MINISTRY OF HEALTH
SINGAPORE

NATIONAL GUIDELINES FOR THE SAFE PRESCRIBING OF OPIOIDS 2021

ACADEMY OF MEDICINE SINGAPORE

COLLEGE OF FAMILY PHYSICIANS SINGAPORE

Singapore Medical Association
For Doctors, For Patients

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Foreword

All of us in clinical practice have prescribed and/or managed the use of opioids for pain, dyspnoea management and cough. However, over the past decade, there have been growing concerns with opioid addiction as a result of indiscriminate medical opioid use. As such, MOH convened a National Committee for the Safe Prescribing of Opioids to develop a set of national guidelines to facilitate the safe prescribing of opioids in Singapore.

In developing these guidelines, the committee has taken reference from international guidelines and contextualised to the local settings, as well as harmonised practices across different institutions and clinical practices. This document will serve as a guide for any healthcare professional that prescribes opioids in their practice. The healthcare professional should exercise discretion and make sound clinical judgment on the recommendations based on the healthcare professional's clinical practice and needs of the patient.

This set of guidelines is a good point of reference for any healthcare professional prescribing opioids. However, it is important to note that it is the responsibility of the healthcare professional to ensure that they have the necessary competencies to manage the patient safely and effectively on opioids. Otherwise, the guidelines strongly recommend prescribing opioids in consultation with a specialist, or to refer to a specialist if the patient's symptoms persist for a prolonged duration (e.g. cough) that would require further investigations.

I would like to thank all who have helped produce these guidelines and hope our healthcare professionals find the 'National Guidelines for the Safe Prescribing of Opioids 2021' useful in their clinical practice.

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SECTION 1: GENERAL

1.1 Introduction to Guidelines

Statement of Intent

These guidelines only serve as a guide to clinical practice and are not intended to set out a prescribed standard of medical care. Medical care accorded to an individual is dependent on available clinical data and is subject to change as scientific knowledge advances and patterns of care evolve. Hence, strict adherence to these guidelines may not ensure a successful outcome in every case.

These guidelines and the suggested information to be provided to patients, are meant as a guide and not intended to be exhaustive. Each medical practitioner is ultimately responsible for the management of his/her unique patient, in light of the clinical data presented by the patient, and the diagnostic and treatment options available.

The contents of this publication are based on the best available evidence at the time of development.

1.2 Objectives of Guidelines

The objectives of these guidelines are to:

a) Improve the safety and effectiveness of opioid therapy and opioid dependence management;
b) Reduce the risks associated with opioid therapy and opioid dependence management, including opioid use disorder and overdose; and
c) Improve communication between healthcare professionals and patients about the risks and benefits of opioid therapy and opioid dependence management.

1.3 Scope of Guidelines

These guidelines are intended to address the following areas in adults:

a) Use of opioids for acute pain;
b) Use of opioids for chronic non-cancer pain;
c) Use of opioids for cancer pain and pain in life-limiting non-cancer diseases;
d) Use of opioids for cough; and
e) Opioid dependence management.

Although these guidelines do not specifically address the use of opioids in children, medical practitioners should endeavour to keep to the same principles and extend their application to children.

1.4 Definition of Strong Opioids

Strong opioids refer to the following:

- Buprenorphine
- Fentanyl
- Hydromorphone
- Methadone
- Morphine
- Oxycodone
- Pethidine
- Tapentadol
- Codeine > 60 mg TDS
- Tramadol > 400 mg/day

1.5 Landscape of Opioid Use and Abuse

Opioids conventionally have a defined role in the management of pain and symptom control. Appropriate treatment with opioids should result in demonstrable improvements in physical, psychological and social functions in the patient. However, the liberal use of opioids in some countries has heralded important concerns.

In the case of acute post-surgical and post-trauma pain, and other painful conditions for patients in emergency departments ("ED") and inpatient wards, recent data has indicated that taking opioids for acute pain, especially in opioid-naïve patients, is associated with a greater likelihood of long-term opioid use. Furthermore, a greater amount of initial opioid exposure (i.e. higher total daily dose, longer duration of prescription) is associated with a higher risk of long-term use[1], misuse, and overdose[2].

In the case of chronic pain, analgesic agents belonging to the opioid class are now the most commonly prescribed medications in the United States of America ("U.S."), where one-third of Americans are inflicted with some form of pain, with the prevalence of chronic pain increasing with increasing age. In 2014 alone, U.S. retail pharmacies dispensed 245 million prescriptions for opioid pain relievers.[3,4] It was of note that 65% of these prescriptions were for short-term therapy (<3 weeks)[5], and that 3-4% of the adult population (9.6-11.5 million persons) were prescribed longer-term opioid therapy.[6] This has led to what is commonly termed the "Opioid Epidemic", where the widespread use of opioids has resulted in addiction and overdose. Although opioid analgesics rapidly relieve many types of acute pain and improve function, the benefits of opioids when prescribed for chronic pain are questionable.

Opioids have been implicated in addiction and overdose. More than a third of the 44,000 drug-overdose deaths that were reported in 2013 (the most recent year for which estimates were available) were attributable to pharmaceutical opioids; and heroin accounted for an additional 19%.[7] At the same time, there has been a parallel increase in the rate of opioid addiction, affecting approximately 2.5 million adults in the U.S. in 2014.[8]

[1] Factors Influencing Long-Term Opioid Use Among Opioid Naive Patients: An Examination of Initial Prescription Characteristics and Pain Etiologies. Shah A, Hayes CJ, Martin BC. J Pain. 2017;18(11):1374. Epub 2017 Jul 13.
[2] Postsurgical prescriptions for opioid naive patients and association with overdose and misuse: retrospective cohort study. Brat GA, Agniel D, Beam A, Yorkgitis B, Bicket M, Homer M, Fox KP, Knecht DB, McMahill-Walraven CN, Palmer N, Kohane. BMJ. 2018;360:j5790. Epub 2018 Jan 17.
[3] Levy B, Paulozzi L, Mack KA, Jones CM. Trends in opioid analgesic-prescribing rates by specialty, U.S., 2007-2012. Am J Prev Med 2015; 49: 409-13.
[4] National Institute on Drug Abuse. The latest prescription trends for controlled prescription drugs. 2015.
[5] Volkow ND, McLellan TA, Cotto JH, Karithanom M, Weiss SR. Characteristics of opioid prescriptions in 2009. JAMA 2011; 305: 1299-301.
[6] Boudreau D, Von Korff M, Rutter CM, et al. Trends in long-term opioid therapy for chronic non-cancer pain. Pharmacoepidemiol Drug Saf 2009; 18: 1166-75.
[7] Volkow ND, McLellan AT. Opioid Abuse in Chronic Pain — Misconceptions and Mitigation Strategies. NEJM 2016; 374;13.
[8] Results from the 2013 National Survey on Drug Use and Health: summary of national findings. NSDUH series H-48. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2014. HHS publication no. (SMA) 14-4863.

1.6 Initiating Opioid Therapy in General

First Line Treatment for Acute and Chronic pain

Opioids should not be prescribed as the first-line treatment for acute and chronic pain. Instead, the following pharmacological and non-pharmacological modalities should be considered, unless contraindicated:

- Pharmacological: Paracetamol, non-steroidal anti-inflammatory drugs ("NSAIDS") including Cox-II inhibitors and anti-convulsants (e.g. gabapentinoids).
    - For acute neuropathic pain, anti-convulsants, tricyclic antidepressants ("TCA"), e.g. amitriptyline, and serotonin-norepinephrine re-uptake inhibitors ("SNRI"), e.g. duloxetine, may be more effective.[9]
- Non-pharmacological: Exercise, physical therapy, acupuncture, relaxation exercises, cognitive behavioural therapy[10] and heat/cold therapy.

Identifying Risk Factors and Patient Factors Before Initiating Opioid Therapy

Medical practitioners should identify and weigh the risk factors for opioid abuse and addiction, before initiating opioid therapy. Risk factors include patients with:

- History of substance abuse*; and
- Psychiatric co-morbidities.

To identify the above risk factors, medical practitioners should:

Step 1: Conduct a patient interview and evaluation, which should include:

- Documenting the patient's medical, dental and prescription drug history;
- Screening the patient for past or current use of opioids, benzodiazepines, sedative-hypnotics, and anxiolytics; and
- Consulting with the patient's primary pain management provider (if any).[11]

Step 2: Check the Electronic Medical Records ("EMR") and the National Electronic Health Records ("NEHR") for prior or concurrent prescriptions of opioids and sedatives, including prescriptions by other medical practitioners.

Medical practitioners should also consider patient factors that may increase the risk of acute adverse events (e.g. overdose, falls), affect the need for opioid analgesics, or influence their prescribed dosages. These include patient factors such as older age, comorbidities, concomitant respiratory depressants, obstructive sleep apnoea ("OSA"), morbid obesity, readiness for opioid treatment and suitability for safe use of opioids in the home.[12] The risk of serotonin syndrome is increased when opioids are taken with serotonergic drugs such as monoamine oxidase inhibitors ("MAOIs") , TCAs and SSRIs/SNRIs (if concurrently used in high doses).[13]

[9] Washington State Health Alliance's Guidelines for Prescribing Opioids for Acute Pain

[10] Pennsylvania Orthopaedic Society. Opioid Recommendations for Acute Pain

[11] Dental Guideline on Prescribing Opioids for Acute Pain Management. Developed by Dr Robert Bree Collaborative and Washington State Agency Medical Directors' Group Sep 2017.

[12] Prescription of opioids for acute pain in opioid naïve patients. UpToDateMay 2018.

[13] US Food and Drug Administration. FDA Drug Safety Communication: FDA warns about several safety issues with opioid pain medicines; requires label changes. March 22, 2016.

** Note: A history of substance use disorder should not exclude a patient from being prescribed opioid analgesics for pain where clinically indicated. It should, however, prompt a discussion with the patient about the increased risk for addiction. If necessary, the patient may be referred for treatment of opioid dependence or addiction[14].*

1.7 Monitoring Required for Patients on Opioid Therapy

1. Monitoring for Efficacy

- Resting pain score
- Dynamic pain score
- Functional activity
- Progress towards achieving therapeutic goals

2. Monitoring for Significant Side Effects

- Sedation leading to increased fall risk (especially in vulnerable populations)

3. Monitoring for Opioid Overdose

- Sedation score - Sedation is the best early clinical indicator of significant opioid-induced ventilatory impairment ("OIVI")
- Respiratory rate ("RR") < 8 bpm

4. Closer Monitoring for High Risk Patients

- Closer monitoring, e.g. in the high dependency unit and/or with the use of continuous pulse oximetry or end tidal carbon dioxide, may be considered for high risk patients
- High risk patients may include, but are not limited to those who:
    - Have undergone surgery or anaesthesia procedures within 24 hours;
    - Are diagnosed with OSA;
    - Are diagnosed with chronic obstructive pulmonary disease ("COPD");
    - Have concomitant use of central nervous system ("CNS") depressant drugs;
    - Are obese; and/or
    - Present with abdominal distension.

1.8 Patient Education[15]

Before initiating opioid therapy, the medical practitioner should educate the patient as follows**:**

A. Discuss the treatment plan

- Discuss realistic goals for pain and function with patients, and help them to understand that pain is a normal part of life and healing.[16]
- Remind them to avoid consuming alcohol and medications that are not part of their treatment plan, e.g. hypnotics and sedatives, as doing so may worsen the side effects of the opioids and increase the risk of overdose.

[14] Pennsylvania Orthopaedic Society. Opioid Recommendations for Acute Pain and New York City Emergency Department Discharge Opioid Prescribing Guidelines. The New York City Department of Health and Mental Hygiene.
[15] Arizona Opioid Prescribing Guidelines. Arizona Dept. of Health Services, 2018.
[16] Washington State Health Alliance's Guidelines for Prescribing Opioids for Acute Pain.

B. Provide information on opioid administration

- Educate patients on how to administer the opioid, preferably with return demonstration.
- Provide patients with information leaflets.
- Explain the role of regular interval (basal) versus breakthrough analgesics, if applicable.

C. Provide information on opioid side effects

- Educate patients on the common side effects of opioids, including the following:

Constipation

- Inform patients that constipation affects nearly all patients receiving strong opioid therapy.
- Prescribe laxative treatment (to be taken regularly at an effective dose) for all patients receiving strong opioid therapy.
- Inform patients that treatment for constipation takes time to work and adherence to treatment is important.
- Optimise laxative treatment for managing constipation before considering switching to strong opioids.

Nausea

- Advise patients that nausea may occur when starting strong opioid therapy but that it is likely to be transient.
- If nausea persists, prescribe and optimise anti-emetic treatment before considering switching to strong opioids.

Drowsiness and Mental Clouding

- Advise patients that mild drowsiness or impaired concentration may occur when starting strong opioid therapy or at dose increase, but that it is often transient.
- Warn patients that impaired concentration may affect their ability to drive and undertake other manual tasks.
- Warn patients that non-compliance with prescribed doses might result in acute respiratory depression or death.
- In patients with either persistent or moderate-to-severe drowsiness, or mental clouding, consider dose reduction if pain is controlled or consider switching opioids if pain is not controlled.

D. Provide information on inappropriate medication combinations

- Educate patients to avoid combining opioids with other medications such as benzodiazepines, sedatives (i.e. hypnotics, anxiolytics) and CNS depressants, including alcohol.

E. Provide information on the risks and management of opioid overdose, dependence and addiction

- Inform patients of the risks of taking opioid analgesics.
- Remind them to take the opioids as prescribed, and not more frequently or in greater quantities.
- Inform patients about the pre-hospital care for opioid overdose found in Table 1.

Table 1: Pre-Hospital Care for Opioid Overdose

Determine Stage	Call 995?	Management
1. "Drowsy"	No	Continue to observe patient. If there is no improvement or if respiratory rate / mental status worsens, proceed to Stage 2 or 3.
2. "Nodding Off"	Yes	Initiate **SAVE** protocol.
3. Unresponsive	Yes	Initiate **SAVE** protocol.

