Management of Chronic Malignant & Non-malignant Pain

Annual Zbeetnoff Drug Therapy Decision Making Conference

Regina, Sask.

March 11-12, 2011

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REMINDERS

- Turn off cell phones & pagers
- Ask questions at any time

Disclosures: none

Outline

1. Principles of chronic pain mgmt
2. Pain:
   - Pathophysiology
   - Types
3. Non-opioids, Opioids, & Adjuvants
4. Common Drug Side-effects

Principles I: Symptom Mgmt

- Directed H & P
  - Look for treatable causes
  - **Severe Distress is an Emergency !!**
- Work w/ interdisciplinary team
  - symptoms are exacerbated by psychological, social, and spiritual stressors
- Communicate effectively
  - MD & Pharm!
- Follow up: what did/did not work

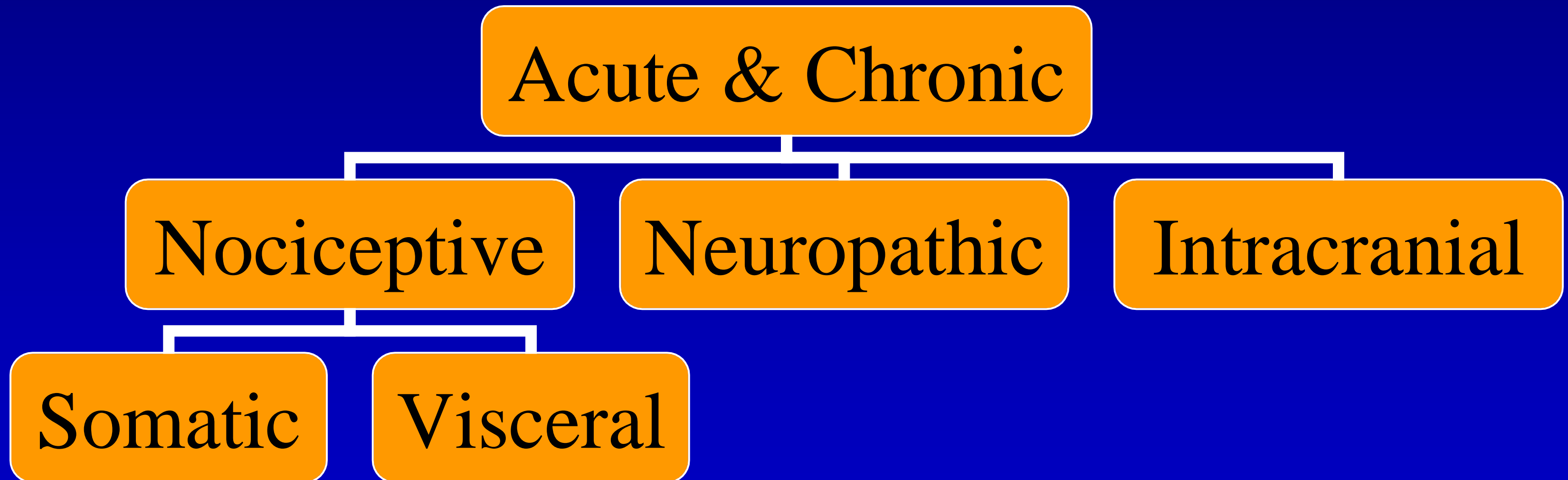
Principles II: **Chronic** Pain Rx

- By mouth
- By the clock – not prn
- By the WHO ladder
- Individualize Rx & Monitor response
- Use Adjuvant drugs
- For ‘constant pain’, need to Rx ‘constantly’
  - 10-30% pts have uncontrolled pain due to s/e
- Anticipate nausea & constipation w/ opioids

Pain pathophysiology

- Acute pain
  - identified event, resolves days–weeks
  - usually nociceptive
- Chronic pain
  - cause often not easily identified, multifactorial
  - indeterminate duration
  - Increased sensitization to all stimuli
    - Hyperalgesia – exaggerated response to noxious stim.
    - Hyperesthesia – exaggerated response to touch
    - Allodynia –non-nociceptive stim. perceived as painful
  - nociceptive and / or neuropathic…

Types of Pain



Nociceptive pain . . .

