Pain and Symptom Control in Palliative Care: New Ways to Think About Old Drugs

Larry C. Driver, MD

Professor, Anesthesiology and Pain Medicine

Medical decision making

Cultural values
- Life is sacred
- Patient autonomy in decision-making
- No one should suffer

What do patients want/expect from their physician?
- Respect as an individual
- Understanding and care
- Not to be abandoned

Kagawa-Singer, 1999

Cancer patients’ symptom burden

- Pain (80%)
- Fatigue (90%)
- Lack of appetite (80%)
- Weight loss (80%)
- Nausea, vomiting (90%)
- Anxiety (25%)
- Shortness of breath (50%)
- Confusion-agitation-delirium (80%)
Cancer pain management

- Barriers related to patient:
  - Expecting cancer to be painful, reluctant to report pain, fear that pain means disease is worst, concern about distracting physicians, concern about "being a good patient", worries about side-effects, poor adherence

- Barriers related to healthcare professionals:
  - Lower priority to pain treatment, inadequate knowledge of pain management, poor assessment of pain, concern about regulations, fears of patient's addiction, concern about side effects and tolerance

- Barriers related to healthcare system:
  - Low priority to cancer pain treatment, inadequate reimbursement, restrictive regulations, problems of availability or access to treatment

Why treat pain (et al. symptoms)?

- Control of pain et al. symptoms is important for
  - Optimizing patient outcomes and satisfaction
    • QOL
  - Moral and Ethical reasons
    • Primum non nocere
    • Nonmaleficence / Beneficence
  - Compliance with guidelines and standards
    • JCAHO

(Blau, SMJ, 1999)

Cancer pain: a significant problem

- Pain interferes with functioning
  (e.g., movement, appetite, sleep, emotional well-being, and relationships)\(^1\)

- Unrelieved pain
  - Impairs quality of life for patients and their families\(^2\)
  - May lead to suicide\(^3,4\)

- Relief of pain improves the quality of life for people who have cancer

1. Ferrell BR et al., Cancer, 1989;63(11 suppl):2321-2327
2. Cleeland CS., Cancer, 1984;54(11 suppl):2635-2641
3. Levin DN., Cancer, 1985;56:2377-2379

The screen versions of these slides have full details of copyright and acknowledgements
Pain in cancer patients

- Most patients with cancer experience cancer-related pain
- 60% to 90% of patients with advanced cancer will experience significant pain.
- A meta-analysis of cancer care over the last 40 years found that 64% of patients with advanced stage disease or metastatic cancer experience pain.
- 30-40% of patients have pain at time of cancer diagnosis.
- 50-70% have pain during treatment.
- 70-80% with advanced disease.

Causes of pain in cancer patients

- Direct tumor invasion of tissue or neural structures (≥75%)
- Aftereffects of cancer therapy (≥20%)
- Unrelated to cancer (≤10%)
- Most patients have more than one type of pain at various times during active cancer treatment, in survivorship, with advanced disease, at end-of-life.

Pain definitions and pathophysiology

- Sensory and emotional experience associated with tissue damage or described in terms of such damage – IASP
- Acute / Chronic
- Nociceptive pain: somatic / visceral
- Neuropathic pain
- Basal pain / Breakthrough pain
Consequences of inadequately managed pain

- ↑HR, ↑BP, ↑RR, sweating, agitation, ↓mobility
- Anxiety / Stress / Depression
- Sleep disorders, drowsiness, fatigue
- Impaired ambulation, falls, ↓mobility/activity
- Cognitive dysfunction, agitation, restlessness
- ↓Socialization
- Patient / family perceptions of patient suffering
- Polypharmacy, ↑nursing time
- ↑Healthcare costs, ↓Productivity
- ↓QOL

Relating pain with function

<table>
<thead>
<tr>
<th>Abilities or activities</th>
<th>Enjoy</th>
<th>Work</th>
<th>Mood</th>
<th>Mood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active</td>
<td>Active</td>
<td>Sleep</td>
<td>Sleep</td>
<td>Walk</td>
</tr>
<tr>
<td>Eat</td>
<td>Eat</td>
<td>Eat</td>
<td>Eat</td>
<td>Eat</td>
</tr>
<tr>
<td>Talk</td>
<td>Talk</td>
<td>Talk</td>
<td>Talk</td>
<td>Talk</td>
</tr>
<tr>
<td>Exist</td>
<td>Exist</td>
<td>Exist</td>
<td>Exist</td>
<td>Exist</td>
</tr>
</tbody>
</table>

Cleeland et al.