- **SAVE** Protocol
  - **S**timulate patient with painful or verbal stimuli and check for responsiveness.
  - **A**irway control is the priority. If there is no pulse, initiate CPR and apply AED pads. If heart rate is adequate but RR is inadequate, initiate rescue breathing and tilt chin up to open airways.
  - **V**entilate patient using bag-valve mask, if available, by bagging 1 breath every 5 seconds until the patient is breathing on his own.
  - **E**valuate patient. If there is no response after rescue breathing for 2 minutes, continue to bag or mask breathing, combined with calling 995.

F. Provide information on opioid storage and disposal[17].

- Educate patients of the need for proper disposal of opioids when the pain has resolved to prevent non-medical use of the medications.
- Encourage patients to return any unused opioids to a licensed pharmacy or the clinic where the opioid was dispensed.

[17] New York City Emergency Department Discharge Opioid Prescribing Guidelines. The New York City Department of Health and Mental Hygiene.

SECTION 2: OPIOID THERAPY FOR ACUTE PAIN

2.1 Definition

Acute pain is defined as pain that normally fades with healing, is related to tissue damage, and significantly alters a patient's typical function.[18] Acute pain is expected to resolve within days to weeks; pain present at or after 12 weeks is considered chronic and should be treated accordingly.

Although the number of opioid doses taken during acute pain episodes and leading to an increased risk of dependence or subsequent misuse is unknown, a recent observational study using a large commercial database suggests that even a few days of opioid use for acute pain can increase this risk.[19] The risk of being on opioids at the one-year mark increases by about one percent for each day of opioid supplied, starting from a three-days' supply of an initial prescription.

Disclaimer: The guidelines in this section excludes patients under active cancer treatment and palliative care. This section covers acute pain management for both inpatient and outpatient settings, including at the ED. Where deviation from these guidelines is necessary, in particular for intra-operative and immediate post-surgery acute pain treatments, as determined by the anaesthetist and surgical personnel, it is imperative that the threats of opioid misuse, and overdose be considered prior to initiating opioid treatment in these situations.

2.2 Opioid Therapy for Acute Pain

Acute pain in many cases may be successfully managed with non-pharmacological treatments and/or non-opioid medications. Opioid therapy should only be considered for patients with moderate to severe acute pain if the pain is not responding to standard non-pharmacologic or non-opioid treatments, or if the pain is not expected to respond to non-pharmacologic and/or non-opioid treatments alone.[20] If the use of an opioid is warranted, medical practitioners should:

1. Refer to the subsequent sections on "Considerations Prior to the Initiation of Opioid Therapy" and "Treatment Algorithm for Acute Pain";
2. Assess patients to determine expected recovery time based on clinical evaluation, literature, medical practitioners' experience and patients' condition;
3. Prescribe opioids in combination with other non-opioid treatments, if appropriate[21];
4. Prescribe the lowest effective dose of short-acting opioids;
5. Avoid initiating therapy with long-acting or extended-release opioids[22];

[18] Indiana Hospital Association, Indiana State Medical Association, Indiana State Department of Health. Indiana Guidelines for the Management of Acute Pain. 2018.

[19] Postsurgical prescriptions for opioid naive patients and association with overdose and misuse: retrospective cohort study. Brat GA, Agniel D, Beam A, Yorkgitis B, Bicket M, Homer M, Fox KP, Knecht DB, McMahill-Walraven CN, Palmer N, Kohane I. BMJ. 2018;360:j5790. Epub 2018 Jan 17.

[20] Arizona Opioid Prescribing Guidelines. Arizona Dept. of Health Services, 2018.

[21] Dental Guideline on Prescribing Opioids for Acute Pain Management. Developed by Dr Robert Bree Collaborative and Washington State Agency Medical Directors' Group Sep 2017.

[22] New York City Emergency Department Discharge Opioid Prescribing Guidelines. The New York City Department of Health and Mental Hygiene.

6. Prescribe and dispense a quantity of opioids no greater than that required for the expected duration of pain, which should be of sufficient severity to justify opioid use[23,24]; and
7. Advise patients on the safe storage and disposal of opioids.

2.3 Considerations Prior to the Initiation of Opioid Therapy

Medical practitioners initiating opioid therapy for acute pain should consider whether the potential benefits of opioid therapy would outweigh its potential risks, by considering the following factors:

- Concomitant drugs and substance use (e.g. benzodiazepines, other opioids, recreational drugs, alcohol, etc.);
- Co-morbidities:
  - (A) Central nervous system – Delirium, dementia, psychiatric co-morbidities
  - (B) Respiratory system – Respiratory insufficiency, known or suspected obstructive sleep apnoea ("OSA")
  - (C) Organ impairment – Chronic liver and renal diseases which may affect metabolism and excretion of opioids; and
- Occupational factors (e.g. requirements for safe driving, and work such as operating machinery, handling hazardous materials, etc.).

In addition, medical practitioners initiating opioid therapy for acute pain should consider the following, where applicable:

(A) Persistent Acute Pain[25]

When presented with challenging acute pain management scenarios (e.g. prolonged severe pain, recurrent episodes of severe acute pain, or in cases with background of chronic pain), medical practitioners should first address exacerbations of chronic or recurrent pain conditions with non-opioid analgesics, non-pharmacological treatments, and/or referral to specialists for follow-up, all as clinically appropriate, before initiating opioid therapy.

If the patient is suspected to be a substance abuser or addict, or presents with any of the factors listed below, the medical practitioner should consider referring the patient to an appropriate specialist (e.g. pain specialist, substance abuse specialist):

- Not meeting the goals of treatment despite escalating doses of controlled substances for pain;
- At high-risk for substance misuse, abuse, diversion, addiction, or overdose as determined by the patient's history;
- Seeing multiple medical practitioners for controlled medications; or
- Prescribed with 2 or more controlled substances.

[23] CDC Guideline for Prescribing Opioids for Chronic Pain.
[24] Arizona Opioid Prescribing Guidelines. Arizona Dept. of Health Services, 2018.
[25] Rule Governing the Prescribing of Opioids for Pain. Vermont Department of Health 2017.

(B) Acute Exacerbations of Chronic Pain[26]

Patients with chronic pain who require opioid analgesics for acute exacerbations should obtain opioid prescriptions from their primary medical practitioner who monitors their pain relief and function. In ad-hoc cases requiring short-acting opioid analgesics, medical practitioners should coordinate opioid therapy with the primary medical practitioner treating the patient's chronic pain.

Note: Prescribing, and particularly initiating, sustained-release or long-acting opioid analgesics from the ED for chronic pain is a form of unmonitored opioid therapy that is not optimal for patient care. Similarly, changing the opioid patients use for their chronic pain relief (e.g. opioid rotation) is complicated and should not be done in the ED.

2.4 Treatment Algorithm for Acute Pain

1. Assessment of Acute Pain
   - Aetiology and nature of pain
   - Appropriate diagnostics
   - Medication history, including past, and current opioid use (including both therapeutic and illegal use)

2. Treatment Based on Pain Rating for Acute Pain

   The recommended opioid doses and frequency listed below only serve as a guide and medical practitioners may exercise discretion as the situation requires. The recommended opioid doses suggested in Table 2 are for **oral formulations**.

Table 2. Recommended Opioid Doses for Acute Pain

Pain Rating for Acute Pain	Possible Scenarios	Treatment Options
Mild	Headaches, soft tissue injuries (e.g. sprains) and minor surgical procedures.	• Treat with non-opioid analgesics, e.g. paracetamol, NSAIDs, anti-neuropathic medications (anti-convulsants, TCAs, SNRIs). • Consider physical therapy, e.g. ice, physiotherapy exercises. • Consider psychological therapy, e.g. relaxation exercises, cognitive behavioural therapy. • Consider interventional treatment. • Reassure patient and provide education, e.g. expected pain duration and warning signs that require immediate medical attention. • Follow-up with primary care medical practitioner and/or referral to specialist.

[26] New York City Emergency Department Discharge Opioid Prescribing Guidelines. The New York City Department of Health and Mental Hygiene.

Moderate	After laparoscopic and minimally invasive surgery, most soft tissue surgery, and non-comminute fractures.	• Provide scheduled non-opioid analgesics if appropriate. • Provide a prescription of short-acting opioids for 3- to 5-days duration*. The recommended opioid doses (oral formulation) are: o Morphine syrup: 5 mg, 3 – 4 times per day; o Oxycodone: 5 mg, 3 – 4 times per day; and o Tramadol: 50 mg, 3 – 4 times per day^. • Doses / dosing frequency should be reduced for the elderly and for other high-risk patients. • If pain is expected to persist beyond 5 days, a prescription for up to 14-days duration can be given, but an early review and re-evaluation should be planned#.
Severe	After major open abdominal and thoracic surgeries, major fractures and trauma, and orthopaedic joint replacements.	• Provide scheduled non-opioid analgesics if appropriate. • Provide a prescription of short-acting opioids for up to 7-days duration*. The recommended opioid doses (oral formulation) are: o Morphine syrup: 5-10 mg, 3 – 6 times per day; o Oxycodone: 5 mg, 3 – 6 times per day; and o Tramadol: 50-100 mg, 3 – 4 times per day^. • Doses / dosing frequency should be reduced for the elderly and for other high-risk patients. • If pain is expected to persist beyond 7 days, a prescription for up to 14-days duration can be given, but an early review and re-evaluation should be planned#.

** From point of admission or surgery/trauma.*

^ Tramadol is an atypical opioid.

 # There may be instances where pain in acute conditions (e.g. rib fractures, long bone fractures, postoperative pain) is expected to last beyond 3-5 days.

3. Additional Considerations When Initiating Opioid Therapy for Acute Pain
   - Maximize the use of appropriate non-opioid treatments first.
   - Exercise caution in the use of opioids in the elderly and other high-risk populations.
   - Apply the principle of starting low and going slow.
   - Always use the lowest effective dose for the shortest possible duration.
   - Educate patient on the opioids' risks and benefits.
   - Monitor for opioid side effects.

2.5 Types of Opioids Used in Acute Pain

The opioid doses for oral and parenteral administration listed in Tables 3 and 4 respectively only serve as a guide, and medical practitioners may exercise discretion as the situation requires. Please note that opioid therapy should be used with caution (with doses adjusted as appropriate) in elderly patients and patients with renal and hepatic impairment.

Table 3. Recommended Opioid Doses for Oral Administration

Opioid	Formulation	Clinical Use	Dose		Caution
Per Oral			**Initiation**	**Maximum**	
Codeine phosphate 8 mg + Paracetamol 500 mg (eg. Panadeine)	Tablet	Mild to moderate pain	1-2 tabs Q4-6H PRN	Limited by maximum daily dose of paracetamol (3-4g/day)	• Remind patients not to combine with other paracetamol containing drugs. • Use with caution in hepatic impairment (max 4 tabs/day for short-term use)
Codeine phosphate 30 mg	Tablet	Moderate to severe pain	15-60 mg Q4-6H PRN	360 mg/day	• Lower dose required for patients with renal or hepatic impairment and/or older patients • This is a pro-drug of morphine and its use should be similar to immediate-release morphine.
Tramadol	Capsule or Tablet	Moderate to severe pain	25-50 mg Q4-6H PRN	• 400 mg/day; • 300 mg/day (Older patients); • 200 mg (Renal impairment); 100 mg (Severe liver impairment)	• Caution in patients with history of seizures. • Lower dose may be required for patients with renal or hepatic impairment and/or older patients
Tramadol 37.5 mg + Paracetamol 325 mg (eg. Ultracet)	Tablet	Moderate to severe pain	1-2 tabs Q4-6H PRN	• 8 tabs per day • In severe renal impairment (i.e. CrCl < 30ml/min) - max 2 tabs Q12H	• Caution in patients with history of seizures. • Remind patients not to combine with other paracetamol containing drugs. • Lower dose may be required in patients with severe liver impairment.

Tramadol 75 mg + Dexketoprofen 25 mg (eg. Skudexa)	Tablet	Moderate to severe pain	1 tab Q8H PRN	• 3 tabs per day	• Caution in patients with history of seizures. • Avoid in patients with contraindications to use of NSAIDs. • Avoid in severe liver / renal impairment.
Morphine	Immediate release (IR) solution	Moderate to severe pain	2.5-5 mg Q4-6H PRN	Titrate to effect	• Lower dose/frequency required for older patients or those with renal/ hepatic impairment. • If patient is already on regular weak opioids (e.g. codeine, tramadol), use opioid conversion table to determine morphine dose.
	Sustained release (SR) Tablet	Moderate to severe pain	Not to start in opioid naïve patients	Titrate based on morphine syrup requirements	Not recommended for use in acute pain.
Oxycodone	Immediate release (IR) Capsule, Solution (1 mg/ml)	Moderate to severe pain	<u>Capsule</u> 5 mg Q4-6H PRN <u>Solution</u> 2-5 mg Q4-6H PRN	Titrate to effect	Lower dose/frequency required for older patients or those with renal/ hepatic impairment
	Sustained release (SR) Tablet	Moderate to severe pain	Not to start in opioid naïve patients	Titrate based on oxycodone requirements	Not recommended for use in acute pain.

Table 4. Recommended Opioid Doses and Frequency for Parenteral Administration

Opioid	Route	Clinical Use	Dose		Caution
Parenteral			**Initiation**	**Maximum**	
Fentanyl (100 mcg/2ml ampoule)	IV	Moderate to severe pain	Bolus: 10-20 mcg every 10-15 min	1-2 mcg/kg	• IV preparations recommended for use in patients with severe acute pain, and only when processes are in place to ensure regular monitoring of patient • Fentanyl is the opioid of choice if patients with moderate to severe renal and liver impairment
	SC/ IM	Moderate to severe pain	25 mcg Q2H PRN	Up to 100 mcg per dose	
Morphine/ Oxycodone	IV	Moderate to severe pain	1-2 mg every 10-15 min	0.1-0.2 mg/kg	
	SC/IM	Moderate to severe pain	2.5-5 mg Q4-6H PRN	Up to 10 mg per dose	
Pethidine^	SC/IM	Moderate to severe pain	25-100 mg Q4H PRN	Up to 400 mg per day	• Caution in patients with renal impairment and history of seizures. • Use should be limited to 48 hours or less in view of potential neurotoxicity.
Tramadol	IM/IV	Moderate to severe pain	25-50 mg Q4-6H PRN	Up to 100 mg per dose, and up to 400 mg per day	Caution in patients with history of seizures.

