SYMPTOM CONTROL IN CANCER REHABILITATION

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CANCER PAIN

- 90% of cancer patients experience pain during their illness
- 30% with pain after curative treatment
- >60% patients with advanced disease have pain.
- High prevalence in spite great medical, pharmacological, and technological advances

National Cancer Institute (NCI)
National Comprehensive Cancer Network (NCCN), American Cancer Soc.
PAIN MAY BE CLASSIFIED AS ACUTE OR CHRONIC

• Acute pain is of short duration, typically resulting from an accident, trauma, surgery, or other injury; protective-alerts one to injury
  • usually resolves on its own as healing occurs
  • patient may experience variations in vital signs and may exhibit signs of discomfort

• Chronic pain is pain that persists or occurs intermittently; an ongoing problem; nonprotective
  • rarely resolves on its own
  • may be associated with cancer or chronic non-malignant illness (eg, arthritis, back pain, pain from nerve damage)
  • patient typically does not show clinical or physical signs of pain

(Curtiss CP. Partners Against Pain®. An Audiotape on Pain Management.Norwalk, CT: Purdue Pharma; 1997)
NEED FOR COMPREHENSIVE ASSESSMENT

• Pain not routinely measured in clinical practice.
• There is no universal accepted tool to assess cancer pain.
• No consensus on how to assess pain in patients with advanced cancer.
• Complex Multifactorial symptoms in elderly patients with malignant disease.

DOMAINS OF CANCER PAIN

- Pain Intensity
- Pain Location
- Cancer Pain
- Pain interference with Function
- Breakthrough Pain
- Treatment Relief/Exacerbation
- Pain Quality/Pain Pathophysiology
PAIN

Pain Receptors

Descending Inhibitory Pathways
Endorphins

Pain Perception
(Somatosensory Cortex)

Psychological Factors
Depression/Anxiety
Chemical Coping

Spiritual Distress
Spiritual Pain

Social Factors
Culture
Family distress

Neuro-cognitive Status
Delirium
Dementia

Cancer and Treatment-related symptoms
Fatigue, Anorexia, Cachexia, Nausea

Painful Stimuli
Primary or metastatic cancer
Treatment-related stimuli

EXPRESSION OF PAIN
PAIN ASSESSMENT: HISTORY

- Onset (and location)
- Provocative or Palliative features
- Quality (pain descriptors)
- Radiation and Related symptoms
- Severity (intensity and effect on function)
- Temporal pattern (Alberta breakthrough pain assessment tool- ABPAT)

National Cancer Institute (NCI)
National Comprehensive Cancer Network (NCCN), American Cancer Soc. (ACS)
PERSONALIZED PAIN GOAL

• Most, PPG is 3
• Stable over time
PAIN ASSESSMENT: PAIN INTENSITY SCALES

Worst Pain and Average Pain last 24 hrs

Simple Descriptive Pain Intensity Scale

• 0-10 Numeric Pain Intensity Scale

• Visual Analog Scale

• Faces Scale

NCCN, ACS
MULTIDIMENSIONAL PAIN ASSESSMENT TOOLS

• **Brief Pain Inventory (BPI):**
  • Used in both clinical and research
  • Reliable and valid for many clinical situations and across cultures and languages.
  • Quick, quantifies pain intensity and disability

• **McGill Pain Questionnaire:**
  • Assesses sensory and affective dimensions of pain.
  • Short form takes only 2-3 minutes

• **Initial Pain Assessment Inventory**

• **Memorial Pain Assessment Card**

• **Pain Drawing**
# EDMONTON SYMPTOM ASSESSMENT SYSTEM (ESAS)

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<tr>
<td>Family Distress</td>
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</tbody>
</table>
CLASSIFYING CANCER PAIN

EDMONTON CLASSIFICATION SYSTEM FOR CANCER PAIN (ECS-CP)

- Mechanism of pain
  - Nociceptive
  - Neuropathic
- Incident Pain
- Psychological distress
- Addictive behavior
- Cognitive dysfunction
PAIN BEHAVIORAL EXPRESSIONS IN COGNITIVE IMPAIRED PATIENTS

- **Facial Expressions**
  - Slight frown, sad, frightened face
  - Rapid blinking
  - Distorted expression

- **Verbalizations, vocalizations**
  - Grunting, chanting, groaning
  - Verbally abusive

- **Changes in interpersonal interactions**
  - Aggressive, combative, decreased social interactions, socially inappropriate, irritable or distressed

- **Body movements**
  - Fidgeting, increased pacing, rocking, restricted movement, gait changes

- **Changes in activities patterns or routines**
  - Refusing food, increase in rest periods, changes in sleep patterns, increased wandering, sudden cessation of common routines

**Cancer patients with cognitive impairment**

**Pain Behaviors**
PAIN ASSESSMENT: PSYCHOSOCIAL ASSESSMENT

• Meaning of the pain to patient and family
• The patient’s previous experiences with pain and past coping responses (CAGE, Hx drug abuse).
• The patient’s knowledge, preferences, and attitudes about analgesic options
• Economic impact of pain and its treatment
• Changes in mood secondary to pain
GENERAL APPROACH

• Allow sufficient time for the assessment.

