


A Pharmacist's Guide to Practical Cancer Pain Management

**Kimberley Stefaniuk, BSP, RPEBC
Clinical Pharmacist, Palliative Care
Princess Margaret Hospital
Toronto, Canada**




Disclosure

- Kimberley Stefaniuk, BSP, RPEBC has received consulting fees from Wyeth and Bayer
- 



Learning Objectives

At the end of this session you will be able to:

- List five common causes of cancer pain
 - Select and justify appropriate therapeutic options for cancer, related pain
 - Implement one new patient counseling strategy and one practice change
- 



Impact of Uncontrolled Cancer Pain

- Functional impairment
 - Mood, sleep, exercise, appetite
- Psychological distress
 - Depression, anxiety, delirium, suicide
- Spiritual distress
- Decreased quality of life
- Burden to family, caregivers



Causes of Acute Cancer Pain

- Diagnostic procedures
- Therapeutic procedures
- Analgesic techniques
- Post, operative pain
- Infection
- Chemotherapy
- Hormone therapy
- Immunotherapy
- Radiation
- Tumor, related pain

Causes of Chronic Cancer Pain

- Nociceptive pain
 - Musculoskeletal pain
 - Paraneoplastic pain syndromes
 - Neoplastic involvement of viscera
 - Osteonecrosis
 - Lymphedema
- Neuropathic pain
 - Peripheral neuropathies
 - Post, surgical pain syndromes
 - Post, radiation pain syndromes
 - Plexopathy
 - Spinal cord compression
 - Shingles



Debility, Related 1 Pain

- Chronic konstipation
- Mucocutaneous ulceration
- Thromboses
- Bedsores
- Cachexia
- Limb1 ischemia
- Candidiasis, 1 infections