^Pethidine is more lipid soluble than morphine, hence there is a more rapid onset of central nervous system effects that increases its abuse potential. The predominant metabolite, norpethidine, is potentially toxic, causing central nervous system excitability such as tremors, myoclonus or seizures.[27] Norpethidine is excreted in the urine and has a terminal half-life of 15 to 20 hours, which can increase in renal failure to as long as 40 hours.[28]

The American College of Surgeons describes pethidine as a suboptimal analgesic and specifically cautions against its use in the elderly. Major national healthcare organisations such as the Centers for Medicare and Medicaid Services, Joint Commission on Accreditation of Health Care Organisations, and Agency for Health Care Policy and Research discourage the use of pethidine in older patients. [29] Studies have also shown that pethidine is no more efficacious in treating biliary or renal tract spasm than comparative mu opioids.[30]

Due to pethidine's poor efficacy, toxicity, and multiple drug interactions, there has been a movement to replace pethidine with more efficacious and less toxic opioid analgesics, such as subcutaneous morphine or subcutaneous fentanyl.[30]

[27] A comparison of the efficacy and safety of morphine and pethidine as analgesia for suspected renal colic in the emergency setting. BMJ Journals.
[28] Accumulation of norpethidine, an active metabolite of meperidine, in patients with renal failure or cancer. Annals of Internal Medicine.
[29] Prevalence of Meperidine Use in Older Surgical Patients. JAMA Surgery.
[30] Meperidine: a critical review. American Journal of Therapeutics.

KEY POINTS

1) Opioid therapy should not be initiated as the first-line treatment for acute pain. Opioid therapy should only be considered for patients with moderate to severe acute pain if the pain is not responding, or not expected to respond to non-opioid treatment.
2) When considering opioid therapy for acute pain, start with the lowest effective dose, and for the shortest possible duration.
3) Initiate opioid therapy for acute pain with short-acting opioids, and not with long-acting opioids.
4) Before initiating opioid therapy, medical practitioners should identify risk factors for opioid abuse and addiction, and screen for use of opioids, benzodiazepines, sedative-hypnotics, and anxiolytics.
5) Exercise caution when initiating opioid therapy in the elderly and other high-risk populations (e.g. obese patients, patients with obstructive sleep apnoea).

SECTION 3: OPIOID THERAPY FOR CHRONIC NON-CANCER PAIN

3.1 Definition

Chronic non-cancer pain ("CNCP") is defined as pain that lasts for a duration of 12 weeks or more, or that persists beyond the period of tissue healing. The prevalence of CNCP in Singapore is at least 8.7% and is more commonly reported in women and older adults. CNCP has a substantial psycho-socio-economic impact on the affected individuals and their families.

Disclaimer: The guidelines in this section exclude patients under active cancer treatment and palliative care. This section covers CNCP management for both inpatient and outpatient settings, including at the ED. Where deviation from these guidelines is necessary, it is imperative that the threats of opioid misuse, and overdose be considered prior to initiating opioid treatment in these situations.

3.2 Opioid Therapy for Chronic Non-Cancer Pain

The limited data from the US and Singapore indicates that approximately 3% of adults receive long-term opioids for CNCP. [31,32]

Opioids should not be recommended as the drug of choice for the management of CNCP. While there is a moderate level of evidence justifying the benefits of short-term administration of opioids in a select group of CNCP conditions, there are risks that should be considered. The level of evidence for long-term opioids use in CNCP is weak and its effectiveness is less established.

When all other options have proven ineffective on their own for CNCP, the addition of opioids may be considered as part of the multi-modal management to improve or maintain patient function and quality of life.

The medical practitioner should consider ceasing opioid therapy if functional outcomes have not been achieved, quality of life has not improved, or when there are grounds for suspect of abuse of opioids.

3.3 Treatment Algorithm for Chronic Non-Cancer Pain

The stepwise approach to initiating opioid therapy in CNCP is described in Table 5.

Medical practitioners who wish to prescribe long-term (more than 4 weeks of 100 mg morphine equivalent daily dose) strong opioids for CNCP should have received training in pain management or treated patients in conjunction with pain medicine physicians or equivalent.

[31] Boudreau D, Von Korff M, Rutter CM, et al. Trends in long-term opioid therapy for chronic non-cancer pain. Pharmacoepidemiol Drug Saf 2009; 18: 1166-75.
[32] George JM, Menon M, Gupta P, Tan MGE. Use of strong opioids for chronic non-cancer pain: a retrospective analysis at a pain centre in Singapore. Singapore Med J 2013; 54(9): 506-510 doi:10.11622/smedj.2013173.

Table 5: Stepwise Approach to Initiating Opioid Therapy in CNCP

Initial Evaluation	• Conduct a thorough evaluation with detailed medical history, physical examination, and appropriate laboratory studies. This should include the nature and intensity of pain, current and previous pain treatment, effect of pain on physical and psychosocial function and history of substance abuse. • Assess the risk of substance abuse, misuse and addiction where appropriate, using screening tools such as SOAPP-R, ORT and DIRE. • Develop a complete and consistent diagnosis.
Informed Discussion	• Discuss and document goals, expectations, risks, benefits and alternatives to opioid therapy for CNCP. Goals should include pain reduction and improved function, as a pain-free state is likely an unreasonable goal. This functional goal varies from one patient to another while returning to work may be a reasonable goal for some patients, the ability to perform more activities of daily living may be a more reasonable goal for others. • Discussion should include the patient's responsibilities, as well as the patient's agreement to provide random urine samples for monitoring.
Initiation	• Initiate strong opioid therapy for a duration exceeding 2 weeks in consult with medical practitioner in the relevant area of speciality or as part of a dedicated multi-disciplinary pain management team, depending on the pain type. • Choose an opioid and its initial dose and titrate based on individual patient's medical condition(s). A short-term trial of opioids lasting from 4 to 8 weeks is recommended. A decision to proceed with long-term therapy should be based on the outcome of the trial (e.g. efficacy, side effects, goal attainment, etc.) • Continue treatment aimed at the specific underlying disease whenever possible. Other pain medications (e.g. partially effective NSAIDS, antidepressants, anti-seizure agents) should be continued as indicated.
Monitoring and continuation	• Monitor patients at a frequency of at least once every 3 to 4 months if they are on stable doses of opioids and are at low risk for adverse outcomes. • Monitor patients at a higher frequency after initiation of therapy, if there are changes in opioid doses and if patients are at higher risk of adverse outcomes (e.g. older adults, patients with comorbidities or risk of aberrant drug-related behaviours, and patients in occupations demanding mental acuity). • Continuation of strong opioids should be done in consultation with a pain specialist, or as part of a dedicated multi-disciplinary pain management team. Where logistically possible, yearly review with a

pain specialist or multidisciplinary pain management team should be considered

- Ideally, a single medical practitioner should be responsible for the continuation of strong opioids. Where a single prescriber is not available, a member of the same multi-disciplinary team should be engaged.

Additional Monitoring for Abuse[33]

- Pill counts, family member or caregiver interviews, and use of NEHR data can be useful supplements.
- Periodic urine drug screening is recommended in high-risk patients for diversion, where drug transfer for illicit distribution or use is suspected.

Monitor for signs of:

- Borrowing or stealing of drugs.
- Repeatedly seeking drugs from other providers or emergency departments via doctor-hopping, forging prescriptions or reporting multiple episodes of loss or theft of prescription drugs.
- Requests for specific drugs, especially a preference for immediate-release over sustained-release medications, not following prescribed dose and schedule, multiple unauthorised dose increases or pushing for higher dose of opioids.
- Non-compliance with non-pharmacological components of pain treatment (e.g. physiotherapy, psychological therapy).
- Showing up only for medication appointments (e.g. misses, cancels, or no-shows at other appointments).
- Concurrent use of illicit drugs (e.g. heroin, cocaine, methamphetamine, marijuana, others), alcohol or tobacco.
- Past history of abuse of prescription medications or illicit drugs.
- Positive urine drug test for illicit drugs or unauthorised drugs.
- Appearing intoxicated.
- Deterioration of function at work, in the family or socially.

Reporting Requirements for Suspected Drug Addicts

- Under Regulation 19 of the Misuse of Drugs Regulations, medical practitioners are required to report suspected drug addicts within 7 days from the date of attendance to Director, Central Narcotics Bureau and the Director of Medical Services, Ministry of Health, through eNOTIF (http://www.enotif.cnb.gov.sg/ENotif).[34]

[33] Ho KY, Chua NHL, George JM, et al. Evidence-Based Guidelines on the Use of Opioids in Chronic Non-Cancer Pain—A Consensus Statement by the Pain Association of Singapore Task Force. Ann Acad Med Singapore 2013;42:138-52.

[34] MH 78:09/10 NOTIFICATION OF SUSPECTED DRUG ADDICTS VIA eNOTIF ONLY (CIRCULAR DATED 09 FEB 2021)

Discontinuation	Opioids should be discontinued when the patient: • Exhibits serious or repeated aberrant drug-related behaviours or drug diversion. • Experiences intolerable adverse effects. • Makes no progress towards meeting therapeutic goals, e.g. taking more than 200 mg morphine or its equivalent per day without any significant pain relief. Method of Opioid Discontinuation • A weekly 10% reduction in dose is generally well tolerated without symptoms of opioid withdrawal in the outpatient setting, in patients without severe medical or psychiatric comorbidities. • In complex cases, detoxification in a rehabilitation setting can be helpful, especially for patients who are unable to reduce their opioid dose in a less structured setting. • Addiction treatment resources should be made available if the aberrant behaviours are related to addiction.

3.4 Types of Opioids Used in Chronic Non-Cancer Pain

The dosing of opioids for oral, transdermal and parenteral administration listed in Tables 6, 7 and 8 respectively only serve as a guide, and medical practitioners may exercise discretion as the situation requires. Please note that opioids should be used with caution (with dosages adjusted as appropriate) in elderly patients and patients with renal and hepatic impairment.

Table 6. Recommended Opioid Doses for Oral Administration

Opioid	Formulation	Clinical Use	Dose		Caution
Per Oral			**Initiation**	**Maximum**	
Codeine phosphate	Tablet	For initiation, breakthrough and maintenance	15-30 mg Q4-6H	Up to 360 mg/day	• Low dose required for patients with renal or hepatic impairment and/or older patients • This is a pro-drug of morphine and its use should be similar to immediate-release morphine. In selected and appropriate cases, maintenance may be considered.

Codeine 8 mg + Paracetamol 500 mg	Tablet	For initiation, breakthrough and maintenance	1-2 tabs TDS-QDS	Max daily dose limited to 3-4 g of paracetamol per day	• Remind patients not to combine with other paracetamol containing drugs. • Use with caution in hepatic impairment (max 4 tabs/day for short-term use)
Tramadol	Tablet	For initiation, breakthrough and maintenance	25-50 mg Q4-6H	• 400 mg/day; • 300 mg/day (Older patients); • 200 mg (Renal impairment); • 100 mg (Liver impairment)	• Caution in patients with history of seizures. • Lower dose may be required for patients with renal or hepatic impairment and/or older patients
Morphine	Immediate release (IR) solution^	For breakthrough pain only	2.5 - 5 mg Q4-6H	Up to 20 mg Q4H	• Lower dose/frequency required for older patients or those with renal/ hepatic impairment. • Initiate with IR opioids before converting to SR tablets. • To consider conversion to SR formulations if required beyond 7 days and to keep IR for breakthrough only. • If patient is already on regular weak opioids (e.g. codeine, tramadol), use opioid conversion table (Appendix A) to determine morphine dose.
	Sustained release (SR) tablet	For maintenance only	Dose depends on daily dose of previous opioid analgesic	Dose depends on daily dose of previous opioid analgesic; SR tablet to be given Q12H.	

Tapentadol	Sustained release (SR) tablet (Note: No immediate release formulation in Singapore)	For maintenance only	50 mg Q12H	• Up to 500 mg/day • Max 100 mg/day in moderate liver impairment.	• Avoid in severe renal /liver impairment.
Methadone	Tablet	For maintenance only	2.5 mg Q8H	Up to 100 mg/day	• Initiate at lower doses and titrate slowly in renal and liver impairment.
Hydromorphone controlled release	Tablet	For maintenance only	8 mg Q24H	Up to 64 mg/day	• In renal and liver impairment, to initiate with lower dose and titrate slowly.
Oxycodone	Immediate release (IR) tablets	For breakthrough pain only	2.5-5 mg Q6H	Up to 30 mg Q4H	• Lower dose/frequency required for older patients or those with renal/ hepatic • Initiate with immediate release opioids before converting to oxycodone SR tablets. • To consider conversion to SR formulations if required beyond 7 days and to keep IR for breakthrough only.
	Sustained release (SR) tablets	For maintenance only	Dose depends on daily dose of previous opioid analgesic	Up to 160 mg/day	
Oxycodone/ Naloxone	Tablet	For maintenance only	Oxycodone HCl 10 mg / Naloxone HCl 5 mg Q12H	Up to oxycodone HCl 160 mg/ naloxone HCl 80 mg per day	• In renal and liver impairment, initiate at lower doses and titrate cautiously. • Avoid in severe renal and liver impairment.

