Nausea & Vomiting
Anorexia & Cachexia
Fatigue & Dyspnea

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Disclosures

I have no financial or other relationships to disclose related to any content provided in this education

Objective

- Explain the pathophysiology of nausea and vomiting as it relates to anti-emetic agent selection
- Define nausea & vomiting, anorexia & cachexia, fatigue & dyspnea
- Discuss common medication dosing and adverse events for after-mentioned palliative care symptom management

Outline

- Topics:
  - Nausea & vomiting
  - Anorexia & cachexia
  - Dyspnea
  - Fatigue
- Outline
  - Overview
    -Definition, prevalence
  - Management
    -Pharmacologic and non-pharmacologic

Nausea & Vomiting

Overview

Definition

- Nausea: subjective experience
  - Unpleasant sensation(s) which precede vomiting
  - Sensations: abdominal discomfort, tachycardia, diaphoresis
- Vomiting: physical event
  - Rapid, forceful evacuation of gastric contents in retrograde fashion from the stomach up to and out of the mouth

Prevalence

- Up to 70% patients with cancer
- Up to 30% end-stare renal disease (ESRD)
- Increasing percentage as closer to end-of-life

Higher Risk

- Females
- Specific tumor types
  - Cancers: gynecological, stomach, esophageal, breast
  - Presence of mets: lung, pleura, peritoneum
- GI pathology
- Intestinal obstruction
- Opioid medications
- Highly emetogenic chemotherapy
  - ”platin”, doxorubicin, cyclophosphamide

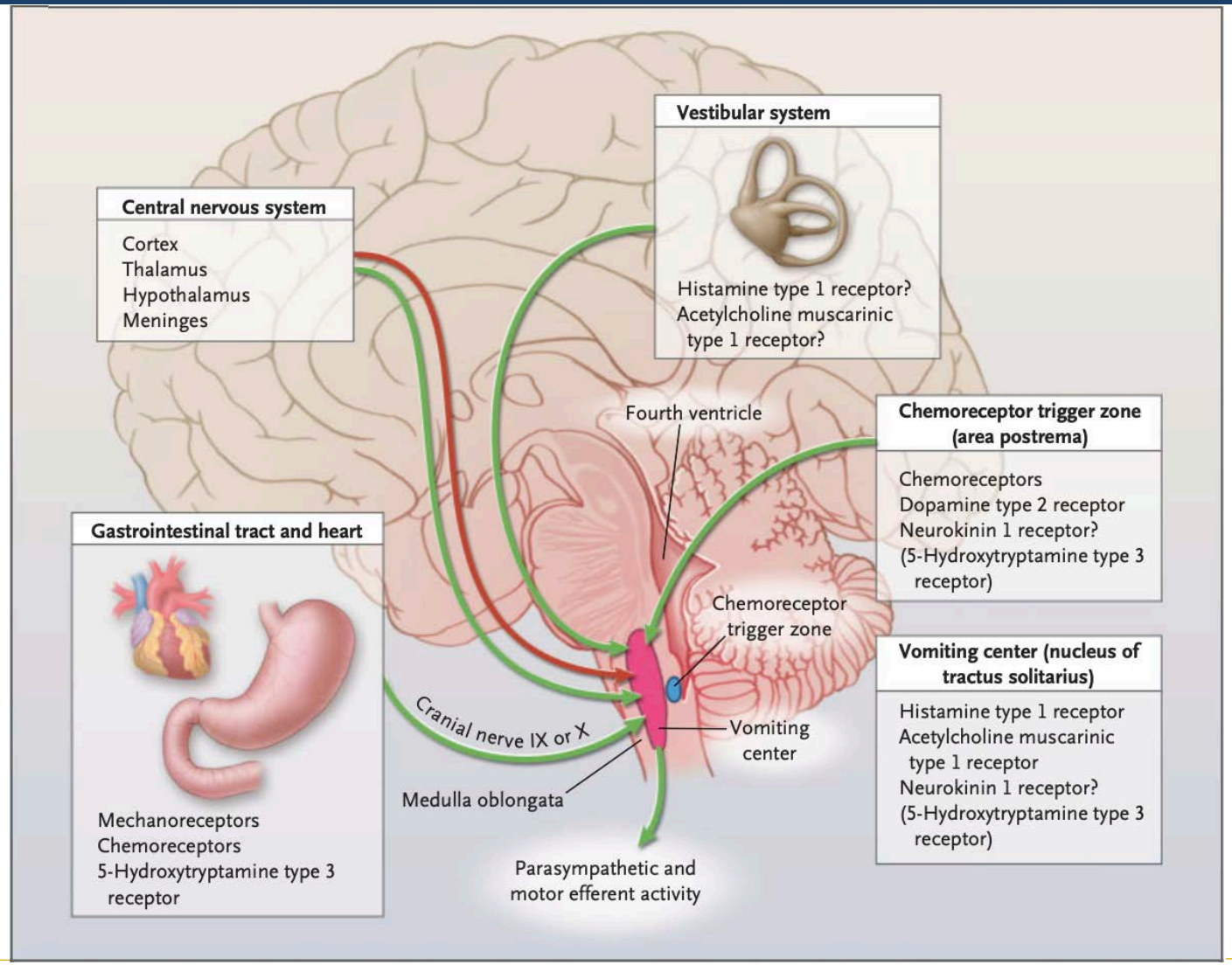
The causes of nausea and vomiting. Fast facts. Available at mypcnow.org. Accessed Oct 2020.

