnolence are temporary side effects that usually resolve within 3–4 days. Constipation is a permanent side effect. Pruritis and urinary retention can persist and may require discontinuation of a particular opioid.

Patients who use the opioid intermittently continue to experience side effects as there is not the opportunity to develop tolerance to those side effects.

*Many side effects diminish or resolve with continued opioid use; conversely, some side effects are more apparent after long-term therapy*

Co-morbidities and concurrent medications that contribute to the incidence and severity of side effects should always be assessed for and treated or discontinued as feasible before considering discontinuing opioid therapy.

Patients should be tapered or weaned off chronic opioid therapy when they experience intolerable adverse effects, or make no progress towards meeting therapeutic goals. When opioids are discontinued, a patient might experience symptoms of opioid withdrawal; these can be very unpleasant but are generally not life threatening.

To avoid these symptoms, it is advisable that opioids are not stopped suddenly but tapered off (known as 'weaning'). Weaning may range from a slow, 10% dose reduction per week to a more rapid 25–50% reduction every few days.

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19 Moore RA, McQuay HJ. Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids. *Arthritis Res Ther* 2005; 7: R1046–51.



## Co-analgesic medications used in pain management

Opioids and non-steroidal anti-inflammatory drugs (NSAIDs) are the standard medicines used to treat pain. NSAIDs are indicated for mild-to-moderate pain and as an adjunct for severe pain, while opioids are indicated for moderate-to-severe pain. The other categories of medication that are used for pain management are referred to as ‘adjuvant’ analgesics because their primary indication is for diagnoses other than pain.

Adjuvants, which are also referred to as ‘co-analgesics’, are medicines administered in conjunction with NSAIDs and opioids that may enhance the analgesic activity of the NSAIDs or opioids, have independent analgesic activity in certain pain states, such as neuropathic pain, or may counteract some of the adverse side effects associated with NSAIDs or opioids.

*The use of adjuvants that target neuropathic pain may be particularly important because such pain is resistant to opioids*

Adjuvants consist of a diverse range of medicine classes, including anticonvulsants (e.g., gabapentin, phenytoin), antidepressants (e.g., tricyclic antidepressants), N-methyl-D-aspartate (NMDA) receptor antagonists (e.g., ketamine), corticosteroids, skeletal muscle relaxants, and local anaesthetics. They are frequently administered with opioids in an effort to diminish the dose required for effective pain management and reduce adverse effects.<sup>20</sup>

Some adjuvant analgesics are useful for treating several painful conditions and are described as multi-purpose adjuvant analgesics (antidepressants, corticosteroids), whereas others are specific for neuropathic pain (anticonvulsants, NMDA receptor antagonists), bone pain (calcitonin, bisphosphonates, radiopharmaceuticals), musculoskeletal pain (muscle relaxants) or pain from bowel obstruction (anticholinergics).

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<sup>20</sup> Lussier D, Huskey AG, Portenoy RK. ‘Adjuvant analgesics in cancer pain management’. *Oncologist* 2004. 9: 571–91.

## Anticonvulsants

Anticonvulsant drugs are useful for neuropathic pain, especially when the pain is lancinating or burning. There is evidence for the effectiveness of a number of anticonvulsants, including carbamazepine, gabapentin, phenytoin and valproate.<sup>21</sup>

The precise mechanisms of action of anticonvulsants in controlling neuropathic pain remain uncertain, but the two standard explanations are: enhanced gamma aminobutyric acid (GABA) inhibition (valproate, clonazepam); or a stabilising effect on neuronal cell membranes. Another possible mechanism of action is via NMDA receptor sites.

In general, when starting an anticonvulsant, it is advisable to start with a low dose and slowly titrate upwards to allow for the patient to adjust to the new medication and decrease the likelihood of adverse side effects. Doses are generally increased until therapeutic effects are seen, or there are limiting adverse effects.

### Gabapentin

Gabapentin acts by binding to calcium channels and modulating calcium influx as well as influencing GABergic neurotransmission. Because of its proven analgesic effect in several types of neuropathic pain, its good tolerability, and a rarity of drug-to-drug interactions, gabapentin is now recommended as a first-line agent for the treatment of neuropathic pain of diverse aetiologies, especially in the medically ill population.

The initial starting dose is typically 300 mg/day given at bedtime. The maintenance dose should be between 1,800 and 3,600 mg/day (taken tid or qid). Most clinicians recommend increasing the dose to at least 1,800 mg/day before assessing the efficacy of the drug.

Because of its short half-life, doses of gabapentin should not be given more than 12 hours apart, and discontinuation of the drug should occur over a week or longer.