Table 7. Recommended Opioid Doses for Transdermal Administration

Opioid Transdermal	Formulation	Clinical Use	Dose		Caution
			Initiation	Maximum	
Buprenorphine	Transdermal patch	For maintenance only	5 mcg/ hour once every 7 days	Up to 20 mcg/hour	Nil
Fentanyl	Transdermal patch	For maintenance only	Dose depends on daily dose of previous opioid analgesic	Patches to be applied Q72H; no optimal or maximum dose	• Lag time of 8-12 hours for analgesia after starting/removal of patch. • Should not be started in an opioid-naïve patient. • Initiate with immediate release opioids before converting to transdermal patch. • Opioid of choice in patients with moderate to severe renal and liver impairment.

Table 8. Recommended Opioid Doses for Parenteral Administration

Opioid Parenteral	Route	Clinical Use	Dose		Caution
			Initiation	Maximum	
Morphine*	IV	For breakthrough pain only.	2.5 mg Q4H	Up to 10 mg/70kg body weight	• IV preparations recommended for use only when processes are in place to ensure regular monitoring of patient
	SC/IM		2.5 – 5 mg Q4-6H PRN	Up to 10 mg per dose	
Fentanyl*	IV		Bolus: 25 mcg Q1-2H	Up to 100 mcg/dose Q1-2H PRN	• Fentanyl is the opioid of choice if patients with moderate to severe renal and liver impairment
Oxycodone*	IV		1 mg Q4H	Up to 15 mg bolus dose, not more frequently than Q4H	• Increased risk of respiratory depression for oxycodone
Tramadol (50 mg/1ml) ampoule	IM/IV	For breakthrough pain only	25- 50 mg Q4-6H PRN	Up to 100 mg per dose, and up to 400 mg per day	• Caution in patients with history of seizures for tramadol

** Note: Not recommended to be used as a sole opioid agent for more than 7 days. Prolonged use for more than 7 days should only be considered for breakthrough pain when patient is already on maintenance opioid use.*

KEY POINTS

1) Chronic non-cancer pain is common and often affects activities and functions of those affected. Goal of treatment should focus on return to function and not just relief of symptoms.
2) A wide variety of treatment options are available for the management of chronic non-cancer pain. Opioids, especially long-term use of strong opioids, should not be prescribed as a first-line treatment due to its potential side effects and risk of misuse.
3) Initiation of strong opioids, especially when patients have multiple presentations, should be done together with a dedicated multi-disciplinary pain management team, preferably with the inclusion of a pain specialist.
4) A thorough evaluation, including an assessment for risk of opioids, should be done before the initiation of strong opioids. It is recommended that the prescriber clearly documents the roles and responsibilities of both patient and the prescriber.
5) Patients with chronic non-cancer pain receiving strong opioids should be reviewed at a frequency of once every 3 to 4 months if the opioid dose is stable, and more frequently if the titration of opioids are required.

SECTION 4: OPIOID THERAPY FOR PATIENTS WITH CANCER AND/OR LIFE-LIMITING DISEASES WHO ARE APPROACHING THE END OF LIFE

4.1 Introduction

Patients with cancer and/or life-limiting diseases often suffer from distressing symptoms, with pain being one of the most common symptoms. Prevalence of pain in cancer ranges from 32% to 93.5%[35] while in non-cancer life-limiting disease, it ranges from 11% to 85%[36]. Symptom control is the cornerstone of good care for patients with cancer and life-limiting diseases who are approaching the end of life, and opioids are an important option in the treatment armamentarium for pain and dyspnoea in these patients. Opioids, when used appropriately, will improve the patient's quality of life without causing significant harm. On the other hand, inappropriate use of opioids may cause more harm due to their adverse effects and potential for misuse, abuse and overdose.

Disclaimer: The guidelines in this section exclude patients in cancer remission. This section covers pain management for both inpatient and outpatient settings, including at the ED. Where deviation from these guidelines is necessary (based on clinical data, including the patient's needs and pre-existing medical conditions), it is imperative that the threats of opioid misuse, and overdose be considered prior to initiating opioid treatment in these situations.

4.2 Definitions

Cancer Pain

Cancer pain is defined as pain caused by the cancer itself or cancer-related treatment or tests. It can be due to the primary tumour, cancer therapies and/or diagnostic procedures.[37]

Pain in Life-Limiting Diseases

Pain in life-limiting diseases is defined as pain related to the underlying advanced diseases. For example, recurrent angina in patients with end-stage heart disease. The pain may also be due to other co-morbidities. For example, lower back pain from osteoporotic vertebral fracture in patients with end-stage chronic obstructive pulmonary disease.

For patients with life-limiting non-cancer conditions not approaching the end of life, but suffer from pain which may be amenable to opioids, please see the section on "Prescribing of Opioids for Chronic Non-Cancer Pain". A different approach is taken for patients approaching the end of life given the disparate therapeutic goals. For pain at the end of life, the primary treatment goal is to maintain an acceptable quality of life.[38] For pain not at the end of life, the primary treatment goal is to improve or maintain the patient's function.

Patients Who are Approaching the End of Life

[35] Marieke H.J. van den Beuken-van Everdingen et al., 'Update on prevalence of pain in patients with cancer: systematic review and meta-analysis', Journal of Pain and Symptom Manage, 51, no.6 (2016), pp.1070-1090.

[36] Katrien Moens, Irene J. Higginson and Richard Harding, 'Are there differences in the prevalence of palliative care-related problems in people living with advanced cancer and eight non-cancer conditions? A systematic review'. Journal of Pain and Symptom Manage, 48, no.4 (2014), pp.660-677.

[37] American Cancer Society, 'Facts about Cancer Pain', https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/pain/facts-about-cancer-pain.html

[38] World Health Organization, 'WHO Guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents', 2019.

For the purpose of this guideline, people who are "approaching the end of life" are those who are likely to die within one year.[39] They include those who have the following:

1) Advanced, progressive, incurable conditions; and
2) General frailty and co-existing conditions.

Please refer to Appendix B for prognostic indicators guidance.[40]

4.3 Opioid Therapy for Cancer Pain and Pain in Life-Limiting Diseases, in Patients Approaching the End of Life

Evaluation

All patients approaching the end of life with cancer and/or life-limiting disease should be assessed for the presence of pain, dyspnoea and other discomfort. The cause of the symptoms should be determined through comprehensive clinical assessment and information gathered from electronic data and/or handoff documents from other healthcare professionals.

Management of Underlying Cause

After identifying the likely cause for pain, dyspnoea or other symptoms, disease-directed treatment should be considered for potentially reversible conditions. In the case of dyspnoea seen in advanced pulmonary and heart disease, identifying the cause and optimising disease-modifying treatment are key approaches[41,42]. If required, opioid therapy can be initiated concurrently to provide symptom relief. When the symptom has improved, one should review the need to continue with opioid therapy.

The burden of disease-directed treatment should be weighed against its benefits and assessed if it is in line with the patient's goals of care, taking into consideration their preference and quality of life. For example, bacterial pneumonia as a precipitating cause for worsening breathlessness in a patient with chronic obstructive pulmonary disease can be treated with appropriate antibiotics with minimal treatment burden. On the other hand, surgery to relieve gastrointestinal obstruction from colorectal cancer, may be deemed too invasive for a patient is approaching the end of life, even if the surgery can reduce abdominal pain. In a situation where the cause is no longer reversible or the disease-directed treatment cannot be optimised further, focus should then be shifted to symptom control.

4.4 Initiating Opioid Therapy for Pain in Cancer and Life-Limiting Diseases in Patients Approaching the End of Life

Assessment

[39] General Medical Council, UK, 'Treatment and care towards the end of life: good practice in decision making', 2010.
[40] Royal College of General Practitioners, 'The GSF Prognostic Indicator Guidance', 2011.
[41] M. Fallon et al., 'Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines', Annals of Oncology, 29, supplement 4 (2018), pp.iv149-iv174.
[42] Healthcare Improvement Scotland, 'Scottish Palliative Care Guidelines', 2020.

The medical practitioner should conduct a comprehensive clinical assessment of pain, including obtaining details about the following:

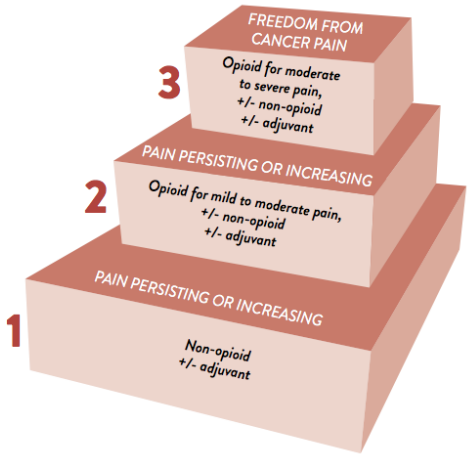
- Onset, frequency, duration, characteristic, intensity of the pain, and aggravating and relieving factors;
- How it impairs one's activities of daily living;
- Psychological concerns;
- Psychiatric history; and
- History of previous analgesia use and substance use.

Management of Cancer Pain and Pain in Life-limiting Diseases in Patients Approaching the End of Life

There is emerging evidence of efficacy for non-pharmacological treatment options for cancer pain and pain in life-limiting diseases in patients approaching the end of life. The experience of pain has multiple contributors and transcends the biomedical dimension to include psychosocial and other issues. Hence cancer pain and pain in life-limiting diseases in patients approaching the end of life is best managed with multiple strategies involving non-pharmacological and pharmacological interventions. Non-pharmacological interventions may include reassurance and offering comfort, physical therapy, and other complementary therapies.

Figure 1: WHO's Pain Ladder

Pharmacological management should be guided by the WHO sequential three-step analgesic ladder (Figure 1)[38]. The ladder provides a framework for prescribing analgesia. In addition, there are other modalities of treatment available for cancer pain including radiotherapy, bisphosphonates for bone pain41 and others. These therapeutic options can be used alone or in conjunction with analgesia.



Although most of the guidelines referenced (in footnotes) refer to opioid therapy in cancer pain, a similar approach has been widely used for pain management in life-limiting non-cancer diseases.

Recommended Opioid Doses and Route of Administration

- For mild to moderate pain or pain not relieved by Step I of WHO's Pain Ladder, consider weak opioids (codeine, tramadol). It can be prescribed together with non-opioid analgesics.

- For moderate to severe pain or pain not relieved by Step 2 of WHO's Pain Ladder, discontinue weak opioids and consider starting strong opioids (e.g. morphine, fentanyl, oxycodone).
- When deciding on the most suitable opioid, consider patient's ability to take medication orally, and their renal and hepatic functions.[43]
- Morphine is recommended because it is easily available and there is wide experience with its use.
- Fentanyl is a safer option in patients with moderate to severe renal and liver impairment.[41,44,45]
- The oral route is the preferred route of administration for opioids.[41,45]
- Oral opioids may not be suitable for patients who are unable to take oral medication, have swallowing problems or impaired gastrointestinal absorption.
- For severe pain requiring urgent relief, opioids should be titrated using the parenteral route, either subcutaneously or intravenous.[41]
- The dose of opioids should be individualised. Initiate opioids at a low dose and titrate dose up, if needed, to achieve a good balance of adequate pain relief with minimal side effects.[46]
- The dose should commensurate with the underlying disease and pain severity.

<u>Opioid Regimen</u>

- Patients with persistent pain should receive opioids on an around-the-clock ("ATC") regimen to prevent the onset of pain.[41]
- Rescue dose of immediate-release opioids should be prescribed for patients with transient exacerbation of pain (breakthrough dose).[45,46]

<u>Communication</u>

- Provide information on the indications for opioids, its effectiveness, potential side effects, treatment regimen and the importance of safe storage of the medications.
- Address any concerns and/or questions the patient or next-of-kin may have with regards to addiction, tolerance, fears and side effects.[45]
- Explain the plan for review of pain control and side effects.

<u>Maintenance of Opioids</u>

- Assess the effectiveness of opioids in pain control and the side effects encountered.

[43] Takashi Yamaguchi et al., 'Clinical Guideline for Pharmacological Management of Cancer Pain: the Japanese Society of Palliative Medicine Recommendations', *Japanese Journal of Clinical Oncology*, 43, no.9 (2013), pp.896-909.
[44] DukeNUS Medical School and Lien Centre for Palliative Care, 'SG Pall eBook', 2020.
[45] National Collaborating Centre for Cancer (UK), 'NICE Clinical Guidelines, No. 140 Opioids in palliative care: safe and effective prescribing of strong opioids for pain in palliative care of adults'.
[46] Augusto Craceni et al., 'Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations for the EAPC', *Lancet Oncology,* 13 (2012), pp.e58-68.

- If pain relief is inadequate, titrate dose up. Consider the total daily dose and rescue doses when deciding on the dose to increase.
- Consider consulting palliative specialist if pain is not controlled and/or the patient remains in severe pain after a few adjustments of medications.
- Review patient and the indication for opioid use regularly. Taper down and stop opioid if there is no more indication for opioid use.
- If indications for opioid use are still present, maintain opioid at the lowest effective dose to achieve an acceptable quality of life.[38]

Chronic Pain in Cancer Survivors

As cancer treatment advances, patients with cancer are surviving longer. Many of these cancer survivors may suffer from chronic pain, some of which are sequelae of cancer treatment. A cancer survivor is defined by the National Cancer Institute's Office of Cancer Survivorship as a person with history of cancer who is beyond the acute diagnosis and treatment phase.

Chronic pain in cancer survivors is complex and is best managed with multiple modalities including non-pharmacological and pharmacological strategies. Currently, there is limited evidence to guide the management of chronic pain in cancer survivors and many of the treatment principles follow the principles for chronic non-cancer pain. When managing chronic pain in cancer survivors, refer to the guideline portion under "Prescribing of Opioids for Chronic Non-Cancer Pain". The following are additional considerations [47]:

- Perform a comprehensive pain assessment for the cancer survivor who has pain to identify the aetiology and mechanism. Consider the possibility of recurrence, second malignancy or late effect from previous cancer treatment.
- The goals of management should include functional improvement in addition to pain reduction.
- Consider referral to other healthcare professionals to provide multidisciplinary care.
- Choices of analgesics should include non-opioid and adjuvant analgesics.
- Consider a trial of opioids after careful selection of patients who had not responded to other management and suffer from pain-related distress and/or functional impairment.
- Assess the risks and benefits if long-term opioids may be required. The risks to be considered include potential adverse effects from long-term opioid use (including but not limited to endocrinopathy, neurotoxicity, etc.) as well as risks of dependence, addiction and abuse.
- Educate patients and family about the long-term risk and benefits of opioid use.
- Taper and stop the dose if opioid use is no longer warranted.

