

Methadone - A Peculiar Drug; But is it too difficult to handle?

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Two Questions

- **Is it justified** to prescribe methadone for this patient with chronic non-cancer pain?



Do you need to be a
rocket-scientist to prescribe
methadone safely?



Why Peculiar?

- Unique, beneficial pharmacology
- Cheap
- Better tolerated – less constipating?
- Still in use after 60 years!




Why Peculiar?

- Highly controlled
- Stigmatized & misunderstood
- **Unpredictable** equivalence dose
- **Accumulation** – difficult to initiate
- Prolonged **QT** Interval
- **Lack of evidence** in chronic non-cancer pain



Methadone – full of promise!

- Potent mu and delta receptor agonist.
- Delta agonism - **counteracts opioid-induced tolerance?**
- **NMDA antagonist** 
- Inhibits reuptake of **5HT & NA** – analgesic effect
- Good option if **tolerant / hyperalgesic** on another opioid.

Methadone – full of promise!

- **Lack of active metabolites** - Small amount of active Methadol & Normethadol. Neurotoxicity occurs with conventional opioids.
- **Long elimination half life** – more forgiving if a dose is missed. Less withdrawal.
- Good choice for management of **dual pathologies**. Lower street value?

Methadone – full of promise!

- **Excellent oral bioavailability 67 – 95%**
- PO, PR routes reliable
- IV, SC, IM , Epidural, Intrathecal routes possible

Adverse Effects

- Nausea / vomiting in 53 patients (23.6%)
- Sedation in 41 patients (18.5%)
- Itching / rash in 29 patients (13%)
- Constipation in 26 patients (11.7%)
- Sweating
- Sexual dysfunction

- **Oral Methadone for Chronic Noncancer Pain:** A Systematic Literature Review of Reasons for Administration, Prescription Patterns, Effectiveness, and Side Effects. Juan Alberto Sandoval, MD, Andrea D. Furlan, MD, and Angela Mailis-Gagnon, MD, MSc, FRCPC. (Clin J Pain 2005;21:503–512)

Equianalgesic doses of opioids

- “....**weak literature evidence base** that exists to support the equianalgesic ratios provided in textbooks, journals, and other medical resources”.



- Gammaitoni AR. Fine P. Alvarez N. McPherson ML. Bergmark S. Clinical application of opioid equianalgesic data. Clinical Journal of Pain. 19(5):286-97, 2003 Sep-Oct.

“Reasonable Dosage Conversions”

Mary Lynch. Pain Res Management Vol 10 2005

Previous Dose of Oral Morphine	Recommended Ratio of Oral Morphine to Oral methadone
Less than 90mg	4
90 – 300mg	8
More than 300mg	12

