To Use or Not to Use is the Question: A "Love Story of Dolophine" Like a Shakespearian Play! Methadone for Analgesia

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Director & Board Chair, Pallium foundation of Canada

Banff
60th Annual Scientific Assembly
Friday 27th January, 2015

Methadone for Analgesia

Other Contributors:
Dr. Neil Hagen (Palliative Medicine)
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Slides reviewed by:
Dr. Lara Cooke (U of Calgary - CPD)
Dr. Janet Wright and Susan Ulan (CPSA)
Drs. Diane Turner, Marie Patton (LTC)

CFPC COI Template - Slide 1

Faculty/Presenter Disclosure

- **Faculty:** **Dr. Srini Chary**
- **Relationships with commercial interests:**
  - **Grants/Research Support:** Not applicable
  - **Speakers Bureau/Honoraria:** Not applicable
  - **Consulting Fees:** Not applicable
  - **Other:** Permission received from Paladin Laboratories to use slides to explain "tissue reservoir."

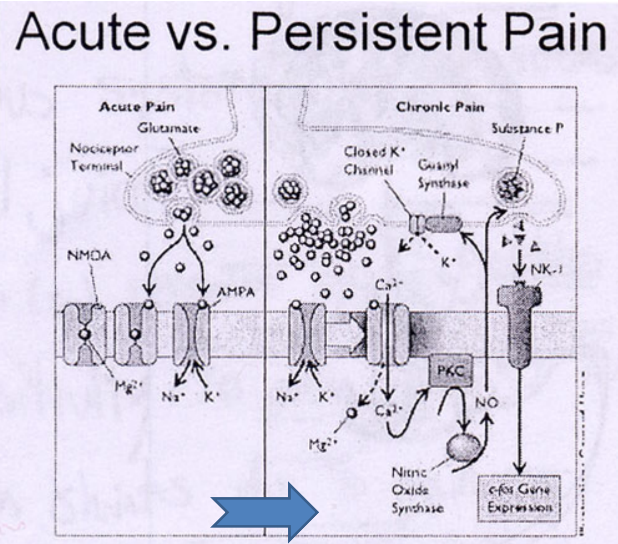
Learning Objectives

1. To learn the challenges associated with chronic pain management

2. To understand the good and bad, associated with the use of Methadone as an analgesic

3. Proficient enough, that an exemption for use of Methadone for analgesia, can be requested

Finally, colleagues from AHS Calgary Zone, Palliative Care & Chronic Pain Clinic are available as mentors and a list is available for you to use



Neuroplasticity: Peripheral sensitization & Central excitation

B.G., 82 yrs - 5

Retired family physician with LBP and previous back surgeries no further surgery possible, seen at RGH and has been using morphine CR & IR, more than 360 mg in 24 hours, Pain relief moderate but "depressed".

Change to hydromorph CR & IR around 24 mg tid, better mood but no improvement in pain. Co-analgesics TCAs and Gabapentinoids led to poor balance and memory.

Any other options: ?

Options - B.G., 82 yrs – 5a

Continue hydromorph & add

Compounded Topical ointment containing:

Voltaren (NSAID)

Lidocaine (Local anesthetic – Na channel)

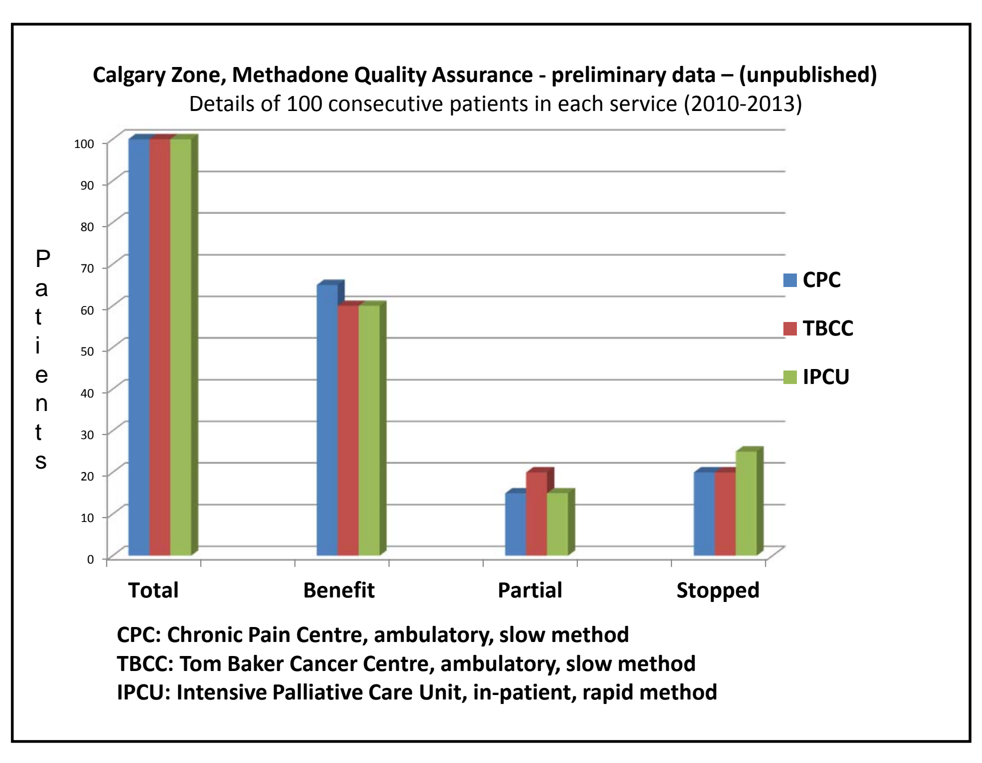
Nortriptyline (TCA)

Gabapentin (Antisieizure – Ca channel)

Clonidine (Sympatholytic)

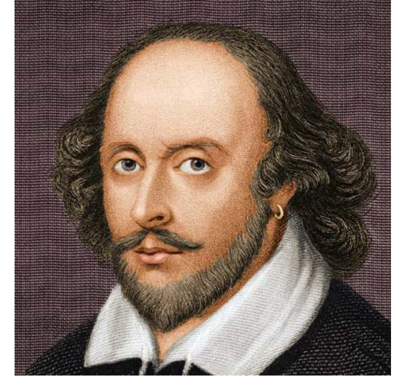
Ketamine (NMDA antagonist)

Consider other opioids including methadone



Opioids & Stages of Use

Opioid Naïve
Opiophobic
Opiophilic
Opioid “Expert”
Opioid Catastrophe
Acquired Opiophobia



Opioid Balance

Harrison Narcotics Tax Act

December 14, 1914

United States Federal law, regulated production, importation and distribution of opiates and Coca products. Act was proposed by ***representative Francis Burton Harrison of New York.***

This clause was interpreted after 1917 to mean that a doctor could not prescribe opiates to an addict, since addiction was not considered a disease at that time. A number of doctors were arrested and some were imprisoned.

METHADONE and the politics of pain | A SEATTLE TIMES SPECIAL REPORT

December 11-13, 2011

Pulitzer Prize:

Michael J. Berens
Investigative Reporting

The Seattle Times

METHADONE and the politics of pain | A SEATTLE TIMES SPECIAL REPORT

December 11-13, 2011

BOOKS of the YEAR

Holiday air-travel tips

No. 7 Duke tops UW, 86-80

The Seattle Times Sunday

DECEMBER 11, 2011

$2.00

Beat down

New law leaves patients in pain

State pushes drug that saves money, costs lives

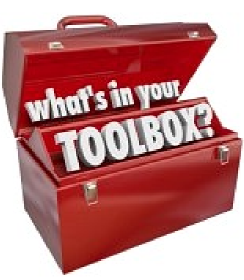
Well-heeled immigrants can invest way to visas

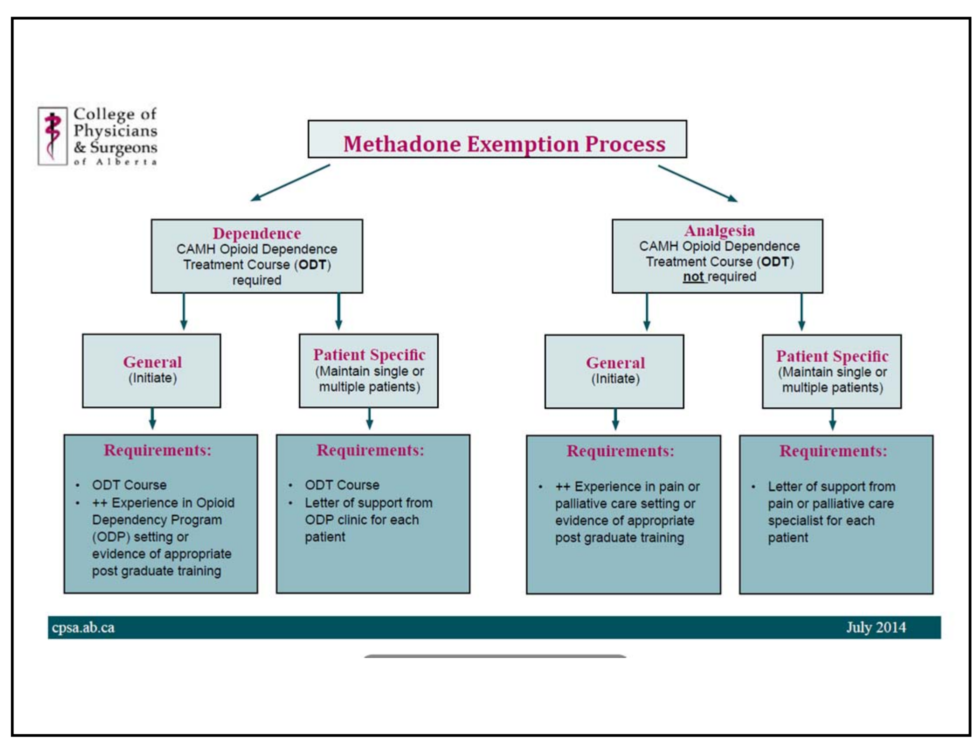
clinic's wake: chaos, deaths

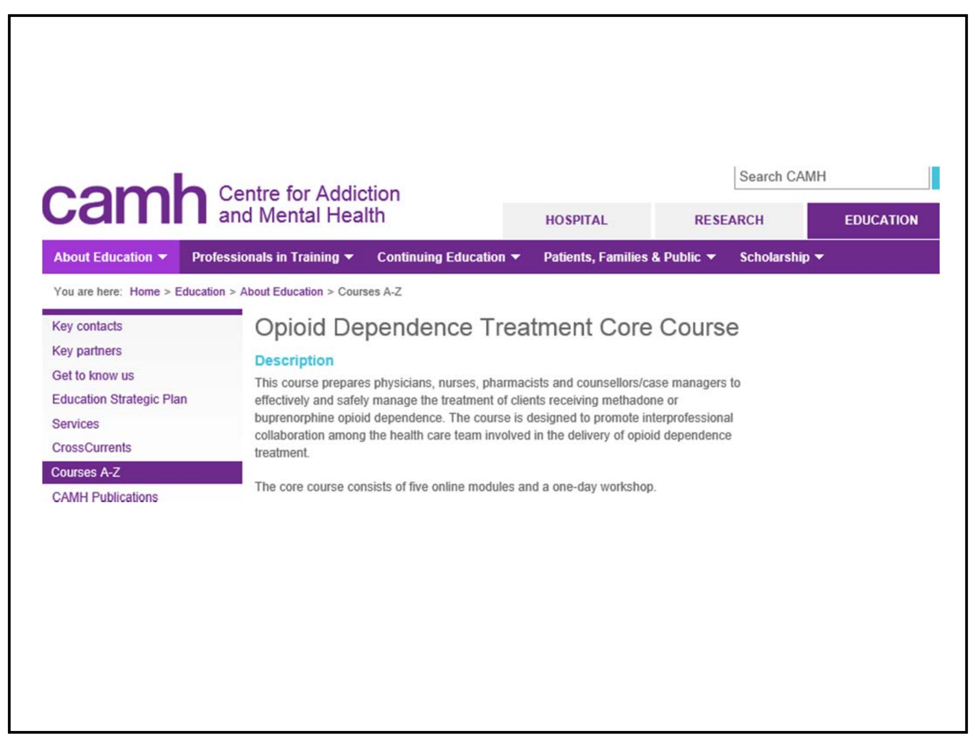
3 FORMER WAMU EXECS REPORTEDLY REACH DEAL

Methadone for Analgesia

Another tool in toolbox – Learn to Use Wisely!