[47] Judith A. Paice et al., 'Management of chronic pain in survivors of adult cancers: American Society of Clinical Oncology Clinical Practice Guideline', *Journal of Clinical Oncology,* 34, no.27 (2016), pp.3325-3347.

4.5 Management of Dyspnoea in Cancer and Life-Limiting Diseases in Patients Approaching the End of Life

The Regional Study of Care for the Dying[48] reported a prevalence of dyspnoea of 54% in patients dying of cancer, and 61% in patients dying of cardiac disease. Dyspnoea is a symptom which usually encompasses multiple components[49] and is often associated with anxiety. Optimal treatment of dyspnoea starts with adequate understanding and identification of these concomitant factors in order to institute appropriate measures to address these factors.

Management of Dyspnoea

Symptomatic treatment of dyspnoea in patients with cancer and life-limiting diseases approaching the end of life include non-pharmacological and pharmacological options. Non-pharmacological therapy includes, but is not limited to, using optimal breathing techniques, ensuring an airy environment, and oxygen therapy for hypoxic patients.

Among the pharmacological options for dyspnoea, opioids are the most widely studied pharmacological therapy. There is modest evidence for use of oral or parenteral opioids to relieve dyspnoea[50, 51] and there is wide clinical consensus for its use in cancer[52] and advanced heart and lung disease[53].

Considerations for the Use of Opioids for Dyspnoea in Cancer and Life-Limiting Non-Cancer Diseases, in patients approaching the end of life

- Prior to initiating opioids, a comprehensive assessment should be performed to determine the cause and aetiology of dyspnoea.
- Treat potentially reversible causes and/or optimise disease-modifying treatment.
- Consider other symptomatic treatment options via non-pharmacological and non-opioid therapies.
- The type of opioid chosen should be determined by the individual patient factors including their ability to take medication orally, and their renal and hepatic functions[43].
- When initiating opioids, morphine is recommended because it is easily available and there is wide experience with its use.
- When considering dosing, opioid-naïve patients require smaller initiation doses for dyspnoea than for pain.[41]

[48] Addington Hall J and McCarthy M. 'Dying from cancer: results of a national population-based investigation', *Palliative Medicine*, 9, no.4 (1995), pp.295–305.
[49] Arif H. Kamal et al., 'Dyspnea Review for the palliative care professionals: treatment goals and therapeutic options', *Journal of Palliative Medicine,* 15, no.1, pp.106-114.
[50] Barnes H et al., 'Opioids for the palliation of refractory breathlessness in adult with advanced disease and terminal illness', *Cochrane Database Systematic Review,* 31, 3 (2016), CD011008.
[51] Vargas-Bermudez A, Cardenal F and Porta-Sales J, 'Opioids for the management of dyspnea in cancer patients: evidence of the last 15 years – a systematic review', *Journal of Pain Palliative Care and Pharmacotherapy,* 29, no.4 (2015), pp.341-352.
[52] M. Kloke and N. Cherny, on behalf of the ESMO Guidelines Committee, 'Treatment of dyspnoea in advanced cancer patients: ESMO clinical practice guidelines', *Annals of Oncology,* 26, supplement 5 (2015), pp.v169-v173.
[53] Mark B. Parshall et al., An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med*. 2012;185(4):435-452. doi:10.1164/rccm.201111-2042ST

4.6 Types of Opioids Used in Cancer Pain and Pain in Life-Limiting Diseases in Patients Approaching the End of Life

The opioid doses for oral, transdermal and parenteral administration listed in Tables 9 -11 only serve as a guide, and medical practitioners may exercise discretion as the situation requires. Please note that opioids should be used with caution (with dosages adjusted as appropriate) in elderly patients and patients with renal and hepatic impairment.

Table 9. Recommended Opioid Doses for Oral Administration

Opioid	Formulation	Clinical Use	Dose		Caution
Per Oral			**Initiation**	**Maximum**	
Codeine phosphate 30 mg	Tablet	Moderate pain, or if pain control not achieved with paracetamol/ NSAIDs	15-30 mg up to Q4-6H	360 mg/day	• Low dose required for patients with renal or hepatic impairment and/or older patients • This is a pro-drug of morphine and its use should be similar to immediate-release morphine. In selected and appropriate cases, maintenance may be considered.
Tramadol	Tablet	Moderate pain, or if pain control not achieved with paracetamol/ NSAIDs	25-50 mg up to Q4-6H	• 400 mg/day; • 300 mg/day (Older patients); • 200 mg (Renal impairment); 100 mg (Liver impairment)	• Avoid use in severe liver impairment • Lower dose may be required for older patients or those with renal/ hepatic impairment.

Morphine	Immediate Release (IR) solution	Moderate to severe pain and/or dyspnoea	2.5-5 mg up to Q4H Frequency may be increased up to Q1H PRN for breakthrough pain	No optimal or maximal dose; Individual maximum dose limited by side effects	• Initiate with IR opioids before converting to SR tablets. To consider conversion to SR formulations if required beyond 7 days and to keep IR for breakthrough only. • Lower dose/frequency required for older patients or those with renal/ hepatic impairment. • When pain is controlled, morphine solution can be converted to SR tablets. • If patient is already on regular weak opioids (e.g. codeine, tramadol), use opioid conversion table to determine morphine dose.
	Sustained release (SR) tablet		Based on conversion from Immediate-Release solution up to Q8H		
Fentanyl	Sublingual tablet	Breakthrough pain, in opioid-tolerant patients already receiving and who are tolerant to continuous opioid therapy for underlying persistent cancer pain	Refer to table by manufacturer; Dose titrated based on individual patient response	Not to exceed 2 doses per breakthrough pain episode, up to 4 episodes/24 hours	• Not equivalent to other fentanyl products on a mcg to mcg basis. • Not recommended as first line for breakthrough cancer pain.

Oxycodone	Immediate release (IR) capsules; solution	Moderate to severe pain and/or dyspnoea	2.5-5 mg Q4-6H PRN Frequency may be increased up to Q1H PRN for breakthrough pain	No optimal or maximal dose	• Initiate with IR opioids before converting to oxycodone SR tablets • To consider conversion to SR formulations if required beyond 7 days and to keep IR for breakthrough only. • Lower dose may be required for patients with renal/ hepatic impairment.
	Sustained release (SR) tablets		Based on conversion from Immediate Release capsules/ solution up to Q8H		
Methadone	Tablet	Moderate to severe pain	2.5 mg Q8H	Up to 100 mg/day	Initiate at lower doses and titrate slowly in renal and liver impairment.
Hydro-morphone	Controlled release Tablet	Moderate to severe pain	8 mg Q24H	Up to 64 mg/day	

Table 10. Recommended Opioid Doses for Transdermal Administration

Opioid	Formulation	Clinical Use	Dose		Caution
Transdermal			Initiation	Maximum	
Fentanyl	Transdermal patch	Moderate to severe pain and/or dyspnoea; Patient who is unable to take opioids orally, and is on a stable dose of strong opioid	Based on opioid conversion table	Patches to be applied Q72H; No optimal or maximal dose	• Lag time of 8-12 hours for analgesia after starting/removal of patch. • Should not be started in an opioid-naïve patient. • Opioid of choice in patients with moderate to severe renal and liver impairment.

Table 11. Recommended Opioid Doses for Parenteral Administration

Opioid Parenteral	Route	Clinical Use	Dose		Caution
			Initiation	Maximum	
Morphine	IV / SC / IM	Severe pain and/or dyspnoea in cancer or advanced diseases where there is need for rapid titration of medication to achieve adequate symptoms control	Bolus: 1 mg Q1-2H PRN Infusion: 0.2-0.5 mg/hour	No optimal or maximal dose	• IV preparations recommended for use only when processes are in place to ensure regular monitoring of patient • Fentanyl is opioid of choice in patients with moderate to severe renal and liver impairment. • Increased risk of respiratory depression for oxycodone
Fentanyl	IV / SC		Bolus: 10 mcg Q1-2H PRN Infusion: 5-10 mcg/hour	No optimal or maximal dose	
Oxycodone	IV / SC		Bolus: 0.5 mg Q1-2H PRN Infusion: 0.2 mg/hour	No optimal or maximal dose	
Tramadol	IM/IV	Moderate to severe pain	25-50 mg Q4-6H PRN	Up to 100 mg per dose, and up to 400 mg per day	Caution in patients with history of seizures for tramadol.

4.7 Referral to Palliative Service or Other Specialists

Assessment and Review of Patients

- Patients should only be started on opioid therapy after an in-person consult with a medical practitioner who is adequately trained in the use of opioids.
- Patients taking opioids should be reviewed at appropriate intervals to strike a balance between adequate monitoring and the burden of frequent reviews.
- Home-based palliative service should be considered for patients with significant disability and have difficulty attending consult sessions.

Referral to Palliative Service or other Specialists

- If the medical practitioner has not received adequate training and/or is unfamiliar with opioids use.
- Patient with complex needs who requires a multidisciplinary team to provide holistic care.
- Patient's symptoms remain poorly controlled.
- Patient has aberrant drug seeking behaviour. In this situation, it is best to have only one medical practitioner for the opioid. Patient may require co-management with a substance abuse specialist.
- Patient's prolonged use of opioids does not commensurate with disease condition.
- Patient requires high doses of opioids.

KEY POINTS

1) Perform a comprehensive assessment to determine the aetiology of pain or dyspnoea and consider disease-directed treatment if potentially reversible conditions are in line with the patient's goals of care.
2) Pharmacological management of pain should be guided by the WHO sequential three-step analgesic ladder.
3) For patients who require strong opioids, morphine is recommended because it is easily available and there is wide experience with its use by medical practitioners. Fentanyl is a safer option in patients with moderate to severe renal and liver failure.
4) Review patients and their indication for opioid use regularly. Taper down and stop if there is no more indication for opioid use.
5) Patients with poorly controlled pain even after strong opioid use and titration should be considered for referral to a palliative care or pain specialist.

SECTION 5: OPIOID THERAPY FOR COUGH

5.1 Introduction

Opioids may be used outside the context of pain management, such as in the treatment of refractory cough or diarrhoea. Codeine is a common example of an opioid prescribed for non-pain indications.

This section outlines the appropriate use of opioid therapy for cough by:

- Recognising the place of opioids in the management of cough; and
- Providing an algorithm for safe practice, specifically in prescribing and monitoring

While this section excludes the use of codeine for management of cough in children, in brief, codeine use in any form for any purpose should be avoided in children under 12 years of age. It is recommended for medical practitioners to **adhere to HSA's prevailing safety alerts to healthcare professionals on the recommendations on the use of codeine-containing products for the treatment of pain and the relief of cough and cold in children and adolescents**[54].

This section also cautions against the use of ephedrine and pseudoephedrine (two main precursors in the manufacture of methamphetamine), which are widely available as combination products in codeine-containing cough medications.

5.2 Definitions and Approaches

The American College of Chest Physicians states that cough can:

- Be an important defense mechanism to help clear excessive secretions and foreign material from airways; and
- Help maintain consciousness during potentially lethal arrhythmias and/or convert arrhythmias to more normal cardiac rhythms[55]

It is hence necessary to understand the protective nature of cough before any attempt is made to suppress it. The American College of Chest Physicians further suggests that ascertaining the duration of cough is the first step in narrowing the list of potential diagnoses, and that cough may be managed using evidence-based guidelines based on their duration[56].

Acute Cough

- Acute cough is defined as cough of less than 3 weeks. It is a common presenting symptom in primary care, and is mostly associated with upper respiratory tract infections.
- In the absence of significant co-morbidities, acute coughs are normally benign and self-limiting. They can however trigger acute exacerbations and even hospitalisations in patients with underlying respiratory conditions.

[54] Recommendations on the use of codeine-containing products for treatment of pain and relief of cough and cold in children and adolescents (HSA's Dear Healthcare Professional Letter issued in July 2016)
[55] Irwin RS, Boulet LP, Cloutier MM et.al. Managing cough as a defense mechanism and as a symptom. A consensus panel report of the American College of Chest Physicians. CHEST 1998; 144: 133S-181S.
[56] Irvin R, French C, Chang AB et. al. Classification of Cough as a Symptom in Adults and Management Algorithms. CHEST Guideline and Expert Panel Report. CHEST 2018; 153(1):196-209

- While dextromethorphan is found to be efficacious in adults with acute cough, codeine (or codeine-containing cough medications) has not been proven effective in these situations.
- Also worth noting is that patients have reported benefits from various over-the-counter ("OTC") medications, even though there is little evidence of specific pharmacological effects.

Subacute cough

- A subacute cough can last between 3 to 8 weeks. Its evaluation is similar to that for chronic cough if there are no obvious precipitating causes.
- For patients with preceding upper respiratory tract infections, post-infectious cough, bacterial sinusitis, and asthma are most common diagnoses[57,58].

Chronic Cough

- Chronic cough is defined as cough lasting more than 8 weeks. Most patients present with a dry or minimally productive cough. The presence of significant sputum production usually indicates a primary lung pathology. In benign chronic cough, a heightened cough reflex is often the underlying abnormality.