• Give patient the opportunity to use a rating scale or other tool appropriate for that population.

• Use indicators of pain according to the following hierarchy of importance:
  ✓ Patient self-report
  ✓ Pathological conditions or procedures known to be painful
  ✓ Pain-related behaviors (e.g., grimacing, restlessness, vocalization)
  ✓ Reports of pain by family members or caretakers
  ✓ Physiological measures (vital signs).
  ✓ Rely on behavioral or objective indicators of pain (e.g., vital signs) only when no suitable alternative exists.
WHEN ASSESSING FOR PAIN...ALWAYS CONSIDER THESE BARRIERS TO EFFECTIVE OPIOID THERAPY

• **Patient Barriers**
  - Save for “when it’s really bad”
  - Fear of addiction
  - Stigma of morphine
  - Side effects
  - Reluctant to report pain

• **Physician Barriers**
  - Fear of addiction
  - Knowledge deficits
  - Regulatory oversight
  - Analgesia low priority compared to cure
Clinicians should give extra attention to the assessment of pain in special populations

• Elderly
• Very young
• Minorities and non-English speakers
• Substance abusers
• Patients with cognitive impairment
1. Identify Patient’s Personal Experience Of PAIN,
2. Identify Therapeutic Goals At Earliest Opportunity
3. Tailor Information To Patient And Family Needs.
4. Interdisciplinary Team Approach
A SIMPLE APPROACH TO PAIN MANAGEMENT - THE WHO ANALGESIC LADDER
Pain score ≥ 4

Opioid Naive
- Oral Route
- IV Bolus

Opioid Tolerant
- Oral Route
- IV Bolus

Dose 5-15mg po short acting Morphine or equivalent
Dose 2-5mg IV Morphine or equivalent
Calculate previous 24 hr total PO requirement and administer 10-20%
Calculate previous 24 hr total PO requirement and convert to total IV equivalent and administer 10-20%
# Commonly Prescribed Opioids

<table>
<thead>
<tr>
<th>Immediate-release</th>
<th>Extended-release</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Morphine</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Tramadol</td>
</tr>
<tr>
<td>Codeine</td>
<td>Hydrocodone</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>Fentanyl</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Methadone</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>Oxymorphone</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Hydromorphone</td>
</tr>
</tbody>
</table>

- Immediate-release: Morphine, Tramadol, Codeine, Hydrocodone, Oxycodone, Oxymorphone, Hydromorphone
- Extended-release: Morphine, Tramadol, Hydrocodone, Fentanyl, Oxymorphone, Hydromorphone, Methadone
DOSING IMMEDIATE RELEASE OPIOIDS

• Dose q 4 hr prn pain or ATC in select cases

• Adjust dose daily until comfortable
  • mild/moderate pain 25%–50%
  • severe/uncontrolled pain 50%–100%
  • adjust more quickly for severe uncontrolled pain

• Warn of temporary sedation, *prescribe a laxative*
• Probably improve compliance, adherence, relief

• Dose q 12 or 24 (product specific)
  • Do not crush or chew tablets
  • May flush time-release granules through feeding tubes; or sprinkle on applesauce

• Adjust dose q 2–4 days

• Absorbed rectally if patient unable to swallow

• Remember the bowels!
OPIOID THERAPY: DRUG SELECTION

• Long-acting opioid around-the-clock plus a short-acting opioid rescue dose prn
  • Preferred approach for patients with cancer pain and selected others with chronic pain
  • Rescue dose may or may not be appropriate for all patients, depending on syndrome and ability to use the drug responsibly
  • Rescue is 5%-15% of total daily dose; usually prescribed “q4h prn” when oral
  • Remember the bowels

Portenoy RK. Opioid prescribing to patients with and without chemical dependency. Presented at: The International Conference on Pain and Chemical Dependency; June 6-8, 2002: New York, NY
# Calculation of Morphine Equivalent Daily Dose (MEDD)

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Calculation of MEDD (multiply by the number below)</th>
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<tbody>
<tr>
<td>PO Morphine</td>
<td>1</td>
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<tr>
<td>PO Hydrocodone</td>
<td>1-1.5</td>
</tr>
<tr>
<td>PO Oxycodone</td>
<td>1.5</td>
</tr>
<tr>
<td>PO Hydromorphone</td>
<td>5</td>
</tr>
<tr>
<td>PO Oxymorphone</td>
<td>3</td>
</tr>
<tr>
<td>IV Morphine</td>
<td>2.5</td>
</tr>
<tr>
<td>IV Hydromorphone</td>
<td>10</td>
</tr>
<tr>
<td>Fentanyl patch µg/hr</td>
<td>2</td>
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<tr>
<td>Opioid</td>
<td>Onset (minutes)</td>
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<tr>
<td>------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Hydrocodone/Acetaminophen</td>
<td>PO: 30</td>
</tr>
<tr>
<td>Hydrocodone ER</td>
<td>PO: 60</td>
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<tr>
<td>Morphine</td>
<td>PO: 30 IV/SC: 5-10</td>
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<tr>
<td>Oxycodone</td>
<td>PO: 10-15</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>PO: 15-30 IV/SC: 15-30</td>
</tr>
<tr>
<td>Methadone</td>
<td>PO: 30-60 IV/SC: 10-15</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>PO: 10-15</td>
</tr>
</tbody>
</table>
OPIOID ADVERSE EFFECTS: USUALLY DOSE-RELATED AND DRUG-SPECIFIC

