Best Practices when using the WHO analgesic ladder

Step 3 analgesics

NCG Palliative Care Committee
Collated by Dr. Nandini Vallath

Best Practices for medical use of strong opioids

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Step 3 opioids are also known as strong opioids OR opioids for moderate to severe pain.

Overview

- Indications, ground rules and best practices
- Individualization in special populations
  - Geriatrics, Patients with kidney disease
- Exercises on prescribing for patients with Persistent moderate to severe Pain

This presentation **does not** cover the following aspects about pain management using step3 opioids.

1. Pharmacology of opioids
2. Differences of chronic pain from acute pain
3. Pathophysiological classification of pains and pathophysiology of chronic pain
4. Pain assessment and documentation
5. Non-pharmacological inputs for managing pain
6. Interventional pain management techniques

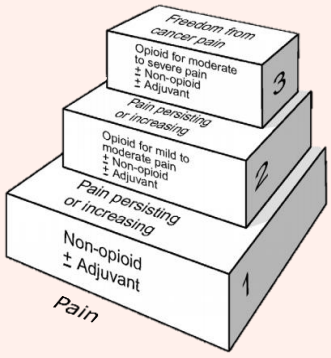
Indications

- Moderate to severe pain
  - Nociceptive, neuropathic or mixed
  - Acute or chronic
- Let the choice be based on intensity and type of pain and not on the stage of disease

We have Morphine, Fentanyl and Methadone available in the Step 3 category in India.

This presentation would emphasize most on usage of Oral Morphine for chronic persistent severe pain.

WHO Analgesic Ladder - 1986



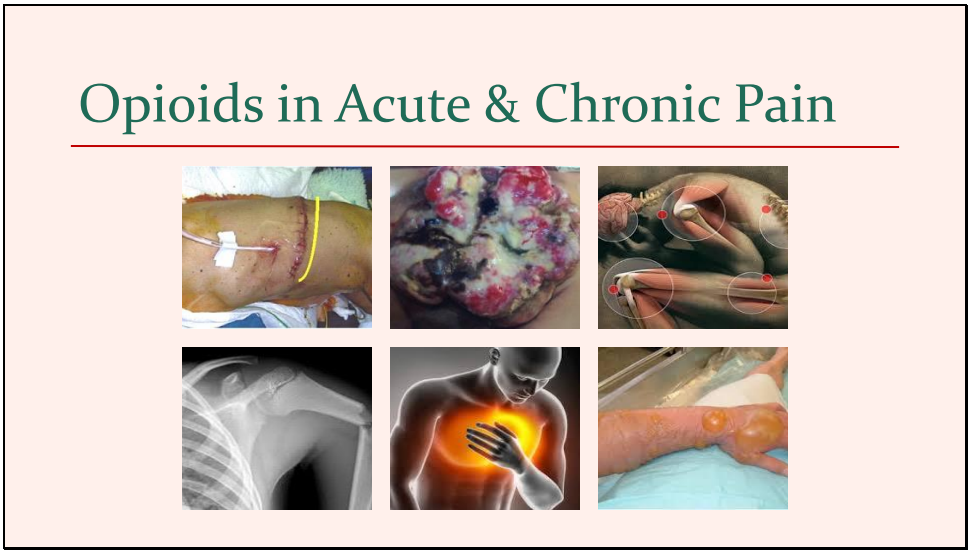
- By Mouth
- By the Clock
- By the Ladder
- Attention to details
- Individualize

WHO recommended the analgesic ladder for a structured approach to managing pain as seen in patients with cancer. The aim was to recommend simple method of utilizing analgesics that are safe, economical and effective. It was meant to empower health professionals across the globe to approach pain with empathy and improve competence in managing pain and relieve the needless suffering due to pain in cancer patients.

BY MOUTH – Ease of drug administration, Manageable by family at home without need for health care professionals – as the drug is needed as long as the pain lasts – which could be life long.

BY THE CLOCK – continuous pain requires continuous analgesia. If prescribed only when patient screams with pain – Pain relief is unsatisfactory AND also, the total analgesic requirement shoots up.

BY THE LADDER – Move up and down the ladder and use the recommended class of drugs based on the type and severity of pain and NOT on poor prognosis or terminality of illness.