Mechanism of Acute Pain

Step 3:
Pain Perception

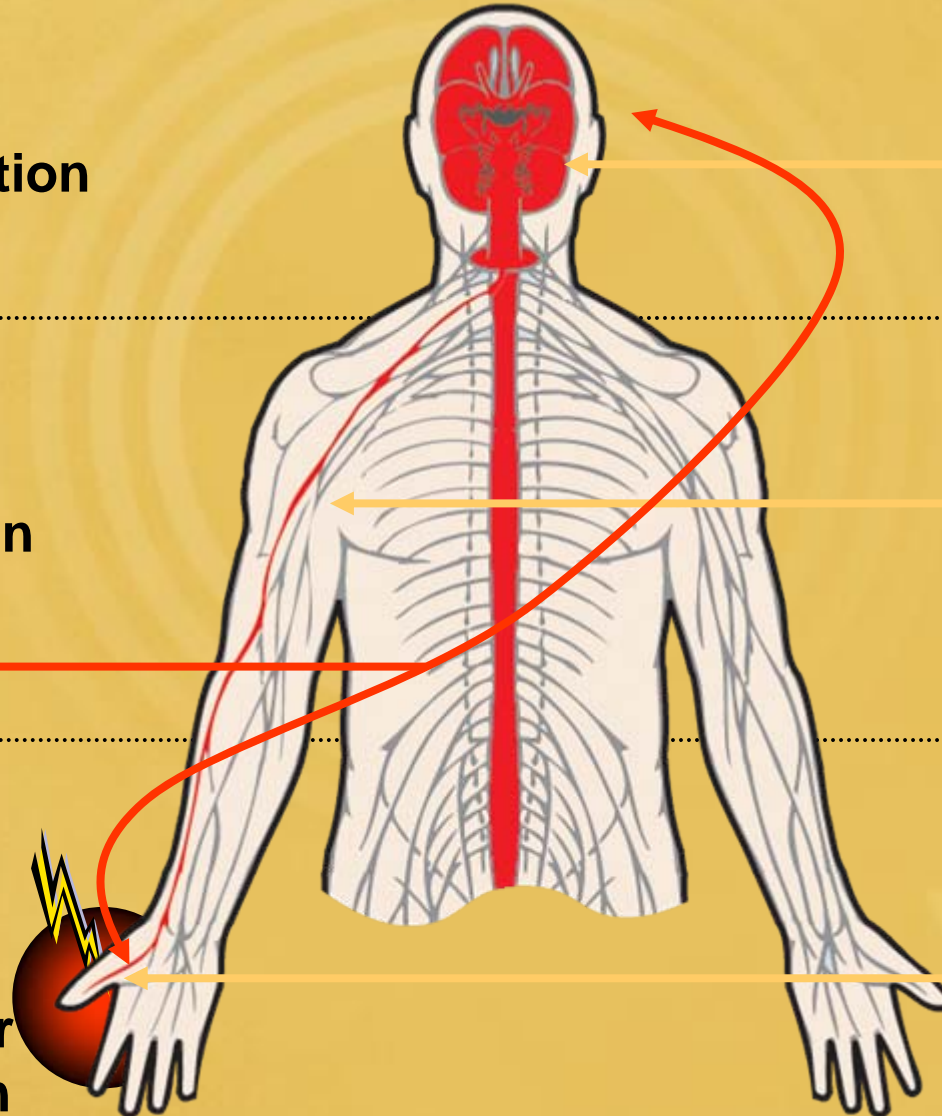
Enkephalins
Endorphins

Step 2:
Signal Transmission
A-delta fibers
& *C-fibers*

Substance P
Glutamate
Aspartic Acid
Nitric Oxide

Step 1:
Peripheral Stimulation & Nociceptor Sensitization

Prostaglandins
Bradykinin
Histamine
Leukotrienes





Mechanism of Chronic Pain

Step 1: Peripheral stimulation and sensitization

Step 2: Signal transmission

Step 3: Pain perception

Step 4: Central sensitization



Classification of Pain

- Nociceptive or neuropathic
 - “Inflammatory” replacing “nociceptive”
- Important to differentiate types of pain
 - Treatment is guided by the pain mechanism/generator
- Acute or chronic



Nociceptive (inflammatory) Pain

- Somatic pain
 - Aching, throbbing, stabbing, pressure
 - Well, localized
- Visceral pain
 - Gnawing, cramping, aching, sharp, and/or stabbing sensations
 - Not well, localized



Neuropathic Pain

- Caused by lesions or damage in the central or peripheral nervous system
 - Burning, numbness, tingling, touch sensitivity, sharp and shooting sensations (lancinating pain), or electric shocks
 - Dermatomal distribution
 - Hyperalgesia, allodynia




Other Considerations

- Multiple pains
- Multiple mechanisms
- Simultaneous mechanisms
- Additional mechanisms
 - Endothelin, in prostate cancer
 - Nerves in bone marrow, periosteum
 - Acidotic environment around tumors
 - Cytokine release from astrocytes



Assessment

- Don't **l**assume **l**it **l**has **l**been **l**done
 - Expect **l**it
 - Look **l**for **l**it
 - Assess **l**it
 - Believe **l**your **l**patient
 - Good **l**assessment **l**is **l**good **l**treatment
- 



Pain Assessment

- Quality
- Onset
- Duration
- Severity
- Location
- Radiation
- Aggravating factors
- Relieving factors
- Description of each pain
- Time frame
- Impact on daily life
- Medication history
- Fears, beliefs
- Other symptoms
- Thorough but rapid



