METHADONE IN THE MANAGEMENT OF CANCER AND NON-CANCER PAIN

Program Outline

00:00	Welcome, Introductions, Housekeeping
00:15	Large Group Interactive Discussion
01:00	Small Group Case Scenarios
02:00	Break
02:15	Small Group Case Scenarios
03:00	Large Group Q & A
03:45	Wrap Up – Program Evaluations

Welcome

- **Program Development**
  - The content and format of this program were developed by Dr. Deborah Robinson, Dr. Larry Librach and Dr. Charmaine Jones
  - Additional collaborative input or shared knowledge from previous Methadone presentations received from Dr. Vincent Maida, Dr. Dwight Moulin, Dr. Donna Ward, and Dr. Brian Kerley, Dr. Paul Daenick
- **Purpose of Program**
  - To improve the knowledge base and clinical skills of physicians who are already using or are considering the use of methadone for pain control

Housekeeping

- **Mainpro C Requirements**
  - This program meets the accreditation criteria of the CFPC for XX Mainpro-C credits
  - Thank you for completing the pre-participation needs assessment
  - Please complete the program evaluation form at the completion of today's events
  - Don't forget to complete the post-participation self-reflective activity in two months time

Housekeeping

- **Course Manual Contents**
  - Welcome Letter
  - Evaluation Forms
    - Pre-participation needs assessment
    - Program evaluation form
    - Post-participation self-reflective activity
  - Introduction Slides and Interactive Presentation Slides
  - Case Scenarios
  - Sample Physician, Pharmacist, Patient Info Sheets
  - References
  - Methadone Exemption Application
  - Additional Handouts – Articles, resources, etc.

Acknowledgements

- The development and administration of this project has in part been made possible by an unrestricted educational grant from Pharmascience

- Special thanks to the local coordinators for today's educational event

Learning Objectives

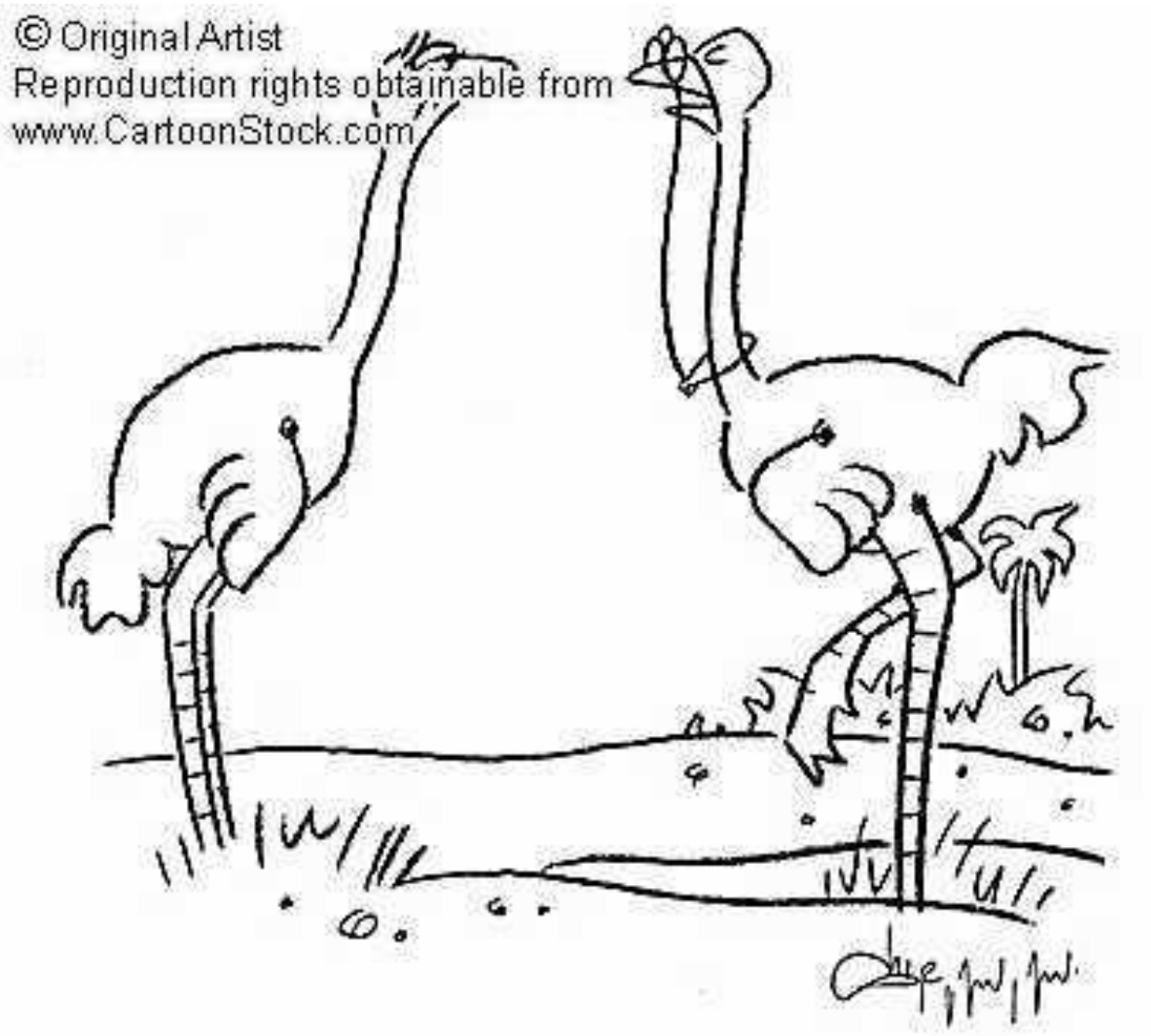
At the completion of the interactive presentation, participants will be able to:

- Describe reasons for using methadone in cancer and non-cancer pain
- Discuss the unique pharmacologic characteristics of methadone including drug interactions, adverse effects, safety issues, available formats and costs

Learning Objectives

After working through the case-based scenarios the participant will be able to:

- Describe how to initiate and titrate methadone safely and effectively
- Describe the process for obtaining exemption from the Canada Health Act to prescribe methadone
- Discuss Some of the practical aspects of prescribing methadone and (ie resource limitations) special circumstances for using methadone (ie the patient going for surgery)



"Take two aspirin and stick your head in the sand."

Presentation Outline

- **Background Information/Review of Pain**
  - Definitions, Classification and Treatment Overview
  - Anatomy and Physiology of Pain
  - Challenges in Pain Control
  - Overview of Opioid Analgesics

- **Methadone**
  - Pharmacology
  - Indications, Contraindications
  - Drug Interactions
  - Schedules for conversion to Methadone

Definitions, Classification and Treatment Overview

The Pain Experience

- **Defining Pain:**
  - An unpleasant sensory and emotional experience associated with actual or potential (tissue) damage
- **The Pain Experience:**
  - Interplay between the actual pain syndrome with physical, psychosocial and spiritual components, technical aspects of taking medication, management of side effects, interaction with caregivers, and interaction with healthcare professionals
- **The Ultimate Goal:**
  - To relieve suffering and improve/optimize quality of life

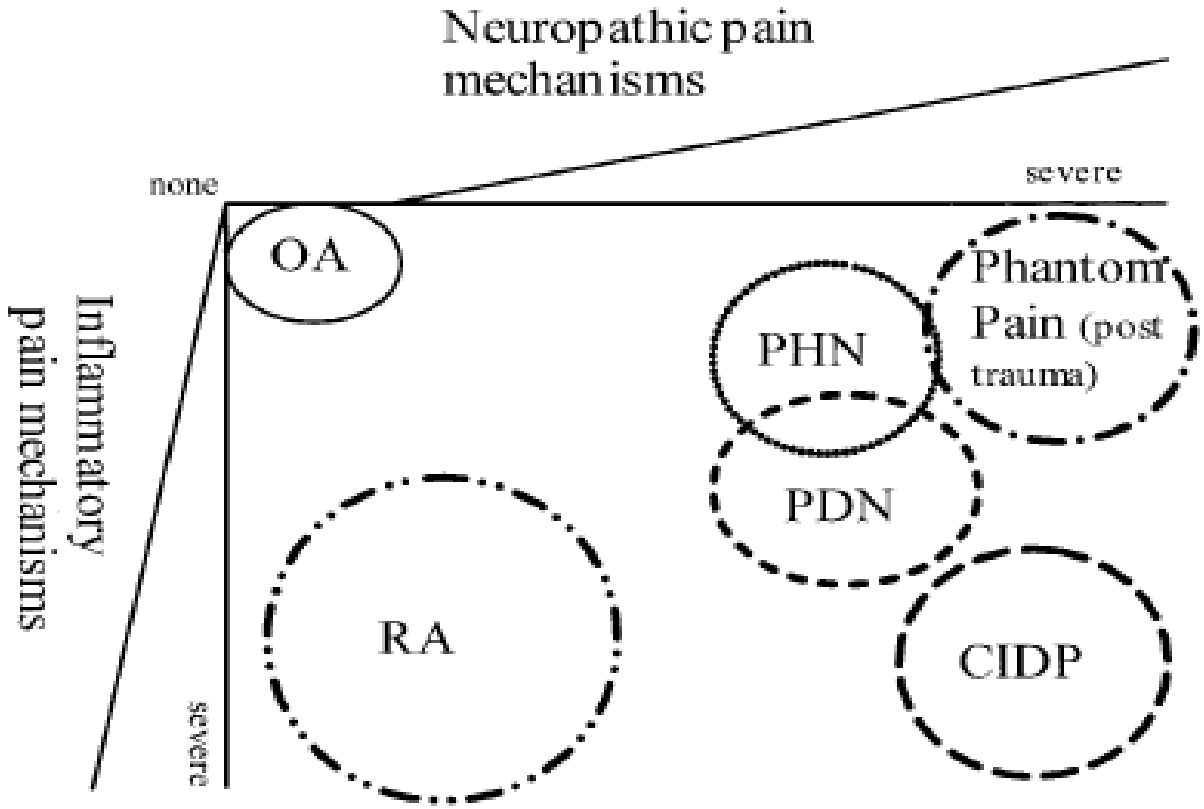
Classification of Pain

- **Inflammatory Pain: Pain in response to tissue injury and the resulting inflammatory process**
  - **Somatic:** constant or intermittent, aching, localized, superficial or deep
  - **Visceral:** constant, aching, squeezing, cramping, poorly localized and sometime referred

Classification of Pain

- **Neuropathic Pain: Pain in response to damage or dysfunction of either peripheral or central neurons**
  - **Dysesthetic:** constant burning, paresthesias, tingling, occasionally radiates
  - **Neuralgic:** lancinating, shooting

Mixed Etiology Pain



"I keep getting pins and needles in my arms."

