SYMPTOM MANAGEMENT NEAR THE END OF LIFE

ASN RENAL WEEK 2010 – PALLIATIVE CARE IN ESRD PATIENTS.

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No Disclosures/Conflicts

- Nearly all drugs mentioned involve off label use except for opioids for pain. Will strive to make clear level of evidence.
- Focus – practical & evidence-based (as much as practical) approach to symptom management for ESRD patients near life's end.
- 'At EOL'…assumption is that underlying cause of symptoms not amenable to disease modification

Symptoms…

TABLE 1. Symptoms of dialysis patients following withdrawal of dialysis

Symptom	Prevalence (%) (7)	Prevalence (%) in last 24 hours without palliative care intervention (15)	Prevalence (%) in last 24 hours with palliative care intervention (7)
Pain	55	42	22
Confusion/agitation	70	30	34
Dyspnea	48	25	28
Nausea	36	13	6
Twitching/seizures	27	28	9
Anxiety/psychological distress	27		6
Pruritus	24		6
Diarrhea/incontinence of stool	21	14	9
Peripheral edema	21		9

You'll see slightly different rates in different series, point is these symptoms are:

1. Common
2. Distressing
3. Treatable

Germain MJ et al. Semin Dialysis. 2007; 20.

Case

- 69 yo woman with ESRD-HD x3 years due to DM2 & HTN. Debilitated, bedbound & nearly blind. Develops rash—ulcerates on L thigh. Hospitalized. Calciphylaxis. Thiosulfate & abx don't help. Given her debility and poor prognosis she agrees to supportive-only care (pain control, wound care). She elects to continue HD 'for now' to tie up her affairs and surprises everyone by continuing to tolerate HD well. Pain is gnawing, burning, 8/10 usually.

Symptom Management

- Our patients go through hell, then they die
- Physical symptoms affect their entire being
  - Ability to experience happiness, joy, emotional intimacy
  - Hope, peace, acceptance. Relationship w/ divinity.
- Our patients are tremendously grateful for the relief they get
- Most patients who understand they are dying want from us: to show up, to try, and to keep showing up

Symptom Management as CQI

- (Almost) Entirely Empiric
  - Evidence guides at best first-choice agents
  - *All sx management is an N of 1 trial*
- Choose an intervention
  - Evaluate at shortest interval for effect/toxicity
    - Dose titrate—re-eval at shortest interval
    - Rotate to new class (5HT3 blockers from D2 blockers)
    - Add new class, respecting polypharmacy
- Show up! Timely reassessments! Ask for help!

Symptom Management

- Acute/uncontrolled sx: rapid-acting meds
- Chronic/peristent sx: long-acting/scheduled meds
- Never forget psychogenic *aggravators* of symptoms – rarely a *sole cause* for patients at EOL but always worsens a bad situation: depression, anticipatory grief, anxiety, spiritual concerns

Pain

- Nociceptive – implies from real or threatened tissue damage.
  - Antiinflammatories
  - Opioids
- Neuropathic – from injury to or pathology of neurons (axons, DRG/spine, brain-thalamus).
  - Opioids
  - Adjuvants (AEDs, TCAs, SNRIs)
- Most nociceptive syndromes involve neural pathology – not a clear distinction.

Pain Assessment: Goals

- Characterize the pain – use standardized scale
- Identify pain syndrome
- Infer pathophysiology – will guide tx choice
- Evaluate physical and psychosocial comorbidities
- Assess degree and nature of disability
  - How is this impacting your life?
  - What can't you do because of the pain?
- Develop a therapeutic strategy – goal oriented
  - Pain level goal (e.g. 4/10)
  - Functional goal

Adapted from R Portenoy www.stoppain.org

Pain non-opioid

- Acetaminophen.
  - Safe.
  - Synergistic to opioids? vs a raindrop in the ocean?
  - Conflicting data. May be synergistic for lower dose opioids (~<50mg morphine equivalents/day)
- NSAIDs.
  - Not safe.
- Glucocorticoids.
  - Pretty safe. Lower dose dexamethasone 4-8mg day – psych-only side effects in short-term. Modest energy, appetite boost. Antiemetic.

