USE OF MORPHINICS AND ITS DERIVATIVES IN THE TERMINALLY ILL CANCER PATIENT

An *adapted* version from the American NCCN Guidelines, 2019

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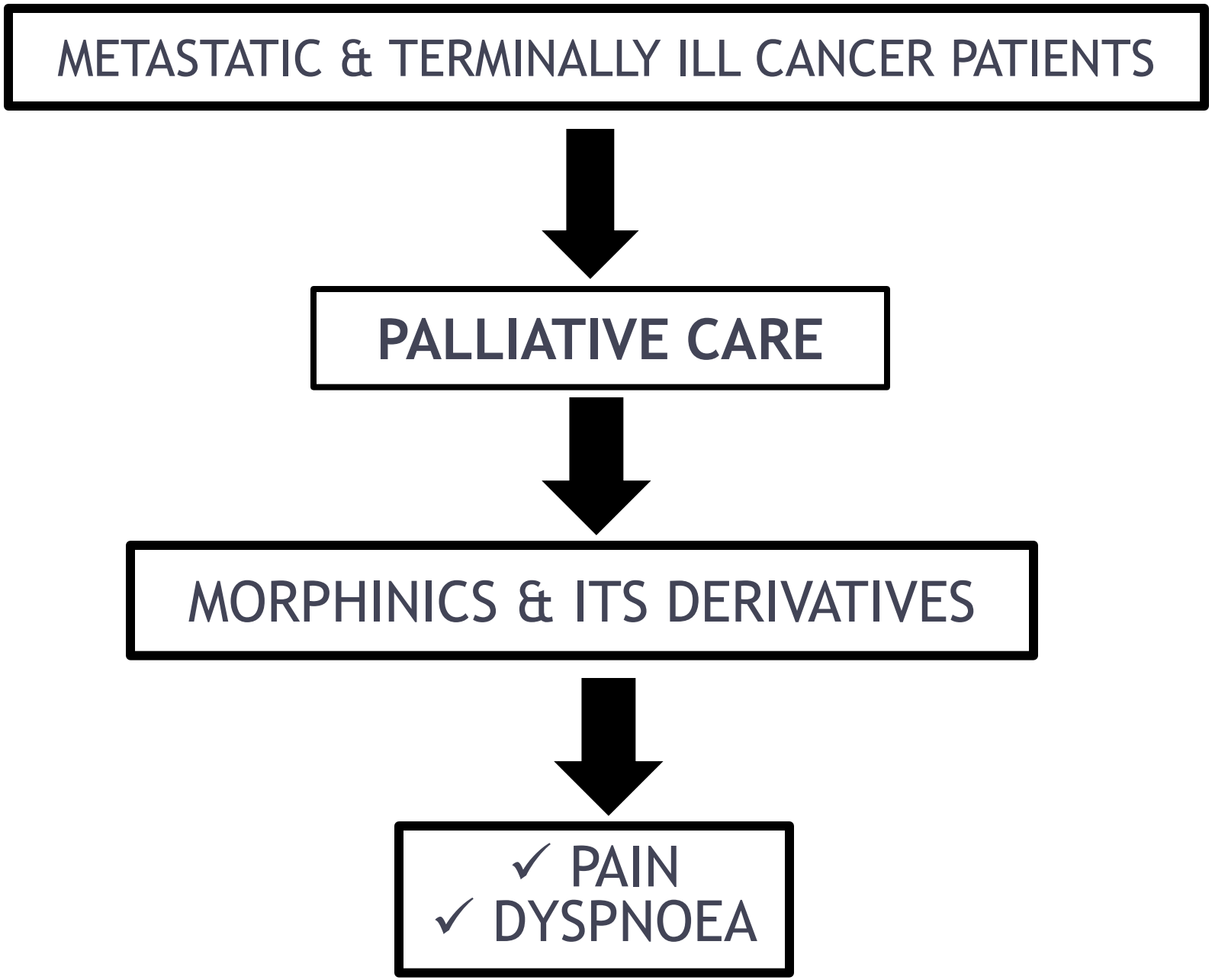
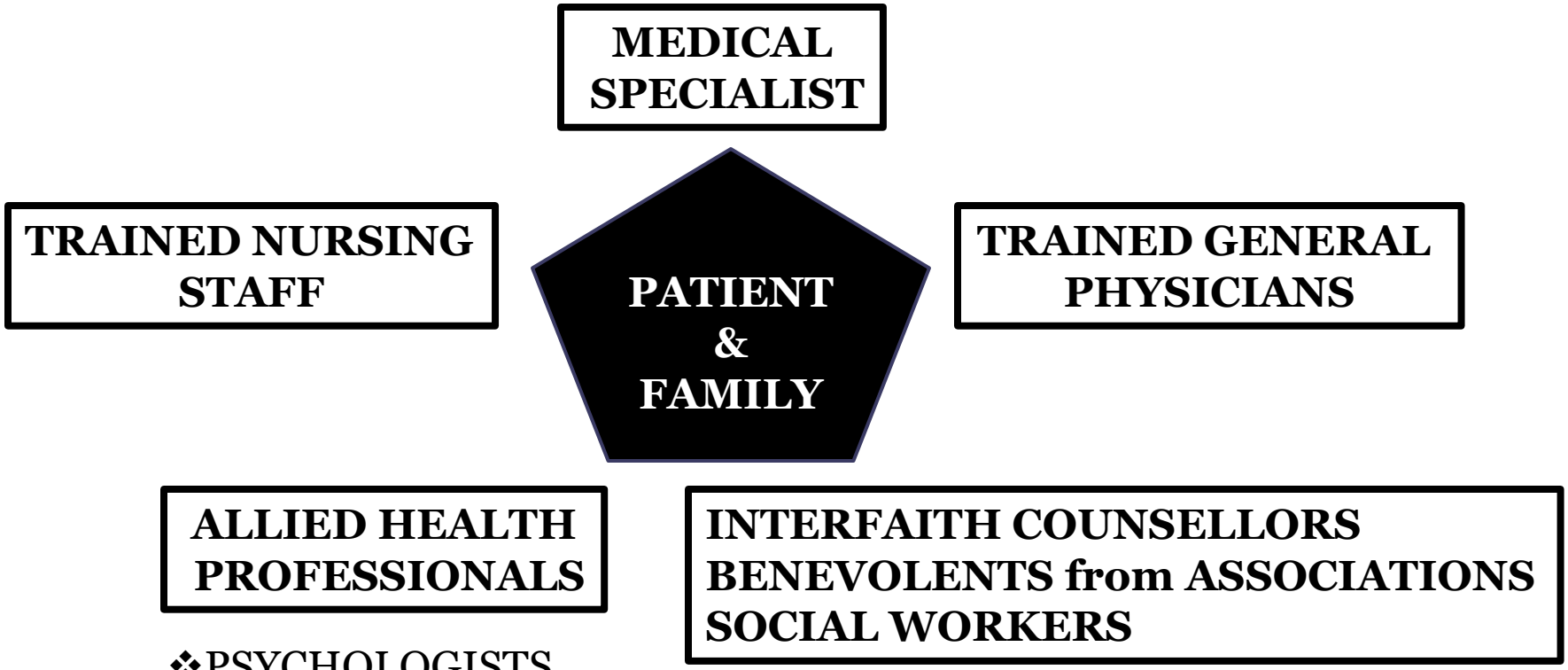