- Direct stimulation of intact nociceptors*
  [*group of cells that acts as a receptor for painful stimuli]
- Transmission along normal nerves
- sharp, aching, throbbing
  - somatic
    - easy to describe, localize
  - visceral
    - difficult to describe, localize

Neuropathic pain . . .

- Disordered or damaged peripheral or central nerves
- Compression, transection, infiltration, ischemia, metabolic injury
- Varied types
  - peripheral, deafferentation, complex regional syndromes

. . . Neuropathic pain

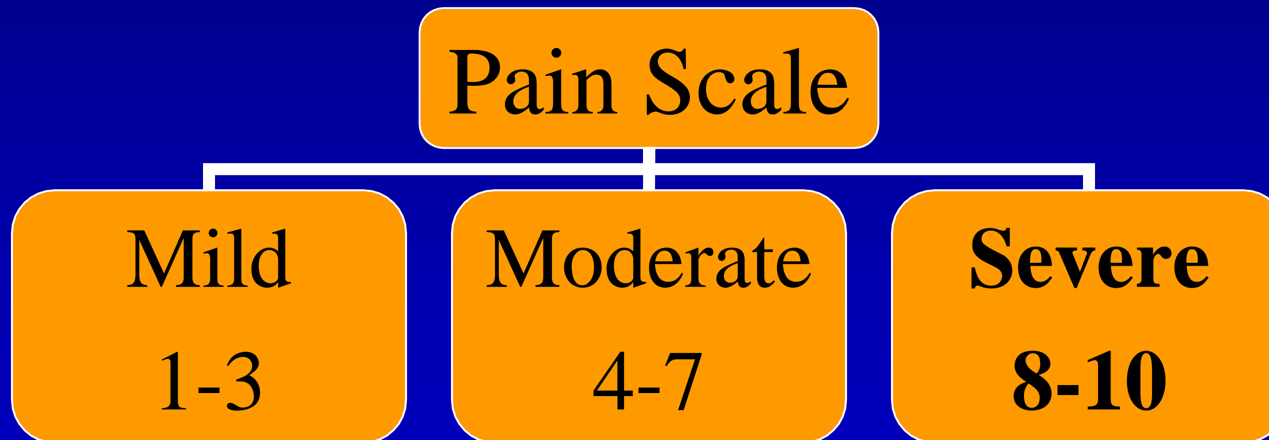
- Pain may exceed observable injury
  - E.g. diabetic neuropathy
- Described as burning, tingling, shooting, stabbing, electrical
- Management
  - opioids
  - adjuvant / coanalgesics often required

Assessing Pain: Chronic TOTAL PAIN

(Applies equally to any symptom assessment)

- Treat all 4 components of Total Pain
  - **P** – physical
  - **A** – anxiety, anger, depression (emotional)
  - **I** – interpersonal (social) – financial/family
  - **N** – non-acceptance of EOL (spiritual)

Assessing Pain



PAIN Severity

- **Do NOT withhold Rx waiting to identify cause !**
- Mr. Carcinoma – pain in back/hips
  - He decided to take chemoRx but now 6 mo later he found boney mets causing pain = 7-8 /10 most days

Consequences of Under Treated Pain

- Untreated pain can cause a patient's emotional and ***spiritual*** death long before the actual end of life – and result in **permanent nerve hypersensitivity**.
- Depression & Agitation/anxiety
- Sleep problems & Anorexia
- Decreased socialization/conditioning

Chronic PAIN types – Rx Guide*

1. Somatic/tissue & bone (nociceptive receptors)
   - Opioids; Bone often needs NSAID or steroid
2. Neuropathic
   - opioid + anticonvulsant +/or TCA
3. Visceral
   - Opioid + anticholinergic

Principles of Analgesics Use in the Tx of Acute Pain and Cancer Pain. Am.Pain Soc., 1999.

