Difficult Pain

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Difficult Pain

- Neuropathic
  - Common in advanced cancer
  - Caused by compression of neural structures
  - Iatrogenic: Cytotoxic induced, surgical
- Bone pain
  - Very common
  - Usually responsive
  - Difficult situations: Metas to wt bearing structures, fractures, compression of neural structures
- Visceral pain
  - Pancreatic pain
  - Bladder spasms

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Stepwise Approach to the Management of Difficult Pain

1. Consider the role of primary therapies to address the underlying cause of the pain
2. Titrate opioids up to maximal tolerated dose
3. Manage side effects through appropriate drug therapy or by trials of alternative opioids
4. Consider the role of adjuvant analgesics
5. Consider the role of regional anesthetic approached
6. Consider the role of invasive neuroablative interventions
7. The use of sedation in the management of refractory pain at the end of life

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Step 1: Consider the Role of Primary Therapies

- The assessment process may reveal a cause for the pain that is amendable to therapy that is directed at the cause
- The therapy may improve comfort, function or duration of survival
- Specific analgesic treatments are usually required as an adjunct to the primary therapy

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Radiotherapy

- Best evidence for:

  Painful bone metastases

  Epidural neoplasm

  Headache due to cerebral metastasis

- In other settings use of RT is largely anecdotal

Chemotherapy

- In responsive cancers, tumor shrinkage is generally associated with relief of pain
- Some reports of analgesic clinical benefit even in the absence of significant tumor shrinkage

Surgery

- Common indications
  - As obstruction of a hollow viscous
  - Unstable bony structures
  - Compression of neural tissues
- Locally advanced disease
  - Total mastectomy
  - Amputation of the effected limb
  - Exanteration +/- sacrectomy in advanced pelvis tumors
- Endoprosthetic treatment with stents
  - Esophageal, biliary, colonic and urethral obstructions

Antibiotic Therapy

- Antibiotics may be analgesic when the source of the pain involves infection
- Clinical context:
  - Cellulitis
  - Chronic sinus infections
  - Pelvic abscess
  - Pyronephrosis
- Occult infection
  - Relative common in head and neck cancer
  - Fungating tumors

Step 2: Titrate Opioids up to Maximal Tolerated Dose

- Opioids should be administered by the least invasive and safest route
- Inadequate relief should be addressed through gradual escalation of dose until adequate analgesia or intolerable SE supervene
- Dose escalations less than 30-50% are not likely to significantly improve analgesia
- The absolute dose is immaterial as long as the balance between analgesia & SE remains favorable

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Step 3: Manage SE Through Appropriate Drug Therapy or by Trials of Alternative Opioids

- Dose reduction of systemic opioid reduction in dose related adverse effects whilst preserving adequate pain relief
  - Addition of non-opioid co-analgesic
  - Addition of an adjuvant analgesics
  - Application of a regional anesthetic or neuroablative intervention
- Symptomatic management of adverse effects
- Opioid rotation

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Drugs Used in the Symptomatic Management of Opioid Side Effects

Side Effects	Management
Constipation	Senna Bisacodyl Lactulose
Nausea and vomiting	Metoclopramide Haloperidol Ondansetron Dexmethasone
Drawsiness	Methylphenidate
Delirium	Haloperidol
Myoclonus	Clonazepam Midazolam

Step 4: Consider the Role of Adjuvant

- Add a non-opioid co-analgesic
  - Paracetamol
  - NSAID
- Non-pharmacological approaches
  - Radiotherapy
  - Nerve block
  - Cognitive-behavioral management
- Multipurpose adjuvant analgesics
  - Corticosteroids: ICP, SCC, SVC obstruction, bone pain, neuropathic pain
- Tropical local anesthetics

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Step 4: Consider the Role of Adjuvant

- Multipurpose adjuvant analgesics

  - Corticosteroids: ICP, spinal cord compression, SVC obstruction, bone pain, neuropathic pain

    - Tropical local anesthetics

- Adjuvant medications used for neuropathic pain

Step 5: Consider Regional Anesthetic Approaches

- Epidural and intrathecal opioids
- Intraventricular opioids
- Regional local anesthetic infusions

Step 6: Consider the Role of Invasive Neuroablative Interventions

- Sympathetic blocks for visceral pain
- Sympathetic blocks for pelvic pain

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Step 7: Use of Sedation in the Management of Refractory pain at the EOL

Original Article

PALLIATIVE MEDICINE

European Association for Palliative Care (EAPC) recommended framework for the use of sedation in palliative care

Palliative Medicine
23(7) 581–593

DOI: 10.1177/0269216309107024
pmj.sagepub.com
SAGE

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Epidemiology of Bone Tumors

- Primary - uncommon
- Secondary (metastatic) - very common
- Third most common site of metastasis (after lungs, and liver)
- Common in patients with
  - Prostate, breast, thyroid, kidney, and lung cancer
  - Myeloma and hematologic malignancies

Sites

- Commoner in axial skeleton
- Vertebral column – most common
  Lumbar thoracic cervical

Anatomical Site	Metastases Presents (n=68)
Vertebrae	**42 (62%)**
Ribs	39 (57%)
Skull	24 (35%)
Femur	15 (22%)
Pelvis	13 (19%)
Humerus	7 (10%)
Clavicle	4 (6%)
Scapula	2 (3%)

