Pain Management: Beyond the Basics

Ed Martin
Common Errors in Pain Management

• Crushing sustained release
• Rapidly titrating patch
• Combining patch and sustained release
• Parenteral/oral calculation
• Long term short acting rx.
• Routine use of opiates for CMO
• Bowel meds
• Use of naloxone
Sustained Release Tabs

• Cannot be crushed
• If unable to swallow must initiate alternative rx.
• Opiate rx can be started with low dose sustained release
Transderm Fentanyl

• Caution in opiate naïve patient
• Cannot rapidly titrate
• Ideal for stable pain in patient unable to swallow
Contraindications

In patients who are not opioid-tolerant

- In the management of acute pain or in patients who require opioid analgesia for a short period of time
- In the management of post-operative pain, including use after out-patient or day surgeries (e.g., tonsillectomies)
- In the management of mild pain
- In the management of intermittent pain (e.g., use on an as needed basis [prn])
Combining Long Acting

- Fentanyl patch plus sustained release morphine or oxycodone
- Makes no sense
- No added benefit
- Side effects are similar
Opiates oral/IV

- Morphine, reduce dose to 1/3 of oral dose when switching to IV
Pumps

• High doses
• Difficulty with oral rx
• Take 24 hr oral dose
• Divide by 3
• Divide by 24 to get hourly rate
• Bolus=hourly dose
• Titrate by 20-30%, not>100% in 24 hrs.
Long Acting Rx

- Attempt to switch to long acting rx
- Evidence supports starting with sustained release products
- Need breakthrough medication
CMO

• Should not equate with routinely starting morphine drip
• Morphine should be started for clear indications
• Dose should be increased in response to symptoms
• Double Effect
Bowel Meds

• Scheduled opiates require scheduled bowel meds
Naloxone

- Caution in opioid dependent patient
- Especially in advanced cancer
- Is sedation due to medication or is the patient dying
- Consider low dose ie 0.1 mg if using in an opioid dependent patient
Opioid Overdose

• 50% in pts never prescribed opioids
• 20% in pts with RX from 5 or more MDs (EMR)

( Hall AJ et al, JAMA.2008;300:2613-20)

Increased risk with increased prescribed dose

Increase risk with dx of depression, substance abuse, use of benzos

(Dunn KM et al, Ann Int Med.2010;152:85-92)
Opioids in Chronic Non-Malignant Pain

• Agreement/contract in place
• Should be based on seeing improved fxn,QOL
• Without improvements, risks>benefits
Opiates and Sedatives: Effects on Survival in Terminally Ill
Double effect

- Assumes opiates and sedatives may hasten death
- Corollary: withholding these meds may prolong survival
High Dose Morphine Use in the Hospice Setting

• Bercovitch M. et al., Cancer 1999;86;871-7
Methods

- Hospice admissions over 2 years
- Cancer patients
- Retrospective chart review
- Scheduled morphine dosing
- Low dose < 300 OME
- Mod high dose 300-599
- Highest dose > 599
Results

• No difference in survival between groups
• Lower doses seen in older patients
• Highest doses with GU cancers, Breast CA
• Higher doses with spinal mets
• Lower doses with lung mets
• Side effects mild, constipation
Limitations

• Retrospective
• Not a control group
• Cancer patients only
Opioid Use in Last Week of Life and Implications for End-of-Life Decision-Making

• Thorns A, Sykes N. Lancet 2000;356:398-9
Methods

• Retrospective chart review
• Inpatient palliative care unit
• 24 hr opioid doses calculated for each day on final week of life
• Increase calculated <1.5, 1.5-2, >2
Results

• No difference in survival from admission, frequency of unexpected death, or description of death between marked increase or no increase patients

• Marked increase group more likely to receive opioids for pain and to receive sedatives
Effects of High Dose Opioids and Sedatives on Survival in Terminally Ill Cancer Patients

Methods

• Retrospective data analysis/chart review
• Use of opioids/sedatives in final 48 hrs
• All sedative medications included
• 209 patients analyzed
• Inpatient setting
• Regression analysis
• OME >600, 240-599,<240 in final 48
• PME >60, 1-59,0 in final 48
Results

- 82% received opioids in final 48 hrs
- 60% received sedative medication (haloperidol, midazolam, hydroxyzine)
Results

