Symptom Management at the End of Life
(for the on-call practitioner)

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Geriatric Grand Rounds
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Objectives

• Utilize current literature to enhance knowledge of symptom management techniques
• Employ existing knowledge base to provide excellent symptom management to patients
• Support skill set of geriatrics fellow on call
Symptoms and Symptom Management to be discussed

- Pain
- Dyspnea
- Agitation/Delirium
- Anxiety
- Fever
- Nausea/Vomiting
- Hyperglycemia
- Hiccups
- Constipation
- Pruritus
- Secretions/Noisy Breathing
- Active dying process
Pain

• Experienced by 71% of patients with incurable cancer at any time in their disease progression
What is the CONTEXT of pain

• Goals of Care

• Care setting

• Caregiver

• Physiology - renal failure, hepatic failure, dementia, delirium, weight or age based dosing
It is absolutely inappropriate to use morphine for symptom management in patients with renal or hepatic impairment

• A. True
• B. False
The “drug of choice” in renal impairment is

• A. Hydromorphone
• B. Methadone
• C. Fentanyl
• D. B or C
Advanced Organ Dysfunction/End Organ Disease

• Hepatic Failure
  – All opioids metabolized by liver
  – Smaller doses and longer dosing intervals may be appropriate
  – Use sparingly with “scrupulous prns”

• Renal Failure
  – Most opioids excreted renally
  – Standard of care – avoid morphine
  – Drugs of choice – methadone, fentanyl

• Delirium
  – Treat with antipsychotics and pain medication
Special Considerations

• Weight based dosing
  – Usually young end of age spectrum

• Age based dosing
  – Creatinine clearance
  – Frailty
  – Usually old end of age spectrum
5 Principles of Pain Relief

• Given by mouth (not SQ/IM)

• “On the clock”

• Use and document pain scales to assess pain pre/post intervention

• Dosing of pain medication is adapted to the individual
  – There is no “ceiling” for dosing opioids

• Pain medications should be prescribed with attention to detail

World Health Organization
Opioid Conversions

• Best to use an equianalgesic table
• There are many
• Learn ONE and use it for all conversions
• Write conversions down
• Check with another provider if you are not sure
Morphine

• Delivery routes
  – Oral, subcutaneous, intravenous, intramuscular, rectal

• Metabolism
  – Metabolized in liver, renally excreted
  – Metabolites accumulate in renal insufficiency

• Histamine release
  – Causes itching
The “conversion factor” from morphine to hydromorphone is

- A. 1:1
- B. 2:1
- C. 5:1
- D. 10:1
Hydromorphone

• Delivery routes
  – Oral, subcutaneous, intravenous, intramuscular, rectal
• 4-7 times more potent than morphine
• Common practice to use in significant renal failure. Not evidence based.
Oxycodone

• Delivery routes
  – Oral
• 1.5 times more potent than morphine
• More expensive than morphine
• Less histamine release
• Common practice to use in significant renal failure. Not evidence based.
The use of transdermal fentanyl can be complicated by

• A. Cachexia
• B. Hirsutism
• C. Hypothermia
• D. All of the above
Fentanyl

• Delivery routes
  – Transdermal, transmucosal, intravenous
• Chronic stable pain – transdermal
  – or in medical setting as IV
• Short T1/2
• Expensive
• Limitations on transdermal fentanyl
  – Cachexia, hyper- or hypothermia, hairy or oily skin
  – Full potency 12-16 hours after application
Methadone

• Delivery routes
  – Oral, subcutaneous, intravenous, rectal
• Long T ½
  – Cannot be rapidly up-titrated or down-titrated
• Direct opioid receptors and NMDA receptors
• Use for high opioid requirements
• Use in advanced renal disease
• Use for mixed pain
Written Pain Plans

• Instructions for pain management are often multi-step

• Medications for pain may influence ability to follow or remember directions

• Illness and fatigue influence ability to follow or remember directions
When to phone the pharmacist...