Opioids – pharmacology in ESRD

- Avoid with ESRD
  - Codeine – it's morphine, just less effective
  - Meperidine – renally excreted normeperidine – agitation, pain, myoclonus, seizures
  - Propoxyphene – as above.
  - Morphine (see below)
  - Hydrocodone – not much is known. Anecdotally safe at low doses
  - Oxymorphone - ?liver ?renally cleared metabolites. Unknown.
  - (Tramadol – safe if renally dosed; ceiling effect; cannot titrate; **best avoided AT EOL for changing symptoms**)

Opioids

- Morphine – **best avoided.**
  - 3-, 6-glucuronides renally excreted
  - Longer $T_{1/2}$ (6-12h), pharmacologically active
  - M3G worsens pain, delirium, myoclonus
  - Advanced CKD without HD: avoid completely**
  - HD: MS, MS-6-G removed by HD but concern M6G accumulates in CNS and not removed well.
  - **THERE ARE BETTER OPTIONS.**
- **?Days to live – no time to accumulate glucuronides - MS may be OK
  - Watch for myoclonus, allodynia…

Opioids

- Oxycodone – CONTROVERSIAL
  - Renally excreted ~active metabolites oxymorphone, noroxycodone.
  - Clinical experience – **avoid in advanced CKD** – delirium, myoclonus, sedation
  - HD: Oxycodone, noroxycodone, oxymorphone are dialyzed…**probably safe**.
  - *Most experts* prefer hydromorphone if methadone, fentanyl impractical for HD patients. Empiric.

Lee MA. Palliat Med. 2005; 19:259-60.

Opioids

- Hydromorphone
  - 3-, 6-glucuronides renally excreted and accumulate in CKD. HM3G likely **neurotoxic, worsens pain.**
  - **Great caution in advanced CKD without HD**.
  - HM & metabolites are dialyzed well – **safer in HD**
  - New, long-acting forumation: NO PUBLISHED EXPERIENCE IN ESRD-HD.
  - …Especially at 'lower doses', even in StageV CKD, some patients will do fine with HM

Davison SN. J Opioid Manage. 2008;4:335-344.

Opioids

- Fentanyl – '100%' liver metabolized.
- Transdermal patch. **Preferred long acting opioid.** Takes 18-24h to work, steady state after a week.
- Transbuccal formulations: Lozenge, effervescent tab, biodispersible film.
  - Fastest acting nonIV. ONLY OPIOID TOLERANT (at least 25mcg/hr td fentanyl, 60mg/day oral morphine).
  - Expense cost-prohibitive for hospices.
  - Generally used if need short acting med & patient proven intolerant to HM, Oxy.

Opioids

- Methadone –'100%' liver.
- 'Both short acting and long-acting'
- Large Vd; Long terminal $t_{1/2}$ (<100h): dose uptitration with caution (>every 3-4d); **switching should be done by experienced clinicians.**
- Blocks NMDA receptor – ?better for neuropathic pain, less delirium, less tolerance, myoclonus re: other opioids?
- Multiple CYP450 interactions…3A4
- **Preferred agent if experienced in its use**

Dosing guidelines

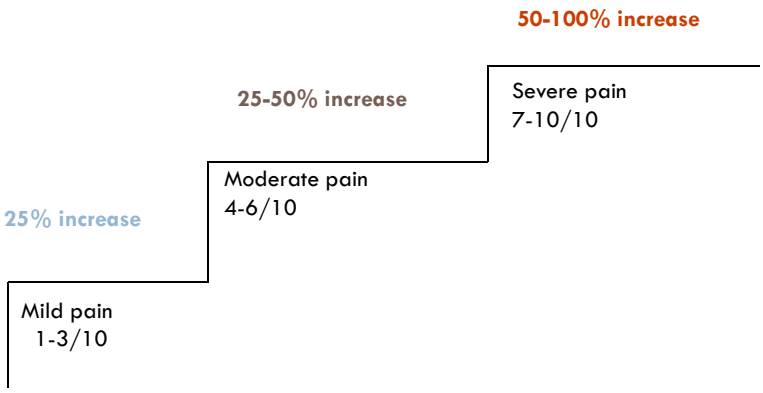
- PRN-only for rare, incident, intermittent pain
- Scheduled &/or Long-acting opioid for continuous/ATC pain
- Pick a starting dose – rapid reassessment and uptitration
- Immediate acting meds for uncontrolled sx
- Long-acting drugs as 'maintenance'/background

Starting doses in ESRD

- Oral oxycodone 5mg q4h** prn. (2.5mg in cognitively frail with ESRD)
- PO HM 2mg q4h** prn (1mg in cognitively frail)
- IV HM 0.2mg q2h** prn (0.1mg)
- IV Fentanyl 25mcg q1h prn (12mcg)
- Transbuccal fentanyl – lowest available and only for opioid tolerant
- OxycodoneER 10mg, Fentanyl patch 12mcg/hr ONLY FOR OPIOID EXPOSED.
- **These are longer intervals than in patients without CKD – would start here **but decrease interval if patient reports <4h of relief.**

