A GUIDE TO THE USE OF STRONG OPIOIDS IN CHRONIC NON-CANCER PAIN

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Malaysian Association for the Study of Pain
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PREFACE

These recommendations were written by a subcommittee appointed by the Malaysian Association for the Study of Pain (MASP). Members of the committee studied several documents on this subject available from around the world (see references), and this final document is the result of several meetings and discussions. The aim of the document is to provide a guide on appropriate use of strong opioids for chronic non-cancer pain to maximise the benefits of opioids in relieving pain and improving function, while minimizing the potential risks of opioid abuse and addiction.

We hope that this document will result in:

- increased awareness among healthcare providers about the current issues involving opioids and non-cancer pain
- improved awareness of opioid benefits and risks among patients and healthcare providers
- improved understanding by patients regarding their responsibilities when taking opioid medications, and
- reduced opioid abuse and diversion.

This document may be used by healthcare professionals involved in the management of patients with chronic non-cancer pain, including members of the multidisciplinary team who may not actually prescribe these drugs, with the aim of having a common understanding regarding the indications and the goals of long term opioid therapy for patients with non-cancer pain.

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SUMMARY OF KEY MESSAGES

1. Long term therapy with opioids is indicated in patients with severe persistent pain which is non-responsive to pharmacological therapy with non-opioids, adjuvant agents, physical therapy and interventional therapy. Consultation with pain specialists is encouraged prior to deciding to initiate opioid therapy.

2. Opioid therapy should provide adequate analgesia with minimum side effects using the lowest possible dose of opioid, with the goal of improved overall functioning and quality of life.

3. Before initiating therapy with strong opioids the following is necessary:

    - Complete clinical evaluation which includes history and physical examination, psychological evaluation and functional assessment.
    - Documentation of failure of other treatments
    - An "opioid agreement", signed by the patient, which outlines the possible risks and benefits of opioid therapy, the responsibility of the patient, required monitoring and the conditions for termination of therapy.

4. During treatment, continuous monitoring of the "4As" should be carried out

    i. Analgesia
    ii. Activity
    iii. Adverse effects
    iv. Aberrant behaviour

5. Avoid combination of opioids with sedative hypnotics like benzodiazepines and barbiturates.

6. Aberrant behaviour and/or no improvement in function and pain after an adequate trial of strong opioids should trigger a consideration to discontinue the opioid.

7. When ceasing therapy with strong opioids, tapering of the dose should be done over an appropriate period to avoid withdrawal symptoms.

INTRODUCTION

Chronic pain is defined as 'pain that persists for three months or more, or beyond normal tissue healing time', and may be due to cancer or non-cancer causes. In Malaysia, the prevalence of chronic pain has been shown to be around 7% of the adult population, higher in women and older adults[1]. Since the introduction of the WHO analgesic ladder in the mid-1970s, it has been well recognised that strong opioids like morphine are essential for the relief of pain in patients with cancer, especially in the advanced stages. There has been an increasing trend to extend the use of strong opioids to patients with chronic non cancer pain (CNCP). Unfortunately, the increase in opioid prescriptions has also led to an increase in opioid misuse, abuse and overdose-related deaths.[2]

Some chronic non-cancer pain conditions which may benefit from long term opioid therapy include:

- Chronic spinal pain - cervical, thoracic, lumbo-sacral
- Osteoarthritis/ joint pain
- Chronic abdominal pain

Long term opioid therapy may also be considered in certain chronic neuropathic pain conditions where pain persists despite maximising non-opioid therapy. It is important to ensure that non pharmacological methods and the dose of anti-neuropathic agents have been optimized before initiating opioid therapy.

In Malaysia, the use of opioids in patients with chronic cancer and non-cancer pain is low. The Malaysian Statistics on Medicine 2008 found that the total opioid consumption in Malaysia was 0.4 DDD/1000 population/day, compared to Australia (8.2 DDD/1000 population /day) and Nordic countries (16.2 to 20.4 DDD/1000 population/day).[3] Data from the International Narcotics Control Bureau (INCB) also indicated that opioid consumption in Malaysia is far below the global average; for example, in 2011 the morphine consumption in Malaysia was 1.48 mg/capita compared to the global mean of 6.11 mg/capita.[4]

However, the use of intermittent short acting opioids (e.g. intramuscular pethidine) for chronic non-cancer pain is not uncommon. This practice is not evidence-based and has the potential to lead to addiction and opioid-seeking behaviour for short term pain relief, and should not be practiced at all.

