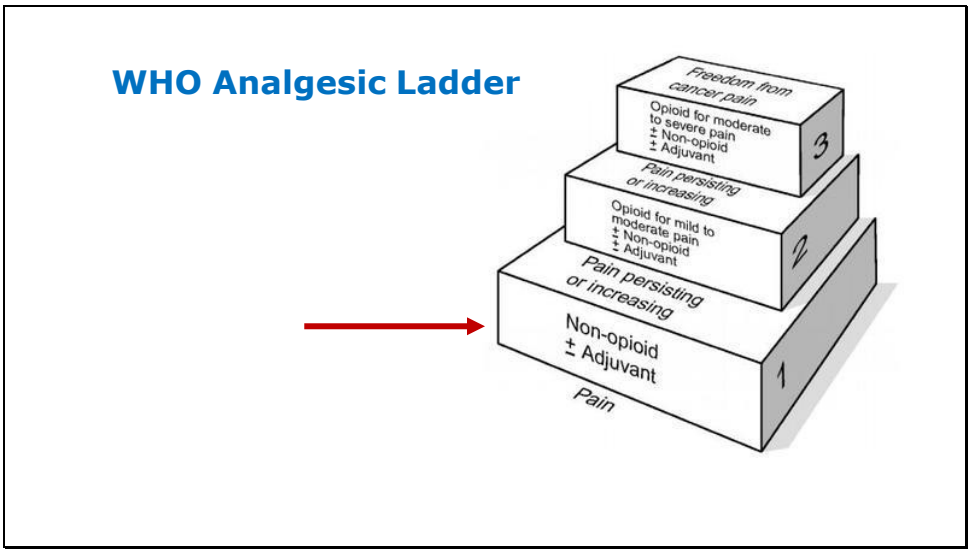
Best Practices when using the WHO analgesic ladder

Step 1 & 2 Analgesics

NCG Palliative Care Committee
Collated by Dr. Nandini Vallath

Step 1 of the WHO Analgesic Ladder



71-76% of patients have “satisfactory” pain relief with the WHO 3 step analgesic ladder.

Ventafridda, Tamburini M, Caraceni A, De Conno F, Naldi F. A validation study of the WHO method of pain relief. Cancer 1987; 59:850-856.
Zech DF, Grond S, Lynch J, Hertel D, Lehmann KA. Validation of World Health Organization Guidelines for cancer pain relief: a 10-year prospective study. Pain. 1995.63(1):65-76.