How can we improve our sensitivity to persistent pain suffered by our patients?

We need to first identify presentations of chronic pain patients, acknowledge their pain and then respond sensitively and competently.

In acute pain states - the patient is seen to be obviously in pain with tachycardia, sweating, higher BP, and distinct emotional expressions such as crying, moaning etc.

Chronic pain patients may not exhibit the typical sweating, tachycardia, crying etc. seen with acute pain. Instead - they move less, sleep less, speak less, eat less. Their ADLs are affected. These aspects can only be elicited through empathetic conversations and not by quick routine objective measurements.

Best Practices: Managing Acute Pain with step-3 opioids

- Control severity until healing brings down the pain -Prescribe for the day and next day only
- Use IR preparations, AVOID SR/TD preparations
- Cover side effects prophylactically
- Review the pain frequently and decide on the need for further opioid prescriptions
- Step down to non-opioid analgesics EARLY

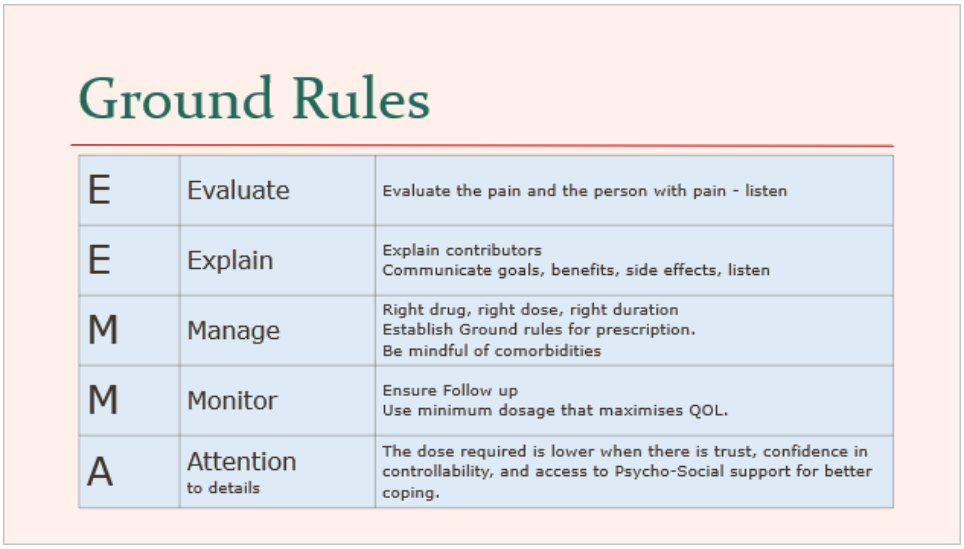
IR – Immediate Release

SR/TD – Sustained Release, Transdermal

Step-3 Opioids for persistent severe pain

Recognize that:

1. Chronic pain is NOT just a long-standing pain. It self-exacerbates, with neuro-plastic changes of Peripheral NS and Central NS with exhaustion of the modulating mechanisms. The frequency and intensity of discharge along the tracts flares up over time and worsens the experience and distress of the patient.
2. Chronic Pain has NO protective role. It is our job to help relieve it.



Ground Rules

E	Evaluate	Evaluate the pain and the person with pain - listen
E	Explain	Explain contributors Communicate goals, benefits, side effects, listen
M	Manage	Right drug, right dose, right duration Establish Ground rules for prescription. Be mindful of comorbidities
M	Monitor	Ensure Follow up Use minimum dosage that maximises QOL.
A	Attention to details	The dose required is lower when there is trust, confidence in controllability, and access to Psycho-Social support for better coping.

EEMMA is the acronym for principles of controlling pain.

