TREATING PAIN in PATIENTS NEARING DEATH

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OBJECTIVES

- Overcome the barriers to treating pain well
- Think of chronic pain as a disease
- Realize that pain is undertreated in the USA
- Know safe and effective Rx for pain
- Appreciate that compassionate palliative care is the standard of care for those nearing death, even during active, aggressive Rx

Definitions

- Chronic pain: persistent (weeks,months,yrs)
  present at least 12 hr daily
  intensity at least 5+ on a 0-10 scale

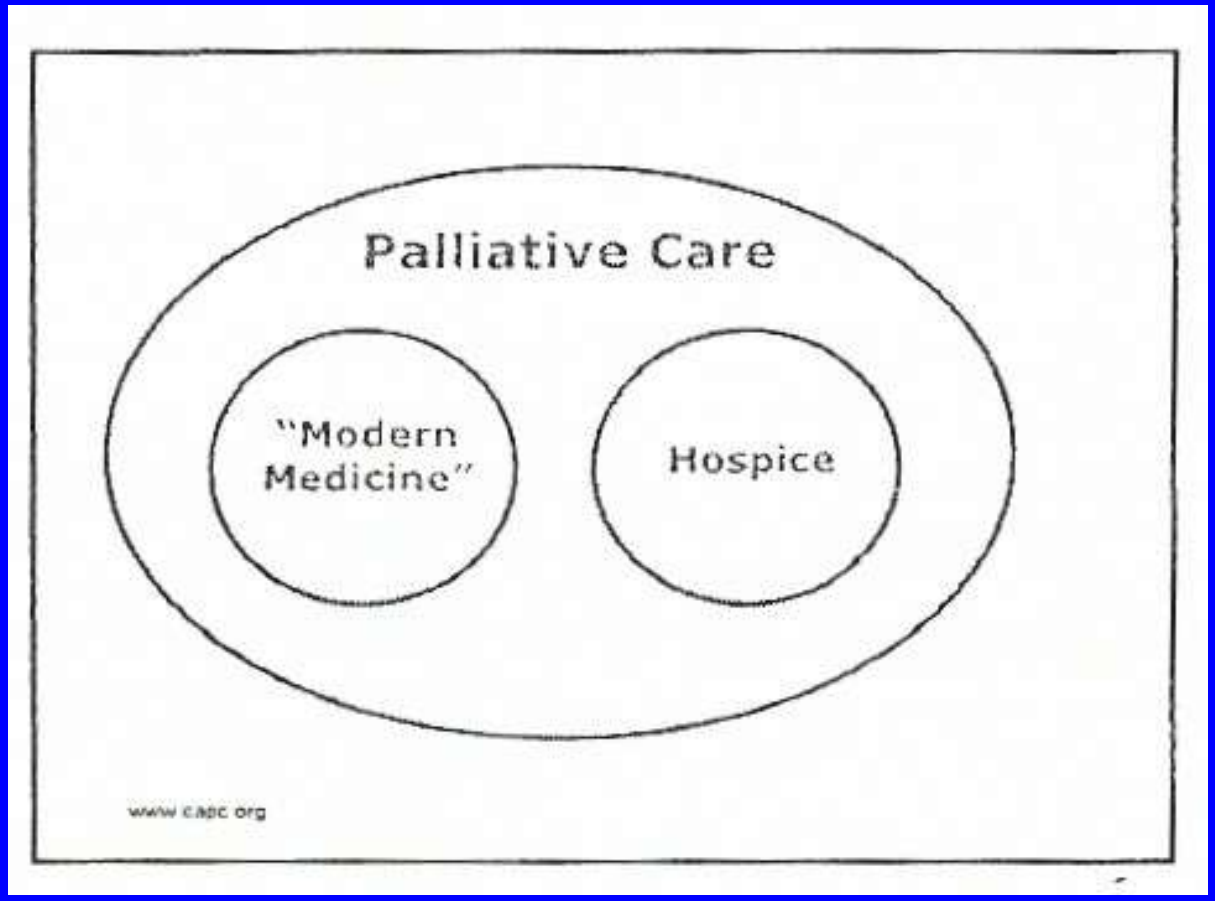
Empathy: feeling another's suffering

Suffering: to feel or endure pain or distress;
can have physical, emotional, or
spiritual components

