Managing Common and Distressing Symptoms in Complex Illness

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Session Outline and Resources

1. Dyspnea
2. Nausea
3. Fatigue
4. Anorexia
5. Depression

Fast Facts: www.eperc.mcw.edu

Managing Symptoms: Meet Mr. G

...a 66 y/o trucker with stage IV esophageal CA and progressive functional decline

- Admitted with “failure to thrive”
- Wife (caregiver) struggling to keep him home
- Prominent symptoms:
  - Episodes of breathlessness, new pleural effusion
  - ↓ POs over 3 wks; “I’m not hungry”
  - Growing fatigue and weakness
- Previously considering experimental chemo, but wife now states: “he’s just given up.”
End-of-Life Symptom Management

- Majority of symptom research in cancer
- Multiple symptoms 'the norm' at end-of-life
- Symptom "complexes" and competing goals
- Physical, mental, emotional, spiritual impact
- Demands comprehensive team-based assessment with individualized plan

A Rational Approach to Symptoms

1. Understand goals and treatment preferences
2. Identify causes and/or contributing factors
3. Treat reversible causes

PHYSIOLOGICAL
- Breathlessness
- Constipation
- Anorexia
- Diarrhea
- Delirium
- Anxiety
- Fever

- Nausea/Vomiting
- Pressure ulcer
- Depression
- Dry mouth
- Agitation
- Fatigue
- Cough
"Now that You Mention it, Doctor"

Studies show that patients do NOT often report symptoms, even when troubling, unless asked.


KEY CONCEPT:
Routinely screen for common symptoms!

Dyspnea (Breathlessness)

- An "uncomfortable awareness of breathing"
- Common: Cancer (21-79%), frequent in end-stage illness even w/o lung involvement
- Highly distressing to patients and families
- Mechanisms:
  - Chemoreceptors (↓PO2, ↑PCO2)
  - Mechanoreceptors (Airway, lung, c-wall)
  - Afferent mismatch


Dyspnea: Pearls

- Respiratory rate, pulse-oximetry, and ABG results do NOT predict dyspnea severity
- Primary symptomatic therapies:
  - Oxygen or moving air
  - Opioids
  - Corticosteroids, +/- benzodiazepines
  - Relaxation, behavioral therapies, pulmonary rehab

Relieving Dyspnea: Oxygen vs. Air

- Randomized, double-blind crossover trial of 51 patients with advanced cancer.
- Patients rated dyspnea and preferences for blinded O2 vs. air (by NC) for 15 min. Results:
  - Symptomatic improvement with BOTH
  - No difference in patient preference.
  - O2 sats improved more with O2 vs. air in hypoxic patients, yet those patients did NOT prefer O2 to air.
  - No correlation between dyspnea score and O2 sat.


Opioids for Dyspnea

**KEY CONCEPT: Opioids are 1st-line treatment for the relief of refractory breathlessness**

- Studies in cancer, COPD, interstitial lung dis.
- ↓ sensation of dyspnea w/o ↓ RR or O2 sats.
- Cochrane review: examined 18 RCTs.
  - ↓ SOB w/ PO or IV opioids vs. placebo (p<0.001).
- Start low: hydrocodone/APAP 1 tab Q4 prn or MSO4 elixir 2-4 mg PO Q2 hrs and titrate.
- Caution in opioid-naïve patients with ↑ PCO2.


Other Therapies for Dyspnea

- Corticosteroids
  - Radiation pneumonitis, SVC syndrome, lymphoma.
- Benzodiazepines: largely unstudied
  - Adjuvant to opioids (anxiety), but ↑ risk sedation.
- Non-pharmacological measures:
  - Pulmonary rehab, chest wall vibration, electrical leg stimulation, walking aids and breathing training.
  - Acupuncture/acupressure (+/-)
  - Relaxation, psychosocial support in lung CA.
  - NPPV in ALS, selected patients with COPD.

Mr. G (continued)

- Pleural effusion drained – only “some” relief
- Neb trials do little to relieve breathlessness
- Liquid morphine 4 mg Q 1-2 hr pm added → dyspnea better ~ 30 mins after each dose
- Patient also w/ moderate nausea after each dose of morphine (which limits his use)
- Last bowel movement yesterday

Now what?

Nausea

- Common (40-70%), distressing at end-of-life
- Complex mechanism based on multiple anatomic pathways:
  1. “Chemoreceptor Trigger Zone” (CTZ) – brainstem; detects toxins, medications, cytokines
  2. Vestibular apparatus – detects motion, vertigo
  3. GI tract – detects irritation, bowel distention
  4. Cortical pathways – ↑ pressure, psychogenic

Dalal et al. JPM, 2006. EPEC, 1999

“Targeted” Nausea Therapy

- Serotonin, Substance P, Acetylcholine, Histamine
- GI tract, Vestibular apparatus, Chemoreceptor Trigger Zone (CTZ)
Nausea Management