- Drug interactions
- Drug selection (“two symptoms, one drug”)
- Methadone conversions
- Other complicated conversions
- Concern over rare adverse effects
  - (serotonin syndrome, anticholinergic toxicity)
Adjuvant Medications

• Antidepressants
  ◦ Duloxetine
  ◦ Tricyclic Antidepressants (TCA)
  ◦ Venlafaxine

• Anticonvulsants
  ◦ Carbamazepine
  ◦ Gabapentin

• Muscle relaxants
  ◦ Baclofen
  ◦ Tizanidine
  ◦ Clonazepam
Adjuvant Medications

• Other
  – Pregabalin
  – Bisphosphonates
  – Calcitonin
  – Capsaicin
  – Lidocaine
  – Cannabinoids
  – Vitamin D
  – Ketamine
Non-Pharmacologic Treatments

• Radiation
• PT/OT
• Acupuncture
• CAM/Integrative Medicine
  – Relaxation
  – Massage
  – Reiki
  – Music
  – Aromatherapy
Dyspnea

• > 30% of patients with cancer experience before end of their lives

• Other disease states also
  – Pulmonary disease
  – Cardiac disease
  – Neurologic disease

Saskia, Symptom Prevalence in Patients with Incurable Cancer, JPM 2007
Oxygen Therapy for Relief of Dyspnea

• Supplemental oxygen can provide relief of dyspnea for patients who are hypoxemic at rest or during minimal activity

Mahler et al. CHEST 2010
Other Non-Pharmacologic Therapies for Relief of Dyspnea

- Pursed lip breathing can be an effective strategy
  - Also consider “tripodding”
- No studies published in peer reviewed journal that have examined use of fan/cool air
- Relaxation can be an effective strategy
  - After each session but not cumulative or long lasting
- Noninvasive positive pressure ventilation can provide relief

Mahler et al. CHEST 2010
Other Non-Pharmacologic Measures

• Look for simple problems
  – Is oxygen turned on? Is tubing kinked?
  – Is there fluid overload from IVF or TPN?
  – Evaluate for acute anxiety episode, severe pain, constipation, urinary retention?
  – New pneumothorax/worsening pleural effusion?

• Understand
  – Where patient is in dying trajectory
  – What are the identified goals of care
It is medically appropriate to use opioids to treat dyspnea

• A. True
• B. False
Non-Opioid Treatments

• Anti-tussives for cough
• Anti-cholinergics for secretions
• Anxiolytics for anxiety
• Diuretics for fluid overload
• Bronchodilators for bronchospasm
• Corticosteroids for reactive airway component
Opioid Medications for Relief of Dyspnea

• Oral and/or parenteral opioids can provide relief of dyspnea
• Opioids should be dosed and titrated for the individual patient with consideration of multiple factors for relief of dyspnea (renal, hepatic, pulmonary function, current and past opioid use)
• Respiratory depression is a widely held concern with the use of opioids for the relief of dyspnea
Agitation/Delirium

• Differential

• Treat reversible conditions
  – Pain
  – Constipation, urinary retention
  – Non-physical causes of distress

• Consider goals of care

• Pharmacologic treatment

• Non pharmacologic treatment

Feldman, PTSD at EOL, JPM 2006
Agitation/Delirium

• Non-pharmacologic options
• In general or with PTSD
  – Education
    • Patient and family “you are not going crazy”
    • Staff
  – Normalize
The “drug of choice” for a patient with delirium at end of life is

• A. Lorazepam
• B. Alprazolam
• C. Haloperidol
• D. Sertraline
Agitation/Delirium

• “Drug of choice” is antipsychotic
  – Most commonly used is haloperidol
  – Benzodiazepines can cause paradoxical agitation
    • Can be used if antipsychotic in place

• Other things to think about
  – Patient with PTSD (up to 84% of all people have experienced trauma)
    • Consider
      – Clonidine
      – Prazosin
      – SSRI
      – TCA

Feldman, PTSD at EOL, JPM 2006
Vrana, Prevalence of traumatic events, J Traumatic Stress 1994
Other Pharmacologic Treatment
Agitation/PTSD

• Lithium
• Anticonvulsants
Anxiety

• Significant anxiety symptoms in 25% of patients with cancer
• Patients with heart failure have elevated rates of anxiety
• Anxiety also found in
  – Depression
  – Other syndromes – OCD, delirium, panic disorder

Block. Psychological Issues in End of Life Care. JPM 2006
Anxiety - Treatment

• How much time do we have?
• Non-pharmacologic
  – Supportive psychotherapeutic interventions
• Pharmacologic
  – SSRI
  – Benzodiazepines
  – IV medications

Block. Psychological Issues in End of Life Care. JPM 2006
It is always appropriate to treat fever in a dying patient

• A. True
• B. False
Fever

• Cause
  – Infection
  – Hypothalamic dysfunction
  – Medication induced
  – Inflammation
    • Aspiration pneumonitis
    • Cancer
    • DVT/PE
Treatment of Fever

• What is a normal temperature?
• Is the patient uncomfortable?
  – If not, who are we treating?
• Non-pharmacologic interventions
  – Ice packs, cooling blankets
    • Active cooling can lead to increased oxygen consumption and plasma catecholamine levels
  – Sponging, fans
    • Distractions from more meaningful interactions?