- Common
  - Constipation
  - Dry mouth
  - Nausea, vomiting
  - Sedation
  - Sweating

- Less common
  - Respiratory depression
  - Hallucinations
  - Dysphoria, delirium
  - Myoclonus, seizures
  - Pruritus, urticaria
  - Urinary retention
  - Amenorrhea
  - Sexual dysfunction
Constipation

• No tolerance to this side effect therefore need to treat through narcotic course
  • Senna, Docusate, Miralax, Lactulose
• Avoid bulk laxatives
• Consider metoclopramide
ANTICIPATE & MANAGE SIDE EFFECTS

Nausea and emesis
• Metoclopramide
• Promethazine, compazine

• Itching
  • Not an allergic reaction
  • Antihistamines
  • Reassure
ANTICIPATE & MANAGE SIDE EFFECTS

• Sedation
  • Tolerance usually develops rapidly
  • Consider asymmetric dosing (smaller a.m. / larger p.m.)
  • Consider psychostimulants
Clinically significant respiratory depression is rare when patients are in severe pain.

Sedation precedes respiratory depression.
PHARMACOLOGICAL MANAGEMENT

• Use the least invasive administration route
• Try to choose long-acting medications for baseline management and always give short-acting medications for breakthrough pain
• Start low dose, one medication, and adjust according to symptoms and tolerance.
• Constant monitoring for side effects, toxicity.
• Avoid Constipation and if present Treat it.
ANALGESIC ADJUVANTS

- Tricyclic Antidepressants-(Amitriptyline, Nortriptyline)
- Anticonvulsants (AEDs)(Gabapentin)
- Lidocaine
- Ketamine
- Capsaicin
- Miscellaneous drugs (psychotropic drugs, benzodiazepines, bisphosphonates, steroids)
ADJUVANT ANALGESICS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Indications</th>
<th>Side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs, e.g. diclofenac (COX-2 inhibitors can be used if high risk of gastrointestinal side-effects)</td>
<td>50 mg TDS orally, 100 mg once daily (OD) per rectum</td>
<td>Bone metastases, hepatic pain, inflammatory pain, soft tissue infiltration</td>
<td>Gastric irritation, headache, fluid retention. Use with caution in renal impairment</td>
</tr>
<tr>
<td>Steroids, e.g. dexamethasone</td>
<td>8–16 mg daily, best used in the morning, Titrate down to the lowest dose that controls pain</td>
<td>Raised intracranial pressure, nerve compression, soft tissue infiltration, hepatic pain</td>
<td>Hyperglycaemia, cushingoid appearance, confusion, gastric irritation if used with a NSAID</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>100–300 mg (at night) titrate to 600 mg TDS. Higher doses may be needed</td>
<td>Nerve pain of any cause</td>
<td>Mild sedation, confusion, tremor.</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Starting dose 25 mg (at night) In elderly start at 10 mg</td>
<td>Nerve pain of any cause</td>
<td>Sedation, dizziness, confusion, dry mouth, constipation, urinary retention. Avoid in cardiac disease Vertigo, sedation, constipation, rash</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Starting dose 100–200 mg (at night)</td>
<td>Nerve pain of any cause</td>
<td></td>
</tr>
</tbody>
</table>

NSAID, non-steroidal anti-inflammatory drug; three times daily, TDS; once daily, OD; nocte.

**Bisphosphonates (Pamidronate, Zoledronic Acid)**

Laird BJA, Fallon MD. Clin Oncol;2008
THERAPEUTIC APPROACHES: CHRONIC PAIN

- Pharmacotherapy
- Rehabilitative
- Psychological
- Anesthesiologic / Surgical
- Complementary and alternative
- Lifestyle changes

NON-PHARMACOLOGICAL ASPECTS

• Interdisciplinary Approach
• Integrative therapy (massage, acupuncture)
• Psychological interventions
• Emotional and spiritual support
• Rehabilitation: Physical and Occupational therapy
• Other interventional procedures (radiation, anesthesia, surgical interventions)
CANCER FATIGUE

• Cancer-related fatigue is a distressing persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning.
CANCER FATIGUE

- Vary from 60% to 90%
  - Lung and ovarian cancer then hematological malignancies
- Chemotherapy - 30% to 91%.
- Radiotherapy - 25% to 93%,
- Combined modality - 59% to 83%.
- Palliative-care setting - 48% to 75%. 
FATIGUE

- Correlated with the
  - a) severity of psychological symptoms (e.g., anxiety and depression)
  - b) pain
  - c) sleep disturbances
  - d) dyspnea
  - e) anorexia
  - f) anemia, and
  - g) opioid dose (if used).
Fatigue

- Deconditioning
- Cachexia
- Mood Disorders
- Inflammation/cytokines/tumor byproducts
- Drugs (e.g. opioids, benzodiazepines); Cancer treatments
- Cancer-related symptoms
- Anemia
- Renal/hepatic/cardiovascular disease
- Infection
ASSESSMENT

• Uni-dimensional scales - dimension of severity.
  
  e.g visual analogue scales (also called a linear analog scale assessment, or LASA).