- Treat/reverse underlying causes (e.g., stop offending medications, treat constipation)
- Symptomatic therapy – mechanistic approach:
  - Targeted therapy 80-90% effective:
    - CTZ: Dopamine or serotonin blockers
    - Vestibular: Histamine or cholinergic blockers
    - GI: Serotonin blockers, prokinetics
    - Cortical: Steroids, benzodiazepines

Dalal et al. JPM, 2006. EPEC, 1999

Targeted Approach to Nausea

(Hallenbeck J, Weissman D, from EPERC Website, FF#5)

<table>
<thead>
<tr>
<th>Anatomical Pathway</th>
<th>Nausea Sources</th>
<th>Target Receptors</th>
<th>Primary Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemoreceptor</td>
<td>Toxins, drugs, cytokines</td>
<td>D, S, others</td>
<td>Haloperidol, Metoclopramide</td>
</tr>
<tr>
<td>Vestibular</td>
<td>Motion, vertigo</td>
<td>H, A</td>
<td>Meclizine, Diphenhydramine</td>
</tr>
<tr>
<td>GI</td>
<td>Gut distention, irritation</td>
<td>A, S, others</td>
<td>Scopolamine, Ondansetron</td>
</tr>
<tr>
<td>Cerebral</td>
<td>CNS pressure, anxiety</td>
<td>?</td>
<td>Dexamethasone, Lorazepam (?)</td>
</tr>
</tbody>
</table>

A=Acetylcholine, H=Histamine, D=Dopamine, S=Serotonin


Antiemetics and Target Receptors

(Hallenbeck J, Weissman D, from EPERC Website, FF#5)

<table>
<thead>
<tr>
<th>EXAMPLE</th>
<th>ANTI-A</th>
<th>ANTI-H</th>
<th>ANTI-D</th>
<th>ANTI-S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scopolamine</td>
<td>+++</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Promethazine</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>+</td>
<td>++</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>+</td>
<td>+++</td>
<td></td>
<td>+++</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>+</td>
<td>+++</td>
<td></td>
<td>+++</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>++</td>
<td>+++</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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LiL Quality Institute
Nausea Management

- Examples of targeted agents and doses:
  - Metoclopramide 10 mg Q6 hrs
  - Medizine 25 mg Q8 hrs
  - Dexamethasone 4 mg BID

- Refractory nausea:
  - Ondansetron, aprepitant (Emend, anti-neurokinin)
  - "BDR" — Benadryl, Dexamethasone, Reglan

- Other interventions:
  - Cannabinoids, olanzapine, acupuncture, TENS

Statkin NE. J Support Oncol., 2007

Cancer Nausea

- Mainstay guidelines recommend combination of serotonin antagonists, dexamethasone, aprepitant

<table>
<thead>
<tr>
<th>Risk</th>
<th>Example Drugs</th>
<th>Acute</th>
<th>Delayed</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (&gt;90%)</td>
<td>Cisplatin, Decarbazine, Cyclophosphamide</td>
<td>Serotonin ant. + dex + aprepitant</td>
<td>Aprepitant + dex days 2–3</td>
</tr>
<tr>
<td>Mod (50-90%)</td>
<td>Anthracyclines, Oxaliplatin, Carboplatin</td>
<td>Serotonin ant. + dexamethasone</td>
<td>Dex days 2–3</td>
</tr>
<tr>
<td>Low (10-30%)</td>
<td>Topotecan, Taxanes, Gemcitabine</td>
<td>Low dose dexamethasone</td>
<td>No routine prophylaxis</td>
</tr>
<tr>
<td>Min (&lt;10%)</td>
<td>Bleomycin, Vinca-alkaloids, Bevacizumab</td>
<td>No routine prophylaxis</td>
<td>No routine prophylaxis</td>
</tr>
</tbody>
</table>


Malignant Bowel Obstruction

- Most common in advanced ovarian, colon CA
- Often inoperable: poor prognosis, ↓ function
- Drug therapy cornerstone for symptom relief:
  1. Analgesia: morphine, hydromorphone, IV/SQ
  2. Anti-nausea: anti-dopamine (haloperidol IV/SQ) and/or anticholinergic +/- dexamethasone
  3. Anti-secretory: scopolamine, glycopyrrolate
- Octreotide for refractory distress
  - 50-150 mcg q 8 hours SQ, 10 mcg/hr IV/SQ gtt

Mr. G (continued)

- Morphine elixir rotated to oxycodone → dyspnea relief retained, nausea resolves
- Senna 2 tabs QD. to prevent constipation
- Patient shares fears: "I'm just so darn tired – I can't do anything anymore. It seems I'm not good for much...and that's hard on Peg."
- Patient's wife: "He eats almost nothing now. It's horrible...he's starving to death."