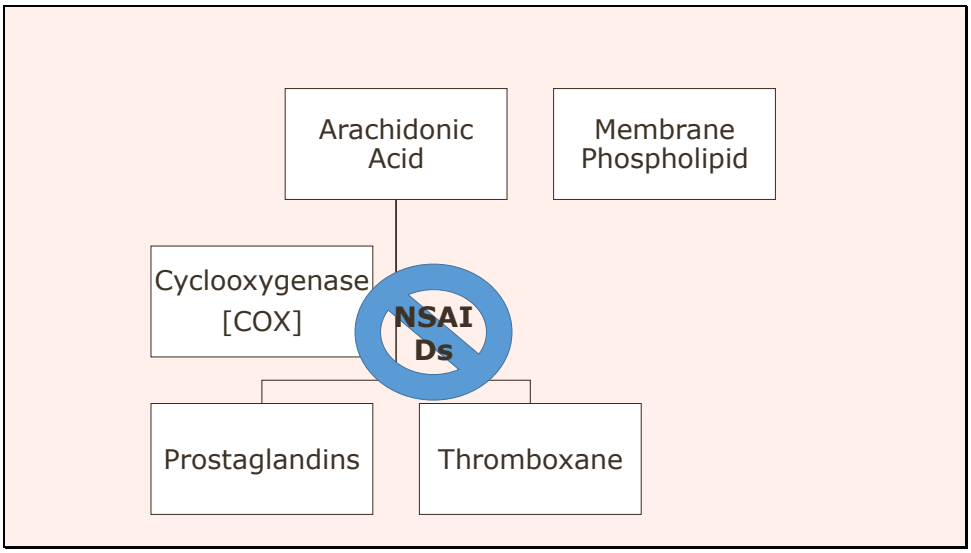
Step 1: Non-Opioids

Paracetamol, NSAIDs, Adjuvants

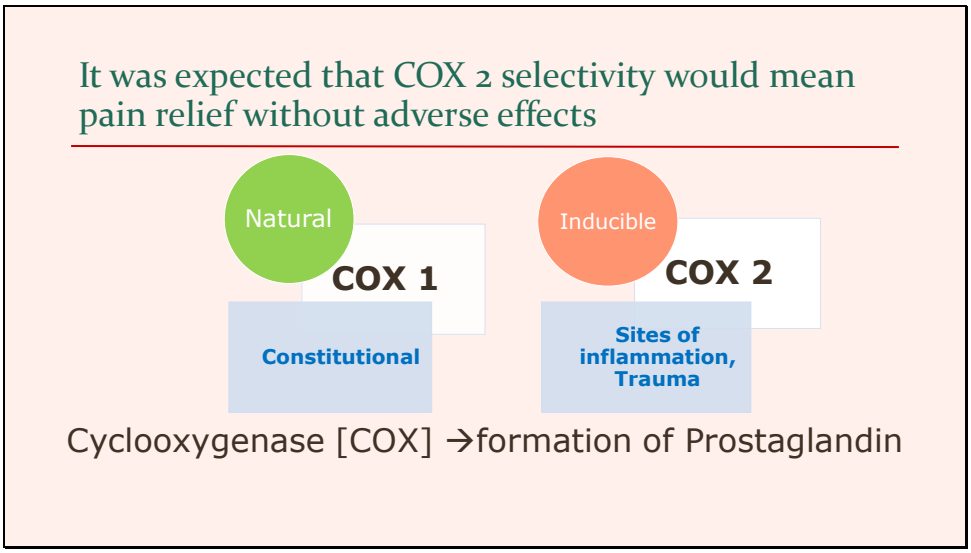
Paracetamol

- Usual Dose: 10-12 mg/Kg Q 6H
- Up to 15 mg/Kg Q 4H when used short term-1 Day
- Maximum dose – 4 Gms/ Day
- Elderly – safe to use not > 2 Gms/ Day

- Paracetamol has predominant central action
- It is available as 500mg/650 mg tablets, 150 mg injections and 1 Gm/ infusion and as suppositories
- It has a significant analgesic action which helps reduce total requirement of NSAIDs and opioids
- Since they are available in combination with innumerable drugs, it would be important exercise to estimate the total dose taken by the patient per day, before prescribing.



COX Inhibition by NSAIDs – Reversible and by Aspirin – Irreversible



The adverse effects caused by;

- COX -1 Inhibition - Gastric irritation, Diminished platelet adhesion
- COX 1 or 2 Inhibition - Renal toxicity
- Anaphylactoid reactions
- Poisoning is known to occur

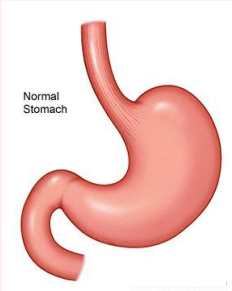
COX 2 selectivity & thrombosis

- Non-selective NSAIDs - worsen bleeding tendency
- COX 2 selective NSAIDs - promote thrombotic events – disturbs Prostacyclin ←→Thromoboxane balance

Just because COX 2 newer does not mean they are safer. The thrombotic complications are higher with COX 2 inhibitors. The risk of renal injury is the same as non-selective NSAIDs.

Risk factors for gastric toxicity – COX1

- High NSAID dose
- History of upper GI symptoms
- Advanced age
- Concurrent aspirin / corticosteroid
- Comorbidities- Rheumatoid arthritis



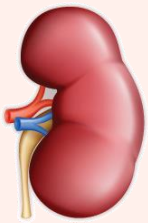
Gastric erosions may be silent

The chances of haemorrhage increases by 3 to 10 fold

- Add gastric protection when using NSAIDs.
- For those without prior history, Histamine antagonist may suffice with adequate follow up.
- For those with history suggestive of Acid peptic disease, Proton Pump Inhibitors are preferred.
- Often patients take PPIs on full stomach. They need special instruction to time it for 30-45 minutes prior to feeding.

Risk factors for Renal toxicity

- Dehydration, Cirrhosis
- Advanced age
- Poorly controlled Diabetes
- Concurrent nephrotoxic drugs e.g. antibiotics, dyes.

