ACCESS TO Methadone for Pain

UBC Division of Palliative Care

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Objectives

- 1. To understand the recent changes in regulatory environment regarding methadone prescribing
- 2. To understand the challenges of and need for transferring patients from a specialist service back to primary care once stabilized
- 3. To learn about some strategies for facilitating that transition safely

Disclosures

- No conflicts of interest to report
- Any honoraria related to my Canadian Virtual Hospice work are donated to cover making the module available for free to physicians in Indian programs run by Dr. Guyatri Palat
- Only bias to mitigate is positive expectations based on 20 years of experience prescribing methadone at BC Cancer

Barriers to Access to Methadone for Analgesia

- Lack of knowledge
- Lack of confidence
- Not knowing an exemption is NO LONGER needed
- Fear of College scrutiny
- Fear of attracting chronic pain patients (“heartsink patients”)
- Fear of attracting “addicts” = people with substance use disorders
- Lack of support from colleagues

CPSBC Statement: first issued June 4th, Revised Oct 17th, 2018

- May 19th, 2018 Health Canada removed requirement for exemption under Section 56 (1) of the Controlled Dugs and Substances Act
- Methadone for Analgesia Guidelines were revised and a new Prescribing Methadone practice standard was issued

BC's Methadone Prescribing Regulations

- "Physicians are expected to acquire the relevant education and training to prescribe methadone for analgesia and/or opioid use disorder as outlined in the standard, be familiar with the Safe Prescribing of Opioids and Sedatives practice standard, and commit to regularly reviewing each patient's PharmaNet profile"
- Need to do "a thorough biopsychosocial assessment", review all meds including OTC
- "It is not recommended to initiate methadone inpatients who are considered opioid-naïve, except in certain palliative or end of life situations"

BC’s Methadone Prescribing Regulations

- “To prescribe methadone for analgesia physicians must use a regular duplicate prescription pad”
- Registrants must clearly document “for pain” or “for opioid use disorder”
- “Naloxone kits must be discussed with an offered to the patient, and (where relevant) naloxone training discussed with friends, family or other care providers”

BC’s Methadone Prescribing Regulations

- Physicians who did not already hold a Section 56(1) exemption, or had not prescribe for more than 3 years, “must” obtain relevant education and training by completing the Methadone for Pain in Palliative Care course, and have read the Colleges Methadone for Analgesia Guidelines
- “Physicians with limited experience are strongly encouraged to consult with an experienced colleague before starting a patient on methadone”

Knowledge

Methadone for Analgesia: Online Training Tool to Support Physician Practice

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An initiative of / Une initiative du

CANADIAN PARTNERSHIP AGAINST CANCER / PARTENARIAT CANADIEN CONTRE LE CANCER

CANADIAN Virtual Hospice

“All You Need To Know About Methadone”

1. It has to saturate your body fat before reaching steady state
2. It has a long and variable half-life
3. It is mostly cleared by the liver
4. It can prolong the QT interval
5. It has more interactions with other drugs than other opioids
6. It has no known active metabolites
7. It often works when other opioids don’t
8. It blocks NMDA receptors, thereby reducing “Wind-Up”

When Should we Consider a Trial?

- Renal failure
- Opioid side-effects
- Lack of effectiveness with other opioid(s)
- Hyperalgesia
- Tolerance
- Anticipation of tolerance (long-term use expected)
- Sometimes cost or other practical concern, e.g. tube-fed

How to prescribe methadone safely…..

“Start Low, Go Slow”

Start Low, Go Slow

- Don’t wait until crisis occurs
- If starting for inadequate pain control, add on to prior opioid, then taper prior opioid once pain controlled
- Start 1mg q8h unless you have a good reason to go higher (or lower)
- If starting for side-effects of prior opioid, do a stepped switch

Start with Equianalgesic Guesstimate Chart, then convert from morphine to methadone

24h Oral Morphine Equivalent	Methadone Dose Ratio
<100mg	3:1
100-300mg	5:1
300-600mg	10:1
600-800mg	12:1
800-1000mg	15:1
>1g	20:1