Etiology

- Medication
  - Opioids
- Disease-related
  - Metabolic (e.g. hypercalcemia, renal failure, liver failure, sepsis)
  - Intracranial (e.g. high ICP, base of skull tumors)
  - GI (e.g. obstruction, hepatomegaly, intra-abdominal masses, constipation, ileus)
  - Chemotherapy & radiation
- Psychogenic
  - Anticipatory nausea & vomiting, anxiety

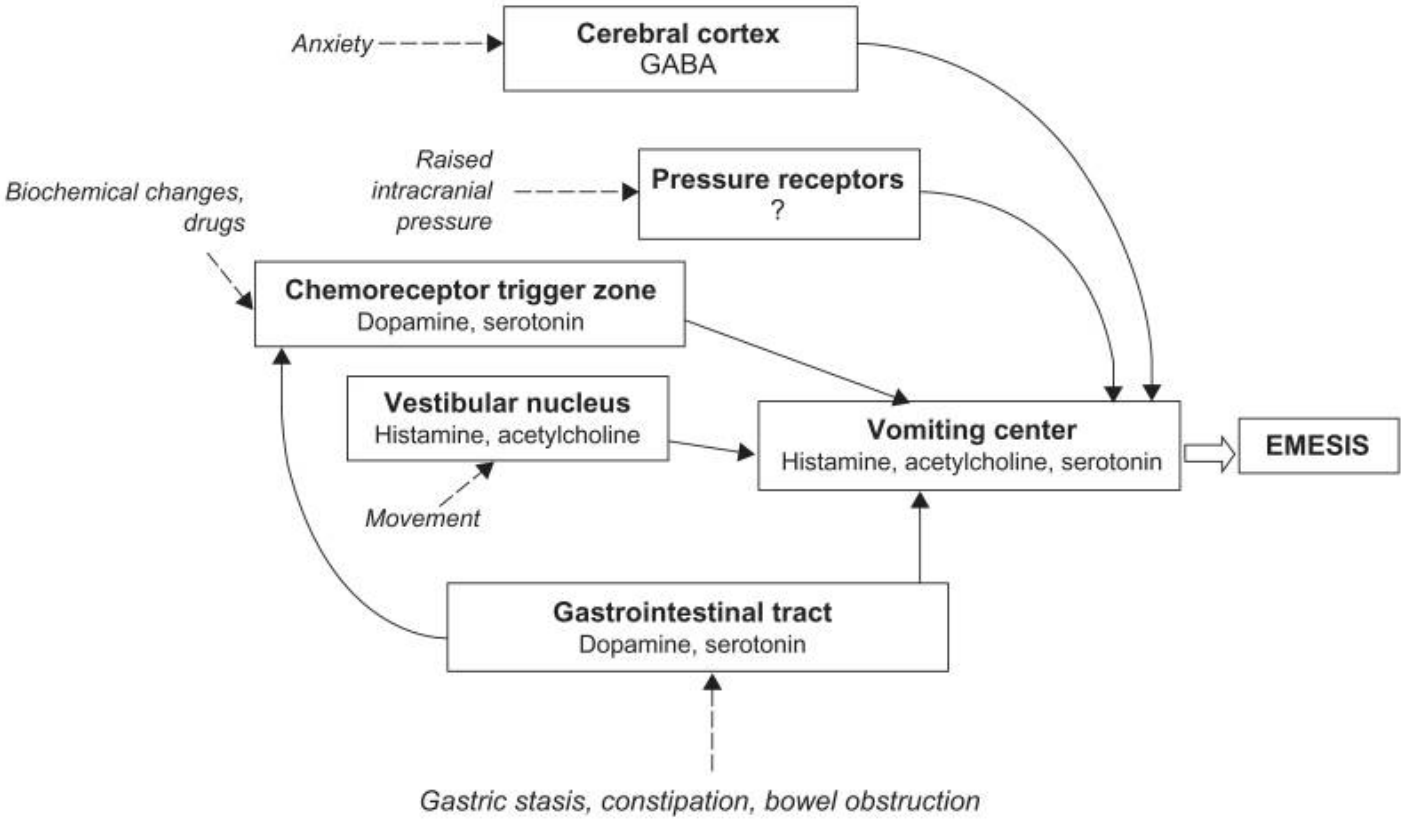
Krakauer, E. L. et al. N Engl J Med 2005;352:817-825