Fine PG. Chronic pain management in older adults. J Pain & Symp.Management. 2009 .

Morrison LJ. Pall.care and pain mgmt. Med.Clinics North Am. 2006

WHO Analgesic Ladder Rx

Start @ #1, push to maximum, then #2,etc.

1. Non-opioid + adjuvant
2. Mild opioid + non-opioid + adjuvant
3. Strong opioid + non-opioid + adjuvant

* Purpose of Step 2 is to go to step 3 !
* **Frail elders = start low & go slow !**

WHO 3-step Ladder

1 mild

- ASA
- Acetaminophen
- NSAIDs
- ± *Adjuvants*

2 moderate

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

3 severe

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

Pain 'Timing' & Rx

- Constant pain has diurnal/circadian pattern
  - Worse during night – so, double hs dose?
- Breakthrough pain – pain increasing before next scheduled dose
- Incidental pain
  - Severe aggravation w/ movement
  - Short duration (seconds – minutes)
    - Difficult to treat

(When Rx, try to stay below sedation threshold)

Analgesics Overview

Non-opioids

- Acetaminophen (max. 4gm/day; 3gm for Srs)

Opioids [3 classes; * synthetics]

1) morphine, codeine, Dilaudid*, hydrocodone, oxycodone*, tramadol [Ultram]
2) Fentanyl*, meperidine* [Demerol]
3) Methadone*, propoxyphene* [Darvon]