[1]Cardosa MS, Gurpreet R, Tee HGT. Chronic Pain, The Third National Health and Morbidity Survey 2006, vol. 1. Kuala Lumpur: Institute for Public Health, Ministry of Health Malaysia; 2008:262.
[2]CDC MMWR2011. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm60e1101a1.htm?s_cid=mm60e1101a1_w. Updated with 2009 mortality and 2010 treatment admission data.
[3]Mary SC, Choy YC, Marzida M et al. Use of Opioid Analgesics. In Pharmaceutical Services Division and Clinical Research Center, Ministry of Health Malaysia, Malaysian Statistics on Medicines 2008, Kuala Lumpur 2013, p 121-122 ; DDD=Defined Daily Dose.
[4]University of Wisconsin-Madison, Pain and Policy Studies Group. http://www.painpolicy.wisc.edu/country/profile/malaysia and http://www.painpolicy.wisc.edu/global, accessed 16 August 2014.

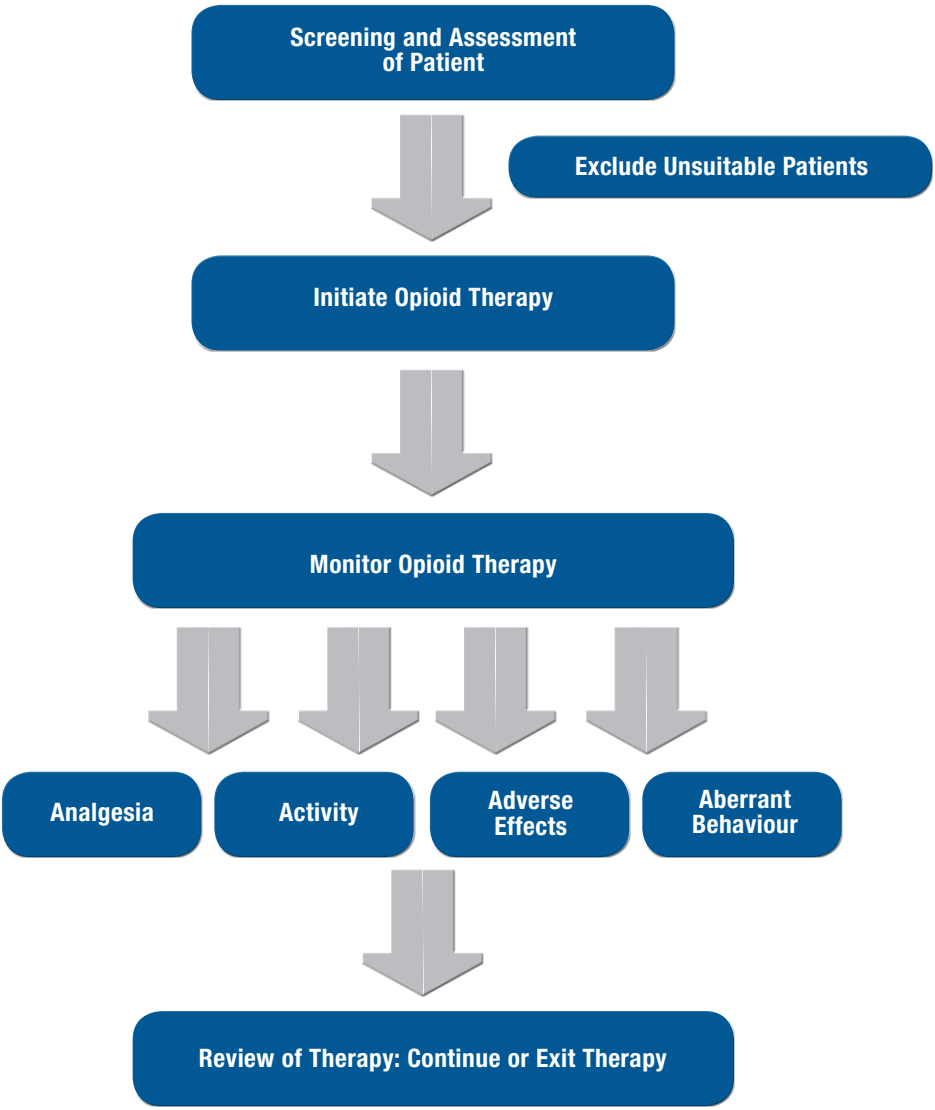
The choices of opioids available in Malaysia has increased in the last decade, and this has the potential to increase the number of opioid prescriptions overall, including prescriptions for CNCP.

The MASP recognises that there is a role for opioids in the management of CNCP and appropriate selection, screening and monitoring of patients on opioid therapy are essential to ensure optimal outcomes. This document aims to provide guidance on the above so as to maximise the benefits of opioids in relieving pain and improving function and quality of life, while minimising the potential risks of opioid abuse and addiction.

