Anorexia/Cachexia, Fatigue, Depression and Advanced Pain Management for the Medical and Hematological Oncologist

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Advanced Pain Management

Case – Jim

- 45-year-old man with metastatic renal cell carcinoma to the pelvis
- Describes severe, deep, stabbing pain in the right buttock that radiates down the right leg
- 9/10 at rest, 10/10 with movement, lies very still in consistent position
- Not a candidate for further radiation
- Referred to our outpatient Palliative Care Clinic

Jim

- On fentanyl patch 125 mcg/hr with Percocet for breakthrough (using 10-15/day – no relief)
- Rotated to hydromorphone based regimen and titrated over next week up to:
  - Hydromorph contin 84mg po q12h
  - Hydromorphone 16mg po q1h prn
- Able to move around in bed somewhat easier
- Continues to rank pain at rest 7/10
- Stabbing/radiating pain not improved

“Opioid Resistant” Pain

- Bony Pain
- Neuropathic Pain
- Incident Pain
- Visceral Pain

Bony Pain

Effective management may require adjuvant medications:

- acetaminophen
- NSAIDs
- bisphosphonates

Bony Pain – Bisphosphonates

- Evidence suggests may reduce metastatic bone pain with certain primary sites
- Optimum dose and duration of treatment are unknown
- Loading doses may reduce refractory bone pain within days

Neuropathic Pain

- A Neuropathic component of cancer-related pain is frequently underdiagnosed and/or inadequately treated
- Patients may have great difficulty finding words to describe the sensation
- May use terms such as “aching,” “burning,” “stabbing,” or “pressure-like”
- Description may include a component of “shooting” or “radiating”
- Location of pain can be anywhere in the dermatomal region innervated by the damaged neural structure

Neuropathic Pain – Pathophysiology

Three primary mechanisms have been proposed re: mediation nerve damage/injury expression and the corresponding receptor(s) serve as medication targets:

1. Peripherally, regeneration after nerve damage can result in the development of neuroma and uncontrolled neuronal firing

    Thought to be mediated mainly through increased expression of both sodium and voltage-gated calcium channels