The dose must be adjusted in patients with renal failure, but no adjustment is necessary in those with liver disease.

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21 Wiffen P, Collins S, McQuay H, Carroll D, Jadad A, Moore A. 'Anticonvulsant drugs for acute and chronic pain'. *Cochrane Database of Systematic Reviews* 2005, Issue 3.



## Pregabalin

Pregabalin, which is an analogue of gabapentin, has a mechanism of action similar to gabapentin, binding to pre-synaptic calcium channels and modulating calcium influx as well as influencing GABergic neurotransmission. It has been found to be very effective in neuropathic pain,<sup>22</sup> and it is more potent than gabapentin and therefore can be used at lower doses.

## Antidepressants

Among antidepressants, ‘tricyclic’ antidepressants (TCAs) – e.g. amitriptyline, imipramine, nortriptyline and desipramine – have been found to be highly effective in the management of neuropathic pain.

Although their definitive mechanism of action of analgesia is unknown, these drugs block the re-uptake of noradrenalin and serotonin, they block hyperalgesia induced by NMDA agonists, and they also have sodium-channel blocking properties. They therefore have analgesic properties independent of their antidepressant effects.

The biggest advantages of TCAs are their low cost, their once-daily dosing, and their beneficial effects on depression (a common co-morbidity with neuropathic pain). TCAs appear to have equivalent analgesic benefits in both depressed and non-depressed patients with neuropathic pain.

The most common side effects of TCAs include sedation, anticholinergic effects (e.g., dry mouth, constipation, and urinary retention) and orthostatic hypotension.

Secondary amine TCAs (nortriptyline and desipramine) are preferred because they are better tolerated than tertiary amine TCAs (amitriptyline and imipramine) but have comparable analgesic efficacy.<sup>23, 24</sup>

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22 Moore RA, Straube S, Wiffen PJ, Derry S, McQuay HJ. ‘Pregabalin for acute and chronic pain in adults’. *Cochrane Database of Systematic Reviews* 2009, Issue 3. Art. No.: CD007076.

23 Watson CPN, Vernich L, Chipman M, Reed K. ‘Nortriptyline versus amitriptyline in postherpetic neuralgia: a randomized trial’. *Neurology* 1998. 51:1166–71.

24 Rowbotham MC, Reisner LA, Davies PS, Fields HL. ‘Treatment response in antidepressant-naive post herpetic neuralgia patients: double blind, randomized trial’. *J Pain* 2005. 6: 741–6.

When treating neuropathic pain, TCAs should be started at low dosages, administered at night and titrated slowly (e.g., dose increased by 25 mg only every 3–7 days, as tolerated).

There is limited data supporting the analgesic efficacy of selective serotonin re-uptake inhibitors (SSRIs).

## Corticosteroids

Corticosteroids possess analgesic properties for a variety of cancer pain syndromes, including bone pain, neuropathic pain from the infiltration or compression of nerves, headache due to increased intracranial pressure, arthralgia, and pain due to malignant obstruction of a hollow viscus<sup>25</sup> (e.g., bowel or ureter) or to organ capsule distension. Corticosteroids act in an anti-inflammatory capacity and in particular assist in reducing swelling and oedema that may be contributing to the pain.

The relative risks and benefits of the various corticosteroids are unknown. Dexamethasone is often selected, a choice that gains theoretical support from the relatively low mineralocorticoid effects of this drug. Prednisone and methylprednisolone can also be used.

Corticosteroids are usually administered either in a high or a low dose. A high-dose regimen has been used for patients who experience spinal cord compression or an acute episode of severe pain that cannot be promptly reduced with opioids. A low-dose corticosteroid regimen (e.g., dexamethasone 2–4 mg once or twice daily) can be used for patients with advanced cancer who continue to have pain despite optimal dosing with opioid drugs.

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25 Feuer DJ, Broadley KE. 'Corticosteroids for the resolution of malignant bowel obstruction in advanced gynaecological and gastrointestinal cancer'. *Cochrane Database of Systematic Reviews* 1999, Issue 3. Art. No.: CD001219.



## **N-methyl-D-aspartate receptor blockers**

The N-methyl-D-aspartate (NMDA) glutamate receptor is a calcium channel closely involved in the development of central (dorsal horn) sensitisation. At normal resting membrane potentials, the channel is blocked by magnesium and is inactive.

Interactions at the NMDA receptor are involved in the development of CNS changes that may underlie chronic pain and modulate opioid mechanisms, specifically tolerance.