Specific objectives of this document are to assist medical practitioners in the following areas:

1. The selection of patients with CNCP who may benefit from strong opioids
2. The assessment of the risk of abuse in these patients before initiation of strong opioids
3. The initiation of therapy with the appropriate opioid
4. The monitoring of these patients in terms of pain control, function, side effects and any aberrant drug-related behaviours.
5. Reduction and cessation of opioid therapy when indicated

ALGORITHM FOR OPIOID THERAPY IN CHRONIC NON-CANCER PAIN



PATIENT SELECTION, SCREENING AND ASSESSMENT

Indications for Strong Opioids

Long term therapy with strong opioids is indicated in patients with severe persistent pain which is non-responsive to pharmacological therapy with non-opioids or weak opioids, adjuvant agents, and including non-pharmacological therapy such as physical therapy and interventional therapy. Consultation with pain specialists is encouraged prior to deciding to initiate opioid therapy.

Patient Selection

It is appropriate to consider starting strong opioid therapy in a patient, in conjunction with ongoing non-pharmacological methods, when there is unsatisfactory pain control despite trying all other modalities. It is important to ensure that the neuropathic component has been adequately treated with anti-neuropathic agents and all non-pharmacological methods have been optimised.

Screening and Assessment

The patients who have been identified should be initially screened for the risk of opioid abuse. Assessment of psychosocial factors and family history is important. Known predictors for opioid abuse are personal or family history of alcohol or drug abuse, age between 16-45 years, history of sexual abuse and co-existing psychiatric illness[5].

The Opioid Risk Tool (ORT)[5] (Appendix C) may be used as a screening tool to stratify patients into low, medium or high risk categories for opioid abuse and aberrant behaviour. Other commonly used tools includes Screener and Opioid Assessment for Patients with Pain (SOAPP)[6] and Diagnosis, Intractability, Risk, and Efficiency (DIRE) Inventory[7].

Before initiation of strong opioid therapy, the following should be carried out:

i. Take a full medical history
ii. Perform a detailed physical examination
iii. Review the outcomes of trials with analgesic and adjuvant medications
iv. Review the results of diagnostic and therapeutic interventional procedures
v. Review other therapeutic modalities used (including physical and psychological modalities)
vi. Review relevant laboratory and radiological investigations

At the onset of therapy a discussion with the patient should include:

i. Expected goals: reduction in pain and functional improvement
ii. Possible adverse effects
iii. Risks associated with long-term opioid therapy
iv. The need for an initial trial period and a specified ceiling dose of opioid equivalent to 200 mg of oral morphine per day.[8]

[5]Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the opioid risk tool. Pain Med. 2005;6(6):432-442
[6]Butler S, Budman S, Fernandez K, Jamison R. Validation of a screener and opioid assessment measure for patients with chronic pain. Pain. 2004; 112: 65-75.
[7]Belgrade MJ, Schamber CD, Lindgren BR: The DIRE score: predicting outcomes of opioid prescribing for chronic pain. J Pain 2006;7:671–681.
[8]Ho KY, Chua NH, 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;42:138-152

When a decision of opioid therapy is agreed upon, it is recommended to have a written opioid treatment agreement (Appendix B) that outlines the responsibilities of both physician and patient with the aim of achieving desired outcomes as well as avoiding and minimising the complications and risks associated with chronic opioid therapy.

Documentation

It is important to keep accurate and complete medical records in order to provide proper patient care and to meet regulatory requirements. It is recommended that there should be detailed documentation of the opioid therapy trial.

History and physical examination, psychological assessment, concomitant medical illness, psychiatric illness and patient's medications should be clearly documented. History should include a detailed pain history, investigations, interventional procedures and previous surgery. Indications for starting opioid therapy should be clearly documented. Any history of substance abuse or alcohol abuse must be documented. The score for the Opioid Risk Tool (Appendix C) should be clearly documented.

In addition to the above, documentation should include the expected goals of therapy, agreed to by the patient, as well as the discussion about possible adverse effects and long term effects of opioid therapy. Last but not least, the conditions under which therapy may be discontinued should also be documented.

INITIATION OF THERAPY

Opioid Treatment Agreement

It is recommended that a written opioid treatment agreement should be obtained prior to initiating opioid therapy. The treatment agreement is a written document that outlines the roles and responsibilities of the physician as well as the patient. (Appendix B)

Initiation of Opioid Therapy

Begin with a trial of therapy and monitor for the reduction of pain and improvement in function, opioid-related side effects and aberrant drug-related behaviours.

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Duration of Trial of Opioid Therapy

The patient should be monitored for improvement in the dimensions that were discussed at the point of commencement. Generally speaking, a trial period (initiation and dose adjustment) of 8 weeks will help the physician to decide whether to continue or discontinue opioid therapy.

Expected Benefits

The patient should have realistic goals and expectations. There must be a thorough discussion regarding the desirable therapeutic effects (usually 30% reduction in pain score is considered as a good outcome), improvement in functional status and quality of life.

It is imperative to highlight to patients with CNCP that the aim of opioid therapy is NOT for total pain elimination but for reduction in pain to achieve functional improvement. The patient must be reminded that self-motivation and active participation in rehabilitation are essential elements in achieving the best outcome, as opioid therapy is only one part of the multidisciplinary approach in pain management.