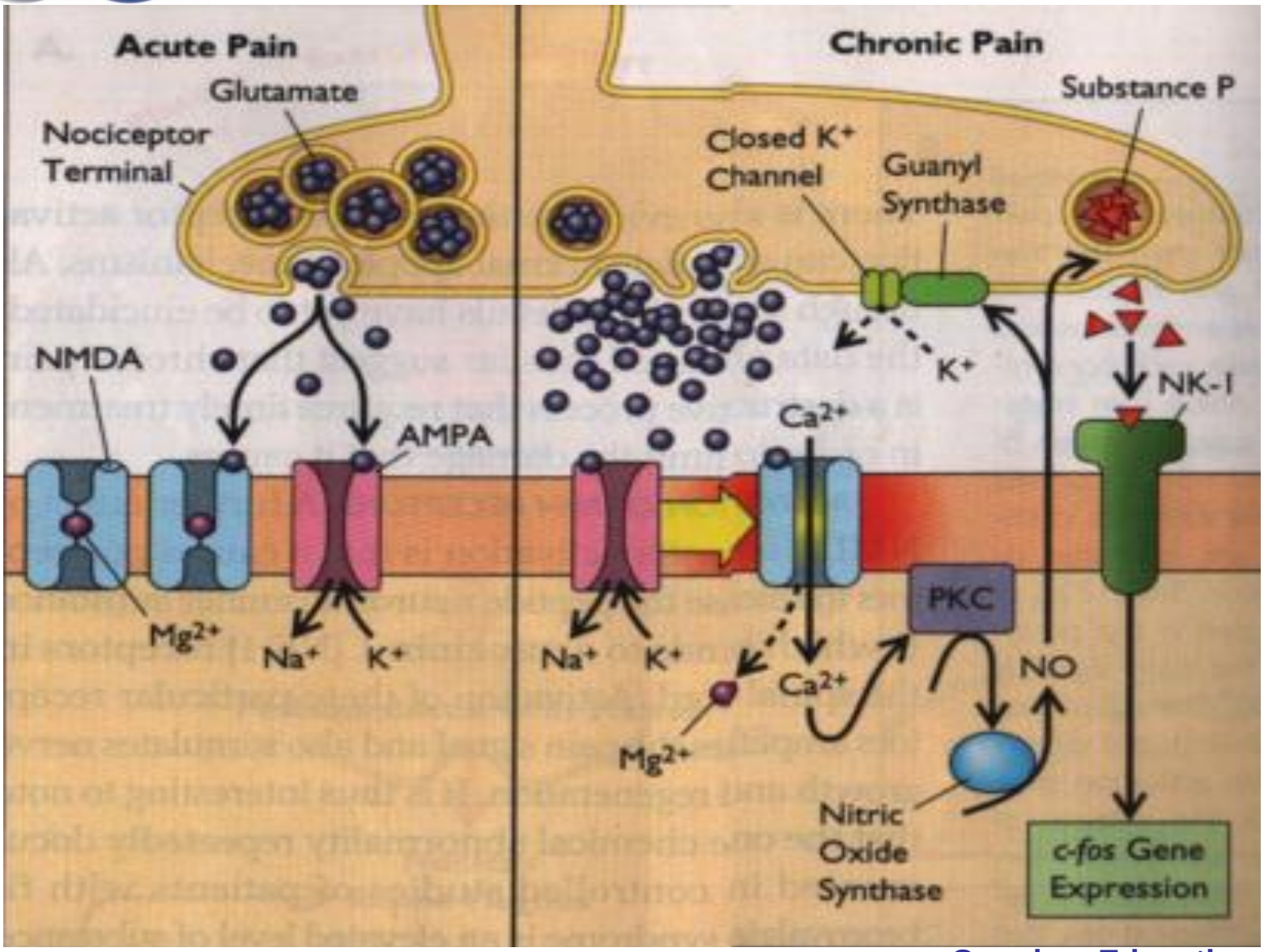
Neuropathic Pain – Pathophysiology

2. Pre-synaptic serotonin and norepinephrine receptors are known to mediate descending inhibition of ascending pain pathways in the brain and spinal cord
3. Central Sensitization (heightened sensitivity of spinal neurons) is mediated by the *N*-methyl-D-aspartic acid (NMDA) receptor

Neuropathic Pain – Pathophysiology

Activation of NMDA Receptor

- Complex activation of multiple neurotransmitters
- Requires maintained C- Fibre stimulus
- Wind up = amplification and prolongation of pain response
- Result is tolerance to opioids
- Clinically may result in hyperalgesia and allodynia


Acute Pain
Glutamate
Nociceptor Terminal
NMDA
AMPA
Mg2+
Na+
K+
Chronic Pain
Substance P
Closed K+ Channel
Guanyl Synthase
K+
NK-1
Ca2+
PKC
Na+
K+
Ca2+
Mg2+
NO
Nitric Oxide Synthase
c-fos Gene Expression

Neuropathic Pain – Management

- Although often used as first-line therapy, opioids may have limited efficacy in the management of neuropathic pain (exception is methadone)
- Improved neuropathic pain management may be achieved by introducing medications that target one or more of the unique chemical pathways that mediate the expression of nerve pain

A note about methadone…

- Improved understanding of the complex pharmacodynamic and pharmacokinetic properties
- Rapidly becoming an essential tool in the management of complex cancer pain
- Methadone exists as a racemic compound
- The non mu-agonist isomer is a NMDA receptor antagnoist and inhibits the pre-synaptic reuptake of both norepinephrine and serotonin

A note about methadone…

- Complex drug interactions, high inter-individual variability in $T_{1/2}$ and unclear opioid conversion ratios = need for special license
- Different than license required for use in management of addiction
- Study comparing methadone and morphine as first-line opioid found equal efficacy for cancer pain in opioid-naïve patients