Willis, 1973

Clinical Features

- Impact on QoL
- Difficult to manage requires multi-model intervention
- Account for 30-35% of all cancer pains *(Twycross & Fairfield, 1982)*
- 1/3 of metastatic CA breast affected the skeleton do not complaint of pain *(Front et al., 1979)*
- The presentation is independent of tumor type, location, number and site of metastases, gender and age *(Oster et al., 1978)*

Pain Characters

- Triad of - Background pain: constant, dull ache, 60% severe, 30% moderate *(Pollen & Schmidt, 1979)*
    - Spontaneous breakthrough pain
    - Incident pain
- Radiation of pain – Hip knee
    - T12/L1 iliac crest/sacroiliac jt
    - Cervical spine occipital region
- Migratory pattern of pain

Break Through Pain

- Bone pain is a major source of BTP & incident pain
- Clinical of BTP:
  Acute onset
  Short duration
  Moderate to severe in intensity
  Often mirror background pain
- Patients with BTP have more functional impairment and more depression

Complications of Bone Pain

- Reduce QoL, psychological morbidity, limited function
- Pathologic fracture
- Spinal cord compression
- BM suppression
- Hypercalcemia
- Deep vein thrombosis, pulmonary embolism

Pathologic Fracture

- Occurs in 8-30% of patients with bone mets *(Mercadante, 1997)*
- Increases with duration of metastasis
- Common in breast CA and myeloma

Mirels' Scoring System for Impending Pathological Fracture (Mirels, 1989)

Variable	Score		
	1	2	3
Site	Upper limb	Lower limb	Peritrochanteric
Pain	Mild	Moderate	Functional
Lesion	Blastic	Mixed	Lytic
Size*	<1/3	1/3 to 2/3	>2/3

*Max destruction of cortex in any view as seen on plain x-ray

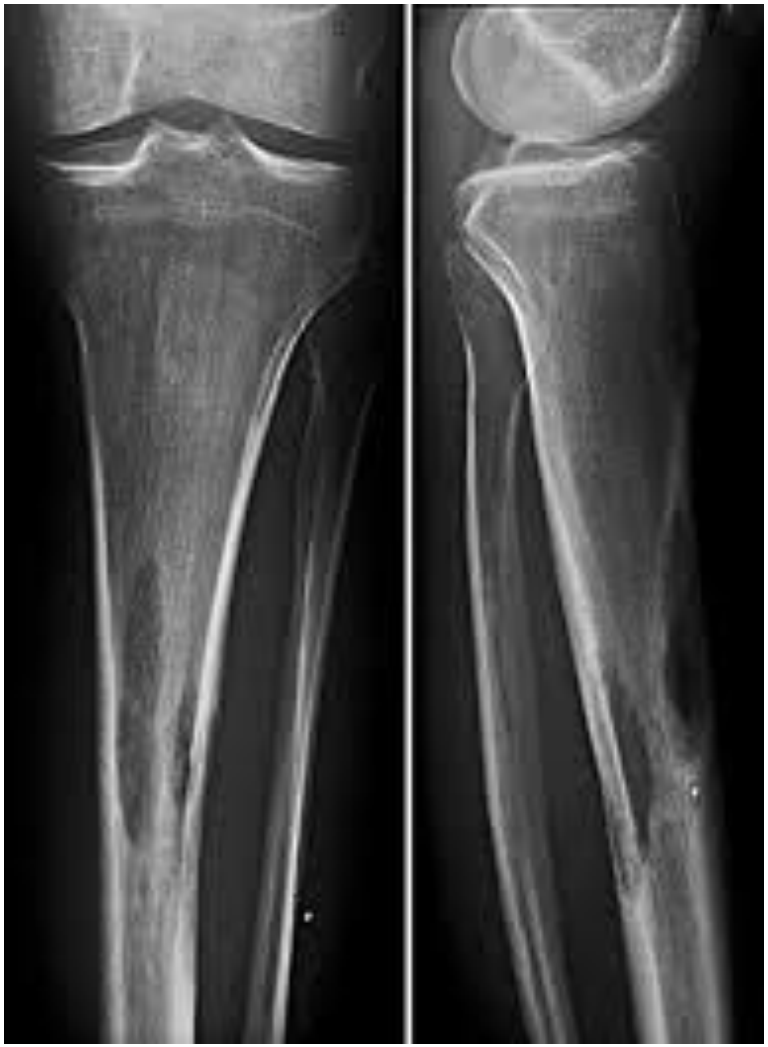
Score $\leq$ 7 indicates that surgery is not needed
Score $\geq$ 9 indicates that surgery is warranted
Score of 8 means that decision has to taken in the context of the patient and his/her disease

Assessment

- Pain details: onset, temporal pattern, site, radiation, quality, intensity, exacerbating factors, relieving factors, response to analgesics, response to other interventions
- Associated psychological symptoms
- Interference with ADL
- General physical exam including neuro exam
- Provocative maneuvers: palpation, passive movement