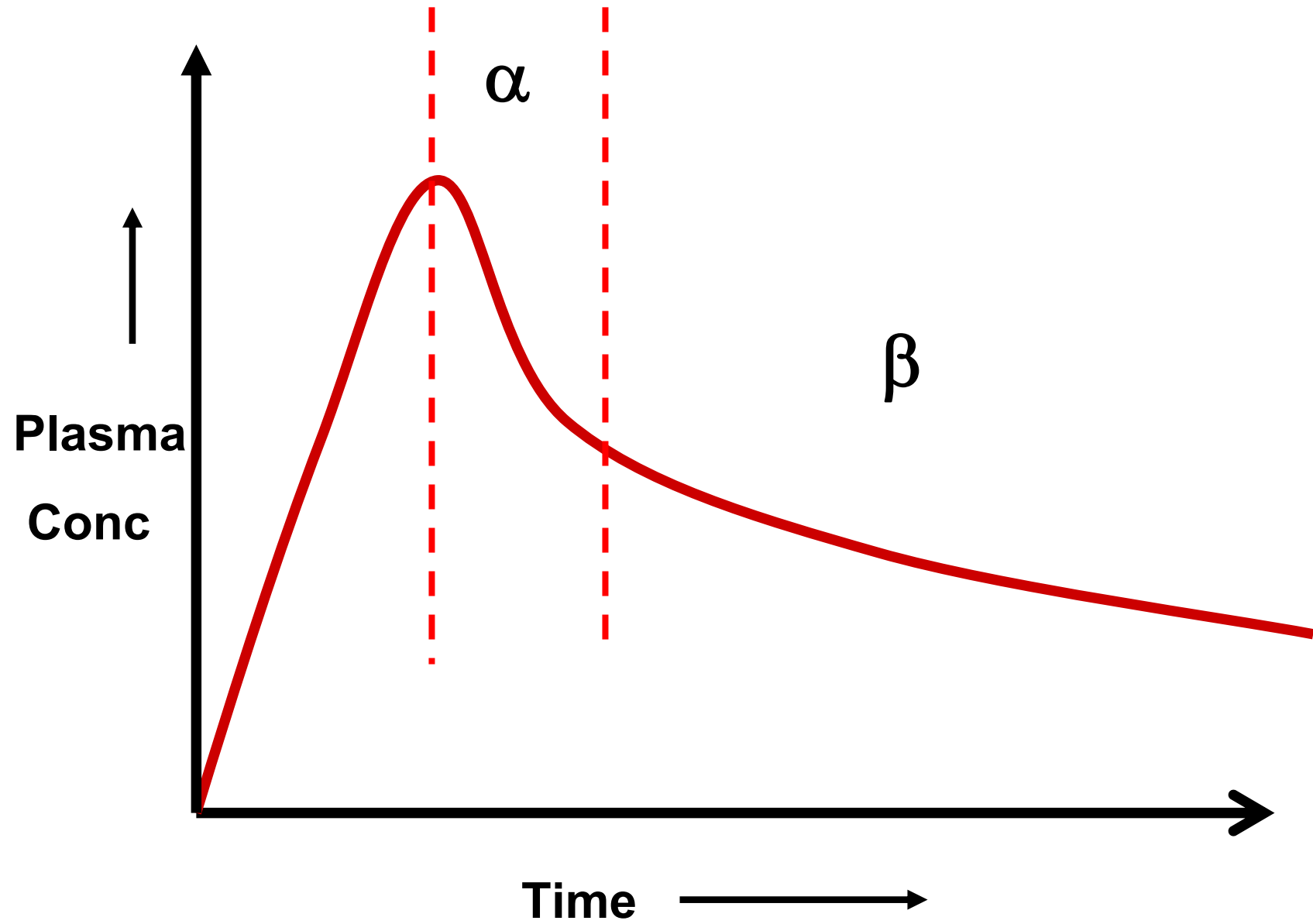
Pharmacokinetics - **accumulation**

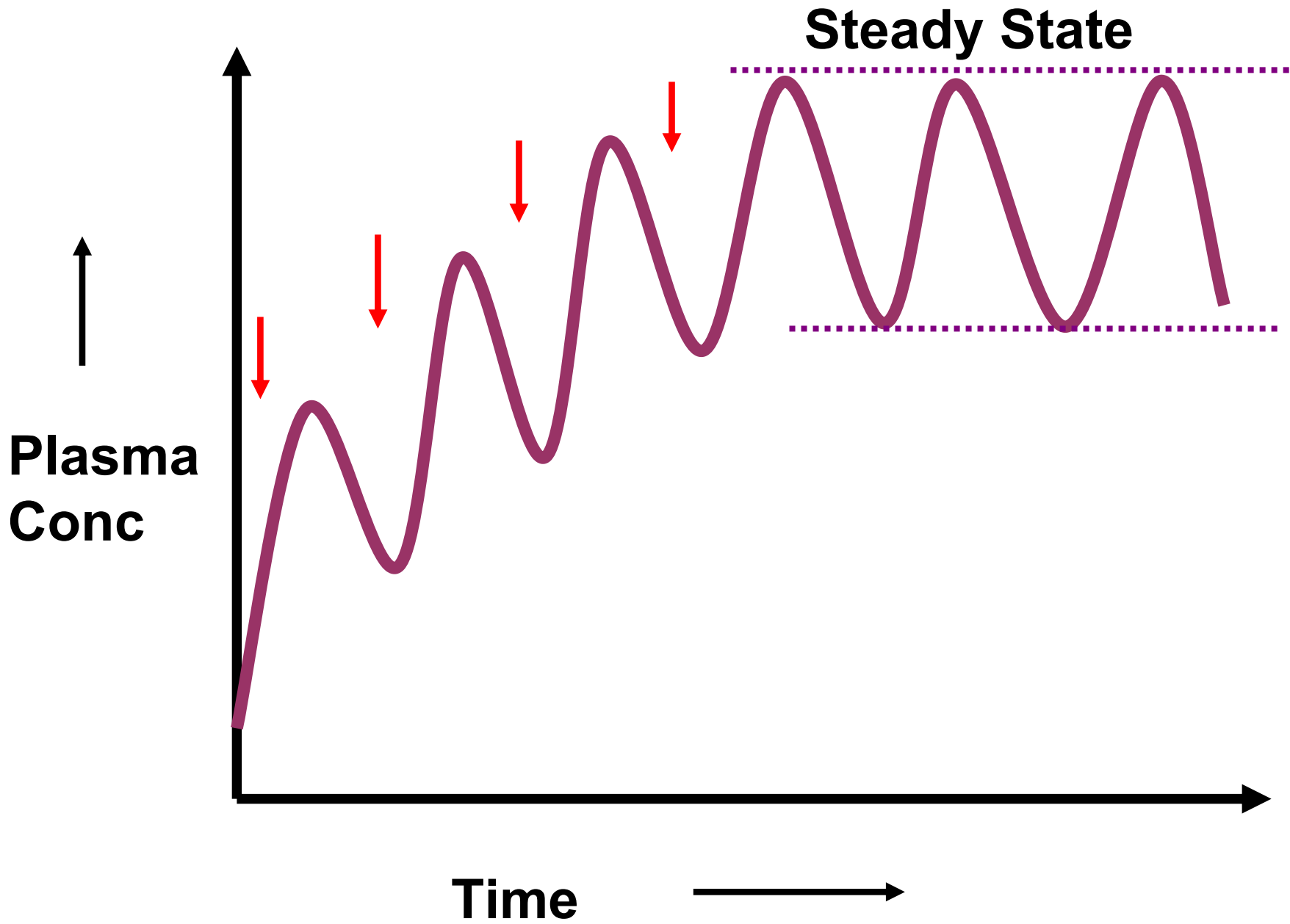
- Peak plasma level 2.5 – 3 hr after oral dose
- Lipophilic & **High volume of distribution**
- Highly bound to alpha1 acid glycoprotein
- Cytochrome enzymes, fecal route
- Variable renal excretion
- Main metabolite is inactive



