Managing Symptoms at End-of-Life

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Disclosures

• Royalty: UpToDate
• Legal Consulting- TASA

Objectives

• Describe prevalence of distressing symptoms at the end of life
• Provide pharmacologic suggestions for management of common distressing symptoms at end of life
• Discuss treatment of refractory symptoms at the end of life
Prevalence of Symptoms End of Life

- Systematic Review 12 studies – 2416 patients in last days to 2 weeks of life
- 43 unique symptoms – highest prevalence
  - Dyspnea 56.7%
  - Pain 52.4%
  - Respiratory secretions - ‘death rattle’ 51.4%
  - Confusion 50.1%


Symptoms – End-of-Life Nursing Homes

- Symptoms worsened toward end of life
- Patients with dementia had more challenging behavior (40.6%) compared to those without (20.65%)
- Delirium occurred in about 30% in both groups

Eastbrooks et al. JAMDA. 2015;16:515e520

Comfort Care Order Sets OR Anticipatory Prescribing

- Consider likely symptoms to occur
- Ensure pharmacologic agents available especially if patient is in the home setting
- Consider risk benefit of prescribing or not prescribing

National Clinical Guideline Centre. Care of dying adults in the last days of life. 2010
PAIN

Prevalence of Pain at End of Life

- Longitudinal study (proxy reported pain)
  - 60% in last year of life
- Systematic review
  - 52% pain in last two weeks of life
- Cross-sectional data 2004 National Nursing Home Survey
  - 36.6% older patients receiving hospice/palliative services had pain, but only 11.4% had cancer as primary diagnosis

Take home – pain is prevalent in serious illness and at the end of life


Pain

- One of most ‘feared’ symptoms for patients
- May be secondary to disease process or toward end of life may be secondary to metabolic derangement, positioning
- May not be easy to assess in the patient at end of life who may cognitive changes
  - Always assume pain present if patient has reason to have pain

Pharmacologic Approaches

• Mainstay of treatment at end of life
• WHO ladder approach to pain management
  o Oral
  o Around the clock
  o Individualized
• Use of multimodal analgesia
  o Non-opioids, adjuvant therapies may provide analgesia
    and be opioid sparing but may be of limited use at the
    end of life


Opioids – General Guides

• Recent RCT – no significant differences in pain
  control/side effects/response in comparison morphine,
  oxycodone, fentanyl, buprenorphine for chronic cancer
  pain
• Substantial individual variation in the response to the
  agent, so rotation may be necessary
• Selection of opioid typically based on clinical
  judgement, formulary access, cost, or availability of a
  parenteral formulation

3 Broglio & Portenoy. UpToDate, 2015.

Mu Opioid Subc or IV PO

<table>
<thead>
<tr>
<th>Mu Opioid</th>
<th>Subc or IV</th>
<th>PO</th>
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</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10 mcg</td>
<td>30 mcg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.5 mcg</td>
<td>1.5 mg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>75 mcg</td>
<td>300 mcg</td>
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<tr>
<td>Oxycodone</td>
<td>10 mcg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Meperidine</td>
<td>100 mcg</td>
<td>1 mcg/hr TD =2 mg/24h morphine</td>
</tr>
</tbody>
</table>

Equianalgesic Dosing Chart

Adapted with Permission Chris Pasero, 2016
A FEW POINTS ABOUT SOME ANALGESICS USED AT END OF LIFE

**Morphine – The Caveats**

- Longest history use for pain
- Active metabolites morphine 3-gluconoride and morphine 6-gluconoride are renally excreted
  - Accumulation causes increased side effects including excess sedation, agitation, confusion
- Use CAUTION with the use of morphine with renal insufficiency and renal failure
  - Changes in renal function in advanced disease even with normal creatinine

*Prommer. Cancer Control. 2015;22(4):412-25*

**Hydromorphone**

- Significantly more potent than morphine
  - 1.5 mg IV hydromorphone = 10 mg IV morphine
  - 7.5 mg oral hydromorphone = 30 mg oral morphine
- Can be concentrated to allow for higher dose infusions subcutaneously
- No clinically relevant metabolites confirmed
- Can be used in renal failure

*Bringle & Portenoy. UpToDate 2015*
Fentanyl

• Synthetic opioid, no active metabolites
  • Tends to be well-tolerated in the older, frail population; renal insufficiency
• Fentanyl transdermal
  • May need to be changed q48h versus q72h
  • Fever/application of heat increase absorption and cause overdose
• Fentanyl oral transmucosal/nasal
  • Not dose equivalent- indicated only for break-through pain related to cancer
  • Quicker onset than immediate release oral opioids
  
Broglio & Portenoy. UpToDate. 2015.