Rule One **Evaluate**

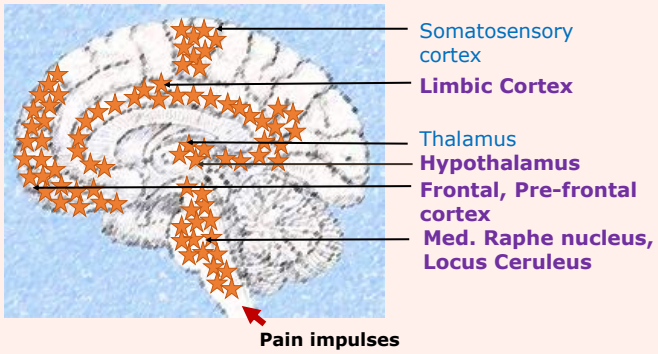
- Opioid prescription is a very responsible decision taken after careful evaluation of the pain and the person in pain
- Is the pain opioid sensitive?
- Is there a non-pharmacological input that would help?
- Are there negative thoughts and emotions? What is the meaning of the pain to the patient?
- How can I follow up this patient?

If psychological morbidity is suspected – manage it through Multi-disciplinary approach including MSW, psychologist, psychiatrist.

Depression lowers the threshold to pain - Mental calm and good sleep brings down the dose of opioids in managing the pain.

The Emotional Experience

Role of psycho-social care influencing appraisal of pain

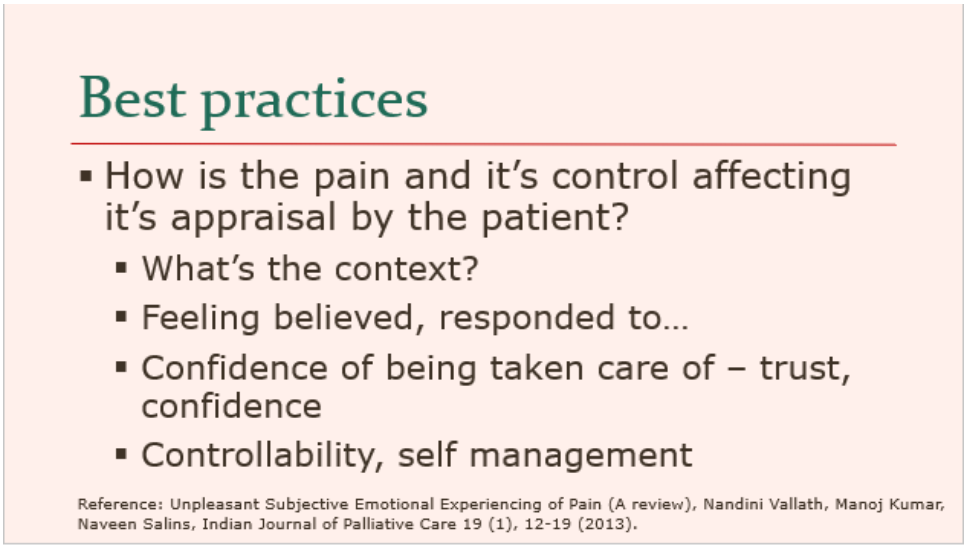


Reference: Unpleasant Subjective Emotional Experiencing of Pain (A review), Nandini Vallath, Manoj Kumar, Naveen Salins, Indian Journal of Palliative Care 19 (1), 12-19 (2013).

It may be noted that pain pathway is projected beyond the thalamus and sensory cortex - into several regions of the brain dealing with affect and emotions.

Pathways also involve Brain stem regions for descending modulatory pathways, dealing with modulation of perceived pain.

The Pain felt by the person is a product of many complex factors influencing perception and modulation.



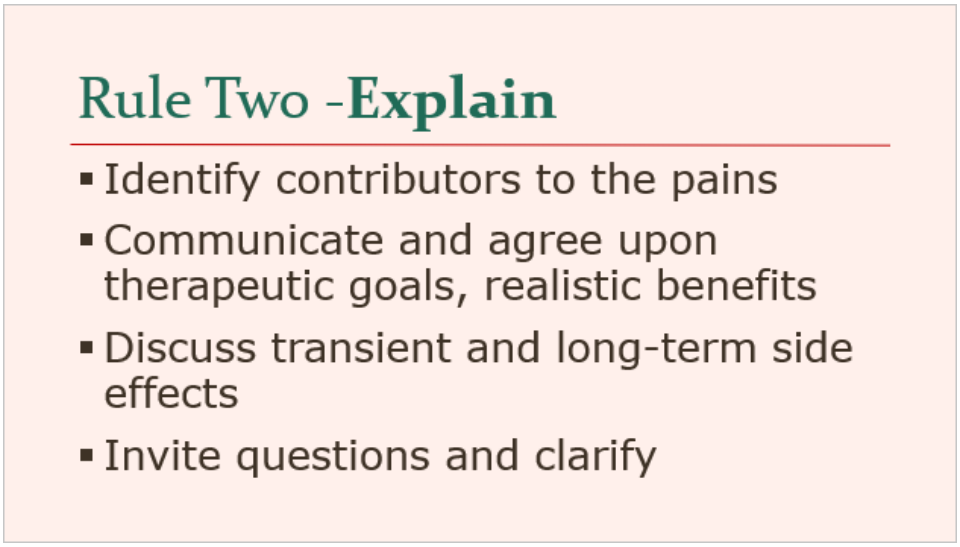
Individuals differ in their appraisal of pain.