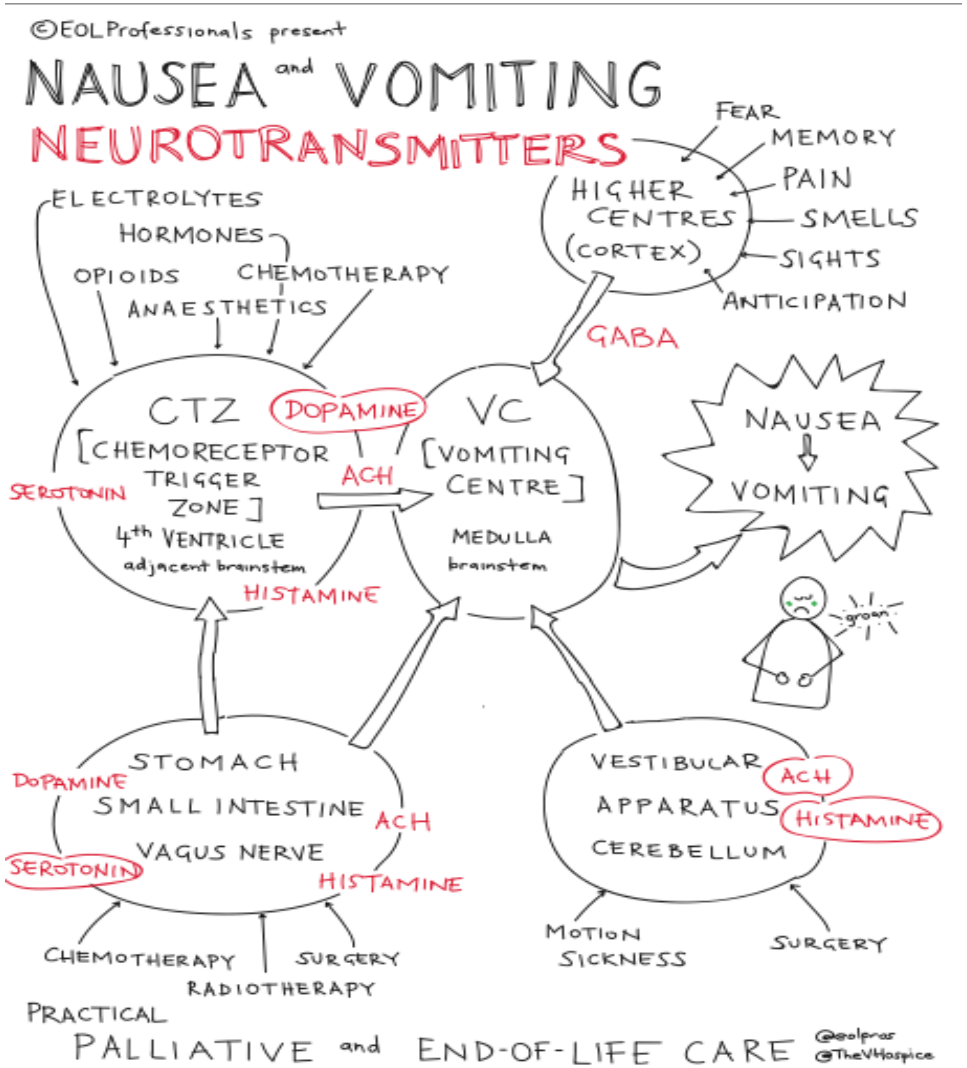
Pathophysiology



Krakauer, E. L. et al. N Engl J Med 2005;352:817-825

Pathophysiology





Images.google.com. Accessed 2020 Oct.

Causes and management: VOMIT

Type of nausea	Receptors involved	Useful drug classes	Examples of anti-emetics
Vestibular	-Cholinergic -Histaminic	-Anticholinergic -Antihistaminic	-Scopolamine patch -Promethazine
Obstruction of bowel by constipation	-Cholinergic -Histaminic -5HT3	-Stimulation of myenteric plexus	-Senna
Dys**M**otility of upper gut	-Cholinergic -Histaminic -5HT3, 5HT4	-Prokinetics	-Metoclopramide
Infection & **I**nflammation	-Cholinergic -Histaminic -5HT3 -Neurokinin 1	-Anticholinergic -Antihistaminic -5HT3 antagonists -NK1 antagonists	-Promethazine -Prochlorperazine
Toxins stimulating CTZ in brain (e.g. chemo, opioids)	-Dopamine 2 -5HT3	-Antidopaminergic -5HT3 antagonists	-Prochlorperazine -Haloperidol -Ondansetron

The causes of nausea and vomiting. Fast facts. Available at mypcnow.org. Accessed Oct 2020.

Management

Non-pharmacologic

- Smaller, more frequent meals
  - Slow eating
  - Cold and bland foods
  - Avoid greasy, fried, spice