Principles of Pain Management

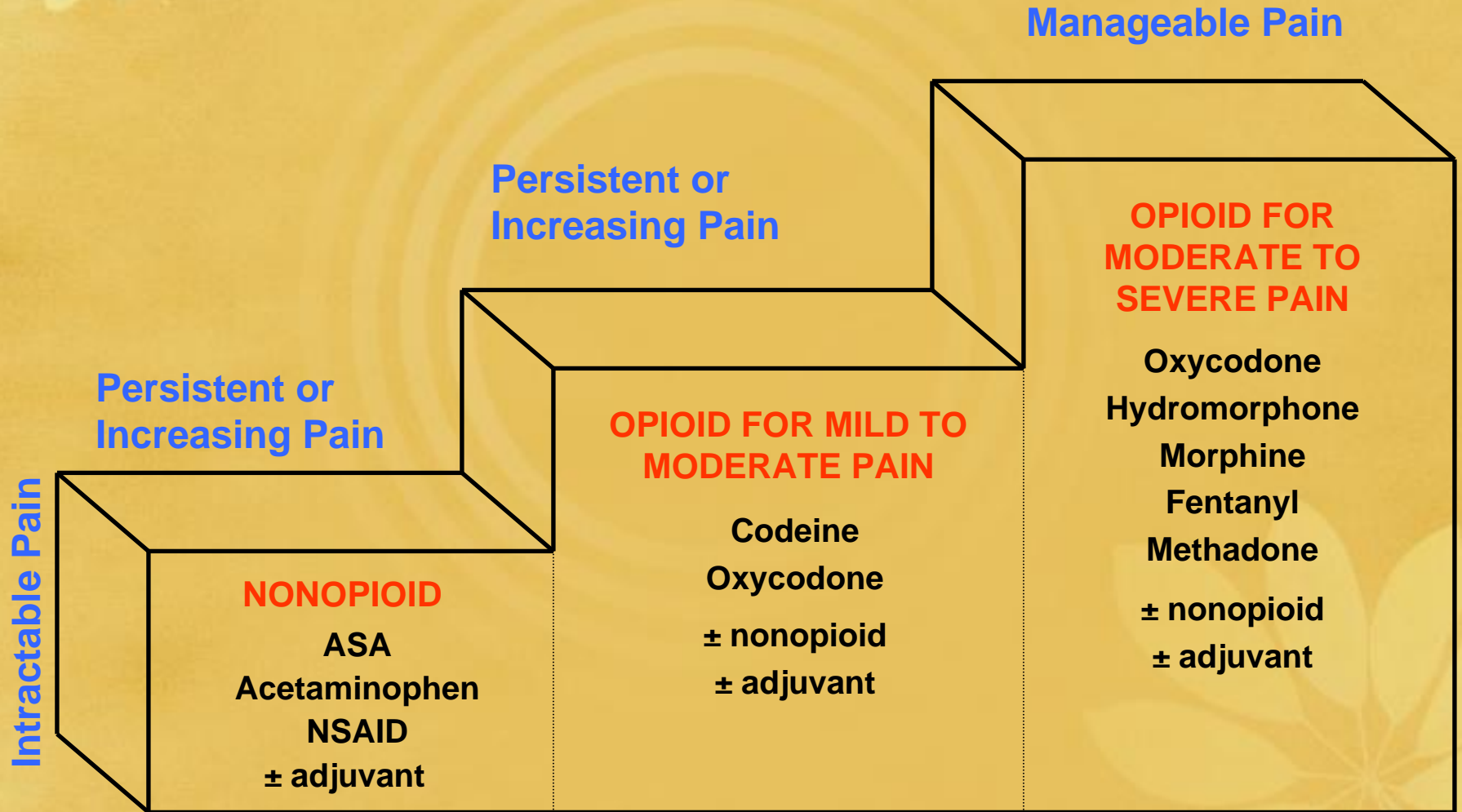
- Intervene promptly
- Match analgesic to pain severity
- Oral whenever possible
- Routine and breakthrough
- Titrate to effect
- Monitor frequently
- Adjuvants at any stage
- Proactive symptom management



Treatment

- Team approach
- Chemotherapy
- Radiation
- Surgery
- Psychological intervention
- Caution!
 - Transcutaneous electrical nerve stimulation (TENS), chiropractic, massage, acupuncture, heat or cold, and other therapies

WHO Analgesic Ladder





Opioids

- Stimulate opioid receptors
- Safe and effective
- No ceiling
- Few drug interactions
- Predictable and manageable side effects
- Allergies, addiction, respiratory depression rare
- Full agonists equivalent equipotent doses

Waller CA, Nunnally J. *Handbook of Palliative Care in Cancer*, 2nd ed. Butterworth-Heinemann, 2000. Gallagher R. *Managing Cancer Pain*. The Canadian Healthcare Professionals Reference, The Canadian Pain Society, 2005.



Equipotent Doses of Opioids

Opioid	Oral Dose	SC/IV Dose
Morphine	10mg	3- 5mg
Codeine	100mg	5- 60mg
Fentanyl	-	0.075-0.125mg
Hydromorphone	2mg	1mg
Oxycodone	5mg	2- 3mg
Methadone	Highly variable	-


Waller A, Caroline, N. Handbook of Palliative Care in Cancer, 2nd ed. Butterworth Heinemann, 2000.; Gallagher R. Managing Cancer Pain. The Canadian Healthcare Professional's Reference, The Canadian Pain Society, 2005; Compendium of Pharmaceuticals and Specialties, Canadian Pharmacists' Association 2008.

SC = subcutaneous; IV = intravenous.