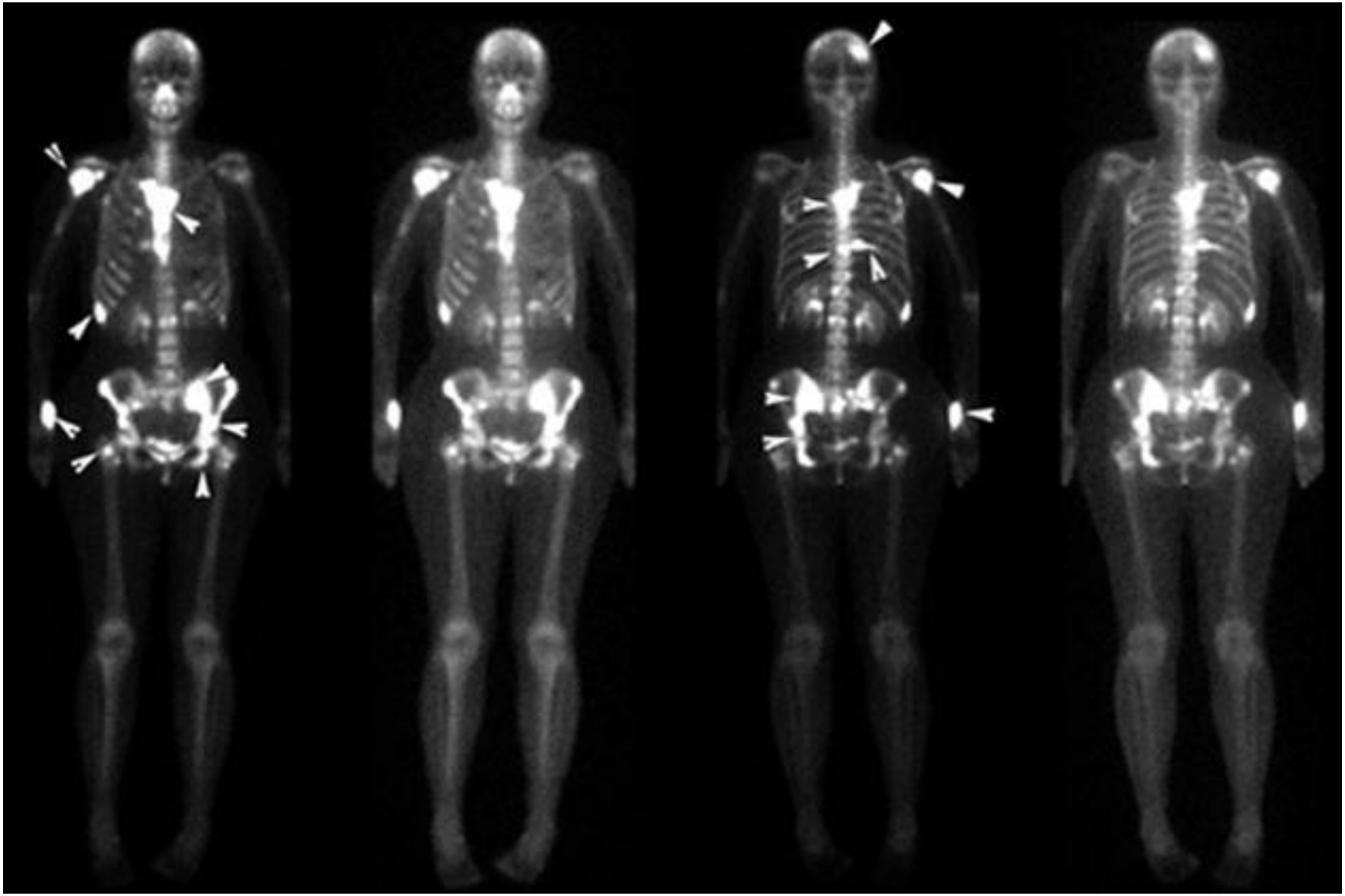
Radiology

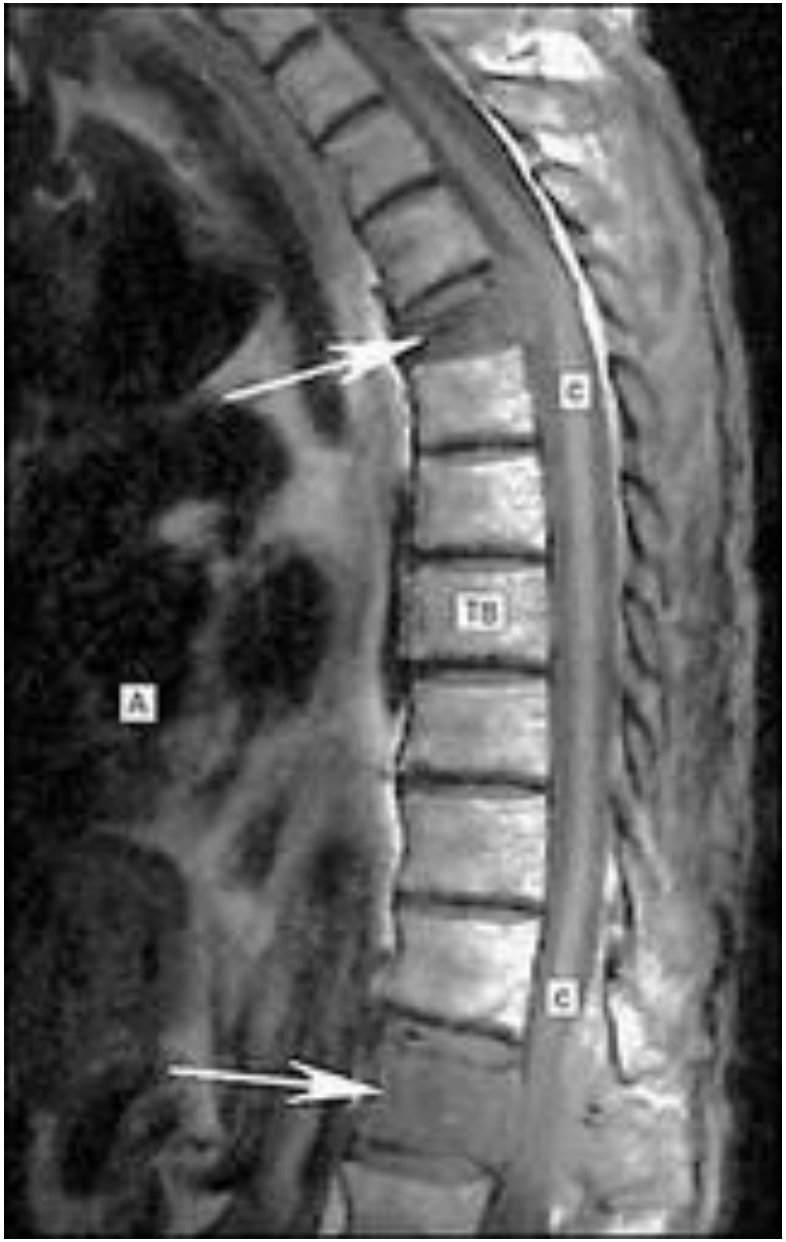
- Imaging plays central role in detection and management
- Typical features: abnormal trabecular pattern, abnormal density, periosteal reaction
- At least 50% of cortical bone must be destroyed before lesion become apparent on plain film



