Drugs & Myths in Hospice & Palliative Care

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Florence, AL

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Outline

I. Drugs used in Hospice & Palliative Care

* Symptom- & Mechanism-based treatments

II. Common Myths in Healthcare & EOLC

* including the myth of ‘informed consent’

REMINDERS

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

Why are we here? To learn from the mistakes of others

Will Rogers said…

- There are 3 kinds of men. The ones who learn by reading. The few who learn by observation. The rest of them have to pee on the electric fence for themselves.

General Goal: provide you w/ the info to counter myths and to understand the rationale for sometimes "doofus" orders!

I. Symptom Controlling Drugs in Hospice & Palliative Care

1. Pain
2. Nausea/Vomiting
3. Dyspnea
4. Constipation
5. Delirium
6. Anorexia

1. Pain

1) Principles of Management
2) Opioids
3) Adjuvants

1) Principles of **Chronic** Pain Rx

- By mouth
- **By the clock – not prn**
  - Pharmacist helps to reinforce to family
- By the WHO ladder [Steps 1, 2, 3]
- Individualize Rx & Monitor response
- Use Adjuvant drugs
- Anticipate nausea & constipation w/ opioids

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

Pain ‘Timing’ & Rx

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

(Try to stay below sedation threshold)

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

Analgesics Overview

- Non-opioids
  - Acetaminophen (max. 4gm/day; 3gm for Srs)
- Adjuvants
  - NSAIDS; Steroids; benzo's; neuroleptics;
  - antidepressants; anti-convulsants
- Opioids [3 classes; * synthetics]

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

*** Hospice & PC Formulary USA 2nd Ed. 2008 ***

Opioids: **Morphine**

- Morphine = gold standard
  - No upper limit dosage e.g. 50mg/hr IV !!
  - Concentrated liquid preferred in hospice
    - 20mg/ml; start 5mg typically;
    - Dispensing issues – no minimum (e.g.600mg)
  - Sublinqual actually a “trickle-down” absorption
  - For pain, anxiety, dyspnea
  - Give scheduled q4h; or TID w/ double dose hs

Opioids: **Methadone**…

- Promoted as DOC 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 ‘’ = $2.40/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 8/day = $2.42/d
- Morph.pump at home = $30/day pump only
- Morph.10mg/ml PLO [topical] 60mg = $5.40/day

* 2010 Avg.Retail Cost – changes !

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]

Breakthrough dosing [BTD]

- If >3 BT doses/day, increase base rate
- 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 Cmax 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 - 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…
  - more sophisticated therapy to counteract adverse effect
  - 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]
  - Should have specific protocol & directions for family

[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

Constipation*

Dry mouth

Nausea / vomiting**

Sedation

Sweats

Uncommon

Bad dreams / hallucinations

Dysphoria / delirium

Myoclonus / seizures

Pruritus / urticaria

Respiratory depression

Urinary retention

* Scheduled laxatives !!

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

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?

3) 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 [~$250/mo]

Adjuvant

Bone pain

- Management
  - opioids
  - NSAIDs
  - **corticosteroids**
  - bisphosphonates
  - Calcitonin [nasal]

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 <u>DM2</u> and <u>CHF</u> – <u>and in elders</u> !**
  - per AGS 2009

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

Rx for Side-effects !

2. Drugs for Nausea / vomiting

- Incidence:
  - Terminal cancer – 62%; 42% in last 6wks
  - PCU admissions – 71%
- Nausea results in vomiting
  - subjective sensation induces neuromuscular reflex
  - Stimulation arises from 4 pathways/ mechanisms:
    - cerebral cortex
    - vestibular apparatus [CN VIII],
    - CTZ [chemoreceptor trigger zone],
    - gastrointestinal lining

[* Wood GJ, et al. JAMA 2007.]