Treatment Options

- **Non-Pharmacologic**
  - Chaplain, music, therapeutic touch, conversation
- **Inteventional**
  - TENS, Capsaicin, Baclofen, Nerve blocks
  - Physiotherapy, Massage, Surgery, Accupuncture
  - Radiation, Behavioural Medicine
- **Management of Other Symptoms**

Treatment Options

- **Pharmacologic**
  - Inflammatory
    - Opioids, NSAIDs, Dexamethasone
  - Neuropathic
    - Opioids, TCAs, SSRIs, Anticonvulsants
    - Lidocaine, NMDA antagonists

Anatomy and Physiology of Pain

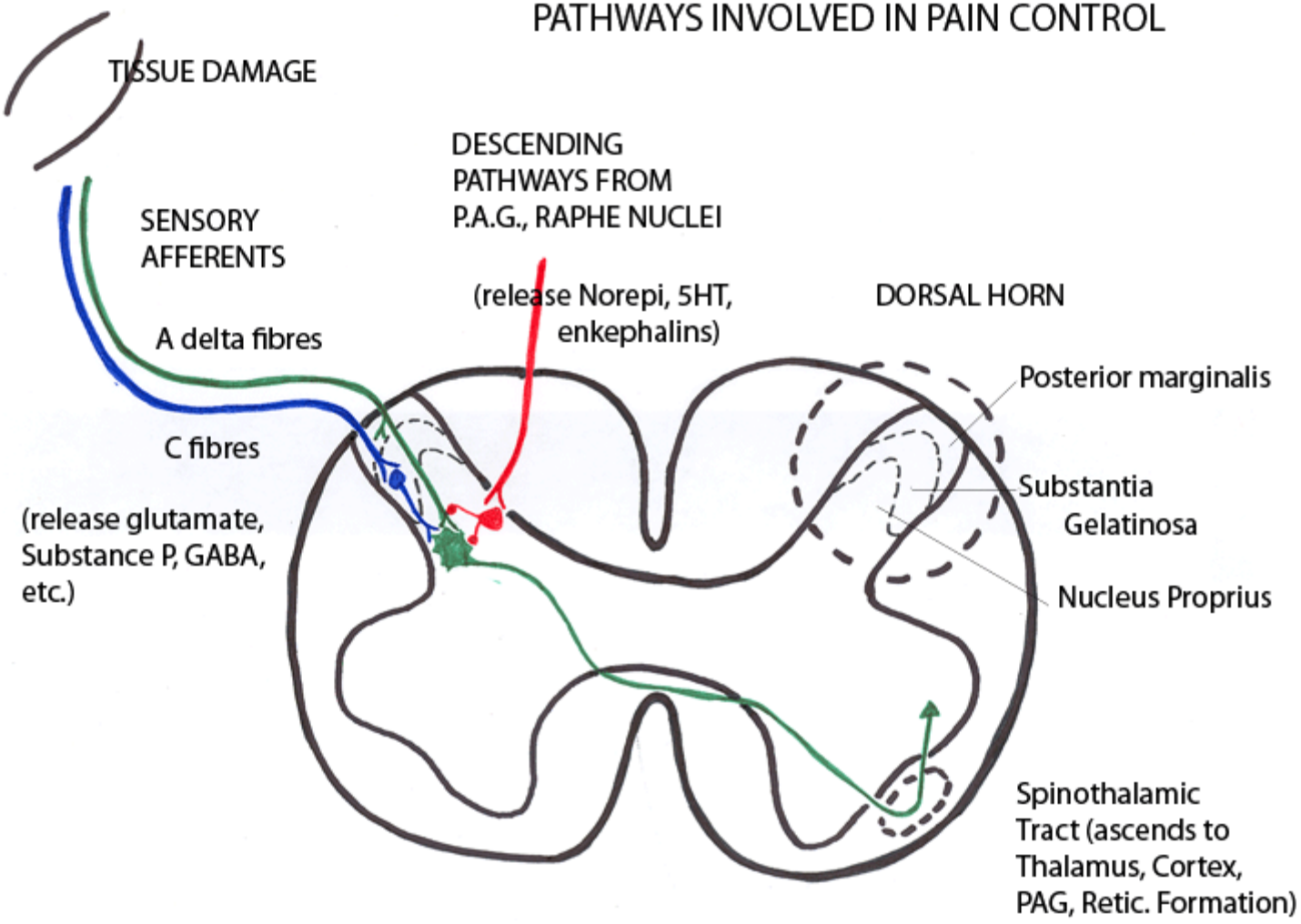
Anatomy & Physiology of Pain

- **The Players in the Ascending Pathway:**
  - Tissue/Nerve Damage and the subsequent release of inflammatory and pain perception mediators which stimulate nociceptors
  - Primary sensory afferents which release glutamate and substance P (tissue to dorsal horn of the spinal cord)
    - Fast A-delta fibres and Slow C fibres
  - Secondary sensory afferents (Spinothalamic tract)
  - Dorsal horn interneurons