Compassion: action that helps relieve the
suffering of another being

Concepts

- Hospice: a philosophy and service based on compassion. Medicare supported; 6 mo. or less life expectancy; ***follows*** aggressive care. A choice.
- Palliative care: a broader concept for ALL patients facing life-threatening illness; focus is to relieve suffering and improve quality of life remaining; It is supportive of, and can be ***concurrent*** with aggressive care, in or out of the hospital
- Palliative Medicine: new subspecialty; over 4,000 physicians members; most are internists, family physicians, or oncologists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Barriers to Treating Chronic Pain

- Education
- Experience
- Fear of Regulators
- Fear of Addicting Patients
- Fear of Opioid use in the Dying

Education, Experience, and Regulators

- Doctors and nurses in the past were given little education and training about pain, and consequently are uncomfortable in prescribing opioids for treating pain, especially chronic pain.
- Changing attitudes and accepting advances in pain Rx may be difficult for many doctors, nurses.
- Fear of DEA, regulatory boards is excessive

Fear of Addiction

- The risk of addiction is over-stated.
- The vast majority of patients with chronic pain are not addicts. 80% of addicts have a familial genetic brain disorder, which is life-long.
- The risk of becoming addicted is estimated at 1-3% in the general pain population when there is no history of prior substance-abuse.
- Normal pain patients follow the rules
- Addicts bend and break the rules

Addiction

- The problem in addiction and substance abusers is not with the substance, it lies within the abuser.
- The reward center in the brain of addicts is not supplied with enough dopamine to enable addicts to feel pleasure as normal persons do.

Addiction

- The addict seeks an activity or substance which boosts dopamine action at the reward center.
- After the boost subsides, the addicts craves that dopamine “high” compulsively, even though the activity or substance may be damaging to him.

Opioids and Respiratory Depression

- Patients receiving opioids for chronic pain and dyspnea tolerate large opioid doses without serious respiratory depression, when titrated appropriately.
- In contrast, observe opioid-naïve patients closely when they receive opioids, as their respiratory center has not developed tolerance to opioids.

Overcome the Fear of Using Opioids in the Dying

- Sleepiness occurs before serious resp. depression. If oversedation occurs, hold opioid until awake, then resume at a lower dose and/or longer dosing interval
- Evidence-based studies indicate that judicious opioid use in the dying does NOT hasten death.
- The benefits of opioids greatly out-weigh the risks.

How to Manage Pain Effectively and Efficiently in Patients Who COULD Die

- Assessing Pain
- Difference between Acute and Chronic Pain
- Treatment of Pain
- Specific Opioids
- Case Examples

Assessing Pain

- Detailed description of pain (from patient, caregiver, staff)- is it somatic, visceral, neuropathic, or mixed? Location? Intensity?
- What makes it better or worse
- Effect on emotional, social status
- How much impairment of function?
- Review diagnostic and lab data
- Reassess often to adjust treatment

Acute Pain

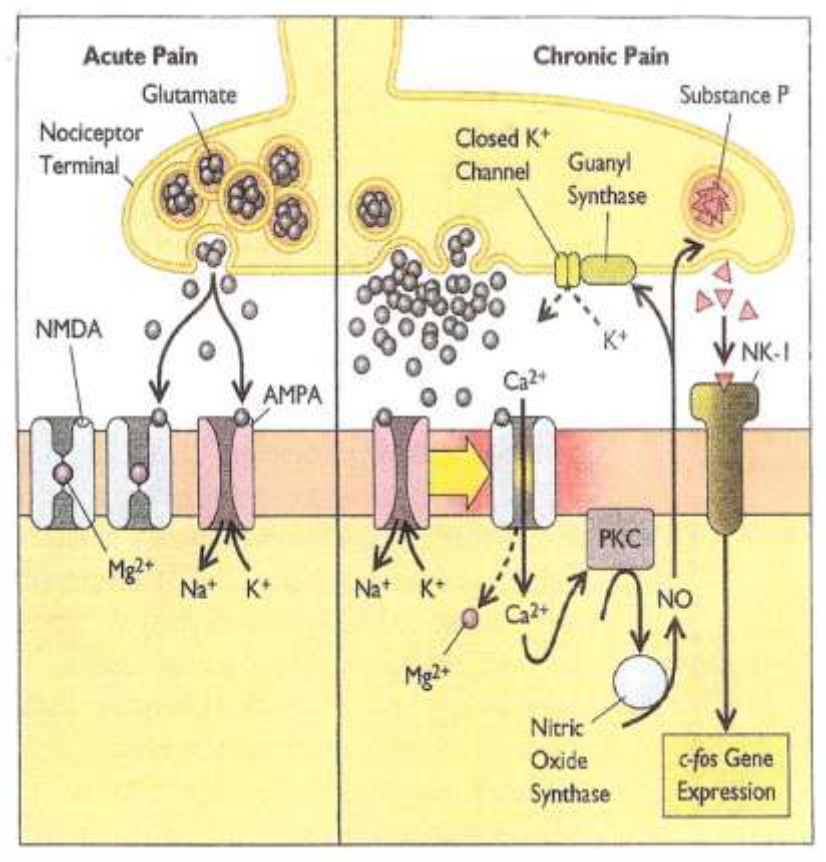
- Pathway for transmission of acute pain in spinal cord and CNS is conventional.
- Duration is short.
- Endorphins and enkephalins are released by CNS to block pain perception.
- All of the opioids are effective for most acute pain.