Radiology

- **CT:**
  More sensitive
  Useful for assessing fractures
  Detecting soft tissue masses
  Lack of sensitivity in detecting BM diseases
- **Bone scan:** Standard investigation
  Classic appearance “Superscan”
- **MRI:** Detect disease before any cortical destruction
  Detecting BM involvement

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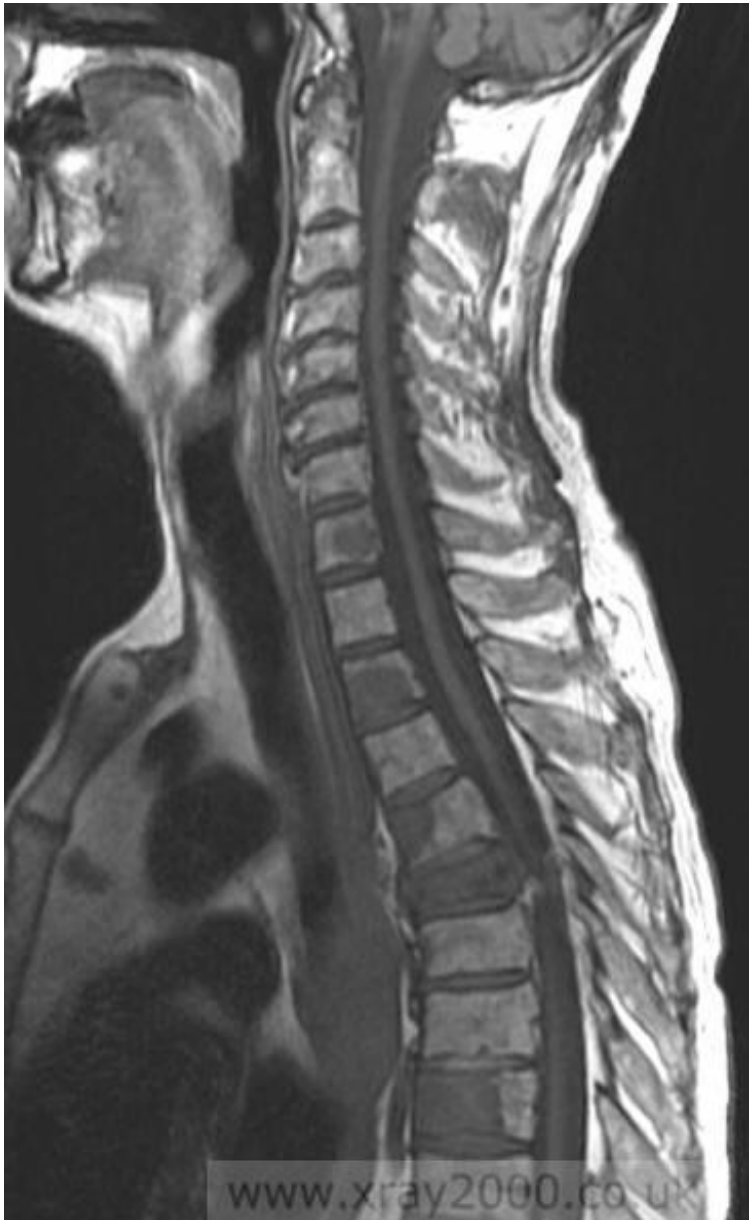

www.xray2000.co.uk

Treatment

- Treatment of underlying cancer
- Treatment of underlying pathology (resorption of bone, fracture of bone)
- Treatment of background pain
- Treatment of any BTP & incident pain
- Treatment of complications (nerve root/spinal cord compression)

Treatment of Underlying Cancer

- Depend on type of cancer
- Radiotherapy – effective in treating bone mets and provide significant pain relief within short period of time.