Opioid Dosing

• Must be individualized
• In hospitalized patient with severe pain frequent dosing with morphine 2-5 mg IV or hydromorphone 0.4-0.8 mg IV every 15-30 minutes may be needed until pain controlled then a “basal” dose should be prescribed with breakthrough medications available


Breakthrough Pain

• Transitory increase in intensity when baseline pain is controlled on a regimen of analgesics
• Causes – multifactorial
  • End-of-dose failure
  • Incident pain
  • Unknown causes
• Incidence
  • Systematic review 59% with cancer experience breakthrough pain

**Breakthrough Medications**

- General principle use 5-15% of total daily dose opioids and utilize same opioid¹
  - In general use single entity agents (i.e; w/o APAP)
- Confirmatory study demonstrated IV morphine tolerated at 20% total daily dose³
- Transmucosal rapid acting fentanyl products may be superior to immediate release oral opioids³
  - Access may be limited due to cost; requires Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) program registration


**Opioid Rotation**

- Consider opioid rotation
  - Pain controlled but adverse side effects
  - Pain not adequately controlled but dose escalation not possible due to side effects
  - Pain is not controlled despite opioid titration
  - Clinical improvement seen in more than 50%¹ to 65%² patients

*Take home: opioid rotation should always be a consideration*


**Opioid Rotation**

- Use equianalgesic table to calculate dose of new opioid
- Dose new agent to 50-75% of equianalgesic dose (except methadone – may need to decrease by 90%)
- If rotating to fentanyl transdermal, do not reduce equianalgesic dose
- Consider further dose reductions if person is older, has organ failure
- Consider less of dose reduction if pain is severe

Opioid Titration

- Consider when using more than 3-4 doses immediate release breakthrough medication daily
- Calculate total amount supplemental medication in last 24 hours and convert into fixed-schedule administration.
- Titration of a dose increment of 25-50% of existing dose usually considered safe
- Titration may be 100% in those with severe pain who are in monitored setting
- Titrated extended release every 2-3 days except methadone


Adjuvant Analgesics

- Component of multimodal pain management
- Include agents such as corticosteroids, anticonvulsants, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and anesthetics – but evidence of efficacy limited for treatment in cancer pain
- Include use of agents to treat side effects such as psychostimulants, antiemetics, sedative hypnotics, benzodiazepines

van den Beuken-van Everdingen et al. Pain Pract. 2016; (epub ahead of print)

Adjuvant Analgesics

- May be of limited utility toward end of life when oral administration may be difficult
- Corticosteroids may provide pain relief in acute neuropathic symptoms toward end of life and can be given intravenously

Intravenous Lidocaine

• Utilized for pain refractory to opioid therapy with reported favorable responses
• Different approaches to therapy including a one time bolus therapy and continuous infusion
• Therapeutic responses without cardiotoxicity at 0.5-1 mg/kg/hr continuously or by short-term infusion


Ketamine

• N-methyl-d-aspartate (NMDA) receptor agent most commonly used as an anesthetic agent; positive effect in the setting of severe, opioid refractory pain
• Difficult side effect profile, including nightmares and delirium
• Start at 0.1 mg/kg/hr by continuous infusion, titrate slowly to 0.5mg/kg/hr
• Pretreat with a low dose antipsychotic or benzodiazepine agent prior to initiation and as needed

Paice. Advance Practice Palliative Care Nursing. 2016;201-252.