Changing from Acute Pain to Chronic Pain

- Acute pain causes release of the neurotransmitter glutamate in the dorsal horn of the spinal cord.
- Glutamate binds to AMPA receptors in cells of the dorsal horn, which triggers pain signals to the CNS
- When AMPA receptors are ‘saturated’ by excess glutamate, normally inactive N-methyl-D-aspartate (NMDA) receptors in the spinal cord become activated by the excess glutamate.
- This begins the change from acute to chronic pain

Acute and Chronic Pain

Brookoff,D:1) Chronic Pain: A New Disease?: *Hosp Pract*: 35(6); Minneapolis,MN; 45-59



Consequences of N-Methyl-D-Aspartate Receptor Activation

- Windup
- Neural Remodeling
- Activation of Neurokinin-1 Receptors
- Afferent becomes Efferent
- Neurogenic Inflammation

Windup

- Less glutamate is required to transmit pain
- More anti-nociceptive input required to stop it
- Endorphins cannot keep up with demand
- Pain relievers lose their effectiveness

- Result: More intense pain, harder to relieve

Neural Remodeling

- Activation of NMDA receptors cause neural cells to sprout new connective endings
  - adds new dimensions to old sensations
  - emotional component of pain can increase
    - new connections channel signals to the reticular activating system of the brain
    - result: diffuse-hard to localize pain

Activation of NK-1 Receptors

- NMDA receptor activation causes nociceptors to release the peptide neurotransmitter Substance P
- Substance P binds to Neurokinin-1 receptors
- This amplifies the pain signal
- Stimulates nerve growth and regeneration

Substance ‘P’

- Induces production of the c-fos oncogene
  - the biochemical footprint for chronic pain
  - marker for central hyper-sensitization
- C-fos
  - levels go higher up the spinal cord with persistence of pain
  - reaches the thalamus…pain is untreatable
- Pain is no longer confined to the original site in some patients
- Detected in fibromyalgia consistently

Afferent becomes Efferent

- NMDA receptor activation causes some afferent neurons to carry signals “backwards” to nociceptors, which can establish a dorsal root pathological reflex
- Substance P is released at the periphery causing inflammation and promotes the cyclic nature of chronic pain

Neurogenic Inflammation

- A tissue reaction caused by Substance P and nerve growth factor, affecting synovia and other connective tissue.
- Doesn’t depend on granulocytes or lymphocytes
- Substance P causes de-granulation of mast cells, releases bradykinin, nitric acid.

Neuropathic Pain

- Damage to sensory nerves
  - **can cause neuropathic pain syndromes**
  - **insensitive to anti-nociceptive suppression**
- After tissue injury
  - **'A Fibers'- large myelinated nerves that carry touch … sprout new terminal branches**
  - **these synapse with pain-sensing cells in the outer dorsal horn which lack opioid receptors, thus endogenous and exogenous opioids are ineffective**
    - examples of pain poorly responsive to opioids are phantom limb and diabetic neuropathy

Pain near the End-0f-Life

- Chronic pain: more complex and difficult to treat than acute pain
- Somatic and Visceral pain (Nociceptive) usually opioids and adjuvants are effective
- Neuropathic pain: adjuvants plus NMDA-receptor blocking opioids (levorphanol, methadone) or ketamine work best