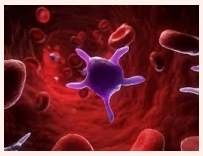


Mechanism: Reduced Renal perfusion and GFR
Leading to Na^+, K^+, water retention, Hypertension, Cardiac failure

- Educate the patient especially about maintaining hydration and urine output.
- Special precautions if they are traveling
- Educate them to withhold the medicines intermittently when there is bearable pain
- Pantaprazole that is often used concomitantly, causes interstitial nephritis

Risk factors for pro-thrombotic effects

- Use of COX 2 drugs
- All NSAIDs have COX 2 inhibition- Diclofenac very strong COXib
- Advanced age, Smokers
- Hypertension, Hyperlipidaemia, Diabetes



Ref: Fosbol et al - International Journal of Stroke Volume 9, Issue 7, pages 943–945, October 2014

Avoid use in patient who are > 65 years

Effect of COX 2 selective drugs

- On the stomach: Less gastric irritation
- On the platelets: No platelet inhibition
- On the Kidney: No Renal protection

Cause-Specific Cardiovascular Risk Associated With Non-steroidal Anti-inflammatory Drugs Among Healthy Individuals

Fosbol E.L et al; Circulation;
Circ Cardiovasc Qual Outcomes 2010;3;395-405

COX inhibitors and coronary and cerebrovascular events - Minimum risk to maximum	
Aspirin	No evidence to support prevention of CVS risk when used concomitantly with NSAIDs
Ibuprofen	Longest experience – relatively safe up to 1200mg/ Day
Naproxen	Relatively lower risk
Diclofenac , Indomethacin, Aceclofenac	COX 2 selective, High Risk
Piroxicam, lornoxicam, Meloxicam	COX 2 selective, High Risk
Celecoxib - COX 2 specific inhibitors	High risk

Ref: Fosbol et al Circulation, June 8 2010

It is important to note that Ibuprofen in doses up to 1200 are safer than the more commonly used Diclofenac Sodium, from cardio-vascular point of view.

About Diclofenac

- 6 deaths from CVS/CNS events/ 100 patient years of Rx
- "The increased risk associated with Diclofenac is of particular importance because it is one of the most commonly used NSAIDs worldwide.
- Diclofenac appears almost as COX-2–selective as Rofecoxib".

Concomittant low dose Aspirin does NOT protect

- NSAIDs affects cardioprotective effect of Aspirin.
- When prescribed together, take the NSAID 30 minutes prior to aspirin.
- Consider additive gastric mucosal protection when using Aspirin with another NSAID.

Recommendations for NSAIDS

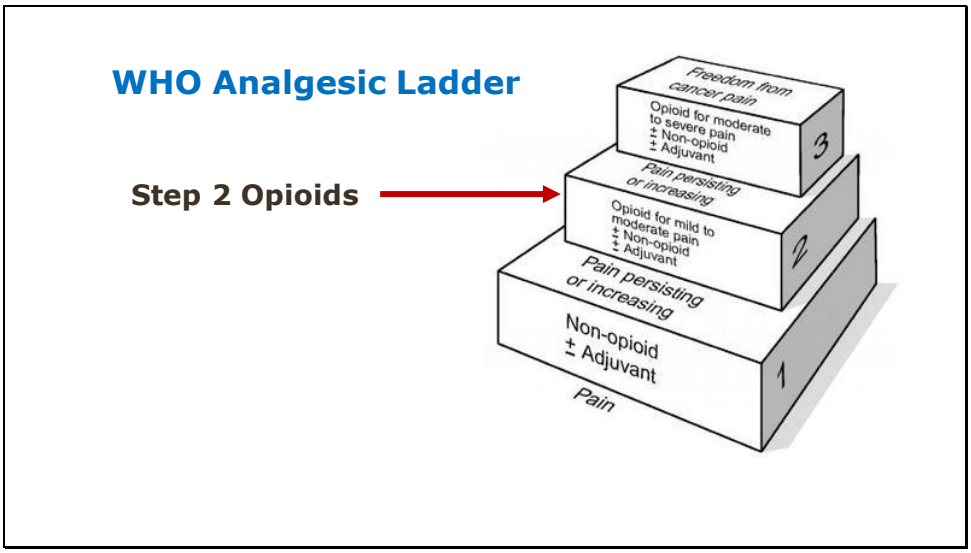
- Lowest dose for the shortest duration
- Use with Proton Pump Inhibitor
- The choice tailored to the GI and CVS/ CNS risks
- Extra caution - Age >65 years, DM, HT, CKD, acute diseases