METASTATIC & TERMINALLY ILL CANCER PATIENTS
PALLIATIVE CARE
MORPHINICS & ITS DERIVATIVES
✓ PAIN
✓ DYSPNOEA

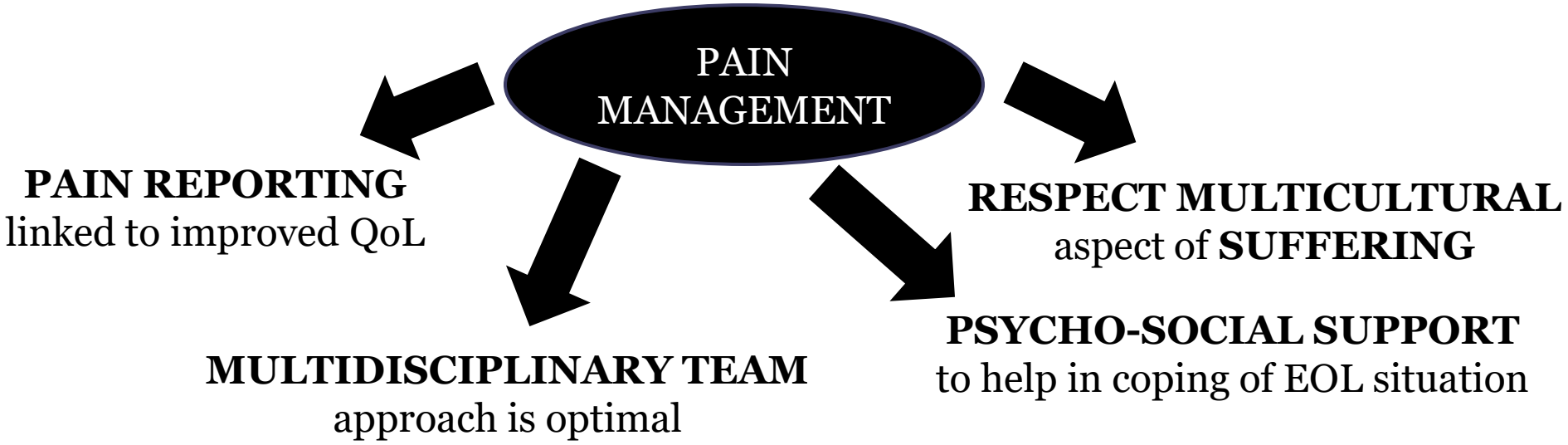
PALLIATIVE CARE: A MULTIDISCIPLINARY APPROACH



- PSYCHOLOGISTS
- DIETETICIANS
- PHYSIOTHERAPISTS
- SPEECH THERAPISTS
- STOMA CARE SPECIALISTS
- CLINICAL PHARMACISTS

PAIN

PAIN (according to IASP): is an unpleasant, sensory & emotional experience associated with actual or potential tissue damage or described in relation to such damage.



5 A's of PAIN MANAGEMENT

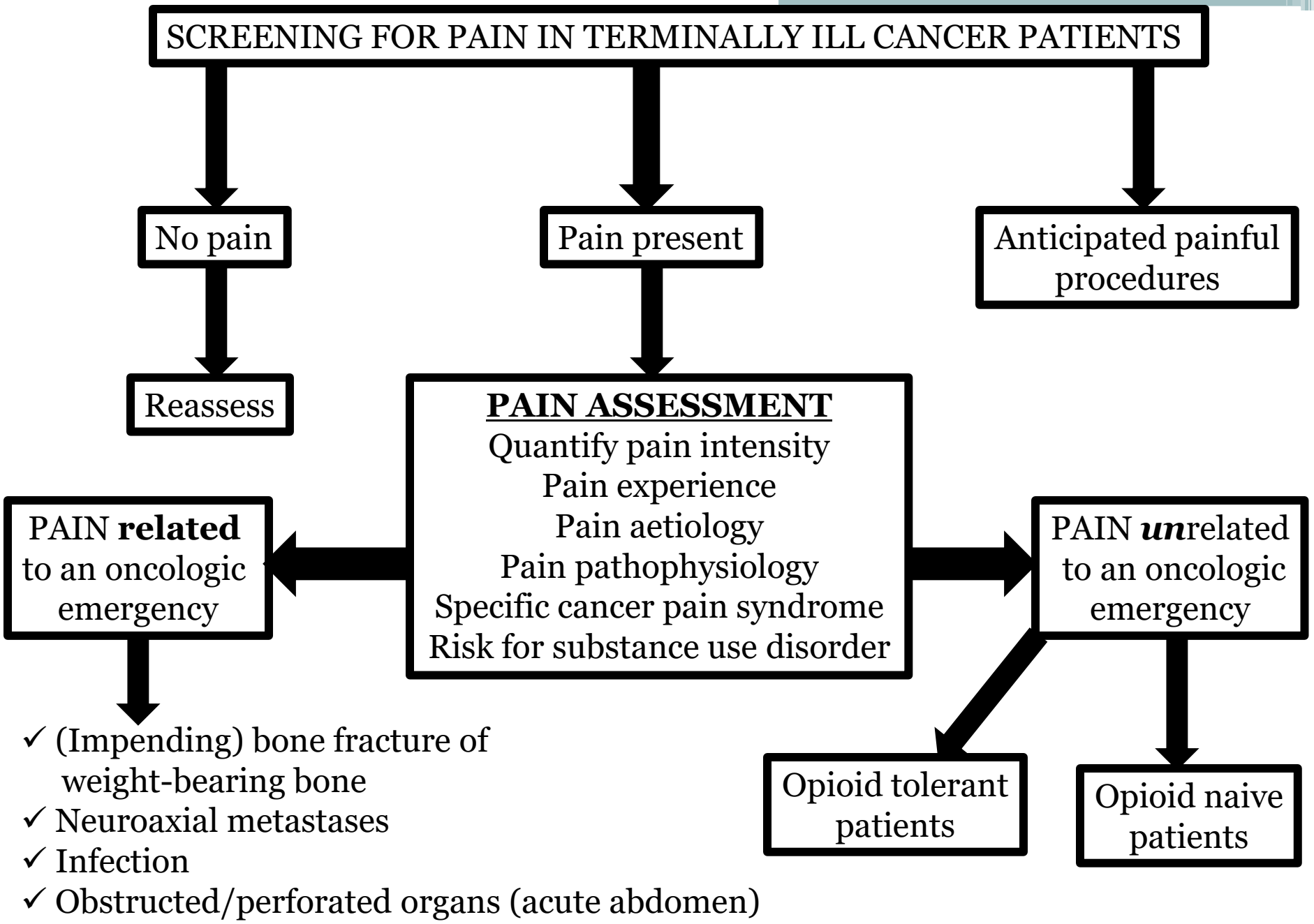
ANALGESIA (optimize analgesia)