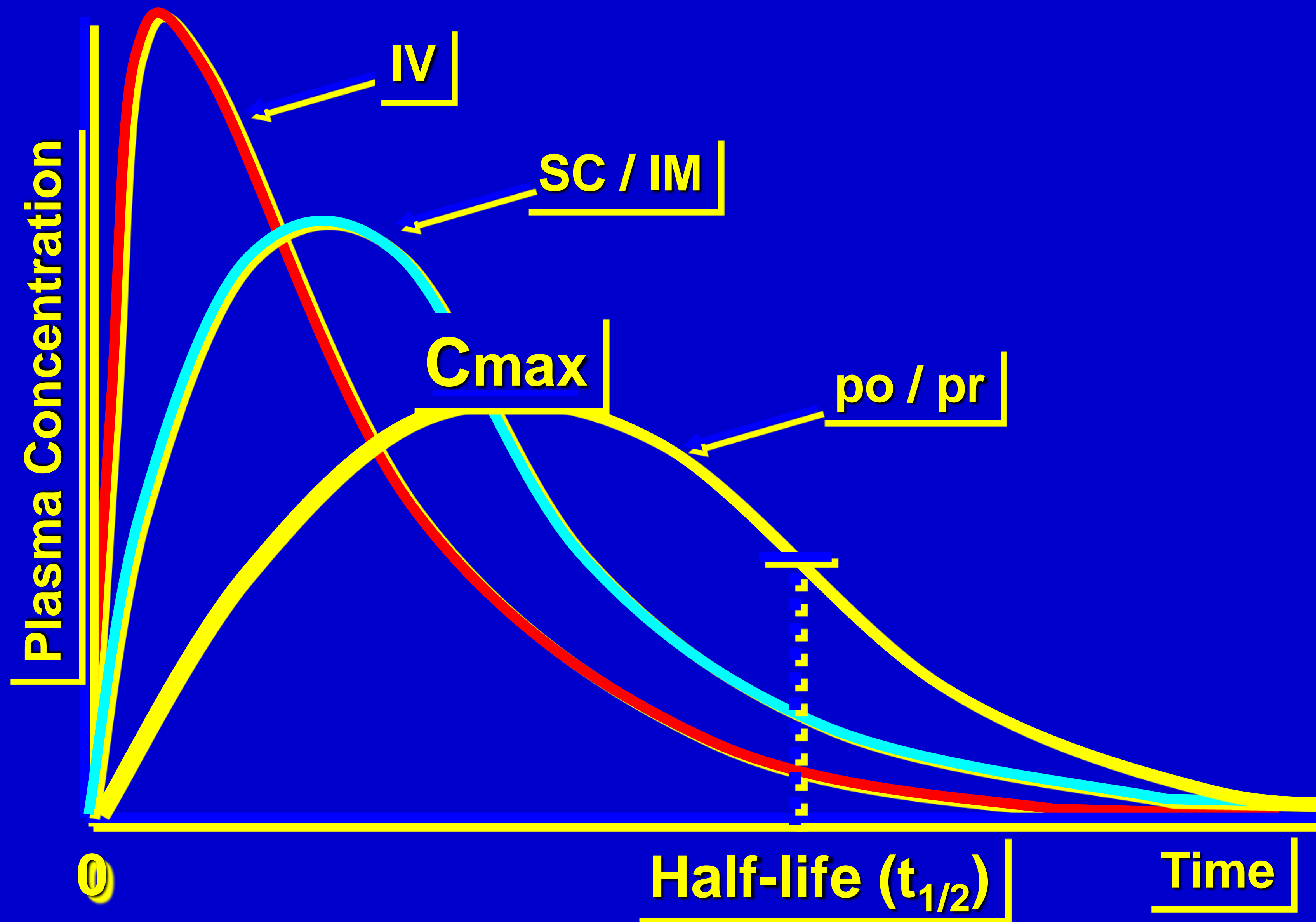
Adjuvants

- NSAIDS; Steroids; benzodiazepines; neuroleptics;
- antidepressants; anti-convulsants

[Hospice & PC Formulary USA 2nd Ed. 2008]

Opioid pharmacology

- Duration of effect of “immediate-release” formulations (except methadone)
  - 3–5 hours po / pr
  - shorter with parenteral bolus
- Steady state after 4–5 half-lives
  = 1 day (24 hours) for IR’s


IV
SC / IM
Cmax
po / pr
Plasma Concentration
0
Half-life ($t_{1/2}$)
Time

Routine oral dosing
immediate-release preparations

- Codeine, hydrocodone, morphine, hydromorphone, oxycodone
  - dose q 4 h
  - adjust dose daily
    - mild / moderate pain ↑ 25%–50%
    - severe / uncontrolled pain ↑ 50%–100%
  - adjust more quickly for severe uncontrolled pain

Routine oral dosing

extended-release preparations

- Improve compliance, adherence
- No better analgesia or reduced S/E [?]

  + 5 times more expensive in USA !
- Dose q 8, 12, or 24 h (product specific)
  - don't crush or chew tablets
  - may flush time-release granules down FT
- Adjust dose q 2–4 days (once steady state reached)

Breakthrough dosing [BTD]

- If >3 BT doses/day, increase sched.dose
- Use immediate-release opioids
  - 10% of 24 hr dose q1h
    - E.g. Morphine 20mg QID + 10mg q1h prn
    - If IV/subQ, can give ¼ of 10%, q15min prn
  - offer after C_{max} reached
    - po / pr ≈ q 1 h
    - SC, IM ≈ q 20-30 min
    - IV ≈ q 10–15 min
- Do NOT use extended-release opioids for BTD

Opioids: **Morphine**

- Morphine = gold standard
  - No upper limit dosage e.g. 50mg/hr IV !!
    … but, watch out for neurotoxicity
  - Concentrated liquid preferred in hospice
    - 20mg/ml; start 5mg typically;
    - Dispensing issues ? (e.g.600mg)
  - Subling poor [10%] - "trickle-down" absorption
  - For pain, anxiety, dyspnea
  - Give scheduled q4h; or TID w/ double dose hs

Opioids: **Methadone**…

- Becoming Drug-of-Choice in many hospice/PC programs
  - Least expensive opioid
  - Give po/sl/IV/SQ/rectal/PLO – bid to tid
  - Best opioid for subling/buccal absorption [lipid solubility]
- Concerns/Risks
  - Long half-life = risk of accidental OD
    - Patient/family must keep log
    - Do Not waken to take it !