Treating Pain with Opioids

- Use the World Health Organization
  3-step analgesic ladder:
- Step 1: Mild analgesics: APAP, NSAIDs
- Step 2: Moderate analgesics: Codeine, Tramadol Hydrocodone/APAP, Oxycodone/APAP
- Step 3: Strong Opioids

WHO 3-step Ladder

3 severe

- Morphine
- Hydromorphone
- Methadone
- Levorphanol
- Fentanyl
- Oxycodone
- ± *Adjuvants*

2 moderate

- A/Codeine
- A/Hydrocodone
- A/Oxycodone
- A/Dihydrocodeine
- Tramadol
- ± *Adjuvants*

1 mild

- ASA
- Acetaminophen
- NSAIDs
- ± *Adjuvants*

Prescribing Opioids for Chronic Pain- General Principles

- Use WHO pain ladder to select analgesic
- Around-the-clock, q. 3-4 hr. (not 4-6 hr)
- Assess frequently, adjust dose to relieve pain
- Add up total opioid taken q. 24hr.
- Select long-acting opioid q. 12 hr.
- Use short-acting opioid for breakthrough pain prn.
- Use one short- and one long-acting
- Reassess to titrate dose

Morphine

- Usual 1st. choice for moderate, severe pain. Begin low, 15mg q 3-4 hr. Titrate ,reassess often.
- No ceiling
- Resp. depression rare in chronic pain patients.
- High doses: metabolites = nausea,dysphoria, muscle jerks; seizures

Dilaudid- hydromorphone

- Beginning dose 2-4 mg q 3-4 hr. Very effective, similar to MS. 2mg = 8mg MS
- Less nausea. No ceiling. Often used orally for breakthrough pain and i.v.
- New long-acting tablet: Exalgo (Covidien)
- Glucuronide metabolite toxicity similar to morphine

Oxycodone

- Starting oral dose 5-10 mg q 3-4 hr. Very effective
- Less nausea, less troublesome metabolites.Combined with ASA and APAP (Percocet,etc.), limits ceiling.
- Expensive sustained-release form (Oxycontin), no ceiling. Watch for illegal diversion. Oxycontin 10,20,40,80mg.
- Liquid concentrate 20mg/ml useful buccally in the dying, as is MS(Roxanol).

Duragesic (Fentanyl)

- Duragesic patch: use care in opioid- naïve patient, only after pain controlled by short-acting opioid.Fever increases absorption. Avoid scant subcut. fat.
- 12 hr delay in onset and offset due to skin reservoir absorption.
- Available as 12, 25, 50, 75,100mcg/hr patch applied q 72 hr (sometimes 48 hr)

Methadone and Levorphanol

- Under-used, not marketed
- NMDA receptor-blocking activity makes these, especially methadone, the best choice for neuropathic and complex chronic pain
- Levorphanol is 4-8x stronger than MS: longer ½ life (q 6 hrs)

Rediscovery of Levorphanol

- Of the 6 major opioids, levorphanol is the least known and least used clinically.
- An excellent opioid marketed since 1958 as Levo Dromoran, levorphanol fell into disuse in the 1980s, when long-acting forms of morphine, oxycodone, and fentanyl dominated the chronic pain market.
- Levorphanol is both a mu opioid agonist like morphine, and an NMDA antagonist like methadone, with recent evidence that it is effective in neuropathic pain.

Levorphanol

- NMDA-receptor blocker and mu-opioid and kappa-opioid agonist
- 2 mg tablet equal to 8-15 mg morphine p.o
- Long half-life (6 hr)
- Recent published evidence (2003) that Levorphanol is effective in chronic neuropathic pain

Methadone

Methadone, a synthetic opioid developed in 1940 has been used worldwide for pain relief.

The development of sustained-action morphine, oxycodone, and fentanyl in the 80s, promoted and marketed by commercial interests in the U.S, relegated methadone to use mainly in substance-abuse until recently.

Short-acting Opioids to Begin Rx or for Breakthrough Pain q 3-4hr

- Hydrocodone/ APAP oral tabs and liquid; 5-10 mg po q 4 hr around-the-clock
- Oxycodone/APAP or Oxycodone oral liq.or tabs 5-10 mg q 4hr ATC
- Hydromorphone: oral tabs,liquid;iv; suppos. 2-4 mg q 3-4 hr ATC
- Morphine: oral tabs,15mg, and oral conc. solution 20mg/ml; iv or s.q.;rectal suppos. Oral conc. most useful at EOL, buccally or subling. 5-10 mg q 2-4 hr prn.