ACTIVITIES (optimize activities of daily living)

ADVERSE EFFECTS (to be minimized)

ABERRANT DRUG TAKING

AFFECT (relationship between pain and mood)


SCREENING FOR PAIN IN TERMINALLY ILL CANCER PATIENTS
No pain
Pain present
Anticipated painful procedures
Reassess
PAIN ASSESSMENT
Quantify pain intensity
Pain experience
Pain aetiology
Pain pathophysiology
Specific cancer pain syndrome
Risk for substance use disorder
PAIN related to an oncologic emergency
PAIN unrelated to an oncologic emergency
✓ (Impending) bone fracture of weight-bearing bone
✓ Neuroaxial metastases
✓ Infection
✓ Obstructed/perforated organs (acute abdomen)
Opioid tolerant patients
Opioid naive patients

PAIN INTENSITY RATING

Always ask patients about : current pain, the worst pain, average pain, the least pain in the past 24h. Use the pain intensity rating.

Also include : worst pain in past week, pain at rest, pain with movement.

Table 1: Numerical Rating Scale

Numerical rating scale:

- Verbal: "What number describes your pain from 0 (no pain) to 10 (worst pain you can imagine)?"
- Written: "Circle the number that describes your pain."

0 1 2 3 4 5 6 7 8 9 10

No pain — Worst pain you can imagine

Categorical scale:

"What word best describes your pain?"

None (0), Mild (1–3), Moderate (4–6), or Severe (7–10)

Table 2: The Faces Pain Rating Scale - Revised[1,2]

0 2 4 6 8 10

Instructions: "These faces show how much something can hurt. This face (point to the left-most face) shows no pain. Each face shows more and more pain (point to each face from left to right) up to this one (point to the right-most face)—it shows very much pain. Point to the face that shows how much you hurt (right now)."

[1]Hicks CL, von Baeyer CL, Spafford P, et al. The Faces Pain Scale - Revised: Toward a common metric in pediatric pain measurement. Pain 2001;93:173-183.

[2]Ware LJ, Epps CD, Herr K, Packard A. Evaluation of the Revised Faces Pain Scale, Verbal Descriptor Scale, Numeric Rating Scale, and Iowa Pain Thermometer in older minority adults. Pain Manag Nurs 2006;7:117-125.

PAIN

CORNERSTONES OF PAIN MANAGEMENT

1. Comprehensive pain management is needed as most patients have multiple pathophysiologies and multiple symptoms (*via* pharmacologic and non pharmacologic modalities).

2. Anticipating analgesic side effects (constipation).

3. Patient and family education as well as psycho-social support.

4. For acute or severe pain or pain crisis, consider hospitalisation.

5. Regularly scheduled analgesics with supplemental doses to manage breakthrough pain.

6. Select the most appropriate medication based on pain diagnosis, comorbidities & potential drug interactions.

7. Analgesic regimen may include an opioid, paracetamol or NSAIDs.

8. Reassessment.

PAIN

Mild
3 or less

1. Consider non opioids.
2. Adjuvant therapies.
3. If persistent, consider short-acting opioids.

Moderate to severe
4 or above

1. Consider hospital admission if acute, severe or pain crisis.
2. Start short-acting opioids.

OPIOID NAIVE PATIENT

Those not chronically receiving opioid analgesic <u>on a daily basis</u> and therefore have not developed significant tolerance

OPIOID TOLERANT PATIENT

Those who are chronically receiving opioid analgesic <u>on a daily basis</u>.

