Atypical Symptoms

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Disclosures

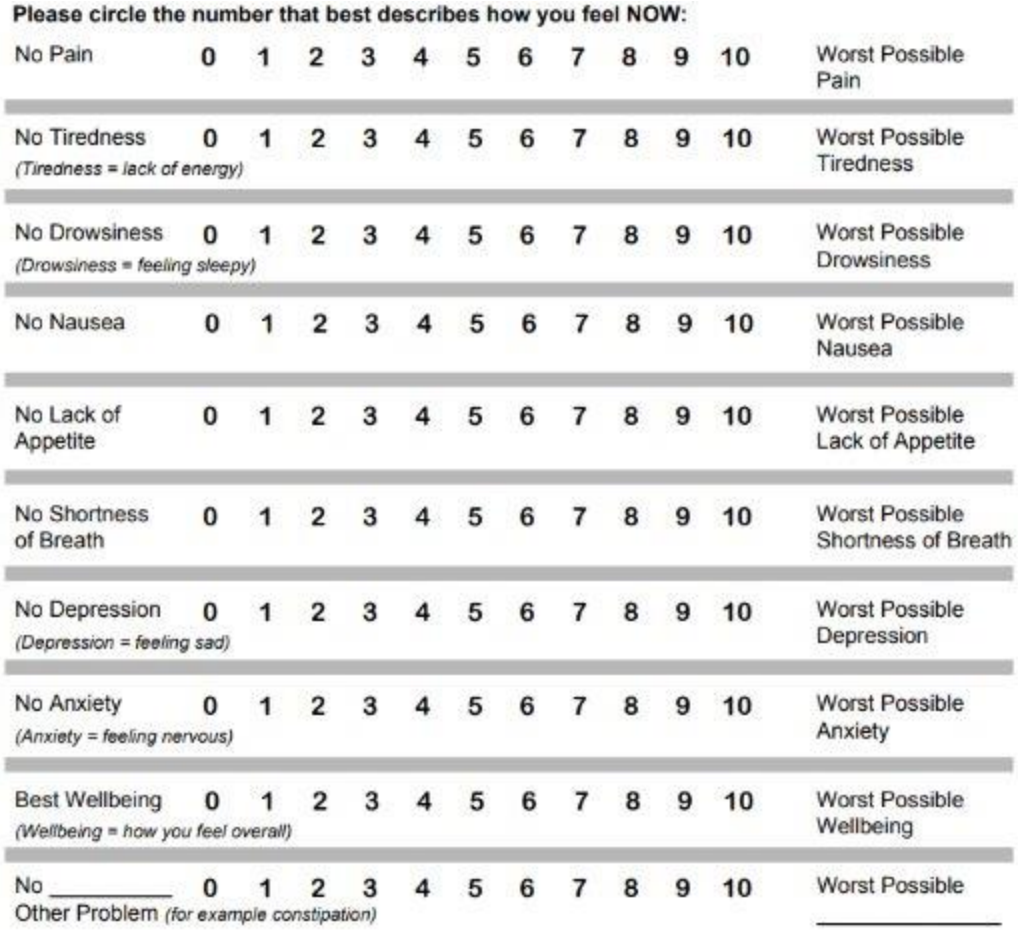
- We have NO financial disclosures
- We will be discussing "off-label" uses of multiple medications given nature of underlying disease

Learning Objectives

- Identify prevalence and epidemiology of some "atypical" palliative care symptoms
- Demonstrate broad overview of pathophysiology of symptoms
- Provide both empiric and etiology-based approach to treatment of symptoms

Introduction

- Many palliative/hospice care visits focus on **pain**, **nausea/vomiting**, **constipation**, and other commonly treated symptoms.
- However, there are less common symptoms that can have a significant effect on quality of life.
- Though they can be less commonly assessed for, as well as less researched in these settings with subsequently less evidence-based guidelines



Please circle the number that best describes how you feel NOW:

No Pain	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Pain
No Tiredness *(Tiredness = lack of energy)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Tiredness
No Drowsiness *(Drowsiness = feeling sleepy)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Drowsiness
No Nausea	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Nausea
No Lack of Appetite	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Lack of Appetite
No Shortness of Breath	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Shortness of Breath
No Depression *(Depression = feeling sad)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Depression
No Anxiety *(Anxiety = feeling nervous)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Anxiety
Best Wellbeing *(Wellbeing = how you feel overall)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Wellbeing
No _____ Other Problem *(for example constipation)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible _____