5.3 Use of Codeine

Efficacy and Safety of Codeine

Codeine is believed to act primarily on the CNS, causing depression of the cough reflex. A Cochrane Review[59] showed lack of good evidence demonstrating the effectiveness of OTC medications in reducing the frequency or severity of cough. In particular, despite widespread usage, there is little evidence supporting anti-tussive activity for orally administered codeine. Biochemically, codeine is a prodrug that is converted to morphine (active component) within the liver by the enzyme cytochrome P450 2D6. As individuals have varying abilities in this aspect of drug metabolism, both over-dosing and under-dosing can occur, often in an unpredictable fashion (with critical safety concerns and poor therapeutic responses respectively). Many countries or agencies such as the European Medicines Agency ("EMA"), Therapeutic Goods Administration ("TGA") and Food and Drug Administration ("FDA") have restricted the use of codeine for precisely these reasons.

Codeine-containing cough medications are not recommended as first-line treatment in all cases. While it may be used with caution for symptomatic relief of distressing cough, medical practitioners should ensure that any underlying condition (examples listed below) is evaluated and managed concurrently.

- Patients with a history of/currently suffering from respiratory-related conditions such as Asthma and COPD
- Patients suffering from gastroesophageal reflux disease ("GERD")
- Suspected and/or confirmed tuberculosis ("TB")

[57] Braman SS. Postinfectious cough. Chest 2006;129:138S-146S.
[58] Irwin RS, Baumann MH, Bolser DC, et al. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. Chest 2006; 129: 1S-23S.
[59] Smith SM, Schroeder K, Fahey T. Over-the-counter (OTC) medications for acute cough in children and adults in community settings (Review). Cochrane Database of Systematic Reviews 2014, Issue 11.

Medical practitioners should always exercise professional judgement before recommending codeine-containing cough medications for symptomatic relief.

Codeine Use in Pregnancy and Lactation

There is a lack of data with regards to codeine use during pregnancy and lactation. Of concern, many women do not consider OTC medications hazardous. The use of codeine by breastfeeding mothers has been found to cause adverse CNS events in breastfed infants[60,61].

Dependence, Misuse and Abuse

Many countries have reported the misuse of codeine-containing cough medications[62] [63]. OTC and prescribed cough medications may contain codeine, alone or in combination with antihistamines and decongestants[64,65].

In relation to decongestants, their presumptive vasoconstrictive action on the nasal mucosa makes both *ephedrine and pseudoephedrine* potentially effective against nasal congestion. However, adverse cardiovascular and neurological effects reported (with unpredictable onset and even at low doses) suggest that their use in the treatment of common colds should be minimised [66].

5.4 Management of Cough (General Information)

- Always try non-pharmacological treatments first, e.g. increasing fluid intake.
- Treat precipitating causes where identified, e.g. reflux disease or post-nasal drip due to allergic rhinitis.
- Initiate pharmacological therapy only if patient is distressed by the cough. Start by using drugs with low addictive potential.
- Prescribe a mucolytic in combination with expectorants for productive cough.
- Consider alternative medications for special populations (e.g. children, pregnancy or breastfeeding women).
- Consider dextromethorphan. Codeine-containing cough medications should be used as a treatment of last resort for dry, hacking coughs.
- Codeine-containing cough medications should be prescribed at the lowest effective dose, and for the shortest possible duration.
- Note the addictive potential of pseudoephedrine in combination medications.

[60] Madadi, P., & Koren, G. (2008). Pharmacogenetic insights into codeine analgesia: implications to pediatric codeine use. Pharmacogenomics, 9(9), 1267-1284

[61] Madadi, P., Shirazi, F., Walter, F. G., & Koren G. (2008a). Establishing causality of CNS depression in breastfed infants following maternal codeine use. Paediatric Drugs, 10(6), 399-404.

[62] Misuse of Prescription Drugs: A South Asia Perspective. United Nations Office on Drugs and Crime. 2011.

[63] Recent Statistics and Trend Analysis of Illicit Drug Markets. 2013.

[64] Elwood, W. N. (2001). Sticky Business: Patterns of Procurement and Misuse of Prescription Cough Syrup in Houston. Journal of Psychoactive Drugs, 33(2), 121-33.

[65] Peters, R. J., Williams, M., Ross, M. W., Atkinson, J., & Yacoubian, G. S. (2007b). Codeine cough syrup use among African-American crack cocaine users. Journal of Psychoactive Drugs, 39(1), 97–102.

[66] Laccourreye O, Werner A, Giroud JP. Benefits, limits and danger of ephedrine and pseudoephedrine as nasal decongestants. Eur Ann Otorhinolaryngology, Head and Neck Diseases 132 (2015) 31–34.

5.5 Management of Persistent Cough[67,68,69,70]

In patients with persistent cough (symptom persists for 3 weeks or more) and are prescribed cough preparations (including codeine-containing medications) for a duration of more than a month[71], the medical practitioner should do the following:

1. Perform chest X-ray (CXR) and/or other relevant test(s) as baseline investigation(s) to exclude other conditions e.g. cancer of lung, tuberculosis etc.

2. Look out for red flags:
   - Haemoptysis
   - > 20 pack-years history of smoking
   - Smoker over 45 years old with a new/altered cough
   - Prominent dyspnoea, especially at rest or at night
   - Substantial sputum production
   - Hoarseness of voice
   - Systemic symptoms: fever, weight and appetite loss
   - Complicated gastroesophageal reflux disease associated with weight loss, anaemia, hematemesis or melena, dysphagia or odynophagia
   - Abnormal respiratory findings on clinical examination

3. Consider these common causes of persistent cough and render appropriate treatment.
   i. Atypical chest infection – perform CXR and treat underlying infection with macrolides / beta-lactams antibiotics as appropriate
   ii. Upper airway cough syndrome (UACS) and CXR normal – rule out history of taking angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), though the latter are associated with a much lower incidence of cough as adverse effect. Consider a trial of antihistamines and decongestants or intranasal steroids.
   iii. Asthmatic cough – perform spirometry and trial of empirical treatment with inhaled bronchodilator or inhaled corticosteroid
   iv. Gastroesophageal reflux disease (GERD) – perform lifestyle modifications and reflux precautions, exercise and reduce body weight. Prescribe H2 receptor blockers or proton pump inhibitors if there are reflux and regurgitation symptoms.
   v. Non-asthmatic eosinophilic bronchitis (NAEB) – perform spirometry and evaluate sputum for eosinophilia. If sputum eosinophilia is present, then give a trial of inhaled corticosteroids

Patients should be referred to a respiratory specialist if cough persists for more than 8 weeks or remains undiagnosed after all of the above have been considered or tried.

[67] Irwin RS, et al. Chest 2006
[68] Kahrilas PJ, et al. Chest. 2016
[69] Poulose V, et al. SMJ. 2016
[70] Gibson PG, et al. BMJ. 2015
[71] This refers to supplying codeine-containing cough medications in cumulative amounts that can be taken daily for up to or more than a month, either in one batch or at repeated intervals

Patients with prolonged cough and have used codeine-containing cough medications daily or almost daily for more than a month have a high likelihood of drug dependence[72]. Given the lack of evidence for codeine-containing cough syrups and/or tablets in chronic cough management, coupled with risk of dependence, codeine-containing cough medications should be discontinued beyond the first month. Medical practitioners can consider prescribing another type of antitussive with lower dependence potential if needed, since existing evidence indicates that efficacies are similar among all antitussives.

Special cases: Prescription of codeine-containing cough medications in Intermediate and Long-Term Care (ILTC) settings such as Home Care and Palliative Care:
Patients receiving end-of-life care and having prolonged/chronic cough may not require a baseline investigation (e.g. CXR) if an infectious aetiology is not suspected clinically. The mobility of such patients should be taken into account when considering investigation(s).

For patients with known diagnosis of chronic lung disease, common secondary causes and triggers (e.g. dysphagia, GERD and heart failure) should be excluded before initiating codeine-containing cough medications. Alternative antitussives (non-codeine based) are preferred choices for long-term use.

Clinical conditions that predispose patients to chronic cough (not exhaustive):

i. Chronic sinusitis
ii. Postnasal drip from allergic rhinitis
iii. Cough variant asthma
iv. Chronic lung conditions e.g. chronic bronchitis, bronchiectasis, interstitial lung disease
v. Immunocompromised patients with opportunistic infections
vi. Intra-pulmonary malignancies, either primary or metastatic
vii. End-stage lung disease from various aetiologies

Some of these conditions are not reversible. Patients may continue to be distressed by persistent symptoms despite disease modifying therapy and conventional drugs used to manage cough. These patients may require continued use of cough medications (including codeine-containing cough medications) under the supervision of a medical practitioner with relevant specialty training (e.g. Respiratory, Infectious disease, Oncology, Palliative Medicine etc.) These specialists, however, are still expected to prescribe cough medications (including codeine-containing cough medications) for extended periods or large quantities with great caution. The same requirements in terms of sound documentation (as listed under Section 5.6) and regular risk assessments for aberrant use apply.

5.6 Required Documentation When Cough Medication is Prescribed

Clinical documentation when cough medication is prescribed should include:

[72] Managing Patients with Regular OTC Codeine Use. Drug and Alcohol Services South Australia 2018.

i. Duration of cough - Acute (lasting less than 3 weeks) vs Subacute (3-8 weeks) vs Chronic (more than 8 weeks)
ii. Associated symptoms, their duration and time course (current and/or previous) – e.g. rhinorrhoea, nasal congestion, facial pain or frontal headaches, sore throat, hoarseness of voice, fever, productive sputum etc.
iii. Red flags (as stated above)
iv. Relevant past history in subacute or chronic cough - e.g. asthma, allergic rhinitis, bronchiectasis, COPD, drugs, environmental factors, symptoms of GERD, smoking history. Sufficient details regarding each of these conditions should be obtained including that of primary disease control (if any, e.g. in asthma/ COPD)
v. Details of investigations (e.g. chest radiograph, spirometry results) and previous treatment (e.g. antibiotic usage, cough syrups, antihistamine use) should be documented as well

In addition, the following clinical documentation for patients who are prescribed codeine-containing cough medications, should include:

i. Strength of codeine-containing cough medications, dosage and duration of use
ii. Indication(s) and/or justification for prescribing or continuing codeine-containing cough medications
iii. Past history of substance abuse: codeine and other opioids, alcohol, benzodiazepines, cannabis, amphetamines, intravenous drug use
iv. Recent codeine-containing cough medication prescriptions from other medical institutions
v. Findings from assessment for mental health problems, like anxiety disorders or depression
vi. Physical examinations (e.g. ENT examination, cervical node, and chest auscultation)
vii. Relevant significant negatives for specific diseases such as clinical signs of cachexia, obstructive lung disease, bronchiectasis, pulmonary fibrosis, and/or cardiac failure

Note: Some of the above information may be obtained from NEHR

5.7 Monitoring Required for Opioid Therapy for Cough

(A) Monitoring for Adverse Effects

Opioids (as constituents or the main drug) used to manage coughs can adversely affect respiratory, gastrointestinal, musculoskeletal, cardiovascular, immune, endocrine, and central nervous systems. The higher the daily dose of opioid consumed (for its anti-tussive properties), the higher the risk of overdose and other adverse effects.

Table 12. Adverse Effects of Opioids

Adverse Effects	Symptoms	Remarks
Respiratory depression	• Drowsiness • Slowed or shallow breathing	• Stop the cough medication immediately • Avoid concurrent use with other CNS depressants, especially benzodiazepines. This combination has been implicated in opioid-related deaths
Mental status changes	• Confusion • Hallucinations	• Stop the cough medication immediately. • Re-evaluate and treat any other underlying causes as appropriate

(B) Monitor for Fitness to Drive

There are no large, randomized studies directly examining the risk of driving while on opioids. Opioids can slow reaction time, cause drowsiness, or cloud judgment when they are first started or increased.

(C) Monitoring for Opioid Misuse, Addiction or Diversion

Medical practitioners are advised to look out for behaviours indicative of opioid misuse / abuse, such as:

- Self-administering increasing doses of opioids
- Obtaining additional opioids from other medical practitioners
- Purposeful sedation
- Early requests for refills
- Misplacing prescriptions

5.8 Important Restrictions to Codeine Prescription

(A) Pregnancy:

Codeine has a US FDA Black Box warning which states that prolonged maternal use can cause neonatal opioid withdrawal syndrome in the new-born.

(B) Lactation:

Mothers taking codeine-containing medications should closely monitor breastfeeding infants for adverse effects, which may include drowsiness, decreased tone, or breathing difficulties.

(C) Geriatric Population[73]:

Codeine should be avoided in patients with history of falls or fractures.

(D) Other Contraindications:

Codeine is contraindicated in the presence of significant respiratory depression, acute or severe bronchial asthma, GI obstruction, including known or suspected paralytic ileus, and concurrent use with monoamine oxidase inhibitors ("MAOI") or use of MAOIs within the last 14 days.

Restrictions on quantity/duration

The prescription of codeine-containing cough medications should be based on the recommended dose of 10ml 3 times a day in the general adult population. It is recommended for medical practitioners to adhere to HSA's prevailing Health Products (Therapeutic Products) Regulations[74] and any other regulatory requirements for the maximum quantity/duration of codeine allowed to be prescribed. Nonetheless, should there be a need to prescribe supra-therapeutic doses of codeine-containing cough syrups that are higher than 10 ml 3 times a day (or equivalent recommended doses of alternative solid codeine-containing cough medications i.e. 60 mg a day), the medical practitioner must document in writing his clinical rationale for using such supra-therapeutic doses.

To minimise the risk of abuse or diversion, it is also recommended that codeine-containing cough medications should not be repeated more than 2 consecutive times without an in-person consultation. The medical practitioner is then expected to assess the benefits and risks as recommended in this guide when extending the duration of treatment.

[73] Beer's Criteria 2015

[74] Prevailing limits on the supply of codeine cough medications may be found under Regulation 14 of the Health Products (Therapeutic Products) Regulations 2016.