<u>Tolerance (according to FDA)</u> : <u>receiving at least</u> :

- 25 μg/h Fentanyl* patch
- 60 mg Morphine* daily
- 30 mg oral Oxycodone daily
- 8 mg oral Hydromorphone
- or an equianalgesic dose of another opioid for a week or longer

INITIATING SHORT ACTING OPIOIDS IN OPIOID NAIVE PATIENTS

PAIN 4 or above (moderate to severe)

ORAL ANALGESIC
(peak effect : 60 mins)

5-15 mg Morphine sulfate or equivalent

Reassess efficacy and side effects at 60 mins

IV BOLUS
(peak effect : 15 mins) or **PCA**

2-5 mg IV Morphine sulfate or equivalent

Reassess efficacy and side effects at 15 mins

Pain unchanged/increased → Increase dose by 50-100% → After 2-3 cycles, (Re)consider IV titration

Pain decreased but inadequately controlled → Repeat same dose

Pain improved and adequately controlled → Continue at current effective dose as needed over 24h

MANAGING PAIN CRISIS IN OPIOID TOLERANT PATIENTS

PAIN 4 or above (moderate to severe)

ORAL ANALGESIC
(peak effect : 60 mins)

Administer oral opioid dose equivalent to 10-20% of total opioid taken in the previous 24h

Reassess efficacy and side effects at 60 mins

IV BOLUS
(peak effect : 15 mins) or **PCA**

Administer IV opioid dose equivalent to 10-20% of total opioid taken in the previous 24h

Reassess efficacy and side effects at 15 mins

Pain unchanged/increased → Increase dose by 50-100% → After 2-3 cycles, (Re)consider IV titration

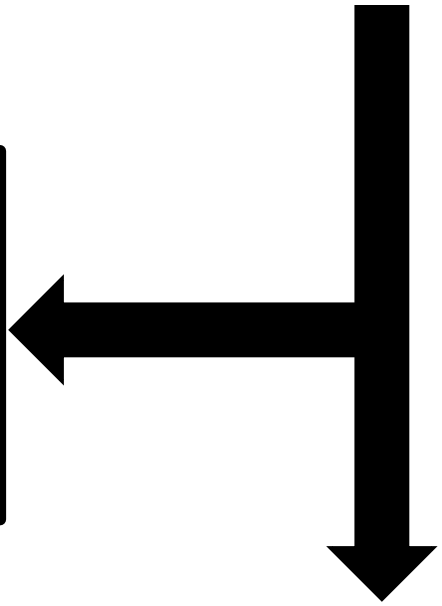
Pain decreased but inadequately controlled → Repeat same dose

Pain improved and adequately controlled → Continue at current effective dose as needed over 24h

SUBSEQUENT PAIN MANAGEMENT

GENERAL PRINCIPLES

- ✓ For persistent pain, initiate regular schedule of opioid with rescue dose.
- ✓ Continue management of constipation & other adverse effects.
- ✓ Provide psychosocial support and patient/family education.
- ✓ Consider adding/adjusting adjuvant analgesics.



If Moderate to severe pain (=/>4)

- ❖ Re-evaluate opioid titration.
- ❖ Pain re-assessment.
- ❖ Consider specific pain syndrome problems.
- ❖ Consider pain speciality consultation.
- ❖ Opioid rotation if dose limiting adverse effects.

If mild pain (0-3)

- ❖ Modify analgesic regimen to minimise adverse effects.
- ❖ Reduce opioids & other treatments when no longer needed.

METABOLISM & EXCRETION OF SOME OPIOIDS

DRUG	METABOLISM	FAECES	URINE
MORPHINE*	Glucuronidation Sulphation N-dealkylation	Trace	90% in 24h (10% morphine, 70% glucuronides, 10% sulphate, 1% normorphine, 3% normorphine glucuronide)
CODEINE*	O-demethylation Glucoronidation	Trace	86% in 24h (5-10% codeine, 60% codeine glucuronide, 5-15% morphine (conjugated)
DIAMORPHINE (Heroin)	O-deacetylation Glucuronidation	Trace	80% in 24h (5-7% morphine, 90% morphine glucuronide)
BUPRENORPHINE (Subutex)	Glucuronidation N-dealkylation	70%, mainly unchanged	2-13% in 7 days
PETHIDINE* (Meperidine)	N-demethylation Hydrolysis	No evidence of excretion	70% in 24h (10% pethidine, 10% normeperidine, 20% mepredinic acid etc)
METHADONE*H	N-dealkylation	30%	60% in 24h (33% methadone, 43% EDDP, 10% EMDP)
FENTANYL*	N-dealkylation Hydroxylation	9%	70% in 4 days (5-25% fentanyl, 50% 4-N-piperidine complex etc)

PAIN ASSESSMENT IN THE NON VERBAL TERMINALLY ILL CANCER PATIENT

- Inability of patients to verbally communicate pain intensity = MAJOR BARRIER relating to pain assessment & management.

- In the absence of self-report, **observation of behaviour** is a valid approach to pain assessment (according to the American Society for Pain Management Nursing).
  CAUTION : Behaviour may indicate other sources of distress (emotional stress, delirium).

- Direct observation, family/caregiver input & evaluation of response to pain medicines or non pharmacologic interventions.

Advanced dementia : http://prc.coh.org/pain_assessment.asp
Checklist of Nonverbal Pain Indicators (CNPI) scale : http://www.ncbi.nlm.nih.gov/pubmed/11706452
Assessment of Discomfort in Dementia (ADD) protocol : http://www.ncbi.nlm.nih.gov/pubmed/11893998
Pain Assessment in Advanced Dementia scale (PAINAD) : http://www.ncbi.nlm.nih.gov/pubmed/12544460

- **Intubated/Unconscious patients** : use of Behavioural Pain Scale (BPS), Critical-care Pain Observation Tool (CPOT).
- Impact of **cultural diversity** in pain reporting.

PROCEDURE-RELATED PAIN & ANXIETY IN THE TERMINALLY ILL CANCER PATIENT

- ✓ Anticipate & offer analgesic (topical, local &/or systemic) and anxiolytic therapy for procedures frequently accompanied by pain & anxiety.
- ✓ Create a calm, comfortable procedural environment.
- ✓ Pre-treatment with an analgesic intervention : wound care, IV-arterial-central line, injection, manipulation, bone marrow aspiration/biopsy, lumbar puncture, skin biopsy, radiation procedure, transportation/change in position with incident pain.

- ✓ **Adm of Analgesics** - *usually* : give the prescribed IV bolus dose 10 mins before or a single sc dose equivalent to 2h basal infusion rate.

- ✓ **Adm of Anxiolytics** - *usually* : Midazolam, oral Lorazepam/Alprazolam, to be given 30-60 mins before a procedure.

- ✓ **Adm of local Anaesthetics** – *usually* : topical local anaesthetic creams (lidocaine, prilocaine or tetracaine) applied to intact skin (as per package insert) & sc adm of Lidocaine with a 27-gauge needle.

