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METHADONE

The Perfect Hospice Medication

HOW METHADONE WORKS

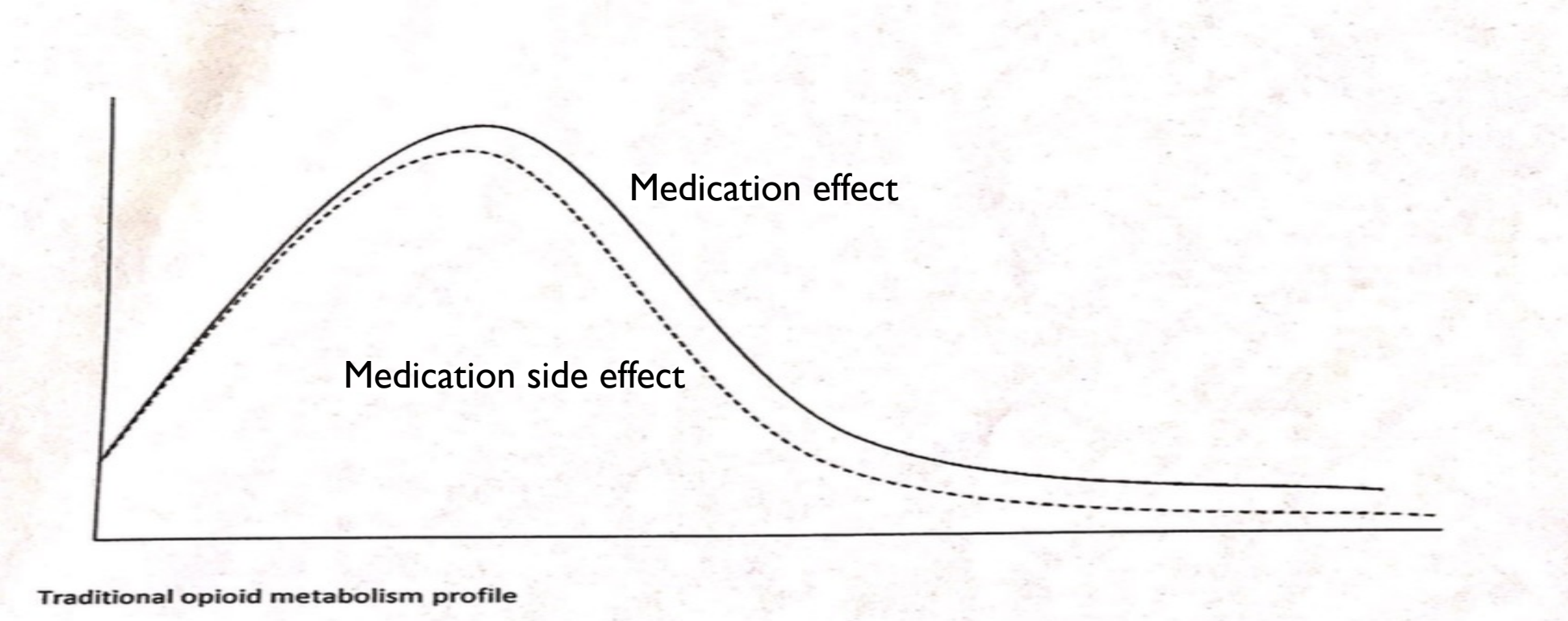
- Works two different ways:
  - Agonizes (turns on) the mu opioid receptor
  - Antagonizes (turns off) the NMDA receptor

HALF LIFE OF METHADONE*

- Immediate release Morphine, Hydromorphone, Oxycodone, and Codeine
  - ½ life ranges between 2-3.5 hours
  - These medications need special coatings to make them extended release or long acting
- Methadone
  - Ranges from 15-60 hours
    - Can last up to 120 hours
    - Average is 20-35 hours
  - Reaches steady state concentrations in 5 to 7 days
    - Wait a week to make dosing changes