Fatigue

- Ubiquitous symptom in advanced illness
  - >90% prevalence in palliative care, CA therapy
  - Longest-lasting and most disruptive symptom
- Subjective sensation:
  - affects physical, cognitive, affective functioning
  - "An overwhelming, sustained exhaustion and decreased capacity for physical and mental work that is unrelieved with rest."
- Mechanisms: complex, cytokine dysregulation

Multiple Causes of Fatigue

[Diagram showing various factors contributing to fatigue]

1. Infection
2. Underlying Disease
3. Cytokines
4. Deconditioning
5. Pain & Symptoms
6. Anorexia/ Cachexia
7. Depression
8. Psychological Stress
9. Poor Sleep
10. Neohormone Dysfunction
11. Thyroid Disease
12. Disease Therapy
13. Medications
14. Anemia
15. Autonomic Dysfunction
16. Metabolic Disorders
Managing Fatigue

• Challenging: think “manage” rather than “fix”
  – Treat reversible causes, concurrent symptoms
  – Beware of depression: strong association!!
• Anemia: not a consistent predictor of fatigue
  – EPO decreases fatigue in CA chemo, ESRD, 
    but delay (6 weeks), $$$, ↑ risk DVT/mortality

KEY CONCEPT: Best evidence treatments for cancer-related fatigue include exercise
and stimulant agents


Stimulants: Methylphenidate

• Centrally acting psychostimulant
• Demonstrated efficacy for depression (elderly), 
  opioid-induced somnolence, and HIV fatigue
• Studied in cancer-related fatigue:
  – Prior open label studies: ↓ fatigue, ↑ QOL
  – Interesting RCT: methylphenidate no different than 
    daily nurse phone call, BUT both ↓ fatigue
  – Recent (2010) RCT in CA helpful in end-stage
  – Starting dose 2.5-5 mg PO QAM/Noon and titrate
• Other stimulants: modafinil


Exercise

• Designed to counter “deconditioning”, muscle 
  wasting, and the paradox of “rest”
• Solid evidence to support effectiveness of 
  exercise for fatigue:
  – In CA and CA therapy, MS, CHF, COPD, others
  – Aerobic and (some) resistance training tested
  – Multiple documented benefits: cardio-respiratory, 
    muscle mass, sleep, mood
  – Questions: best “dose”? Adherence?

Steroids

- Corticosteroids
  - Unclear mechanism, short duration relief (4 wks)
  - Dexamethasone 4 mg PO BID
- Megestrol acetate
  - Advanced cancer: ↑ energy and ↑ well-being
  - Start at 160 mg/d and titrate to 800 mg/d, $\$
- Testosterone (T) and anabolic steroids
  - Hypogonadism, opioids associated with fatigue
  - Helpful in COPD combined with exercise


Cachexia

- Cachexia: a complex metabolic syndrome
  - Involuntary loss of >10% premorbid weight
  - Profound loss of lean muscle mass, appetite
  - Common in cancer (80%) and advanced illness
- Mechanisms:
  - Tumor/advanced illness ↔ Cytokine dysregulation
  - Metabolic and neuroendocrine abnormalities
- Nutritional supplementation and appetite stimulation can NOT overcome catabolic loss

Del Fabbro et al. JPM, 2006. EPEC, 1999

Assessing Anorexia

- Subjective loss of appetite
  - Elicit both patient and family perspective
  - Assess distress related to changes in body image
- Nutritional and weight history, BMI
- Seek and understand major contributors:
  - Chronic nausea, constipation, SOB
  - Taste alteration, early satiety
  - Deconditioning, functional losses
  - Depression, loss of self-esteem

Treating Cachexia/Anorexia

- Clarify goals: (e.g., ↑ weight vs. appetite vs. strength)
- Treat reversible causes/ symptoms (where possible)
- Non-pharmacological therapies:
  - Education, emotional support (not "starving to death")
  - Nutritional counseling, frequent small meals
- Medically assisted nutrition (PEG or TPN)
  - Rarely appropriate in advanced CA or dementia
  - TPN during chemo: ↑ infections and ↓ survival
  - Role in obstructive GI, carcinoid tumors, ALS


Appetite Stimulants

- Megestrol acetate
  - Safe and effective in cancer, AIDS for ↑ appetite and weight gain – BUT does NOT ↑ function
  - Start low dose (160 mg/d); titrate to 800 mg/d
  - Side effects: edema, ↑ glucose and LFTs

**KEY CONCEPT:** Appetite stimulants and medically assisted nutrition (PEG, TPN) do not lengthen life or improve function for most patients with advanced illness


EOL Depression: A Few Pearls

- Common (~30%) (but so is sadness and grief)
- End-of-life assessment different:
  - **KEY CONCEPT:** Somatic symptoms (fatigue, insomnia, loss of appetite, apathy) do NOT reliably predict end-of-life clinical depression
  - Predictors: hopelessness, "Are you depressed?"
- Therapies:
  - Cognitive behavioral therapy in cancer
  - Psychosocial/ spiritual support + antidepressants:
    - SSRIs; mirtazapine (Remeron) → sleep/appetite
    - Methylphenidate (Ritalin) for rapid response

Mr. G (continued)

- Responds “probably” to 1-question screen
- Methylphenidate 5 mg BID helps with energy and mood after 3rd dose, lorazepam stopped
- Mirtazepine started: mood, sleep, appetite
- Family counseling re: nutrition, expectations
- Home resistance training ordered (PT)
- Patient “hopeful”, motivated at discharge
- Mr. G + wife agree to home palliative support, grateful for “a new day.”

Questions and Comments