- Plastic > metallic utensils
- Oral care
- Avoid known triggers, strong odors
- Acupuncture

Pharmacologic

- Anti-emetics
  - Dopamine antagonists
  - Serotonin antagonists
  - Histamine antagonists
  - Acetylcholine antagonists
  - Cannabinoids
  - Benzodiazepines
- Optimize dose, frequency
- Opioid rotation

Athavale A, Athavale T, Roberts DM. Antiemetic drugs: what to prescribe and when. Aust Prescr. 2020 Apr;43(2):49-56.

Pharmacologic Management: Serotonin Antagonists

Medications

- Ondansetron (Zofran®):
  - 4mg PO/IV/ODT q6h

Indications

- Nausea & vomiting, acute
- Chemotherapy-induced nausea and vomiting
- Post-operative nausea and vomiting

Adverse Effects

- Constipation
- Headache
- QTc prolongation (ondansetron)
  - Reversible
  - Dose-dependent
  - FDA-warning (32mg IV Zofran dose)

FDA Drug Safety Communication. Ondansetron. Accessed 25 Oct 2020.
Athavale A, Athavale T, Roberts DM. Antiemetic drugs: what to prescribe and when. Aust Prescr. 2020 Apr;43(2):49-56.
Glare P, Miller J, Nikolova T, Tickoo R. Treating nausea and vomiting in palliative care: a review. Clin Interv Aging. 2011;6:243-59.