Context

The situation in which pain is experienced also affects the severity – e.g. Pain of major trauma in a war front – with immediate possibility of return to safety, is experienced as less severe by the soldier; than when a person is diagnosed with a life-threatening illness like cancer.

Controllability

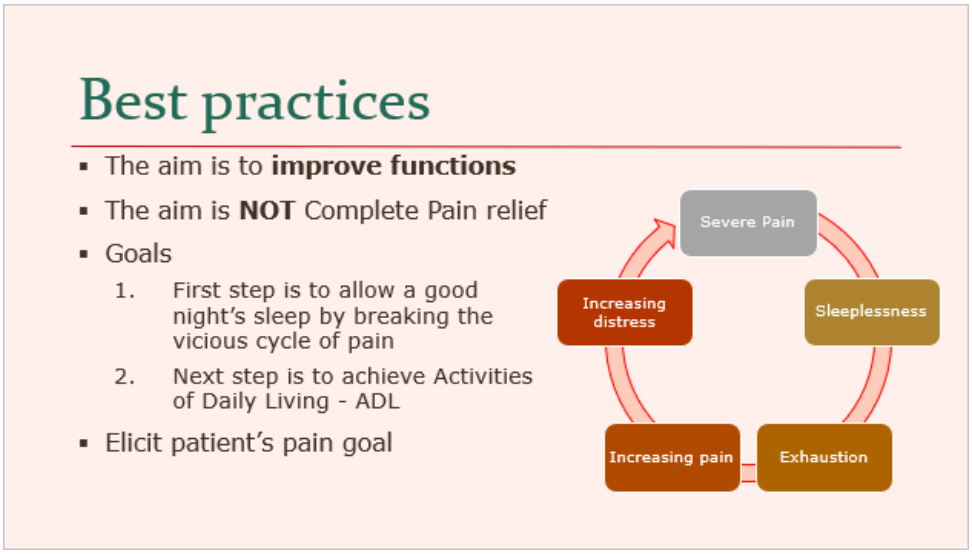
By acknowledging, validating their experience and responding to it early - we are contributing to raising their pain threshold.



Elicit and respond to questions by the patient and family

Compliance is possible only when we understand details, explain situation and how the medicine would help, elicit fears in the patient and family in starting the opioid medications and respond to them satisfactorily.

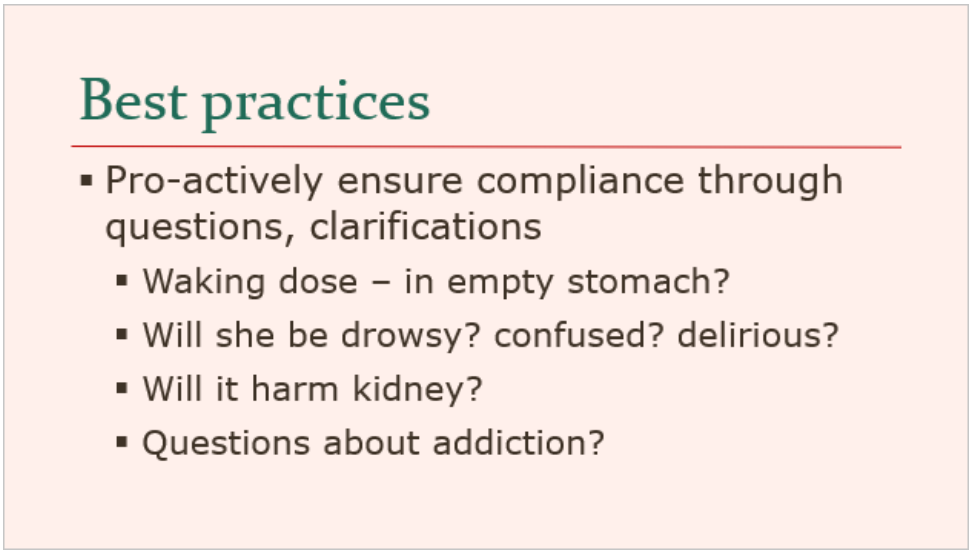
Refer to the **Frequently Asked Questions** in the Palliative Care section on the NCG website. This includes FAQs by patients as well as professionals.