No Fatigue 0 | ---------------------------------------------- | 10 Worst Possible Fatigue
ASSESSMENT

- Multidimensional Fatigue Inventory
- Multidimensional Fatigue Symptom Inventory
- Revised Piper Fatigue Scale
- Revised Schwartz Cancer Fatigue Scale
- Brief Fatigue Inventory
- Cancer Fatigue Scale
- Fatigue Symptom Inventory
- Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)
CUT OFF FOR CLINICALLY SIGNIFICANT FATIGUE

• 4/10 on a 0-10 scale (NCCN)
• 5/10 on a 0-10 scale (Butt and Cella, 2008)
• >3 on usual fatigue, >4 on a worst fatigue scale (Hwang, 2001)
# INVESTIGATIONS

<table>
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<tr>
<th>Medical Condition</th>
<th>Assessment Modality</th>
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<tbody>
<tr>
<td>Anemia</td>
<td>Complete blood count, serum vitamin B&lt;sub&gt;12&lt;/sub&gt;, 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>
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<tr>
<td>Mood disorders</td>
<td>Assessment of depression and anxiety following the DSM IV criteria</td>
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<tr>
<td>Side effects of primary disease treatment</td>
<td>Recent radiation therapy, chemotherapy, surgery</td>
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<tr>
<td>Malnutrition</td>
<td>Serum albumin, pre-albumin, cholesterol</td>
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<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>
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</table>
### MANAGEMENT

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

#### Symptomatic Treatment

**Pharmacological**
- Corticosteroids
- Psychostimulants(?)

**Non-pharmacological**
- Counseling
- **Physical Activity** *
- O.T/ PT

* Level 1 Evidence
SPECIFIC MANAGEMENT

- Anemia – transfusions and erythropoietic agents
- Deconditioning - exercise
- Depression - antidepressants
- Infections - antibiotics
- Dehydration - fluids
- Hypoxia - oxygen
- Metabolic and endocrine disorders - correction
- Insomnia - sleep hygiene
- Pain - opioids
- Hypogonadism - testosterone
FATIGUE AND EXERCISE

Exercise reduces fatigue by:

• maintaining or restoring functional capacity,
• improving depression and anxiety,
• enhancing quality of life.
• low to moderate intensity of exercise such as aerobic exercise (walking, cycling, swimming, etc.) for at least 20 minutes duration for 6 weeks to 6 months

Winningham ML, Oncol Nursing Forum. 1994
Oldervoll LM
PSYCHOSOCIAL INTERVENTIONS

Found to be effective in the treatment of CRF

These include:

a) Cognitive behavioral therapy,
b) energy conservation
c) exercise/yoga/meditation
SLEEP THERAPY

• Cognitive Behavioral therapy

• Stimulus control
  – going to bed when sleepy
  – going to bed at approximately the same time each night, and
  – maintaining a regular rising time each day

• Sleep restriction
  – avoiding long or late afternoon naps
  – limiting total time in bed

• Sleep hygiene
  – avoiding caffeine afternoon
  – promoting environment conducive for sleep (dark, quiet and comfortable)
NUTRITION

Patients with CRF with cachexia:

- Frequent small meals that are calorie dense
- Ideal – 34 cal/kg/day or 1.5x REE [or as customized by dietician for a given patient]
- Arginine-, glutamine-, and leucine-related products rich products increase the lean body mass
- Nutrition counseling and consultation
- Adequate hydration and electrolyte balance
PSYCHOSTIMULANTS