Antagonists at the NMDA receptor may offer another innovative approach to the treatment of neuropathic pain in cancer patients. There are presently four commercially available NMDA receptor antagonists: dextromethorphan (antitussive); ketamine (dissociative anaesthetic); amantadine (antiviral drug); and memantine (a drug approved for the treatment of Alzheimer's disease).

Of particular interest is ketamine, which, when administered by intravenous infusion or orally, is effective in relieving cancer pain and reducing opioid requirements.<sup>26</sup> Ketamine should only be used by clinicians experienced in its use because of the sometimes daunting side effects, particularly in the medically frail.

Ketamine is often started in a low dose taken orally (PO) – an oral formulation is available pre-prepared in some health centres or it can be prepared by the pharmacy as required. Sterility is not necessary for PO administration of ketamine.

Oral ketamine can be given direct from a vial, or after dilution (for convenience) to 50mg/5ml, as follows:

- Starting dose: 10–25 mg 8-hourly to 6-hourly
- Increase dose in steps of 10–25 mg up to 50mg 6-hourly
- Maximum dose 200 mg 6-hourly.

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<sup>26</sup> Laurettil, Gabriela R. MD, MSc, PhD; Lima, Izabel C. P. R. MD, MSc; Reis, Marlene P. MD, MSc, PhD; Prado, Wiliam A. MD, MSc, PhD; Pereira, Newton L. BPharm, MSc, PhD. 'Oral ketamine and transdermal nitroglycerin as analgesic adjuvants to oral morphine therapy for cancer pain management'. *Anesthesiology* 1999. 90: 1528–33.

### **Preparation of ketamine oral solution**

Use ketamine 100mg/ml 10ml vials.

To prepare 100ml of 50mg/5ml oral solution:

- 10ml vial of ketamine 100mg/ml for injection
- 90ml purified water

Store in refrigerator with expiry 1 week from manufacture

### **Key points to note when using adjuvants**

- Consider optimising the opioid regimen before introducing an adjuvant analgesic.
- Consider the burdens and potential benefits in comparison with other techniques used for pain that is poorly responsive to an opioid, including:
  - Opioid rotation
  - More aggressive side-effect management
  - A trial of spinal drug administration
  - Trials of varied non-pharmacological approaches to pain control (e.g., nerve blocks, rehabilitative therapies, and psychological treatments).
- Select the most appropriate adjuvant analgesic based on a comprehensive assessment of the patient, including any inferences about the predominating type of pain and associated factors (co-morbidities) or symptoms.
- Prescribe an adjuvant analgesic based on a knowledge of its pharmacological characteristics, actions, approved indications, unapproved indications accepted in medical practice, potential serious adverse effects, and interactions with other drugs.
- The adjuvant analgesics with the best risk–benefit ratios should be administered as first-line treatment.
- Avoid initiating several adjuvant analgesics concurrently.
- In most cases, initiate treatment with low doses and titrate gradually according to analgesic response and adverse effects.
- Reassess the efficacy and tolerability of the therapeutic regimen on a regular basis, and taper or discontinue medications that do not provide additional pain relief.
- Consider combination therapy with multiple adjuvant analgesics in selected patients.



## Myths about using opioids

### **Myth No. 1 – Morphine is offered to patients only when death is imminent**

It is not the stage of a life-threatening illness, but the degree of pain, that dictates which medicine to use. Patients are usually started on morphine when it is appropriate; some people never need morphine, while others will require it for quite a while. Patients can live for a long time while using morphine to control pain, which allows them a more active life.

### **Myth No. 2 – Healthcare providers do an adequate job of providing adequate pain control**

There are healthcare provider barriers to good pain control. Doctors may neglect to ask whether a person suffers pain and might well assume that disease-oriented treatment will control pain, such as antiretroviral treatment for the HIV-positive patient (whereas antiretrovirals are not analgesics). In some cases, too, if physicians prescribe a dose range for analgesia, most nurses tend to give lower doses. This results in the under-treatment of acute pain (oligoanalgesia), which eventually causes chronic pain because of subsequent alterations within the central nervous system.

When a patient states he has pain, the patient must always be believed and be treated through prompt implementation of adequate pain modalities.

### **Myth No. 3 – Pain medications always lead to addiction**

The fact is that there is no sufficient evidence that opioids lead to addiction, when prescribed appropriately in a dose sufficient to relieve pain, especially for those patients using opioids for short-term acute pain management.<sup>27</sup>

When clinicians believe that appropriate use of narcotics leads to addiction, they become reluctant to prescribe these medications, hence depriving the patients of their right of freedom from pain.