Routes of Administration

• Oral preferred route but rotation to other routes may be necessary in up to 70% of cases
• Preferred non-oral routes - subcutaneous, intravenous and enteral
• Mixed evidence for preference buccal, rectal and transdermal gel routes
• Systematic review alternative routes
• Subcutaneous as effective as intravenous
• Rectal route comparable to parenteral route
• Take home – multiple routes available to provide analgesia

Sublingual Opioids

- Sublingual opioids often chosen at end of life when no intravenous access
- Sublingual morphine – only 18% absorbed through sublingual mucosa
- Sublingual absorption of other agents:
  - Fentanyl 51%
  - Buprenorphine 55%
  - Methadone 34%
  - Oxycodone 16%


DYSPNEA

Definition

- Dyspnea (or breathlessness)
  - a subjective experience of breathing discomfort that consists of qualitatively distinct sensation that varies in intensity
  - 'experience of dyspnea derives from interactions of physiological, psychological, social and environmental factors that may induce secondary physiological and behavioral responses'

Pathophysiology

- Mechanism/pathways not well understood
- Changes in activity central chemoreceptors
- Hypercapnia/hypoxia induce ‘air hunger’
- Changes in mechanoreceptor activity in lung, chest wall, upper airway, facial receptors
- Neuromechanical dissociation
- Similar neural networks may mediate pain and dyspnea


Opioids

- Opioids – first line treatment
  - Decrease respiratory drive
  - Alter responses to hypoxia and hypercapnia
  - Changes in bronchoconstriction
- In Systematic review/meta-analysis opioids efficacious
  - Morphine most widely studied
  - Other studies confirm efficacy: hydromorphone, subcutaneous oxycodone, fentanyl


Opioids

- CHF- RCT comparing morphine, oxycodone, and placebo did not demonstrate efficacy but no adverse effects
- Multi-site RCT chronic dyspnea (54% with COPD) treated with morphine ER 10-30 mg daily-effective over time
- Results studies COPD, cancer, heart failure no relationship opioids - respiratory compromise

Opioid Dosing

- Start with low dose morphine 2.5-5 mg PO or hydromorphone 0.5-1 mg PO q2h PRN and titrate to effect
- If unable to take PO can administer subcutaneously or intravenously – utilize 50% of PO dose


Benzodiazepines

- Although evidence does not support use for management– may treat affective response
- Prospective non-randomized trial (n = 26) cancer combination lorazepam/opioids significant reduction dyspnea
- Retrospective review hospitalized patients palliative care (n = 115), those receiving benzodiazepine/opioids better relief


Benzodiazepines

- Lorazepam recommended
  - Short half life
  - Available IV, tablet, liquid
  - Can start as low as 0.25 PO or IV mg q4h

Take home – consider as adjunct to opioids especially when affective component anxiety

Quill et al. In: Primer of Palliative Care, 6th Ed. 2014:52
Oxygen

• Chronic Obstructive Pulmonary Disease–Systematic Review (18 studies, \( n = 431 \)) and (4 studies \( n = 331 \) – overlap 2 studies)\(^2\)
  – dyspnea improved with oxygen when mildly or not hypoxemic
• Multisite RCT (\( n = 211 \)) compared oxygen versus room air delivered by nasal cannula
  – subjective feeling dyspnea relieved at same rates for those receiving room air \(^2\)


Fans

• Hypothesis – cool air on nasoreceptors may decrease feeling of dyspnea
• Randomized controlled cross-over study (\( n = 50 \)) evaluated handheld fan on leg and face – positive result on face\(^1\)

Take home – trial warranted due to low cost and low risk


DELIRIUM
Delirium

- Definition – disturbance in cognition that evolves over short period of time; most often associated with a medical condition
- Subtypes: hyperactive, hypoactive, mixed
- Prevalence at end of life - 58.8%- 88%
- Multifactorial causes at end of life – multi-organ failure, CNS pathology, metabolic derangement, infectious pathology

References:

Delirium Management

- If death not imminent and consistent with goals of care – identify causes and initiate treatment if benefits outweigh risks
  - Electrolyte imbalance, polypharmacy, infections, pain, constipation, urinary retention
- No approved medications; antipsychotics utilized but mixed evidence.
- No strong evidence for non-pharmacologic techniques in delirium at end-of-life

References:

Terminal Delirium Management

- Haloperidol – first line use (0.5-1 mg q2-12h) may not be as sedating as atypical antipsychotics
- Atypical antipsychotics – olanzapine (2.5-5 mg q12/24h), quetiapine (12.5-100 mg q12/24h); risperidone (0.25-1 mg q12/24h) may be more sedating than haloperidol
- Aripiprazole 5-30 mg q24h – may be more effective hypoactive delirium