Long-acting Opioid Preparations

- Morphine sustained- release (q 8-12 hr) (MsContin);24hr(Avinza);12-24 hr (Kadian)
- Oxycodone sustained- release (q 8-12 hr) (Oxycontin)
- Fentanyl transdermal patch (q 72 hr) (Duragesic)
- Methadone (q 6-12 hr)
- Levorphanol (q 6-8 hr)

How to Convert From One Opioid to a Different Opioid

- Add up all the opioids currently prescribed in the previous 24 hrs
- Use the equi-analgesic tables to convert all opioids to their oral morphine equivalent
- Select the new opioid, and use the tables to calculate the 24hr dose of that opioid
- Use a long-acting, and a short-acting version (if available), dosed appropriately for that opioid

Equianalgesic Doses if Morphine = 10 mg p.o.

- Hydromorphone= 2 mg- 2.5 mg (I use 2.5 mg)
- Oxycodone = 5-10 mg (I use 10 mg)
- Hydrocodone =15 mg
- Codeine = 60 mg
- Ultram(tramadol) =50 mg
- Demerol(merperidine) =50 mg
- Fentanyl(duragesic)=see slide 24
- Levorphanol = see slide 25

Fentanyl: converting to and from Morphine

12 mcg/hr Transderm patch = 25 mg oral Morphine per 24 hr.

25 mcg/hr Transderm.patch = 50 mg oral Morphine per 24 hr.

50 mcg/hr Transderm.patch = 100 mg oral Morphine per 24 hr.

75 mcg/hr Transderm.patch = 150 mg oral Morphine per 24 hr.

100 mcg/hr Transderm.patch = 200 mg oral Morphine per 24 hr.

CONVERTING TREATMENT: from oral MORPHINE to oral LEVORPHANOL

Morphine (MS)/24 h to Levorphanol (LEV)/24 h

- MS < 100 mg 12:1 (12 mg MS:1 mg LEV)
- MS 101-300 mg 15:1 (15 mg MS:1 mg LEV)
- MS 301-600 mg 20:1 (20 mg MS: 1 mg LEV)
- MS 601-800 mg 25:1 (25 mg MS: 1 mg LEV)
- MS 801-1000 mg No data
- MS > 1000 mg No data

MD Anderson Ratios to Convert Oral Morphine to Oral Methadone:

- Morphine Equivalent Daily Dose (oral):
- <30mg: ratio MS to Methadone = 2:1
- 30-99 : " " " = 4:1
- 100-299: " " " = 8:1
- 300-499: " " " = 12:1
- 500-999: " " " = 15:1
- >1000 : " " " = 20:1

Adjuvants for Neuropathic Pain

- ANTICONVULSANTS:
- Gabapentin, Lyrica, Valproic Acid, Lamotrigine, Tegretol

TRICYCLIC ANTIDEPRESSANTS:

Amytryptiline Imipramine
Nortryptiline Desipramine

OTHERS: Duloxetine (Cymbalta)
Lidocaine

Adjuvants for Nociceptive Pain

- Tricyclic Antidepressants (desipramine or nortryptiline preferred)
- NSAIDS
- Corticosteroids (dexamethasone preferred)
- Metoclopramide (for visceral pain)

Case 1

- 86 yr WF, readmitted from nursing facility; dementia, debility, dehydration, UTI, sacral and heel decubiti, 3rd hospitalization in 3 mo. Grimaces and cries out when turned and bathed. Lortab elixir 5 mg q 6hr not helpful.
- Rx: parenteral fluids, antibiotics, iv morphine, haloperidol, wound care, Foley
- Sepsis worsens, more agitation, family notified of decline and asks for comfort care at home with hospice.

Palliative Care at Home with or without Hospice for Case 1

- Hospice or palliative care team assessment; develop plan of care with MD:
- Pain: Morphine oral conc. Roxanol 0.25 ml (5 mg) buccally q 2-4 hr prn pain; titrate up 0.25 ml stepwise as needed
- Haloperidol oral conc. 2mg/ml.; 1-2 mg q 4-8 hr buccally, for agitation or nausea.
- Lorazapam oral conc. 2mg/ml; 0.5-2.0 mg may or may not be helpful for anxiety.