Cough

Cough: Physiology

- Coughing is a protective mechanism of our respiratory tract to clear irritants, mucus, foreign bodies, etc.
- It is a complex process:
  - Either mechanical or chemical receptors are stimulated and the afferent signals are carried by vagus nerve to cough center in the medulla
  - After processing, an efferent signal is sent down vagus, phrenic, and spinal motor nerves to produce the cough
  - Sometimes hypersensitivity can develop which can contribute to chronic cough

Cough: Etiologies

- Common Causes
  - Medication-related
  - Proximal
    - Upper airway cough syndrome (post-nasal drip)
      - Season allergies
      - Infection
    - GERD
  - Distal
    - Asthma/COPD
    - Postinfectious cough
    - Smoking
    - Environmental triggers
- Less common (palliative world)
  - Bronchiectasis
  - Interstitial pulmonary fibrosis
  - Lung abscess
  - Sarcoidosis
  - Cancer-related
    - Direct tumor effects
      - Endobronchial tumor
      - Parenchymal infiltration
      - Pleural disease
      - Lymphangitis
      - Pleural effusion
    - Treatment-related
      - Post-radiation
      - Chemotherapy

Cough: Evaluation

- If history and exam present clear and convincing cause, treat the cause first (i.e. stop the ACE-I, prescribe antibiotics, inhaler, PPI, etc)
- If concern for pulmonary cause or if above treatment in step above fails, traditionally a chest x-ray would be done [if consistent with goals]
- For non-palliative/hospice patients, if chest imaging is unrevealing for a reason for chronic cough, the next step is to cycle through treatment for the most common causes of chronic cough (post-nasal drip, GERD, etc.)

Cough: Treatment

Step 1: Determine etiology

Step 2: treat the underlying cause (if applicable):

- Post-nasal drip with antihistamines vs decongestants vs nasal corticosteroid
- Treating pneumonia with antibiotics (dependent on goals)
- GERD with H2 blockers or PPI
- COPD/asthma with appropriate inhalers +/- systemic steroids
- Stopping offending medication like ACE inhibitor.

Step 3: Empiric treatment/cough suppressant for refractory

- There are causes where the cause is unlikely to be resolvable such as lung cancer/metastases, interstitial lung disease, recurrent aspiration, or end-stage COPD. **These are the cases that will be focused on here**

Cough: Refractory Management (Opioids)

- Only clear central acting anti-tussive medications are opioids.
  - Mechanism: are thought to work by suppressing the brainstem cough center through mu and kappa opioid receptor agonism
    - Examples: morphine, oxycodone, hydromorphone, etc.
  - Common adverse effects: sedation, constipation, nausea
  - Other notes:
    - Short-acting ones are the most effective and most studied; long-acting ones are not as studied or commonly used for this indication
    - Other opioids
      - Codeine: trials support its effectiveness for cough, and it may be easier to prescribe.
        - But due to safety concerns, especially with children, experts suggest using low-doses of the full agonist opioids above

Cough: Refractory Management (non-opioid management)

Central acting

- Gabapentin:
  - Mechanism of action: voltage-gated calcium channel blocked->increased GAB synthesis=GABAnergic.
  - It is thought that chronic cough can be related to central sensitization as in neuropathic pain.
    - A double blind controlled study did show that it can improve cough frequency/severity and cough-related quality of life
  - Dosing: Starting dose of 300 mg BID; Study looked at doses up to 1800mg per day
- Other (non-evidence based/anecdotally) neuromodulating agents: paroxetine, amitriptyline and benzodiazepines

Cough: Refractory Management (non-opioid management)

Peripheral Acting

- Sweet syrups such as honey or those at the store which are often combined with guaifenesin.
  - Mechanism of action: unknown, but thought to act as a protective barrier to mechanical cough sensory receptors in the throat

Cough: Refractory Management (non-opioid management)

Peripheral Acting

- Benzonatate (Tessalon Perles):
  - Mechanism of action: anesthetizing stretch receptors in the respiratory tract
  - Duration of action is 3-8 hours
  - Dosed at 100-200 mg three times a day.
  - Administration: Capsules must be swallowed whole; chewing or sucking them can cause fatal oropharyngeal anesthesia, choking, or harm if released in the mouth
  - **No published controlled studies confirm its effectiveness, but multiple uncontrolled studies support its use**
  - Side effects are uncommon but include sedation, headache, bronchospasm, and nausea. Empirically many experts recommend adding it to an opioid

Cough: Refractory Management (non-opioid management)