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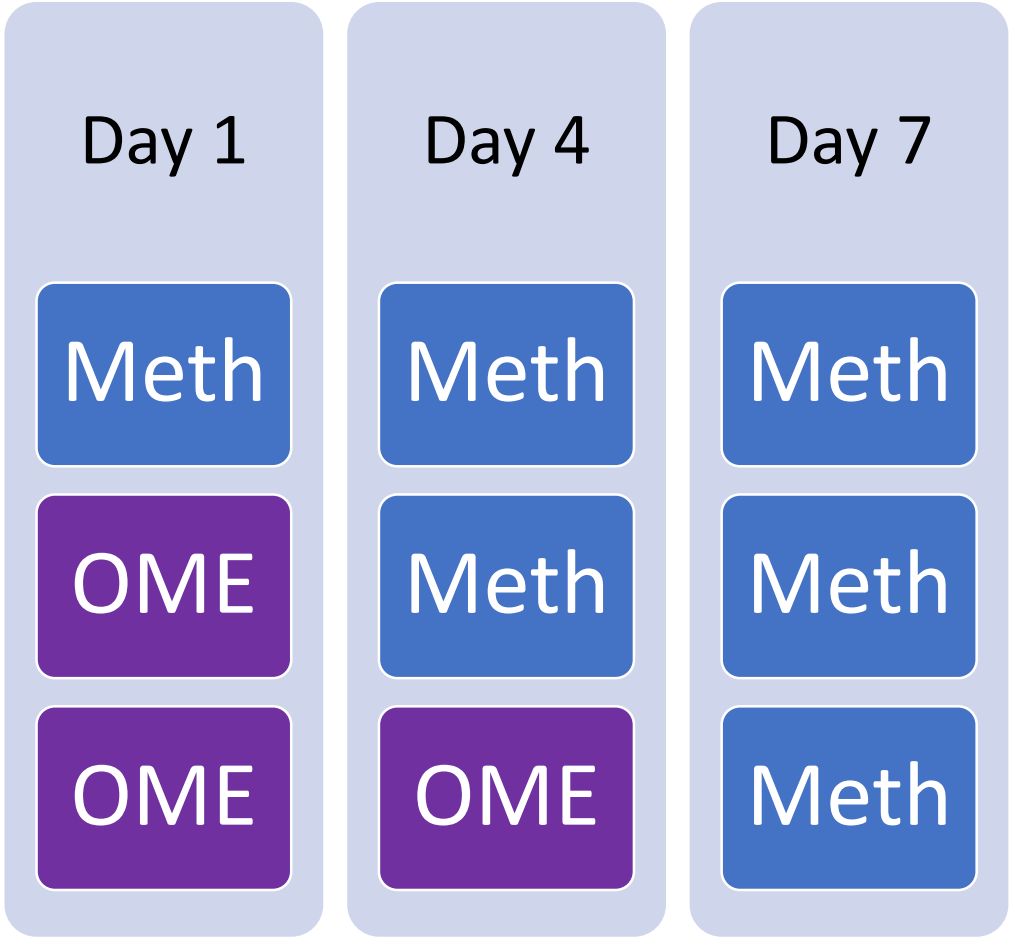
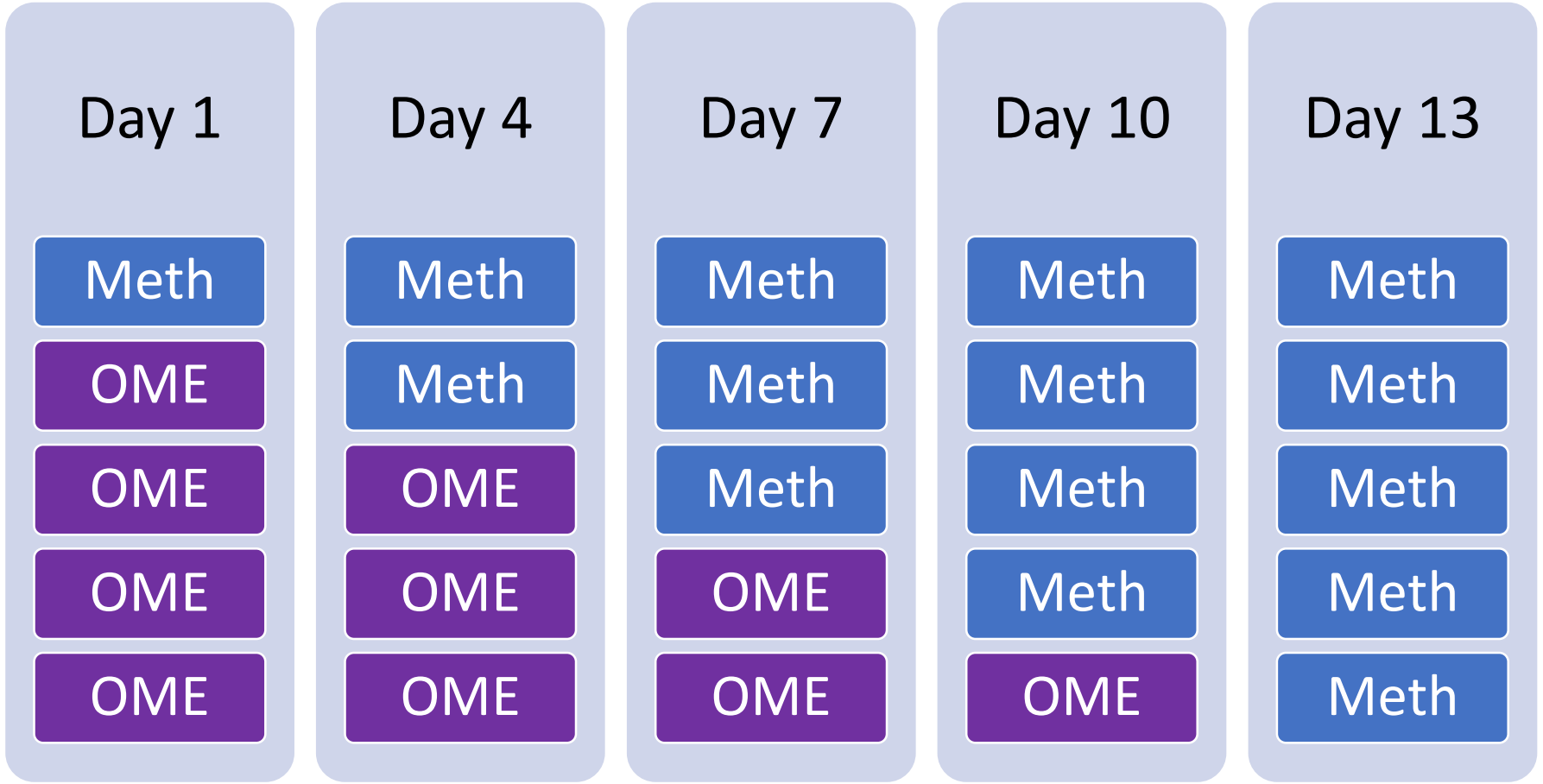
A 3-step switch

