CHRONIC NAUSEA
Common Causes of Chronic Nausea

- Anxiety
- Autonomic dysfunction
- Bowel Obstruction
- Constipation
- Opioids
- Metabolic abnormalities: e.g., uremia, liver failure, hypercalcemia
  - Peptic ulcer disease
  - Radiation Therapy
  - Delayed CINV
  - Other drugs 5-HT3 antagonists
    - Antibiotics
    - NSAIDS
• Chemo, Opioids
• Uremia, ↑Ca
• Toxins

Higher Cortical Centers

↑ ICP
• sensory stimuli
• psychogenic stimuli

NAUSEA/EMESIS

GI obstruction
Gastric stasis,
Metastatic ds,
Bacterial toxins, drugs,
chemo agents
XRT

Receptors:
5-HT3
D2
M
NK1
H-1

VOMITING CENTRE

area postrema of the medulla

Gastrointestinal Tract

Vestibular Apparatus

Motion
Opioids
## Specific Treatment

Treat underlying etiology........Are there multiple etiologies?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercalcemia</td>
<td>Hydration, bisphosphonates</td>
</tr>
<tr>
<td>Opioid toxicity</td>
<td>Opioid rotation/decrease dose</td>
</tr>
<tr>
<td>Constipation</td>
<td>Aggressive bowel regimen. ? Xrays</td>
</tr>
<tr>
<td>Gastric ulceration</td>
<td>PPIs, H2-antagonists</td>
</tr>
<tr>
<td>Infection</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Tense ascites</td>
<td>Paracentesis, consider IP catheteror</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Counseling, Anxiolytics</td>
</tr>
<tr>
<td>Brain metastases</td>
<td>Radiation therapy, Steroids</td>
</tr>
<tr>
<td>Malignant bowel obstruction</td>
<td>? Pt prognosis; Resection, bypassing, or stenting, venting gastrostomy</td>
</tr>
</tbody>
</table>
# Anti-emetic Agents

<table>
<thead>
<tr>
<th>Class</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine antagonist</td>
<td>With prokinetic effects</td>
</tr>
<tr>
<td></td>
<td>▪ Metoclopramide</td>
</tr>
<tr>
<td></td>
<td>▪ Without prokinetic effects</td>
</tr>
<tr>
<td></td>
<td>▪ Haloperidol, Prochlorperazine, Chlorpromazine, Promethazine</td>
</tr>
<tr>
<td><strong>Mainly acts CTZ</strong></td>
<td></td>
</tr>
<tr>
<td>H1 receptor blockers</td>
<td>Promethazine, Diphenhydramine, Meclizine, Hydroxazine,</td>
</tr>
<tr>
<td>Ach antagonist</td>
<td>Scopolamine (transdermal), Hyoscyamine, Glycopyrrolate</td>
</tr>
<tr>
<td>5HT3 antagonists</td>
<td>Ondansetron, Granisetron, Dolasetron</td>
</tr>
<tr>
<td>Other useful agents...</td>
<td>Dexamethasone, Dronabinol, Lorazepam</td>
</tr>
</tbody>
</table>
CANCER RELATED FATIGUE
<table>
<thead>
<tr>
<th>Medical Condition</th>
<th>Assessment Modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>Complete blood count, serum vitamin B\textsubscript{12}, folate, iron, transferring saturation, ferritin levels, fecal occult blood tests, and, if positive, further evaluation for blood loss</td>
</tr>
<tr>
<td>Medication side effects and polypharmacy</td>
<td>Anticholinergics, antihistamines, anticonvulsants, neuroleptics, opioids, central α antagonists, beta-blockers, diuretics, SSRI and tricyclic antidepressants, muscle relaxants and benzodiazepines</td>
</tr>
<tr>
<td>Cognitive or functional impairment</td>
<td>Assessments such as ADL, IADL, MMSE, and “get up and go” test</td>
</tr>
<tr>
<td>Mood disorders</td>
<td>Assessment of depression and anxiety following the DSM IV criteria</td>
</tr>
<tr>
<td>Side effects of primary disease treatment</td>
<td>Recent radiation therapy, chemotherapy, surgery</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Serum albumin, pre-albumin, cholesterol</td>
</tr>
<tr>
<td>Infections</td>
<td>Blood cultures, urine culture, chest radiography, HIV antibody, RPR, PPD skin test</td>
</tr>
<tr>
<td>Other contributing medical conditions</td>
<td>Directed based on clinical finding</td>
</tr>
</tbody>
</table>

Yennu & Bruera JAMA 2007
CRF Management

Specific treatment of underlying causes
- Cachexia
- Autonomic failure
- Anemia
- Infection
- Hypoxia
- Hypogonadism
- Depression
- Others

Symptomatic Treatment

Pharmacological & Complementary
- Corticosteroids
- Psychostimulants (?)
- New agents - Ginseng?

Non-pharmacological
- Energy conservation
- Physical Activity (Aerobic or Resistance)*; Yoga*
- Psychosocial:
  - Cognitive Behavioral therapy* (CBT-BT-CBT-I)
  - Mindfulness based stress reduction
- Psycho-educational
- Supportive Expressive Therapy
- Massage?
- Acupuncture?
- Qigong?