- ✓ **Adm of general anaesthesia** by trained personnel.

SPECIFIC CANCER PAIN SYNDROMES

Pain associated with inflammation

Trial with NSAIDs/corticosteroids

Bone pain without oncologic emergency

- NSAIDs, Paracetamol or Steroids.
- Consider Bisphosphonates, Denosumab.
- Diffuse bone pain : consider hormonal therapy, chemotherapy, corticosteroids, radio-isotopes.
- Local bone pain : local RT, nerve block, vertebroplasty, RF ablation.
- Orthopaedic consultation for stabilization.
- Refer to pain specialist.

SPECIFIC CANCER PAIN SYNDROMES

Bowel obstruction

- ❖Evaluate aetiology, if resulting from cancer, consider surgery.
- ❖If partial bowel obstruction, consider Corticosteroids &/or Metoclopramide.
- ❖<u>Palliative management</u> :
  - ✓ Bowel rest
  - ✓ Nasogastric suction
  - ✓ Percutaneous gastrostomy drainage
  - ✓ Corticosteroids
  - ✓ H2 blockers
  - ✓ Anticholinergics (scopolamine, hyoscyanine, glycopyrrolate)
  - ✓ Octreotide

Nerve pain

- ❖Corticosteroids for nerve pain/inflammation
- ❖Antidepressants/Anticonvulsivants/Topical agent for Neuropathic pain
- ❖If still refractory, consider referral to pain sp.

Painful lesions likely to respond to anti-neoplastic therapies

Consider RT, hormones or Chemothp

Severe refractory pain in the imminently dying

Consider palliative sedation

OPIOID PRESCRIBING, TITRATION & SAFETY

- The appropriate opioid dose **is** the *lowest dose* that relieves the patient's pain.
- Titrate with caution those with decreased renal/hepatic function, chronic lung disease, upper airway compromise, sleep apnoea & poor PS.
- Generally, the **oral route** is the *most common*, however IV, SC, IR, TD, TM routes can be considered as indicated to maximise **patient comfort**.
- Calculate dosage increase based upon total opioid dose (around the clock/scheduled and as needed) taken in the previous 24h & increase both doses as required.
- The rapidity of dose escalation should be related to the severity of symptoms, expected analgesic onset & duration, and ability to monitor during dose titration.

OPIOID PRESCRIBING, TITRATION & SAFETY

- Consider opioid rotation if pain is inadequately controlled & further dose titration is limited by adverse effects. Other causes of opioid rotation : out-of-pocket costs, limitations based upon insurance formularies, change in patient's condition (dysphagia, *NPO* status, initiation of tube feeding, renal/hepatic function).

- Initial patient evaluation : assess risk factors for aberrant use of pain medications and use of screening tools (SOAPP-R, ORT,…).

- Monitor for aberrant drug-taking behaviours (COMM tool).

- Educate patients/caregivers about safe use, storage & disposal of opioids.

- Use caution when combining other sedatives (BDZ) with opioids.

POTENTIAL RISK FACTORS for MISUSE/ABUSE OF MORPHINICS

- History of prescription, illicit drug or alcohol dependence/substance abuse.
- History of binge drinking or peers who binge drink.
- Familial history of substance abuse.
- History of psychiatric disorder (anxiety, depression, ADHD, PTSD, bipolar or schizophrenia).
- History of sexual abuse victimization.
- Age < 45 years old.
- Patients with a history of legal problems or incarceration.

OPIOID DOSE REDUCTION

When possible, consider 10-20% opioid dose reduction.

Situations that warrant dose reduction :

- ❖ patient does not need breakthrough analgesic.
- ❖ completion of acute pain event.
- ❖ improvement of pain control through use of non-opioids.
- ❖ well-controlled pain in the setting of stable disease.

If patient has unmanageable adverse effects but pain is mild (3 or below)

- ➢ consider 10-25% downward dose titration & re-evaluate.
- ➢ close follow-up to ensure that pain does not escalate &
- ➢ patient does not develop symptoms of withdrawal.

If patient has significant issues (marked sedation due to sepsis) :

- ✓ consider 50-75% opioid dose reduction.

If patient experiences worsening pain with INCREASING DOSE :

- ❑ consider opioid HYPERALGESIA.
- ❑ opioid dose reduction/rotation should be considered.

MINIMISING THE RISK OF OPIOID MISUSE & ABUSE DURING CHRONIC OPIOID USE

- ❖ Clinical judgement must be exercised.
- ❖ Use caution when combining opioid medications with sedating drugs – BDZ.
- ❖ Educate the patient/family regarding benefits/adverse effects of opioid therapy.
- ❖ Educate regarding **NOT** sharing opioids with family members/friends.
- ❖ Educate about the addictive potential associated with opioids.

Screening tools have been devised, *viz.*

- ➢ **S**creener & **O**pioid **A**ssessment for **P**atients with **P**ain-**R**evised (**SOAPP-R**).
- ➢ **O**pioid **R**isk **T**ool (**ORT**).
- ➢ **C**urrent **O**pioid **M**isuse **M**easure (**COMM**).
- ➢ Comprehensive psychological evaluation can be also helpful.

Provide support for high-risk patients :

- ❑ Educate them.
- ❑ Refer them to Cognitive-Behavioural psychotherapists.
- ❑ Refer to addiction specialists.
- ❑ Encourage **Naloxone** availability for administration by caregivers for patients taking opioids who are at high risk for respiratory depression & sedation.

➢ So as to increase the patient's ability to implement problem-solving strategies.

MINIMISING THE RISK OF OPIOID MISUSE & ABUSE DURING CHRONIC OPIOID USE

- ✓ Urine drug testing at baseline & during treatment, should be considered.
- ✓ Reduce quantity of drug prescribed per prescription.
- ✓ Increase frequency of outpatient visits weekly (if possible).
- ✓ Recommended : pain medication diaries (document dose, no. of tablets, date and time taken).
- ✓ Recommended : electronic medication dispensers.