Recommendations for NSAIDS

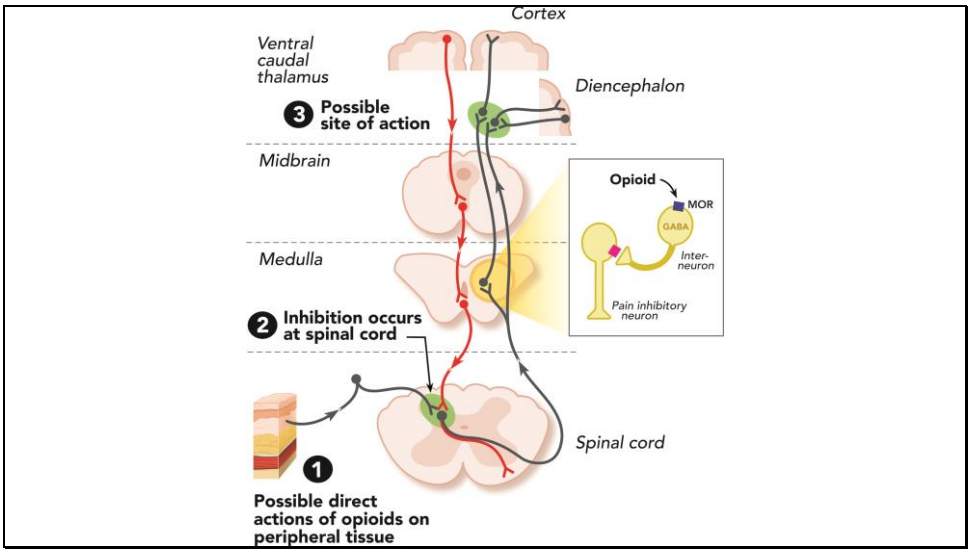
- Avoid combinations
- Ensure hydration - educate the patient
- Monitor kidney – baseline S.Creatinine, and 3 monthly or if physical signs or symptoms
- Look for additive adverse effects with other medications

Recommendations for NSAIDS

- Routinely use gastroprophylaxis – Proton Pump Inhibitor / Antihistaminics
- Ibuprofen (≤1200 mg / Day) & Naproxen are safer.
- Consider Diclofenac as COX 2 selective.
- Use NSAIDs at the lowest dose for shortest duration



- When pain is persisting or increasing despite rational use of step 1 drugs in adequate doses, move to step 2 – add a weak opioid to the existing analgesic regime.
- Weak Opioids are
  - Codeine
  - Dihydrocodeine
  - D-Propoxyphene
  - Tramadol
  - Tapentadol



The presence of Opioid receptors is widespread across the body – including peripheral tissues.
This explains the possibility for using opioids by direct local administration too at tissues / spinal cord levels.

Opioids for moderate pain

- Some Step 2 opioids have prescription advantage
  - Tapentadol -u+NERI agonist–50 mg 6hrly / 8hrly [Max-500mg/D]
- Tramadol [50-100 mg 6hrly / 8hrly;Max- 400mg/D] requires triplicate prescription
- Codeine, Dihydrocodeine [30-60 mg 6hrly] are strictly controlled drugs.

- Codeine is one of the drugs in the notified list of “Essential Narcotic Drugs” – which may be accessed, stocked and dispensed by institutions specifically “Recognised” for this.
- The “Recognized medical Institutions – RMIs” are authorized by the State Drug Controller.

Opioids for moderate pain

- Not commonly used
  - Pethidine
    - Short acting, high side effects
  - Pentazocin
    - Agonist + Antagonistic
    - short acting, poor oral efficiency
    - limited by ceiling dose
    - psychotomimetic effects
- Useful but not available
  - Dextropropoxyphene
  - Need for lifting the legal ban

WHO ladder drugs - Step II

Step 2 Drug	Side Effects
Codeine	Constipation
Proxyvon	Cumulative, Q-T interval prolongation
Tramadol	Expensive Serotinergic syndrome
Tapentadol	μ + NE pathway; less N / V

- Dextropropoxyphene has had several decades of safe use before it was banned. The issue of prolonged QT interval has been sighted as important reason for the ban.
- Efforts are on to make this medicine available as a cheaper effective alternative to other medicines in the group.
- Tramadol can lower the seizure potential

Step 2 analgesic for children

- The Step 2 does not exist in the WHO Recommendations when treating cancer pain in Children
- Step 3 drugs are used directly in the right dosage, if Step 1 medicines are ineffective.