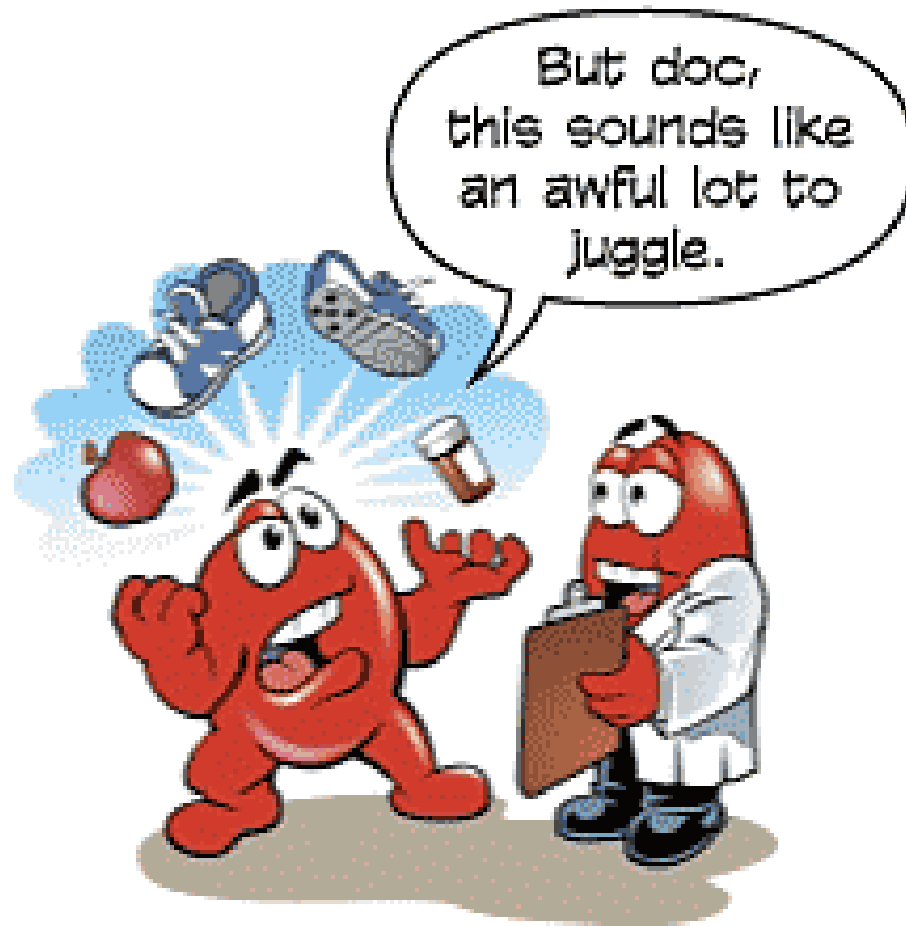
Pharmacokinetics - **accumulation**

- Methadone - biphasic pattern of elimination:
- Slow distribution **α -elimination phase (8–12hr)**
(Analgesia similar time period)
- **β -elimination phase (30–60 hr).**