Opioid Dosing

- Around the clock dosing
 - Sustained release products
 - Immediate release products for breakthrough pain
- “Start low and go slow”
 - Elderly or children
 - Hepatic or renal dysfunction
- No ceiling effect



Opioid Dose Adjustments

- Dependent on time to, peak effect of medication
 - SR: 14-72 hours, SR Oxycodone: 12-24 hours
- Can make earlier if patient is experiencing troublesome adverse effects
- Consider metabolite accumulation in renal dysfunction

Waller A, Caroline N. Handbook of Palliative Care in Cancer, 2nd ed Butterworth Heinemann, 2000. Gallagher R. Managing Cancer Pain. The Canadian Healthcare Professional's Reference, The Canadian Pain Society, 2005.



Opioid Adverse Effects


- Sedation
- Nausea and vomiting
- Constipation
- Myoclonus
- Confusion
- Respiratory depression



Opioid Rotation

- Why?
 - Intolerable adverse effects
 - Lack of response to increasing doses of a particular opioid
- How?
 - Calculate total daily opioid dose
 - Determine equivalent dose of new opioid
 - Decrease dose by 25 to 50%

Waller A, Caroline, N. *Handbook of Palliative Care in Cancer*, 2nd ed. Butterworth Heinemann, 2000.; Gallagher R. *Managing Cancer Pain*. The Canadian Healthcare Professional's Reference, The Canadian Pain Society, 2005.





Adjuvant Analgesics

- Acetaminophen
- NSAIDs/COX-2 inhibitors
- Tricyclic antidepressants
- Anticonvulsants
- Bisphosphonates
- Steroids
- Others


Waller CA, Nunn JH. *Handbook of Palliative Care in Cancer*, 2nd ed. Butterworth-Heinemann, 2000. Gallagher R. *Managing Cancer Pain*. The Canadian Healthcare Professional's Reference, The Canadian Pain Society, 2005.



Nonopioid Analgesics

- Acetaminophen
 - Use carefully in hepatic dysfunction
 - Caution patients about hidden acetaminophen
- NSAIDs
 - Traditional NSAIDs, COX, 2
 - No ASA
 - Caution in renal dysfunction, GI upset, lowered platelets

Waller A, Caroline, N. *Handbook of Palliative Care in Cancer*, 2nd ed. Butterworth Heinemann, 2000.; Gallagher R. *Managing Cancer Pain*. The Canadian Healthcare Professional's Reference, The Canadian Pain Society, 2005.



Limitations of Nonopioids

- Not effective alone for moderate to severe pain
- Minimal efficacy in neuropathic pain
- Ceiling effect
- Adverse effects

Gallagher R. *Managing Cancer Pain*. The Canadian Healthcare Professional's Reference, The Canadian Pain Society, 2005; Gehdod R. *Cancer Pain Management*. *Indian J Anaesth*, 2006; 150(5):375,390.





Antidepressants

- Tricyclics— best documented therapy for neuropathic pain
 - Amitriptyline, nortriptyline, imipramine, desimipramine equally efficacious
 - Effect independent of antidepressant activity
 - Titrate to effective dose q 3 to 4 days
 - Importance of oral hygiene and managing xerostomia and constipation

Tricyclic Antidepressant Dosing

Drug	Dosing Steps	Comments
Amitriptyline Desipramine Imipramine Nortriptyline	Titrate to effect <70 years: 25, 50, 75, 100, 125, 150 mg qd, 3, 4 days >70 years: 10, 20, 30, 40, 50, 75 mg qd, 3, 4 days	Generally, amitriptyline should not be used, especially in elderly. There is less severe dry mouth and sedation with other drugs. Do not use if 2° or 3° heart block on ECG, arrhythmias, ↑ QTc.

ECG = electrocardiogram.

Dworkin RH, et al. *Arch Neurol.* 2003;60:1524-34.



Other Antidepressants

- Disappointing results with SSRIs, SNRIs
 - Higher NNT than TCAs
- Role for duloxetine in diabetic neuropathy
 - At 60 mg daily, 15% of patients treated reported a 30% sustained reduction in pain
 - BUT over 87% of patients experienced marked treatment adverse effects
- More study needed for trazodone, mirtazapine and others


SSRI = selective serotonin reuptake inhibitors; SNRI = serotonin-norepinephrine reuptake inhibitors; NNT = number needed to treat; TCA = tricyclic antidepressants.