<u>Educate regarding safe manipulation, storage & disposal of controlled substances</u> :

- ❖ contributes in maintaining a safe community.
- ❖ minimises opioid misuse & abuse in the society.
- ❖ encourage community take-back programs for disposal of unneeded controlled substances.
- ❖ FDA recommends *flushing down the toilet* unneeded opioids !

MISCELLANEOUS ANALGESICS

NON-OPIOID ANALGESICS

KETAMINE

- A non competitive NMDA receptor antagonist which blocks Glutamine.
- **Low** (i.e. sub-anaesthetic) **doses** produce :
  - analgesia.
  - modulate central sensitisation.
  - modulate hyperalgesia.
  - modulate opioid tolerance.

- **NB**: limited data regarding use of Ketamine as an *adjuvant* to opioids for management of cancer pain.

LIDOCAINE

IV Lidocaine infusion may be a useful therapy for :

- Refractory pain.
- Neuropathic pain.

OPIOID ROTATION

- ✓ Determine the amount of current opioid taken in a 24h period.
- ✓ Calculate the equi-analgesic dose of the new opioid.

Pain **in**sufficiently controlled

↓

Begin with 100%-125% of equi-analgesic dose

↓

During the first 24h, titrate liberally & rapidly to attain analgesic effect

Pain effectively controlled & patient is opioid tolerant

↓

Reduce dose by 25%-50%

(allow for incomplete cross-tolerance between different opioids)

NB: Always consider if patient is renal impaired.

OPIOID ROTATION

For Oral opioids

$$\text{Individual dose} = \frac{\text{Total daily dose of new opioid needed}}{\text{Number of doses per day}}$$

Eg. 6 doses for regular PO Morphine every 4h
approx = 2 doses of ER Morphine every 12h.

From Oral opioids to Transdermal Fentanyl

1. Determine the 24h analgesic requirement of Morphine.
2. Consider ratio : **200 mg/d oral Morphine = 100 μg/h Fentanyl patch**.
   NB: Insufficient clinical data to recommend specific ratio to convert from Fentanyl to Oral Morphine.

NB: Due to patient variability, for all opioid rotations, clinical judgement must be used to titrate to the desired response. Conversion info tables are approximate.

CONVERSION TABLE (USA)

Opioid Agonists	Parenteral dose	Oral dose	Factor (IV to PO)	Duration of action
Morphine*	10 mg	30 mg	3	3-4h
Hydromorphone	1.5 mg	7.5 mg	5	2-3h
Fentanyl*	100 µg	-	-	-
Oxycodone	-	15-20 mg	-	3-5h
Hydrocodone	-	30-45 mg	-	3-5h
Oxymorphone	1 mg	10 mg	10	3-6h
Codeine*	-	200 mg	-	3-4h
Tramadol*	100 mg	300 mg	3	-
Tapentadol	-	75-100 mg	-	-
Methadone*$_H$	-	-	-	-

NB: Table of conversion to be used with caution; dose may vary among patients. Consultation with a Palliative care/Pain specialist is recommended.

OTHER CONVERSION TABLES (Australian)

ORAL MORPHINE TO OTHER ORAL OPIOIDS		
ORAL TO ORAL	**CONVER-SION RATIO**	**EX.**
Morphine to Tramadol	1:5	Oral Morphine 10 mg = Oral Tramadol 50 mg
Morphine to Codeine	1:8	Oral Morphine 7.5 mg = Codeine 60 mg
Morphine to Methadone	-	CONSULTANT REQUIRED
Morphine to Oxycodone	1.5:1	Oral Morphine 15 mg = Oral Oxycodone 10 mg
Morphine to Hydromorphone	5:1	Oral Morphine 5 mg = Oral Hydromorphone 1 mg

NB: Table of conversion to be used with caution; dose may vary among patients. Consultation with a Palliative care/Pain specialist is recommended.

OTHER CONVERSION TABLES (Australian)

TRANSDERMAL FENTANYL TO MORPHINE

Fentanyl Patch strength	Dose	IV Morphine equiv. (mg/24h)	Oral Morphine equiv. (mg/24h)	Breakthrough pain management
12 µg/h	288 µg/24h	10-15	20-45	5 mg IR Oral Morphine 1 hourly p.r.n.
25 µg/h	600 µg/24h	30-40	60-100	10 mg IR Oral Morphine 1 hourly p.r.n.
50 µg/h	1200 µg/24h	60-80	120-200	20 mg IR Oral Morphine 1 hourly p.r.n.
75 µg/h	1800 µg/24h	90-120	180-300	30 mg IR Oral Morphine 1 hourly p.r.n.
100 µg/h	2400 µg/24h	120-160	240-400	40 mg IR Oral Morphine 1 hourly p.r.n.

200 mg/24h (NCCN)

NB: Table of conversion to be used with caution; dose may vary among patients. Consultation with a Palliative care/Pain specialist is recommended.

Eg: CONVERTING IV MORPHINE TO IV HYDROMORPHONE

Patient on 8 mg/h IV Morphine and needs to be converted to IV Hydromorphone.

1. In a 24h period : 8 x 24 = 192 mg/day.
2. From conversion tables, 10 mg IV Morphine = 1.5 mg IV Hydromorphone, hence
   192 mg/d IV Morphine = 28.8 mg/d IV Hydromorphone.
   Dividing by 24h = 1.2 mg/h IV Hydromorphone.

3. Now, if the patient was **effectively controlled** with IV Morphine (192 mg/d), *reduce the dose of Hydromorphone by 25%-50%*.
   i.e. 28.8 mg/d reduced by 25% = 21.6 mg/d IV Hydromorphone
   = 0.9 mg/h IV Hydromorphone.
   i.e. 28.8 mg/d reduced by 50% = 14.4 mg/d IV Hydromorphone
   = 0.6 mg/h IV Hydromorphone.

4. If dose of IV Morphine was **ineffective**, *begin with 100% equi-analgesic Hydromorphone dose*.
   i.e. 28.8 mg/d IV Hydromorphone = 1.2 mg/h IV Hydromorphone.
   or increase the dose by 25%,
   i.e. 36 mg/d IV Hydromorphone = 1.5 mg/h IV Hydromorphone.

From Oral Morphine to Transdermal Fentanyl

Patient on 30 mg ER Oral morphine every 12h, & needs to be converted to TD Fentanyl.