Pain and symptom assessment

- Pain is a multidimensional experience
  - Physical
  - Psychological
  - Spiritual
  - Social
  - Cultural
  - Situational
  (Collateral symptoms may be multifactorial)
2 Patients: pain intensity 8/10
(Both patients same cancer and stage)

<table>
<thead>
<tr>
<th></th>
<th>Patient #1</th>
<th>Patient #2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nociception</td>
<td>85%</td>
<td>30%</td>
</tr>
<tr>
<td>Somatization</td>
<td>5%</td>
<td>20%</td>
</tr>
<tr>
<td>Chemical coping</td>
<td>5%</td>
<td>30%</td>
</tr>
<tr>
<td>Tolerance</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>Incidental Pain</td>
<td>0%</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Pain and symptom assessment

- Collect the data
  - Pain history / Medical history
  - Physical examination
  - Imaging studies
- Integrate the findings
- Develop the therapeutic strategy
  - Single modality
  - Multimodality

ABCs of pain and symptom assessment and management

- Ask about pain et al symptoms regularly; Assess systematically
- Believe the patient and family in their reports of pain and other symptoms
- Choose treatment options appropriate for the patient, family, and setting
- Deliver interventions in a timely, logical, and coordinated fashion
- Empower patients and their families; Enable them to control their course to the greatest extent possible
Therapeutic approaches: cancer pain

- Pharmacotherapy
  - Opioids / Nonopioids / Adjunct co-analgesics
- Rehabilitation
- Psychological
- Anesthesiologic / Surgical
- Complementary / Alternative (Integrative)
- Education / Lifestyle changes

Pharmacotherapy

- Guidelines – WHO, NCCN, AHCPR, APS...
- Nonopioid analgesics
- Opioid analgesics
  - Low potency → High potency
  - CR, ER, SR / IR
  - Route of administration
  - Side effects: predictable, manageable

Principles of opioid therapy for effective pain management

- Treat persistent basal pain with around the clock scheduled extended-release opioids
- Treat episodic breakthrough pain with prn regular-release opioids
- Consider rapid-onset opioid as an alternative breakthrough opioid, or as a back-up rescue opioid
- Titrate dosage to optimal pain relief
- Use least invasive and best tolerated route of administration to meet patient needs
- Anticipate and proactively treat opioid side effects
- Provide rational co-analgesic polypharmacy and add multidisciplined pain treatment approaches for balanced analgesia

Adapted from AHCPR 1994, WHO 1996, APS 1999
Pain and Symptom Control in Palliative Care: New Ways to Think About Old Drugs

Larry C. Driver, MD

Commonly prescribed opioids

- Immediate-release
  - Morphine
  - Tramadol
  - Codeine
  - Hydrocodone
  - Oxycodone
  - Oxymorphone
  - Hydromorphone
  - Fentanyl
  - Tapentadol

- Extended-release
  - Morphine
  - Tramadol
  - Oxycodone
  - Oxymorphone
  - Hydromorphone*
  - Hydrocodone*
  - Fentanyl
  - Methadone

Extended-release opioids for basal pain

- Morphine: 10, 15, 20, 30, 40, 50, 60, 80, 100, 200 mg, Q24h, q12h, (q8h)
- Tramadol: 100, 200, 300 mg, Q24h, (q12h)
- Oxycodone: 10, 15, 20, 30, 40, 60, 80 mg, Q12h, (q8h)
- Oxymorphone: 5, 7.5, 10, 15, 20, 30, 40 mg, Q12h, (q8h)
- Fentanyl: 12, 25, 50, 75, 100 mcg/h patch, Q72h, (q48h)
- Hydrocodone: pending?
- Hydromorphone: pending?

Regular-release opioids for breakthrough pain

- Morphine: 10, 15, 30 mg
- Tramadol: 50 mg
- Codeine: 15, 30, 60 mg (+APAP)
- Hydrocodone: 5, 7.5, 10 mg (+APAP)
- Oxycodone: 5, 7.5, 10, 15, 20, 30 mg (+APAP)
- Oxymorphone: 5, 10 mg
- Hydromorphone: 2, 4, 8 mg
- Tapentadol: 50, 75, 100 mg

- Future “tamper-resistant” and “abuse-deterrent” opioids
Rapid-onset Fentanyl for breakthrough pain or rescue
- Fentanyl "lozenge on a stick"
- Breakthrough pain in opioid-tolerant cancer patients
- Rapid onset (~10-15 minutes)
- Useful in emergency setting as an alternative to IV
- 200 mcg approximately equal to MS 2 mg IV
- No exact equianalgesic conversion, (Start low and titrate to effect)
- Proper administration important!
- OTFC lozenge: 200, 400, 600, 800, 1200, 1600 mcg
- Buccal tablet: 100, 200, 300, 400, 600, 800 mcg