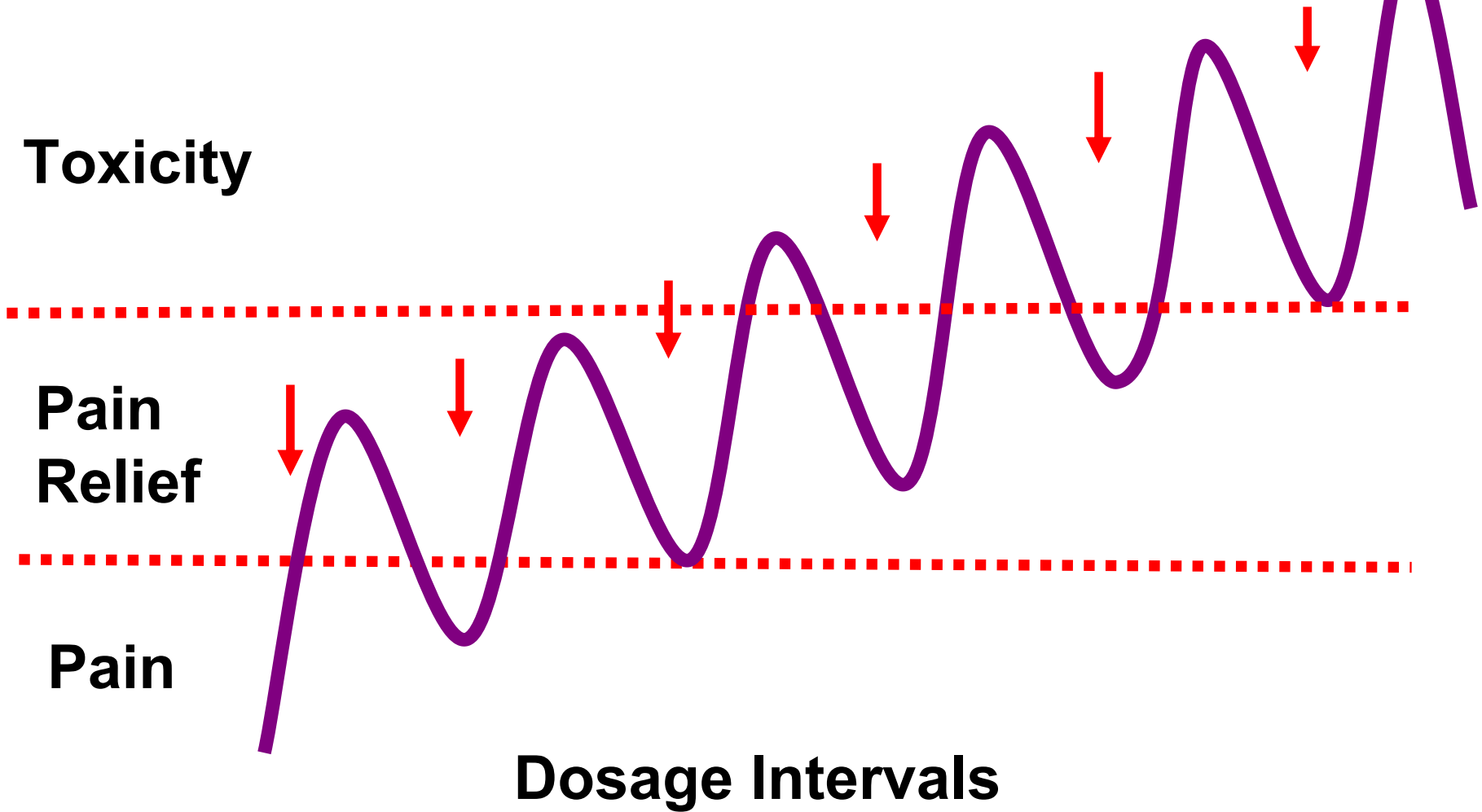
How do you switch from another opioid to methadone?



Methadone Rotation regimes are various!

- The “No No”
- “Stop, Load and Go” Mercadante’s “Rapid Switch”
- Substitute by thirds over 3 days + / - prns
Ripamonti, Lawlor, Bruera and others
- Some simple, some complicated.