* Level 1 evidence
ANOREXIA - CACHEXIA
International Consensus Definition

- Two group:
  1. Cachexia (>5% WL < 6 months OR >2% + BMI < 20)
  2. No cachexia

- Four group:
  1. No cachexia
  2. Pre- cachexia (<5%)
  3. Cachexia (>5% OR >2% + BMI < 20)
  4. Refractory (>15% + BMI < 23 OR >20% + BMI < 27)
Cachexia: Clinical Significance

**Prevalence in Cancer:**
- 50-80%; 4 of 5 pts in adv stages
- GI > lung > breast 80%/60%/40%

**Clinical Outcomes: “Bad Condition”**
- Shortened survival
  - leading cause of death; 20-30%
- Impacts Rx decisions, and outcomes of cancer Rx
- ↑ Morbidity
- ↓ QoL
- Psychological distress ~35-75%.

*DeWys 1980; Vigano 2000; Wigmore 1997, Andreyev 1998; Bruera 1997*
Figure 4 | Cachexia as a multi-organ syndrome. In addition to skeletal muscle and adipose tissue, other organs are affected by the cachectic process. In fact, the wasting that takes place in muscle could well be dependent on alterations in other organs or tissues, such as white adipose tissue (see the main text). Abnormalities in heart function, alterations in liver protein synthesis, changes in hypothalamic mediators and activation of brown adipose tissue are also involved in the cachetic syndrome.
## Anorexia / Cachexia: Metabolic Alterations

<table>
<thead>
<tr>
<th></th>
<th>Cachexia</th>
<th>Starvation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Energy expenditure</strong></td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Proteinsynthesis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• overall</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>• muscle proteins</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>• acute phase proteins</td>
<td>↑</td>
<td>⇔</td>
</tr>
<tr>
<td><strong>Proteolysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• muscle proteins</td>
<td>↑</td>
<td>↑↑</td>
</tr>
<tr>
<td><strong>Lipogenesis</strong></td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Lipolysis</strong></td>
<td>↑</td>
<td>↑↑</td>
</tr>
<tr>
<td><strong>Glucose turnover</strong></td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Ketone bodies</strong></td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>

Cachexia
Cachexia

Immunosuppression → Infections

Inflammation Decreased Activity → Thromboembolism → CancerDeath

Autonomic Failure → Sudden Death

Cachexia
Weight loss / Cachexia

Fatigue, physical weakness

Body image

Sign of illness evolution

Family / caregivers

Physical symptoms (anorexia, nausea, early satiety)

Patient emotional distress

Patient QOL
Management of Anorexia-Cachexia

Single modality/agent unlikely to be successful

- Treat causes of secondary cachexia
- Appetite stimulants
- Appropriate nutrition
- Identify and treat deficiencies
  - Testosterone, Thyroid, Vitamin D, B-12, folate
- Empiric treatment with multivitamin and omega-3 fish oil
- Exercise
- Anti-catabolic/Anti-metabolic agents/Anabolic agents
## Treatment of secondary cachexia

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Examples of Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early satiety</td>
<td>Metoclopramide, small frequent meals</td>
</tr>
<tr>
<td>Nausea</td>
<td>Metoclopramide</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>Swallow evaluation as appropriate; Antifungal, antiviral agents</td>
</tr>
<tr>
<td>Mucositis</td>
<td>Opioids, antifungal, antiviral</td>
</tr>
<tr>
<td>Constipation</td>
<td>Laxatives</td>
</tr>
<tr>
<td>Delirium</td>
<td>Identify cause, haloperidol, atypical agents (olanzapine)</td>
</tr>
<tr>
<td>Depression</td>
<td>Counseling, anti-depressants</td>
</tr>
</tbody>
</table>
Appetite Stimulants

- Progestational agents - megestrol acetate
- Corticosteroids – dexamethasone, prednisone
- Dronabinol
- Ghrelin or ghrelin mimetics

- None of the above prevent muscle loss
- No improvement in survival
Cannabinoids

- Delta-9-tetrahydrocannabinol (THC): Dronabinol

- Indications for dronabinol (FDA approved):
  - AIDS related anorexia
  - Chemotherapy-induced Nausea

- AIDS patient study (n=139): oral dronabinol vs. placebo *
  - significant improvement: *Appetite, mood and Nausea*
  - no body weight gain

Side effects: Somnolence, dizziness, confusion, perceptual disturbance

*Beal. JPSM 1995*
Other Agents

- **Psychotropics: Mirtazapine and Olanzapine:**
  Via beneficial receptor antagonistic activities
  - Appetite (5-HT2, H-1)
  - Nausea (5-HT3)
  - Insomnia (H-1, 5-HT2)

- Mirtazapine useful if depressed mood or insomnia, nausea also present

- Olanzapine useful if presence of delirium or insomnia, nausea; Well designed randomized controlled trials awaited

- Investigational agent: Oral Anamorelin (Ghrelin agonist) 100mg
  (Temel JS et al 2016; Takayama K et al 2016) has been found to improve lean body mass, QOL anorexia (FAACT) and fatigue (FACIT-F) scores. No improvement in function (Hand grip strength test)
Nonpharmacological-interventions

- **Compassionate communication**
  - reframe “starving to death” to the more complex one of irreversible (usually) metabolic abnormalities.

- **Nutritional counseling**
  - Remove dietary restrictions
  - Small and frequent meals
  - 25 to 30 calories/kg per day 1.5 to 2.0 g of protein/kg per day

- **Exercise**: aerobics and resistance training

- **Parenteral Nutrition**