Methadone: why it's better

- Mu opioid agonist, NMDA [N-Methyl-d-Aspartate] receptor antagonist; inhibits reuptake serotonin, Norepineph.
- No active metabolites
- Better pain control than morphine, but more sedating
- As good as morphine for breakthrough pain q3h
- Reduce risk of opioid-induced neurotoxicity
- Low cost !!

[Bruera et al, 2000; Hospice & PC Formulary USA. 2nd Ed. 2008; Cleary JF. Methadone: the ideal long-acting opioid? AAHPM Bulletin, winter 2002.]

FYI: Relative Opioid Costs

• Morph.liq.20mg/ml 100mg/day		= $5.00/day
• Morph.MSIR 15mg	‘’	= $1.40/day
• Methad.liq.10mg/ml	30mg/day	= $2.08/d
• Methad.tabs 10mg	‘’	= $ .80/d
• Fent.patch 50mcg q3d		= $5.66/d
• Duragesic 50mcg		= $10.60/d
• Fentanyl buccal [Fentora 100mcg]		= $20 each
• Dilaudid liq 1mg/ml	15mg/day	= $4.37/d
• Dilaudid tab 2/4/8mg	16mg/day	= $6.00/d
• Lorcet 10/325 qid		= $1.21/d
• Morph.pump at home		= $30/day pump only
• Morph.10mg/ml PLO [topical] 60mg		= $5.40/day

* 2010 Avg.Retail Cost

Opioid Equianalgesic doses*

po / pr (mg)	Analgesic	**SC** / IV / IM (mg)
100	Codeine	60
15	Hydrocodone	-
4	Hydromorphone	1.5
15	**Morphine**	**5**
10	Oxycodone	-
150	Meperidine	40
25mcg	Fentanyl	= 50mg/day MS

Methadone – see separate formula scale…

*[*Prescriber's Letter, Sept.2004. AAHPM Equianalgesic Table for Adults. 2003]*

Converting Morphine to Methadone

< 100mg MEDD* = 4:1 [e.g. MS 100mg/d = 25mg methadone]

101 – 300mg/day = 8:1

301 – 500mg = 12:1

501 – 1000mg = 15:1 [e.g. 600mg/d = 40mg methadone]

>1000mg = 20:1

Rx conversion e.g. - methadone 10mg tid + 5mg q3h prn.

[* MEDD = Morphine Equivalent Daily Dose = convert & add all opioids to total MEDD]

Opioids - Why not Demerol !!

- Short duration
- Low potency – but addictive!
- Not recommended by any national CPG since 1990: for elders, >3days, CPS, CRI
- Medical myth re pancreatitis & biliary colic
- Toxic metabolite – normeperidine
  - CNS Excitation Syndrome – tremors, myoclonus, delirium, seizures

Also Not recommended . . .

- Mixed agonist-antagonists
  - Pentazocine [Talwin], butorphanol [Stadol], nalbuphine [Nubain], dezocine
    - compete with agonists → withdrawal
    - high risk of psychotomimetic adverse effects with pentazocine, butorphanol
- Propoxyphene [Darvon]
  - no better than ASA, acetaminophen
  - toxic metabolite at high doses
  - FDA removed from sales Nov/10

Tolerance

- Reduced effectiveness to a given dose over time
- 9 different mu receptors
  - opioids bind in different proportion often leading to tolerance to one opioid
  - **rotating opioids helps treat tolerance**
- Usually not clinically significant with chronic dosing
- If dose increasing, suspect disease progression

Pain poorly responsive to opioids

- As dose escalates → adverse effects; so…
  - Need changes to counteract adverse effect
  - Avoid mixing opioids [if possible]
  - alternative
    - route of administration
    - **opioid ("opioid rotation" - <u>methadone</u>)**
  - Adjuvants
  - use a non-pharmacologic approach
  - Look for other causes/factors

…Pain poorly responsive to opioids

- Lidocaine 1% IV option [cancers]
  - 1-2mg /kg slow push over a few minutes,
    or, in 25ml saline over 15-30min.
  - May follow w/ continuous infusion 1-2mg/kg/hour
  - Will reduce dose of opioid needed !