Anatomy & Physiology of Pain

- **The Players in the Descending Pathway:**
  - Descending inhibitory neurons release endorphins, enkephalins, and dynorphin which bind to opioid receptors
  - Dorsal Horn Interneurons
    - Enkephalins bind to delta opioid receptors on inhibitory interneurons
  - Primary afferent nerve terminals and cell bodies of secondary afferents
    - Endorphins bind to mu opioid receptors found on both 1° and 2° afferents

PATHWAYS INVOLVED IN PAIN CONTROL

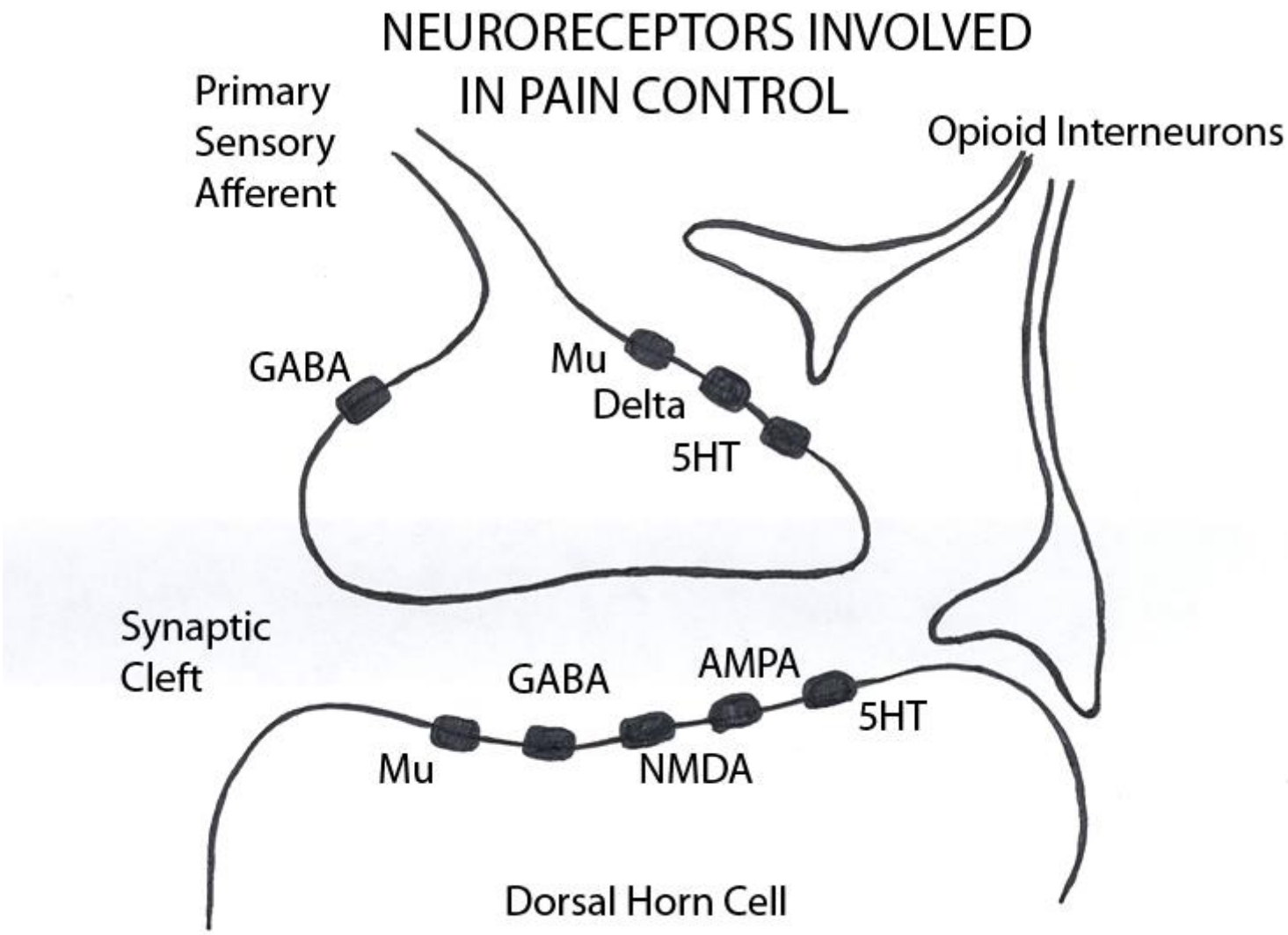


Anatomy & Physiology of Pain

- **Glutamate Receptors:**
  - Generally found on the post-synaptic membranes in the dorsal horn
  - AMPA receptors are rapidly desensitized and transmit rapid and short-lived excitatory effects
  - NMDA receptor activation requires repeated stimulation of the post-synaptic membrane by AMPA receptors in order to be activated (slowly desensitized and transmit a more sustained excitatory effect)