A note about methadone…

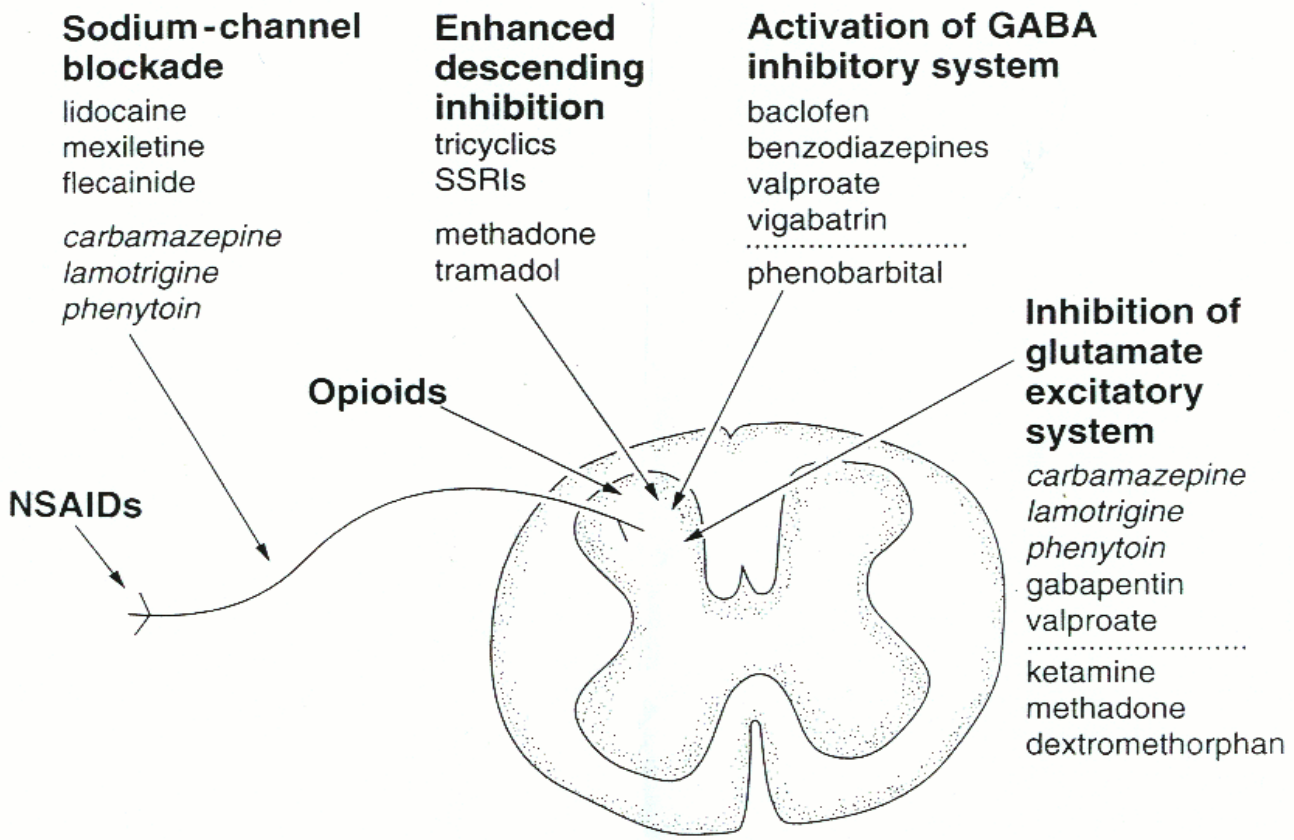
MS Contin™	1000mg/d	$820
Kadian™	1000mg/d	$960
OxyContin™	800mg/d	$1066
Duragesic™	250mcg/h	$1499
Methadone tabs	100mg/d	$22

Neuropathic Pain – Management
Adjuvant Medications

- Anticonvulsants:
  - Gabapentin
  - Pregabalin
  - Phenytoin
  - Carbamezapine
- Antidepressants
  - TCAs (Nortriptyline, Amitriptyline)
  - SSRIs
- Cannabinoids
- Ketamine

Neuropathic Pain – Management
Dorsal Horn

- Primary site of action of analgesics and adjuvant analgesics on peripheral nerves and the dorsal horn
- Drugs in italics act both peripherally and centrally
- Drugs below the dotted lines are channel blockers at their respective receptor-channel complex


Sodium-channel blockade
lidocaine
mexiletine
flecainide
carbamazepine
lamotrigine
phenytoin
Enhanced descending inhibition
tricyclics
SSRIs
methadone
tramadol
Activation of GABA inhibitory system
baclofen
benzodiazepines
valproate
vigabatrin
phenobarbital
Inhibition of glutamate excitatory system
carbamazepine
lamotrigine
phenytoin
gabapentin
valproate
ketamine
methadone
dextromethorphan
Opioids
NSAIDs

Neuropathic Pain – Management
Anticonvulsants

Gabapentin:

- Requires 3-times-daily dosing
- Excreted unchanged by the kidneys requiring dosing adjustment in the setting of renal insufficiency
- No enzymatic metabolism occurs in the liver
- No significant drug interactions
- Clear evidence for efficacy over TCAs in management of diabetic neuropathy
- No randomized trials examining efficacy in the setting of cancer pain