camh Centre for Addiction and Mental Health
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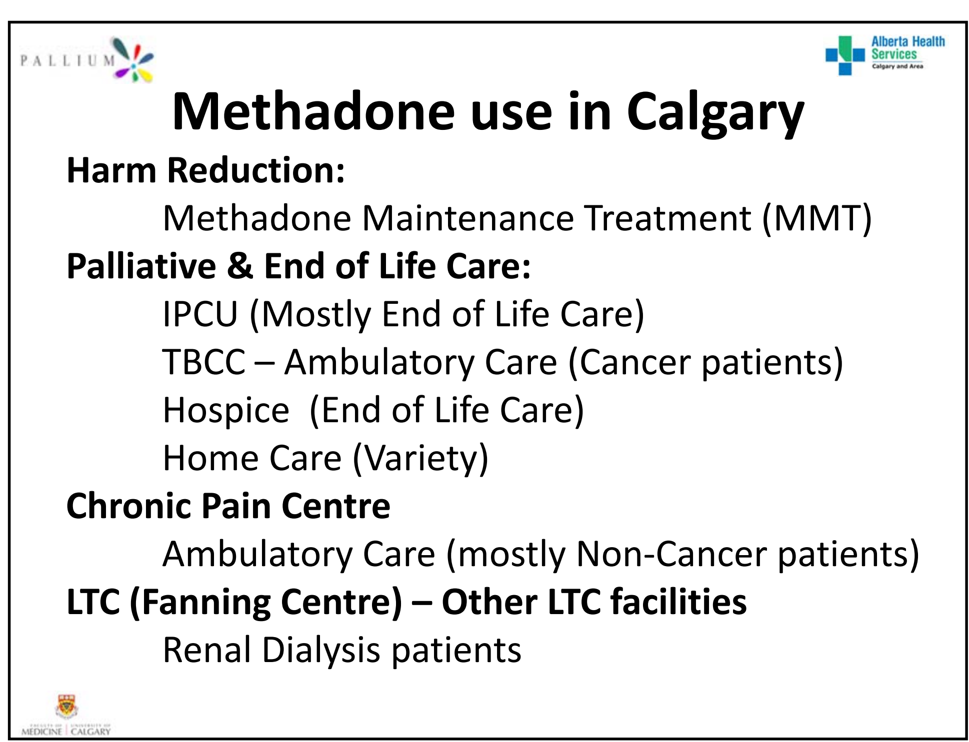
Get to know us
Education Strategic Plan
Services
CrossCurrents
Courses A-Z
CAMH Publications
Opioid Dependence Treatment Core Course
Description
This course prepares physicians, nurses, pharmacists and counsellors/case managers to effectively and safely manage the treatment of clients receiving methadone or buprenorphine opioid dependence. The course is designed to promote interprofessional collaboration among the health care team involved in the delivery of opioid dependence treatment.
The core course consists of five online modules and a one-day workshop.


PALLIUM
Alberta Health Services
Methadone use in Calgary
Harm Reduction:
Methadone Maintenance Treatment (MMT)
Palliative & End of Life Care:
IPCU (Mostly End of Life Care)
TBCC – Ambulatory Care (Cancer patients)
Hospice (End of Life Care)
Home Care (Variety)
Chronic Pain Centre
Ambulatory Care (mostly Non-Cancer patients)
LTC (Fanning Centre) – Other LTC facilities
Renal Dialysis patients
MEDICINE CALGARY

Methadone use in Calgary

Methadone Maintenance Treatment (MMT)

MMT: Physician Specific education & practice

Part of Addiction Medicine

Daily liquid methadone or suboxone wafers

Patient is being seen to have taken

Behaviour modification & Harm reduction

If Urine drug screens are OK weekend carries

Some patients longer period carries

Some patients have dual disorder-pain & SUD

Methadone use in Calgary

Palliative & End of Life Care:

FMC - IPCU (Mostly End of Life Care, In-patients & rapid opioid switch). Neuraxial analgesia etc.

Hospice (End of Life Care, similar to IPCU)

TBCC Ambulatory Care (Cancer palliative & end of life care) slow opioid switch

Palliative Home Care (Variable)

Methadone use in Calgary

<u>Chronic Pain Centre:</u>

Ambulatory Care (mostly Non-Cancer patients)
Multi disciplinary care
Education & Groups
Physical & Psychological modalities
Slightly different equianalgesia
Avoid Opioid breakthrough after titration

Methadone guidelines: Internal website - AHS

Calgary Challenge!

Patients in an acute care facility, TBCC, Chronic Pain Clinic who are stable on methadone for analgesia, move to community and face difficulty ….

In 2013 the methadone for analgesia education project commenced:

Drs. Diana Turner, Marie Patton (LTC) requested initiation of education
Palliative Care, Chronic Pain Service & (Transition Service) AHS, Calgary Zone
Janet Wright & Susan Ulan (CPSA)
Lara Cooke (U of C - CPD)

Methadone for Analgesia Workshops Capacity building

-2013-14 Three workshops were conducted

-A total of 40 physicians have attended

-4 physicians had exemption already

-"Survey Monkey" of 40 physicians 18 replied and 10 obtained methadone exemption

-In Calgary, at the start of the program patient from acute care site could not move to LTC and now five (5) LTC sites are able to accept and continue methadone

The Problem

- Pain and Addiction *CAN* and do coexist
- Addiction in General Population
  - Varies 3-16% prevalence
  - Varies with the drug, gender, economic status, race, age…
- Addiction in the Chronic Pain Population
  - Extent not well known
  - Same terms often used but with different meanings
- Lack of precision in definitions around abuse/dependency/addiction

- **Perceived and Real Barriers**

Barriers to Effective Pain Management

- Fear of iatrogenic problems
  - Abuse/Addiction/Diversion
- Fear of regulatory sanction
- Concern over long-term efficacy
- Lack of time
- Inadequate compensation
- Others …

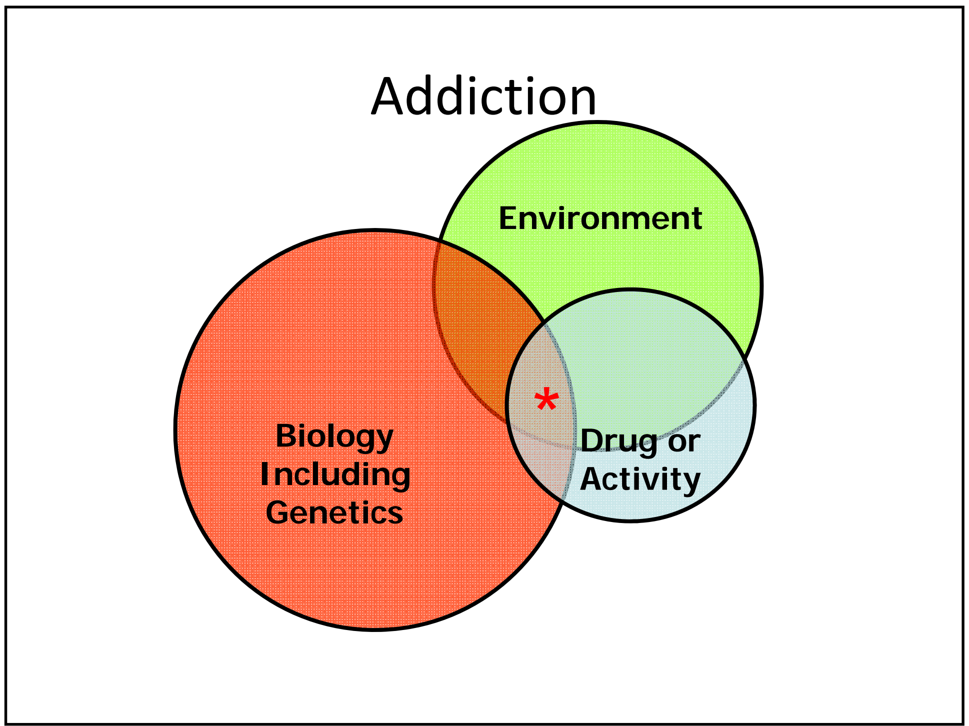
Chronic Cancer and Non-cancer Pain:

Most patients with chronic cancer and non cancer pain obtain improved comfort and function with chronic administration of analgesics, including opioids

The risk of aberrant behavior is overall low

It is the exceptions that cause major clinical challenges

As health care professionals we need to be prepared for these important exceptions



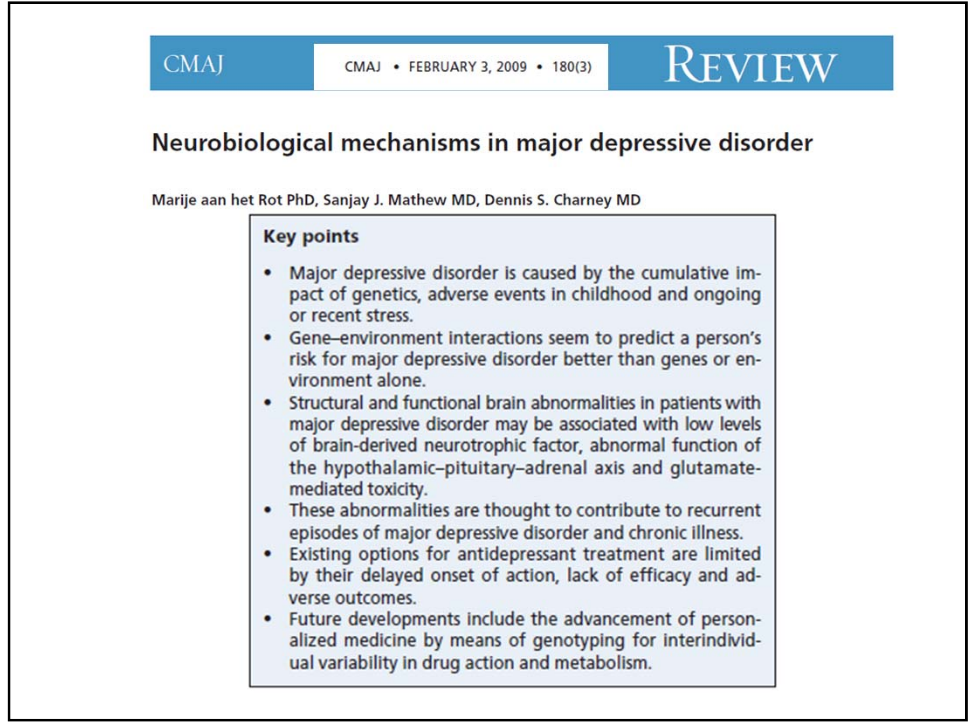
Definition

Addiction:

- Addiction is a primary, brain disorder, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations
- It is characterized by behaviours that include one or more of the following:

  Impaired control over drug use, compulsive use, continued use despite harm, and craving