Anatomy & Physiology of Pain

- **Opioid mu Receptors:**
  - Found on the pre-synaptic C-fibre terminals where their activation helps diminish release of glutamate
    - Chronic stimulation of sensory afferents results in the ‘down regulation’ of mu receptors found on C-fibre terminals
  - Also found on the post-synaptic membrane of the dorsal horn cells where their activation inhibits stimulation of the spinothalamic tract neurons
    - Chronic stimulation of mu receptors results in the upregulation of NMDA receptors


NEURORECEPTORS INVOLVED
IN PAIN CONTROL
Primary
Sensory
Afferent
Opioid Interneurons
GABA
Mu
Delta
5HT
Synaptic
Cleft
GABA
AMPA
5HT
Mu
NMDA
Dorsal Horn Cell

Challenges in Pain Control

Challenges in Pain Control

- **Side Effects of Opioids**
  - Nausea, vomiting, sedation, constipation, urinary retention, biliary colic, hypertension, pruritis, xerostomia, mental clouding
- **Toxicity of Opioids**
  - Myoclonus, respiratory depression, delirium
- **Complex Pain Issues**
  - Tolerance, Hyperalgesia, Allodynia, Wind-up

Complex Pain Issues

- **Tolerance**
  - Diminished response to a drug's effects due to physiologic changes induced by prolonged exposure to the drug
- **Allodynia**
  - a state of altered perception such that normally innocuous stimuli (ie light touch) cause pain.
- **Hyperalgesia**
  - Perception of abnormally high levels of pain in response to normal noxious stimuli such as a small scratch

Complex Pain Issues

- **Wind up**
  - Hyperexcitability of spinothalamic neurons due to repeated C fibre stimulation felt to be mediated in part by NMDA receptors
  - Less glutamate is required to transmit pain and more anti-nociceptive input is required to stop it
  - Neuronal plasticity occurs

OPIOIDS

Classification of Opioids

- **Naturally Occurring**
  - Morphine, Codeine
- **Semi-synthetic**
  - Hydromorphone, Oxycodone
- **Synthetic**
  - Fentanyl, sufentanyl, methadone

Opioid Receptors

Receptor	Endogenous Ligands	Exogenous Ligands
μ (mu)	B-endorphin	All opiates
δ (delta)	Enkephalin	Methadone Hydromorphone
κ (kappa)	Dynorphin	Oxycodone Morphine

Opioid Pharmacokinetics

Opioid	Terminal Half-Life	Oral Bioavailabilty	Active Metabolites
Morphine	2 – 4	1 0 – 50	M6G, M3G
Meperidine	3 – 4	30 – 60	Normeperidine
Methadone	6 – 150	60 – 90	None known
Fentanyl	3 – 7	<2	Norfentanyl
Codeine	3 – 4	60 – 90	Morphine
Oxycodone	2 – 6	40 – 80	Oxymorphone
Hydromorphone	2 – 4	35 – 80	H3G

THAT OTHER PAINKILLING METHOD IS OF COURSE A LOT MORE EXPENSIVE

Methadone

Historical Context

- Invented in Germany during WWII
- Has been used as an analgesic since the early 1940s
- Became popular in the treatment of narcotic addiction in the 1960s
- Lost favour in the 1970s
- Increased interest with better understanding of pharmacology in the 1980s

Methadone for Pain Guidelines

Pharmacodynamics

- **Methadone is a very strong mu receptor agonist**
  - analgesia, sedation, tolerance, respiratory depression
- **Methadone is an NMDA receptor antagonist**
  - Blocks tolerance, prevents hyperalgesia and wind-up
  - Plays a role in treating neuropathic pain
- **Methadone inhibits re-uptake of Norepi and 5HT**
  - Monoamine uptake inhibition has been shown to provide analgesia in patients with neuropathic pain

Physicochemical Properties

- **Racemic Mixture**
  - L-methadone: Analgesia (8 to 50 times more potent than the D isomer)
  - D-methadone: antitussive, NMDA antagonist and tolerance reversal