Neuropathic Pain – Management
Gabapentin Titration

- Day 1 - Initiate 300 mg at HS for 3 days
- Day 4 - Increase to 300 mg BID for 3 days
- Day 7 - Increase to 300 mg TID
- Continue to titrate based on response to a maximum of 3600 mg daily*

***if creatinine clearance normal – dose reduce if not**

Jim

- At time of initial referral gabapentin was initiated
- Titrated to 1200mg TID over four weeks
- Stabbing/radiating pain improved minimally
- Disease progressing on systemic therapy

Neuropathic Pain – Management
Anticonvulsants

Pregabalin:

- Lipophilic analogue of gabapentin
- Designed to improve diffusion across BBB
- Six times more potent than gabapentin
- Initiate 75mg QHS or BID
- Titrate to 150mg BID over 1 week
- Maximum 600 mg/day

Neuropathic Pain – Management
Anticonvulsants

Pregabalin:

- Onset of action as early as 1 week
- Rapid dose titration
- BID dosing
- No efficacy data in cancer population
- No head to head data with gabapentin

Neuropathic Pain – Management
Anticonvulsants

General Considerations:

- If discontinuing gabapentin or pregabalin, taper over 1-3 weeks to prevent withdrawal syndrome:
  - symptoms include nausea, headache, diarrhea
- Reimbursement issues: many drug benefit plans will not cover gabapentin or pregabalin for neuropathic pain unless documentation of poor response to less-expensive medications is provided

Neuropathic Pain – Management
Anticonvulsants

- Other agents including carbamazepine, phenytoin, valproate, and clonazepam are occasionally used in the setting of cancer pain
- Efficacy evidence is limited
- Potential side effects and drug interactions often limit the clinical utility of these agents
- Should be considered for complex neuropathic pain syndromes

Neuropathic Pain – Management
Antidepressants

TCAs:

- No single TCA has greater efficacy than any other for neuropathic pain
- Side effects tend to be the limiting factor
- Nortriptyline tends to have the least anticholinergic properties
- Initiating dose should be 10–25 mg once daily, taken at night

Neuropathic Pain – Management
Antidepressants

- Selective serotonin and serotonin–norepinephrine reuptake inhibitor, have been studied in the setting of diabetic neuropathy and trigeminal neuralgia
- Moderate efficacy evidence supports using these medications for neuropathic pain
- Should be considered for complex neuropathic pain syndromes

Neuropathic Pain – Management
Cannabinoids

Sativex:

- Cannabinoid CB1 receptor acts on pathways that partly overlap with those affected by opioids
- Buccal cannabinoid spray approved for use in cancer pain
- Dose for an adult is not more than 1 spray every 4 hours (average 8/day)

Neuropathic Pain – Management
Ketamine

- Effect as a NMDA receptor antagonist is thought to be mechanism responsible for role in management of neuropathic pain
- Trials have used intrathecal, epidural, intravenous, subcutaneous and oral routes of administration
- Most trials have low numbers of patients but for these patients benefit has been significant

Neuropathic Pain – Management
Ketamine

- Adverse effects include tachycardia, hypertension, raised intracranial pressure, and nausea
- Psychotomimetic effects such as hallucinations, confusion, and sedation are most concerning
- Continuous ketamine infusion has been shown to be a successful option for refractory pain
- Initial hospitalization and specific monitoring may be required
- Oral ketamine may have a role in cancer pain management, has not been well studied

Jim

- Opioid rotated from hydromorphone to methadone
- Titrated methadone up to 45mg PO TID
- Improved pain to 4/10 at rest but incident pain remained 10/10
- Addition of oral ketamine 30mg TID was not beneficial (no side effects)

Interventional Cancer Pain Management Techniques

- Nerve blocks
- Vertebroplasty/cementoplasty
- Intraspinal analgesia
  - Epidural
  - Intrathecal

Jim

- Referred to interventional pain team (anesthesia and/or radiology)
- Two psoas blocks completed one month apart
- No improvement in pain

Jim

- Decision to proceed with intraspinal analgesia
- Two day admission for insertion
- Intrathecal catheter tunneled and connected to pump providing continuous infusion of opioid and anesthetic
- Home care agency – competencies achieved
- Jim cared for and died at home 6 weeks later