The “No No” - Fixed dose and interval

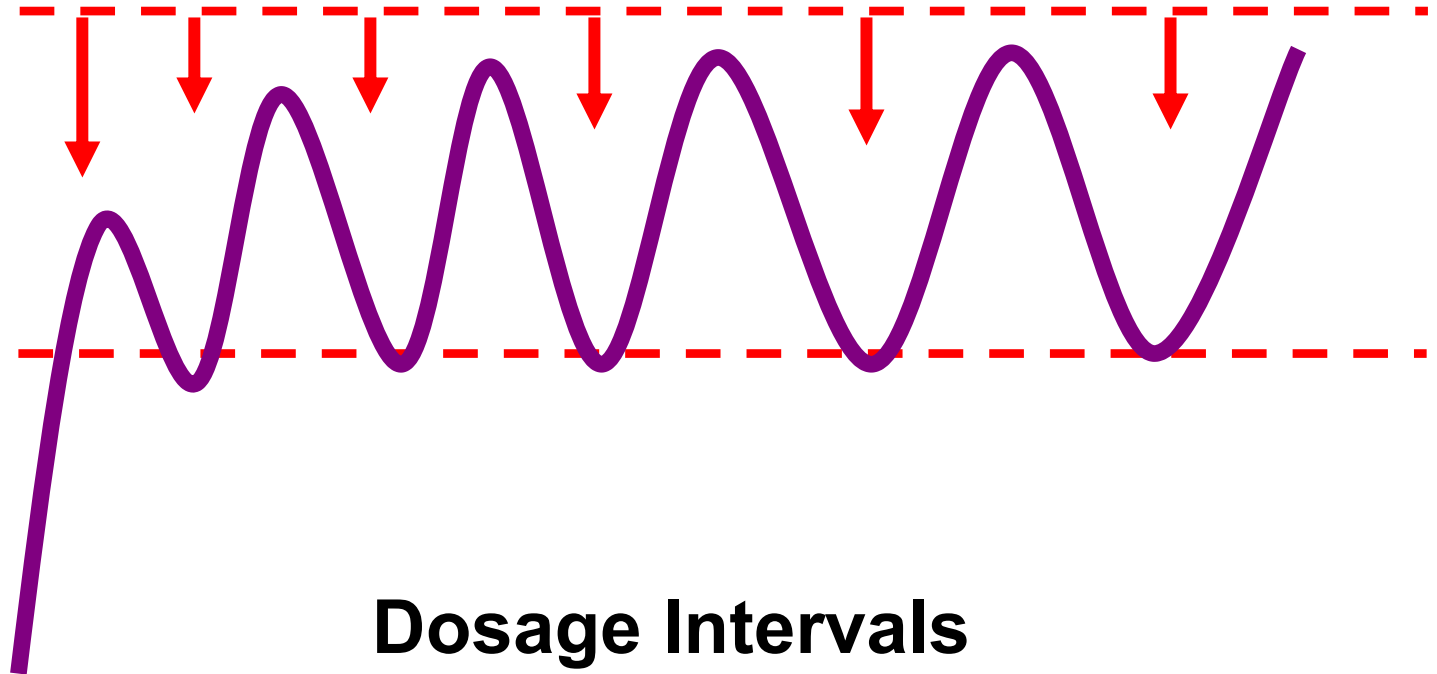


Fixed Dose and Patient-Controlled Intervals (PRNs)

Toxicity

Pain Relief

Pain



Supervision and titration is the key

– hospital admission for difficult rotations?



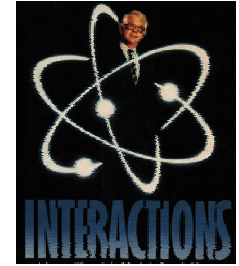
Outpatient rotation is possible

“...opioid rotation to methadone can be safely performed in a home care setting without intensive monitoring when an experienced team is involved. A schedule of twice-weekly visits for the first 2 weeks of follow-up should be enough to ensure safety”

Hernansanz S. Gutierrez C. Rubiales AS. Flores LA. del Valle ML. Opioid rotation to methadone at home. Journal of Pain & Symptom Management. 31(1):2-4, 2006 Jan



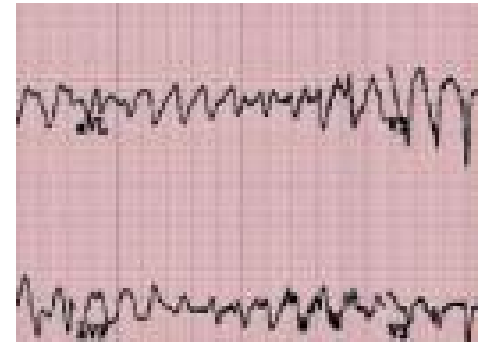
Interactions



- Increased Methadone Effect
- Diazepam
- SSRIs
- Omeprazole
- Grapefruit Juice
- Cipro / Erythromycin
- Amitriptyline **
- Decreased Methadone Effect
- Carbamazepine
- Phenytoin
- Rifampicin
- Risperidone

Gabapentin OK, Pregabalin expected to be OK

QT prolongation – risk of ventricular arrhythmia?



- Methadone may prolong the QTc interval in specific subpopulations but poses little risk of serious prolongation (> 500ms).

Cruciani RA. et al Measurement of QTc in patients receiving chronic methadone therapy. *Journal of Pain & Symptom Management*. 29(4):385-91, 2005 Apr.

QT prolongation – risk of ventricular arrhythmia?



- **Known risk factors associated with TDP found in found in 44 (75%)**
 - Female
 - Interacting medications
 - Hypokalemia
 - Hypomagnesemia
 - Structural heart disease
- **Dosages for 10 of 42 cases (29%) were within the recommended range** for methadone maintenance treatment
- (8%) were fatal.

Pearson EC. Woosley RL. QT prolongation and torsades de pointes among methadone users: reports to the FDA spontaneous reporting system. [Pharmacoepidemiology & Drug Safety. 14(11):747-53, 2005 Nov.

Methadone Fatalities

- Almost exclusively, deaths associated with methadone also involve a cocktail of drugs such as alcohol and benzodiazepines
- Schwartz RP, Brooner RK, Montoya ID, Currens M, Hayes M. 1999. A 12-year follow-up of a methadone maintenance program. *Am J Addict* 8: 293–299.



ADDICTION MEDICINE

Tighten Ontario's methadone program states inquest

Ontario's methadone maintenance program needs additional funding and more precise treatment guidelines for physicians, a coroner's jury has concluded after investigating 4 deaths related to the program.