Radiotherapy for the Palliation of Painful Bone Metastasis

- 20 trials, 43 different RT fractionation schedules and 8 studies of radioisotopes.
- Complete pain relief at 1 month in 395/1580 (25%) patients, and at least 50% relief in 788/1933 (41%) patients at some time during the trials.
- NNT to achieve complete relief at 1 month = 4.2 (95% CI 3.7-4.7).
- No obvious differences of SE and efficacy between the various fractionation schedules.

The Cochrane Library, 2002.

Treatment of Background Pain

- Pharmacologic management: WHO GL
  - “By the mouth”
  - “By the clock”
  - “By the ladder”
  - “For the individual”
  - “Attention to detail”
- Adjuvant analgesic – Bisphosphonates, corticosteroids
- Non-pharmacological management: rubbing, massage, heat/cold compression, TENS,

NSAIDS

- Difficult to determine the value of NSAIDS in bone pain because bone pain is typically not separated from cancer pain
- NSAIDS - medication of choice for mild pain
- If the pain becomes more severe, or if there is a risk for GI, hepatic or renal toxicity, the patient should be started on an opioid.

Is Bone Pain Responsive to Opioids?

- Bone pain not complicated by any neural involvement is a somatic pain, and is typically very responsive to opioids

Treatment of BTP (Davies, 2006)

- Pharmacological:

  1. Modification of the background analgesic regimen

     (a) increase dose of analgesic drugs;

     (b) addition of analgesic drugs;

     (c) addition of co-analgesic drugs

  2. Use of rescue analgesics

     (a) non-opioid

Bisphosphonate

- Pamidronate - most widely studies have shown a reduction of pain from bone mets in most patients with multiple myeloma or breast cancer. *(Palliat Med 2001; 15(4):297-307.)*
- Pamidronate and clodronate can potentiate the effects of analgesics in the treatment of bone pain, although no significant decrease in analgesic consumption.*(J Urol 2001)*

Are Bisphosphanates Effective for Bone Pain? *(Cochrane Review, 2002)*

- 30 RCT with 3682 subjects
- Efficacy NNT at 4 wks of 11 [95% CI 6-36] and at 12 wks of 7 [95% CI 5-12].
- Adverse drug reactions, NNH was 16 [95% CI 12-27]
- One study showed improvement in QoL at 4 wks
- Evidence to support the effectiveness in providing some pain relief for bone metastases.
- Insufficient evidence to recommend as first line therapy
- Bisphosphonates should be considered where analgesics and/or radiotherapy are inadequate for the

Steroids in the Treatment of Bone Pain

- Adjuvant analgesic for cancer-related bone pain
- Dosage (Expert opinions):

  Oral methylprednisolone 16 mg PO bd.

  Dexamethasone 4-8 mg PO 2-3 times/day,

  Prednisone 20-30 mg PO 2-3 times/day.
- If no benefit is seen within 5-7 days the drug should be discontinued. If beneficial, the drug should be tapered to the lowest effective dose

Complementary Approaches

- To improve mobility: bracing, prostheses, wheelchairs
- Physical therapy & occupational therapy
- Relaxation, imagery, biofeedback, hypnosis and music therapy

Management of Incident Pain

What is Incident Pain?

- Incident pain is pain that can be predicted and occurs with specific activities.
- can be pre-medicated with a quick-acting, short term-lasting pain medication before activities that cause pain.