Pharmacologic Management: Dopamine Antagonists

Medications

- Haloperidol (Haldol®): 0.5 to 1 mg PO/IV q12h
- Metoclopramide (Reglan®): 5 to 10mg PO/IV q6h
- Prochlorperazine (Compazine®): 10mg PO q6h; 25mg PR q12h
- Olanzapine (Zyprexa®): 5mg PO qhs

Indications

- Opioid-induced nausea/vomiting
- Gastroparesis
  - Metoclopramide

Adverse Effects

- Extrapyramidal symptoms/movement disorders (IV > PO)
  - Akathisia
  - Dystonic reactions
  - Parkinsonism
  - Tardive dyskinesia
- QT prolongation
  - BBW : haloperidol, droperidol
- Sedation
- Renal dose adjustment (CrCl<60): metoclopramide

Athavale A, Athavale T, Roberts DM. Antiemetic drugs: what to prescribe and when. Aust Prescr. 2020 Apr;43(2):49-56.
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Pharmacologic Management: Histamine Antagonists

Medications

- Meclizine (Antivert®): 25 to 50mg PO q6h
- Promethazine (Phenergan®):
  - 25mg PO/PR q6h
  - 12.5 to 25mg IV q6h

Indications

- Vestibular, motion sickness
- Movement-related

Adverse Effects

- Sedation
  - Promethazine
- Anticholinergic effects with promethazine

Athavale A, Athavale T, Roberts DM. Antiemetic drugs: what to prescribe and when. Aust Prescr. 2020 Apr;43(2):49-56.
Glare P, Miller J, Nikolova T, Tickoo R. Treating nausea and vomiting in palliative care: a review. Clin Interv Aging. 2011;6:243-59.

Pharmacologic Management: Cholinergic Antagonists

Medications

- Scopolamine (Transderm Scop®): 1 patch q72h
  - Do not cut patches

Indications

- Vestibular nausea
- Adjuvant to control symptoms of malignant bowel obstruction

Adverse Effects

- Sedation
- Blurred vision
- Urinary retention
- Dry mouth
- Constipation
- Confusion/delirium
  - *increased risk of cognitive impairment, falls

Athavale A, Athavale T, Roberts DM. Antiemetic drugs: what to prescribe and when. Aust Prescr. 2020 Apr;43(2):49-56.
Glare P, Miller J, Nikolova T, Tickoo R. Treating nausea and vomiting in palliative care: a review. Clin Interv Aging. 2011;6:243-59.

Pharmacologic Management: Benzodiazepines

Medications	Indications	Adverse Effects
• Lorazepam (Ativan®): 0.5 to 1mg PO/IV q8h	• Anticipatory nausea/vomiting in patients receiving chemotherapy • Anxiety playing role in nausea	• Confusion • Sedation • Delirium

Athavale A, Athavale T, Roberts DM. Antiemetic drugs: what to prescribe and when. Aust Prescr. 2020 Apr;43(2):49-56.
Glare P, Miller J, Nikolova T, Tickoo R. Treating nausea and vomiting in palliative care: a review. Clin Interv Aging. 2011;6:243-59.

What about cannabinoids?

- Dronabinol (Marinol)
  - Initial: 2.5 to 5mg PO q12h
  - Indication: chemotherapy-induced nausea and vomiting
  - Allergy
    - Capsules - sesame oil
    - Oral solution - alcohol
  - Adverse effects: sedation, diarrhea, euphoria

Dronabinol. Lexi-Comp. Accessed 2020 Oct.

Take Away Points

- Identify cause behind nausea & vomiting to lead appropriate medication selection
- Multiple agents:
  - Choose agents of different classes
  - identify place in therapy (1st vs 2nd line)

Anorexia & Cachexia

Overview

Definition

- Anorexia: loss of appetite/desire to eat
- Cachexia: physical wasting with loss of skeletal and visceral muscle mass
  - Involuntary loss of >5% original body weight
  - BMI<20 kg/m^2 or sarcopenia with weight loss>2%

Prevalence

- Occurs in ~30% of patients with cancer
  - Up to ~80% of patients with metastatic disease
- Greatest incidence with solid tumors (gastric, pancreatic, lung, colorectal, head & neck)

Classification

- Primary: hypercatabolic state
- Secondary: starvation-mediated

Del Fabbro E, Inui A, Strasser F., Cancer Cachexia. Pocket book for cancer supportive care. Springer Healthcare 2012.
Argilés JM, Olivan M, Busquets S, López-Soriano FJ. Optimal management of cancer anorexia-cachexia syndrome. Cancer Manag Res. 2010 Jan 22;2:27-38.