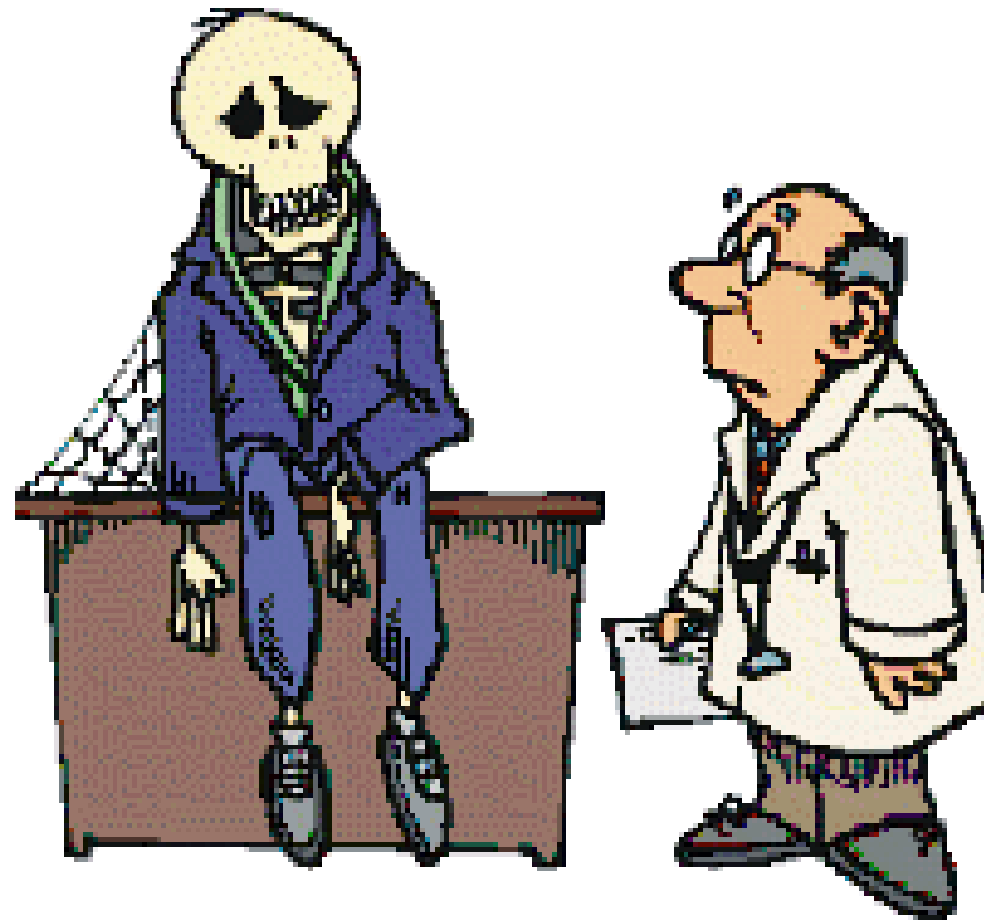
The Office of the Chief Coroner's month-long November inquest found that physicians treating patients in methadone maintenance deviated from current guidelines by allowing patients an excessive number of "carries" (take-home methadone) and not following guidelines for initiating patients into therapy.

The jury's 46 recommendations also identified systemic problems, including stagnant



Coronair

The majority of patients in Ontario's methadone maintenance program used to be addicted to heroin; now it's prescription opiates.



Outcomes?

Oral Methadone for Chronic Noncancer Pain

Juan Alberto Sandoval et al Clin J Pain 2005;21:503–512

Morley et al. Palliative Med 2003.17:576 - 587

- 13 case reports, 7 case series and 1 RCT
- 545 patients rotated to methadone
- Max 20 – 930mg / day

- Ineffective previous opioid - 344 patients
- First choice - 34 patients
- In addicted patient already on MMT - 3 patients
- Multiple reasons - 155 patients
- No details - 9 patients

Oral Methadone for Chronic Noncancer Pain

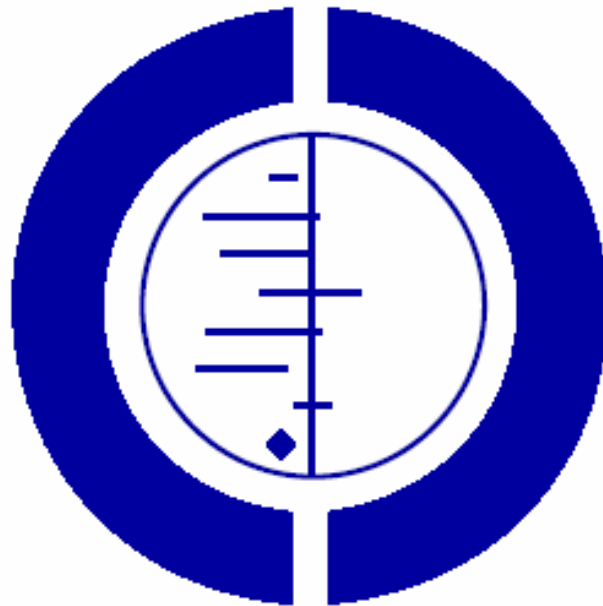
Juan Alberto Sandoval et al Clin J Pain 2005;21:503–512