Opioid Dose Escalation

Always increase by a percentage of the present dose for uncontrolled pain based upon patient's pain rating and current assessment



Adapted from Weissman DE. 2003. www.eperc.mcw.edu

Dosing guidelines

- Example: taking 4mg PO HM prior to dressing change. Reports pain remains 8/10. No sedation. Increase to 8mg. If minor sedation ~6mg.
- If mild sedation – choose lower range of escalation.
- If moderate relief, not perfect, but moderate sedation – continue same dose and monitor
- If dose-limiting sedation & uncontrolled pain
  - **Different opioid**
  - **Expert help –** non-opioid analgesics, blocks, topicals, rotation to methadone, assessment of 'non somatic' causes of pain/distress

Titration Intervals – Uncontrolled Sx

- IV bolus opioid (any of them)
  - Peak CNS within 15 minutes.
  - In closely monitored setting can uptitrate this often.
  - Once effective dose established – should last patient 1-4h – Can titrate with each dose.
- Oral dosing. Oxy, HM peak within 2h.
  - HM, Oxy reduced clearance can be up to 4h.
  - Ask patient – will be able to tell you onset, peak, duration of acceptable analgesia.
  - Safe to increase dose every ~3h. Once it has peaked, ok to redose

Titration Intervals – Long-acting

- 'Roll' PRN doses into long-acting doses vs Increase by %
- Oxycodone ER – q48h in ESRD (ie don't uptitrate any faster than this)
- Fentanyl patch – q72h
- Drips – for HM q24h in ESRD. Fentanyl IV q8h.
- Methadone – **expert** – >q3-4d.

Equianalgesic Table

PO/PR (mg)	Analgesic	SC/IV/IM (mg)
30	Morphine/Hydrocodone	10
4-6	Hydromorphone	1.5
20-30	Oxycodone	-
"15mcg/hr TD"	Fentanyl**	100mcg

**Half the *24 hour Oral Morphine-equivalent dose in mg* approximately equals the *Fentanyl patch dose in mcg/hr*

Adapted from Portenoy R. Beth Israel Medical Center. www.stoppain.org

Equianalgesia

- There is no equianalgesic dose of transbuccal fentanyl – always start at lowest and titrate
- Methadone – no established equianalgesic doses either – rotation to/from only by those experienced with it
- With any conversion between opioids DEFAULT should be to conservative range
- *Many add a 25-50% dose reduction from the 'equianalgesic dose'*
- Watch closely, prepare to increase if underdose

Examples

- 50mcg/hr TD fentanyl. Continues to report moderate 5/10 pain, minimal sedation. Taking 2mg PO HM 3x a day.
  - Increase HM 50% to 3mg; encourage using q3h. **OR** -
  - Increase TD fentanyl by 50% to 75mcg/hr.
- Using 0.4mg/hr IV HM with 2mg/day extra prn. (0.4x24 = 9.6 mg…11.6mg/24h IV HM).
  - 11.6 x 20 = 232mg PO MS "=" 115mcg/hr transdermal fentanyl. I'd prescribe 62 to 75mcg/hr fentanyl patch…decision based on how cognitively robust they are

Alternative Routes

- PO tabs: HM, Oxycodone, Methadone, MS
- PO liquid: Oxy, MS, methadone. HM(compounded)
- Sublinqual: HM, oxy/MS/methadone, fentanyl transbuccal formulations
- Rectal: HM, methadone, oxy, MS
- Subcut: HM, MS, fentanyl (Home continuous subcutaneous infusion – uses PCA device, subcut catheter)

Side Effects

- Constipation – stimulant laxatives are cornerstone
  - 2-8 tabs/d sennakot
  - Osmotic agents – avoid MOM, Fleets in ESRD
    - PEG 3350 – 17gm day ***is the healthy adult dose – many terminally ill/opioid users need 34-68gm or more***
    - Lactulose – more flatulance, cramping
- Nausea – Limited to first several days

Side effects – sedation & resp depression

- Great source of concern
  - Respiratory depression is rare if rational dosing used.
  - Drowsiness→somnolence→obtundation→respiratory depression→apnea. *Apnea doesn't just sneak up on you.*
  - Drowsiness worst first 24h – rapidly attenuates *with a stable dose*
  - However: dying patients often don't have a stable dose, and have progressive encephalopathy from other causes

Sedation & Respiratory Depression

- Zero evidence that opioid use at EOL hastens death (multiple hospice and palliative unit studies): **don't tell this to your patients**
- Educate patients/families, and focus on goals.
  - Reassure doses are chosen carefully and not to 'drug'
  - Caution that as death nears sedation occurs from 'dying process' itself, although deepened by meds
  - Clarify goals: symptom relief vs. being as aware as possible – symptom relief virtually always preeminent
- If a patient/family wants sedation – that is a red flag for extreme suffering/psychoemotional distress

Adjuvant analgesics

- Classically thought of as for neuropathic pain
- Limited role at EOL – not enough time to titrate.
- Would not introduce in those with days/weeks to live
- Continue them if patient already on them, adjusting for lack of dialysis and residual GFR.
  - Pregablin 25mg/day, Gabapentin 100mg/day, Duloxetine – recommended to stop, Nortriptyline & amitriptyline – continue regular strength.