It will require prospective diagnosis of behaviour & Recovery

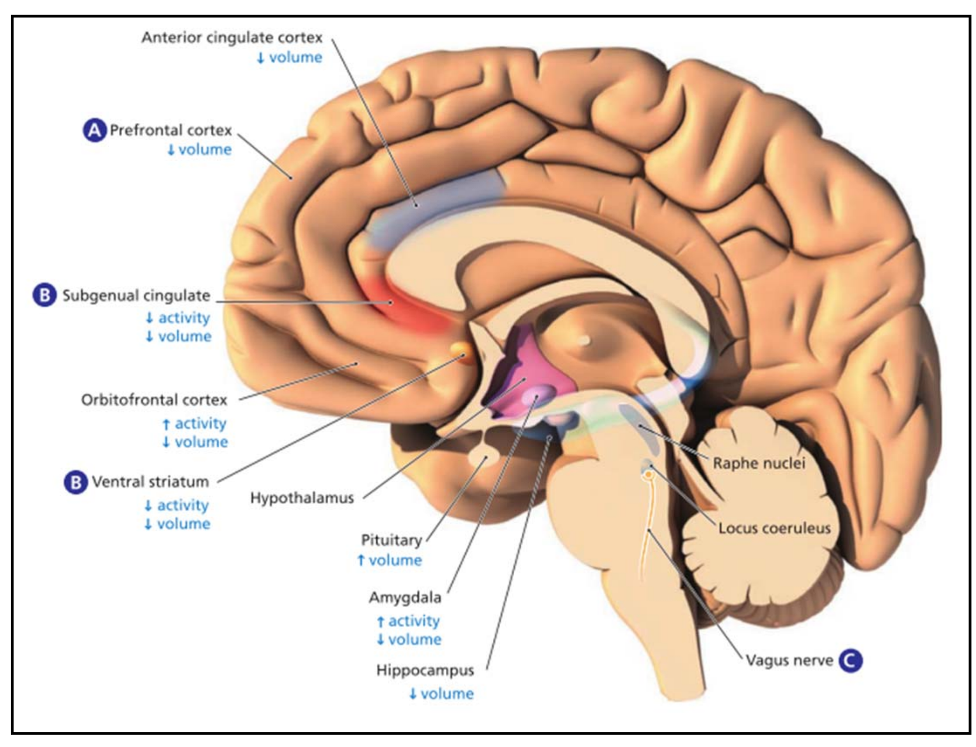

CMAJ
CMAJ • FEBRUARY 3, 2009 • 180(3)
REVIEW

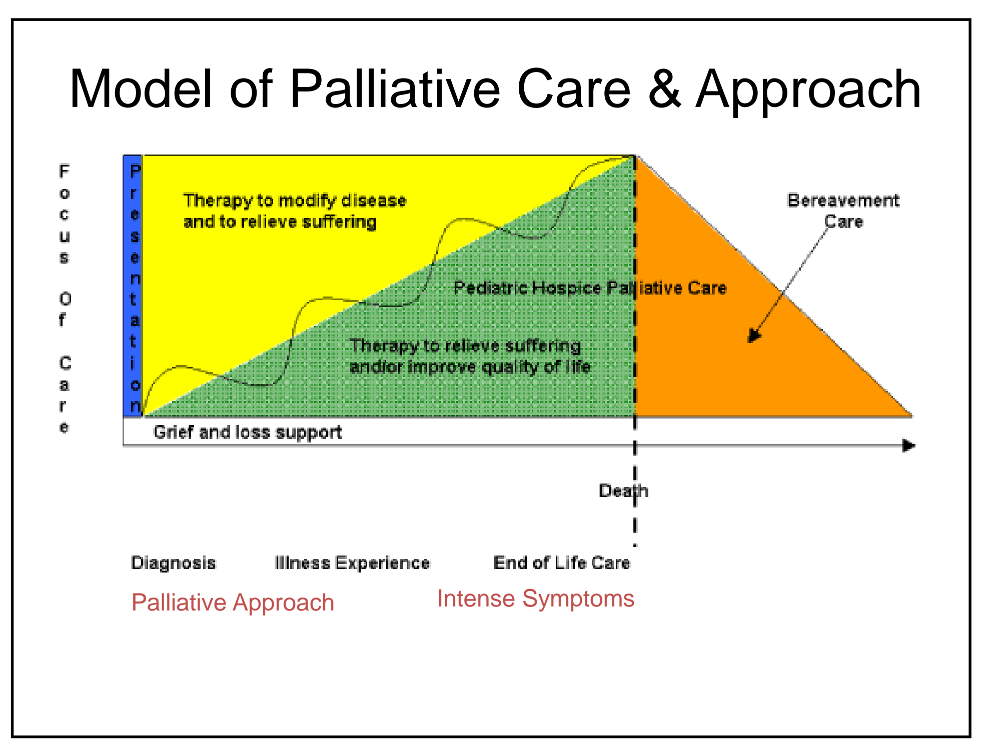
Neurobiological mechanisms in major depressive disorder

Marije aan het Rot PhD, Sanjay J. Mathew MD, Dennis S. Charney MD

Key points

- Major depressive disorder is caused by the cumulative impact of genetics, adverse events in childhood and ongoing or recent stress.
- Gene–environment interactions seem to predict a person's risk for major depressive disorder better than genes or environment alone.
- Structural and functional brain abnormalities in patients with major depressive disorder may be associated with low levels of brain-derived neurotrophic factor, abnormal function of the hypothalamic–pituitary–adrenal axis and glutamate-mediated toxicity.
- These abnormalities are thought to contribute to recurrent episodes of major depressive disorder and chronic illness.
- Existing options for antidepressant treatment are limited by their delayed onset of action, lack of efficacy and adverse outcomes.
- Future developments include the advancement of personalized medicine by means of genotyping for interindividual variability in drug action and metabolism.




Model of Palliative Care & Approach
Focus Of Care
Presentation
Therapy to modify disease and to relieve suffering
Pediatric Hospice Palliative Care
Therapy to relieve suffering and/or improve quality of life
Bereavement Care
Grief and loss support
Death
Diagnosis
Illness Experience
End of Life Care
Palliative Approach
Intense Symptoms

PALLIUM
Alberta Health Services
Chronic Pain
3 sides of a coin!
Physical Pain
Coping
Emotional Pain

Assessment & Management
(Universal Precautions for Chronic Pain)

History & Clinical Examination

Investigations including risk assessment (SUD)

Empathic listening

Neuropathic and/or Nociceptive pain

Goal setting & Intervention

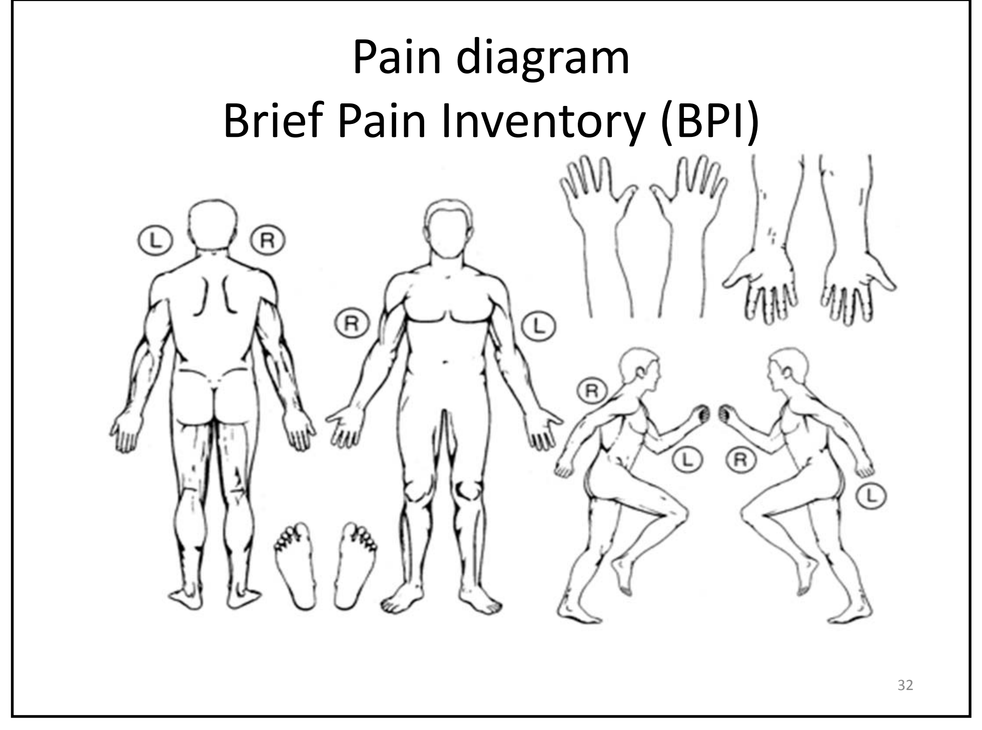
Boundaries as needed (UDTs, frequent dispensing)

Follow-up

Make patient work: Self management skills & not dependant, if at all possible

Gourlay DL, Heit HA, Almahrezi A. Universal precautions in pain medicine: A rational approach to the treatment of chronic pain. Pain Medicine 2005;6:107-112

Pain diagram
Brief Pain Inventory (BPI)



32

What things make your pain feel worse?
What things make your pain feel better?
What treatments or medications are you currently receiving for your pain?

BPI

Please rate your pain by circling the one number that best describes your pain at its **WORST** in the past 24 hours.
No pain 0 1 2 3 4 5 6 7 8 9 10 Worst pain you can imagine
Please rate your pain by circling the one number that best describes your pain at its **LEAST** in the past 24 hours.
No pain 0 1 2 3 4 5 6 7 8 9 10 Worst pain you can imagine
Please rate your pain by circling the one number that best describes your pain on the **AVERAGE**.
No pain 0 1 2 3 4 5 6 7 8 9 10 Worst pain you can imagine
Please rate your pain by circling the one number that tells how much pain you have **RIGHT NOW**.
No pain 0 1 2 3 4 5 6 7 8 9 10 Worst pain you can imagine
In the last 24 hours, how much relief have your pain treatments or medications provided?
Please circle the one percentage that shows most how much **RELIEF** you have received.
No relief 0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% Complete relief

Interference Scale
Circle the one number that describes how, during the past 24 hours, pain has interfered with your:
A. General activity
Does not interfere 0 1 2 3 4 5 6 7 8 9 10 Completely interferes
B. Mood
Does not interfere 0 1 2 3 4 5 6 7 8 9 10 Completely interferes
C. Walking ability
Does not interfere 0 1 2 3 4 5 6 7 8 9 10 Completely interferes
D. Normal work (includes both work outside the home and housework)
Does not interfere 0 1 2 3 4 5 6 7 8 9 10 Completely interferes
E. Relations with other people
Does not interfere 0 1 2 3 4 5 6 7 8 9 10 Completely interferes
F. Sleep
Does not interfere 0 1 2 3 4 5 6 7 8 9 10 Completely interferes
G. Enjoyment of life
Does not interfere 0 1 2 3 4 5 6 7 8 9 10 Completely interferes

Source: Adapted from Pain Research Group, 1997.[12] Reprinted with permission.

Opioid Risk Tool
Clinician Form

(includes point values to determine scoring total)

Mark each box that applies:

	Female	Male
1. Family History of Substance Abuse:		
Alcohol	☐ 1	☐ 3
Illegal Drugs	☐ 2	☐ 3
Prescription Drugs	☐ 4	☐ 4
2. Personal History of Substance Abuse:		
Alcohol	☐ 3	☐ 3
Illegal Drugs	☐ 4	☐ 4
Prescription Drugs	☐ 5	☐ 5
3. Age (mark box if between 16-45)	☐ 1	☐ 1
4. History of Preadolescent Sexual Abuse	☐ 3	☐ 0
5. Psychological Disease		
Attention Deficit Disorder, Obsessive-Compulsive Disorder, Bipolar, Schizophrenia	☐ 2	☐ 2
Depression	☐ 1	☐ 1
Scoring Totals	_____	_____

The patient can be placed into one of three opioid risk categories based on their total score.

Low Risk = 0 - 3 points
Medium Risk = 4 - 7 points
High Risk = 8 points and above

Lynn R. Webster, MD: Medical Director of Lifetree Medical, Inc.; Sal Lake City UT 84106

Essential Follow-up Documentation The "6 A s" Modified: "Sleep" is added

1. Analgesia (pain relief)
2. Activities (physical and psychosocial functioning)
3. Adverse Effects (and your advice)
4. Ambiguous Drug Taking Behaviour (and your response)
5. Accurate medication record
6. Affect
7. Sleep

Jovey R. et al. Managing Pain. 2002 p. 121
Gourlay DL, Heit HA, Almahrezi A. Universal precautions in pain medicine: A rational approach to the treatment of chronic pain. Pain Medicine 2005;6:107-112.