- Fatigue
- Opioid induced sedation*
- Depression
- Hypoactive delirium

* Level 1
<table>
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<tr>
<th>Authors (year)</th>
<th>Study Design (cancer type, sample size, outcome measure)</th>
<th>Intervention</th>
<th>Main Result</th>
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<tbody>
<tr>
<td>Psychostimulants</td>
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<tr>
<td>Spathis et al, 2014</td>
<td>Advanced lung cancer; N=208; placebo controlled RCT; FACIT–Fatigue score</td>
<td>Modafinil (100 mg/day on days 1 to 14; 200 mg/day on days 15 to 28) or matched placebo</td>
<td>No significant difference between modafinil and placebo (p=0.20; 95% CI, -3.56 to 3.97) was found.</td>
</tr>
<tr>
<td>Escalante et al, 2014</td>
<td>Mixed solid tumors; N=42; placebo controlled RCT; BFI</td>
<td>Methylphenidate sustained release (18mg/day)-placebo or placebo-methylphenidate sustained release (18mg/day) for 4 weeks. Patients crossed over after 2 weeks</td>
<td>Low-dose methylphenidate did not improve cancer-related fatigue.</td>
</tr>
<tr>
<td>Bruera et al, 2013</td>
<td>Mixed solid tumors; N=141; placebo controlled RCT; FACIT-F</td>
<td>Methylphenidate +Nursing telephone intervention, Placebo +NTI, MP + control telephone intervention, and PL+CTI. Methylphenidate dose was 5 mg every 2 hours as needed up to 20 mg per day.</td>
<td>Methylphenidate and Nursing telephone intervention alone or combined were not superior to placebo in improving CRF.</td>
</tr>
<tr>
<td>Kerr et al, 2012</td>
<td>Mixed solid tumors; N=30; placebo controlled RCT; Piper Fatigue Scale</td>
<td>Methylphenidate 5mg at 8 am and 1 pm or placebo. Doses of MP were titrated every three days (dose range 10-40mg) according to response and adverse effects.</td>
<td>Patients taking Methylphenidate were found to have significantly lower fatigue scores (Piper Fatigue Scale) at Day 14 compared with baseline.</td>
</tr>
<tr>
<td>Moraska et al, 2010</td>
<td>Mixed solid tumors; N=148; placebo controlled RCT; BFI</td>
<td>Methylphenidate sustained release (target dose, 54 mg/d) or placebo for 4 weeks.</td>
<td>Methylphenidate was not significantly better than placebo in improvement of cancer-related fatigue in this patient population.</td>
</tr>
</tbody>
</table>
CORTICOSTEROIDs

• Dose and Type unknown
• Mechanism unknown
• Duration of benefit unclear
• Use high dose – short time?
<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Study Design</th>
<th>Intervention</th>
<th>Main Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yennurajalingam, 2013</td>
<td>Mixed solid tumors; N=132; Randomized double blind placebo – controlled; FACIT-F</td>
<td>Dexamethasone 8mg/day orally for 2 weeks</td>
<td>Dexamethasone is more effective than placebo in reducing cancer-related fatigue in patients with advanced cancer. There was a significant improvement in quality of life, physical well-being, and physical distress scores.</td>
</tr>
<tr>
<td>Della Cun et al, 1989</td>
<td>Mixed solid tumors; N= 403; Randomized double blind placebo – controlled parallel; NOSIE; LASA</td>
<td>Methylprednisolone 125mg/day intravenously for 8 weeks</td>
<td>Methylprednisolone was significantly more effective than placebo in improving quality of life as measured by the changes from baseline in the NOSIE and LASA total scores. (P less than 0.05) and by the Physicians’ Global Evaluation (P less than 0.001).</td>
</tr>
<tr>
<td>Bruera et al 1985</td>
<td>Mixed solid tumors; N= 40; Randomized double blind crossover; NRS 1-100 scale for pain and other cancer related symptoms including activity(fatigue).</td>
<td>Methylprednisolone 32 mg/day orally for 14 days</td>
<td>Following the 14-day, double-blind phase, appetite and daily activity (fatigue) significantly improved among patients who received Methylprednisolone.</td>
</tr>
<tr>
<td>Authors (year)</td>
<td>Study Design (cancer type, sample size, outcome measure)</td>
<td>Intervention</td>
<td>Main Result</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>----------------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Barton et al, 2013</td>
<td>Mixed solid tumors and cancer survivors; N=132; Randomized double blind placebo – controlled; general subscale of the MFSI-SF</td>
<td>American ginseng 2000mg/day orally or placebo for 8 weeks</td>
<td>Improvement in the Ginseng arm compared to placebo was seen at 4 weeks (P = .07) and at 8 weeks (P = .003).</td>
</tr>
<tr>
<td>de Oliveira Campos et al, 2011</td>
<td>Breast cancer undergoing systemic chemotherapy; N=75; randomized cross-over design; FACIT-F</td>
<td>Guarana 50 mg orally twice daily (32 patients) or placebo (43 patients) for 21 days. After a 7-day washout period, patients were crossed over to the opposite experimental arm.</td>
<td>Guarana significantly improved the FACIT-F, and BFI global scores compared to placebo on days 21 and 49.</td>
</tr>
<tr>
<td>Cruciani., et al. 2009</td>
<td>Mixed solid tumors, N= 60; RCT; FACT- An</td>
<td>L-Carnitine (initial dose 0.5 g/day for two days, followed by 1g/d for two days, then 2 g/d for 10 days or Placebo)</td>
<td>No difference between groups was found.</td>
</tr>
<tr>
<td>Del Fabbro et al 2013</td>
<td>Mixed solid tumors; N=43; placebo controlled RCT; FACIT-F</td>
<td>Testosterone was administered intramuscularly using a weight-based dose titrated every 14 days to a bioavailable testosterone goal of 70–270 ng/dL. Gluteal injections of 150 or 200 mg testosterone enanthate or matching placebo (sesame seed oil) were administered at baseline, day 15, day 29, day 43, and day 57.</td>
<td>No statistically significant difference was found for FACIT-fatigue scores between Placebo and Testosterone arms.</td>
</tr>
<tr>
<td>Drug</td>
<td>Initial dose</td>
<td>Side effects</td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td>---------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
<td>Dexamethasone - 8 mg/day for 2 weeks</td>
<td>Severity of most toxic effects is dose-dependent. Adverse effects include</td>
<td></td>
</tr>
<tr>
<td>disease-related fatigue</td>
<td></td>
<td>infection, oral thrush, insomnia, mood swings, myalgia, and elevation of blood</td>
<td></td>
</tr>
<tr>
<td>(off-label use)</td>
<td></td>
<td>glucose.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prolonged use (more than 1 month): gastritis (especially with concurrent use</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>of non-steroidal anti-inflammatory drugs), hiccups, edema, muscle weakness,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>easy bruising, dizziness, hirsutism and slow wound healing.</td>
<td></td>
</tr>
<tr>
<td><strong>Methylphenidate</strong></td>
<td>5 mg/day</td>
<td>Common adverse effects include loss of appetite, slurred speech, abnormal</td>
<td></td>
</tr>
<tr>
<td>Cancer-related fatigue</td>
<td></td>
<td>behavior, and restlessness.</td>
<td></td>
</tr>
<tr>
<td>(off-label use)</td>
<td></td>
<td>Serious adverse effects include hypertension, tachyarrhythmia, thrombocytopenia,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>and hallucinations.</td>
<td></td>
</tr>
<tr>
<td><strong>Megestrol acetate</strong></td>
<td>480-800 mg/day</td>
<td>Common adverse effects include hypertension, sweating, hot flashes, weight</td>
<td></td>
</tr>
<tr>
<td>FDA-approved treatment for</td>
<td></td>
<td>gain, dyspepsia, nausea, vomiting, insomnia, mood swings, and impotence.</td>
<td></td>
</tr>
<tr>
<td>cachexia in patients with</td>
<td></td>
<td>Serious adverse effects include thrombophlebitis, adrenal insufficiency, and</td>
<td></td>
</tr>
<tr>
<td>AIDS and as a treatment for</td>
<td></td>
<td>pulmonary embolism.</td>
<td></td>
</tr>
<tr>
<td>breast and endometrial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cancer; also used for</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>treating cancer-associated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cachexia and anorexia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(off-label use)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Modafinil</strong></td>
<td>200 mg/day</td>
<td>Common adverse effects include diarrhea, nausea, dizziness, headache,</td>
<td></td>
</tr>
<tr>
<td>fatigue related to cancer</td>
<td></td>
<td>insomnia, agitation, anxiety, nervousness, and rhinitis.</td>
<td></td>
</tr>
<tr>
<td>and multiple sclerosis</td>
<td></td>
<td>Serious adverse effects include cardiac dysrhythmia, hypertension, and</td>
<td></td>
</tr>
<tr>
<td>(off-label use)</td>
<td></td>
<td>infectious disease.</td>
<td></td>
</tr>
</tbody>
</table>
SLEEP DISTURBANCE AND PALLIATIVE CARE