Potential Risks

Discussing the potential adverse effects is also paramount to the success of opioid therapy. Patients should be counseled on the common opioid related adverse effects (e.g. constipation, nausea, vomiting, sedation and pruritus) as well as other serious risks and complications (e.g. tolerance, dependence, abuse, addiction or life-threatening overdose). The management of complications and adverse events must also be conveyed to patients.

Patients should be cautioned against operating heavy machinery and driving when initiated with strong opioid therapy. They should also be advised that concomitant administration of benzodiazepines or antidepressants (which are common among CNCP patients) increases the risk of central nervous system (CNS) depression.

It is important to educate the patient and family members about the risks of overdose and concomitant use of alcohol and/or CNS depressants with strong opioids, as these have been shown to result in opioid-related deaths.

Potential risks of long-term opioids[9] should also be discussed. These include:

a) Hormonal changes (low testosterone levels in males which may affect mood, stamina, physical performance and libido)
b) Immunosuppression
c) Opioid-induced hyperalgesia
d) Cognitive impairment

Opioid Selection

Opioid selection, dosing, and titration should be based on each patient's health status, previous opioid experience, and side effects of opioid therapy.

Strong opioids currently available in Malaysia are morphine, oxycodone, methadone, buprenorphine, nalbuphine, pethidine and fentanyl. However, pethidine, nalbuphine and fentanyl/transdermal fentanyl are not recommended for use in chronic non-cancer pain (see below).

When selecting opioids, the following principles apply:

1. Opioids are to be started at low doses and titrated upward slowly, both in opioid-naïve as well as opioid-tolerant patients.
2. Oral opioids are preferred over injectable opioids.
3. Sustained-release (SR) formulations are also preferred over immediate-release (IR) formulations as steady plasma drug concentration can be achieved.
4. IR formulations may be useful for initiating therapy in opioid-naïve patients with renal impairment or in elderly patients for a short period of time before changing to the SR formulation.

Opioids to be Avoided in CNCP

- Pethidine should not be used for chronic pain management because it is only available in the injectable form, and there are no clinical advantages over other opioids such as morphine. In fact, accumulation of its active metabolite (norpethidine) can be neurotoxic, resulting in convulsions. It may precipitate serotonin syndrome when used concomitantly with monoamine oxidase inhibitors or tricyclic antidepressants. Pethidine also possesses a higher potential for abuse compared to other opioids as it produces more intense euphoria[10].

- Agonist-antagonist opioids e.g. nalbuphine, because they may precipitate withdrawal symptoms in opioid tolerant patients.

Opioids with Special Considerations

- In the Ministry of Health Malaysia, transdermal fentanyl is only approved for use as a second line drug in the management of chronic cancer pain, with use restricted to pain specialists, palliative medicine specialists and oncologists.[11]

- Methadone should only be used by pain specialists for patients with CNCP as it is a difficult drug to titrate. In Malaysia, the indication for methadone is only for harm reduction therapy; therefore, a special permission from the Director General of Health is required if methadone is used for the treatment of CNCP.[11]

[9]Trescot AM, Boswell MV, Atluri SL, et al. Opioid guidelines in the management of chronic non-cancer pain. Pain Physician. 2006 Jan;9(1):1-39.
[10]Walker DJ, Zacny JP. Subjective, psychomotor, and physiological effects of cumulative doses of opioid mu agonists in healthy volunteers. J Pharmacol Exp Ther 1999;289:1454-64.
[11]Ministry of Health Malaysia Drug Formulary 2014. Available at http://www.pharmacy.gov.my/v2/ms/dokumen/formulari-ubat-kementerian-kesihatan-malaysia.html. Accessed on 10 Jan 2015.

Using Strong Opioids in Patients with Co-morbidities

- Chronic opioid therapy should be avoided in patients with decompensated respiratory disease and in patients with history of substance abuse.

- In patients who are taking concomitant benzodiazepines or other CNS depressants, the sedative effects may be enhanced with opioids.

- Patients with impaired drug clearance are at a higher risk of opioid accumulation and serious side effects; therefore lower doses should be used and the patient should be monitored frequently for efficacy and side effects. These include patients with renal impairment, liver impairment, elderly patients and patients with chronic heart failure.

Commonly Used Opioids

Morphine

Morphine is a pure opioid agonist that binds to the mu-opioid receptor in the CNS causing inhibition of ascending pain pathways. It is commonly used for moderate to severe pain. For patients with CNCP, it is recommended that a sustained release formulation of morphine (morphine SR) (e.g. MST Continus®) that has a longer duration of action be used.

Morphine should be avoided in patients who have impaired renal function as accumulation of the active metabolite of morphine (morphine-6–glucoronide) may lead to overdose.