Complete pain relief may lead to unacceptable levels of adverse effects.

The adverse effects can make the patient non-compliant- e.g. patient may refuse medications due to severe nausea / vomiting. Such a patient may prefer tolerable reduction in pain with minimal side effects.

Patient's Pain Goal is the best guide to plan our dose and titration.



Explanation that waking up dose means not having to wait until breakfast. That it can be taken in empty stomach without harm.

Many patients generalize pain killers into one group as toxic to kidney – this needs explanation that opioids do not harm kidney function.

Differentiate addiction seen for the euphoric effect with peak CNS plasma levels of parenteral opioids in prone personalities Vs. the gradual plateau levels of the Morphine 3 or Morphine 6 Glucuronide released after liver metabolism of the orally taken drug.

Refer to the Frequently Asked Questions in the Palliative Care section on the NCG website. This includes FAQs by patients as well as professionals.

Rule Three - **Manage**

- Prescribe appropriately, safely
- Clear prescription - continuous pain relief for continuous pain
- Provide SOS dose for breakthrough pain
- 24-hour subcutaneous dose is ½ -1/3rd of oral dose

Oral Morphine – it is safe, economical and effective. It is available in most formats –immediate and sustained release tablets, oral solutions, injections. It may be administered by most routes used for giving medicines – oral, parenteral – IV, SC, epidural, intrathecal, topical, intraarticular etc.

It is effective per rectum. We should request manufacturers for PR formats too. This formulation would be useful in very sick patients and in small children.

Morphine is NOT calculated according to mg / Kg body weight. It is gradually titrated based on the severity of pain and relief experienced.

In an adult without comorbidities who has persisting pain despite appropriate prescription of step – 2 medications and multi-disciplinary inputs, we may start with 10 mg of immediate release Morphine 4 hourly. Extra SOS doses would be required for covering breakthrough pains and this needs to be explained clearly. This is 1/6th of the 24-hour dose

The number of regular doses and the extra doses used is best recorded in a book - for adjusting the total dose during the next review.

Best practices

- Continue step I drugs when indicated
- Long acting preparations [SR tab, Transdermal] are NOT SUITABLE as 1st line therapy
- Prescribe Prophylactically for known Side Effects
- Provide written Precautions

Always prescribe stimulant laxatives for constipation that occurs in 99% of patients. Do not wait for constipation to happen.

Nausea/ vomiting is seen in 1/3rd of patients only. Providing antiemetic - haloperidol / metoclopramide and instructing to take it if required adds to compliance to prescription by the patient.

Sedation is a self-limiting effect. Patient may also sleep more in the first few days to compensate for the lost sleep of weeks/months spent with severe pain. It would be important to advice on not using machinery [including driving] during this period.

If sedation continues after the 1st week, it is important to review the patient, look for other drugs /contributory factors, and reduce the dose when appropriate.

Date	Medicine	On waking	8 AM	10 AM	12 PM	2 PM	6 PM	Bed time	SOS NRS>5/ 10	What for
24th Oct	T PARACETAMOL 650 MG			1		1		1		Pain Relief
	T. METOCLOPRAMIDE 10 MG								1	Vomiting
	T. MORPHINE 10 MG	1		1		1	1	2	1	Pain relief
	T. IBUPROFEN 400 MG		1			1		1		Pain relief
	T. BISACODYL 5 MG							2		Motion
	Review Date, Dr. Name, Sign, Reg. No.			10.30 AM on 27th Oct						

This is a sample of prescription of strong opioids. The timing and explanation for each drug is clearly indicated.