- **Defined** as interference of normal sleep either by a symptom or condition
- The prevalence of sleep disturbances - 24% to 95%
- Frequency at least twice the normal population
- More frequent in Lung cancer and Breast cancer pts.

Sela RA, Watanabe S, Vena et al 2006
Yennurajalingam 2013
SLEEP DISTURBANCE

- Presentations -
  - Somnolence
  - Decreased night time sleep
  - Decreased sleep quality
  - Difficulty falling asleep
  - Being easily awakened.
SD AND QUALITY OF LIFE

• Decline in cognitive function
• Inability to engage in work or recreational activities,
• Loss of hedonic capacity
• Adverse alterations to immune and neuroendocrine function

Lianqi, et al.
Berger AM. 2005
ETIOLOGY IN ADVANCED CANCER

Multifactorial

**Predisposing Factors:** age, gender, family history, psychiatric disorders

**Precipitating Factors:**

- Common symptoms including pain, delirium, anxiety, depression, nausea & vomiting, dyspnea
- Medications - opioids, corticosteroids, psychostimulants (modafinil, methylphenidate), caffeine, herbal remedies, diuretics, benzodiazepines, medication withdrawal including alcohol, sedative hypnotics
- Issues affecting sleep wake cycle such as polyuria, nocturia, disruption in normal schedule e.g., multiple hospital admissions, poor sleep hygiene
- Conditions affecting sleep – brain metastasis, sleep apnea, restless leg syndrome, heart failure, severe COPD

**Perpetuating Factors:** maladaptive behaviors

Meuser et al.
Savard et al.
Bottomley et al.
ASSESSMENT

- **Intensity** - (0-10) scale
- **Type and duration** - sleep diaries/logs e.g., difficulty initiating sleep, recurrent nocturnal awakenings.
- **Tools** - Edmonton Symptom Assessment Scale, Pittsburg Sleep Quality Index, Insomnia Severity Index (differ by anchors)
- **Comprehensive history, exam, labs** (e.g., Ferritin levels)
- **Tests** - Actigraphy, Polysomnography as indicated
PHARMACOLOGICAL TREATMENTS