Morley et al. Palliative Med 2003.17:576 - 587

- Pain outcomes were meaningful in 59% of the patients in the uncontrolled studies.
 - Morley JS. Bridson J. Nash TP. Miles JB. White S. Makin MK. **Low-dose methadone has an analgesic effect in neuropathic pain: a double-blind randomized controlled crossover trial. Palliative Medicine. 17(7):576-87, 2003 Oct.**
- “..1 DB RCT showed a statistically significant improvement on methadone for neuropathic pain”.
(10mg bid, 18 patients, 20 days)

Methodadone for cancer pain (Review)

Nicholson AB



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COLLABORATION®**

The Cochrane Library 2006



“There is evidence to suggest that methadone is an analgesic with similar efficacy to morphine and a comparable side effect profile”.

“...no trial evidence to support the proposal that methadone has a particular role in neuropathic pain of malignant origin”.

Methadone treatment of chronic non-malignant pain & opioid dependence - A long-term follow-up.

European Journal of Pain **Vol10, Issue 3, Pages 271-78. April 2006**

A. Rhodin, L. Grönbladh, L.-H. Nilsson and T. Gordh

- 75% “good” pain relief
- 5 started work
- 7 “got out of bed”
- 2 discarded their wheelchairs
- Mean global health score of 50.8 (73.7 Gen Pop)



Case Scenario

- 47 year old female. Patient of mine for 20 years.
- Chronic mechanical back pain.
- Previous extensive back surgeries in her teens and twenties for scoliosis.
- Rods “in and out”. Nothing surgical left to do.
- 2 years ago had a mastectomy, chemo, DXR for breast cancer and is left with neuropathic post-surgical pain. She is declared “clear of disease” by Oncology
- Probably abused street drugs in her youth but this is a thing of the past.
- Married once and now divorced. No kids. Has a very tolerant boyfriend who copes with her bipolar mood disorder which is generally well controlled.
- Takes Citalopram (Celexa) and regularly attends her psychiatrist.

Case Scenario

- Has not worked for years. Previously held various clerical posts. Not very active and has a very limited lifestyle.
- Has tried controlled release Morphine, Codeine, Hydromorphone, Oxycontin, Fentanyl patch.
- Now back on **Hydromorph Contin 36mg TID**. Not as effective as it was, terrible constipation, dose escalated by 100% in last 6 months with no benefit. “It used to work quite well”. Getting very expensive.
- Also takes Gabapentin 1200mg tid, Cesamet 2mg bid.
- Not a candidate for spinal cord stimulator, IT pump. Back injections.
- Generally very compliant and turns up to appointments. Only once asked for an early refill.
- **UNABLE TO GET PAIN CLINIC APPOINTMENT FOR 18 MONTHS**

Rotation

- Hydromorphone 108mg / day / po =
- Morphine 540mg /day /po =
- Methadone 45mg / day /po
- Reduce by 25% = 36mg Methadone / day
- Day 1 HM 36mg, HM 36mg, Me 12mg,
- Day 2 HM 36mg, Me 12mg, Me 12mg,
- Day 3 Me 12mg , Me12mg, Me 12mg,
- + \ - BTA HMIR 10mg po Max 3 / Day.