1. Total amount of current oral Morphine/24h = 30 x 2 = 60 mg/d.
2. From conversion tables, 200 mg/d Oral Morphine = 100 μg/h Fentanyl patch.
   Hence 60 mg/d Oral Morphine = 30 μg/h Fentanyl patch.

Round down to the closest equivalent patch, i.e. 25 μg/h Fentanyl patch.

NB: Fentanyl patch is available in 12, 25, 50 & 100 μg/h, therefore begin with 25 μg/h patch.

WORDS OF CAUTION REGARDING FENTANYL PATCH

- ✓ Use Fentanyl patch only in patients tolerant to opioid therapy.
(initiate short-acting opioid and control the pain; if insufficient start the TD Fentanyl)

- ✓ Fever, topical application of heat or extreme exertion may accelerate TD Fentanyl absorption & are c-i for TD Fentanyl.

- ✓ The patch is not to be punctured nor cut.

- ✓ NOT recommended for unstable pain requiring frequent dose changes.

- ✓ During the first 8-24h, provide an as-needed dose of morphine or other short-acting opioid.

- ✓ When converting from continuous parenteral infusion Fentanyl to TD Fentanyl, a 1:1 ratio is applied. For some patients, additional dose titration may be required.

- ✓ Analgesic duration of TD Fentanyl = 72h. Some patients might experience end-of-dose failure. Hence they should replace the patch after 48h instead.

From Oral Oxymorphone to Transdermal Fentanyl

Patient on 10 mg ER Oral Oxymorphone every 12h, & requires conversion to TD Fentanyl.

1. Total amount of current Oral Oxymorphone/24h = 10 x 2 = 20 mg/d.
2. From conversion tables, 10 mg Oral Oxymorphone = 30 mg Oral Morphine,
   Hence, 20 mg/d Oral Oxymorphone = 60 mg/d Oral Morphine.
3. From conversion tables, 2 mg/d Oral Morphine = 1 μg/h TD Fentanyl,
   Therefore, 60 mg/d Oral Morphine = 30 μg/h TD Fentanyl.

Hence begin with 25 μg/h TD Fentanyl patch.

ORAL METHADONE

- Commercially available in 5 mg & 10 mg tablets, 1 mg/mL, 2 mg/mL & 10 mg/mL oral solution.
- Associated with many drug-drug interactions.
- Utility to educate patients/family about the ANALGESIC effect of Methadone, besides its use for maintenance of addiction.
- The conversion rate varies with the amount of Morphine (or other opioid) a patient has been using chronically.
- The higher the dose of Morphine a patient used, the more potent Methadone is.

- Has a long & variable half-life AND VARIABILITY WITHIN THE PATIENT OVER TIME, its use is reserved for palliative care/pain specialists.
- Titrate up every 5-7 days by 5 mg/dose. More rapid titration may be required.
- Given at reguler intervals with additional doses of a short-acting opioid (as needed).
- ECG to be done prior to initiation/opioid rotation (! Increased QTc).
- American Pain Society Guidelines recommend a Methadone starting dose that is no more than 30-45 mg/d.

OPIOID ROTATION : from ORAL MORPHINE to ORAL METHADONE

Patient on oral morphine at 30 mg every 4h & needs to be converted to oral methadone.

1. Total dose of Oral Morphine per 24h = 30 x 6 = 180 mg/d.
2. From conversion tables, the conversion ratio is 8:1. Hence, 180/8 = 22.5 mg/d oral Methadone.
3. Reducing the dose by 50% to account for incomplete cross-tolerance, dosing ratio variability & patient variability, 22.5 /2 = 11.25 mg/d oral Methadone, approx. = 15 mg/d oral Methadone.
4. Divide the total daily oral Methadone dose into 3 daily doses, viz. 15/3 = 5 mg oral Methadone every 8h.

Table 2. Dose Conversion Ratios for Total 24-hour Oral Morphine to Oral Methadone[24,25,26]

ORAL MORPHINE	DOSE CONVERSION RATIO (total 24-hour oral morphine:oral methadone)
30–90 mg	4:1
91–300 mg	8:1
300–600 mg	10:1
600–800 mg	12:1
800–1000 mg	15:1
>1000	20:1

Note: If the total daily dose equivalent of morphine is greater than 400 mg, a pain or palliative care specialist should be consulted.

MANAGEMENT OF OPIOID ADVERSE EFFECTS

General principles of opioid adverse effect management :

- adverse effects are common, must be anticipated and be treated accordingly.
- patient/family education is essential.
- opioid adverse effects generally improve over time, except constipation.
- If opioid adverse effects persist, consider opioid rotation.
- Multisystem assessment is necessary.
- Dose adjustment & treatment of adverse effects rely also on patient/family reporting.

Common opioid-induced adverse effects :

- **G-I** : nausea, vomiting, constipation.
- **Autonomic** : xerostomia, urinary retention, postural hypotension.
- **CNS** : drowsiness, cognitive impairment, hallucinations, delirium, respiratory depression, myoclonus, seizure, hyperalgesia.
- **Cutaneous** : pruritus, sweating.

COMORBIDITIES MIMICKING OPIOID-INDUCED ADVERSE EFFECTS

CNS

Cerebral & Leptomeningeal metastases : drowsiness, cognitive impairment, nausea, vomiting.
Cerebro-vascular event & Extradural haemorrhage : drowsiness, cognitive impairment.

METABOLIC

Dehydration/Hypoxemia : drowsiness, cog. impairment.
Hypercalcaemia : drowsiness, cog. impairment, nausea, vomiting.
Hyponatremia : drowsiness, cog. impairment.
Renal/Liver failure : drowsiness, cog. impairment, nausea, vomiting, myoclonus.

SEPSIS/INFECTION

Drowsiness, cog. impairment, nausea, vomiting.

MECHANICAL

Bowel obstruction : nausea, vomiting.

IATROGENIC

Tricyclics : drowsiness, cog. impairment, constipation.
BDZ : drowsiness, cog. impairment.
Antibiotics : nausea, vomiting.
Vinca alkaloids/Flutamide : constipation.
Steroids : agitated delirium.
NSAIDs : nausea, drowsiness.