- Ketamine po [use inj. form po; not usually given IV/SQ when in hospice] - effective in Complex Regional Pain Synd !
  - Should have specific protocol & directions for family [see website]

[Thomas J, etal. IV Lidocaine relieves severe pain. J Pall Med. 2004]
[McCleane G. IV Lidocaine: an outdated or underutilized tx for Pain. J Pall Med. 2007.]
[Fine PG. Ketamine: from anesthesia to palliative care. AAHPM Bulletin 2003]

Opioid adverse effects

Common	Uncommon
Constipation*	Bad dreams / hallucinations
Dry mouth	Dysphoria / delirium
Nausea / vomiting**	Myoclonus / seizures
Sedation	Pruritus / urticaria
Sweats	Respiratory depression
	Urinary retention

* Scheduled laxatives !!

* * Scheduled anti-emetic for 1st wk !!

Opioid-induced Nausea / vomiting

- Onset with start of opioids
  - tolerance develops within days
- Prevent or treat with dopamine-blocking antiemetics for first week of tx
  - Prochlorperazine [**Compazine**], 5 mg q 6 h
  - Haloperidol [Haldol], 1 mg q 6 h
  - Metoclopramide [**Reglan**], 5-10 mg q 6 h

Opioid allergy

- Nausea / vomiting, constipation, drowsiness, confusion
  - adverse effects, not allergic reactions
- Anaphylactic reactions are the only true allergies
  - bronchospasm
- Urticaria, bronchospasm can be allergies; need careful assessment

Urticaria, pruritus

- Mast cell destabilization by morphine, hydromorphone
- Treat with routine long-acting, non-sedating antihistamines
  - fexofenadine, 60 mg po bid, or
  - loratadine 10mg
- Sedating antihistamines or doxepin if sleep desired

Sedation

- Onset with start of opioids
  - **distinguish from exhaustion due to pain**
  - tolerance develops within days
- If persistent, try alternative opioid
- Psychostimulants may be useful
  - Methylphenidate [Ritalin], 2.5 mg q am and q noon, titrate

Respiratory depression

- Opioid effects differ for patients treated for pain
  - pain is a potent stimulus to breathe
  - loss of consciousness precedes respiratory depression
  - pharmacologic tolerance rapid

Alternative routes

- Enteral feeding tubes
- Transmucosal / Sublingual / buccal
- Rectal
- Transdermal - PLO *
- Parenteral – **SubQ** , IM , IV
- Intraspinal

* PLO: Pluonic Lecithin Organogel; Permanent Latrine Orderly; Palestine Liberation Organization;

SubQ - Hypodermoclysis

- For subQ meds and fluids
- Fluids for rehydration – NS, D5/NS
  - Up to 125ml/hr, +/- KCl; equal absorption
- Meds = anything that can be given IV except abx and a few others
  - Place #23-25 butterfly access – chest best; change only if red/draining
  - Rarely need IV; **No IM injections**

- *AAHPM Bulletin, Winter 2003*

Transdermal patch

- Fentanyl [*Duragesic*]
  - peak effect after application ≈ 24 hours
  - patch lasts 48–72 hours
  - ensure adherence to skin
  - NOT for opioid naïve !!!
  - Overrated and $$$
  - 25mcg patch = 50mg MS/day
  - More delirium?

Adjuvant analgesics

- Medications that supplement primary analgesics
  - may themselves be primary analgesics
  - use at any step of WHO ladder
  - Antidepressants, anticonvulsants, steroids

Tricyclic antidepressants for burning (neuropathic) pain . . .