Methadone
- Dual action: mu-agonist / NMDA antagonist
- Better response for neuropathic pain? / Less tolerance?
- Other long-acting opioids are actually short-acting drugs in a time-release matrix
- 6-8 h analgesic α-t½, 48-60+ h elimination β-t½
- Careful dosing because of long t½; usual dosing interval 6-12 h
- Difficult titration (up to 1 week to reach steady-state)
- Dose-response relationship between methadone and other opioids is not linear
- Rotation to or from methadone is challenging
- Cardiac rhythm issues with ↑dosages
- Can be very effective in experienced hands
- Clinically effective; less tolerance? cost-effective

Methadone: conversion
- Edmonton Model: Bruera
  - Calculate target final methadone dose using Morphine Equivalent Dose (MED) guideline
  - Reduce dose of current opioid by one-third each day until discontinued
  - Add dosing of methadone
    - One-third target dose day one
    - Two-thirds of target dose day two
    - Full target dose day three

Opioid adverse effects
(Often dose-related)

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

- Less common
  - Respiratory depression
  - Bad dreams, hallucinations
  - Dysphoria, delirium
  - Myoclonus, seizures
  - Pruritus, urticaria
  - Urinary retention
  - Amenorrhea
  - Sexual dysfunction

Opioid rotation

- Rationale for opioid rotation
  - Differences in receptor activity, cross-tolerance
  - Different intrinsic activity, metabolites
- Development of intolerable side effects despite adequate analgesia
- Choice of rotation empirical although strong opioids should be rotated with other strong opioids
- Reduce equianalgesic dose by 25%–50% with provisos:
  - Reduce less if pain severe
  - Reduce more if medically frail
  - Reduce fentanyl less
  - Reduce methadone more: 75%–90%

Managing the poorly responsive patient

- Better side-effect management
- Opioid rotation
- Pharmacologic strategy to lower opioid requirement
  - Spinal route of administration
  - Add non-opioid or adjuvant analgesic
- Nonpharmacologic strategy added to lower opioid requirement

Pain and Symptom Control in Palliative Care: New Ways to Think About Old Drugs
Larry C. Driver, MD

Adjuvant analgesics / co-analgesics
- Antidepressants (TCAs, SNRIs, SSRIs)
- Anticonvulsants (AEDs)
- NSAIDs
- Steroids, Bisphosphonates
- Topicals (lidocaine, capsaicin, etc.)
- Cannabinoids
- Psychotropics: benzodiazepines, stimulants
- etc.

Procedural interventions
- Nerve blocks – local anesthetics, steroids, alcohol / phenol, etc.
- Tunneled / Implanted spinal infusion systems
- Implanted neural stimulation systems
- Vertebro / Kyphoplasty
- Noncancer e.g., spine pain interventions

et al. Nonpharmacologic treatment
- Education
- Physical therapy
- Psychological approaches
- CAM
- Integrative pain care
- Spiritual care
Collateral opioid issues

- Physiologic dependence
- Psychologic dependence
- Addiction
- Tolerance
- Pseudoaddiction
- Realistic expectations / Hope
  - Cure / Comfort / Care

Cancer fatigue

- “An unusual, persistent, subjective sense of tiredness related to cancer or cancer treatment, despite adequate rest, that interferes with usual functioning”, NCCN
- Generalized weakness, resulting in inability to initiate certain activities
- Easy fatigability and reduced capacity to maintain performance
- Mental fatigue resulting in impaired concentration, loss of memory, and emotional labiality

Fatigue pathophysiology

- Fatigue is a multidimensional syndrome, often with multiple contributing factors
  - Severity of psychological symptoms (anxiety and depression)
  - Pain
  - Sleep disturbances
  - Dyspnea
  - Anorexia
  - Anemia
  - Opioid dose
  - Cytokine dysregulation – IL-6, IL-1β, TNF-α
  - HPA- Axis and neuroendocrine axis dysregulation
  - Autonomic failure
  - Drug interaction – (Benzodiazepines)
Symptomatic treatment of fatigue

- Established drugs-
  - corticosteroids, megestrol acetate
- Investigational drugs-
  - thalidomide, methylphenidate, modafinil, melatonin, fish oil, l-carnitine,
- Counseling
- Physical and occupational therapy

Problem-specific management of fatigue

- 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

Corticosteroids

- Mechanism unknown
- Dose and type unknown
- Duration of benefit unclear
- Use high dose – short time / lower dose – longer time?