Alternative Rx for Case 1

- Don’t use Fentanyl patch until stable pain control with short-acting opioid- remember 25mcg/hr patch is equal to 50mg oral morphine/24hr
- Oxycodone oral conc. 20mg/ml SL or buccally
- Hydromorphone 2mg tabs(crushed) or oral solution, 1-2mg q 3-4 hr. A conc. sol. available (1mg per drop) when large dose needed
- Levorphanol 2mg tab (crushed) ½ tab q 8hr subling.
- Methadone 2.5mg (crushed) or oral conc.q 12hr

Case 2
Lung cancer with spread to Pleura and Ribs

- 61yr WM, Dx 1 mo., seen in Onc. Clinic: Pain at 7, aching, sharp with activity and with cough. Lortab10 q 4-6 hr prn not helping over past 2 wks.
- Percocet 5 one or two q 4hr ATC helps after 3 days; taking 8 tabs/ 24 hr.(40 mg in 24 hr)
- Convert to Oxycontin 20 mg q 12 hr,and 1 Percocet q 4 hr prn breakthrough pain.

Case 2 Worsens

- Despite aggressive Rx, he developes mets to liver and spine; pain becomes severe, with somatic, visceral, and neuropathic elements
- Oxycontin increased stepwise, 80 mg q 8hr
- No relief, so Dilaudid by PCA pump, and finally an intrathecal pump is helpful until he becomes septic and pump is removed.

Case 2 near- terminal

- Dilaudid PCA not controlling pain; 2 mg/hr plus 20mg demand, for total 68mg/24hr.
- Morphine equivalent=68 x20=1,360 mg po
- Convert to Methadone: conversion ratio is 20 to 1, so Methadone dose is 68 mg in 24hr
- Could dose po 20mg at 6am and 2pm and at 10pm, or half that dose q 8hr subcut. Reassess often to adjust dose up or down,

Case 3
End-stage COPD

- 78yr WF, smoker, anxious and fearful, housebound, oxygen-dependent, on nebs, prednisone, in and out of hospital with pneumonia, gets frequent bouts of dyspnea.
- She and family are afraid of narcotics (addiction, hastening death).
- Lorazepam helps some with anxiety and hyperventilation, but sx worsen.

Case 3: Comfort

- Educating family and patient by nurse and doctor that benefit of Morphine is great and risk is very small takes time and diligence
- They finally agree with a test dose of 5mg, either Roxanol or MSIR tab, when in distress and with nurse present
- In 30 min, patient gets calm, more relaxed, with much better relief of dyspnea, and thereafter she allows morphine prn for dyspnea or pain.

Case 4: Breast Cancer with Spread to Bone and Liver

- 54 yr BF admitted to Hospice from hospital with constant mod.severe pain in upper back, rib cage and upper abdomen.
- She was on a Morphine PCA pump, and was converted to MsContin 90mg q 12hr, with 30mg MSIR q 4hr prn breakthrough pain.
- Over next mo., pain increased despite 600mg MsContin in 24 hr. Muscle spastic contractions develop, signalling morphine toxicity: Must rotate to another opioid (Dilaudid).

Case 4: Side-effects

- Dilaudid tried orally, then by PCA pump, but metabolites of Dilaudid cause similar side-effects, leading to seizures. Must calculate rotation to another opioid (Levorphanol)and stop Dilaudid. Dilaudid dose is equal to 480 mg oral morphine in 24 hr.
- Consultant rotates her to oral Levorphanol. Ratio of MS:Lev is 20:1, so Lev dose is 24 mg/ day, or 6mg q 6 hr. Pain reduced, with no adverse effects

“Symptom Control Kit”

Morphine solution 20mg/ml (subling) (15ml)

Chlorpromazine suppository 25mg (2)

Diazepam suppository 10mg (2)

Hyoscyamine [1-atropine] tab 125mcg (4), or
Atropine 1% drops (5 ml)

Lorazepam Sol., 2mg/ml (buccally),(15ml)

Haloperidol tabs 2mg (6)

Summary

- The standard of care for the treatment of pain is changing every year.
- Pain, particularly chronic pain, is undertreated by most physicians.
- Non-interventional pain treatment is safe, effective, and cost-efficient.
- Most primary care MDs can treat most patients with chronic pain, whether malignant or non-malignant.
- Palliative Care team can help relieve complex chronic pain even in patients who may die soon.

UNDERSTANDING METHADONE