(SSRIs usually not helpful)

- **Nortriptyline** > Amitriptyline
- 10–25 mg po q hs, titrate (escalate q 4–7 d)
  - analgesia in days to weeks
  - Fewer anticholinergic adverse effects, cardiac toxicity
  - Sedation helpful at hs
  - May exacerbate RLS

… Neuropathic Pain

- Anticonvulsants
  - Gabapentin [Neurontin]
    - 100 mg po tid, titrate to 2400-3600mg
  - Carbamazepine [Tegretal]
    - 100 mg po bid, titrate
  - valproic acid [Depakote]
    - 250 mg po q hs, titrate
  - pregabalin [Lyrica]
    - 25mg po tid [$$$]

Bone pain

- Management
  - opioids
  - NSAIDs
  - **corticosteroids**
  - Bisphosphonates [alendronate/Fosamax]
  - Calcitonin [nasal – Miacalcin – for vert.comp.fx/mets]

Adjuvant

Corticosteroids . . .

- Many benefits: bone pain, nausea, anorexia, tumor related swelling pain
- Side effects less important in PC [but usually try weaning off <6wks]
- Dexamethasone [*Decadron*]
  - long half-life (>36 h), dose once / day
  - minimal mineralocorticoid effect
  - doses of 2–20 + mg / d

NSAIDs . . .

- Step 1 analgesic, co-analgesic
- If one class ineffective, change to dif. class (5)
  - E.g. ibuprofen [Motrin] to diclofenac [Voltaren]
- Inhibit cyclo-oxygenase (COX 1 & 2) [PG's]
  - vary in COX-2 selectivity
- All have analgesic ceiling effects
  - effective for bone, inflammatory pain
  - individual variation, serial trials

NSAID adverse effects

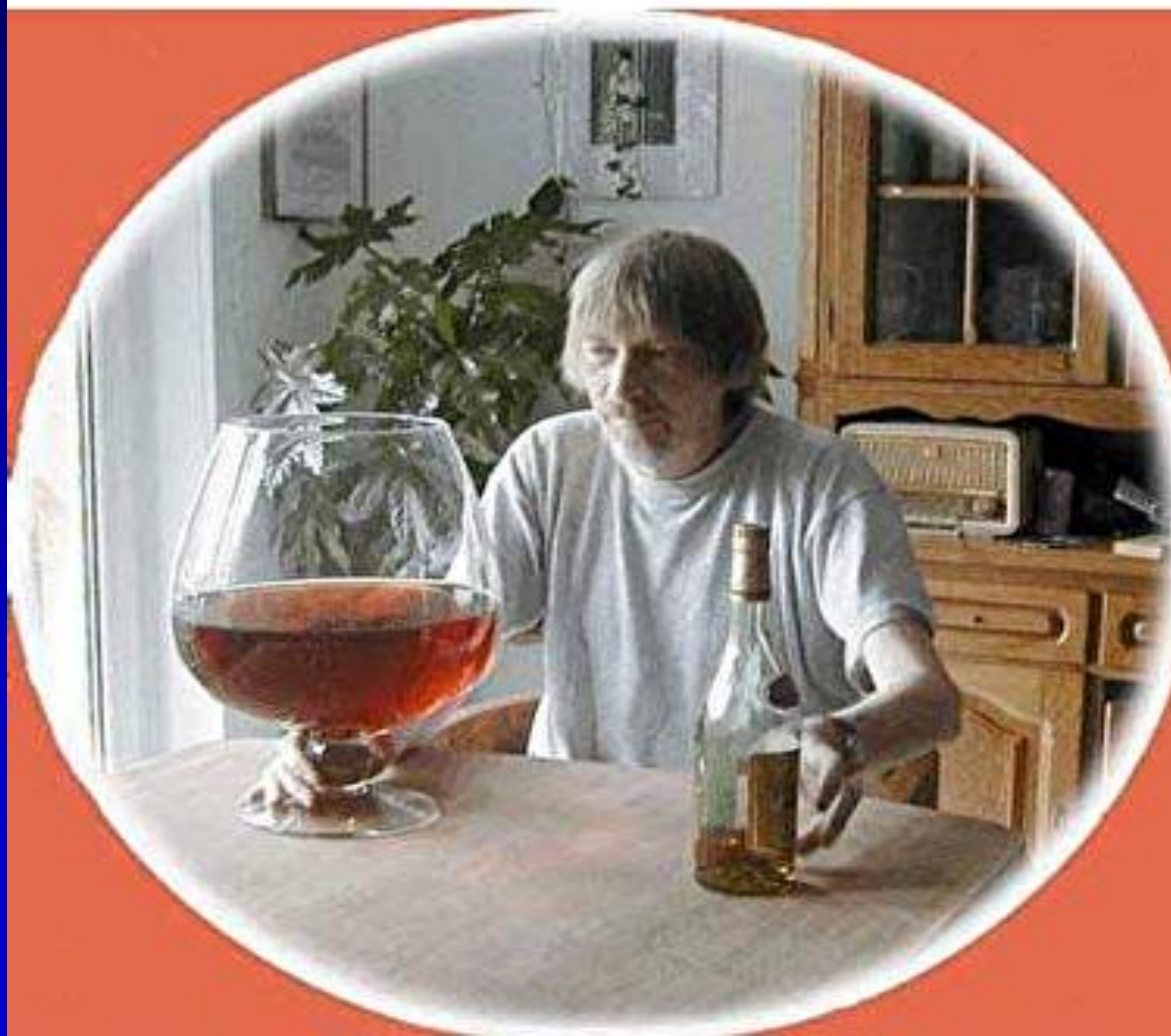
- Renal insufficiency & edema
  - maintain adequate hydration
  - COX-2 selection inhibitors
- Inhibition of platelet aggregation
  - assess for coagulopathy - GI Bleed
- Confusion/delirium in elders
- **Avoid in DM2 and CHF – and in elders !**
  - per AGS 2009