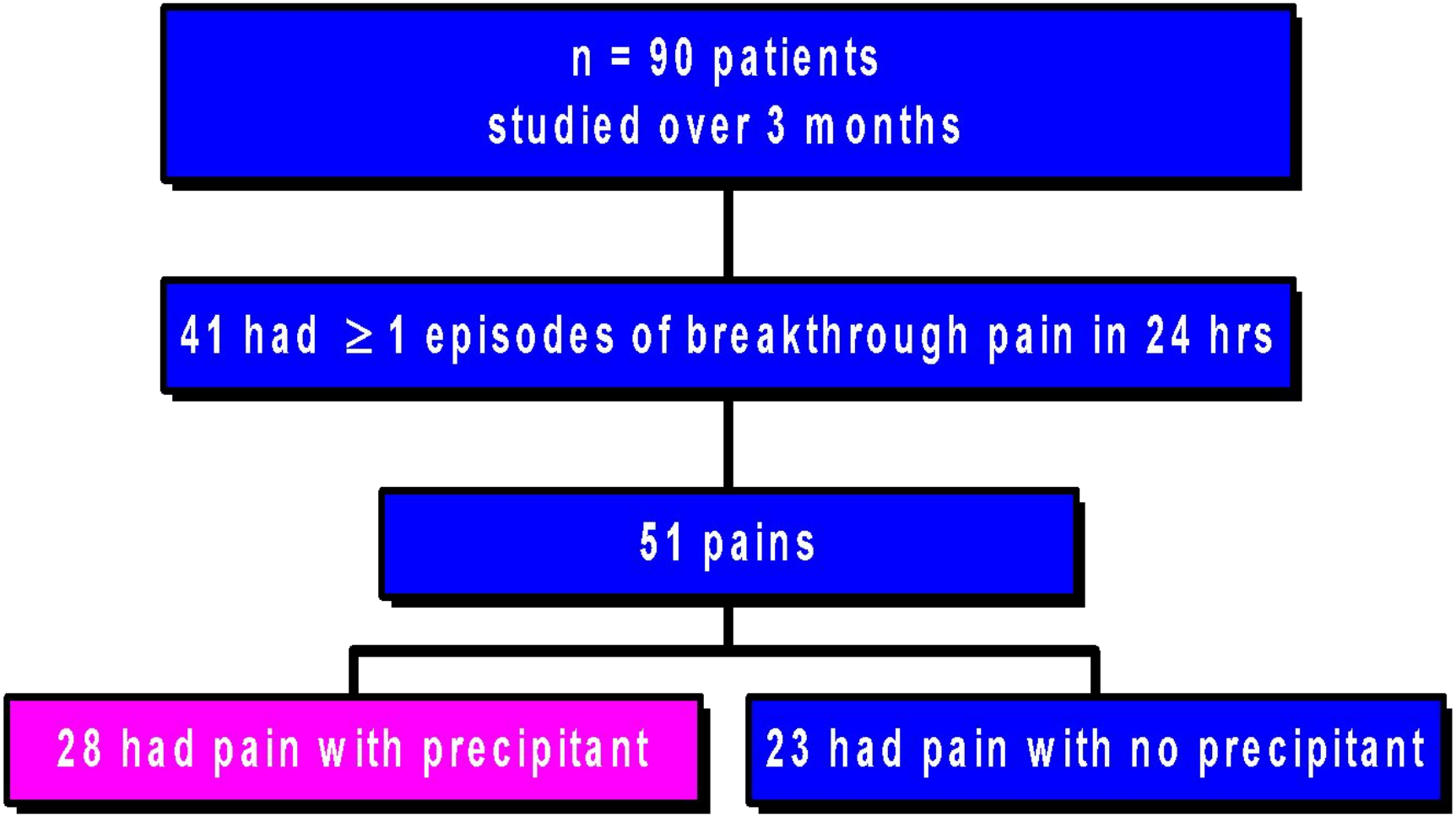
Types of Breakthrough Pain

Type	Characteristics	Solution
Incident	Activity-related Has identifiable precipitant Usually nociceptive	Anticipate and premedicate with short-acting agent
Idiopathic/ Spontaneous	Unpredictable Usually neuropathic or visceral	Add adjuvant medication
End-of-dose failure	Predictable return of pain before next scheduled dose of medication	Increase dose or shortening the time between doses of the long-acting agent (eg. q 8 h. instead of q 12 h.)

Causes of Incident Pain

- Bone metastases
- Neuropathic pain
- Intra-abdominal disease aggravated by respiration
- Skin ulcer, dressing change, debridement
- Bowel disimpaction
- Catheterization

How Common is Incident Pain?



Portenoy RK, Hagen NA. Pain 1990 42:135-144

Management of Incident Pain

- Treat underlying problem eg. Bone pain:

  Radiation Tx, chemotherapy

  Bisphosphonates

  Orthopedic intervention

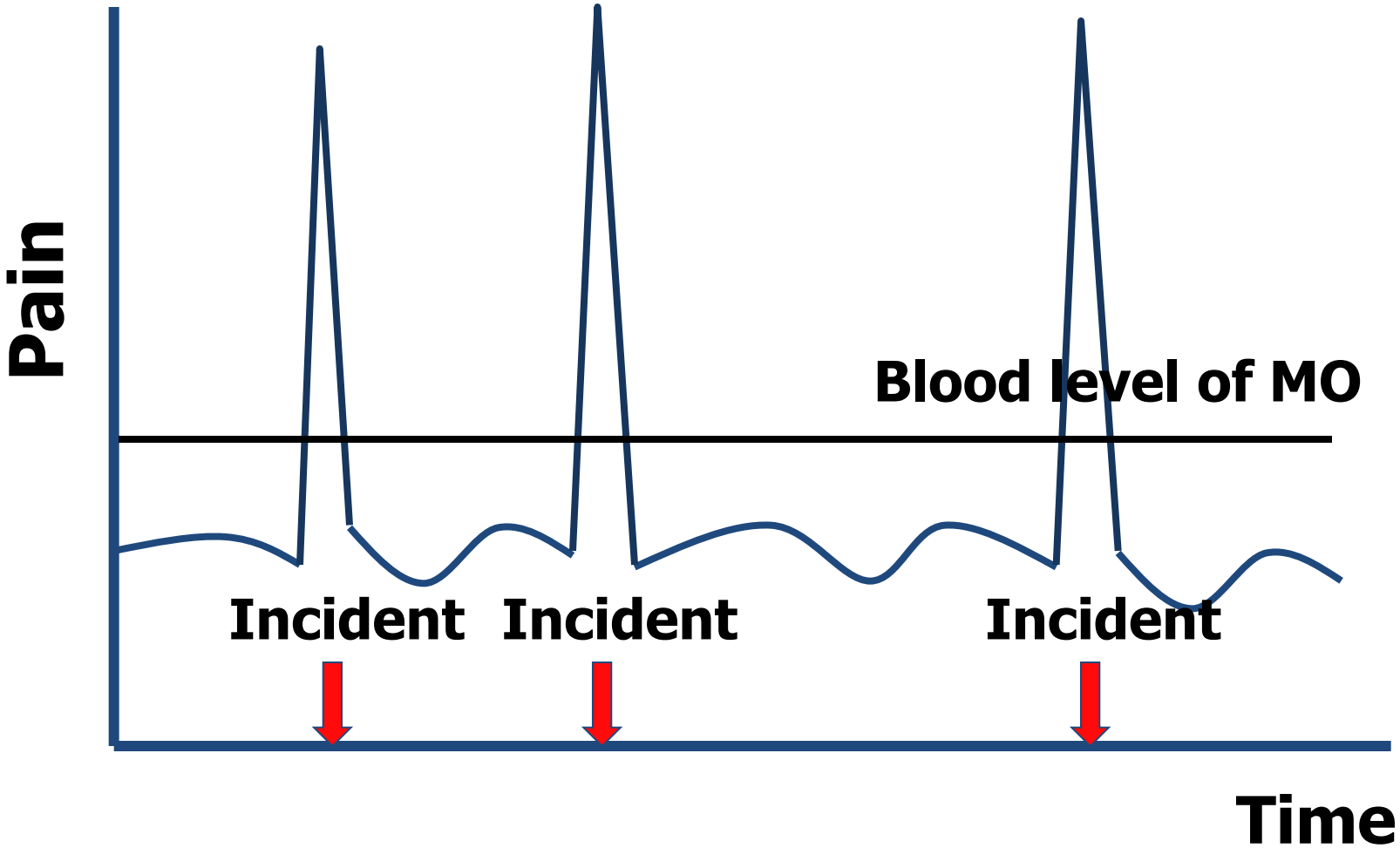
  Nerve blocks

- Premedication before activity

Ideal Analgesic for Incident Pain

- Easily administered
- Rapid onset, early peak effect
- Short-duration of action
- In patient’s control
- Save for patients

Incident Pain



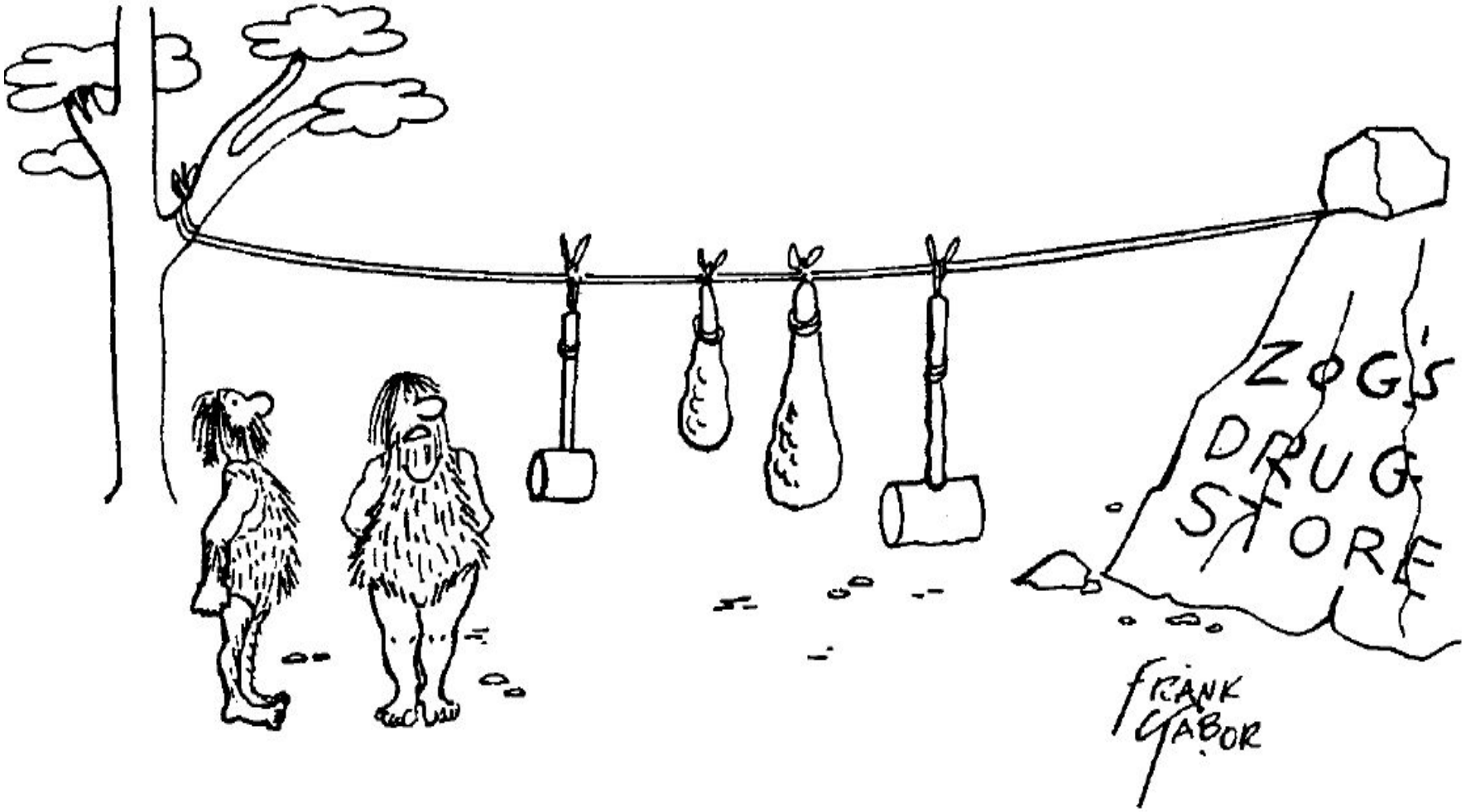
Clinical Features of BTP

Clinical feature	Average
• Time to peak severity	• 3–5 minutes
• Intensity	• Severe or excruciating
• Duration of episode	• 15–30 minutes
• Number of episodes/day	• 1–5
• Precipitated by an event†	• 55–60%
• Predictable†	• 50–60%

Morphine for BTP?