Pharmacological management: Megestrol acetate (Megace)

Megestrol acetate (Megace®)

MOA:
-Synthetic progestin

Indications (palliative care):
-Anorexia/cachexia

Dosing:
-Suspension: ES (625mg/5mL) vs Megace (40mg/mL)
-Tablet: 40mg
-Initial dose: 400 to 800mg suspension po daily
- 625mg daily (of 125mg/mL ES suspension) or 400mg daily (of 40mg/mL) suspension

Pharmacokinetics (PK):
T ½: 20 to 50 hours

Adverse Drug Reactions (ADR):
-edema, mortality, VTE (hypercoagulability)
-nausea, diarrhea, impotence, peripheral edema, HTN

Clinical Pearls

Appetite improvement ~1 week
Weight gain ~2 to 4 weeks
- Water gain > skeletal/lean muscle gain
- Drug-drug interaction with anticoagulant
- Suspension used for cachexia while tablets used for cancer-related diagnosis
- Doses > 800mg/day show no benefit and higher ADRs
- Studies shown equally efficacious with fewer side effects than corticosteroids

Tazi E, Errihani H. Treatment of cachexia in oncology. Indian J Palliat Care. 2010 Sep;16(3):129-37.
Megestrol acetate for cancer anorexia/cachexia. Fast facts. Available at mypcnow.org. Accessed Oct 2020.

Pharmacological management: Mirtazapine

Mirtazapine (Remeron®)
MOA: -Tricyclic antidepressant (TCA) -Antagonizes noradrenergic, H1, 5HT receptors -Increases NE and serotonin receptors
Indications (palliative care): -Anorexia/loss of appetite -Depression -Insomnia
Dosing: -Initial: 7.5 to 15mg PO qhs -Max dose 45mg PO qhs
PK: T ½: 20 to 40 hours
ADR: -Dry mouth, daytime sedation, constipation, confusion/dizziness, blurred vision

Clinical Pearls

- Option for concomitant depression + cachexia ("skinny elderly person")
- Antidepressant effects may be faster (1 to 2 weeks) than the 4-8 weeks with SSRI/SNRI
- Sedation is inversely related to dose
  - Low doses - high binding affinity to histamine receptor
    - Tolerance develops 7-10 days after treatment start
  - High doses – NE > 5HT
    - Change to qAM administration

Tazi E, Errihani H. Treatment of cachexia in oncology. Indian J Palliat Care. 2010 Sep;16(3):129-37.

Pharmacological management: Other

- Dronabinol
  - Appetite and nausea improvement
  - Well tolerated, especially by patients with prior marijuana experience
  - Evidence surrounding CINV or AIDS-associated cachexia
  - Initial dose: 2.5mg po before lunch and before dinner
    -Maximum dose: 10mg po q12h
- Cyproheptadine (Periactin)
  - No renal/hepatic impairment however q8h dosing
  - Initial: 2mg PO (tablet/syrup) q8h
- Dexamethasone
  - Initial: 2 to 4mg po daily
  - Higher rate of toxicity and adverse effects (when compared with Megace)
  - Increase in appetite without weight gain
- *No benefit seen in combining cachexia/anorexia medication

Tazi E, Errihani H. Treatment of cachexia in oncology. Indian J Palliat Care. 2010 Sep;16(3):129-37.