KEY POINTS

1) Codeine-containing cough medications should only be prescribed when all other cough medications have proven ineffective and/or are contraindicated due to allergy or adverse effects.
2) Codeine-containing cough medications should be prescribed at the lowest effective dose, and for the shortest possible duration when indicated.
3) Prescription history should be checked using the National Electronic Health Record (NEHR) where available, whenever a codeine-containing cough medication is supplied.
4) Patients should be appropriately counselled and educated on the risks of taking long-term codeine-containing cough medications.
5) Prescription of codeine-containing cough medications should not be repeated more than 2 consecutive times without a physical consultation to minimise the risk of abuse or diversion.
6) Use of codeine-containing cough medications should be discontinued after a month due to the lack of evidence in the efficacy of codeine-containing cough medication in chronic cough management and increased risk of dependence.
7) Patients should be referred to a respiratory specialist if cough persist for more than 8 weeks or remains undiagnosed after all red flags are considered and relevant work up completed.

SECTION 6: MANAGEMENT OF OPIOID DEPENDENCE

6.1 Introduction

This set of guidelines provides medical practitioners with step-by-step guidance through the opioid dependence treatment decision-making process, specifically, to enable medical practitioners to perform initial screening and assessment of patients with opioid dependence; and treat patients with opioid dependence appropriately and effectively. The goal of treatment and management plan for opioid dependence should be total abstinence.

These guidelines are intended for the use of medical practitioners managing patients with dependence to opioids, including heroin and prescription pain medications.

6.2 Definitions

Tolerance

Tolerance is defined in DSM-5 as either a need for markedly increased amounts of opioids to achieve intoxication or desired effect, or a markedly diminished effect with continued use of the same amount of an opioid [75].

Dependence

Often refers to both the physical and psychological elements of drug dependence.
Psychological dependence is defined as a subjective sense of need for a specific psychoactive substance, either for its positive effects or to avoid negative effects associated with the substance.
Physical dependence is defined as a state of adaptation, manifested by a drug class-specific withdrawal syndrome produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug substance, and/or administration of an antagonist.[76] Physical dependence underlies the physiological adaptations accountable for withdrawal symptoms emerging from the abrupt discontinuation of opioids. Withdrawal symptoms (e.g. insomnia, chills, diarrhoea, nausea, vomiting, myalgia, piloerection) may occur 1 to 14 days upon discontinuation and vary in severity depending on the opioids prescribed. Therefore, opioid dose tapering in anticipation of discontinuation would be required to prevent these withdrawal symptoms. [77]

Opioid dependence or addiction occurs when an individual persists in the use of opioids despite significant substance-related problems such as tolerance, withdrawal and compulsive drug taking behaviour. The ICD-10 criterion for the diagnosis of substance dependence is as follows: A cluster of physiological, behavioural, and cognitive phenomena in which the use of a substance or a class of substances takes on a much higher priority for a given individual than other behaviours that once had a greater value. A central descriptive characteristic of the dependence syndrome is the desire (often strong, sometimes overpowering) to take psychoactive drugs (which may or may not have been medically prescribed), alcohol or tobacco. There may be evidence that return to substance

[75]American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.
[76] American Society of Addiction Medicine (2020). The ASAM National Practice Guideline for the Treatment of Opioid Use Disorder: 2020 Focused Update. J Addict Med, 2020;14(2S), :1–91.
[77]Volkow, N. D. & McLellan, A. T. (2016). Opioid Abuse in Chronic Pain — Misconceptions and Mitigation Strategies. *New England Journal of Medicine*, 374(13), 1253–1263.

use after a period of abstinence leads to a more rapid reappearance of other features of the syndrome than occurs with nondependent individuals. [78]

Abuse

The essential difference between opioid abuse, as compared to opioid dependence, is the absence of tolerance, withdrawal or pattern of compulsive use although there have been clinically significant adverse consequences such as failure to fulfil major role obligations, multiple legal problems, recurrent social and interpersonal problems.

6.3 Misconceptions Regarding Opioid Dependence and Addiction

These misconceptions were drawn directly from questions submitted by physicians to two major websites for pain-management specialists (the American Academy of Pain Management and the American Pain Society).

1) ***Addiction is the same as physical dependence and tolerance.*** This misconception leads some medical practitioners to avoid prescribing opioids to patients who would benefit from them and many patients to be afraid of taking opioids as prescribed.

2) ***Addiction is simply a set of bad choices***. This misconception contributes to the discrimination against patients with addiction and to the wilful ignorance by medical practitioners about modern treatment methods. It also promotes mistrust of patients by medical practitioners and prevents affected patients from seeking help for their addiction.

3) ***Pain protects patients from addiction to their opioid medications.*** This misconception can lead to overconfidence and overprescribing among medical practitioners as well as failure to monitor and recognize addictive behaviours or to intervene properly when they emerge. Research has shown that patients who are prescribed opioid medications for pain can become addicted to them even when the drugs are taken as prescribed.

4) ***Only long-term use of certain opioids produces addiction.*** The misconception that addiction is simply the property of certain opioid drugs promotes overprescribing of certain types of opioids that may be as risky as types that are well known to be associated with addiction. An improved prescribing practice in the management of acute pain is a necessary step in the control of opioid diversion and overdose, since the over-prescription of opioids for acute pain is the main source of drug diversion.

5) ***Only patients with certain characteristics are vulnerable to addiction***. Certain conditions do increase the vulnerability to addiction. These include substance-use disorder (including abuse of alcohol, nicotine, and illicit drugs), developmental stage (adolescents are more vulnerable than adults), and certain mental illnesses (e.g., attention deficit–hyperactivity disorder and major depressive disorder). Although some patients are more vulnerable than others, no patient is immune to addiction.

[78] World Health Organization (n.d.). *Management of substance abuse*. 2021.

6.4 Managing Opioid Diversion and Abuse

Mitigating Strategies against Opioid Diversion and Misuse

Several mitigation strategies for risk assessment of opioid misuse include the following[77,79]:

1. **Screening Tools for Identification of Patients with Substance-Use Disorder**
   - Such tools include the Opioid Risk Tool[80]; the Screener and Opioid Assessment for Patients with Pain (SOAPP), version 1.0; SOAPP-Revised[81]; and the Brief Risk Interview[82]; or the use of a simple question such as "How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?" since patients who score above a certain threshold (e.g. ≥1 to the question) may be at increased risk for opioid abuse.

2. **Use of NEHR Data**
   - Patient prescription history can be used to identify doctor-hopping, which is frequently an indication of drug misuse or diversion.

3. **Use of Urine Drug Screening**
   - Such screening, which can be performed before prescription of opioids and periodically as part of regular follow-up, can provide information on drug use not reported by patients and may help in identifying patients who are not taking their prescribed opioids and might be diverting them.

4. **Doctor-Patient Agreement on Adherence**
   - Such personal contracts can help medical practitioners in monitoring a patient's adherence to prescribed opioid medications.

5. **Role of Urine Drug Testing**
   - Urinary drug testing ("UDT") is the most practical and objective tool available to prescribers for medically assessing, at any given point in time, whether a patient is taking prescribed medications or unauthorised controlled medications, or using illicit substances. However, UDT only provides a snapshot of the person's medication usage. A better diagnosis can be made after careful history taking, physical examination, acquisition of collateral information from family members, and the use of screening questionnaires. This can be used at the medical practitioner's discretion.

[79]George, J. M., Menon, M., Gupta, P. & Tan, M. G. E. (2013). Use of strong opioids for chronic non-cancer pain: a retrospective analysis at a pain centre in Singapore. *Singapore Medical Journal*, 54(9), 506–610.

[80]Webster, L. R. & Webster, R. M. (2005). Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the Opioid Risk Tool. *Pain Medicine*, 6(6), 432–442.

[81]Akbik, H., Butler, S., Budman, S., Fernandez, K. & Jamison, R. (2005). Validation and comparison of the SOAPP (Screener and Opioid Assessment for Patients with Pain) in two pain centers. *J Pain*, 6(3) supp.

[82]Jones, T. & Moore, T. (2013). Preliminary data on a new opioid risk assessment measure: The Brief Risk Interview. *Journal of Opioid Management*, 9(1), 19–27.

6.5 Identification of Opioid Dependence

Signs and Symptoms of Opioid Dependence

- Salience of behaviour in obtaining opioids, e.g. repeatedly seeking drugs from other providers or EDs via doctor-hopping, forging prescriptions or reporting multiple episodes of loss or theft of prescription drugs, showing up only for medication appointments.
- Requests for specific drugs, especially a preference for immediate release over sustained-release medications, not following prescribed dose and schedule, multiple unauthorised dose increases or pushing for higher dose of opioids.
- Concurrent use of illicit drugs, concurrent use of alcohol, tobacco use, past history of abuse of prescription medications or illicit drugs, or positive urine drug test for illicit drugs or unauthorised drugs.
- Non-compliance with non-pharmacological components of pain treatment (e.g. physiotherapy, psychological therapy).
- Physical dependence as shown by an increase in tolerance to opioids or physical withdrawal symptoms in the absence of opioids.
- Use of opioids negatively affecting their physical, social or occupational functioning.
- Other features as specified in the ICD-10 for opioid dependence.

6.6 Treatment Strategies for Managing Opioid Dependence

- Treatment for each patient should be individualised and decided by factors such as medical practitioner's assessment of patient's motivation, as well as the presence of medical and psychiatric comorbidities.
- Treatment should only be prescribed by the following:
    - Addiction specialist under the section of Addiction Psychiatry of College of Psychiatrists and/or accredited under NAMS; or
    - Other psychiatrists who have experience in the management of opioid dependence
- The treatment and management of opioid dependence should be carried out under the care of a multi-disciplinary team consisting of, but not limited to the following:
    - Substance abuse specialist
    - Counsellor
    - Nurse
    - Pharmacist
    - Clinical psychologist
    - Medical social worker

Detoxification

- Detoxification and subsequent abstinence should be offered to opioid-dependent people who are motivated to become abstinent. This can be done either in an inpatient or outpatient setting depending on the severity of the patient's condition.
- Detoxification should always be with the patient's agreement and be tailored to meet the needs of the patient. It is important to clarify treatment objectives with the patient, e.g. expectations, concerns and aftercare/support needs at the onset.
- Detoxification involves the symptomatic treatment of withdrawal signs while ensuring complete abstinence from opioids.

Detoxification with Symptomatic Treatment

- For symptomatic treatment of withdrawal signs, e.g. diarrhoea, vomiting, body aches, anxiety, medications can include but are not limited to the following:

Table 13. Treatment of Withdrawal Symptoms

Symptom(s)	**Suggested Medication(s)**
Diarrhoea	Diphenoxylate with Atropine/Loperamide
Pain	• Paracetamol/other pain relief medications • For patients with paracetamol allergy, other pain killers such as NSAIDs might be considered.
Nausea/vomiting	Metoclopramide/Promethazine
Anxiety/agitation	Hydroxyzine/Promethazine
Anxiety and insomnia	• Diazepam in tapering doses • Other benzodiazepines can be considered for patients with liver impairment.

- Patients should be seen as often as necessary. The schedule of treatment is determined by the medical practitioner in consultation with the patient. Sometimes a period of inpatient treatment is necessary if there are severe physical dependence symptoms.

Education, Counselling and Psychotherapy

- Non-pharmacological modalities of treatment such as, psychoeducation, counselling, crisis intervention, liaison with other social service agencies, enhancing problem solving and social skills are recommended for all patients in addition to any existing pharmacological measures.
- Sound general counselling principles such as reflective listening, empathetic alliance and a client-centred approach are likely to contribute to the rehabilitative process and are recommended for all patients.
- During abstinence, cognitive-behavioural psychotherapy when given with opioid antagonist therapy improves the retention in treatment and success of abstinence in patients who have undergone successful detoxification and may be used in conjunction with therapy.
- A relationship with clients based on trust contributes to an effective therapeutic alliance.
- Focus of counselling is on external matters such as case management, problem solving and help in addressing practical issues.

Community Psychosocial Services

- Referrals and liaison with social service agencies (e.g. half-way houses, therapeutic communities, medical social workers) are useful treatment strategies to be considered in the management of opioid dependent individuals.
- Self-help groups such as Narcotics Anonymous can be considered for the holistic management of opioid dependent individuals.
- Updated information of these resources can be found on the web sites of Singapore Anti-Narcotics Association (www.sana.org.sg) and National Addictions Management Service (www.nams.sg).

Opioid Antagonist Therapy[83]

- Opioid antagonists are drugs which competitively displace opioids from opioid receptor sites. This interrupts the reinforcing effects of opioid consumption and reduces the craving associated with chronic opioid abuse.
- It is used for opioid-dependent individuals who have undergone detoxification and increases the efficacy of cognitive-behavioural therapy-based abstinence programmes for motivated individuals.[84]
- Naltrexone is currently the only oral opioid antagonist available in Singapore.
- Opioid antagonists reduce the reinforcing effects of opioid consumption and reduce the cravings associated with chronic opioid abuse.
- An opioid antagonist like naltrexone can be used for patients who have undergone detoxification and whose compliance is not an issue.

Acupuncture

This is used as an adjunct treatment for selected patients who are suitably inclined towards acupuncture. Such individuals will still continue with standard treatment as usual but with acupuncture added on to help relieve symptoms of cravings and withdrawals, insomnia etc.

6.7 Balancing the Need for Adequate Pain Relief versus Treatment of Opioid Dependence

Treatment for opioid dependence should have the end goal of abstinence in mind. If there is a situation where the patient being treated for opioid dependence requires opioids for pain relief, treatment should be done in consultation with the patient's pain management team to balance the need for adequate pain relief.

[83]American Society of Addiction Medicine (2020). The ASAM National Practice Guideline for the Treatment of Opioid Use Disorder: 2020 Focused Update. *J Addict Med*, 14(2S), 1–91.

[84]Dutra, L., Stathopoulou, G., Basden, S.L., Teresa, M. L., Powers, M. B. & Otto, M. W. (2008). A meta-analytic review of psychosocial interventions for substance use disorders. *Am J Psychiatry*, 165, 179–187.