- Palliative Performance Scale, oral intake, edema, dyspnea at rest, delirium were independent prognostic factors
- No difference in survival between opioid groups
- No difference in survival in sedative groups
Limitations

• Retrospective
• Not a control group
• Cancer patients only
Sedative Use in the Last Week of Life and the Implications for End-of-Life Decision Making

- Sykes N, Thorns A, Arch Intern Med 2003;163:341-344
Methods

• Retrospective Chart Review
• 237 consecutive patients
• Died in an inpatient hospice
• Midazolam, haloperidol, methotrimiprazine
Methods: 4 Groups

- Little or no sedation
- Significant sedation for 7 days
- Significant sedation only in final 48 hrs
- Significant increase in dose in final 48 hrs
Results

• No survival difference between no significant sedation group and sedation in last 48 hr group
• 7 day sedation group had longer survival
Limitations

• Retrospective
• Not a control group
• Cancer only?
Patterns of High-Dose Morphine Use in a Home-Care Hospice Service

• Bercovitch M, Adunsky A. Cancer 2004;101:1473-7
Methods

• Retrospective chart review
• 661 hospice patients with cancer
Results

• Higher morphine doses associated with longer survival
Limitations

- Unclear timing of morphine dose
- Cancer only
- Retrospective
- No control group
Effects of Opioids and Sedatives on Survival in an Australian Inpatient Palliative Care Population

Methods

• Retrospective chart review
• Inpatient hospice deaths
• Looked at sedatives and opiates
• Cancer was the most common dx.
• Looked at meds given in final 24 hrs
Results

• OME>300 mg/day had longer survival from admission
• Sedative use did not influence survival
Limitations

• Retrospective
• Diagnoses unclear
• No control group
Opioid Use and Survival at the End of Life: A Survey of a Hospice Population

Methods

• Retrospective cohort
• National Hospice Outcomes Project
• Looked at patients on opioids who underwent a dose change
• Interval between last dose change and death was key variable of interest
• Total daily dose included prns
Methods

• 1306 patients in sample
• 1163 received opioids
• 725 had a dose change
• 640 patients had dose < 200 IVME per day
• 85 patients > 200 IVME
• 19 patients > 600 IVME
Results

- Higher dose opioid group were younger (67.1 vs 77.9) and had longer lengths of stay on hospice (46.6 days vs 28.1 days)
- 42% of patients had cancer, higher percentage in high dose group
- Higher PPS score in the high dose opioid group
Results

• Multivariate analysis:
• Absolute dose change and percent dose change not associated with survival
• Higher final dose, cancer diagnosis, unresponsiveness associated with shorter survival
• Pain score < 5 associated with longer survival
• Explained only 6% of survival variance
Summary

• Need to invoke doctrine of double effect
• Efforts to prolong survival by holding meds
Methadone

Back to the Future
History

- Germany 1938
- 1950’s re for opioid withdrawal
- 1960’s opioid addiction
- 1990’s neuropathic pain
Pharmacology

• No active metabolites
• Oral bioavailability 80% but unpredictable
• T1/2 27 hrs.
• Biphasic elimination alpha 6-8 hrs, beta 30-60 hrs.
• Beta phase prevents withdrawal but not analgesic
• Dose q 24 hrs for withdrawal q 6-8 hrs for pain
• Hepatic metabolism type 1 cytochrome P450
• Excreted via fecal route
• Urinary excretion increases with acidification
• Present in breast milk
Drug-Drug Interactions

• SSRI’s increase levels
• Phenobarb, phenytoin, carbamazepine decrease
Methadone Advantages

- Renal Failure
- Cost
- Neuropathic Pain
Neuropathic Pain

• Low-dose methadone has an analgesic effect in neuropathic pain: a double-blind randomized controlled crossover trial
• Poor responders?
• Efficacy with methadone vs placebo
• ?NMDA activity
Methadone Side-effects

• QT prolongation (? Risk of Torsades)
• Constipation(? Less)
• Nausea
• Sedation/CNS (?less)
Methadone Conversion

- Varies with opiate dose
- More potent with higher opiate dose
Methadone Conversion

- Edmonton Palliative Care Unit
- Replace 1/3 of morphine dose each day for 3 days
- Use 10/1 MS to methadone ratio
Methadone Conversion