MORPHINIC USE FOR DYSPNOEA IN THE DYING PATIENT

- Provide Oxygen if hypoxic &/or subjective relief is reported.
- Use of fans.
- Emotional/Spiritual support to the dying patient : distress reduction.
- If opioid naive = provide Morphine.
- If on chronic opioids, consider increasing dose by 25%.
- Consider BDZ.
- Reduce excessive secretions (death rattle) with anti-secretory agents.
- Consider time-limited trial of mechanical ventilation.
- Consider sedation for intractable symptoms (NCCN guidelines).

PALLIATIVE SEDATION

- In the imminently dying patient, palliative sedation (to induce a deep sedation) remains controversial.
- It is better that prognosis be confirmed by two physicians (NCCN guidelines).
- Discuss & obtain informed consent for sedation from the patient/family, before imminent death occurs.
- Sedation will consist of the continuous parenteral administration of [Midazolam/Propofol] rendering the patient unconscious.

- There are no state regulations in Mauritius.
- Explain that consent for sedation **must be** accompanied by consent for :
  - discontinuation of life-prolonging therapies [artificial nutrition/hydration].
  - withholding of Cardiopulmonary resuscitation (**DNR**).

- Reassign health care professionals who cannot provide sedation due to personal, professional values and beliefs, as long as patient care is cared for.
- Provide ongoing psycho-social & spiritual support for the patient's family.

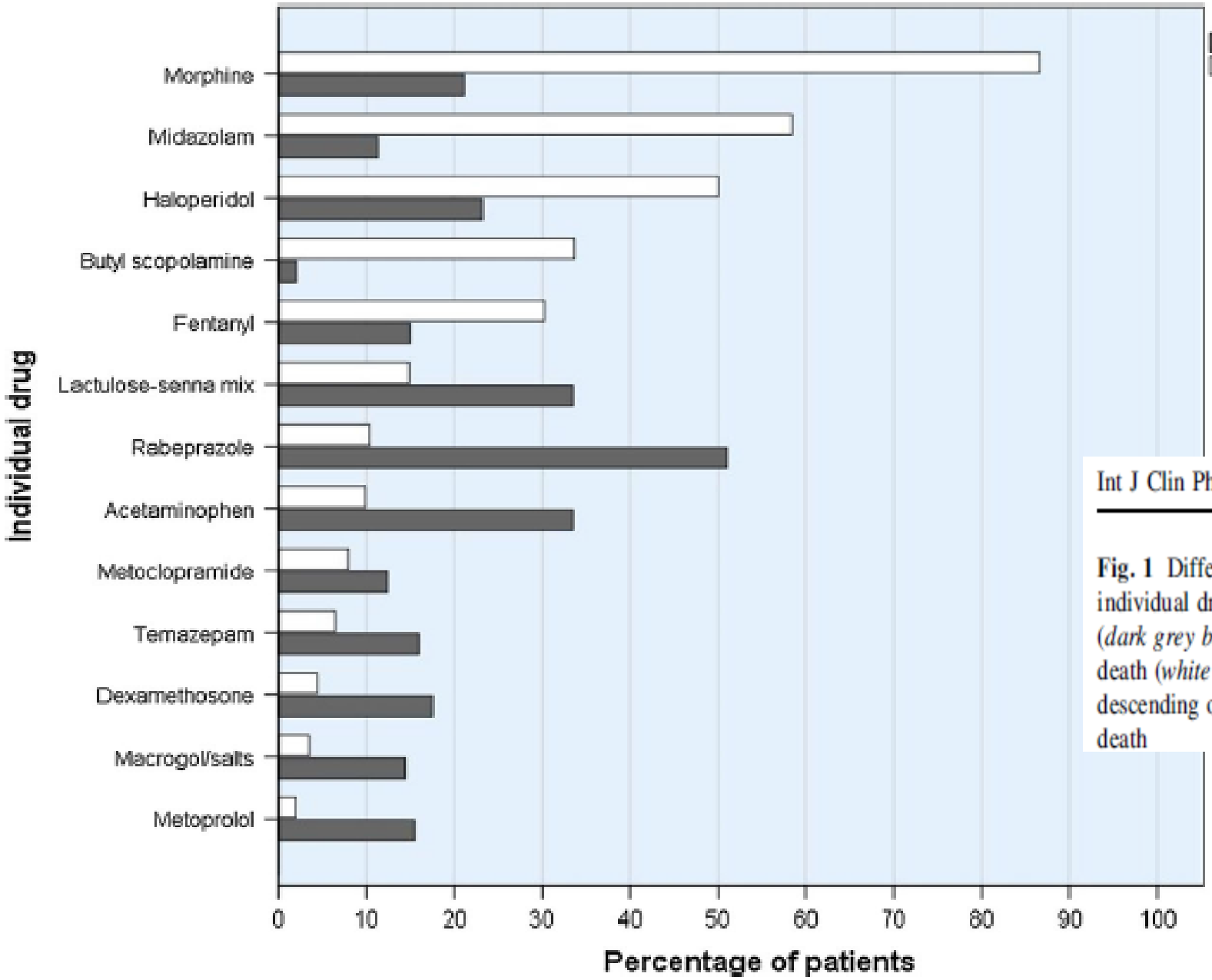


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Fig. 1 Differences in top-10 individual drugs at admission (*dark grey bars*) and at day of death (*white bars*); shown in descending order for the day of death

CONCLUSIONS

- Morphine and its derivatives are ESSENTIAL in the management of pain & dyspnoea in the terminally ill cancer patient (palliative care setting).
- Screen for pain in the verbal/non verbal patients, assess opioid naive/tolerant status of patients, re-assess pain as required.
- Recognise risk factors for misuse/abuse of opioids.
- Consider opioid rotation when necessary & seek specialist advice.
- METHADONE is a potent analgesic, besides its use in addiction.
- Recognise comorbidities that mimick opioid-induced adverse events.
- Dyspnoea : use of Morphine for sedation in the *agonising* dying patient…

Open question : **Palliative sedation** *v/s* **Euthanasia**.

THANK YOU FOR YOUR ATTENTION