References:
Terminal Delirium Management

Agitation

- Chlorpromazine (12.5-50 mg q4h-6h) – use for agitated delirium not responsive to less sedating antipsychotics
- Short acting benzodiazepine in combination with antipsychotic may be indicated – generally not used alone as can worsen delirium


RESPIRATORY SECRETIONS

“DEATH RATTLE”

Death Rattle

- Definition – increased respiratory secretions at the end of life – also known as ‘noisy secretions’, ‘increasing retained secretions’
- Prevalence in studies ranged from 12%-92%
- Impact – may not be distressing to patients, but distressing to family members and professionals

Death Rattle Treatment

- High quality studies lacking
- Antimuscarinic medications often utilized (scopolamine, hyoscine butylbromide, glycopyrrolate, atropine), but evidence for efficacy equivocal
- No agent proved superior
- Management including repositioning, suctioning and decreasing hydration also lack of evidence for efficacy
- Reassurance to family members important

Lohse et al. / Pall Symptom Manage. 2014;47:105-122

Medication Dosing

- Atropine 1% ophthalmic  1-2 drops sublingual every 2 hours PRN (may be the least expensive)
- Glycopyrrolate 1-2 mg PO  BID-TID PRN or 0.2-0.4 mg Subcut/IV q4-8h PRN (costly)
- Scopolamine 1.5 mg TD q72h (takes time for onset)
- Hyoscyamine – 0.125-0.25 mg PO/SL q4h PRN (may have less CNS side effects)

Quill et al. In: Primer of Palliative Care, 6th Ed. 2014:57

ANXIETY AND INSOMNIA
Anxiety

- Fears and worries common in those near death
  - Treating distressing symptoms may decrease anxiety
- Minimal evidence for pharmacologic treatment – however expert consensus opinion support use of benzodiazepines


Insomnia

- Common toward end of life and may be related to physical discomfort and anxiety
- Research into appropriate treatment lacking
- Benzodiazepines may be useful if anxiety is contributing to insomnia


Medication Management

- Lorazepam – 0.5-1 mg up to 4 times daily (available PO/SL/IV)
- Clonazepam 0.25-2 mg two to three times daily (may help for sleep at night due to longer duration of action)

NAUSEA AND VOMITING

Nausea and Vomiting

- Multiple causes ranging from inflammation, obstruction, medications, constipation, bleeding, metabolic changes, intracranial pressure, anxiety, vestibular disease
- Evaluation includes trying to reverse potential causes if possible while still treating symptoms


Management

- Treat underlying pathology when indicated if benefit outweighs burden of treatment
  - Opioid induced nausea – rotation
  - Obstruction – surgical intervention when indicated
  - Constipation - bowel regimen
  - Hypercalcemia – hydration, bisphosphonates
  - Ascites - paracentesis
  - Brain metastases - corticosteroids, radiation
  - Peptic ulcer disease- PPIs treatment
  - Infection – antibiotics
  - Anxiety – anxiolytics, supportive counseling

Pharmacologic Treatment

- Mechanistic approach – treat based on etiology limited as may be multifactorial
  - If using multiple anti-emetics, select anti-emetics with different mechanisms of action
- Most treatment has been based on clinical preference
- No specific guidelines for drug selection and dosing – limited high quality evidence

Example Medication Management

- Gastroparesis or medication induced
  - Metoclopramide 10 mg IV/PO q6h
- Medication induced/toxins/unspecified
  - Haloperidol 1.5-5 mg PO or 0.5-2 mg IVTID PRN
  - Ondansetron 8 mg PO/ODT q8h PRN
  - Dexamethasone 4-8 mg IV/PO daily
- Increased intracranial pressure/bowel obstruction
  - Dexamethasone 4-8 mg IV/PO daily

Pharmacologic Pearls

- Eliminate any medications that may be contributing to nausea
- Consider cardiac effects of anti-emetics (if death not imminent)
  - QTc prolongation – ex; ondansetron
- Consider anti-emetic effects on bowels
  - Constipation – ondansetron
- Consider use of medication to treat more than one symptom
  - Example – haloperidol if also has delirium, dexamethasone if has pain secondary to bony metastases


Blumen & Millogo. NEJM. 2015;373(26): 2549-61
CONSTITUTION

**Definition**

- Defined as infrequent bowel movements or difficult moving bowels or incomplete evacuation
- Defined by patient experience
- Prevalence in advanced cancer estimated 70-100%