Topicals & Patches

- Lidocaine 5% patch. Minimal systemic, safe in ESRD. Only established (RCT) benefit is for post herpetic neuralgia and painful diabetic neuropathy.
  - Probably strong placebo effect…so what?
  - 30 patches ~$220
- Diclofenac patch. Minimal systemic absorption (1/1000th of oral dose).
- Know your compounding pharmacist – morphine, methadone, gabap, ketamine, etc. gels – ulcers
  - Systemic absorption occurs. No data in ESRD.

Case – 69yo with calciphylaxis

- Pain probably mixed neuropathic nociceptive
- IV HM 0.2mg q1h prn. Reassess in 2h.
- Pain 8→6/10 with 2 doses. Analgesia for 45mins. No sedation.
- IV HM 0.4mg IV q1h prn.
- Reassess 2h pain 4/10 with 1 dose, lasted 90 mins – drowsy.
- Continue this dose

Case

- After 1 day used 3.4mg IV HM with mild drowsiness and pain 3-5/10.
- 3.4mg x20 = 68 mg ('oral morphine equiv')
- 25mcg/hr TD fentanyl
- (vs methadone)
- HM 2-4mg po q3h prn
- May live for many weeks – renally dosed gabapentin
- Talk with wound specialist and compounding pharmacist about topicals
- Add a bowel regimen

Case

- 3 weeks later she decided to stop HD; wounds have worsened; pain has been 'ok' at best. She asks – what is going to happen and how can you make sure I am comfortable?

Dyspnea

- Non-drug
  - Fans, O2 or even air by NC, open doors/windows
  - Non-hypoxic dyspneic patients – compressed air by NC as good as O2 by NC
- Drug
  - Opioids and Benzodiazepines
- Dyspnea←→anxiety/panic
  - Most use opioids as 1st line, benzos as adjuncts
  - Benzodiazepines dosed as for anxiety.
    - SL lorazepam, midazolam elixir available

Dyspnea

- Opioids – approach is exactly like for pain
- No head to head studies but clinical observation is that no opioid (ie morphine) is superior for dyspnea
- Opioid studies for dyspnea reinforce observation that (for opioid naïve patients) small opioid doses are often effective (e.g. 2.5-5mg oral morphine) **and safe.** No ESRD data.
- **Labored breathing** in obtunded/comatose patients need more

Clemens. *J Pain Sympt Man* 2007;33:473-81. Jennings. *Thorax* 2002;57:939-44. Navigante. JPSM 2006;31:38-47.

Secretions ('death rattle')

- Differentiate from pulmonary edema
- Retained oropharyngeal secretions – pool in back of throat due to reduced/failing swallow
- Reposition, **gentle** oral suctioning
- Antimuscarinic agents
  - Scopolamine patches, 1-3 (can cause delirium)
  - Atropine ophth soln 1-2 gtt orally (systemic)
  - Hyoscyamine, 0.125-0.25 PO, ODT, SL elixir q4h
  - Glycopyrrolate: IV in hospital – no CNS effect – 0.2-0.4mg q4h prn

Nausea

- D2 blockers are first line agents – many do not need dose adjustments
  - Prochlorperazine (PO, IV, PR)
  - Haloperidol (PO, SL, IV, SC): 0.5-2mg
  - Olanzapine (PO, ODT): 'dirty' pharmacology including serotonin blockade. 2.5-5mg
  - Metoclopramide – renally dosed. 5mg q12h.
- 5HT3 blockers: Experience and low-quality data supporting use in uremia/ESRD
  - Ondansetron 4-8mg PO, IV, ODT (no renal adjustment)
  - Granisetron transdermal – renally excreted, no data.

Andrews. Nephrol Dial Transpl 1995;10:140. Ljutic D. Kidn Blood Press Res 2002;25:61-4.