[Hospice & Palliative Care Formulary USA, 2nd edition. 2008]

Substance users

- Can have pain too
- Pain history NB – screen for chronic pain syndrome ? - CAGE score 2+ = poor pain control
- Treat with compassion
- Protocols, contracting
- Consultation with pain or addiction specialists

My Doctor said "Only 1 glass of alcohol a day". I can live with that.



Nonpharmacologic pain management…

- Palliative Radiotherapy – localized cancers bone
  - Only for those >2mo prognosis;
  - Single dose usually as effective as multiple
  - 40% have 50% pain decrease [1-2wks]
- Neurostimulation
  - TENS, acupuncture
- Anesthesiologic
  - nerve block
- Surgical
  - cordotomy
- Physical therapy
  - exercise, heat, cold

. . . Nonpharmacologic pain management

- Psychological approaches
  - cognitive therapies (relaxation, imagery, hypnosis)
  - biofeedback
  - behavior therapy, psychotherapy
- Complementary therapies
  - Massage; mentholated creams
  - art, music, aroma therapy

Pain Management Problems – Mr. Charles Carcinoma

- NB to document doses and responses !!!
- Started on morphine 15mg q4h po (8/10)
- Reglan 10mg po q8h [*anticipatory*]
  - Can reduce or wean off after a week
- Added dexamethasone 4mg bid
- Pain still 5/10, not sleeping; (goal=3/10)
  - **Add nortriptyline 25mg hs = slept and 3/10**

Coping w/ Pain & Aging

Hope is eternal & life is a circle.

Definition of success changes…

- At age 4, success is…not peeing your pants
- At age 12, success is…having friends
- At age 16, success is…a driver's license
- At age 20, it's…having sex
- At age 35, it's having money…

…Defining Success as we age

- At age 50, success is…having money
- At age 60, it’s…having sex
- At age 70, it’s…having a driver’s license
- At age 75, it’s…having friends
- At age 80, success is not peeing your pants!

“Growin’ old ain’t for sissies” **– Bette Davis**

Thank you !