6.8 Process Workflow for Reporting of Patients with Suspected Opioid Dependence

Drug users may occasionally present at pain clinics with chronic pain conditions seeking opioid-based analgesics. Medical practitioners should be vigilant for such presentations and prescribe opioid-based analgesics judiciously.

- If suspected of drug abuse, patient should be referred to the National Addictions Management Service at the Institute of Mental Health for assessment and treatment (call 67326837 for appointment). Under Regulation 19 of the Misuse of Drugs Regulations, medical practitioners are required to report patients with suspected opioid dependence within 7 days from the date of attendance to Director, Central Narcotics Bureau and the Director of Medical Services, Ministry of Health, through eNOTIF (http://www.enotif.cnb.gov.sg/ENotif).[85]

KEY POINTS

1) Anyone who takes opioids is at risk of developing physical dependence.
2) The difference between opioid abuse and opioid dependence is the presence of strong or irresistible craving for the drug, developing significant tolerance and withdrawal symptoms, and continued and compulsive use of opioids despite repeated, harmful consequences.
3) Medical practitioners should be able to identify the signs and symptoms of opioid dependence and abuse such as repeatedly requesting for opioids from multiple providers, preference for immediate release over sustained-release opioids, asking for higher doses, coming for frequent refills with unreliable excuses, showing signs of neglect, presence of withdrawal symptoms, and non-compliance with non-pharmacological components of pain treatment (e.g. physiotherapy, psychological therapy).
4) History of substance use and other associated psychosocial stressors (e.g. poverty, unemployment), history of antisocial behaviour and certain mental illness (e.g. attention deficit-hyperactivity disorder and major depressive disorder) increases a person's vulnerability to dependence. Although some patients are more vulnerable than others, no patient is immune to dependence.
5) Treatment of opioids dependency should be individualised. If there is a situation where the patient being treated for opioid dependence requires it for pain relief, withdrawal from opioids should be encouraged with the help of addiction treatment specialists and this should be done in consultation with pain management team to balance the need for adequate pain relief with alternative non-opioid choices.

[85] MH 78:09/10 NOTIFICATION OF SUSPECTED DRUG ADDICTS VIA eNOTIF ONLY (CIRCULAR DATED 09 FEB 2021)

APPENDICES

A. Opioid Conversion Table

*Table 14: Opioid conversion**

Drug	Route	Conversion Factor (drug: oral morphine)	Approximate Dose (mg) Equivalent to Oral Morphine 30 mg
Codeine	Oral	10:1	300
Tramadol	Oral	5:1	150
Hydromorphone	Oral	1:5	6
Oxycodone	IV/SC	1:4	7.5
Morphine	IV/SC	1:3	10
Oxycodone	Oral	1:2	15
Fentanyl	IV/SC	1:100	0.3

** These equivalent doses are only approximations. There is wide and unpredictable inter-individual variability of different opioids. Medical practitioners should practise caution by reducing the calculated equivalence dose further (25-75%) to avoid unintentional overdose caused by incomplete cross-tolerance and inter-individual pharmacokinetic variability.*

B. Identifying Patients Approaching End of Life

Adapted from Gold Standard framework

General Indicators of decline

- Decreasing activity – functional performance status declining (e.g. Barthel score) with limited self-care, in bed or chair 50% of day and increasing dependence in most activities of daily living
- Multiple co-morbidities as indicators of mortality and morbidity
- Advanced disease - unstable, deteriorating complex symptom burden
- Decreasing response to treatments, decreasing reversibility
- Limited benefit from further active treatment
- Progressive weight loss (>10%) in past six months
- Repeated unplanned/crisis admissions
- Serum albumin <25g/L

Specific Clinical Indicators

A) Advanced Cancer- predictable decline

For patients with advanced cancer with poor performance status and functional ability (if patients are spending more than 50% of their time in bed/lying down), their prognosis is estimated to be about 3 months or less.

B) Organ Failure – erratic decline

(The list below is not exhaustive)

1) Advanced COPD
2) Advanced Heart Disease
3) Advanced Renal Disease
4) Advanced Neurological Diseases- Parkinson Disease, Motor neuron disease, massive stroke etc
5) Advanced Dementia
6) Frailty

1) Advanced Chronic Obstructive Pulmonary Disease

At least 2 of the following

- Forced Expiratory Volume <30% predicted
- Long term oxygen therapy
- Medical Research Council Dyspnoea scale grade 4/5*
- Right heart failure from Cor Pulmonale
- Recurrent hospital admissions (at least 3 in last 12 months due to COPD)

*MRC Dyspnoea scale grade 4 is breathless after walking for about 90m.
*MRC Dyspnoea scale grade 5 is too breathless to leave house or breathless when dressing or undressing

2) Advanced Heart Failure

At least 2 of the following

- New York Heart Association Classification III/IV
- Repeated hospital admissions
- Optimal therapy but poor symptom control

3) Advanced Renal Failure

Stage 5 Chronic Kidney Disease (CKD) whose condition is deteriorating with the following:

- Patients choosing the 'no dialysis' option or discontinuing dialysis
- Symptomatic Renal Failure – nausea and vomiting, anorexia, pruritus, reduced functional status, intractable fluid overload.

4) Advanced Neurological Disease (Parkinson Disease, Motor Neuron Disease, massive stroke etc)

- Progressive deterioration in physical and/ or cognitive function despite optimal therapy
- Swallowing problems (dysphagia) leading to recurrent aspiration pneumonia, sepsis, breathlessness or respiratory failure
- Speech problems: increasing difficulty in communications and progressive dysphasia

5) Advanced Dementia

Dementia at Functional Assessment Staging Tool (FAST) Stage 7C* and

- Recurrent infections
- Severe pressures sores – stage three or four

*Fast 7C: Non ambulant and total dependent on all activities of daily living.

6) Frailty

Frailty with:

- Deteriorating Karnofsky score or Clinical Frailty Score >6
- Increasing weakness and fatigue

Clinical Frailty score 7 is a patient who is severely frail—Complete dependent for personal care from whatever cause.

C. Case Scenarios for Prescribers: Putting these Guidelines into Practice

With Suggested Answers

These scenarios have been put together to illustrate how the recommendations from these guidelines could be implemented and situations where practice could deviate from recommendations.

Case study 1

A 60-year-old man who has chronic severe low back pain after three failed lumbar laminectomies has been functioning well for past 3 years on a fentanyl patch 12 mcg/hr once every 72 hours.

He presents at emergency department after slipping and falling in toilet at home. He was diagnosed to have a proximal non-displaced left humeral fracture. Patient complains of severe pain with pain score of 9 out of 10.

1. How would you manage the pain in the emergency department?

Suggested answer:

Consider the following before initiating pain treatment

1) Medical co-morbidities e.g. renal impairment, respiratory illness, obstructive sleep apnoea, frailty
2) Medication history
3) History of chronic opioid treatment
4) History of substance abuse
5) History of benzodiazepine use

Multimodal acute pain treatment options

Non-pharmacological, non-opioid modality

1) Arm sling
2) Ice pack

Pharmacological modality

1) Paracetamol
2) NSAIDs / COX-2 Inhibitors – e.g. Parenteral ketorolac, parenteral parecoxib

2. Despite the above measures, patient still complained of severe pain, you have decided to give the patient parenteral opioids for more rapid relief.

Suggested answer:

Possible options

1) IV fentanyl 10-20 mcg every 10-15 min until pain improves (there **must** be regular 5-10 min monitoring and review for sedation, respiratory rate, other vital signs, and pain scores).

OR

2) IV morphine 1-2 mg every 10-15 min until pain improves (there **must** be regular 5-min monitoring and review for sedation, respiratory rate, other vital signs, and pain scores).

OR

3) Subcutaneous morphine 2.5 to 5 mg stat and can then be given every Q4-6H PRN (there **must** be regular 15-min to 30-min monitoring and review for sedation, respiratory rate, other vital signs, and pain scores).

OR

4) Subcutaneous oxycodone 2.5 to 5 mg stat - can be given Q4-6H PRN (there **must** be regular 15-min to 30-min monitoring and review for sedation, respiratory rate, other vital signs, and pain scores).

OR

1) IM tramadol 25 – 50 mg stat - can be given Q4-6H PRN (there **must** be regular 15-min to 30-min monitoring and review for sedation, respiratory rate, other vital signs, and pain scores).

3. Do you remove the fentanyl patch?

Suggested answer:

No. In a patient taking extended release/long acting opioids for chronic pain, treatment of unrelated, severe pain will require a moderate-to-high dose of a short-acting analgesic at a short dosing interval – for a temporary basis.

4. The patient is to be discharged back home from the ED after a stay of about 8 hours; his pain has improved to pain score of 3-4 with an arm sling. He was given a follow-up appointment for the orthopedic surgeon in 5 days. What would you provide for post-discharge pain relief?

Suggested answer:

Multimodal treatment options

Non-pharmacological, non-opioid modality

1) Arm sling
2) Ice pack (if feasible)

Pharmacological modality

3) Continue chronic low back pain therapy with fentanyl patch 12 mcg/hr once every 72 hours
4) Paracetamol
5) NSAIDs / COX-2 Inhibitors – e.g. oral diclofenac, oral naproxen, oral etoricoxib, oral celecoxib
6) Opioids for acute pain secondary to humerus fracture
    1) Oral morphine 2.5-5 mg Q4-6H PRN for 3-5 days

OR

2) Oral oxycodone capsule 5 mg Q4-6H PRN for 3-5 days

OR

3) Tramadol 25-50 mg Q4-6H PRN for 3-5 days

Case study 2

A 22-year old university student was seen at the clinic for severe acute low back pain (ALBP). A few days prior to the onset of the ALBP, she was helping a friend to shift house.

Her pain score is currently 7-8 out of 10, and she can walk, but only over a short distance. There is no pain radiation to the lower limbs. She said that she is unable to attend classes.

She has no history of low back pain, or other co-morbidities. Her BMI is 32.

1. How would you manage her pain?

Suggested answer:

Considerations before initiating pain treatment

1) Medical co-morbidities e.g. renal impairment, respiratory illness, obstructive sleep apnoea, frailty
2) Medication history
3) History of chronic opioid treatment
4) History of substance abuse
5) History of benzodiazepine use
6) Red flags for low back pain – e.g. fall, fever, persistent unremitting pain, night pain, pain not associated with movements, history of cancer, bowel / bladder dysfunction, weakness lower limbs

Consideration for multimodal treatment of ALBP

1. Non-pharmacological, non-opioid modality (not exhaustive)
   1) Encourage normal activities as much as tolerated
   2) Provide information about LBP
   3) Physical methods - ice pack, heat pack, manual therapy (manipulation, massage)
   4) Psychological methods – cognitive behavioural approaches
   5) Physiotherapy
2. Pharmacological modality
   1) Paracetamol (do not provide paracetamol alone)
   2) NSAIDs / COX-2 Inhibitors – e.g. oral naproxen, diclofenac, celecoxib, etoricoxib
   3) Muscle relaxants e.g. orphenadrine, eperisone, baclofen (short term)

If patient's pain does not improve with the above modalities, we can then consider the use of short-term opioids; however, an assessment of her respiratory system is warranted, especially to diagnose obstructive sleep apnoea. We can also consider prescribing weaker opioids first, like codeine and tramadol.

Suggested options

1) Oral codeine 8 mg + paracetamol 500 mg tablets – 1-2 tablets Q4-6H PRN per day for 3-5 days
2) Oral codeine phosphate 15-30 mg Q4-6H PRN capsule 5 mg TDS to QDS for 3-5 days
3) Tramadol 25-50 mg Q4-6H PRN for 3-5 days

Case study 3

A 69-year-old lady with a history of Stage 3C1 High grade serous carcinoma left tubal primary involving left ovary, s/p THBSO infracolic omentectomy and currently on adjuvant Paclitaxel/carboplatin, presents for surveillance follow up.

She complains of RA flare not responding to prednisolone, and the pain was also not well managed despite regular oral tramadol 50 mg TDS. She was started on low dose IV morphine continuous infusion for pain relief. Her pain was better controlled, and the morphine dose was subsequently reduced and discontinued with an increase in the dose of prednisolone.

1. What could have been considered prior to initiation of IV morphine?

Suggested answer:

The use of paracetamol and orphenadrine combination (Anarex) or a weak opioid, together with adjustment of steroid, should be able to help the patient achieve pain relief in RA flare management. If the patient experiences worsening of pain from RA flare despite adjustment of steroid and analgesic, further investigations should be carried out to rule out any other underlying cause or issues such as septic joint and OA instead of initiating a strong opioid.

Case study 4

A 32-year-old lady with a history of Zoster infection presents for neuralgia pain. She has no known drug allergies nor any organ impairment.

1. How would you manage her pain?

Suggested answer:

The ideal choice of analgesia for post Zoster infection neuralgia pain would be a neuropathic agent such as PO Gabapentin or Pregabalin (unless otherwise indicated e.g. allergy, renal impairment etc).

2. If the patient is on NGT feeding, what options would you then consider?

Suggested answer:

For patients who are unable to take medication orally, a weak opioid could be offered to manage the neuropathic pain. It is recommended to follow up with a chronic pain specialist for dose titration of the opioid and management of side effects. The use of transdermal analgesia is not advisable unless prescribed by a pain specialist.

Case study 5

A 42-year old man with a history of severe contracture is suffering from incidental pain, unresponsive to paracetamol and NSAIDs. Oral morphine was prescribed to be given prior to dressing change or any major change in position.

1. Was the initiation of morphine appropriate in this case?

Suggested answer:

- Patients with chronic musculoskeletal conditions with no alternative treatment options may require prolonged use of opioids to improve quality of life.
- In this instance, a referral to the home care hospice team (for Nursing Home/Homecare patients) is recommended to ensure there is monitoring of opioid effectiveness and toxicity in the management of chronic incidental pain in patients with severe contracture/other chronic pain conditions. Recommended analgesia regime would be to administer short-acting low dose opioid prior to major activities.

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