Recommended starting dose for opioid–naïve patients:
- Morphine SR 10 mg 12-hourly
- For elderly patients (>65 years old), Morphine SR 10 mg OD may be used initially

For patients who are not opioid-naïve, a higher starting dose may be considered, depending on the previous dose of opioid used, for example
- Morphine SR 20mg 12-hourly for patients who have been taking Tramadol 300-400mg/day.(cease tramadol when starting morphine)

Morphine dose should be calculated according to opioid conversion tables (Appendix D) if switching to morphine from another strong opioid (e.g. oxycodone).

Oxycodone

Oxycodone is a pure opioid agonist that binds to the mu-opioid receptor in the CNS causing inhibition of ascending pain pathways. Sustained release oxycodone, which is available as Oxycontin®, and immediate release oxycodone which is available as Oxynorm® may be used for moderate to severe CNCP. Targin® is a sustained release preparation containing a combination of oxycodone and naloxone; naloxone in the tablet may prevent or reduce opioid induced constipation.

Recommended starting doses:

For opioid naïve patients:
- Oxycodone SR (Oxycontin®): 10 mg 12-hourly
- Oxycodone IR (Oxynorm®): 5 mg 6 to 8-hourly in patients with renal impairment.

For patients who are not opioid-naïve, a higher starting dose may be considered, such as Oxycodone SR 20mg 12-hourly.

For the elderly or patients with renal impairment, a lower starting dose is possible using Targin (oxycodone/naloxone) 5mg/2.5mg 12 hourly.

Transdermal Buprenorphine

Buprenorphine is a mixed agonist-antagonist which exerts partial agonistic effects at the mu-opioid receptors and antagonistic effects at the kappa-opioid receptors.

Transdermal buprenorphine takes about 3 days to reach steady state and lasts up to 7 days.

Recommended starting dose
- In opioid-naïve patients: 5 mcg/hour patch
- In non-opioid-naïve patients:10 mcg/hour patch

See Appendix A for further prescribing information on the above drugs.

MONITORING OF THERAPY

Monitoring the 4A's

Patients who are on long term opioid therapy should be monitored using the "4A's":

i. **Analgesia** - review dosage of medications and the adequacy of analgesia
ii. **Activity** - monitor improvement in function and quality of life.
iii. **Adverse Effects** - common side effects of opioids and its management
iv. **Aberrant Behaviour**[12] (see list below)

Aberrant Behaviour

- Uses illicit drugs and /or abuses alcohol
- Hoards medications
- Runs out of medications early
- Uses more opioid than prescribed
- Has self-escalated the dose of opioids
- Obtains opioids from more than one provider
- Appears sedated or confused (eg, slurred speech, unresponsive)
- Expresses worries about addiction
- Expresses a strong preference for a specific type of analgesic or a specific route of administration
- Expresses concern about future availability of opioid
- Reports worsened relationships with family members
- Indicates that she or he "needs" or "must have" analgesic medications
- Requests frequent clinic appointments primarily to discuss analgesic medication
- Exhibits lack of interest in rehabilitation or self-management
- Reports minimal/inadequate relief from opioids
- Indicates difficulty with complying with Opioid Treatment Agreement.

[12]Managing chronic pain with opioids in primary care. http://www.painedu.org/manual.asp#OpioidGuide

Frequency of Follow Up

After initiating opioid therapy, patients should be reviewed on a weekly basis to optimise analgesia and monitor for side effects. Once analgesia is optimised and a stable dose determined, they can be seen once a month. Patients who are adherent to the treatment regime and progressing towards agreed goals of therapy may be reviewed less frequently.

Criteria for Continuation or Discontinuation of Therapy

Continue therapy when you have desirable outcomes with minimal tolerable side effects.
Continuous monitoring of the "4A's" is mandatory, i.e. Analgesia, Activity, Adverse effects and Aberrant behaviour.

Consider discontinuation of therapy in patients who:

- Develop intolerable adverse effects or dangerous complications
- Fail to adhere to treatment regime
- Exhibit aberrant behaviour related to drug use
- Fail to meet the goals that had been laid out
- Fail to comply to the terms of the opioid treatment agreement

SPECIFIC MANAGEMENT ISSUES

Breakthrough Pain

Breakthrough pain should preferably be managed by non-pharmacological methods. However, additional analgesics like paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) may be used on a PRN basis. Unlike in cancer pain, short acting immediate release opioid should be avoided.

Opioid Related Side Effects

Nausea and vomiting

Patients might need anti-emetics for nausea and vomiting when initiating opioid therapy.

Constipation

Routine prescription of laxatives is imperative as constipation can be very troublesome and distressing. If Targin® (SR oxycodone/naloxone) is used, laxatives may not be required; it may be considered as an alternative to Oxycontin® or SR morphine in patients where constipation is a problem despite the use of laxatives.

Sedation

Drowsiness may occur when first starting strong opioids so patients should be warned about not driving and not operating heavy machinery when initiated on opioids.

Tolerance will develop for all side effects of long term opioid therapy except constipation.