Pharmacokinetics

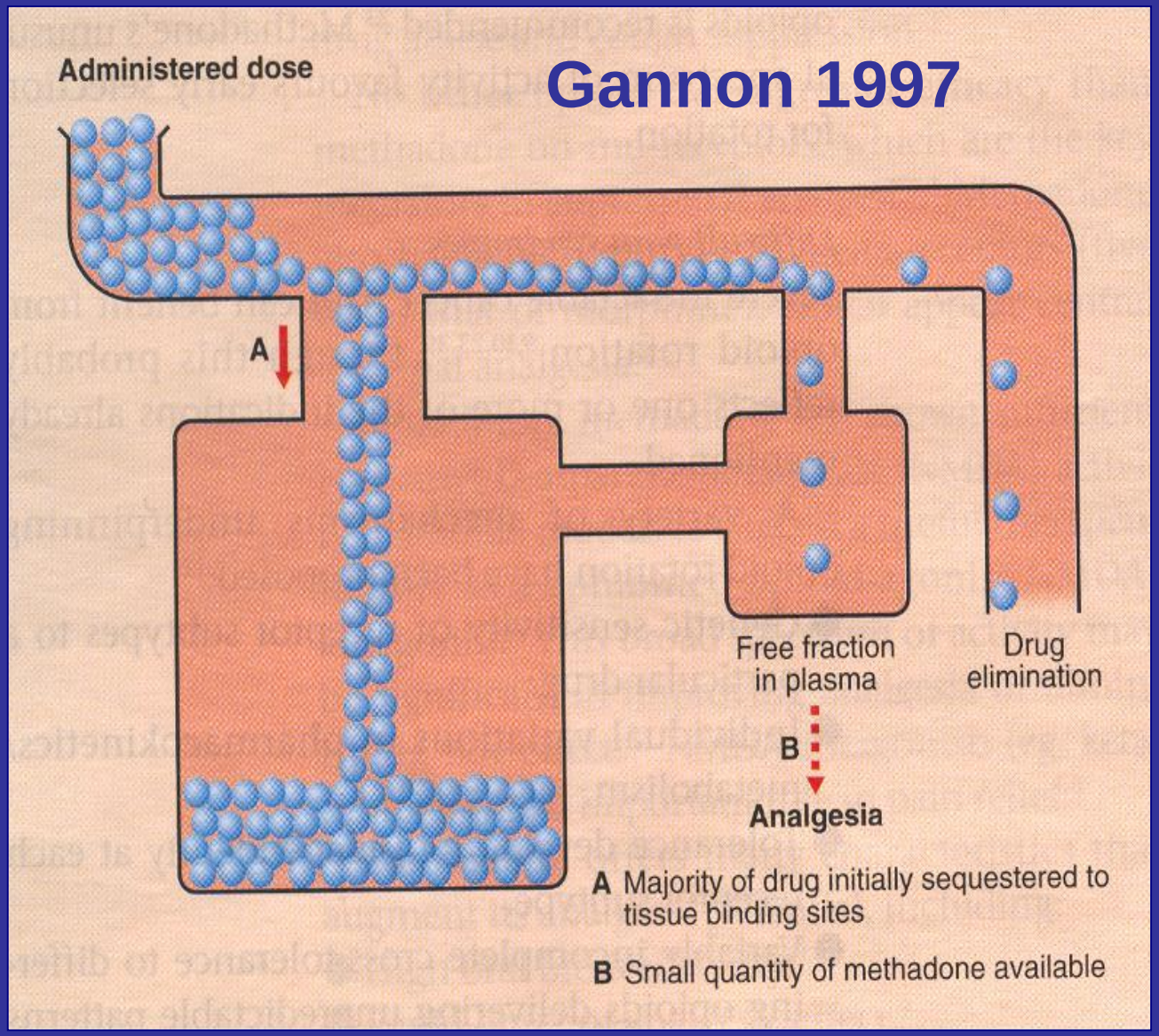
- **Absorption**
  - Gut absorption is nearly complete (80% bioavailability)
  - When taken orally, absorbed within ~30 minutes
  - Very lipophilic

- **Distribution**
  - Rapid and extensive distribution (1% in blood)
  - Highly bound in plasma to AAG
    - AAG is an acute phase reactant
  - Very lipophilic

Pharmacokinetics

- **Methadone is very lipophilic**
  - Easily absorbed across mucous membranes such as oral and rectal mucosa
  - Concentrates in multiple organs with slow transfer from tissue to blood
  - Steady state achieved in 2 – 10 days
  - After 3 to 5 days tissue reservoirs are full and subsequent doses reach higher plasma peak

Gannon 1997


Administered dose
A
Free fraction in plasma
Drug elimination
B
Analgesia
A Majority of drug initially sequestered to tissue binding sites
B Small quantity of methadone available

Lipid Solubility of Some Common Opioid Drugs

DRUG	*HEPTANE - BUFFER PARTITION COEFFICIENT*
• Morphine	• 0.00001
• Hydromorphone	• 0.0001
• Fentanyl	• 19.6
• Methadone	• 44.6

Onset of Action

- **Parenteral**
  - 10 to 20 minutes with a peak concentration in brain within 1 to 2 hours
- **Oral**
  - 30 to 60 minutes with a 2.5 to 4 hour time to peak plasma concentration (both tablets and liquids)

Pharmacokinetics

- **Metabolism and Elimination**
  - Methadone is predominantly metabolized in the liver
  - Methadone is eliminated in the urine and feces
- **Extensive Hepatic Metabolism (90%)**
  - P450 enzymes (primarily CYP3A4)
  - Metabolites are inactive
- **Renal**
  - Methadone is filtered through glomerulus and reabsorbed depending on pH
    - pH > 6 renal clearance 4% of methadone
    - pH <6 renal clearance 30% of methadone

Large Interindividual Variation

- **Fluctuations from day to day and week to week even in a single individual**
  - Varying AAG plasma level
  - Drug interactions
  - Duration of treatment

Indications

- Moderate to severe cancer pain
- Chronic non-malignant pain
- Inflammatory, neuropathic or mixed pain
- Failure to respond to morphine
- Tolerance, toxicity or allergy to morphine
- Renal failure, bowel obstruction
- Patients with history of drug abuse
- Hyperalgesia

Contra-indications

- Allergy to methadone (???)
- Respiratory depression
- Severe COPD, Acute Asthma
- Concurrent administration of MAOI
- Poor compliance
- Raised ICP
- Prolonged QT

Prolonged QT Interval

- **Monitor patients with the following characteristics carefully while on methadone:**
  - Heart or liver disease
  - Electrolyte abnormalities
  - Concomitant treatment with CYP3A4 inhibitors
  - Medications that may cause prolonged QT
  - Patients who require >100 mg methadone/day
    - *check ECG, Calcium Magnesium, Potassium and other drugs that can affect QT interval*