Neuropathic Pain
Treatment – Related Syndromes

- Chronic pain syndromes related to treatment (systemic therapy, radiation, surgery) are mostly neuropathic in classification
- Predisposing factors for chronic neuropathic pain following nerve injury are unknown
- Syndrome can appear months or years after treatment

Chemotherapy Induced Peripheral Neuropathy (CIPN)

- Taxanes – 50-70% pts experience mild to moderate numbness, tingling, burning/stabbing in hands and feet
- Vinca Alkaloids – 25%; high doses associated with absent Achilles reflex, weak distal muscles, foot drop
- Platinum (Oxaliplatin) – Sx can occur after prolonged therapy and may develop 3-8 weeks after last dose

CIPN – Management

- ***Cancer, 2007:*** One placebo controlled RCT – gabapentin (max dose 2700mg) for six weeks – no benefit
- ***JCO, 2004:*** Case series, gabapentin used as secondary prophylaxis with 90% reduction in taxane-induced arthralgias/myalgias (300mg TID; 2 days prior to start to 5 days following completion of chemo)

Anorexia/Cachexia, Fatigue and Depression

Janice

- Referred to Palliative Care Clinic for management of bony pain related to metastatic breast CA
- 3rd visit, pain well controlled, ESAS screen:
  - depression 8/10
  - anxiety 6/10
  - appetite 9/10
  - fatigue 8/10
  - well-being 8/10

pain, nausea, SOB, drowsy all <4

Janice

- Symptoms did not change with improvement in pain management
- Further social history – single mother of two teenage female children who are not aware of patient's diagnosis
- Unable to work for the past two years
- Sleeps most of the day, cooks minimally
- "Are you depressed?" – "Yes"
- Denied suicidal ideation or DHD

Anorexia/Cachexia

- More common in GI malignancies and advanced disease (25%, 45%)
- Often accompanied by malnourished states and cachexia
- Nutritional interventions, in general, do NOT affect survival
- May benefit pts:
  - whose difficulty eating is due to GI obstruction
  - those who have treatment adverse effects
  - when anorexia affects QoL

Anorexia/Cachexia

- RCTs have found a significant improvement in anorexia and QoL in colorectal CA and H&N patients receiving dietary counseling
- MBO patients with a prognosis of more than six weeks have a higher QoL with home TPN
- TPN as a routine element of a nutritional intervention for weight loss in patients with advanced cancer has not shown improvement in survival or QoL

Anorexia/Cachexia

- Large body of literature supporting effective treatments for poor appetite however experts do not support a specific role for this intervention as a quality standard
- Pharmacologic agents include:
  - megestrol
  - dronabinol
  - fluoxymestrone
  - medroxyprogesterone
  - steroids?

Fatigue

- A subjective sensation characterized by:
  - pervasive and persistent sense of tiredness
  - not relieved by sleep or rest
  - can adversely effect a person's emotional, physical and mental well being
- Incidence is at least 60% for those receiving systemic therapy

Fatigue

- Multifactorial nature in cancer population has led to difficulties clarifying underlying mechanism
- Two most plausible mechanisms include:
  - abnormal or prolonged inflammatory response
  - disruption to the hypothalamic pituitary adrenal axis
- Clinical support for these theories is lacking

Fatigue

- Given number of reversible causes, screening should occur at initial visit and at regular intervals in follow up
- Large body of literature examining impact of exercise on fatigue
- Evidence = not strongly supportive of exercise as an intervention for fatigue
- RCTs with paroxetine and methylphenidate did not show benefit

Depression

- Use of quality standards depends on accuracy of diagnosis
- Difficult to differentiate from adjustment disorder as well as prevalence of disease-related vegetative symptoms
- Limited evidence supporting use of short-term antidepressants – no RCT data

Depression

- Screening should occur AT LEAST:
  - Newly diagnosed patients
  - Patients starting on systemic therapy and/or radiotherapy
  - Patients with newly identified advanced disease
  - Patients expressing DHD (see Lecture 4)
- For patients diagnosed with depression, treatment plans should be documented and appropriately followed

Janice

- Agreed to begin:
  - methylphenidate 5mg 8AM and noon
  - mirtazapine 30mg hs
- Follow up in two weeks – fatigue 4/10
- Follow up in four weeks – depression, anxiety and well-being 4/10
- Titrated off methylphenidate