Opioid Rotation

If the patient has intolerable side effects with one opioid, it is acceptable to rotate or switch to a different opioid to achieve analgesia with more tolerable side effects. This is known as “Opioid switching” or “Opioid rotation”. Opioid rotation may also be useful in patients who have been on long term opioids and are escalating the dose with no added benefit. When converting from one opioid to another, the equi-analgesic dose is calculated using opioid conversion tables (Appendix D). The starting dose of the new opioid is usually 25-50% lower because of incomplete cross-tolerance between different opioids.

Troubleshooting Common Problems

Compliance Problems
- Reinforce Opioid Treatment Agreement
- Reassess suitability of patient for opioid therapy and consider exit strategy if compliance problems persist

Unacceptable Side Effects
- Decrease dose
- Consider opioid rotation or discontinuation

Inadequate Pain Relief (Without Significant Side Effects)
- Increase dose

Inadequate Pain Relief (With Side Effects)
- Decrease the dose of opioid and add a non-opioid analgesic
- Anticipate and treat specific side effects
- Reinforce non-pharmacological therapy
- Consider opioid rotation or discontinuation

Frequent Breakthrough Pain
- Increase maintenance dose
- Avoid giving short acting opioids - encourage patient to use non-pharmacological techniques for breakthrough pain / flare-ups
- Reinforce use of non-pharmacological techniques

Sleep Problems
- Reinforce use of non-pharmacological techniques including relaxation
- Review sleep patterns and discuss sleep hygiene
- Avoid using anxiolytic drugs e.g. benzodiazepines

REVIEW OF THERAPY

Continuation of Therapy

Continuation of opioid therapy is appropriate under the following circumstances:
- Reduction in pain intensity
- Improvement in function and quality of life
- Progressing towards agreed goals
- Tolerable side effects
- Generally complying with the Opioid Treatment Agreement

Discontinuation of Therapy

If one or more of the following criteria are present, discontinuation of opioid therapy should be strongly considered:
- Intolerable opioid-related side effects or dangerous complications even if there is some reduction in pain
- Failure to achieve adequate analgesia with acceptable side effects, even after opioid rotation
- Failure to meet agreed goals of therapy
- Persistent escalation of opioid dose with inadequate analgesia
- Aberrant behaviour related to drug use
- Persistent non-compliance with Opioid Treatment Agreement
- Deterioration in physical, emotional or social functioning

Cessation of Therapy

Once a decision has been made to discontinue opioid therapy:
- Initiate detailed discussion with the patient about the need for discontinuation of opioid therapy.
- Review exit criteria agreed upon in Opioid Treatment Agreement with the patient.
- Clarify that ceasing therapy is for the patient's benefit and that this does not mean we are abandoning pain management or abandoning the patient.

Opioid medications need to be tapered down and ultimately discontinued. Abrupt discontinuation of opioid therapy will result in varying degrees of opioid withdrawal syndrome.

A medication reduction plan (current dose till medication is stopped completely) should be made with the patient and should be followed as closely as possible. Weaning can be carried out on an outpatient basis, with weekly follow-up of the patient and weekly dose reduction. If withdrawal symptoms occur, the previous dose may be continued for a longer period of time and a slower dose reduction plan made.

See Appendix E for examples of medication reduction plans. Refer the patient to a pain specialist or addiction specialist if there is difficulty in weaning off opioids. In some cases, the medication reduction and cessation can be done more effectively if combined with a cognitive behaviour-based pain management program.

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4. Managing chronic pain with opioids in primary care. http://www.painedu.org/manual.asp#OpioidGuide. Accessed on 10 Jan 2015

5. Trescot AM, Boswell MV, Atluri SL, et al. Opioid guidelines in the management of chronic non-cancer pain. Pain Physician 2006;9(1):1-39.

APPENDIX A
DOSAGE GUIDE FOR RECOMMENDED OPIOIDS
MORPHINE

AVAILABLE FORMULATION	STRENGTH	DOSING	PHARMACOKINETICS	COMMON SIDE EFFECTS
Immediate Release Aqueous Formulation	2mg/ml *Aqueous formulation is prepared by individual institution. Concentration may differ.	**Initial dose:** 5mg - 10mg q4-6 h	**Onset of action** Within 30mins **Duration** Immediate release: 2 - 4 h Extended release: 8 - 12 h **Bioavailability** 17% to 33% **Metabolism** Hepatic (Active metabolite: morphine-6-glucuronide) **Excretion** 90% renal (caution in renal impairment; increased risk of toxicity due to dose accumulation)	**Dermatologic** Pruritus **Gastrointestinal** Constipation Nausea and Vomiting **Neurologic** Somnolence Dizziness Headache **Renal** Urinary retention (<5%) **Respiratory** Depression
Sustained Release (SR) Tablet	10mg 30mg	**Initial dose:** 10 mg q12h **Maintenance:** Titrate based on patient's response and administer daily dose in divided doses (q12h) *To be swallowed whole. Do not chew, crush or dissolve tablet		