Goal Setting

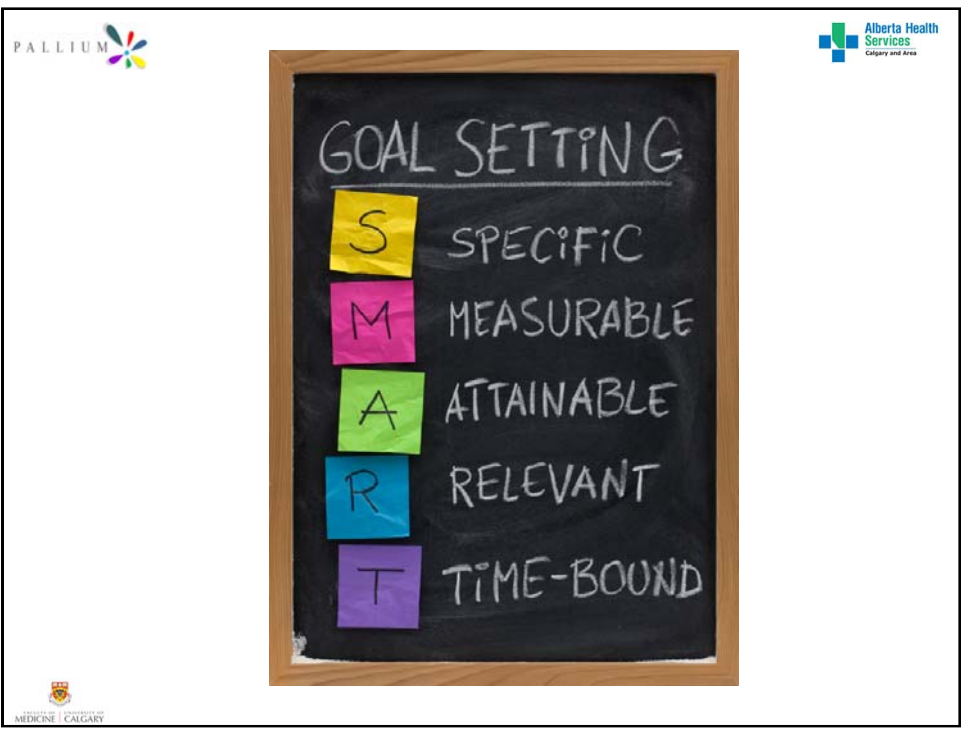
Restful sleep at night

Affect being better than neutral

Pain reduction by >30% (highest or average)

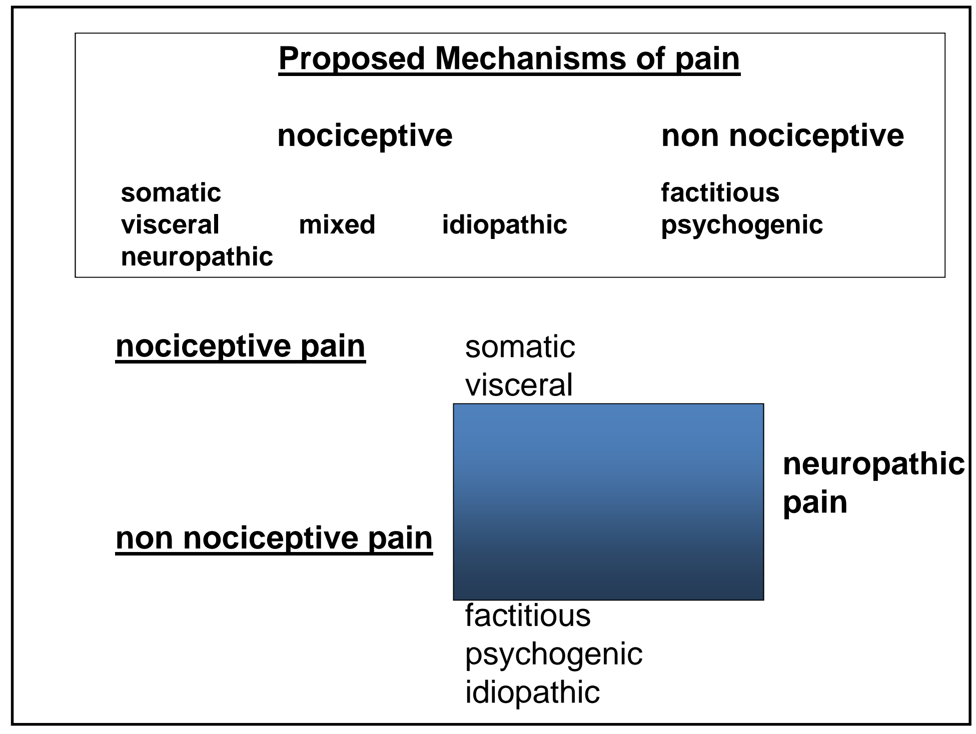
Improved activity/ function

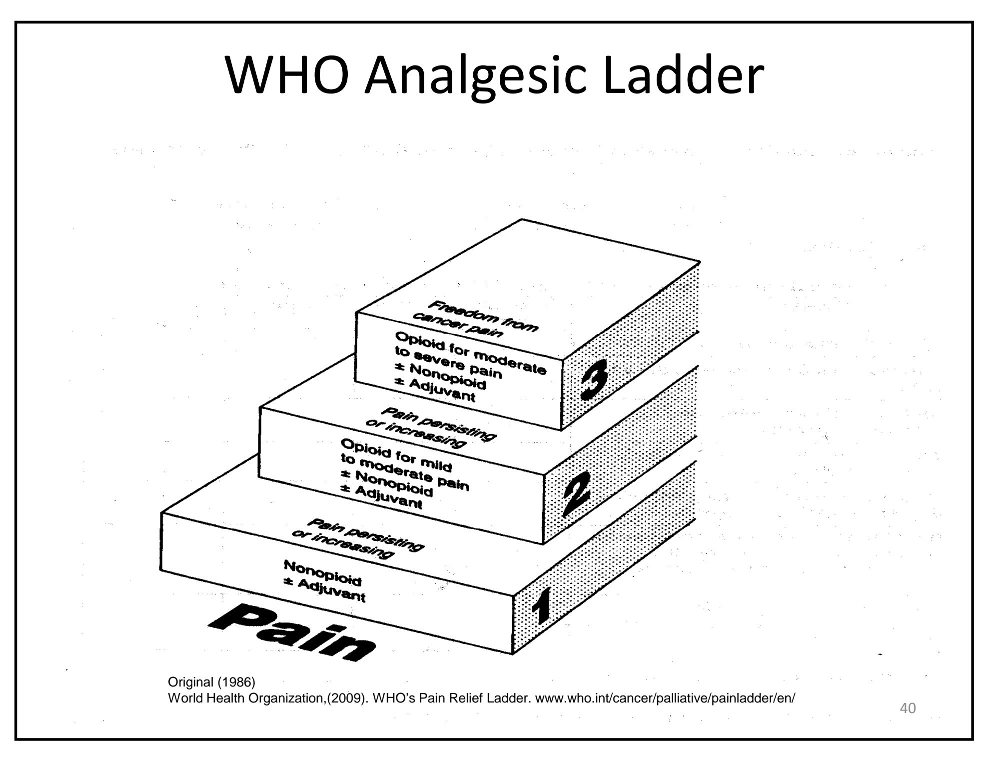
SMART Goals

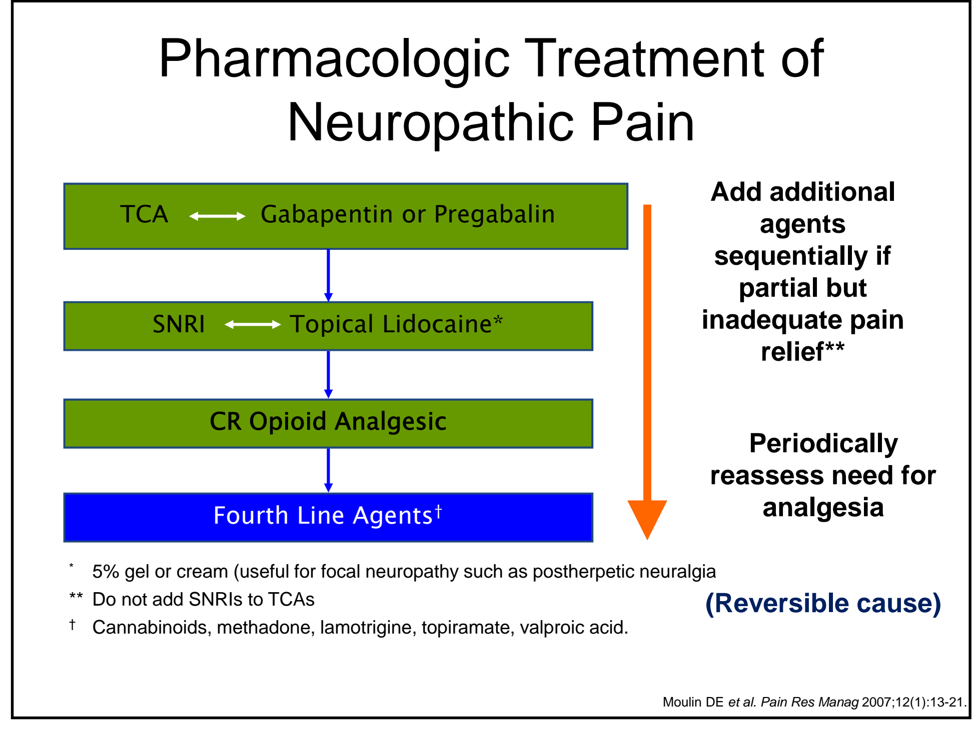


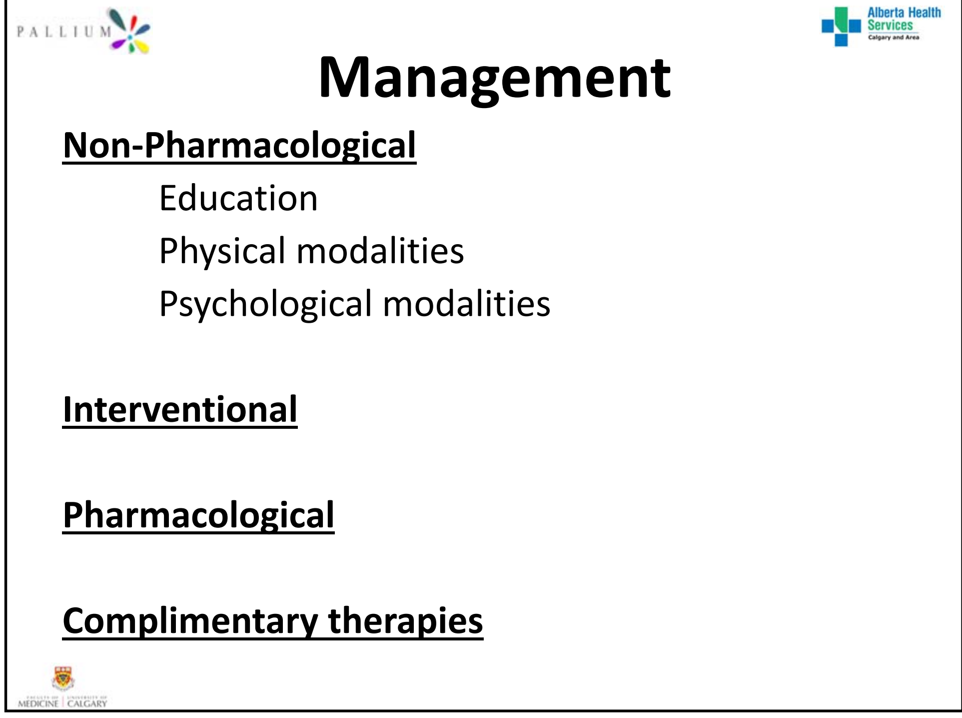
Boundary Setting

- 90%+ of patients don't need strict boundary setting
  - Most patients have their own internal limits
- For remaining ~10%
  - Strict boundary setting is essential
- Included could be
  - Treatment agreements, Urine Drug Testing (UDT), Interval/Contingency Dispensing


Proposed Mechanisms of pain
nociceptive
non nociceptive
somatic
visceral
neuropathic
mixed
idiopathic
factitious
psychogenic
nociceptive pain
somatic
visceral
neuropathic pain
non nociceptive pain
factitious
psychogenic
idiopathic


WHO Analgesic Ladder
Freedom from cancer pain
Opioid for moderate to severe pain
± Nonopioid
± Adjuvant
3
Pain persisting or increasing
Opioid for mild to moderate pain
± Nonopioid
± Adjuvant
2
Pain persisting or increasing
Nonopioid
± Adjuvant
1
Pain
Original (1986)
World Health Organization,(2009). WHO's Pain Relief Ladder. www.who.int/cancer/palliative/painladder/en/
40


Pharmacologic Treatment of Neuropathic Pain
TCA ⟷ Gabapentin or Pregabalin
SNRI ⟷ Topical Lidocaine*
CR Opioid Analgesic
Fourth Line Agents†
Add additional agents sequentially if partial but inadequate pain relief**
Periodically reassess need for analgesia
* 5% gel or cream (useful for focal neuropathy such as postherpetic neuralgia
** Do not add SNRIs to TCAs
† Cannabinoids, methadone, lamotrigine, topiramate, valproic acid.
(Reversible cause)
Moulin DE et al. Pain Res Manag 2007;12(1):13-21.