Goldstein DJ, et al. *Pain*. 2005;116:109-18; Raskin J, et al. *Pain Med*. 2005;6:346-56; Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. Cochrane Database of Systematic Reviews, The Cochrane Collaboration 2005, Issue 3.





Anticonvulsants

- Similar mechanism for seizure control
 - Gabapentin: 1300 to 1400 mg/day
 - Pregabalin: 150 to 1600 mg/day
 - Carbamazepine: 1600 mg/day
 - Valproic acid: 1100 to 12000 mg/day
 - Lamotrigine: 150 to 1600 mg/day
- 

Bisphosphonates and Steroids

- Bisphosphonates
 - Pamidronate: 90 mg iv q 4 weeks
 - Zoledronate: 4 mg iv q 4 weeks
 - Clodronate: up to 1600 mg po daily
- Steroids
 - Dexamethasone 4 to 16 mg/day



Tramadol


- Potency = codeine 30 mg + acetaminophen 325 mg
- Short, term indication only
- Drug interactions, potential seizure
- Limited role in cancer pain

Waller A, Caroline, N. Handbook of Palliative Care in Cancer, 2nd ed. Butterworth Heinemann, 2000.





Methadone

- Opioid and NMDA receptor activity
 - Use for opioid tolerance, neuropathic or refractory pain
 - Variable equipotency
 - At lower doses, 1:1 with morphine; at morphine doses of >300 mg, methadone is at least 10X potency of morphine
 - CYP 450 metabolism: many drug interactions
- 




Morley and Makin

- Use one-tenth of 24-hour oral morphine equivalent (maximum 30 mg per dose) q 3h prn
- If patient uses >300 mg oral morphine per day, convert to 30 mg q 3h prn
- On day 6, add up 24-hour total of methadone on days 4 and 5
- Convert daily amount to q 12h dosing schedule
- Use 1/4 of routine methadone dose q 3h prn for breakthrough pain

prn = as needed.

Morley J, Makin M. The use of methadone in cancer pain poorly responsive to other opioids. *Pain Rev* 1998;5:51, 58.





Edmonton Method

- Rotating from another opioid
 - Day 1: ↓ morphine by 50%; replace with methadone at 10:1 ratio q 18h
 - Day 2: ↓ morphine by 50%; ↑ methadone only if moderate, severe pain. Use short-acting opioid for breakthrough pain
 - Day 3: D/C morphine. Give methadone q 18h + 10% of daily dose as rescue q 13h prn

Bruera E, Pereira J, Watanabe S, Belzile M, Kuehn N, Hanson J. Opioid rotation in patients with cancer pain. A retrospective comparison of dose ratios between methadone, hydromorphone, and morphine. *Cancer* 1996;78:852, 7.1

DC = discontinue.




Very, Very, Very Approximate Methadone Dosing and Conversion

Total Daily Oral Morphine Equivalent	Estimated Daily Oral Methadone Requirement
<100mg	20- 30%
100-300mg	10- 20%
300- 600mg	8- 12%
600- 1000mg	5- 10%
>1000mg	<5%



Ketamine

- Rapid, acting general anesthetic with analgesic properties
 - NMDA receptor antagonist
 - May attenuate as well as reverse opioid tolerance, resulting in sedation and respiratory depression
 - Decrease opioid dosage by 25 to 50% when ketamine is commenced
 - Monitor frequently
- 




Ketamine

- Decrease opioid dosage by 25 to 50% when ketamine is commenced
- Maintain opioid breakthrough
- Consider haloperidol 1 mg po bid or midazolam 2.5 to 5 mg sc for CNS effects
 - Vivid dreams, hallucinations, delirium, agitation, excess sedation

CNS = central nervous system; bid = twice daily.

Fitzgibbon E, Viola R. *J Pall Med.* 2005;8:49-57.

Bell RF. *Pain.* 1999;83:101-3.