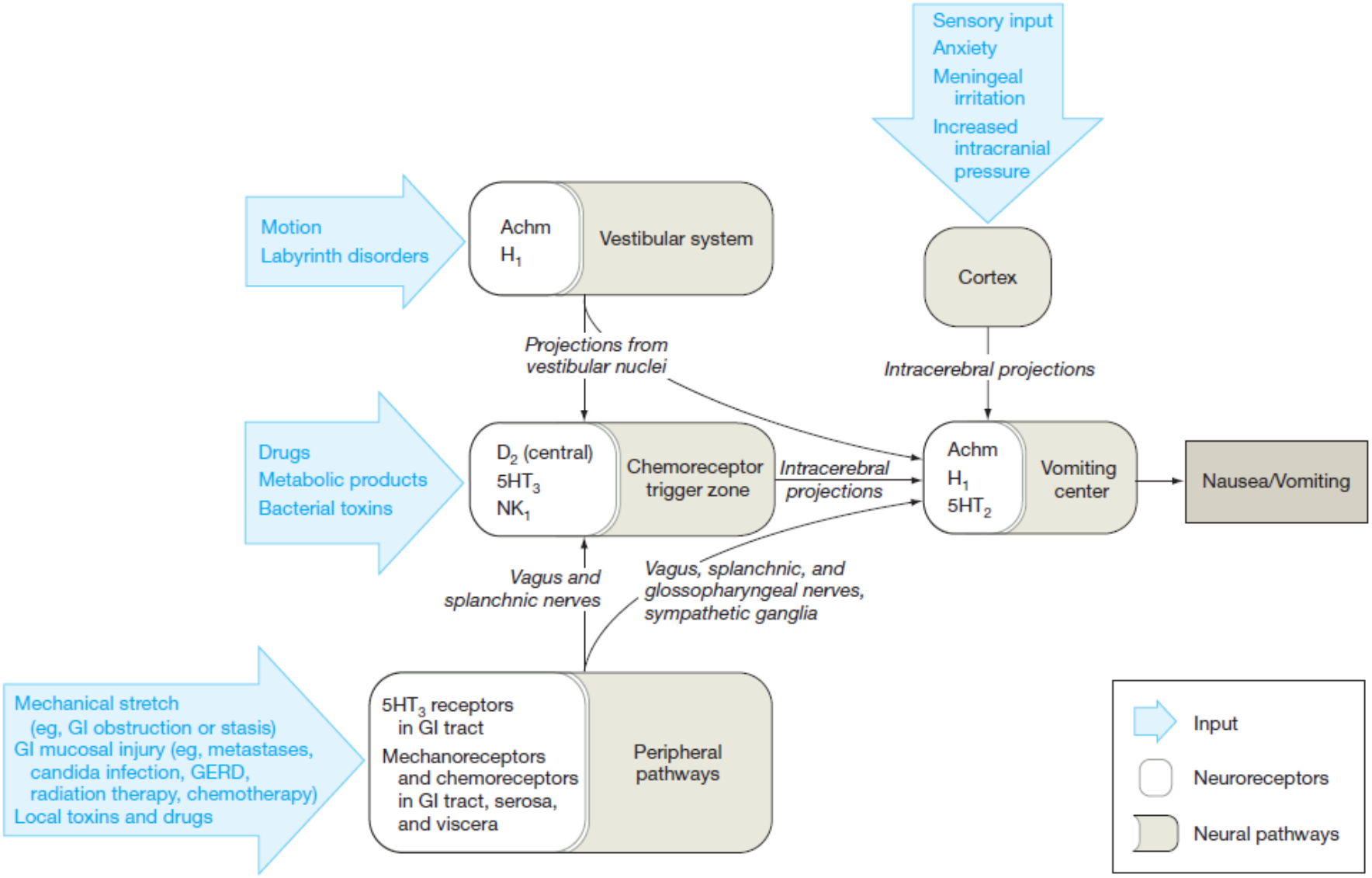
…Vomiting Pathophysiology/Mechanisms

- Psychologic stimuli = ***Cerebral***
- Motion/positional stimuli = ***Vestibular***
- Drugs/Uremia/Ketosis/Carcinomatosis = ***Chemoreceptor Trigger Zone***
- Gastric irritation/distension/Hepatitis = ***GI***

All stimulate Vomiting Center

Treat the underlying mechanism

Figure. Interrelationships Between Neural Pathways That Mediate Nausea and Vomiting



Achm indicates muscarinic acetylcholine receptor; D_2, dopamine type 2 receptor; GERD, gastroesophageal reflux; GI, gastrointestinal; H_1, histamine type 1 receptor; NK_1, neurokinin type 1 receptor; $5HT_2$, 5-hydroxytryptamine type 2 receptor; and $5HT_3$, 5-hydroxytryptamine type 3 receptor.

Mechanism-based Treatment

- *Cerebral*: Ativan; decadron
- *Vestibular*: Benadryl, Meclizine, Dramamine
- *CTZ*: Compazine, Haldol, Reglan [dopamine antagonists]; decadron; Zofran
- *GI*: antacids, Zantac, Reglan, PPI, Levsin, scopolamine; laxatives/enemas !