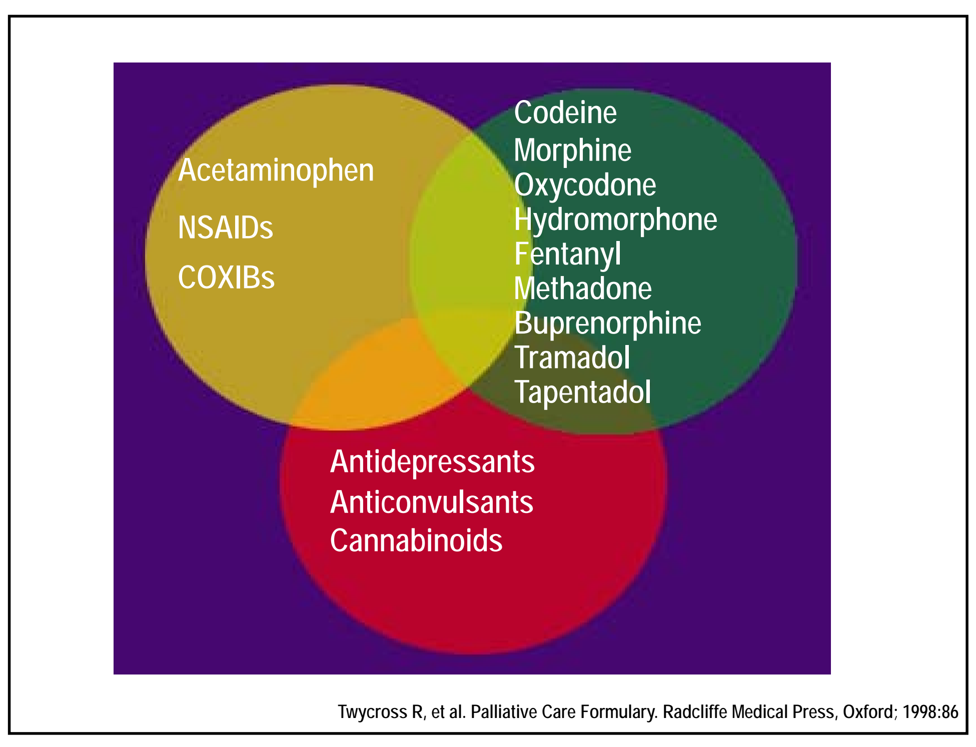

PALLIUM
Alberta Health Services
Management
Non-Pharmacological
Education
Physical modalities
Psychological modalities
Interventional
Pharmacological
Complimentary therapies

Treatment Options for Chronic Pain

Pay attention to Mental Health & Substance Use Disorder

EDUCATION: AHS Calgary Zone "Living Well" Program -CDM

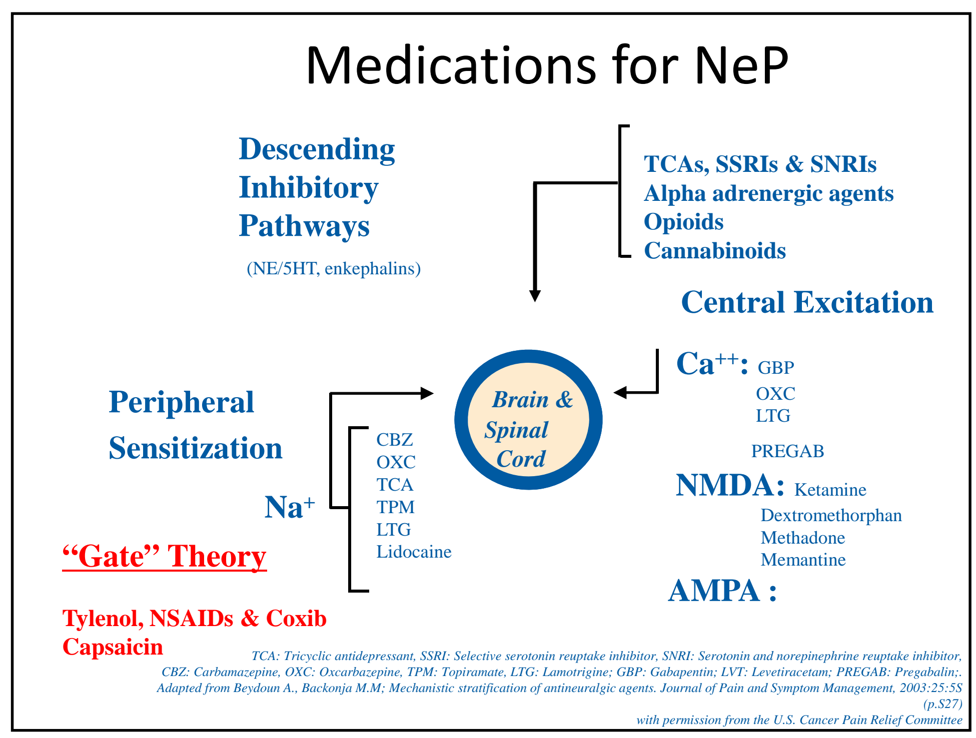
PHYSICAL	PSYCHOLOGIC	PHARMACOLOGIC	INTERVENTIONAL
Normal activities Splinting / Taping Aquafitness Physio • Passive • Active Stretching Conditioning Weight training Massage TENS Transcranial Magnetic Stimulation Chiropractic Acupuncture	Hypnosis Stress Management Cognitive-Behavioural Family therapy Psychotherapy Mindfulness- Based Stress Reduction	OTC medication Topical medications NSAIDs / COXIBs Immune modulators Tricyclics Anti-epileptic drugs Opioids Local anesthetic congeners Muscle relaxants Sympathetic agents NMDA blockers CGRP blockers Migraine medications	I.A. steroids I.A. hyaluronan Trigger pt. therapy IntraMuscular stim. Prolotherapy Nerve blocks BOTOX Epidurals Orthopedic surgery Radio frequency facet neurotomy Neurectomy Implantable neurostimulators Implantable pain pumps
Complimentary:	Vit D3, Cumin, Omega 3-Fatty acids, Magnesium etc.		



Twycross R, et al. Palliative Care Formulary. Radcliffe Medical Press, Oxford; 1998:86

Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain

- **Summary of Recommendations**
- Cluster 1: Deciding to Initiate Opioid Therapy
- Cluster 2: Conducting an Opioid Trial
- Cluster 3: Monitoring Long-Term Opioid Therapy (LTOT)
- Cluster 4: Treating Specific Populations with LTOT
- Cluster 5: Managing Opioid Misuse and Addiction in CNCP Patients



Classification of Opioids

	Considering action on Receptors				
Origin	**Agonist μ**	**Ago-anta μ**	**Partial-ago μ**	**Anta μ**	**Antagonist NMDA & *5HT only**
Naturally occurring	Codeine, Morphine				
Semi-synthetic	Hydro-morphone, Oxycodone	Nubain	Bupre-norphine		
Synthetic	Fentanyl, Methadone Tramadol	Talwin		Naloxone, Naltrexone *M Naltraxone*	Methadone *Tramadol

Hepatic excretion: Buprenorphine & Methadone

48

Classification of Opioids

	Considering action on Receptors				
Origin	Agonist μ	Ago-anta μ	Partial-ago μ	Anta μ	Antagonist NMDA & *5HT only
Naturally occurring	Codeine, Morphine				
Semi-synthetic	Hydro-morphone, Oxycodone	Nubain	Bupre-norphine		
Synthetic	Fentanyl, **Methadone** Tramadol	Talwin		Naloxone, Naltrexone *M Naltraxone*	**Methadone** *Tramadol

Hepatic excretion: Buprenorphine & Methadone

49

Alberta Health Services Calgary and Area

Methadone

Discovery
Pharmacology
Clinical challenges
Calgary use and experience
Clinical studies
Adverse effects
Case studies

Discovery of Methadone

Eisleb & Schaumann: 1939 Hoechst scientists, one of 105 antipyretics & analgesics #Va 10820: later known as methadone.

“Dolophine or Adolphine” names seem to have been used in the streets of New York.

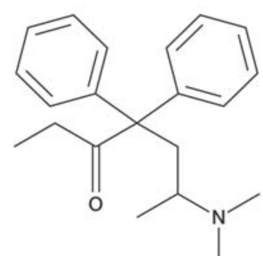
“Amidon” as a pain killer sold in Europe.

Eli-Lilly, US - obtained the production rights for $ 1, as ? “spoils of War!”

Methadone: Chemical Composition

Racemic Mixture R & S

- R-methadone: analgesia
- S-methadone: antitussive, NMDA antagonist, prevents reuptake of NE and 5-HT



Methadone

- mu and delta opioid receptor agonist
  - Analgesia and typical opioid SE profile; may have more diaphoresis and flushing
- NMDA receptor antagonist
  - May help to prevent or reverse opioid tolerance and hyperalgesia
  - Theoretical advantage for neuropathic pain
- Inhibits re-uptake of norepinephrine & serotonin
  - Evolving evidence for this mechanism-based analgesia via descending modulation in neuropathic pain

Opioid Pharmacokinetics

Opioid	Terminal Half-Life (hours)	Oral Bioavailabilty or transdermal (%)	Active Metabolites
Morphine	2 – 4	10 – 50	M6G, M3G
Meperidine	3 – 4	30 – 60	Normeperidine
Methadone	6 – 150	60 – 90	None known
Fentanyl Transdermal	17	92 – 95	Norfentanyl
Codeine	3 – 4	60 – 90	Morphine
Oxycodone	2 – 6	40 – 80	Oxymorphone
Hydromorphone	2 – 4	35 – 80	H3G?, H6G

Opioid Pharmacokinetics

Opioid	Terminal Half-Life (hours)	Oral Bioavailabilty or transdermal (%)	Active Metabolites
Morphine	2 – 4	10 – 50	M6G, M3G
Meperidine	3 – 4	30 – 60	Normeperidine
Methadone	6 – 150	60 – 90	None known
Fentanyl Transdermal	17	92 – 95	Norfentanyl
Codeine	3 – 4	60 – 90	Morphine
Oxycodone	2 – 6	40 – 80	Oxymorphone
Hydromorphone	2 – 4	35 – 80	H3G?, H6G

Pharmacokinetics: Plasma Concentrations

Bi-exponential absorption

1. Rapid alpha-phase = transfer of drug from the central compartment to the tissue compartment and to the beginning of elimination
   - T 1/2 of this phase varies from 1.9-4.2 hours (avg 3 hrs)
2. Slow beta-phase = corresponds to elimination
   - T 1/2 varies from 8.5-47 hrs

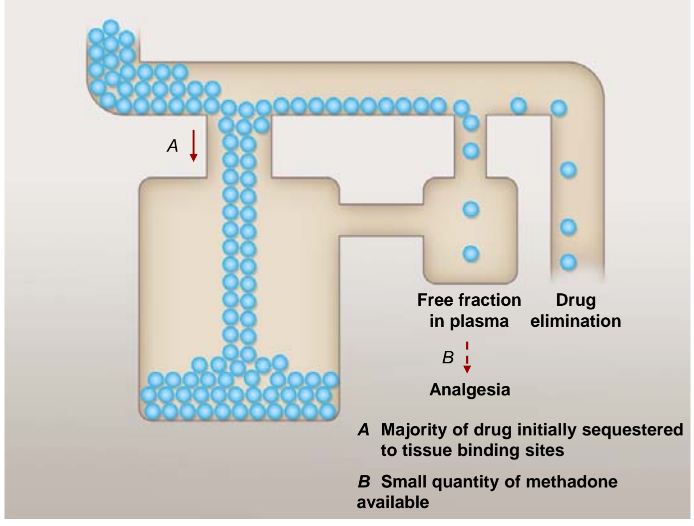
Pharmacokinetics: Absorption and Distribution

- Absorption
  - Oral absorption results in 80% bioavailability with a range of 41-99% and is detected in plasma in ~30 minutes
  - T-max varies from 1-6 hours (avg 2.5-4.4h)
  - Very lipophilic so absorbed easily across mucous membranes (mouth/rectum)
- Distribution
  - Rapid and extensive initial distribution occurs within 1-2 hours
  - 89% is bound in plasma to A1G (an acute phase reactant whose level fluctuates)
  - Prolonged elimination phase lasting for 15-60 hours

Davis M. Support Care Cancer 2001; 9:73-83. Peng P. Can J Anesth 2005; 52:513-523. Toombs J. Amer Fam Phys 2005; 7(7):1353-1358. Ferrari A. Pharmacological Research 2004; 50:551-559

57

Methadone Pharmacology During Initial Dosing Period (0 to 1 day)



Gannon C. Eur J Palliative Care 1997; 4:152-8

58

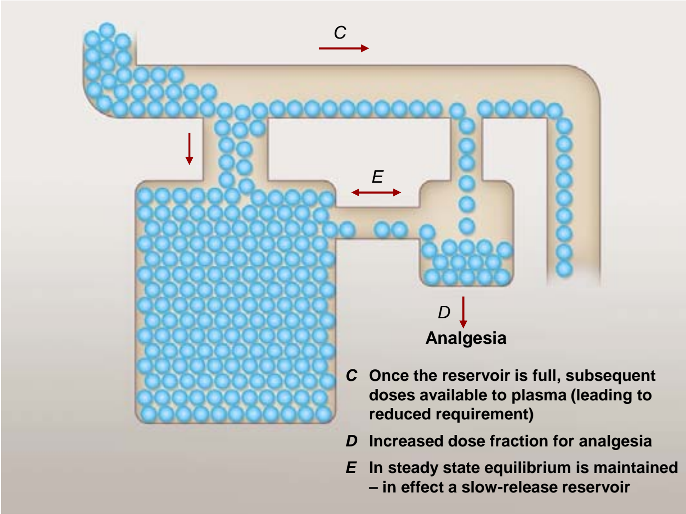
Pharmacokinetics: Plasma Concentrations

- Once absorbed, 98% is transferred to tissues, primarily liver, kidneys and lungs
- 1-2% remains in the blood
  - 60-90% of that is bound to plasma proteins
  - Only the unbound methadone is active
- Anything reducing plasma alpha 1 globulins will increase the available methadone; heroin addiction and stress both increase the alpha 1 globulins and decrease free, active methadone