Advantages

- **NMDA receptor antagonist properties**
- **Long half-life**
  - Less frequent dosing required in stable dosing
- **No active metabolites**
  - Fewer side effects/toxicities
- **Highly lipophilic**
  - Good oral/bucal/rectal absorption

Clinical disadvantages

- Variable elimination half-life (delayed toxicity)
- Variable potency (increases with higher doses of previous opioid)
- Regulatory approval required
- Bitter taste
- SC infusion – local toxicity
- Ventricular Arrhythmias
- Historical stigma

Drug Interactions

- **Largely due to inhibition or induction of P450 cytochrome CYP3A4**
  - 3A4 inhibitors are drugs that will increase methadone levels (risk toxicity)
    - Grapefruit juice, cannabis, antifungals, SSRIs…
  - 3A4 inducers are drugs that will decrease methadone levels
    - Risperidone, corticosteroids, phenytoin, barbiturates
- **Benzodiazepines increase risk of respiratory depression**

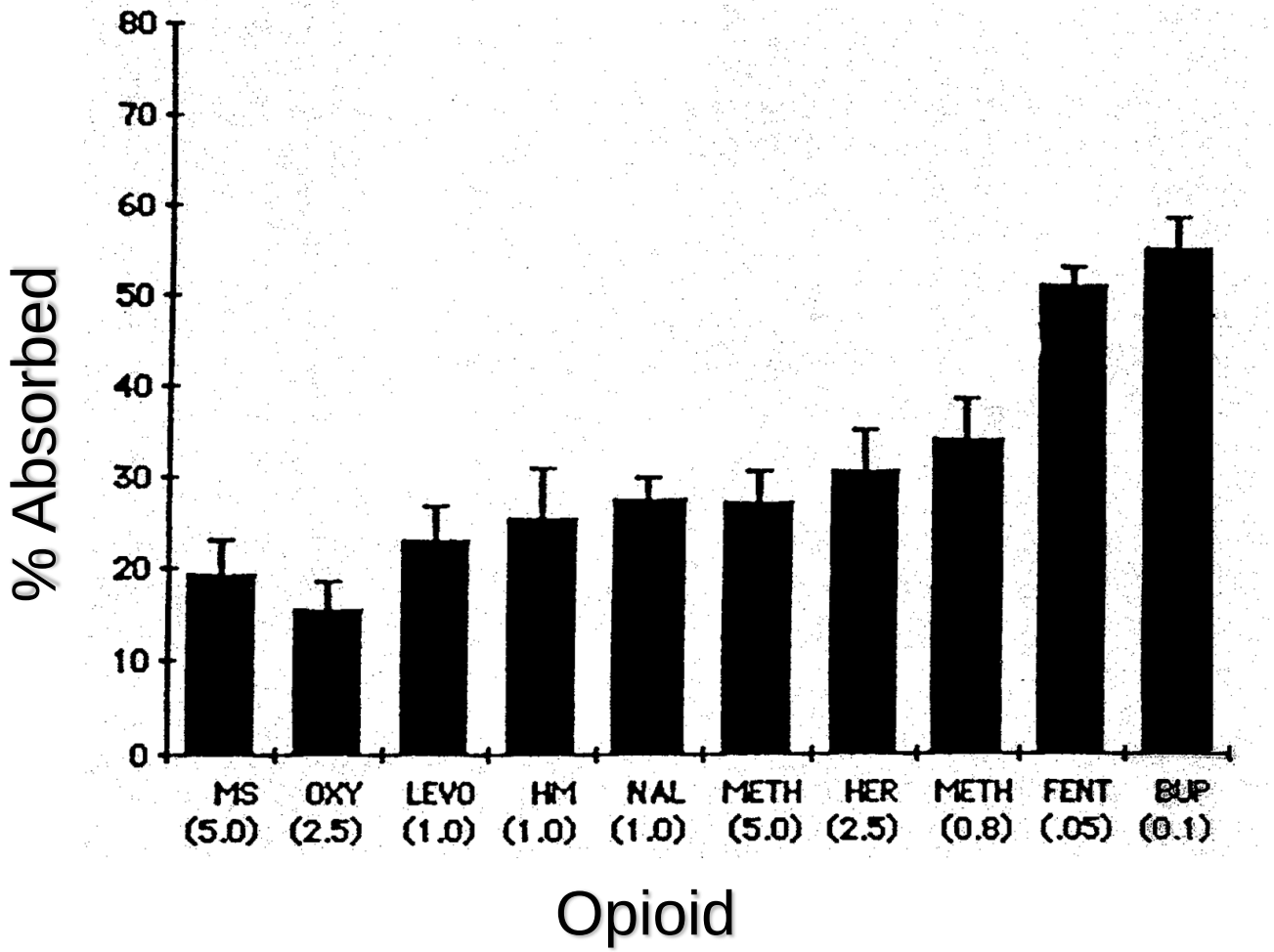
Routes of Administration

- **Oral and sublingual (buccal, rectal)**
  - Use powder to make capsules or solution of any strength
  - Tablets: 1, 5, 10 and 25 mg
  - Liquid: 1 mg/ml, 10 mg/ml
  - ?Mouthwash
    - *Methadone Mouthwash*
      - *Gallagher R. JPSM 2004 27(5):390-391*