Peripheral Acting

- Anticholinergics (e.g., hyoscyamine/scopolamine)
  - Mechanism of action: block acetylcholine, which can inhibit secretions
  - Other notes:
    - Due to the mechanism, they can also cause constipation, urinary retention and confusion
    - If cough reflex is weak or impaired, the thickened secretions can be harder to clear
- Expectorants (e.g., guaifenesin)
  - Mechanism of action: can thin bronchial secretions and make them easier to cough up.
  - Though given the thinning, if the cough reflex is diminished, this could lead to aspiration or fluid going further down respiratory tract

Cough: Refractory Management (non-opioid management)

Peripheral Acting

- Nebulized local anesthetics
  - Mechanism of action: anesthetizing afferent receptors in the respiratory tract
  - Systematic review found effective and generally well-tolerated, though difficult to generalize given limited RCTs, variety of cough etiologies, and wide range of doses used
  - Dosage: Published regimens include lidocaine 2% solution, 5 mL nebulized every 6 hours; and bupivacaine 0.25%, 5 mL nebulized every 8 hours.
    - Administration tips: using a mouthpiece to avoid contact in with tongue/mouth, doing swish and spit afterward, using candies/sweets to help with taste afterward, and the warning that in the first couple minutes it might trigger a cough with the irritation from administration
  - Side effects/complications (generally transient): bronchospasm, dysgeusia or oropharyngeal numbness

Cough: Summary

- Treatment for cough should be directed at underlying cause if feasible and consistent with patient's prognosis and goals of care.
- When symptomatic treatment is needed for distressing cough in a patient with terminal illness, it is reasonable to start with an opioid and add benzonatate if needed
- A targeted trial of anticholinergics or expectorants may be reasonable if clinically indicated but should be stopped after a couple days with no effect
- Sweet syrups may be helpful with upper respiratory infections but otherwise their role is uncertain
- If these strategies fail to control distressing symptoms, gabapentin should be tried for coughs lasting greater than 8 weeks

Secretions

Secretions: Physiology and Etiology

- Mucus consists mostly of water mixed with glycoproteins and lipids to protect respiratory tissues and remove unwanted material with the help of cilia

Failed clearance:

- The mucociliary clearance can become impaired with age, smoking, COPD, etc.
- Dementia and neurogenerative disorders can impair cough reflex

Overproduction:

- Bronchitis, GERD, and allergies can stimulate excessive secretions

Secretions: Physiology and Etiology

- "Death Rattle"
- Caused by loss of swallowing and inability to clear oral secretions
- This is known due to sounds being observed in non-terminal patients who lose this ability due to injury

Secretions: Pharmacological Treatment for non-EOL patients

Expectorants:

- Guafenesin

Anticholinergics:

- Scopolamine, glycopyrrolate

Inhaled agents

- Bronchodilators can increase ciliary clearance
- N-acetylcysteine lowers viscosity of mucus making it easier to clear
- Cystic fibrosis:
    - Hypertonic saline (secretions thick due to decreased saline secondary to disease)
    - DNAase agents can be helpful in CF (breaks down DNA from dead neutrophils thickening secretions)

Secretions: Non-pharm treatment for non-EOL patients

- Gentle suctioning can be helpful, but deep suctioning can cause irritation and more secretions
- Chest physiotherapy can loosen secretions for clearance/suctioning
- in COPD, parenteral hydration has not been shown to make a difference with mucus production or clearance

Secretions: Non-pharm treatment for EOL patients

Given lack of evidence for pharmacological treatments, these should be considered first-line therapies:

- Discontinue IV or enteral fluids
- Gentle suctioning, but not deep suctioning
- Repositioning to facilitate drainage
- REASSURANCE to family and caregivers about nature of secretions and that while it is bothersome to us, it is likely not for the patient

Secretions: Pharmacological treatment for EOL patients

Anticholinergic agents:

- Centrally acting:
  - hyoscyamine (PO), scopolamine(PO or TD), atropine (PO)
- Peripherally acting:
  - glycopyrrolate (much more effective IV than PO)

Centrally acting ones are generally cheaper, though are much more likely to cause delirium and sedation. They all can have the same peripheral adverse effects of constipation, urinary retention, etc.

Diarrhea

Diarrhea: Introduction

Constipation is a large focus in hospice and palliative care given the use of opioids.