• Consider use of hypnotics on an individual basis but only for short term use.
• Caution as drug interaction, drug pharmacokinetics and pharmacodynamics, drug side effect profile, tolerance, addiction and dependency are common
# HYPNOTICS

<table>
<thead>
<tr>
<th>Classification</th>
<th>Example Drugs</th>
<th>Dosages</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultra-short-acting</td>
<td>Zaleplon</td>
<td>5–10 mg</td>
<td>Little to no anxiolytic effect. Costly</td>
</tr>
<tr>
<td>Short-onset, brief duration</td>
<td>Triazolam</td>
<td>0.125 mg</td>
<td>Rapid sleep induction</td>
</tr>
<tr>
<td></td>
<td>Alprazolam</td>
<td>0.5-1 mg</td>
<td>Limited effect on sleep maintenance.</td>
</tr>
<tr>
<td>Short-onset, intermediate duration of action</td>
<td>Zolpidem</td>
<td>5-10 mg</td>
<td>No clear advantage over benzodiazepines. Costly</td>
</tr>
<tr>
<td></td>
<td>Zopiclone</td>
<td>5-7.5 mg</td>
<td>Minimal anxiolytic effect</td>
</tr>
<tr>
<td></td>
<td>Eszopiclone</td>
<td>3 mg</td>
<td>Minimal anxiolytic effect</td>
</tr>
<tr>
<td>Intermediate onset, duration</td>
<td>Lorazepam</td>
<td>0.5-4 mg</td>
<td>Adequate effect in sleep induction and maintenance. Risk of daytime drowsiness</td>
</tr>
<tr>
<td></td>
<td>Temazepam</td>
<td>7.5-15 mg</td>
<td>Adequate effect in sleep induction and maintenance. Risk of daytime drowsiness</td>
</tr>
<tr>
<td>Longer latency to onset, prolonged</td>
<td>Clonazepam</td>
<td>0.5-2 mg</td>
<td>Slow sleep induction with increased risk of accumulation of metabolites</td>
</tr>
<tr>
<td>activity (half-life, metabolites)</td>
<td>Chlordiazepoxide</td>
<td>50-100 mg</td>
<td>Slow sleep induction with increased risk of accumulation of metabolites</td>
</tr>
<tr>
<td></td>
<td>Diazepam</td>
<td>5-10 mg</td>
<td>Slow sleep induction with increased risk of accumulation of metabolites</td>
</tr>
</tbody>
</table>
### ANTIDEPRESSANTS AND ANTIPSYCHOTIC AGENTS

<table>
<thead>
<tr>
<th>Category</th>
<th>Medication</th>
<th>Dosage</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longer latency to onset, prolonged activity (off label treatment for insomnia)</td>
<td>Amitryptiline</td>
<td>25-100 mg</td>
<td>Increased risk of daytime sedation, confusion, and cardiac conduction abnormalities.</td>
</tr>
<tr>
<td></td>
<td>Imipramine</td>
<td>25-100 mg</td>
<td>Start with 15 mg at bedtime.</td>
</tr>
<tr>
<td></td>
<td>Doxepin</td>
<td>25-100 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trazodone</td>
<td>25-100 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mirtazapine</td>
<td>15-30 mg</td>
<td></td>
</tr>
<tr>
<td>Variable activity (off label treatment for insomnia)</td>
<td>Haloperidol</td>
<td>0.5-5 mg</td>
<td>Used mainly in sleep disturbance related to delirium/psychosis.</td>
</tr>
<tr>
<td></td>
<td>Risperidone</td>
<td>0.5-1 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Olanzapine</td>
<td>5-10 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quetiapine</td>
<td>25 mg</td>
<td></td>
</tr>
</tbody>
</table>
NON-PHARMACOLOGICAL TREATMENTS

- Sleep hygiene
- Stimulus control
- Cognitive behavioral therapy
- Muscle relaxation training
- Biofeedback
- Supportive brief psychotherapy
- Exercise interventions

Morin et al 2009
Savard et al. 2005
Berger AM 2009
Treatment
Non pharmacological measures

Commonly Recommended Sleep Hygiene Measures

1. Maintain a regular bed and wake time schedule including weekends.
2. Establish a regular, relaxing bedtime routine such as soaking in a hot bath or hot tub and then reading a book or listening to soothing music.
3. Create a sleep-conducive environment that is dark, quiet, comfortable and cool.
4. Sleep on a comfortable mattress and pillows.
5. Use your bedroom only for sleep and sex.
6. Finish eating at least 2-3 hours before your regular bedtime.
7. Exercise regularly. It is best to complete your workout at least a few hours before bedtime.
8. Avoid caffeine (e.g. coffee, tea, soft drinks, chocolate) close to bedtime. It can keep you awake.
9. Avoid nicotine (e.g. cigarettes, tobacco products). Used close to bedtime, it can lead to poor sleep.
10. Avoid alcohol close to bedtime.