Suggested Ketamine Order

- Ketamine 10 mg/mL concentration via infusion pump as a continuous subcutaneous infusion
- Usual initial rate 2 mg/hour subcutaneously
- Titrate q 24 hours in 1 mg/hour increments until 4 mg/hour
 - If needed to effect or intolerable side effects
- Thereafter, increase by 2 mg/hour up to a maximum daily dose of 700 mg/day



Ketamine “Burst”

- Test dose of 12.5 to 15 mg subcutaneous ketamine
- Commence escalating doses of ketamine
- When stable, consider reducing opioid by 50% daily if possible
- May switch to oral but **CAUTION:**
 - When converting from subcutaneous TO oral, DECREASE dose by 50%

Ketamine1 “Burst”

Starting dose 100 mg.

- a. If effective, continue three days then cease.

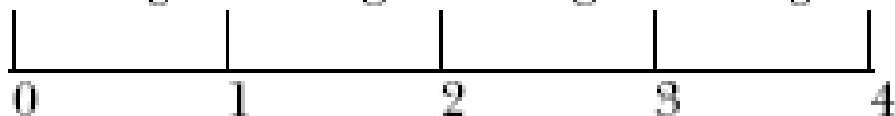
100 mg 100 mg 100 mg Stop



If 100 mg ineffective after 24 hours, increase to 300 mg.

- b. If 300 mg effective, continue three days then cease.

100 mg 300 mg 300 mg 300 mg Stop



If 300 mg ineffective after 24 hours, increase to 500 mg.

- c. 100 mg 300 mg 500 mg 500 mg 500 mg Stop



Cease at day 5 whether effective or not, or earlier if ineffective and significant adverse effects.



Cannabinoid Receptors

- **CB₁ receptors in pain pathways**
 - Brain, spinal cord, nerve terminals in the CNS
 - Controls synaptic neurotransmission by retrograde signaling
 - ↓ pain neurotransmitters, eg, GABA, glutamate, etc
- **CB₂ receptors in immune cells**
 - Central and peripheral
 - B and NK cells
 - Modulate immune function through release of cytokines

CB = cannabinoid receptor; GABA = gamma-aminobutyric acid.

Russo EB, Guy GW. *Med Hypotheses*. 2006;66:234-46; Walker JM, et al. *Pain Res Manage*. 2001;6:74-9;

Pertwee RG. *Pharmacol Ther*. 1997;74:129-80.



Effects of Δ^9 -Tetrahydrocannabinol (THC)

- Psychoactivity
- Analgesic
 - Neuropathic pain
- Antispasticity
- Antiemetic
- Anti-inflammatory
- Appetite stimulation
- Reduced intraocular pressure
- Bronchodilation
- Oxytocic



Effects of Cannabidiol (CBD)

- Anti-inflammatory
- Analgesic
- Anticonvulsant
- Sedative
- Anxiolytic
- Antipsychotic
- Anorectic
- Antimicrobial



Available Cannabinoids

- Dronabinol
 - Synthetic Δ^9 -tetrahydrocannabinol
 - Absorption slow, unpredictable
 - Dysphoria with higher doses
 - Equivocal study results

- Nabilone
 - Synthetic cannabidiol
 - Better oral absorption
 - Analgesic trials underway



Available Cannabinoids

- Medical marijuana
 - Smoking may not be possible for very ill patients
 - Variable dose
- SativexTM
 - 9, tetrahydrocannabinol and cannabidiol 1:1

Cannabinoids

Drug	Formulations	Usual Daily Dose
Dronabinol (Marinol™)	5 and 10 mg capsules	5- 20 mg
Nabilone (Cesamet™)	0.5 and 1.0 mg capsules	Rarely beyond 4 mg
THC/CBD 1:1 (Sativex™)*	Buccal spray: 2.7 mg THC and 2.5 mg CBD per spray	4- 8 sprays per day. Dose may be increased up to 21 sprays per day
* Only cannabinoid approved for use in cancer pain		

Marinol™ (dronabinol) Product Monograph, Solvay Pharma, 2007.

Cesamet™ (nabilone) Product Monograph, Valeant Pharmaceuticals, 2007.

Sativex™ Product Monograph, Bayer Inc, 2007.