Ferrari A. Pharmacological Research 2004; 50:551-559

59

Methadone Pharmacology At Steady State (3 – 5 days +)



Gannon C. Eur J Palliative Care 1997; 4:152-8

60

Methadone: Large Inter- and Intra-individual Variation

- Factors involved in variable blood concentrations include:
  - Varying A1G plasma level
  - Drug interactions
  - Duration of treatment
  - Genetic factors regulating both pharmacokinetics (metabolizing enzymes and transporters) and pharmacodynamics (receptors and signal transduction elements)

Somogyi AA. Clin Pharmacol Ther 2007; 81(3):429-44.
Coller JK. Clin Pharmacol Ther 2006; 80(6):682-90

61

Methadone and Prolonged QT

- Mechanism not yet fully identified
- Significant QTc prolongation is defined as > 500 msec
- Risk factors include: low K+ or Mg+ (a side-effect of cisplatinum therapy), hx of CHF, bradycardia or baseline long QT, advanced liver disease, and concomitant disuse or use of medications or a reduction in plasma protein levels which then increase methadone concentration
- Appears to be rare in methadone doses of < 50 mg/day and more common in doses > 80 mg/day

Krantz M. Lancet 2007; 369(9559):336-7.

62

Methadone and Prolonged QT

Suggested Guidelines:

- Baseline ECG before or around, initiating methadone or the dose exceeds 80mg in 24 hrs
- Recheck with methadone dose increases
- Recheck if possible drug interaction that could increase effective dose
- If QT between 450-500 msec, consider increasing methadone with caution and ECG reassessment
- If QT > 500 msec, consider reducing dose of methadone

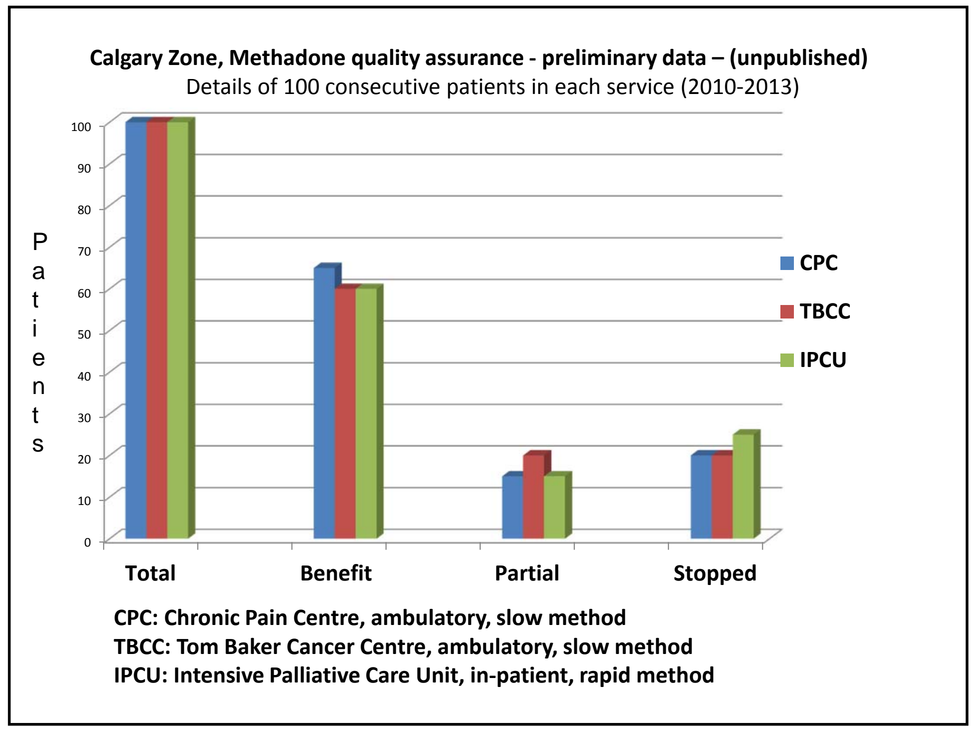
Iskamdar S. Tennessee Medicine, 2007; Feb: 35-42.

Evidence and Methadone use

Cancer Chronic Pain

Non-Cancer Chronic Pain

Neuropathic pain & Opioid induced Hyperalgesia



Methadone for Cancer Pain: Retrospective Study

- ***Subjects:*** 196 advanced cancer outpatients with moderate to severe pain (retrospective)
- ***Key results:***
  - Mean dose of oral methadone ranged from 14 mg at day 7 to 23.65 mg at day 90
  - Reduction in pain intensity with respect to baseline occurred at each analysis time
  - In 55.1% of the patients the reduction during the follow-up period was ≥ 35% according to the Palliation Index
  - A high percentage of patients reported an amelioration of insomnia

De Conno F, et al. J Clin Oncol 1996; 14(10):2836-42

Methadone vs. Morphine for Advanced Cancer Pain

- ***Subjects:*** 40 patients with advanced cancer requiring strong opioids for pain management
- ***Key results:***
  - Methadone patients had opioid escalation indices significantly less than morphine patients
    - 7 methadone patients maintained initial dosage until death; 1 morphine patient did not require opioid dose escalation
  - Symptom frequencies and intensities were similar in the two groups

Mercadante S, et al. J Clin Oncol 1998; 16(11):3656-61. 67

Methadone for Refractory Neuropathic Pain

- ***Subjects:*** 18 patients with a diverse range of chronic neuropathic pain syndromes
  - All had responded poorly to traditional analgesics
- ***Key results:***
  - Analgesia was seen after each dose of methadone
  - Compared to placebo, methadone 10 mg bid significantly improved maximum pain intensity, average pain intensity and pain relief
  - Analgesic effects extended over 48 hours
  - Analgesic effects were not restricted to any particular type of neuropathic pain

Morley JS, et al. Palliat Med 2003; 17(7):576-87. 68

Low-Dose methadone for prevention of Opioid Hyperalgesia

A retrospective study of 240 patients with Cancer and Non-Cancer diagnosis with chronic pain and opioid therapy at MD Anderson Centre, Texas:

Patients who are on opioid other than methadone

Methadone maximum 15 mg/day &
Haloperidol 2 to 6mg/day, along with methadone

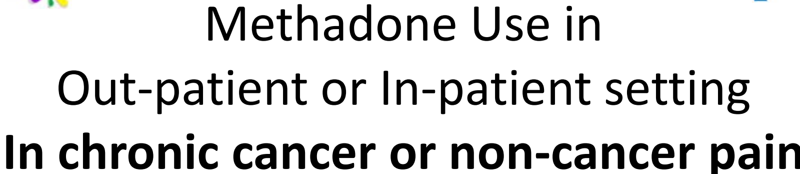
Hyperalgesia was not reported with improved pain control

Salpeter S R, Burera E, et al, J Pall Med, 16, Number 6, 2013 69

Patient-specific Considerations Methadone for Analgesia

Methadone Prescribing, Dosing and

Drug Interactions



Methadone Use in Out-patient or In-patient setting **In chronic cancer or non-cancer pain**

Opioid tolerant

Toxicity from other opioids

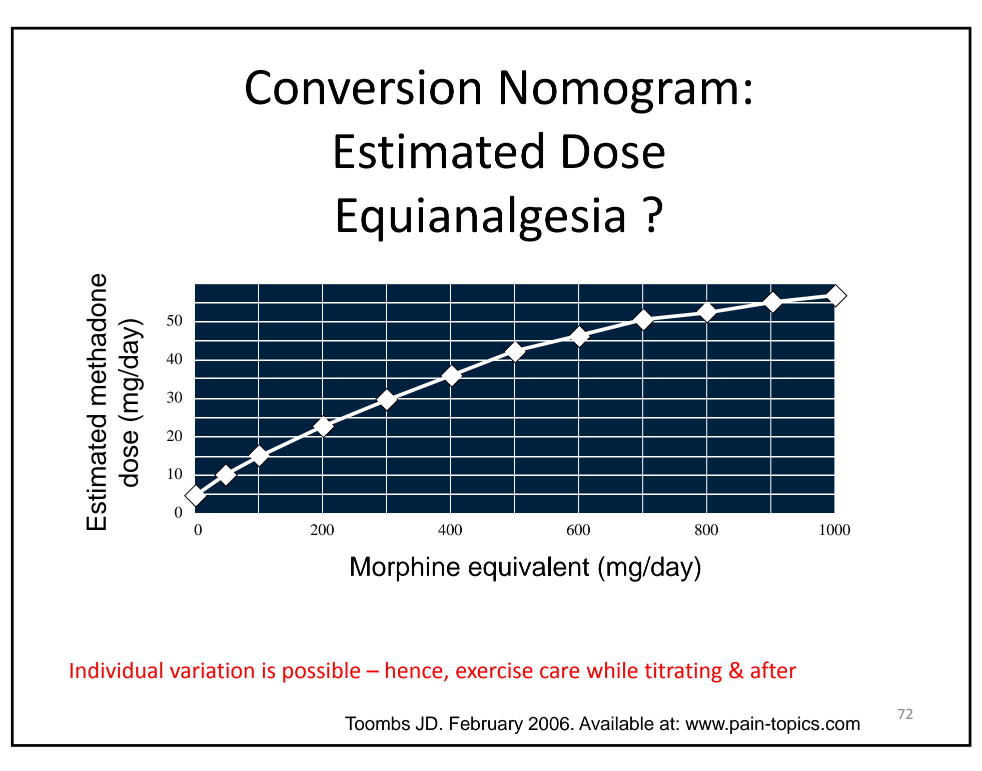
Elderly & frail

Renal disease & dialysis

Substance use disorder

Hyperalgesia

Conversion Nomogram: Estimated Dose Equianalgesia ?



Individual variation is possible – hence, exercise care while titrating & after

Toombs JD. February 2006. Available at: www.pain-topics.com

72

Methadone titration

Slow titration

ambulatory patient, hospital or clinic

Rapid titration (in patients)

German method

Edmonton or Modified German method

Morley & Makin

Methadone for Analgesia

Patient Information:

Can use printed information relating to:

- Methadone use in general
- Initial observation & follow-up
- Goals: mutually agreed
- Oipoid use agreement
- Side-effects
- When and how to stop methadone
- Non-pharmacological interventions
- Self management Skills

General Considerations for Methadone Dosing in Pain

- “Start Low Go Slow”
- No reliable conversion factors for other opioids
- Any new side effects related to sedation or respiratory depression is more likely due to methadone and NOT to the previous opioid
- Methadone blood levels continue to rise for approximately 5 days after starting treatment

Starting Methadone – (Slow Method) morphine-equivalent < 100 mg/day)

- **Frail elderly: consider a lower start dose**
- Week 1 Rx: 1 mg or 2.5 mg od to tid
- Titrate up by 1mg or 2.5 mg/dose q 5-7 days
  - (i.e., week 2 dispense 5 mg tid, week 3 dispense 7.5 mg tid)
- May cautiously use BT opioids if necessary for additional pain relief during titration as the situation warrants

Starting Methadone in Opioid-experienced Patients (Rapid Method)

- Consider MEDD and calculate the need for methadone using nomogram
- **In-patient - can consider rapid titration**
- Use appropriate regular q4h dose & BT methadone as needed
- Titrate up the regular dose and/or BT methadone next day or two
- At the end of 3 or 5 days, 24 hrs dose given in 3 divided doses with or without BT medication

Options for Breakthrough Pain During Methadone Therapy

- ***During methadone titration:*** Use an alternative short-acting oral opioid with short half-life (*e.g.,* morphine 10 mg) every hour as needed for breakthrough pain and to provide pain relief
- ***At stable methadone dose:*** Give 10% of total daily methadone as prn drug every hour for breakthrough pain
  - Instruct the patient to call you if they need to use more than 5 breakthrough doses per day

vonGunten CF. J Palliative Med 2004; 7(2):304-5

Methadone in opioid novice

Methadone can be used, starting at a lower dose and gradually titrating.