- Codeine is not recommended by WHO for treating cancer pain in children because,
  - It is not a reliable analgesic as it depends on conversion to Morphine, forit's pharcological effect. The corresponding enzyme is found to be lacking in children.
- Tramadol is not recommended by WHO for treating cancer pain in children because,
  - There have not been adequate studies to show safety for use in children

EAPC recommendations – Step II Weak Recommendations

- All are equally efficacious; max Side Effects with tramadol
- Amongst step 2 drugs, Codeine is a controlled drug
- Total Codeine dose not to exceed 360mg / D [S E]
- Codeine not >240mg /D IF COMBINED with 600mg PCM

- Note that Paracetamol is a common combination drug.
- Ensure the dose does not cross . 4 Gms / Day in healthy adults

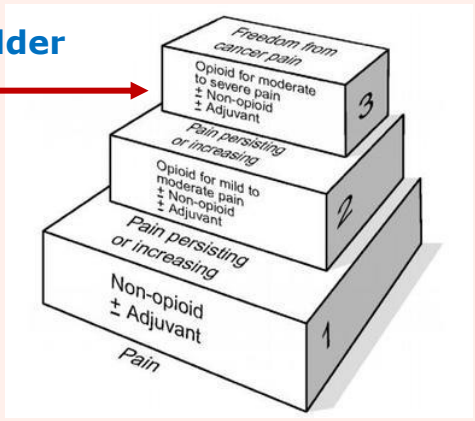
EAPC recommendations – Step II Weak Recommendations

- Tramadol may be combined with PCM, daily doses < = 400
- The division into weak or strong opioids is for convenience of use
- Morphine ≤ 30 mg per day can be used as Step 2 opioid.
- Pre-emptively handle SE of Opioids

- Morphine may be used in opioid naïve patients;
- It is a cheaper and effective Step 2 option in India

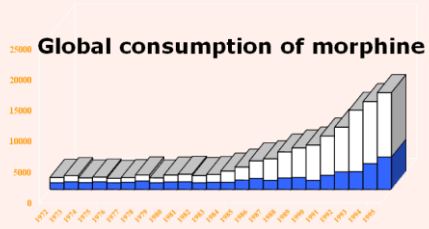
WHO Analgesic Ladder

Step 3 Opioids

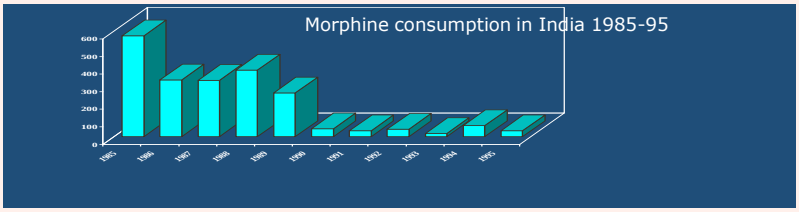


- Step 3 opioids are the strong opioids.
- When patient has pain that is persisting or worsening despite adequate doses of Step 2 medicines [non-opioids and weak opioids] then it is time to move from Step 2 to step 3.
- This done by discontinuing the Step 2 and replacing it with a strong opioid.
- The step 1 medications may be continued if not contra-indicated
- Step 3 opioids are Strong Opioids
    - Morphine, Fentanyl, Methadone
    - Not available in India – Oxycodone, Hydrocodone

FACTs about Opioid Access and availability



96% adults, 99% children with severe cancer pain do not have access to opioid medicines in India



Contributors to poor availability

- Medical Institutions faced stringent regulations - maintaining multiple licenses for acquiring, stocking, prescribing and using opioids.
- Harsh punishment prescribed in the NDPS Act 1985 (e.g. possible10 years of rigorous imprisonment even for clerical errors) alienated institutions and pharmacists from stocking these medicines.
- Attitude and knowledge of professionals towards using opioids were negative:
    - Exposure of professionals was restricted to injectable opioids as used in acute or emergency situations. This led to exaggerated fears about addiction and respiratory depression for all formats.
    - Lack of availability of opioid formats like oral Morphine at medical colleges and hospitals, prevented exposure and training of professionals in using them for managing chronic pain.
    - This developed into unfounded fears opiophobia.
- The public associate opioids with addiction or as the last resort and are reluctant to use the drug even if it meant great degree of suffering. This fear was often reinforced by professionals.

Why is there so much needless suffering due to persistent unrelieved pain?

- Despite the Amended NDPS Act in 2014, the situation has not changed much.
- This because, most regions in India still follow the old Rules with all it's complexities.
- Generations of doctors still do not have practical knowledge on prescribing and using oral Morphine long term.
- Opiophobia is strong amongst professionals and public – even now
- ***The guidelines for stocking opioids are available in NCG website under the section on Palliative Care.***