Instead of time – we can use face of the clock too

Avoid using formulations which contain drug combinations. As it hampers individual drug titrations. They are also costlier.

The early morning and night doses ARE NOT TIMED specifically as 6 am or 10 pm – so that patients are not unnecessarily disturbed from sleep just to give medications. Disturbed sleep can lower the pain threshold.

The night dose may be doubled – so that patient need not wake up with pain in the middle of the night. The drowsiness due to the extra dose may be advantageous.

The review date – to ensure clarity in review and for record for the nurse in charge to follow up if the patient does not show up.

Prescribing - Best practices

Instructions on the backside of Prescription

1. Medications such as Morphine are effective only if taken in the prescribed dosage at the prescribed time intervals
2. If there is excessive sleepiness, irrelevant talking, or if there are difficulties with passing urine, vomiting etc. please stop the medications and contact the clinic at the earliest.

Prescribing - Best practices

Instructions on the backside of Prescription

3. If for any reason, the tablets are unused, they have to be returned to the clinic
4. Store them safely in closed containers without moisture
5. Do not share these drugs with anyone else
6. Keep the tablets strictly away from children

Patients and family care givers should be aware of the strength of the medicines they hold.

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Ensure there is a person committed to daily record keeping. The registers are maintained meticulously. This is very important requirement as per the NDPS Rules. The guidelines are available at the NCG site.

Risk of abuse in a patient is discussed in more detail in the document on Safe Usage of Opioids.

Refer to the Palliative Care section on the NCG website.

- Patient's Name
- Registration details
- Number of dispensed tablets?
- Daily account of stock

Sample of daily record keeping

The number on the right-end column indicates the reducing number of stock of tablets of Morphine Sulphate. The next day's register begins with the end stock of the previous day.

Interruptions in supply leads to needless suffering. The doctor in charge of the stocks should stay mindful of the quantity of opioids in the institution. Application for fresh stock early would prevent interruptions in the supply to patients who require the medicine for their pain relief.

Rule Four **Monitor**

- Review, review, review
- Do not start if review is impossible
- If direct review is difficult,
  use family carer, general practitioner
  or community volunteer

Monitoring – Best Practices

- Is the Analgesia satisfactory?
- Oral Immediate Release [IR] Morphine - Dose is usually modified after 36 hours.
- This allows steady blood levels to be achieved as per the T ½ life of the drug before escalating the dose.

Frequency for upscaling daily dose

- Approximate duration for steady state blood levels = 5 times T-half life
- For oral IR Morphine - 5 X half life = 5 X 6 hours = 30 hours
  - Hence - wait for at least 36 hours before stepping up the dose by 25-50%
  - Exception – escalating uncontrolled pain
- For SR Morphine- 5 X 16 -20 hours = 80 -100 hours
  - Step up not earlier than 4-5 days

Difficulty with titration is another reason why Fentanyl patch is not a good 1st line Step -3 drug.

Monitoring – Best Practices

- Is the **A**nalgesia satisfactory?
- Is the pain relief improving patient's **A**ctivity?
- Pain relief and **A**dverse effects -Right balance??
- Is there an **A**buse potential?
  - **A**berrant behaviour
    - Trust but verify

The 4 As guide the decision to continue opioids as well as the dose.

The most important factor is that the relieved pain improves prioritized functions of the patient.

Goal of opioid therapy

Lowest dose that achieves analgesia with **maximum function** and **minimum side effects**

Aim of therapy is NOT complete pain relief; it is enhancing function due to satisfactory pain relief. Hence it is important to elicit patient's pain goal.

Rule Five **Attention to Details**

- **Individualize:** understand meaning attributed to the pain, psycho-social contributors, patient's pain goal, abuse potential to attain the right dose
- Understand and foster dignity → maximise QOL
- Progress of disease, function of systems e.g. kidney

Often the meaning attributed by the patient for his/her suffering contribute to unrelieved pain. There may be guilt and pain may be internalised as a punishment. This needs to be elicited and addressed

Enquire

What is it that I should know about you, that would help me care for you better?

If Pain persists?