OXYCODONE

AVAILABLE FORMULATION	STRENGTH	DOSING	PHARMACOKINETICS	COMMON SIDE EFFECTS
Immediate Release (IR) Tablet (Oxynorm®)	5mg 10mg	**Initial dose:** 5 – 10 mg q4-6 h **Maintenance:** Titrate based on patient's response	**Onset of action** Immediate release: 10 - 15 mins Sustained release: 1 h **Duration** Immediate release: 3 - 5 h Extended release: ≤ 12 h **Bioavailability** 60% to 87% **Metabolism** Hepatic (Active metabolite: negligible) **Excretion** 83% renal	**Dermatologic** Pruritus **Gastrointestinal** Constipation Nausea and Vomiting **Neurologic** Somnolence Dizziness Headache **Respiratory** Depression
Sustained Release (SR) Tablet (Oxycontin®)	10mg 20mg 40mg	**Initial dose:** 10 mg q12h **Maintenance:** Titrate based on patient's response and administer daily dose in divided doses (q12h) *To be swallowed whole. Do not chew, crush or dissolve tablet		
Sustained Release Oxycodone / Naloxone Tablet (Targin®)	5/2.5 mg 10/5 mg 20/10 mg	**Initial dose:** 5/2.5 mg or 10/5mg q12h **Maintenance:** Titrate based on patient's response and administer daily dose in divided doses (q12h) **Maximum daily dose:** 80/40mg * To be swallowed whole. Do not chew, crush or dissolve tablet		

BUPRENORPHINE

AVAILABLE FORMULATION	STRENGTH	DOSING	PHARMACOKINETICS	COMMON SIDE EFFECTS
Transdermal patch	5 mcg/h 10 mcg/h	**Opioid-naïve:** Initiate with 5 mcg/h patch **Opioid-tolerant:** i) Oral morphine equivalent <30mg/day: initiate with 5 mcg/h patch ii) Oral morphine equivalent 30mg – 80mg/day: initiate with 10 mcg/h patch Titrate based on patient's response at a minimum interval of 72 hours **Maximum dose:** 20 mcg/h *Replace patch every 7 days at a different site *Each site can be re-used after 3 weeks	**Onset of action** 17 hours **Duration** 7 days (steady state reached after 3 days) **Bioavailability** 15% **Metabolism** Hepatic (Active metabolite: nor-buprenorphine) **Excretion** Renal 30%, Fecal 70%	**Dermatologic** Application site; Erythema Irritation Rash Pruritus **Gastrointestinal** Constipation Nausea Vomiting Dry mouth **Neurologic** Somnolence Dizziness Headache

APPENDIX B:
OPIOID TREATMENT AGREEMENT

We are committed to do our best to manage your chronic pain condition. It is often difficult to achieve complete pain relief, but our goal is for you to have meaningful pain reduction and a better quality of life.

In your case we have decided that long term opioid therapy is appropriate at this stage of your treatment. Because these drugs have potential for abuse and serious side effects, strict accountability is necessary. The purpose of this agreement is to facilitate this therapy.

I, _____ agree to the following:

1. I have been explained and counseled on the potential benefits of opioid therapy.
2. The goals of opioid therapy are reasonable pain reduction and improvement of function; failure to achieve these may result in cessation of opioid therapy.
3. The common side effects of opioid therapy include nausea, vomiting, drowsiness, giddiness, constipation and itch.
4. Other potentially serious side effects include: tolerance and dependence, and 'withdrawal syndrome' upon sudden cessation of the opioid medication.
5. I will obtain the opioid medication only from you and your unit in your hospital.
6. I will not take more medication than what is prescribed and advised by your unit.
7. I will attend scheduled follow-up appointments and offer information honestly.
8. I agree to undertake certain tests for monitoring of the effects of treatment.
9. I will keep the opioid medication in a safe place.
10. I will not engage in any unlawful activities involving the prescribed medication.

I have understood this agreement and agree to comply with the statements above.

I understand that you or other doctors in your unit have the right to cease prescribing the medication if I fail to comply with this agreement.

Signature of patient: _____

Patient's name: _____

Date: _____

Signature of doctor: _____

Doctor's name: _____

Date: _____

APPENDIX C:
OPIOID RISK TOOL

OPIOID RISK TOOL	Mark each box that applies ✓		Item Score If Female	Item Score If Male
1. Family History of Substance Abuse	Alcohol	☐	1	3
	Illegal Drugs	☐	2	3
	Prescription Drugs	☐	4	4
2. Personal History of Substance Abuse	Alcohol	☐	3	3
	Illegal Drugs	☐	4	4
	Prescription Drugs	☐	5	5
3. Age (Mark box if 16 - 45)		☐	1	1
4. History of Preadolescent Sexual Abuse		☐	3	0
5. Psychological Disease	Attention Deficit Disorder, Obsessive Compulsive Disorder, Bipolar Disorder, Schizophrenia	☐	2	2
	Depression	☐	1	1
	TOTAL			

Total Score Risk Category
Low Risk 0 - 3
Moderate Risk 4 - 7
High Risk > 8

Reference:
Webster LR. Predicting aberrant behaviors in opioid-treated patients: Preliminary validation of the opioid risk tool. Pain Medicine. 2005;6(6):432-442.