Observation capacity by a family member for the first 24 to 48 hrs.

Good information given to patient/ family

Methadone Drug Interactions

There are 2 ways to cause an effect:

1. By starting a medication which will alter the metabolism, e.g.,:
   - Starting **fluconazole or paroxetine** may reduce clearance resulting in increased serum levels and sedation/toxicity
   - Starting **retonavir or dilantin** may increase clearance resulting in decreased levels and may reduce analgesia or withdrawal symptoms

Methadone Drug Interactions

2. By **stopping** a medication which will alter the metabolism, e.g.,:
   - Stopping **fluconazole or paroxetine** may increase clearance resulting in decreased serum levels and reduced analgesia or withdrawal symptoms
   - Stopping **retonavir or dilantin** may decrease clearance resulting in increased levels and may increase analgesia or cause sedation/toxicity

Methadone Drug Interactions

3. Consider medications that **prolong QT/QTc** interval including hypokalemia or hypomagnesaemia

Medications include:

Haloperidol, Paroxetine, Diltiazam, etc.

4. **Serotonin syndrome**:

Concomitant use of: TCAs, MAOIs, SSRIs etc.

OPIOID ADVERSE EFFECTS

Most Common side effects:

- Constipation (requires ongoing laxatives)
- Nausea
  - Usually resolves after a few days
  - Metoclopramide or Haloperidol in the first few days
- Somnolence (usually resolves after a few days)
- Dry mouth

Less common side effects:

- Sweating, Pruritis

Rare: (especially with appropriate dosing)

- Respiratory depression

OPIOID ADVERSE EFFECTS

Sleep Apnoea

Common with opioid use including methadone

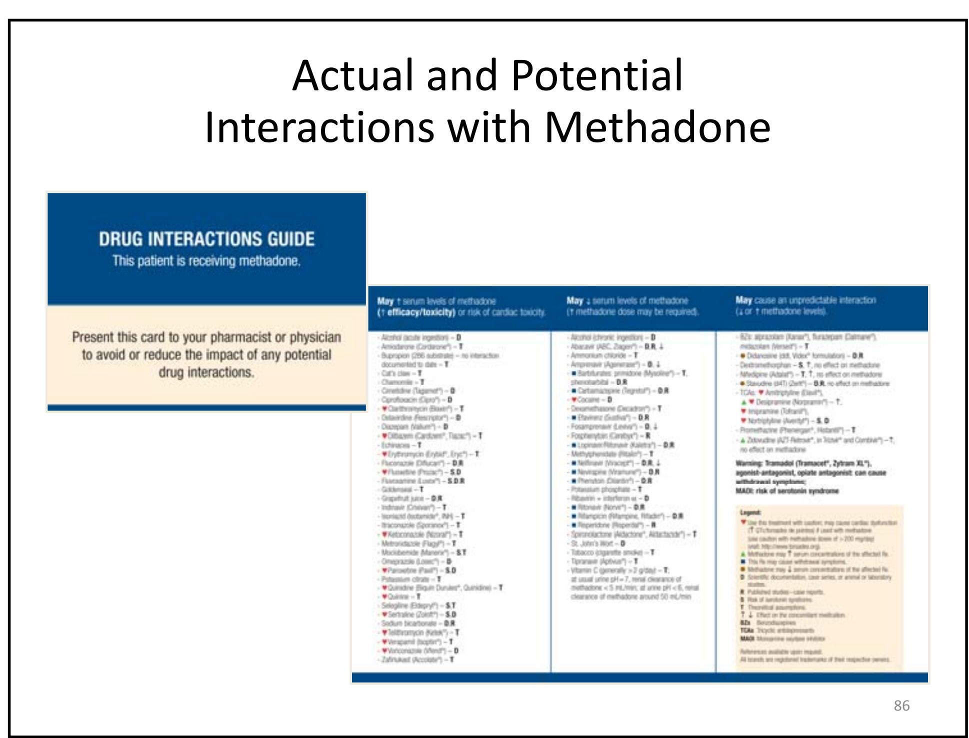
Endocrine:

Associated with long term use of opioids
May need hormone replacement eg. Testosterone

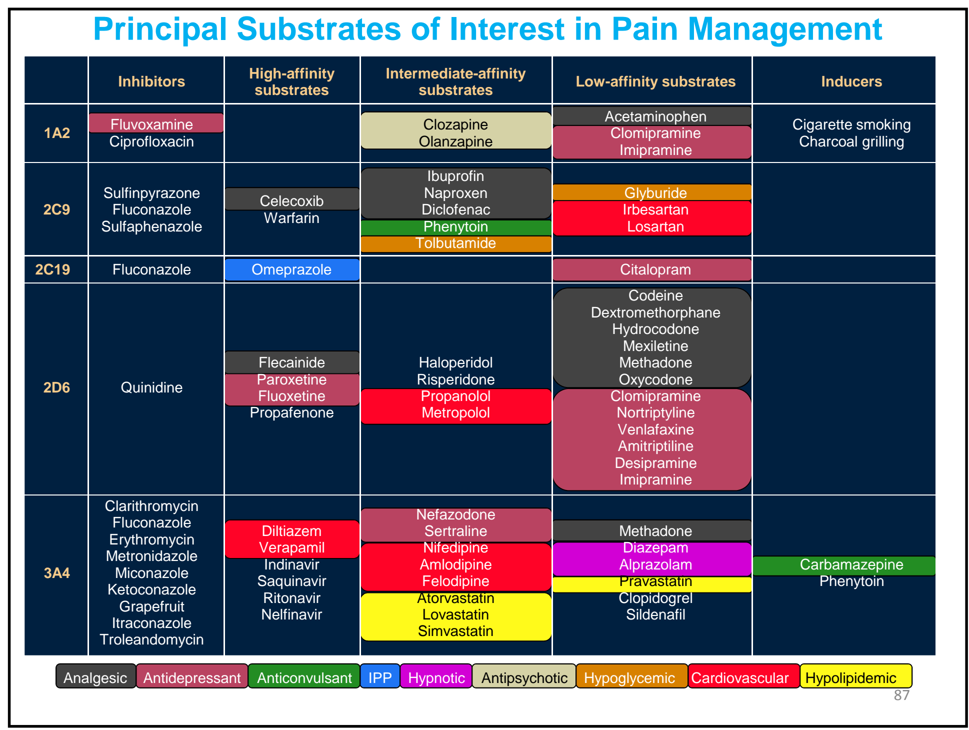
Methadone Toxicity

- Sedation always proceeds respiratory depression
- Monitor for and concern if:
  - Lack of response to tactile or vigorous stimuli
  - RR < 10/min
  - Systolic BP < 90 mmHg or 20% less than baseline
  - O_2 saturation levels occasionally helpful but can be falsely reassuring
  - Consider in patients with history of sleep apnea, obesity or any condition which decreases ventilation capacity

Actual and Potential Interactions with Methadone



86



Principal Substrates of Interest in Pain Management

	Inhibitors	High-affinity substrates	Intermediate-affinity substrates	Low-affinity substrates	Inducers
1A2	Fluvoxamine Ciprofloxacin		Clozapine Olanzapine	Acetaminophen Clomipramine Imipramine	Cigarette smoking Charcoal grilling
2C9	Sulfinpyrazone Fluconazole Sulfaphenazole	Celecoxib Warfarin	Ibuprofin Naproxen Diclofenac Phenytoin Tolbutamide	Glyburide Irbesartan Losartan	
2C19	Fluconazole	Omeprazole		Citalopram	
2D6	Quinidine	Flecainide Paroxetine Fluoxetine Propafenone	Haloperidol Risperidone Propanolol Metropolol	Codeine Dextromethorphane Hydrocodone Mexiletine Methadone Oxycodone Clomipramine Nortriptyline Venlafaxine Amitriptiline Desipramine Imipramine	
3A4	Clarithromycin Fluconazole Erythromycin Metronidazole Miconazole Ketoconazole Grapefruit Itraconazole Troleandomycin	Diltiazem Verapamil Indinavir Saquinavir Ritonavir Nelfinavir	Nefazodone Sertraline Nifedipine Amlodipine Felodipine Atorvastatin Lovastatin Simvastatin	Methadone Diazepam Alprazolam Pravastatin Clopidogrel Sildenafil	Carbamazepine Phenytoin

Analgesic | Antidepressant | Anticonvulsant | IPP | Hypnotic | Antipsychotic | Hypoglycemic | Cardiovascular | Hypolipidemic

87

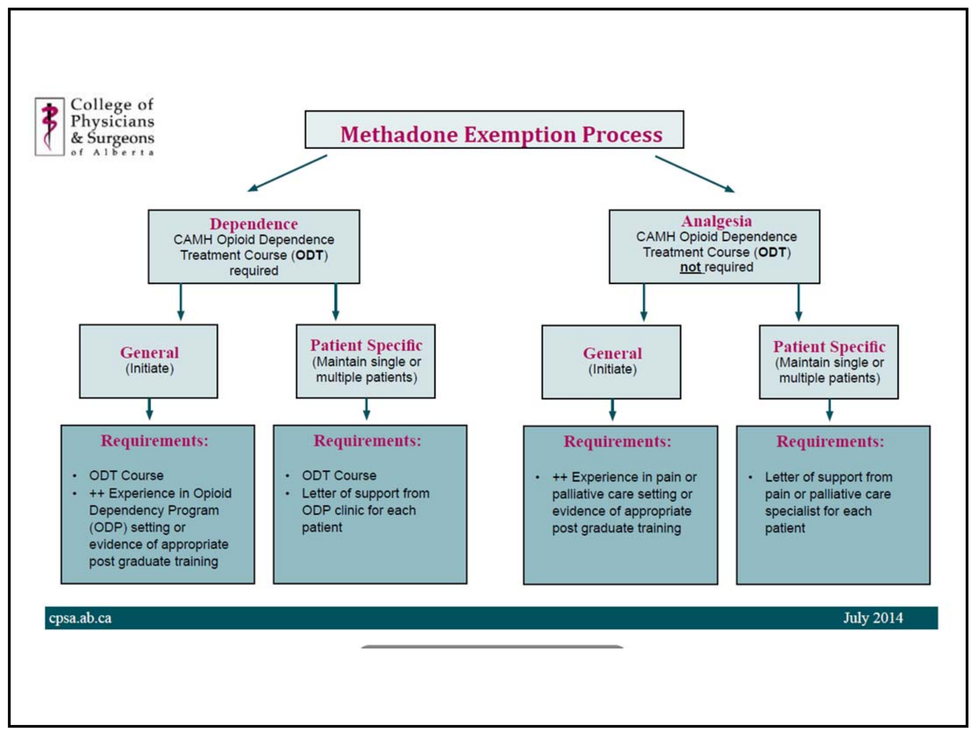
Methadone for Analgesia

CDSA

Exemption

CDSA: Controlled Drugs & Substances Act

Canadian Federal Act, Section 56


College of Physicians & Surgeons of Alberta
Methadone Exemption Process
Dependence
CAMH Opioid Dependence Treatment Course (ODT) required
Analgesia
CAMH Opioid Dependence Treatment Course (ODT) not required
General
(Initiate)
Patient Specific
(Maintain single or multiple patients)
General
(Initiate)
Patient Specific
(Maintain single or multiple patients)
Requirements:
• ODT Course
• ++ Experience in Opioid Dependency Program (ODP) setting or evidence of appropriate post graduate training
Requirements:
• ODT Course
• Letter of support from ODP clinic for each patient
Requirements:
• ++ Experience in pain or palliative care setting or evidence of appropriate post graduate training
Requirements:
• Letter of support from pain or palliative care specialist for each patient
cpsa.ab.ca
July 2014

PALLIUM
Alberta Health Services
Methadone Program
Overview
Standards & Guidelines
Resources
The CPSA Methadone Program is designed to support physicians in providing safe, accessible, effective and consistent clinical care to patients who may benefit from treatment with methadone. This program will be relevant to physicians who:
• practice addiction medicine
• treat patients with chronic pain
• look after patients in a palliative care setting
• treat patients admitted to hospital who are already on methadone
Practice of Addiction Medicine
Treat Patients with Chronic Pain
Look after patients in palliative care setting
Treat patients admitted to hospital who are already on methadone

Prescribing Methadone: CDSA* Exemption

Temporary exemption (hospital/institutional per-patient use):

In Calgary, AHS acute care sites; physician can continue the existing dose with or without exemption

At present this applies to Acute care sites only

- Physicians wishing to prescribe methadone for analgesic use in their patients must obtain a Federal Ministerial exemption per section 56 of the Controlled Drugs and Substances Act (call 1-866-358-0453)

