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

Larry C. Driver, MD

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

THE UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER *Making Cancer History™*

Larry C. Driver, MD

Professor, Anesthesiology and Pain Medicine

1

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 **2**

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%)

3

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

Larry C. Driver, MD

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**

4

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)

5

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**:2337-2339
4. Breitbart *et al*. *Cancer*, 1989;**63**(11 suppl):2336-4232

6

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

Larry C. Driver, MD

Pain in cancer patients

- Most patients with cancer experience cancer-related pain
- 60% to 90% of patients with advanced cancer will experience significant pain[1-7]
- A 2007 meta-analysis of cancer care over the last 40 years found that 64% of patients with advanced stage disease or metastatic cancer experience pain[8]
- 30-40% of patients have pain at time of cancer diagnosis[9]
- 50-70% have pain during treatment[9]
- 70-80% with advanced disease[9]

1. Daut RL *et al.*, *Cancer* 1982;**50**:1913-1918
2. Cleeland CS. *Cancer* 1984;**54**(11 suppl):2635-2641
3. Foley KM., *N Engl J Med* 1985;**313**:84-95
4. Peteet J., *et al.*, *Cancer* 1986;**57**:1259-1265
5. Donovan M *et al.*, *Pain* 1987;**30**:69-78
6. Greenwald HP *et al Cancer*, 1987;**60**:2563-2569
7. Portenoy RK., *Cancer* 1989;**63**(11 suppl):2298-307
8. van den Beuken-van Everdingen MH *et al.*, *Pain* 2007;**132**:312-320
9. Svendsen KB *et al.*, *Eur J Pain* 2005;**9**(2):195-206

7

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

8

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

9

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

Larry C. Driver, MD

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

10

Relating pain with function

Abilities or activities

Enjoy						
Work						
Mood	Mood					
Active	Active					
Sleep	Sleep					
Walk	Walk	Walk				
Eat	Eat	Eat	Eat	Eat		
Talk	Talk	Talk	Talk	Talk		
Exist	Exist	Exist	Exist	Exist	Exist	
Level 0	Level 2	Level 4	Level 5	Level 6	Level 8	/10

Cleeland *et al.*

11

Pain and symptom assessment

- Pain is a multidimensional experience
  - Physical
  - Psychological
  - Spiritual
  - Social
  - Cultural
  - Situational

  (Collateral symptoms may be multifactorial)

12

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

Larry C. Driver, MD

2 Patients: pain intensity 8/10

(Both patients same cancer and stage)

	Patient #1	Patient #2
Nociception	85%	30%
Somatization	5%	20%
Chemical coping	5%	30%
Tolerance	5%	0%
Incidental Pain	0%	20%
	100%	100%

13

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

14

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

Adapted from AHCPR 1994

15

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

Larry C. Driver, MD

Therapeutic approaches: cancer pain

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

Joint Commission on Accreditation of Healthcare Organizations; pain management today; in: *Pain Assessment and Management: An Organizational Approach;* Joint Commission in Accreditation of Healthcare Organizations. Oakbrook Terrace, IL; 2000:1-6

16

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

17

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

18

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

19

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?

20

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

21

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

Larry C. Driver, MD

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

22

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-$t_{½}$,48-60+ h elimination β-$t_{½}$
- Careful dosing because of long $t_{½}$; 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

McDonnell FJ, Sloan JW and Hamann SR (2000), *Curr Oncol Rep* **2**(4): 351-7; Hewitt DJ (2000); *Clin J Pain* **16**(2 Suppl): S73-9; *Hematol Oncol Clin North Am* 2002 Jun;**16**(3):543-55

23

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

24

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

Larry C. Driver, MD

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

25

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%

Mercadante S, *Cancer* 1999;**86**:1856-66

26

Managing the poorly responsive patient

- Better side-effect management[12]
- Opioid rotation[12]
- Pharmacologic strategy to lower opioid requirement
  - Spinal route of administration
  - Add non-opioid or adjuvant analgesic[8,9]
- Nonpharmacologic strategy added to lower opioid requirement[8]

8. McCaffery M, Portenoy RK. Overview of three groups of analgesics; in: McCaffery M, Pasero C. *Pain: Clinical Manual*. 2nd ed. St. Louis, MO: Mosby, Inc; 1999:108-128
9. American Cancer Society. Nursing principles of pain management; available at: http://www.acs-tx.org /Texas.nsf/pages/PainManagementCourse; accessed August 15, 2002
12. American Pain Society; *Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain;* 4th ed. Glenview, IL: American Pain Society; 1999

27

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.*

28

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

29

et al. Nonpharmacologic treatment

- Education
- Physical therapy
- Psychological approaches
- CAM
- Integrative pain care
- Spiritual care

30

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

Larry C. Driver, MD

Collateral opioid issues

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

31

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

32

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)

33

Symptomatic treatment of fatigue

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

34

Problem-specific management of fatigue

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

35

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

36

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

Larry C. Driver, MD

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

DeWys 1980; Vigano 2000; Wigmore 1997, Andreyev 1998; Bruera 1997
MacDonald *et al.*, JACS, July 2003

37

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)

38

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

39

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

Larry C. Driver, MD

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

40

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%)

41

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

42

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

43

Problem-specific treatment

Hypercalcaemia	Hydration, bisphophonates
Opioid toxicity	Opioid rotation/decrease dose
Constipation	Aggressive bowel regimen, ? X-rays
Gastric ulceration	PPIs, H2-antagonists
Infection	Antibiotics
Tense ascites	Paracentesis, consider IP catheter
Anxiety	Counseling, Anxiolytics
Brain metastases	Radiation therapy, Steroids
Malignant bowel obstruction	? Pt prognosis; Resection, bypassing, or stenting, venting gastrostomy

44

Anti-emetic agents

Class	Medication
Prokinetic agent	**Metoclopramide (Reglan)**
Dopamine antagonists	***Haloperidol (Haldol),*** Prochlorperazine (Compazine), Chlorpromazine (Thorazine)
Histamine H1 receptor blockers	Diphenhydramine (Benadryl), Meclizine (Antivert), Hydroxazine (Atarax, Vistaril) Promethazine (Phenergan)
Acetylcholine antagonist	Scopolamine (transdermal), **Hyoscyamine,** Glycopyrrolate
Serotonin antagonists	Ondansetron (Zofran), Granisitron (Kytril) Dolasetron (Anzemet)
Other useful agents…	**Dexamethasone (Decadron),** Dronabinol (Marinol), Lorazepam (Ativan), Octreotide (Sandostatin)

Dickerson; *Eur J of Palliat Care* 1993

45

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

Larry C. Driver, MD

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

46

HENRY STEWART TALKS

47