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<sup>27</sup> Joranson, D., Ryan, K., Gilson, A., Dahl, J. 'Trends in medical use and abuse of opioid analgesics'. *The Journal of the American Medical Association*, 2000. 290: 1710–14.

### **Myth No. 4 – People on morphine die sooner because of respiratory depression**

Respiratory depression is very uncommon except in opioid-naïve patients commenced on intravenous morphine. Respiratory depression will not occur if morphine is given orally in a low starting dose and titrated carefully against a patient's response. Indeed, low doses of morphine can be safely used in patients with end-stage COPD or lung cancer to relieve dyspnoea; it makes breathing more comfortable.

### **Myth No. 5 – Pain medications always cause heavy sedation**

The fact is that because chronic pain can cause sleep deprivation, most opioids will cause initial sedation. However, once the patient catches up on lost sleep, continuing treatment with adequate opioid doses will allow them to resume normal mental alertness and orientation.

### **Myth No. 6 – People should not take morphine before their pain is severe, lest it lose its effect**

There is no upper dose limit to the use of morphine or other strong opioids. If pain increases, the dose can be increased – a unique feature of strong opioids such as morphine.

Using opioids when they are needed early in the course of a terminal illness does not mean that they will fail to work later in the disease. Tolerance to the analgesic effect of morphine is unusual.

### **Myth No. 7 – Some kinds of pain cannot be relieved**

All pain is not the same and therefore all pain medications do not have the same effect. Some pain may require a different approach, such as combining opioids with NSAIDs and/or adjuvants. A thorough pain assessment can help a healthcare worker prescribe a medication regimen that will allow the patient to keep pain at a manageable level.<sup>28</sup> A difficult-to-control need for pain relief requires more in-depth assessment and regular review of the patient's response to pharmacological and non-pharmacological interventions.

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<sup>28</sup> Vilensky, W. 'Opioid "mythstakes": Opioid analgesics – current clinical and regulatory perspectives'. *Journal of the American Osteopathic Association*, 2002. 102(9): S13–4.



### **Myth No. 8 – Opioids shouldn't be used in pregnancy**

The fact is that a woman should not necessarily stop taking opioids when she discovers she is pregnant. Indeed, withdrawal effects from opioid cessation can trigger uterine contractions that, in the first trimester, can lead to spontaneous abortion (or, in the third trimester, can lead to premature labour).

### **Myth No. 9 – Effective pain management can be achieved on an 'as needed' basis**

Effective pain management requires medications that are provided around the clock (and according to the medicine half-life) in a prophylactic manner in order to prevent pain. Opioids that are given by the clock tend to have fewer side effects because lower effective doses are given. Prescribing medication for chronic pain only as needed (prn) condemns the patient to episodes of pain when the analgesic effect wears off.

### **Myth No. 10 – Opioid analgesics in older patients should be avoided**

Chronic moderate-to-severe pain frequently requires strong opioids and this should be no exception for the elderly. However, due to pharmacokinetic and physiological changes in older patients, the titration of opioids in such cases should be undertaken with greater caution. The best approach is to begin with a low dose (5–10mg 4-hourly) of an immediate-release opioid and then to slowly titrate according to analgesia and side effects.<sup>29</sup>

For all opioids except buprenorphine, the half-life of the active drug and its metabolites is increased in the elderly and in patients with renal dysfunction. It is therefore recommended that – except for buprenorphine – doses be reduced, a longer time interval be used between doses, and creatinine clearance be monitored.<sup>30</sup>

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29 Fallon M, Hanks G, Cherny N. 'Principles of control of cancer pain.' *BMJ* 2006. 332: 1022–4.

30 Pergolizzi et al. 'Opioids and the Management of Chronic Severe Pain in the Elderly: Consensus Statement of an International Expert Panel with Focus on the Six Clinically Most Often Used World Health Organization Step III Opioids (Buprenorphine, Fentanyl, Hydromorphone, Methadone, Morphine, Oxycodone)'. *Pain Practice* 2008. 8(4): 287–313.

## **Other myths**

Other myths that have currency in some medical circles but that are not true include:

1. Morphine hastens death in a terminally ill patient.
2. Injectable morphine works better than morphine by other routes.
3. Strong analgesics such as morphine should be withheld until death is imminent.
4. A patient who is sleeping cannot be in pain.
5. A patient who is watching television or laughing with visitors is not in pain.
6. Infants and children don't experience pain as adults experience pain.
7. Once you start pain medications, you always have to increase the dose.
8. Alterations in vital signs are reliable indicators of pain in a patient.



## Notes

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NGO Registration Number 4231



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