• UK Hospice Model
• Stop opiate
• Methadone q3h prn
• Use 10/1 MS to methadone ratio
• Dose not to exceed 30 mg of methadone
• At 6 days review total daily dose and convert to bid/tid dosing
Methadone Versus Morphine As a First-Line Strong Opioid for Cancer Pain: A Randomized Double-Blind Study

Eligibility

• Uncontrolled pain due to advanced CA
• > 4 week life expectancy
• Normal renal and cognitive function
• Not receiving strong opioids
• No chemo or RT to improve pain
Treatment

- Methadone 7.5 mg q 12 hrs and 5 mg q 4h prn pain
- Morphine SR 15 mg q 12 hrs and ms 5 mg q 4 hrs prn pain
- Dose increase if > 2 prns daily
- Dose decrease if c/o sedation
- 4 weeks
Dosing

- Methadone mean: 20 mg qd
- Morphine mean 40 mg qd
- Breakthrough = 0 at day 29
Efficacy

- No difference in pain relief
- No difference in neuropathic pain patients
Side-effects

- Delayed sedation with methadone
- Higher drop-out rate with methadone
Conclusion

• “Methadone did not produce superior analgesic efficiency or tolerability at 4 weeks compare with morphine”
Sustained Release Oral Morphine Versus Transdermal Fentanyl and Oral Methadone in Cancer Pain Management

• Mercadante S et al
• European Journal of Pain in press
Methods

• 2003-2006
• 108 advanced cancer patients
• Had received rx including codeine, tramadol now needing strong opioids
• Excluded liver, renal disease, cognitive impairment, expected survival < 3 months, needing RT or new chemo
Methods

- 36 patients MSSR 60 mg per day
- 36 patients Fentanyl Transdermal 25 mcg/hr
- 36 patients Methadone 5 mg tid
- Given prn morphine and meds titrated based on prn use
Results

• 108 patients recruited
• 38 patients withdrew, lost to follow-up
• 22 morphine, 25 fentanyl, 23 methadone completed 4 week study
• Within groups similar losses to opioid change and loss to follow up
• Opioid increase smallest in methadone group but some required a decrease so most changes in this group
Results

- No difference in quality of life scores and side effects
- Methadone, least costly,
- Fentanyl most costly
Conclusion

• All three are effective for first line therapy with similar side effects
• Methadone, less costly, required more up/down adjustment and may require more expertise to use
Problem

• Patient can no longer swallow sustained release opiate
• How about a patch
• But the patient has advanced cancer and is very thin
• Will the fentanyl be absorbed?
Addition of Methadone to Another Opioid in the Management of Moderate to Severe Cancer Pain: A Case Series

• 20 patients (16 neuropathic)
• Mean morphine dose 338 mg /day
• Mean methadone dose 15.5 at evaluation
• Methadone well tolerated in 17/20
• 40% had improved pain (≥2) initially, 35% at an additional time
Too thin for a patch?
Transdermal Fentanyl in Cachectic Cancer Patients

• T Heiskanen et al. Pain. 2009: 144; 218-222
Methods

• Prospective
• Cancer patients with pain requiring opiates
• 10 normal weight, 10 cachectic patients
• Excluded: cognitive impairment, fever, pregnancy/lactation, renal, cardiac, hepatic failure, skin diseases, CYP3A4 drug use (erythromycin, diltiazem, fluoxetine, fluvoxamine, verapamil)
Methods

- Transdermal fentanyl dose based on opiates taken
- Blood levels of fentanyl tested
Results

- Transdermal fentanyl dose was higher in the cachectic patients (pt had longer duration of illness)
- Adjusted for dose the plasma fentanyl concentration were significantly lower at 48 and 72 hours
- No difference at 4 and 24 hours
Results

• No difference in local skin blood flow, skin temperature or local sweating
• Cachectic patients had thinner upper arm skin fold
• Pain scores similar in both groups
• Amount of subcutaneous tissue has not been shown to influence absorption
• Blood flow and skin permeability have been shown to influence absorption
• Skin permeability may be influenced by other factors in cachectic patients
• “not the opioid of choice for cachectic cancer patients with pain”
Topical Analgesics
NSAIDs