Causes of nausea / vomiting

- Metastases
- Meningeal irritation
- Movement
- Mental anxiety
- Mucosal irritation
- Medications
  - 30% of narcotics wk 1
- Mechanical obstruction
- Motility – 44%
- Metabolic/Microbes/ Meds – 33%
- Myocardial

*[*Stephanson J, et al. Supp.Care Cancer 2008]*

Management of nausea / vomiting

- Dopamine antagonists
  - First choice for most
- Antihistamines
- Anticholinergics
- Serotonin antagonists

- Prokinetic agents
- Antacids
- Cytoprotective agents
- Other medications

- Tx effective 84% in 3 days

- If one pathway fails, try different path

Dopamine antagonists

- Haloperidol [Haldol] – 0.5-1mg
- Prochlorperazine [Compazine] 5mg
- Droperidol [Inapsine]
- Promethazine [Phenergan – discouraged]
- Trimethobenzamide [Tigan]
- Metoclopramide [Reglan]

Histamine antagonists (antihistamines)

- Diphenhydramine [Benadryl] – 25mg q4h
  - Caution in elderly or dementia
- Meclizine [Antivert]
- Hydroxyzine [Atarax/Vistaril]

Acetylcholine antagonists (anticholinergics)

- Scopolamine [0.4mg subQ, q4h prn]
  - Also, Transderm V patch
- Glycopyrrolate [0.4mg subQ, q4h prn]
  - Doesn’t cross blood-brain barrier

Serotonin [5HT3] antagonists

- Ondansetron [Zofran - $$$ 22/4mg tab; 8mg tab = $39; generic $2 /4mg tab & $0.29/4mg IV]
  - Not FDA approved for ‘routine’ use – only for post-op, radiation therapy and chemotherapy
  - No more effective than combination of others in Palliative Care
- Granisetron [Kytril - $$$ 50/1mg tab]

Prokinetic agents

- Metoclopramide [Reglan] [10mg = $0.17/tab]
  - Caution in Parkinson's or Lewy body dementia

Antacids

- Antacids
  - Gaviscon [coating upper mucosa]
- H_2 receptor antagonists
  - Cimetidine [Tagamet]
  - Famotidine [Pepcid]
  - Ranitidine [Zantac]
- Proton pump inhibitors
  - Omeprazole [Prilosec]
  - Lansoprazole [Prevacid]

  *[3 signif. risks for seniors]

Other medications for N/V

- Dexamethasone [Decadron]
  - Anti-inflammatory - peri-tumor edema
  - Often helpful in cancers
- Dronabinol
- Lorazepam [Ativan]

- Octreotide [somatostatin analogue for malignant bowel obstruction]
  - $$$ 46.24 per 0.1mg [0.1-0.6mg/day usual]

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

3. Breathlessness (dyspnea)

- May be described as
  - shortness of breath
  - a smothering feeling
  - inability to get enough air
  - suffocation
- Only reliable measure is patient self-report
  - SaO2 doesn't often correlate

Causes of breathlessness

- Anxiety
- Airway obstruction
- Bronchospasm
- Hypoxemia
- Pleural effusion
- Pneumonia
- Pulmonary edema
- Pulmonary embolism
- Thick secretions
- Anemia
- Metabolic
- Family / financial / legal / spiritual / practical issues

Management of breathlessness

- Treat the underlying cause
- Symptomatic management
  - oxygen
  - opioids
  - Anxiolytics
  - Nebulizer – ipatropium vs albuterol – increase jitters in seniors? ASK.
  - Non-pharmacologic interventions

Treating Dyspnea - Morphine

- Morphine 3-10mg q4h po prn
  - Relaxes bronchial smooth muscles
  - Provides a euphoria, reduces “suffocation”
  - Reduces other pains
  - Can increase by 50% q4h till improvement
    - If dyspnea constant, give morphine scheduled RTC
  - Nebulized MS occasionally better than subQ/po
    - 5mg of sugar-free liq (or inj.solution) in 5ml NS
    - Crisis comfort kit

Anxiolytics

- Safe in combination with opioids
  - lorazepam
    - 0.5-2 mg po/subQ q 1 h prn until settled
    - then dose routinely q 4–6 h to keep settled
    - Can give subling crushed – crisis kit

Nonpharmacologic interventions

- Reassure, work to manage anxiety
- Behavioral approaches, e.g., relaxation, distraction, hypnosis
- Limit the number of people in the room
- Open window; fans
- Anticipate events and plan responses !!!
  - Crisis Mgmt !