	Breakthrough cancer pain episode (typical)[1]	Immediate-release morphine
Onset	Rapid and abrupt	Onset of analgesia after ≥30 minutes[2]
Peak	Peak intensity reached within 3–5 minutes	Peak analgesic effect after 40–60 minutes[3]
Duration	15–30 minutes	4 hours[2]

1. Bennett D *et al. P&T* 2005;30:296–301
2. Bennett D *et al. P&T* 2005;30:354–361
3. Coluzzi PH. *Am J Hosp Palliat Care* 1998;15:13–22

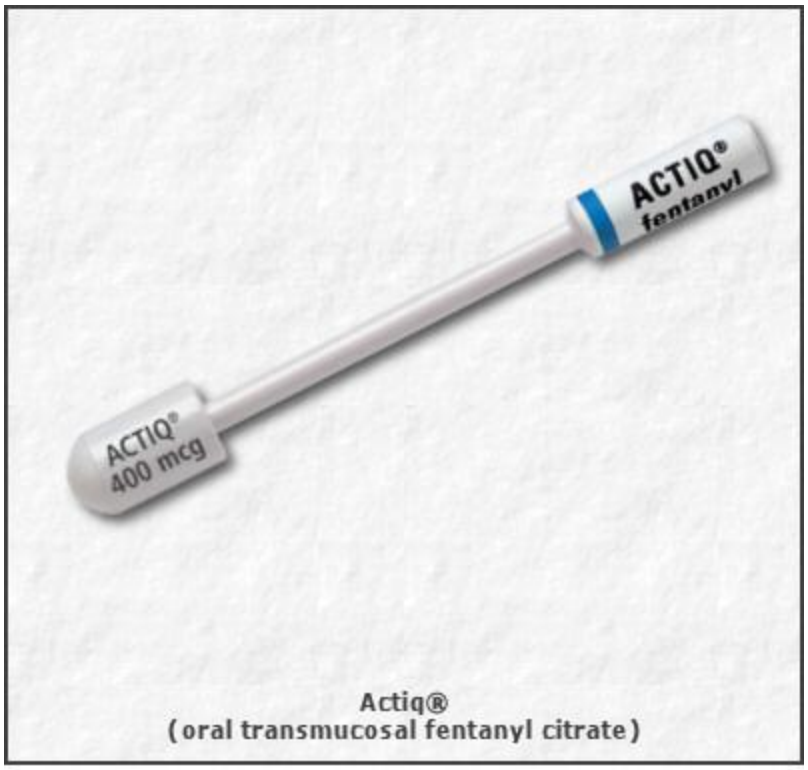


"Actually, all the leading pain relievers act the same, though some may be quicker-acting than others."

Fentanyl

	Breakthrough cancer pain episode (typical)[1]	Oral transmucosal fentanyl citrate[2,3]
Onset	Rapid and abrupt	Onset of analgesia after ~5–10 minutes
Peak	Peak intensity reached within 3–5 minutes	Peak analgesic effect after ~20 minutes
Duration	15–30 minutes	1–2 hours

Transmucosal Fentanyl



Actiq®
(oral transmucosal fentanyl citrate)

Photo: usdoj.gov

Steps of the Incident Pain

Step	Medication	SL (50 mcg/ml)
1	Fentanyl	50
2	Sufentanil	25
3	Sufentanil	50
4	Sufentanil	100 *

http://palliative.info/IncidentPain.htm

Sublingual Fentanyl Citrate For the Management of Incident Pain

- The parenteral form of Fentanyl can be used subcutaneously or sublingually
- Onset of action ~ 5-15 min. peak ~ 20 min. duration of action up to 45 min.
- Before applying the “Incident Pain Protocol”, the dose of the around-the-clock opioid should be maximized and other appropriate adjunct analgesics included as necessary

http://akecity.blogspot.com/2011/03/blog-post_31.html

Application of the Incident Pain Protocol

- Administered SL 5-10 min prior to anticipated activity
- Hold the medication under the tongue for 5-10 min without swallowing
- After 5-10 min, if pain not controlled, then that same dose may be repeated up to 2 doses, at 5-10 min intervals
- Consider moving to the next step if the max number of doses (three) is required to achieve comfort
- The Protocol may be used up to q1h prn.

http://akecity.blogspot.com/2011/03/blog-post_31.html

Steps of the Incident Pain Protocol

- **Step 1:** Fentanyl 12.5mcg (0.25 mL of 50ug/mL parenteral solution)
- **Step 2:** Fentanyl 25 mcg (0.50 mL of 50ug/mL parenteral solution)
- **Step 3:** Fentanyl 50 mcg
- **Step 4:** Fentanyl 100 mcg (2 ml volume may necessitate giving the medication in 2 doses of 50mcg/1ml at an interval 5-10minutes apart)

http://akecity.blogspot.com/2011/03/blog-post_31.html

Sublingual/Buccal Ketamine

- Indications: Movement or procedure related pain
- Dose: 0.25-0.5 ml of ketamine inj add with syrup to 2 cc. SL
- Rapid onset peak blood level
- Dyspholic type side effects