- Is there compliance to the medicine?
- Is it reaching the site of action?
  - Alimentary absorption – nausea, vomiting?
  - Edema / poor circulation affecting subcutaneous injection?
- Under-dosing? improper choice?
- Have we missed major distress?

Despite impeccable assessment and rational and adequate prescriptions – Rule out 1st - Poor compliance with medication or a new pain

Consider emotional contributors - fear, anxiety, depression.

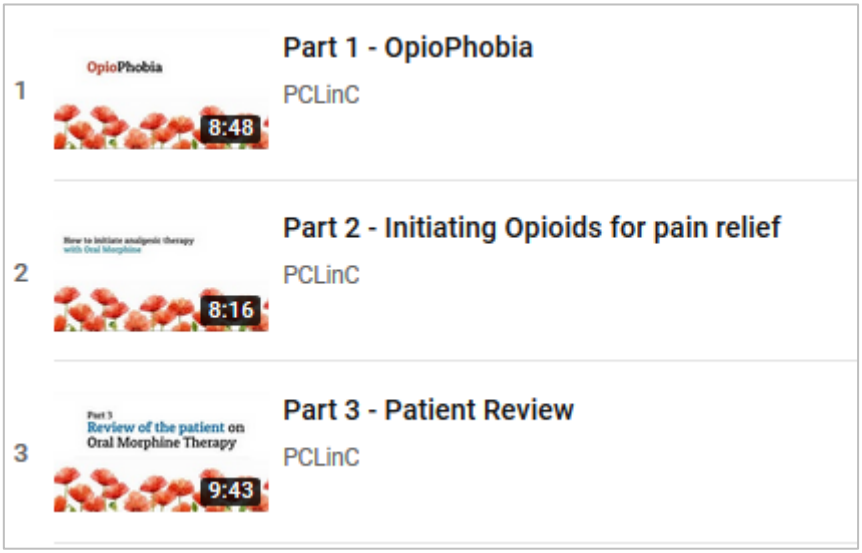
Pain will not be adequately managed unless patients feel heard and participates to control their situation.

If Pain disappears?
Weaning - Best Practices

- Opioids given for even = or > 1 week needs weaning
- Wean when pain-free for > 4 weeks on a regular unchanged dose, OR post intervention
- Decrease by 25–50% and observe for a week.
- If pain relief continues, decrease by 25% or 10% [when long term] every 1-2 weeks - until it is stopped, or until the pain recurs.
- If pain recurs, increase to the previously satisfactory dose.

Patient on long term opioids may have total relief of pain through an intervention e.g. radiotherapy for bone pain / interventional Nerve Block.

Opioids should not be stopped suddenly, unless used for very short duration of < 4 days.



YouTube Video Link

This set of 3 videos help understand the sequence of interactions usually required when starting a patient on oral Morphine.

Best Practices for Older Patients

Best practices - older patient

- Pain may masquerade as abrupt changes in behavior and function
  - Instability; Incontinence; Immobility
  - Confusion, restlessness, aggression, anorexia, and fatigue
- Patient may not complain – Assess carefully

Older patient do not always complain of pain even as they suffer. It may surface as changes in routines.

Step 1 Drugs

- PCM not > 2 g/D – [liver dysfn, alcohol]
- Avoid - Nonselective NSAIDs and COX-2 Inhibitor
  - Gastrointestinal and renal toxicity, hypertension, heart failure
  - Naproxen, Ibuprofen safer with CAD / CVD

AUGUST 2009–VOL. 57, NO. 8 PHARMACOLOGICAL MANAGEMENT OF PERSISTENT PAIN IN OLDER PERSONS - **American Geriatric Society**

PCM- Paracetamol

CAD – Coronary Artery Disease

CVD – Cerebrovascular Disease

COX-2 – CycloOxygenase 2 Inhibitor

Step 1 Drugs

- Avoid Diclofenac Na
- Avoid taking NSAIDs with
  1. Aspirin
     if necessary, take 20 min before
  2. Steroids

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Using Step 3 Drug

- Morphine has slower onset and takes longer for peak levels
  - Start with 2.5 mg – then titrate …
- TD Fentanyl – onset -18-24 hours; duration 72-96 hours