Barone, Fever: Fact and Fiction. Trauma 2009
eperc.mcw.edu/FastFacts
Treatment of Fever

- Pharmacologic interventions
  - Discontinue non-essential medications
  - Time limited trial of antibiotics
  - Acetaminophen
  - NSAIDs
  - Glucocorticoids
Nausea/Vomiting

• Not everyone will benefit from ondansetron (Zofran)
Vomit center

CTZ

Dopamine, serotonin
Toxins e.g. opioids, changing levels, not steady state

CNS

? mediators?
Peaceful environment, Adjust food presentation – sour, cool, easy to digest

GI tract

Acetylcholine, histamine, serotonin, substance P, mechanoreceptors/Chemoreceptors
Stop anticholinergics
Consider “squashed stomach”
Try coating agents

Vestibular apparatus

Intrinsic
Substance P, acetylcholine, histamine

Acetylcholine, histamine

adapted from Hallenbeck. Palliative Care Perspectives 2003
## Etiology of Nausea/Vomiting

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<thead>
<tr>
<th>Metastases</th>
<th>Meningeal irritation</th>
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<tbody>
<tr>
<td>Movement</td>
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<tr>
<td>Mentation</td>
<td>Metabolic</td>
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<tr>
<td>Medications</td>
<td>Microbes</td>
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<tr>
<td>Mucosal irritation</td>
<td>Myocardial</td>
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<tr>
<td>Mechanical obstruction</td>
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</table>

EPEC Project, 2003
<table>
<thead>
<tr>
<th>Drug</th>
<th>Receptor</th>
<th>Where useful?</th>
<th>Other</th>
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<tbody>
<tr>
<td>Chlorpromazine</td>
<td>Dopamine, histamine</td>
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<td>Very sedating, no use in PD</td>
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<tr>
<td>Haloperidol</td>
<td>Dopamine, very weak histamine</td>
<td>CTZ</td>
<td>No use in PD</td>
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<tr>
<td>Lorazepam</td>
<td></td>
<td>CNS-anticipatory nausea</td>
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<tr>
<td>Metoclopramide</td>
<td>Dopamine, very weak histamine</td>
<td>Upper GI gut dysmotility</td>
<td>No use in PD, caution in CKD</td>
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<tr>
<td>Ondansetron</td>
<td>Serotonin</td>
<td>CTZ, gut inflammation from chemo/XRT</td>
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<tr>
<td>Prochlorperazine</td>
<td>Dopamine, very weak histamine</td>
<td>CTZ, infection, inflammation</td>
<td>No use in PD</td>
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<td>Promethazine</td>
<td>Histamine, acetylcholine</td>
<td>Vestibular, infection, inflammation</td>
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<tr>
<td>Scopolamine</td>
<td>Acetylcholine</td>
<td>Vestibular</td>
<td>Minimize movement</td>
</tr>
<tr>
<td>Senna</td>
<td>Local stimulation (myenteric plexus)</td>
<td>Obstruction esp constipation</td>
<td></td>
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<tr>
<td>Other – older</td>
<td></td>
<td></td>
<td>adapted from Hallenbeck. Palliative Care Perspectives 2003</td>
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<tr>
<td>antihistamines,</td>
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<td>dronabinol, coating</td>
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<td>agents</td>
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</table>
Evidence shows that it may be appropriate (in a hospice patient who is not actively dying) to *not* treat an asymptomatic blood glucose level of

- A. 170
- B. 200
- C. 270
- D. 370
Hyperglycemia

• Compare life expectancy to period of time for therapeutic effect to occur
  – UKPDS 33 and 34
  – ACCORD
  – ADVANCE

• Compare treatment burden to benefit

• Conclusion: Treat symptomatically!

Vandenhauwe, Palliative Care and Type II Diabetes, American Journal of Hospice & Palliative Medicine, 2010
Hiccups

• Causes
  – Close to a hundred
  – Most common GI in nature - GERD
  – Metabolic derangements
    • Hypokalemia/calcemia/carbia, uremia, DM
  – Pharmacologic agents
    • Corticosteroids, benzodiazepines most common, also chemotherapy, opioids
  – Diaphragmatic irritation
    • Tumor, infection, inflammation

Smith. Management of hiccups in the palliative care population. AM J Hospice and Palliative Care 2003
Hiccups – Pharmacologic Treatment