- Evidence for diclofenac, ibuprofen, ketoprofen
- Ibuprofen topical similar in efficacy to oral
Lidocaine

• Good evidence for post herpetic neuralgia and diabetic neuropathy
• Often used for back pain, joint pain
• Limited evidence (no controlled trials) and unclear mechanism of action
Capsaicin

• Evidence with post herpetic neuralgia and diabetic neuropathy
• Burning discomfort noted in most
Opiates

- Morphine not absorbed through intact skin
- No better than placebo when applied to painful ulcers (J Wound care 2005;4:279-283)
Neuropathic Pain
Nociceptive Pain

• Normal activation of the nociceptive system by noxious stimuli
Neuropathic Pain

• Pain due to damage to or dysfunction of the nervous system
Neuropathic Pain

- Negative and positive sensory systems
- Spontaneous pain
- Stimulus provoked pain
Allodynia

• Pain in response to nonpainful stimuli
Hyperalgesia

• Increased sensation of pain in response to painful stimuli
Nerve Injury

- Inflammation
- Hyperexciteability of primary afferent neurons (sunburn)
• Increased primary afferent nociceptor firing
• Decreased inhibition centrally, loss of inhibitory neurons
• Central sensitization (normal sensory input amplified and sustained)
• Wide dynamic range neurons in spinal cord: input from nociceptive and non-nociceptive neurons
• After sensitization mild tactile stimuli can activate spinal cord signaling
• Inhibitory neurons release serotonin and norepinephrine
Tricyclic Antidepressants

- First meds to show effect vs. placebo
- Don’t use amitriptyline
- Anticholinergic side effects
Nortriptyline

• Start 10-25 mg at hs
• Titrate to 100+ mg at hs
• Sedation, dry mouth etc.
Gabapentin

- FDA approval PHN
- Start as low as 100 mg at hs
- 100-300 mg tid
- Increase by 100-300 mg every 1-7 days
- Can load hs dose to decrease sedation
- 1800 mg/day assoc with efficacy
Gabapentin

- Need to get to therapeutic dose and maintain for > 1 week (may take 2 months)
- Side effects: somnolence, dizziness, less common GI sx., edema
5% Lidocaine Patch

- FDA: PHN
- Minimal blood levels on intact skin
- Side effects: skin rash
- Dose: up to 3 patches on for 12 hours applied to area of maximal pain
- Trial 2 weeks
- Mexilitine, IV lidocaine
Opiates

• Good evidence for efficacy
• Long acting preferred
Opiate Side Effects

- Cognitive Impairment
- Hallucinations
- Constipation
- Nausea
- Pruritis
- Myoclonus
- Sedation
- Respiratory Depression
Tramadol

• Norepi/serotonin reuptake inhibitor
• Major metabolite is a mu opioid agonist
• Start at 50mg once or bid
• Maximum dose 100 mg 4 times daily
• Side effects: dizziness, nausea, constipation, orthostatic hypotension
Tramadol

- Lowers seizure threshold
- Caution with SSRI!
Duloxetine

- FDA:PDN
- Side effects: sedation, confusion, hypertension
- 60 mg daily
Effect of Duloxetine on Pain, Function, and Quality of Life Among Patients With Chemotherapy-Induced Painful Peripheral Neuropathy

• Smith et al. JAMA 2013;309:1359-67
• Chemotherapy induced peripheral neuropathy
• 30 mg daily for 1 week then 60 mg daily for 4 weeks vs placebo
• Decreased pain, less pain interference with fxn, higher quality of life
• Side effects slightly higher in placebo group
Pregabalin

- Side effects similar to gabapentin
- FDA: PHN. PDN
- 50 mg tid to 100 mg tid
Neuropathic Pain and Methadone

- Low-dose methadone has an analgesic effect in neuropathic pain: a double-blind randomized controlled crossover trial
- Poor responders?
- Efficacy with methadone vs placebo
- ?NMDA activity
Opiate Neurotoxicity

- Sedation
- Myoclonus
- Delirium/agitation
- Hyperalgesia
- Allodynia
- Seizures
Opiate Neurotoxicity

Due to metabolites?
But also seen with fentanyl and methadone
Other etiologies in terminally ill
Opiate Induced Hyperalgesia

- May be seen with myoclonus, delirium
- Change in pain pattern
Hydromorphone
Neuroexcitation