Delirium/Encephalopathy

- Prepare families; normalize
- Distraction, redirection, reassurance
- Restlessness, agitation, fear/anxiety – consider drug therapy IF DISTRESSING
- Neuroleptics are cornerstone.
  - Starting doses are same for nausea
  - May need higher doses – 5mg haloperidol q4h; 10mg olanzapine q6h.
  - Chlorpromazine: sedating, low-potency neuroleptic
    - 25-50mg PO/IV/SC q6h prn to start
    - Used when/if no longer trying to avoid sedation
    - No renal dose adjustments.

(Concerns about) Hunger and Thirst

- Intractable hunger, thirst exceedingly rare.
- Diminished PO exceedingly common – distressing to families (rarely patient): **Educate & Reassure**
  - It's normal; Effect of dying process (NOT its cause); 'Force-feeding' usually worsens sx (nausea, edema); Encourage patients to eat as much as they want not more.
  - **Be positive and focus on goals** – 'The best way to help her be comfortable right now is to help her eat what she feels like, but listening to her when she says she is full. This way she won't be hungry and it will reduce the amount of fluid build-up.'
- ?Sodium and water restriction in the final days/weeks? **Individualized decision.**

Myoclonus

- If on Morphine, Hydromorphone, Oxycodone consider fentanyl, methadone especially if severe (multiple 'jerks' a minute)
- Benzodiazepines – titrate to effect
  - Lorazepam 0.5-2mg PO/SL/IV/PR/PN
  - Diazepam 5-10mg PO, PR
- Refractory myoclonus – multifocal/constant –
  - Rapid benzodiazepine escalation
  - Pentobarbitol, phenobarbitol

Pruritus

- Observation: not a particular problem at EOL for previously well-dialyzed patients who did not chronically have pruritus…?
- Extensive amount of 'modest' quality research – virtually none specific to EOL
- There are no EOL tricks, just cautions due to lack of RRT
- Continue what they are already on
- Avoid naltrexone if on systemic opioid analgesics

Pruritus

- Gabapentin – well established
  - Continue for those already on.
  - New pruritus – would give 100mg once and re-eval in 48h.
- Acupuncture:
  - Moderate evidence; One blinded, sham-controlled trial of acupuncture (quchi LI11) near elbow vs sham point 2cm away. TIW x1mo.
- Pramoxine lotion, camphor-menthol lotion, capsaicin, ondansetron, thalidomide

Kim KH. J Pain Sympt Manag 2010. PMID 20684872. Vila R Ann Pharmacother 2008;42:1080-4

Pruritus

- Methylnaltrexone – **no data yet in ESRD – 50% dose reduction CrCl<30….**
  - Peripherally acting opioid antagonist (No reversal of analgesia or withdrawal)
  - Approved for opioid induced constipation
  - Some early suggestion it is effective for opioid pruritus (although this has thought to be a central effect in the past)
  - Endogenous opioid, kappa receptor may be involved in uremic pruritus
  - **Stay tuned.**

Moss J. Mayo Clinic Proc 2008;83:1116-30. Friedman JD. Ann Pharmacother 1001;35:85-91. Yuan CS. Drug Alcoh Depend 1008;52:161-5.

Intractable suffering

- Patients at EOL with severe symptoms refractory to standard tx (dyspnea, agitation, pain)
- Deliberate sedation to alleviate these symptoms can be indicated
  - Proportionate sedation – just enough to get some rest, some relief – routine benzodiazepine doses, chlorpromazine
  - Continuous & deep sedation ('Terminal' or 'Palliative' sedation) – deliberate pharmacologic coma induction - should be done by experts. True CDS is RARE.
    - This is different from accepting sedation as an inevitable side effect of escalating doses of opioids for pain, dyspnea at EOL
    - Opioids are terrible sedatives anyway

Psychoexistential Suffering

- Loss of meaning, grief, anger, overwhelming sadness, lack of acceptance of death, concerns for family well-being, loss of opportunity to mend familial problems, God/religious beliefs, abandonment
- As physicians, we have little control over any of this
  - Even 'clinical' depression, when it develops at life's end – no time to address

Psychoexistential suffering – the role of the medical professional

- 1. Not make it worse
  - Abandonment
  - Poor communication – confusing language, avoiding talking about death & time (for interested patients),
- 2. Do what we can – show up & try
  - Symptoms
  - Good communication – plain-spoken, timely communication about prognosis, options, realistic outcomes, and your recommendation. We tell our patients all the time what to do – it shouldn't be any different at EOL.

Psychoexistential suffering – the role of the medical professional

- 3. Hear our patients' & families' suffering and help them find resources which can ameliorate the sources of their suffering –
  - Social work,
  - Chaplaincy,
  - Mental health professionals,
  - Bereavement workers,
  - Child Life Specialists,
  - etc.

Key References

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