Fatigue

Overview

Definition

- Persistent sense of tiredness/diminished energy despite rest

Prevalence

- Over 75% of patients with metastatic disease

Classification

- Cancer-related fatigue
  - Radiation
  - Chemotherapy
  - Related to disease state progression
- Opioid induced constipation

Non-pharmacological

- Energy conservation
- Control of contributory factors
- Exericse

Pharmacological

- Methylphenidate
- Modafinil
- Dexamethasone

Pharmacological management: Methylphenidate

Methylphenidate IR (Ritalin, Methylin)

MOA:
Inhibits dopamine and norepinephrine reuptake

Indications (palliative care):
- Fatigue
- Depression
- Opiate-induced sedation

Dosing:
- Methylphenidate IR 2.5 to 5 mg PO before breakfast and lunch
- Renal adjustment: none
- Hepatic adjustment: give lower range of normal dosing

PK:
Onset: within 1 hour
Duration of action: 3 to 6 hours

ADR:
>10%: headache, irritability, weight loss / decreased appetite
>5%: HTN, tachycardia, tremors, dry mouth, nausea

Clinical Pearls

- Titrate based on patient response tolerability:
  - Can titrate as fast as daily (usually q3 days)
- Avoid administration past noon to prevent insomnia
- Fast onset of action (within 1-4 days) for depression compared to other antidepressants
- ADRs/co-morbid risks should not be seen as contraindications
- Weigh benefits-vs-risks and patient's goals of care

Pharmacological management: Modafinil

Modafinil
MOA: - Inhibits NE and dopamine transporters - Increases synaptic concentrations of norepinephrine, dopamine, serotonin, glutamate, decreases GABA
Palliative care indications: - Fatigue - Opiate-induced sedation
Dosing: Modafinil 100 to 200mg PO qAM - Increase to 200mg after 3 to 7 days (- Hepatic: reduce dose by 50% in severe dysfunction
PK: Onset: within 1 hour
ADR: -Headaches (34%), nausea (11%), nervousness (7%), diarrhea (6%)

Clinical Pearls

- Less abuse potential compared to amphetamines (modafinil is non-amphetamine stimulant)
- Lower risk of insomnia
- Convenience of once daily dosing
- Provides an alternative if methylphenidate is contraindicated

Pharmacological management: Dexamethasone

Dexamethasone (Decadron®)

MOA:
Inhibits prostaglandin synthesis

Indications:
- Fatigue
- Loss of appetite
- Nausea

Dosing:
Dexamethasone 2 to 4 mg PO once or twice daily

PK:
Efficacy onset: within 24 hours
T 1/2: 36-54 hours

ADRs: (high doses, chronic use)
- GI toxicity
- Hyperglycemia
- Infection
- Osteoporosis
- Psychological disturbances
- Perianal discomfort

Clinical Pearls

- Often administered for bone pain, tumor burden, inflammatory pain
- Give last dose before 1700 to avoid insomnia
- Decision between burst dose versus chronic dose depends on risk-vs-benefit
- Initiate with gastroprotective agent if patient with multiple risk factors for GI toxicity
- Lower mineralocorticoid activity than other steroids
- Discontinue after 5 to 7 days if no benefit occurs

Dyspnea

Overview

Definition

- Subjective experience
  - Breathlessness
  - Chest tightness
  - Air hunger
  - Feeling of suffocation or breathing discomfort

Prevalence

- Between 29% to 74% patients with advanced cancer
- Common in last six months of life
- Negative impact on quality of life

Etiology/Cause

- Multifactorial etiology- triggered by anxiety, pain, sense of impending doom

Management

Non-pharmacological

- Relaxation
- Supplemental oxygen
- Therapeutic room air -> fan

Pharmacological

- Pure agonist opioids
- Benzodiazepines

Management

Opioids

- MOA: Diminish the chemoreceptor response to hypercapnia and hypoxia in the brain stem
- Dosing:
  - Opioid naïve:
    - Morphine 2.5 to 10mg PO q1h PRN
    - Morphine 1 to 3mg IV q2h PRN
    - *Titrate to effect
  - Baseline opioids: Increase opioid dose by 25% and titrate to effect
  - Chronic dyspnea: long-acting formulation for baseline control with 10% of TDD for breakthrough dyspnea

Benzodiazepines

- MOA: Reduction of anxiety which may worsen breathlessness
- Dosing:
  - Lorazepam 0.25 to 1 mg PO Q4H PRN
  - Midazolam 5 mg IV Q4H PRN

Thank you!

Questions?

Nausea & Vomiting
Anorexia & Cachexia
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