- Convert previous opioid to Morphine using good chart
- Reduce previous opioid by 1/3 at same time as starting methadone at 1/3 of predicted equianalgesic dose
- After 3 days, double up on the methadone, and halve the previous opioid (i.e. replacing 2/3)
- After further 3 days stop the previous opioid and add the final 1/3 of the methadone



More steps, more time



What to Prescribe

- Use pills if possible, as less risk of administration error than liquid
- Liquid is 10mg/m oral solution “Methadose” in BC, cherry flavour, unless requested otherwise
- Beware non-standard strengths
- Pills only covered by BC Palliative Drug Benefit Program (“Plan P”) or Extended Health
- Liquid is very cheap
- Need to give clear instructions re. measurement, and ensure 1ml syringes are supplied. Demonstrate if possible.

Slow Switch has Built-In Safety Net

- Clinical assessment of how much tolerance and how much hyperalgesia is present can be very difficult
- Dose escalation with incrementally less effectiveness in the absence of apparent worsening cause suggests tolerance
- Hyperalgesia suggested by “Everything hurts!”
- Non-cross-tolerance can lead to inadvertent over-dosing when starting methadone if tolerance is not taken into consideration
- Some patients have little to no tolerance and can be under-dosed with routine dose reduction
- Hyperalgesia takes a while to settle, may need to back off once comfortable

If patient is dying and oral route expected to be lost…..

- Other routes perfectly fine
  - Rectal
  - Buccal
  - Sublingual
- Absorption ~80% for all routes, may need minor adjustment
- Topical route not so predictable (Lipoderm®)

Rare Side-Effects

- Depression
- Hypoglycemia
- Sweats
- Rash
- Edema
- Dyspnea

Drug Interactions

- Some drugs can **decrease** clearance of methadone
  - Ciprofloxacin
  - Fluconazole
  - Grapefruit
- Some can **increase** clearance
  - Enzalutamide
- Don’t try to remember them all, look it up
- M4P course has printable ref, also in Methadone for Analgesia Guideline from CPSBC

Drug Interactions

- QT-prolonging effect rarely clinically significant, but may add to congenital or acquired Long QT Syndrome
- Beware of hypomagnesemia
- If in doubt do ECG before and after starting

Confidence

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Original Article

Clinical Outcomes of Start-Low, Go-Slow Methadone Initiation for Cancer-Related Pain: What's the Hurry?

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Abstract

Background: Methadone has been shown to be effective for cancer pain. Most published switching methods are complete in less than three days, requiring very close supervision, usually in an inpatient setting. This need for hospitalization is a barrier to access. We present a large retrospective study of slow outpatient methadone starts and describe our starting method.