Titrate methadone

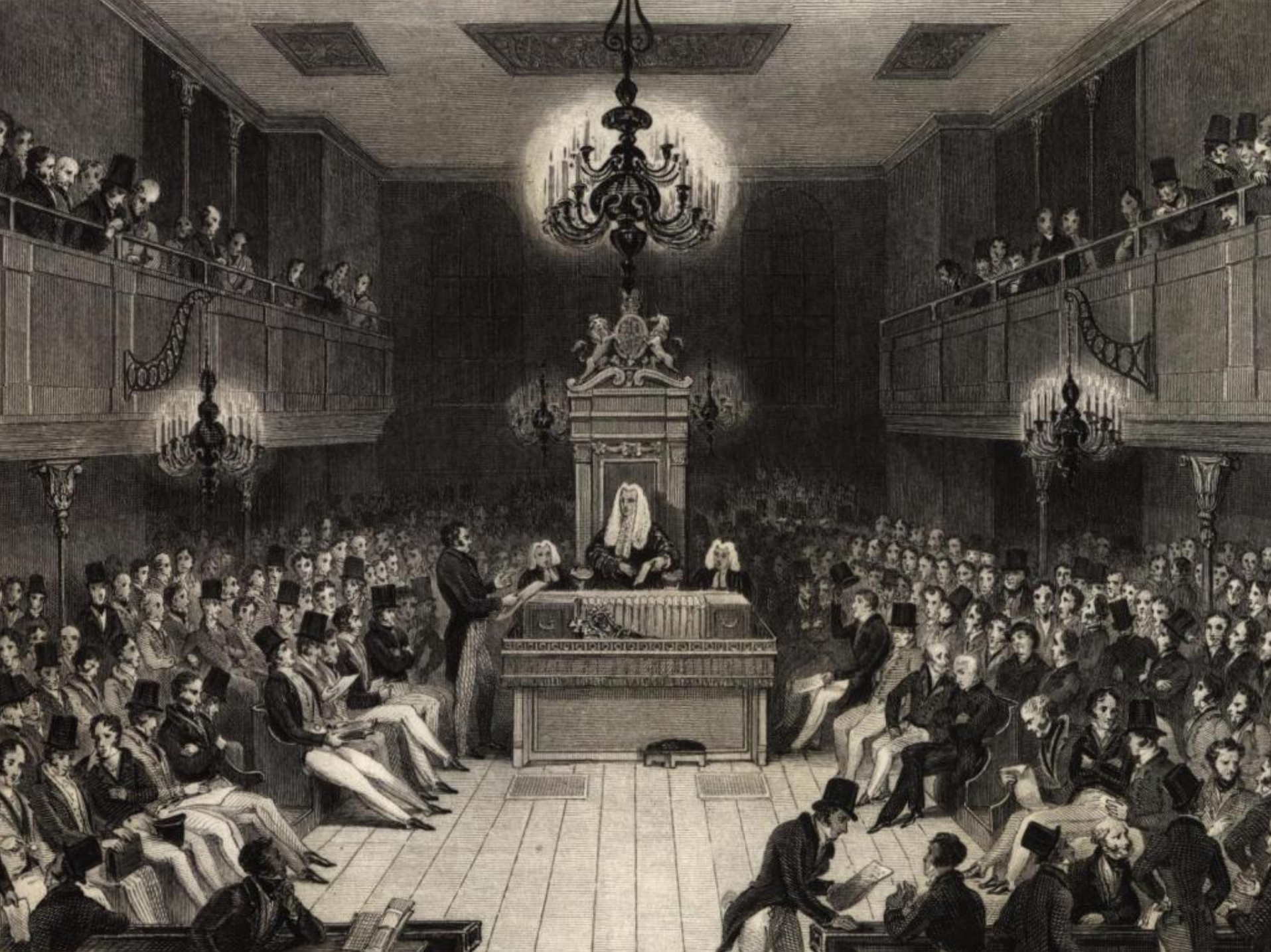
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References

- Lynch ME. **A review of the use of methadone for the treatment of chronic noncancer pain.** Pain Research & Management. 10(3):133-44, 2005.
- Peng P ,Tumer P, Gourlay D. **Perioperative pain management of patients on methadone therapy.** Can J Anesth. 52.(5): 513-523. 2005.
- Sandoval JA ,Furlan AD, Mailis-Gagnon A, **Oral Methadone for Chronic Noncancer Pain; A Systematic Literature Review of Reasons for Administration, Prescription Patterns, Effectiveness, and Side Effects.** Clin J Pain. 21:503–512.2005.
- Fishman SM, Wilsey B, Mahajan G, Molina P. **Methadone reincarnated: novel clinical applications with related concerns.** Pain Med. 3: 339–48.2002.
- Fredheim Olav Magnus S Fredheim . **Opioid switching from oral slow release morphine to oral methadone may improve pain control in chronic non-malignant pain: a nine-month follow-up study** Palliative Medicine. 20: 35/41. 2006.
- Watanabe S. **Methadone the Renaissance.** Journal of Palliative Care. 17:2; 117-120. 2001.
- Garrido MJ Troconiz IF, **Methadone: a review of its pharmacokinetic / pharmacodynamic properties.** Journal of Pharmacological and Toxicological Methods. 42, 61-66. 1999.
- Corkery JM, Schifano F, Hamid Ghodse A, oyefeso A. **The effects of methadone and its role in fatalities.** Human Psychopharmacology. Clin Exp.19: 565 – 567. 2004.
- Gammaitoni AR et al. **Clinical application of opioid equianalgesic Data.** The Clinical Journal of Pain, 19: 286-297.2003.
- Ferrari A et al. **Methadone - Metabolism, pharmacokinetics and interactions.** Pharmacological Research, 50; 551-559. 2004.
- Pearson EC, Woosley RL. **QT prolongation and torsades de pointes among methadone users: reports to the FDA spontaneous reporting system.** Pharmacoepidemiology and Drug Safety. 14: 747 – 753. 2005.
- Hernansanz S et al. **Opioid rotation to methadone at home.** J Pain Symptom Management. 31(1) .2-3. 2006.