CURRENT INVESTIGATIONAL INTERVENTIONS FOR SLEEP DISTURBANCE IN ADVANCED CANCER

Non-Pharmacological

• **Cognitive behavioral Therapy**
  Likely benefit in advanced cancer, but limited impact

• **Physical Activity**
  Likely benefit in advanced cancer, but issues with adherence

• **Light therapy**
  Likely benefit in advanced cancer, but limited evidence

Pharmacological

• **Melatonin**
  Likely benefit in advanced cancer, but limited impact

• **Methylphenidate**
  Likely benefit in advanced cancer, but limited evidence

---

Bruera, JCO 2006
Bruera., JCO , 2003
Garfinkel Lancet, 1995
Sleep Disturbances
Combination Treatments

- Pain
- Dyspnea
- Fatigue

Inflammation

Behavioral Problems
- Decreased daytime activity
- Increased time in bed

Psychiatric Symptoms
- Anxiety
- Depression

Patient Characteristics
- Age, gender, race
- Comorbidities (obesity)
- Prior sleep disturbances
- Addictions (tobacco, coffee)

Brain

Sleep Disturbance (PSQI)

Cancer

Melatonin

Methylphenidate

CBT

Light Therapy
MANAGEMENT

- **Interdisciplinary and multimodal approach**
- Treat the underlying symptom and/or cause
- Combination of pharmacological and non-pharmacological approach should be explored if the “primary” cause cannot be treated.
ANOREXIA-CACHEXIA

• Prevalence in cancer: 50-80%; 4 of 5 patients in advanced stages
  • GI>lung>breast 80%/60%/40%

• Characterized by ongoing loss of skeletal muscle mass with or without fat loss

• Cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment

• Pathophysiology is characterized by negative protein and energy balance driven by variable combinations of reduced food intake and abnormal metabolism

Fearon, Lancet Oncology 2011
MECHANISMS OF CACHEXIA

- 2 major categories:
  - Tumor-Host interactions
    - Immune-endocrine-metabolic alterations (including hepatic/renal dysfunction)
  - Decreased oral intake (secondary cachexia/starvation component)
Cytokines and Cachexia Syndrome

**Tumor**
- Hepatic Acute Phase Protein Response
- **Muscle Wasting**
- **FAT LOSS**

**Cytokines** (IL-1, IL-6, TNF-α)
- **Resting Energy Expenditure**

**Brain**
- Sickness Behaviors
  - Anorexia, Fatigue, Cognitive failure, Sleep Issues, Depression
- **Neuro-endocrine Alterations**
  - ↑ stress hormones
  - ↓ testosterone, growth hormone,
CONTRIBUTORS TO “SECONDARY CACHEXIA”

• Uncontrolled nutritional impact symptoms
  • Nausea, vomiting, early satiety, pain, dysphagia, mucositis, constipation, taste alteration

• Mechanical obstruction – intrinsic or extrinsic

• Psychosocial factors
  • Depression, access to food, dietary restrictions

• Effects and complications of treatments
  • XRT, chemo, infections, surgery
## ASSESSMENT QUESTIONS

<table>
<thead>
<tr>
<th>Question?</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>How the patient feels?</td>
<td>Symptom Assessment</td>
</tr>
<tr>
<td>Intake?</td>
<td>History, observation, food diary, calorie recall</td>
</tr>
<tr>
<td>Body weight?</td>
<td>Ht, wt, BMI</td>
</tr>
<tr>
<td>Body composition?</td>
<td>Anthropometry, bioelectric impedance, CT imaging</td>
</tr>
<tr>
<td>Function?</td>
<td>Performance status, functional tests</td>
</tr>
</tbody>
</table>
MANAGEMENT OF ANOREXIA-CACHEXIA

• Multimodality needed

• Treat causes of secondary cachexia

• Appetite stimulants***
  • Megestrol, steroids, marinol (none prevent muscle loss; no improvement in QOL or survival)
  • Mirtazapine

• Appropriate nutrition

• Identify and treat deficiencies
  • Testosterone, thyroid, vitamin D, B12, folate

• Empiric treatment with multivitamin, carnitine, fish oil

• Exercise

• Anti-catabolic, anti-metabolic 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; antifungal/antiviral agents</td>
</tr>
<tr>
<td>Taste</td>
<td>Zinc; trial of different food</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>Pilocarpine, saliva substitute</td>
</tr>
<tr>
<td>Mucositis</td>
<td>Opioids, antifungal/antivirals</td>
</tr>
<tr>
<td>Constipation</td>
<td>Laxatives</td>
</tr>
<tr>
<td>Delirium</td>
<td>Correct cause, haloperidol, atypical agents (e.g. olanzapine)</td>
</tr>
<tr>
<td>Depression</td>
<td>Counseling, anti-depressants</td>
</tr>
</tbody>
</table>