Psychostimulants

- Fatigue
- Opioid induced sedation
- Depression / Hypoactive delirium
Cancer Anorexia-Cachexia

- Widely prevalent -
  - Cancer: 50-80%; 4 of 5 pts in adv stages
  - GI > lung > breast 80/60/40
- “A wasting syndrome characterized by loss of muscle and fat caused by an aberrant host response to a wide variety of chronic illnesses”
- “Anorexia usually accompanies cachexia, and is caused by related mediators acting upon the hypothalamus”
- Clinical Outcomes: “Bad Condition”
  - Psychological distress ~35-75%
  - ↓ QoL
  - Shortened survival – leading cause of death: 20-30%
  - Impacts treatment decisions and outcomes of cancer treatment
  - ↑ Morbidity

MacDonald et al., JACS, July 2003

Cachexia a “common pathway” for deteriorating energy balance in end stage disease

- Cachexia not unique to cancer
- RA, SLE, COPD, CHF, HIV, TB, critical illnesses…
- Chronic inflammation is a common link
- Progress on 2 major fronts:
  - Cytokines: major cachexia mediators
  - Elucidation of signaling mechanisms involved in skeletal muscle wasting

Argiles 2005; O’Riordain 1999; Tisdale 2003; Wigmore 2002; Acharyya et al., 2004

Starvation vs. Cachexia

- Starvation:
  - Calorie deficiency due to decreased oral intake
  - Host adapts metabolically
    - Conserves lean mass and increases fat breakdown
  - Appropriate nutrition may reverse these changes
- Cachexia:
  - Loss of fat AND muscle
  - Defective host adaptation
    - Increase acute phase response, muscle loss occurs early
    - feeding does not reverse the macronutrient changes

The screen versions of these slides have full details of copyright and acknowledgements
Management of Anorexia-Cachexia

- Multidimensional syndrome
- Single modality/agent unlikely to be successful
- Multiple domains of treatment preferred
  - Treatment of secondary cachexia
  - Appetite stimulants
  - Anti-catabolic/Anti-metabolic agents
  - Anabolic agents
  - Appropriate nutrition
  - Exercise

Chronic nausea/vomiting

Fainsinger et al., J Palliat Care 1991
71/100 pts (PCU) required Rx for nausea in last wk of life

Reuben et al., (National Hospice Study): Arch Intern Med 1986
62% of terminal cancer patients; prevalence rates of 40% in the last 6 weeks of life; women and younger patients had higher rates

Grond et al., JPSM 1994
1635 pts (pain clinic); Frequency of 27% for nausea, 20% for vomiting

Meuser et al., Pain 2001
- 593 cancer patients treated by a pain service
- nausea (23%), constipation (23%) and dry mouth (20%)

Opioid induced nausea (OIN)

- Opioid initiation or dose escalation
- Tolerance develops rapidly
  - Most nausea abates in 3-4 days
- Risk factors: Higher doses, renal failure
- Mechanisms involved
  - Decreased bowel motility: Gastroparesis, Constipation
  - Stimulation of the Chemoreceptor Trigger Zone
  - Removal of inhibitory input from medulla to the CTZ
  - Increased sensitivity of vestibular center
  - Cortex: memory of previous unpleasant feeling
Pain and Symptom Control in Palliative Care: New Ways to Think About Old Drugs
Larry C. Driver, MD

Nausea management

- General supportive measures in all
  - Oral hygiene, comfortable environment for the patient
  - Frequent small volume food and fluid intake at regular intervals; IV fluids
  - Correct metabolic abnormalities
  - Discontinue unnecessary medications
- Specific interventions as appropriate
  - Etiology, are there multiple etiologies?
  - Manage complications of prolonged N/V
  - Pharmacological agents
  - Non-pharmacological agents
  - Reassessment

Problem-specific treatment

<table>
<thead>
<tr>
<th>Condition</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercalcaemia</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, X-rays</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 catheter</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>Patient 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>Prokinetic agent</td>
<td>Metoclopramide (Reglan)</td>
</tr>
<tr>
<td>Dopamine antagonists</td>
<td>Haloperidol (Haldol), Prochlorperazine (Compazine), Chlorpromazine (Thorazine)</td>
</tr>
<tr>
<td>Histamine H1 receptor blockers</td>
<td>Diphenhydramine (Benadryl), Meclizine (Antivert), Hydroxyzine (Atarax, Vistaril), Promethazine (Phenergan)</td>
</tr>
<tr>
<td>Acetylcholine antagonist</td>
<td>Scopolamine (transdermal), Hyoscyamine, Glycopyrrolate</td>
</tr>
<tr>
<td>Serotonin antagonists</td>
<td>Ondansetron (Zofran), Granisetron (Kytril), Dolasetron (Akozemil)</td>
</tr>
<tr>
<td>Other useful agents...</td>
<td>Decamethasone (Decadron), Dexamethasone (Marine), Lorazepam (Ativan), Ondexolide (Sandostatin)</td>
</tr>
</tbody>
</table>
Acknowledgements

- Sriram Yennu MD* (Fatigue)
- Shalini Dalal MD* (Anorexia-Cachexia, Nausea)

*Department of Palliative Care and Rehabilitation Medicine
The University of Texas M. D. Anderson Cancer Center