Methods: Charts were reviewed of patients referred to the Pain and Symptom Management/Palliative Care clinics at the six BC Cancer Agency's regional centers that underwent initiation of methadone for analgesia over a 14-year period. Patient characteristics, method of start, and outcomes of methadone treatment were recorded.

Results: Of the 652 identified patients, we were able to determine outcomes of methadone initiation in 564 (86.5%). Among these, 422 (74.8%) were deemed successful initiations, as determined by whether or not the patient remained on methadone at follow-up with subjective improvement in pain control, on a stable dose of methadone. Of the unsuccessful trials, 97/142 were primarily due to adverse events, 16 of which were considered serious enough to require hospitalization, including two due to sudden cessation of opioid therapy leading to withdrawal. Some of the included adverse events were not necessarily causal from the initiation of methadone, for example, development of bowel obstruction or delirium. Only one death occurred from a deliberate overdose of multiple medications, including methadone.

Conclusions: Initiation of methadone for analgesia in ambulatory cancer patients can be done safely in an outpatient setting using a start-low go-slow method, and can be expected to be helpful in ~75% of patients. Discontinuation is more likely to be for side effects than for inadequate analgesia. Access to methadone therapy can safely be widened by slow initiation, avoiding more dangerous rapid switching protocols and reducing the need for hospitalization.

BCCA Chart Review

- Of 652 identified patients, we were able to determine outcomes of methadone initiation in 564 patients (86.5%)
- Vast majority were SLGS or stepped switches
- Among these, 422 (74.8%) were deemed successful initiations and 142 (25.2%) were not, as determined by whether or not they remained on methadone, with subjective improvement in pain control, on a stable dose

BCCA Chart Review

- 96 patients (15%) had at least one documented side effect, but only 16 (2.6%) had a potentially related adverse event considered serious enough to require hospitalization, 2 of which were due to sudden cessation of the methadone
- Most hospitalizations were only tenuously associated with the methadone, for example delirium
- One death occurred, from a deliberate overdose of multiple medications, including methadone
- No patient characteristics identified which would help predict those at higher risk of adverse events

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Original Article

The Association between Patient Characteristics and Opioid Treatment Response in Neuropathic and Nociceptive Pain Due to Cancer

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Abstract

Background: Cancer pain remains a difficult problem, for which opioids are often necessary. At present it is difficult to predict the effectiveness of opioid therapy.
Objectives: We aim to assess the association between patient characteristics and opioid treatment response in cancer patients, and develop a model to predict probability of response.
Subjects: We used data from two previously published randomized clinical trials, in which patients with head and neck cancer were treated with fentanyl or methadone (total $N = 134$).
Measurements: Treatment success was defined as ≥50% pain reduction at one and five weeks. We analyzed patient characteristics (age, sex, depression, and anxiety), treatment characteristics (having had chemotherapy, radiotherapy, surgery, methadone, or fentanyl) and pain characteristics (neuropathic and nociceptive).
Design: Based on univariable and multivariable regression analyses determinants of therapy success were assessed. Based on these analyses a prediction model was developed.
Results: Our analyses show that one-week therapy success was associated with methadone (odds ratio [OR] = 5.21), duration of pain in months (OR = 1.12), neuropathic pain (OR = 3.36), and age of the patient in years (OR = 0.95). Inclusion of these four characteristics into our prediction model resulted in an area under the curve of 81.6%.
Conclusions: Careful analyses of patient attributes, treatment, and pain type of patients with head and neck cancer resulted in a prediction model that allowed to predict short-term pain relief and the opioid treatment response in neuropathic and nociceptive pain owing to cancer.

Methadone vs Fentanyl in head and neck cancer

- 134 patients from 2 RCTs combined
- Methadone patients 5.12 times more likely than the Fentanyl patients to have >50% pain reduction at 1 week

Efficacy and Safety of Two Methadone Titration Methods for the Treatment of Cancer-Related Pain: The EQUIMETH2 Trial

- Philippe Poulain et al, Nov 2016
- 146 patients
- 2 methods, both fast:
  - Stop and go using aggressive conversion chart
  - 3-step 24hr interval steps

Poulain study outcomes

- Eventually 80% experienced better pain control……
- But 13% required naloxone infusions

- No comparative studies of 3-day stepped starts vs faster starts/switches

Summary

- Do the course: Methadone4pain.ca
- Think of methadone well before a pain crisis occurs
- Recruit your colleagues
- Start low-go slow unless very good reason for urgency
- If switching, do as many steps as you have time for
- Avoid stepping up any more often than q 3 days
- Check for interactions
- If it’s not working, try something else

- Enjoy!