APPENDIX D:
OPIOID CONVERSION TABLES

ORAL MORPHINE TO OTHER ORAL OPIOIDS			
	Conversion Ratio	Comments	Reference
Morphine to Tramadol	1 : 5	Oral Morphine 10mg = Oral Tramadol 50mg	1, 2, 3
Morphine to Dihydrocodeine	1:10	Oral Morphine 10 mg = Oral dihyrocodeine 100mg	3
Morphine to Codeine	1 : 8	Oral Morphine 15mg = Oral Codeine 120mg	1, 2
Morphine to Oxycodone	1.5 : 1	Oral Morphine 30mg = Oral Oxycodone 20mg	1, 2, 4

OTHER OPIOIDS TO ORAL MORPHINE			
	Conversion Ratio	Comments	Reference
Oral to Oral			
Tramadol to Morphine	5 : 1	Oral Tramadol 200mg = Oral Morphine 40mg	1,2
Dihydrocodeine to Morphine	10 : 1	Oral Dihydrocodeine 120mg = Oral Morphine 12mg	3
Oxycodone to Morphine	1 : 1.5	Oral Oxycodone 20mg = Oral Morphine 30mg	1,2,4
Parenteral to Oral			
Morphine to Morphine	1 : 3	IV or SC Morphine 10 mg = Oral Morphine 30 mg	2,4
Oxycodone to Morphine	1 : 3	IV or SC Oxynorm 10 mg = Oral Morphine 30 mg	2
Pethidine to Morphine	0.4 : 1	IV or IM Pethidine 100 mg = Oral Morphine 25 mg	2
Transdermal to Oral			
Transdermal Fentanyl to Morphine	1 : 100	Transdermal Fentanyl 25 mcg/hour ≈ approximately Oral Morphine 30- 60 mg/day	3,4
	Transdermal Fentanyl 25 mcg x 24 hour = 600mcg/day = Oral Morphine 60 mg		4
Transdermal Buprenorphine to Morphine	1 : 75-100	Transdermal Buprenorphine at 5mcg/hour ≈ approximately Oral Morphine 10 mg/day	3,4
	5 mg patch = 5 mcg/hour for 7days 5mcg/hour = 120 mcg/day 120mcg/day x75 (conversion ration) = 9000mcg Morphine= 9 mg Morphine		4

ORAL MORPHINE TO TRANSDERMAL BUPRENORPHINE			
Approximate Oral Morphine Equivalence	**Patch Strength**	**Delivery Rate**	**Reference**
10mg / 24 hours	**Buprenorphine 5mg / 7days 120mcg / 24 hours**	**5mcg / hour**	**2, 3**
20mg/24 hours	**Buprenorphine 10mg/7 days 240mcg/24 hours**	**10mcg / hour**	**2, 3**
40mg / 24 hours	**Buprenorphine 20mg/7days 480mcg/24 hours**	**20mcg / hour**	**2, 3**

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2. Opioid Conversion 2014, Faculty of Pain Medicine ANZCA. Accessed online 18 January 2015 www.fpm.anzca.edu.au/resources/pdfs/FPM%20opioid%20conversion%202014.pdf/view?searchterm=opioid+conversion

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4. Opioid Conversion Ratios – Guide to Practise 2013, Eastern Metropolitan Region Palliative Care Consortium. Accessed online 18 January 2015. www.emrpcc.org.au/wp-content/uploads/2014/12/EMRPCC-Opioid-Conversion-2013-V2-November-2014.pdf

APPENDIX E :
EXAMPLES OF MEDICATION REDUCTION PLANS

Example 1: A slow reduction in a patient on SR morphine

Time	Drug	Dose
Week 1	Morphine SR	30 mg BD
Week 2	Morphine SR	20 mg OM, 30 mg ON
Week 3	Morphine SR	20 mg BD
Week 4	Morphine SR	10 mg OM, 20 mg ON
Week 5	Morphine SR	10 mg BD
Week 6	Morphine SR	10 mg ON
Week 7	OPIOID MEDICATION CEASED 10 mg ON	

Example 2 : A more rapid reduction in a patient on Oxycontin

Time	Drug	Dose
Week 1	Oxycontin	30 mg BD
Week 2	Oxycontin	20 mg BD
Week 3	Oxycontin	10 mg BD
Week 4	OPIOID MEDICATION CEASED 10 mg ON	

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