- **Parenteral**
  - sc/iv to oral ration = 1 to 1-2
  - Sc may cause inflammatory reaction
  - Need to constitute from powder in Canada

Sublingual Absorption of Opioids

CLIN PHARM THER 44, 1988: 335-342



Side Effects

- **Similar to other Opioids**
  - Generally thought to cause less nausea and constipation
  - Less risk of neurotoxicity (e.g. myoclonus)
  - Sedation most common
  - Prolonged QT interval
  - Sweating, diarrhea, anxiety

Making the Conversion

- **The fact that there are so many published right answers about conversion to methadone is a signal that it is for the moment quite empirical**

- **Consider**
  - Setting of care, skill of prescriber, monitoring, urgency of change

http://palliativedrugs.com/download/100304methadone.pdf

United Kingdom (Morley & Makin) Protocol (1998)	
Step 1	**Stop Morphine**
Step 2	**Give fixed doses of methadone at 1/10th of the 24 –h oral morphine dose when the 24 h dose is less than 300 mg (oral)**
Step 3	**When the 24 h morphine dose is >300mg (oral) the fixed methadone dose should be 30 mg**
Step 4	**The fixed dose is taken as needed but not more frequently than every 3 hours**
Step 5	**On day 6, add the total dose of methadone administered in the last 48 h, divide by 4 and give at 12 h intervals**
Step 6	**If additional doses are needed after day 6 adjust the doses as for sustained-release morphine**
Step 7	**If ≥ 2 doses/day of prn methadone continue to be needed, the dose of regular methadone should be increased by about ¼ to 1/3 once a week, guided by prn use**

Palliative Drugs . Com Guidelines (2005)	
Step 1	**Stop Morphine**
Step 2	**Give methadone loading dose 1/10 of the previous 24 hour total to a maximum of 30 mg.**
Step 3	**Give fixed doses of methadone at 1/3rd of the loading dose of oral methadone q3h p.r.n.**
Step 4	**For patients in severe pain unable to wait 3h before giving the next dose, options include:** –Previous opioid q1h p.r.n. (50-100% of previous p.r.n. dose) –If neurotoxicity was a problem, use an alternative strong opioid –ketamine
Step 5	**On Day 6, the amount of methadone taken over the previous 2 days is noted and divided by 4 to give a regular q12h dose, with ¼ of the regular q12h dose given q2h p.r.n.**
Step 6	**If ≥2 doses/day of p.r.n. methadone continue to be needed, the dose of regular methadone should be increased q weekly**

Ottawa Protocol (Modified Morley & Makin)	
Step 1	**Stop regular dosing of previous opioid**
Step 2	**Methadone dose = 1/30 of the 24 hour oral morphine-equivalent dose (maximum methadone dose 30 mg)**
Step 3	**Give this dose q3h prn for inadequately controlled pain**
Step 4	**Give previous prn opioid q1h prn for break-through pain occurring within 3 hours of the last methadone**
Step 5	**Monitor for pain, sedation, and respiratory depression q3h**
Step 6	**On day 6 sum up total methadone used in the previous 48 hours and divide it by 6 to get the new methadone dose**
Step 7	**Prescribe this new dose q8h routinely; stop previous prn opioid**
Step 8	**Methadone prn dose = 10% of daily dose given q1h prn**
Step 9	**Increase dose by 25-33% every 4 to 6 days if inadequate analgesia**

Edmonton Protocol	
Day 1	**Decrease the original opioid daily dose by 30% and replace it with oral methadone every 8 hours using a 10:1 ratio**
Day 2	**If pain control is good, decrease the original dose of morphine by another 30% and increase the methadone dose only if the patient experiences moderate to severe pain.** **Treat transient pain with rescue dose of short-acting opioid.**
Day 3	**Discontinue last 30% of the original morphine dose and maintain the patient on regular methadone administered every 8 hours. Use methadone as breakthrough (10% of daily dose)**

Librach's Modified Edmonton Protocol	
Day 1	**Decrease the original opioid daily dose by 30% and add oral methadone at a dose of 5 to 10 mg every 8 hours (10:1 ratio) and use original opioid for breakthrough.** **Wait three days to judge initial stabilization.**
Day 4	**Decrease original opioid by a further 30% and increase the methadone dose by 5 to 10 mg per dose. Use methadone 5 to 10 mg every 4 to 6 hours for breakthrough**
Day 7	**Stop the original opioid. Depending on response, increase methadone dose and continue using methadone for breakthrough.**

Making the Conversion

- **Rule of 15:**
  - Estimated oral methadone per day (mg) =

15 + [Daily oral MDE divided by 15]

Some General Guidelines for Initiation of Methadone…

- **Starting Methadone in Opioid Naïve patients:**
  - Start methadone at 2.5mg po TID (Cancer Pain)
- **Starting methadone in patients on low morphine daily dose equivalents:**
  - Consider stopping original opioid prior to initiation of methadone (ie Ottawa protocol)
- **The Patient on high dose MDDE (>200 mg):**
  - Consider a gradual approach (ie Edmonton protocol)