4. The ‘anti-bunged up’ drugs

- Common to all opioids
- Opioid effects on CNS, spinal cord, myenteric plexus of gut
- Easier to prevent than treat

Constipation . . .

- Prokinetic agent
  - Metoclopramide [**Reglan**] – 5-10mg q6h
- Osmotic laxative
  - MOM, lactulose, sorbitol,
  - **Miralax (17gm QDay)**
    - **MegaMiralax – 68gms in 250ml juice/water**
- Other measures – castor oil

Constipation - if on opioids:

- Diet usually insufficient
- Bulk forming agents not recommended
  - NO METAMUCIL [impacted concrete torpedo !]
- **Stimulant laxative**
  - **senna**, bisacodyl, glycerine, casanthranol, etc
- Stool softeners (docusate)
  - Not as helpful in seniors [all *mush* w/ no *push*]
  - Only use if hard stools are hard to push out

5. DELIRIUM

- A syndrome with acute disruption of attention and cognition **(cognitive failure !)**
- Diagnostic criteria *[DSM IV]*
  - 1. disturbance in consciousness w/ reduced ability to focus, sustain or shift attention
  - 2. change in cognition (e.g. memory/speech) with new perceptual disturbance
  - 3. develops over hours to days and fluctuates in severity
  - 4. has underlying medical cause

Delirium - prevalence

- Prevalence = 25% avg. (14-56%)
  - Undetected in 32-67% of those admissions
- May occur in up to 88% of terminally ill
- Mixed syndrome in PC:
  - Delirium + Depression + Dementia + Pain
  - A manifestation of other problems

[Brown TM. Delirium. BMJ 2002;325:644-7.]
[Inouye SK. The Dilemma of Delirium. Am J Med 1994;97:278-88]
[Bruera et al. J Pain Sympt Mgmt 1992]

Delirium - Common Causes

- **Drugs** – anticholinergics, anticonvulsants, anti-parkinsons, steroids, opiates, alcohol, benzo's
- Drug withdrawal – sedatives, opiates, alcohol
- Metabolic – Hypoxia, hypoglycemia, hypothyroid, fluid & electrolytes, ARF, hepatic failure, etc.;

Delirium - Causes cont'd

- Infections – especially UTI in dementias
- Head trauma; Rectal/Bladder Trauma !!!
  - i.e. Impaction or Retention
- Epilepsy
- Neoplasms
- Vascular – TIA/CVA, PTE, AMI, CHF

Management - Drugs

No drug is FDA-approved! Tx for the GOAL!

- Haldol = Drug of Choice [caution L.B.Dementia]
  - Give ROUTINELY, 1-2mg subQ (or po), & use prn for breakthrough [s/a for pain]
  - Review Q 24hrs
- "Avoid" benzodiazepines [paradoxical]
  - Unless alcohol withdrawal
  - Use only if Haldol alone ineffective

Terminal Delirium

- Signs of active dying process
- Hyperactive/agitated (or hypoactive)
- R/O opioid-induced neurotoxicity
  - Rapid increase in opioid dosing, dehydration; myoclonus, hyperesthesia, delirium
  - Trial reduction opiate 50%, increase fluids, Ativan

…Terminal Delirium: Tx Options

- Haloperidol [Haldol]– 1mg q30min subQ until controlled, then 2mg q6h x 24h, then prn [max = 100mg/day] [occasional paradoxical effect]
  - Thorazine [chlorpromazine] – 50mg q30min prn until controlled, then 100mg q6h; [max = 2000mg/day]
- Chlorpromazine [Thorazine] 100mg PR q4h prn
- Phenobarbital 100mg PR q4h prn
- Palliative Sedation: Principle of "double effect" in EOLC

6. Drugs to 'make mom eat'

Treating Anorexia – Cachexia Options

- Megace [megestrol] – 80-200mg qid
  - Increase risk DVT; $$$[$7/400mg]; 'false' wt gain
- Decadron [dexamethasone] – 2-16mg/day
- Alcohol – patient preference (homemade cough preparations !!)
- Others – metoclopramide; dronabinol; thalidomide.

*Cross KL. Eating & drinking at the EOL. AAHPM Bulletin. 2001.

Persons RK. Should we use appetite stimulants for malnourished elderly patients? J Fam Prac. 2007.

If comfort is Goal for many Seniors ?

Take a Break !!!

- 10 min. ?
- Then, Part II - Myths