Using Opioids in elderly

- **Prefer Immediate Release preparations**
- Evaluate Hydration, malnutrition
- Look for co-morbidity, other medications
- **Care - with administration of medicine**
- Simplest regime, bunch medicines together, check understanding
- Cognitive dysfunction, depression
- Who is the personal care giver? Is the patient alone?
- **Gradual and slower titration to the right dose**

Cockcroft-Gault Equation

82 year old male with serum creatinine of 1.2

$$\frac{140 - 82 \times 62(\text{Weight})}{72 \times 1.2(\text{S. Creat})}$$

Estimated GFR = 41.6
(moderate to severe renal failure)

22 year old male with serum creatinine of 1.2

$$\frac{140 - 22 \times 62(\text{Weight})}{72 \times 1.2(\text{S. Creat})}$$

Estimated GFR = 84.6
(mild renal failure)

Alteration in the estimated GFR in two patients of different ages, with the same creatinine levels.

FACTOR IS 1 IN MALES AND 0.85 IN FEMALES. Hence value to be multiplied by 0.85 in females

Opioids in renal impairment

Drug	Effect	Comments
Fentanyl*	Drug may accumulate Not removed by dialysis	Not significant with bolus dose. Caution with infusion. RECOMMENDED
Methadone*	No accumulation Not removed by dialysis	Usual caution. 50% reduction. Learned vigilance. RECOMMENDED

*Ref: OTPM & PCF-5th

OTPM – Oxford Text Book of Palliative Medicine

PCF 5th – Palliative Drug Formulary – 5th edition

Opioids in renal impairment

Drug	Effect	Comments
Codeine* Morphine	M3G and M6G accumulates Removed by dialysis	M3G – neurotoxic Prolonged narcolepsy **NOT RECOMMENDED** ↓ dose, ↑ interval
Tramadol* MAY USE	Parent and metabolite accumulates	↑ Epileptogenicity **NOT RECOMMENDED** Not > 50 mg BD

*Ref: OTPM & PCF-5th

Fentanyl Citrate TD Patch

Fentanyl is not a 1st line medicine. It is used for suitable candidates after the 24 hour dose for satisfactory pain has been established through titrated use of oral Morphine.

The conversion is then based on the efficacy formula – Morphine: Fentanyl of 1: 100.

60 mg oral Morphine = 25 ug/hour patch

The patch has to be placed without wrinkles, on non-hairy, non-irradiated skin. After application of the patch. there is waiting period of 8-12 hours for the drug to reach steady blood level.

*TD – Transdermal system

Fentanyl Citrate TD Patch

- Specific indications
  - Difficulty with oral intake, Tablet phobia / poor compliance, Renal failure
  - Intolerable side effects - nausea, vomiting, severe constipation, hallucinations
- The dose may need to be adjusted in patients with fever or has high core body temperature
- It is costly

Fentanyl is very expensive. The average weekly cost of using 25 ug/hour patch is > Rs.2000/- which could be the average weekly income of Indian families.

As the medications are required for long periods, cost is a very important consideration.

The cost involved long term is an important consideration. If the prescription is given to the patient, without this consideration, we may be contributing to the poverty of the family. As the meagre earnings would get used up for pain medications as crisis expenditure. Children may be pulled out of schools and the family may compromise on food – so that the suffering patient gets relief.

Oral Morphine is cheap and there is always a dose for most pain patients –that may be arrived at with meticulous evaluation of pain and titration of medications.

Further Reading

- **Managing pain in children - WHO**
  http://apps.who.int/iris/bitstream/10665/44540/1/9789241548120_Guidelines.pdf
- **Cancer Pain Relief - WHO**
  http://apps.who.int/iris/bitstream/10665/37896/1/9241544821.pdf

What can we do prevent needless suffering due to persistent unrelieved pain?

1. By committing to learn more about pain and about using opioids
2. Understand guidelines for stocking and dispensing and help to get it stocked at our institutions. Step wise details are available in NCG website.
3. Attend Palliative care settings to experience the practicalities of using it. There are videos uploaded on the NCG online portal to understand some of these aspects.
4. Most important requirement – we have got away with not treating pain! Transform this apathy of healthcare systems by acknowledging and responding to patient's pain and improve their quality of life.
5. Educate others on rational and safe use of medications in the WHO ladder.