Pharmacokinetics:1 Cannabis

Cannabis Form	Onset	Peak	Duration
Smoked	Seconds to minutes	15 – 30 minutes	2 – 3 hours
Oral	30 – 90 minutes	2 – 3 hours	4 – 12 hours
THC/CBD 1:1	30 – 150 minutes	1.5 – 4 hours	6 – 8 hours




Sativex™

- Contains 9, tetrahydrocannabinol and cannabidiol in a 1:1 ratio
- Substantial clinical data, including over 101 Phase II/III trials
 - Over 2500 patients participated to date
 - Over 1000 patient-years of safety data
 - Intractable, treatment-resistant patients who remained on current medication throughout trial



Dose

- High inter, patient variability
- Day 1: maximum 1 spray q 4h, 4 doses maximum
 - Maximum 10 sprays per day???
- Doses spread evenly throughout day
- Titrate gradually as needed and tolerated
- Most patients require 2 sprays or less





Adverse Effects

- Dizziness
- Sleepiness
- Fatigue
- Bad taste
- Feeling intoxicated
- Hold doses until resolved
- May increase interval or reduce subsequent doses
- No evidence of clinically relevant drug-drug interactions between cannabinoids and opioids




Role of the Pharmacist

- Distribution functions
 - Prompt, efficient medication supply
 - Adequate stock
 - Accurate dispensing
 - Compounding
 - Storage and transport
 - Explaining laws to patients
- 




Drug Access

- Opioids, methadone
 - Unique preparations
 - Regional pharmacy list
 - Drug access algorithm
 - Educate about processes
- 





Pharmacy Considerations

- Drug selection
 - Dosage forms, characteristics and routes
 - Compliance aids
 - Tips to aid swallowing
 - Snap caps
 - Q18h vs q12h
- 




Role of the Pharmacist

- Clinical functions
 - Recommend drugs and doses
 - Conversions
 - Anticipate/prevent side effects
 - Medication history
 - Minimize polypharmacy
 - Drug information and education
 - Seamless care
- 




Role of the Pharmacist

- Advocacy
 - Speak up
 - Don't back down
 - Communicate, negotiate
 - Educate
 - Cultural issues
 - Link to services
 - Empower
- 




Counseling

- Not just opioids
 - Written and verbal
 - Patient, family, and caregiver
 - Medication schedule
 - Simple, frequent
 - Pain control objectives
 - Resources available
- 




Counseling Your Patients

- Dose
 - Tapering or escalating
 - Administration
 - Routine and prn
 - Proper use of route
 - Dosage form
 - Can the medication be crushed or administered via tube
 - Unusual features
- 

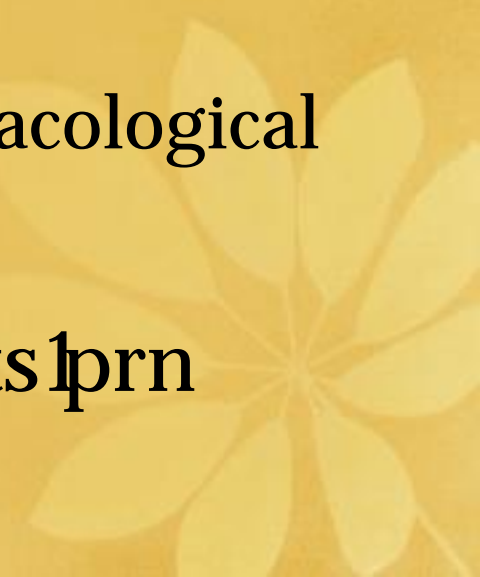


Counseling Your Patients

- Indication
 - Expected time to benefit
 - Duration of therapy
 - Treatment goals
 - Compliance
 - Drug interactions
 - Side, effect management
- 




Counseling Your Patients

- Monitoring parameters
 - When to call the doctor
 - Address fears, issues
 - Addiction, social stigma, costs, safety
 - Multimodal approach
 - Adjuvants and opioids, nonpharmacological
 - Storage
 - Modify patient information sheets prn
- 




Monitoring

- Follow, up crucial
 - Appropriate time frame
 - Frequent until stable
 - Issues, effects
(therapeutic and adverse)
 - Communicate
 - Right things in place?
- 




Developing a Pharmacy Care Plan

- Assessment
 - Medication history
 - Patient's understanding of condition
 - Issues
 - Treatment plan
 - Pharmacological and nonpharmacological
 - Monitoring strategy
- 



Conclusion

- Multidisciplinary, multimodal therapy is most effective
 - Cancer patients have unique needs and considerations when managing pain
 - Pharmacist is vital member of interdisciplinary pain team
- 



**Make a difference for your
patients**



Contact Information

kimberley.stefaniuk@uhn.on.ca