However, diarrhea can significantly decrease quality of life:

- interference with participation with social activities
- skin breakdown
- dehydration
- fatigue
- exacerbating mood and anxiety concerns

Diarrhea: Physiology

- Types
  - Osmotic (unabsorbed solutes – examples include lactulose, lactose for the intolerant, MiraLAX, etc.)
  - Secretory (hormones or toxins stimulate cells in intestines to secrete more solutes than they should - examples include cholera, rotavirus, VIPoma, carcinoid, etc.)
  - Inflammatory - autoimmune or infectious (intestinal cells are damaged leading to leakage of mucus, blood as well as decreasing capacity to absorb)
  - Increased motility (examples include functional bowel disorders, overuse of stimulant laxatives, short gut syndrome, hyperthyroidism)

Diarrhea: Etiologies

- Iatrogenic
  - Overuse of laxatives
  - Overflow leakage from constipation
  - Enteritis from chemo or immunotherapy
  - Radiation enteritis
  - Celiac plexus block
  - Tube feeding
  - Short bowel syndrome
- Infectious
  - Viral
  - Bacterial (campylobacter, E. coli, etc.)
  - Parasites (advanced HIV/immunocompromised)
  - C difficile from antibiotic use

- Structural/Physiologic
  - Inflammatory bowel disease
  - GI bleed
  - Partial obstruction
  - Hormone-secreting tumors (e.g. carcinoid)
  - Pancreatic insufficiency

Diarrhea: Evaluation

- history and physical exam to assess most likely causes -> treat most likely presumptive cause if clear
- If large volume diarrhea, can get labs to assess for electrolyte imbalances
- If concern for obstruction, can get abdominal imaging.
- If there is concern for an enteric infection, can check stool labs including C difficile

Note: amount of work up for diarrhea will be dependent on patient goals

Diarrhea: Treatment

Step 1: Determine etiology

Step 2: General principles to keep in mind while evaluating and treating

- Ensure adequate hydration, with parenteral fluids if needed
- Avoiding lactose for a time given likely temporary lactase deficiency
- Protective skin care for those with pressure ulcers

Step 3: treat the underlying cause (if applicable)

Treatment should be directed at cause if possible (antibiotics for infectious causes, dose-reduction of cancer-directed therapy as determined by oncology, surgery/bowel rest for obstruction, etc.). More specifics to follow.

Diarrhea: First-line Empiric Pharmacological Treatment

- Opioids
  - Loperamide
    - weak systemic absorption and works by slowing down peristalsis.
    - available over the counter, but can be used in higher doses than those on the packaging. Up to 54mg has been used in palliative care setting with minimal adverse effects.
    - Caution if infection is thought to be the cause.
  - Diphenoxylate/atropine
    - former is a peripherally acting opioid that also functions to slow down the GI tract, promote fluid absorption and stool formation. Atropine is included to discourage overuse.

Studies show that loperamide is to be preferred given better effectiveness and side-effect profile.

Diarrhea: Refractory to opioids

Octreotide

- somatastatin analogue that inhibits secretion of GI and pancreatic digestive hormones and also reduces motility.
- Recommended initial doses are 100-150mcg TID SC/IV but can be increased.
- particularly effective for VIPomas, carcinoid, and other GI hormone secreting tumors (also gets used with bowel obstructions)
- In one study 30 of 32 chemotherapy-induced diarrhea, patients who failed loperamide had resolution within 72 hours with octreotide.
- There is a depot IM version that can be dosed every 4 weeks that could be considered as frequent injections might not be feasible at home

Diarrhea: Inflammatory causes

Mesalamine

- Related to aspirin (inhibits COX/LOX pathways and proinflammatory molecules) and made to work specifically in the bowels

Budesonide

- topical steroid that can be taken orally
- Some studies have shown good effects for loperamide-refractory diarrhea on certain chemotherapies

Systemic steroids (dexamethasone, prednisone, etc.)

- effective for immunotherapy-related inflammation of the GI tract, though use should be coordinated closely with oncology given effect on cancer-directed treatment

Diarrhea: Infectious causes

Note:

- Only recommended for certain infectious causes - based on species of bacteria/parasite

For C. difficile specifically:

- two preferred therapies are antibiotics which are poorly absorbed systemically and stay in the GI tract:
  - oral vancomycin and fidaxomicin
  - Former is likely less expensive
  - Dosing guidelines and suggestions for what to do when repeat treatment is needed are available via medical references

Diarrhea: Other agents

For pancreatic insufficiency:

- use supplemental enzymes to help with digestion
- Diet alterations

Cholestyramine:

- originally a cholesterol-lowering medication that binds bile acids in the stool used before advent of statins
- one of the biggest side effects was constipation
- can be helpful for radiation-induced enteritis, ileal resection, and post-cholecystectomy.

Thanks and Questions!!

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