• If possible, direct at specific cause
• Baclofen – only drug studied in double blind randomized placebo controlled study
• Chlorpromazine – only FDA approved drug for hiccups
• Other – anti-convulsants such as gabapentin or phenytoin, metoclopramide, nifedipine
Hiccups
Non-Pharmacologic Treatment

• Vagal stimulation
• “Interruption” of phrenic nerve transmission
• Interrupting the respiratory cycle
• Other
  – Acupuncture, diaphragmatic pacing electrodes, surgical ablation of the reflex arc
Constipation is a cause of morbidity in this percentage of cancer patients treated with opioids

- A. 25%
- B. 50%
- C. 75%
- D. 95%
Constipation

• Common cause of morbidity in palliative care setting

• Approximately 40% of patients referred to palliative care service (up to 87% in another study)

• Greater than 95% of patients treated with opioids for cancer related pain

• Unrelieved constipation complications can be life threatening

Hjalte et al. The Direct and Indirect Costs of Opioid-Induced Constipation. Journal of Pain and Symptom Management. 2010
Opioid Induced Constipation

• Opioids cause constipation by
  – Increasing ring contractions (segmenting activity)
  – Decreasing propulsive intestinal activity
  – Enhancing resorption of fluid and electrolytes

What’s the Evidence? (chronic constipation)

• Grade B recommendations
  – Fiber
  – Stool softener
  – Stimulant laxative

• Grade A recommendations
  – Polyethylene glycol
  – Lactulose

What’s the Evidence? (constipation in Palliative Care)

• Treatment of constipation in palliative care is based on inadequate evidence

• There persists and uncertainty about the “best” management

• Based on consensus best practices, health care provider should select laxatives based on the individual patient’s symptoms, performance status, and preference

Miles et al. Laxatives for the management of constipation in palliative care patients. Cochrane Database Systematic Review 2006
It is medically appropriate to use an antihistamine in all patients who experience pruritus

• A. True
• B. False
Pruritus

– Prurioresponsive
  • Itch originates in the skin
  • Histamine, serotonin, cytokines, opioids, neuropeptides such as substance P
  • Some release of histamine from mast cells, other independent

– Neuropathic
  • Damage anywhere along the afferent pathway
  • Postherpetic, paraneoplastic

– Neurogenic
  • Centrally induced – reset of itch threshold
  • Unresponsive to antihistamines
  • Uremic itch, cholestatic itch

– Psychogenic
  • Associated with psychiatric disorders

Seccareccia, Pruritus in Palliative Care, Canadian Family Physician, 2011
Treatment of Pruritus - Nonpharmacologic

• Regularly lubricate skin, especially after bathing
  – Substitute itch with another sensation
    • Menthol for cooling, lidocaine for small areas, capsaicin to block substance P, topical steroids

• Nonpharmacologic
  – UVB therapy
  – Biliary stent vs itch caused by cholestasis
Treatment of Pruritus - Pharmacologic

- H1 receptor antagonists
- SSRI – Paroxetine
- SNRI – Mirtazepine
- TCA - Doxepin
- Ondansetron
- Cholestyramine
- Neuroleptics (gabapentin/pregabalin)
- Naltrexone and naloxone
- Opioid rotation
- Spinal opioid administered with bupivacaine

Seccareccia, Pruritus in Palliative Care, Canadian Family Physician, 2011
Secretions/”Noisy Breathing”

• Inability to handle normal secretions
• Change in muscle tone leading to pooling
• Suctioning doesn’t help
• Pharmacologic treatment – no evidence base
  – Anticholinergics “drug of choice”
• Non-pharmacologic treatment
  – Positioning
  – Education

Active Dying Process

• Stages – early, middle, late
• Time course – 24 hours to 14 days
• Family concerns
• Treatment
  – Confirm treatment goals, adjust treatments
  – Communicate clearly “patient is dying”
  – Treat symptoms as they arise
  – Excellent mouth and skin care
  – Counseling and support to families
Ethical Issues for Relief of Symptoms at End of Life

• Concerns about contributing to addiction and/or physical dependence should never limit effective treatment or palliation of symptoms.

• The “principle of double effect” provides a rational for using opioids or sedatives that might hasten death, provided that the purpose of increasing doses is to relieve symptoms.

Mahler et al. CHEST 2010
Ethical Issues for Relief of Symptoms at End of Life

• Anxiety and depression frequently accompany symptoms such as pain or dyspnea and require evaluation

• Clinicians should understand that some cultures may have different perspectives on
  – the role of the family and
  – who should be involved in decisions about treating symptoms at the end of life
Questions

(and thank you!)