*CDSA: Controlled Drugs and Substances Act

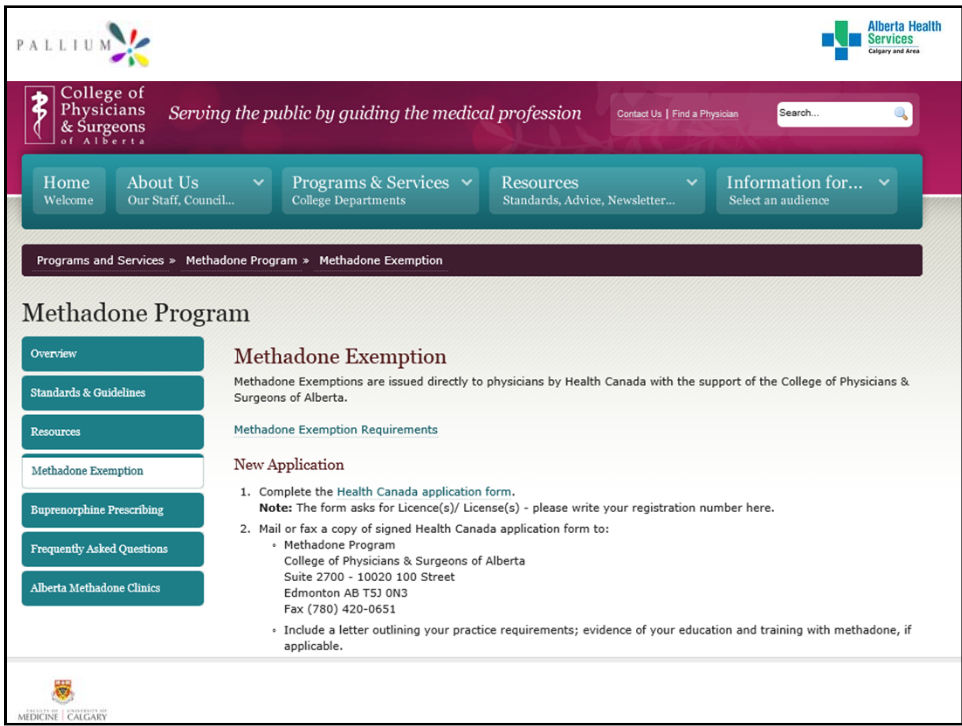
Prescribing Methadone: CDSA* Exemption

General exemption (per practitioner):

- Conditions/process vary provincially; inquire at provincial College and/or federal methadone program.

- Alberta: CPSA 1-780-423-4764

*CDSA: Controlled Drugs and Substances Act



Application for exemption

A copy of application

Apply through the College of Physicians and Surgeons of Alberta (Enquire other provinces)

A copy certificate of attendance at this workshop attached to the application

Methadone – Case Scenarios

In chronic cancer or non-cancer pain

Neuropathic & Neuralgic pain

Opioid tolerant

Toxicity from other opioids

Renal disease & dialysis

Substance use disorder

Opioid induced Hyperalgesia

B.G., 82 yrs - 5

Retired family physician with LBP and previous back surgeries, seen at RGH and has been using morphine CR & IR, more than 360 mg in 24 hours, Pain relief moderate but "depressed".

Change to hydromorph CR & IR around 24 mg tid, better mood but no improvement in pain. Co-analgesics TCAs and Gabapentinoids led to poor balance and memory.

Any other options: ?

Options - B.G., 82 yrs – 5a

Continue hydromorph & add

Compounded Topical ointment:

Voltaren (NSAID)

Lidocaine (Local anesthetic – Na channel)

Nortriptyline (TCA)

Gabapentin (Antisieizure – Ca channel)

Clonidine (Sympatholytic)

Ketamine (NMDA antagonist)

Options - B.G., 82 yrs – 5b

Continue hydromorph & added

Compounded Topical ointment:

Lidocaine (Local anesthetic – Na channel)

Gabapentin (Antisieizure – Ca channel)

Ketamine (NMDA antagonist)

Could afford as there is cost to go with compounded ointments

Breakthrough pain was better but baseline pain still high 5-6/10

Options - B.G., 82 yrs – 5c

Hydromorph due to side effects and poor baseline pain relief, was switched to Methadone, commencing at 1mg tid and final dose of 15mg tid, Hydromorph withdrawn over 6 weeks.

Remains on Methadone 15 mg tid – 5 years and no dose escalation & better baseline pain 2-3/10. Uses Tylenol arthritis and ointment for breakthrough pain.

Recently admitted to FMC with GI bleed and recovering but worries about his wife who has dementia.

LB, 65 yrs - 1

Recurrent Endometrial Ca with groin pain with neuralgic pain

HM CR 15mg tid, wishes to reduce due to nausea and tried Morphine and Fentanyl and could not tolerate. Also on Gabapentin 300mg tid with little benefit

Nausea has not improved variety of anti-emetics including maxeran, haloperidol and ondensetron have been tried

Options – LB – 1a

MEDD: HM 45mg X 5 = 225mg

Low risk for SUD

Not suited for tramadol, Tapentadol or buprenorphine patch as the dose is high

Oxycodone CR, needs more than150mg in 24hrs

Methadone a possibility?

Options – LB – 1b

Methadone was commenced at 2.5mg tid and gradually increased to 10mg tid and hydromorph was reduced and stopped

16 months, remains at 10mg tid with restful sleep, better mood, pain & function improved

Personal goals of returning to play golf materialized

RK, 70 yrs - 2

- Follicular lymphoma chemotherapy with peripheral sensory neuropathy and had back surgeries with LBP & now, no radiculopathy
- Had been on Morphine 900mg in 24 hrs
- Sleep is poor, average pain still reports around 6-7/10
- No other health issues & UDS negative
- What other options?

Options - RK, 70yrs – 2a

- MEDD=900, Moderate risk for SUD
- Consider Hydromorph or Fentanyl with Co-analgesics like TCAs and/or Anti-seizure medications
- Fentanyl: needs more than 4 patches of 100mcg/hr!
- Methadone
- Implantable pump?

Methadone – RK, 70 yrs-2b

Did try Hydromorph, alone did not control neuropathic pain, addition of TCAs and Gabapentin some benefit but side effects did not allow increased dosage

Commenced on methadone 5mg tid and titrated up to 15mg tid and remains (28 months) at this dosage with no other analgesics except Tylenol arthritis occasionally, for flare-up

SD, 54yrs – 3a

Rectal Ca, AP resection with neuropathic pain in the perineum. Had been on Oxycontin 160mg bid and had noted tablets in the colostomy bag, some were “dummy pills” and pain control was poor

Changed to OxyNeo, when older preparation was stopped and noted “hydrogel” in the colostomy; again with poor pain control. Had not been on any co-analgesics

What other options?

Options – SD, 54yrs – 3b

MEDD=480mg – Low risk for SUD

Co-analgesics: TCAs, Anti-seizure meds
Liquid/tabs morphine or CR (480mg/24hrs)
Liquid/tabs hydromorph or CR (96mg/24hrs)
Fentanyl patch (250mcg/hr)
Add co-analgesics for neuropathic pain

Methadone liquid or tabs?

Methadone – SD, 54yrs – 3c

Patient chose liquid methadone

Started, Methadone (liquid) at a dose of 5mg tid while remained on OxyNeo and at a dose of 10mg tid in two weeks, noticed improvement in night time sleep and OxyNeo was reduced to 80mg bid and another two weeks 15mg tid and OxyNeo was reduced to once a day and stopped after 3 weeks and remains on steady dose of methadone 15mg tid over 2 years.

JD, 42yrs – 4a

LBP, mechanical back with no radiculopathy and multi site myofascial pain for more than 10 years

She lives with her mother and has 12 year old daughter. Hardships in childhood, on AISH

Had been using 120mg Oxycontin tid and now OxyNeo and OxyIR, 10-20mg X 4 times a day

JD, 42yrs – 4b

Major Depression and on antidepressants

Labile emotions, still uses marijhuana

High risk for substance use disorder

Family physician is concerned and the dose of Oxycodone IR, increasing

Tried Morphine and Hydromorphone but did not like them

What options can we consider?

Options – JD, 42yrs – 4c

MEDD = 540 mg, High risk for SUD!

Urine drug screens: positive for cocaine some times and marijuana

Fentanyl patch

Methadone

Options – JD, 42yrs – 4d

Opioid switch to Fentanyl, noted skin rash and stopped

Methadone commenced and reached up to 25mg tid and the dose of OxyNeo reduced to 60mg bid and the use of OxyIR to 10mgX5 a day

Patient was asked to see the addiction counsellor from ADAC and admission to inpatient service for detoxification was suggested and patient did not agree.

Options – JD, 42yrs – 4e

Two weeks later, patient arrived with her mother with Oxycodone withdrawal symptoms and refused to take methadone.

Patient and mother after a lengthy conversation agreed to stop methadone and continue OxyIR with boundaries.

Continue OxyIR not more than 100mg/day, can take 10 to 20mg q4h, (no OxyCR) and weekly dispensing

Learning Objectives

1. *To learn the challenges associated with chronic pain management*

2. *To understand the good and bad, associated with the use of Methadone as an analgesic*

3. *Proficient enough, that an exemption for use of Methadone for analgesia, can be requested*

Finally, colleagues from AHS Calgary Zone, Palliative Care & Chronic Pain Clinic are available as mentors and a list is available for you to use

Conclusions

Chronic Pain must be considered not in isolation but as "total pain and suffering" with physical and mental health included

Methadone, an opioid with biphasic absorption with hepatic excretion and associated enzyme system & QT prolongation requires careful titration

Methadone is associated with advantages and disadvantages, learning to use it wisely may add another tool in your toolbox & mentors can assist in your further learning

List of colleagues

"expressed an interest to mentor"

email : first.last name@albertahealthservices.ca

Palliative Care

Clinical Pharmacists at TBCC:

Dean England 403 521 3432

Chris Ralph 403 521 3432

Physicians:

Srini chary, 403 473 2771

Ayn Sinnarajah 403 944 1147

Martin LaBrie 403 944 2304

Lyle Galloway 403 944 1147

Chronic Pain Centre (CPC)

Clinical Pharmacist at CPC

Joyce Cote 403 943 9935

Physicians:

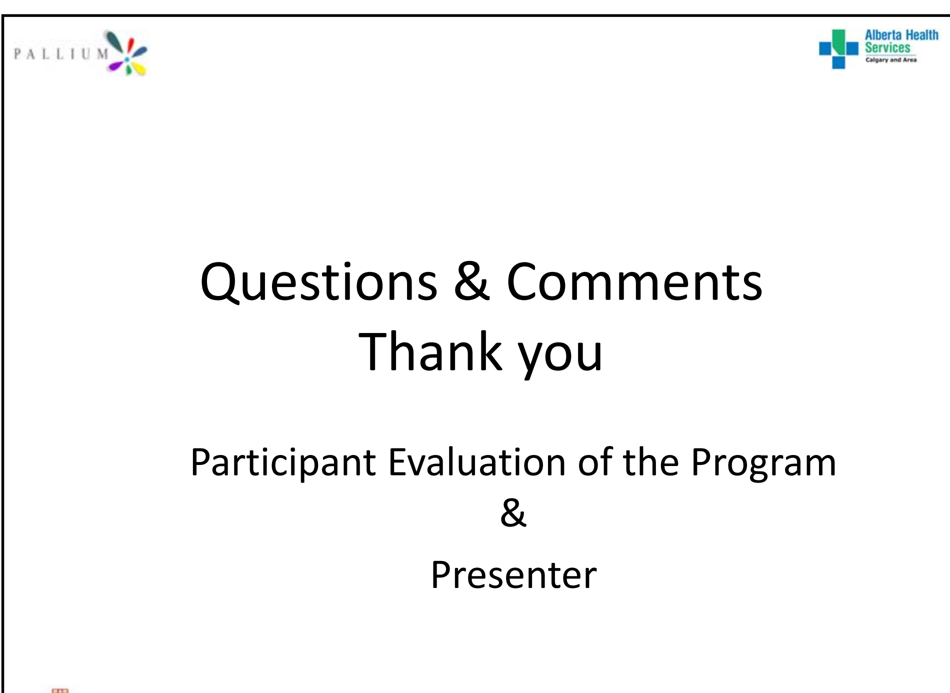
Chris Spanswick 403 943 9960

Lori Montgomery 403 943 9922

John Pereira 403 943 9913

Kelly Shinkaruk

In the event of emergency Palliative Care physician on call via FMC switchboard


PALLIUM
Alberta Health Services
Questions & Comments
Thank you
Participant Evaluation of the Program
&
Presenter
MEDICINE
CALGARY