**Causes**

- Drugs: opioids/anticholinergics/chemotherapy
- Neurogenic disorders/autonomic dysfunction
- Decreased oral intake
- Dehydration
- Immobility
- Electrolyte imbalance: hyperkalemia/hypercalcemia
- Endocrine abnormalities
- Bowel obstruction

Pharmacologic treatment

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
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<tbody>
<tr>
<td>Osmotics</td>
<td>Polyethylene glycol (may be superior to lactulose)</td>
</tr>
<tr>
<td></td>
<td>Lactulose</td>
</tr>
<tr>
<td></td>
<td>Magnesium sulfate</td>
</tr>
<tr>
<td>Stimulants</td>
<td>Senna (can take up to 8 daily)</td>
</tr>
<tr>
<td></td>
<td>Bisacodyl</td>
</tr>
<tr>
<td>Surfactants</td>
<td>Docusate sodium (no evidence of increased efficacy when added to senna)</td>
</tr>
<tr>
<td>Suppositories</td>
<td>Glycerin, Bisacodyl</td>
</tr>
<tr>
<td>Enemas</td>
<td>Tap water, mineral oil</td>
</tr>
<tr>
<td></td>
<td>Saline, sodium phosphate (not recommended older – cause dehydration – need)</td>
</tr>
<tr>
<td>Opioid receptor agonists</td>
<td>Methylnaltrexone (caution if obstruction – can cause perforations)</td>
</tr>
<tr>
<td>Chloride channel activator</td>
<td>Lubiprostone</td>
</tr>
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</table>

Clinical Pearls

- Consider treatment in the last days of life if benefit outweighs burden
- Rectal suppositories or methylnaltrexone (if opioid induced) may be necessary if oral intake is decreased

CACHEXIA - ANOREXIA
Prevalence

- Prevalence not well studied
- Heart failure or COPD 5-15%
- Cancer
  - 50-85% patients GI, pancreatic, lung colorectal cancers at diagnosis
- Advanced cancer – 60-80%
  - Weight loss – part of disease trajectory incurable malignancies


Cachexia-Anorexia Syndrome

- Complex incompletely understood multidimensional syndrome – progressive over time
  - Muscle wasting
  - Negative protein-energy balance (decreased intake, abnormal metabolism)
  - Decreased food intake
  - Hypercatabolism


Pharmacologic Management

- NO one medication consistently effective –
- At end of life consider corticosteroids
  - May increase food intake
  - Suitable short duration advanced disease

Clinical Pearls

• Educate family and caregivers
• Encourage patient to eat for pleasure, but do not force toward the end of life

IN THE LAST HOURS OF LIFE

Most important medications for home at the end of life...

• Pain
  — Opioids such concentrated liquid (morphine 20 mg/ml)
• Anxiety
  — Lorazepam liquid 2 mg/ml
• Nausea-restlessness
  — Haloperidol or lorazepam liquid
• Secretions
  — Atropine ophthalmic (give sublingual) or glycopyrrolate

WHEN SYMPTOMS ARE REFRAC TORY TO TREATMENT

Palliative Sedation

• Utilized at the end-of-life when symptoms are refractory to treatment
• Goal is to reduce suffering in dying patient
• Level of sedation proportional to need to decrease symptom distress
• Sedation to level of unconsciousness only in cases of severe intractable suffering at end of life


Palliative Sedation

• Should only be initiated if severe symptoms refractory to treatment
• Life expectancy is hours to days
• Requires interdisciplinary approach; informed consent
• Palliative care specialists should be involved
• Institutions should have palliative sedation policy

Palliative Sedation

- Medications utilized include barbiturates, benzodizepines and anesthetics
- Intravenous or subcutaneous route preferred
- Opioids should be continued if utilized for management of pain or dyspnea
- Goal of medication is to induce sedation without untoward side effects


The Double Effect

- Recognize the goal is to relieve suffering
- Treatment may include sedation, but not with purpose of hastening death
- Use of sedation to relieve intractable suffering outweighs risk of hastening death


Conclusion

- Palliation of symptoms is important component of end of life care
- “Comfort” care at the end of life often requires intensive symptom management
- Develop a comfort order set to address distressing symptoms at the end of life