• Thwaites D, McCann S, Broderick P. Journal of Palliative Medicine 2004;7:545-50
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<th>No symptoms</th>
<th>Neuroexcitatory symptoms present</th>
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<td>Mean duration (SD)</td>
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Dose < 20 mg/hr

- Seizures 0
- Agitation 18% (11% if < 15 days)
- Myoclonus 3% (0 if, 15 days)
Dose > 20 mg/hr, > 15 Days

- Agitation 50%
- Myoclonus 60%
Opioid Induced Pain

- Pain now exceeds preexisting pain without disease progression
- Pain now diffuse
- Not tolerance
- Dose increase results in no reduction of pain
- ? Less likely with methadone
Opioid Induced Pain

- Dose increase should improve analgesia at least short term
- If not: consider dose reduction and adjuvants
- If not: consider methadone
Ketamine

• Anesthetic
• Produces analgesia
• No effect on pharyngeal-laryngeal reflexes
• Minimal respiratory depression
Ketamine

- Dissociative anesthesia
- Interrupts association pathways
- Somatesthetic sensory block
- NMDA, mu, delta, kappa receptors
Ketamine

- “Emergence reaction”
- Dream-like state
- Vivid imagery
- Hallucinations
- Delirium
- Benzos used to control this
Parenteral Ketamine as an Analgesic Adjuvant for Severe Pain: Development and Retrospective Audit of a Protocol for a Palliative Care Unit

Edward J. Fitzgibbon, Raymond Viola
Ketamine Protocol

- Palliative Care Unit
- Terminally Ill Patients
- Uncontrolled Pain
- Contraindications: Uncontrolled Seizures, symptomatic increased intracranial pressure
Ketamine Protocol

• Primarily given sc
• Starting Dose 50-100 mg/24 hrs
• Increase by 50-100 mg/24hrs no sooner than 24 hrs after last increase
• Consider d/c if no effect with 700 mg/24 hrs
• Consider decrease in opiate by 25-50%
• Consider prophylaxis with haldol 1mg bid
• Consider prophylaxis with lorazepam 0.5mg bid
Ketamine Audit

• 16 patients in a 1 year period.
• All but 1 CA
• M/F 9/7
• 14 with some neuropathic component
Effectiveness criteria

- Pain decreased by 4/10
- Decreased prn use by 50%
- Documentation of improved comfort
Effectiveness

- All 3 criteria 11/16
- Reduced pain 15/16
- Decreased prn 12/16
Side Effects

- Drowsiness: 7/16 (resolved in <5 days)
- Hallucinations: 3/16
- Agitation: 1/16
- Discontinued: 1 drowsiness, 1 hallucinations
Safety and Efficacy of Prolonged Outpatient Ketamine Infusions for Neuropathic Pain

- Walker LR, Walker MJ. AM J Ther.
- 2006; 13 (4):300-305
• Retrospective chart audit
• 13 non-cancer patients with neuropathic pain
• Mean Dose .12 mg/kg/hr ( 8 mg/hr for 70 kg adult)
• Duration 5-55 days
• Supervision required first 24 hrs
• Irritation in sc patients
• 11/13 patients had improved pain
• Morphine dose decreased
• Side effects: fatigue, dizziness, confusion, spinal pain
72 yo female, Metastatic Renal Cancer

- Pain in hips, back, pelvis
- Uncontrolled on duragesic, oxycontin
- MS 4mg/hr sc to 40 mg/hr: bolus not helpful, myoclonus, paranoia
- Decadron 8mg tid, haldol 2mg tid
- Ketamine 4mg/hr to 16 mg/hr complete relief
- MS decreased to 16 mg/hr, less myoclonus
Military use of Ketamine

- Battlefield anesthetic (wound debridement/exploration, fracture/dislocation reduction)
- IM 5mg/kg onset 5-10 minutes, duration 20-30 minutes
- IV 2 mg/kg over 60 seconds, onset 60 seconds, duration 5-10 minutes
Ketamine

- There is evidence for use but controlled trials would be helpful
Effective Pain Control

- May require more than one class of drugs
- Ketamine may provide relief for patients with opiate refractory pain
- May provide additional analgesia to patients in crisis ie. pathologic fracture, sudden escalation of pain