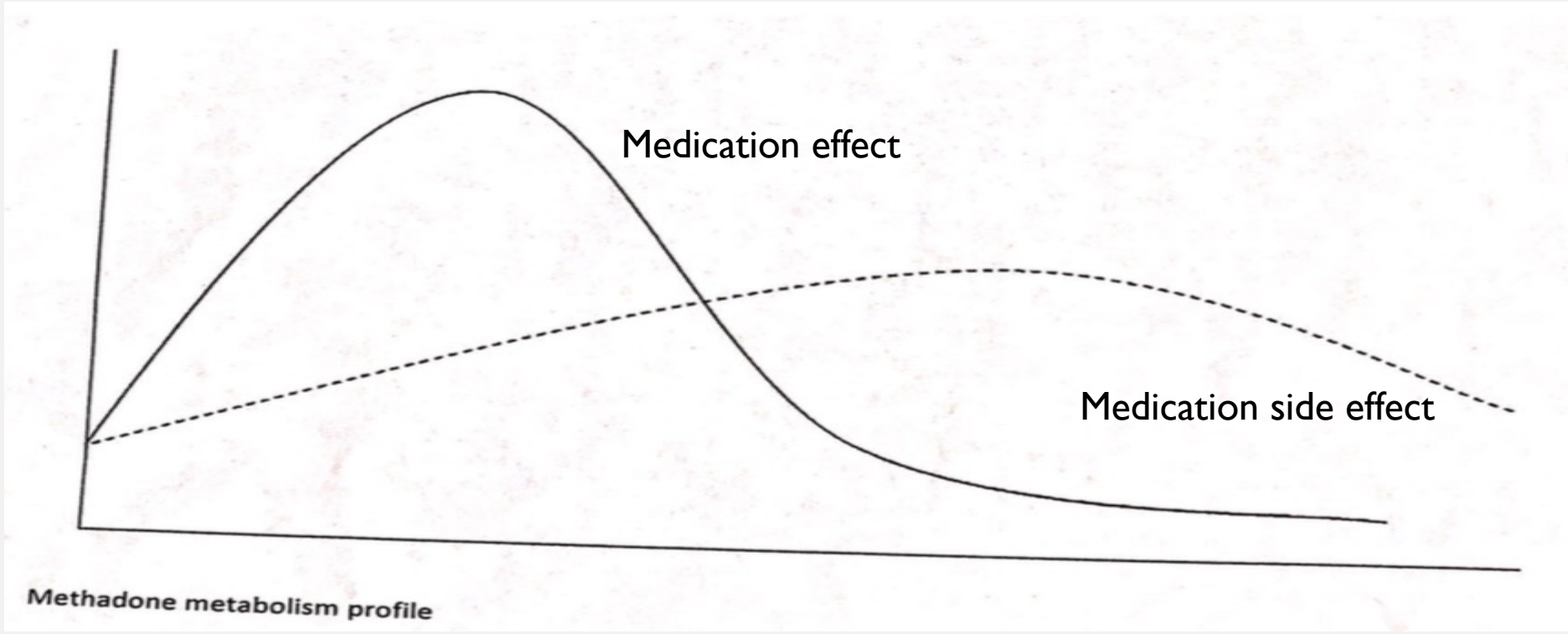
*Methadone (Lexi-Drugs). Available at: http://online.lexi.com.webproxy2.ouhsc.edu/lco/action/doc/retrieve/docid/patch_f/7262?cesid=7c1xv9WCk92&searchUrl=/lco/action/search?q=methadone&t=name&va=methadone

TRADITIONAL OPIOID METABOLISM



Traditional opioid metabolism profile

METABOLISM OF METHADONE



ONSET OF ACTION VS STEADY STATE CONCENTRATION*

- Onset of action is around 6-8 hours
- Steady state concentration is generally 5-7 days, can be longer based on liver function
- Methadone can be started even after patient has transitioned
  - Useful for covering the patient's opioid tolerance and providing pain management
  - May consider using as an adjuvant depending on patient's specific situation

*McPherson, Mary Lynn, Kathryn A. Walker, Mellar P. Davis, Eduardo Bruera, Akhila Reddy, Judith Paice, Kasey Malotte et al. Safe and appropriate use of methadone in hospice and palliative care: Expert consensus white paper. Journal of Pain and Symptom Management 57, no. 3 (2019): 635-645.

PHARMACOKINETICS OF METHADONE*

- Long half-life
- Oral bioavailability of 80%
- Time to peak concentration up to 7.5 hours
- Metabolized by the Cytochrome system in the liver
- Excreted in the urine

*Methadone. Available at: https://www-micromedexsolutions-com.webproxy2.ouhsc.edu/micromedex2/librarian/PFDefaultActionId/evidencexpert.DoIntegratedSearch?navitem=topHome&isToolPage=true#

ADVANTAGES OF METHADONE*

Nociceptive pain coverage

Neuropathic pain coverage

No active metabolite

Re-sensitizing opioid receptor

Can be crushed or given rectally

Cost efficient

*McPherson, Mary Lynn, Kathryn A. Walker, Mellar P. Davis, Eduardo Bruera, Akhila Reddy, Judith Paice, Kasey Malotte et al. Safe and appropriate use of methadone in hospice and palliative care: Expert consensus white paper. Journal of Pain and Symptom Management 57, no. 3 (2019): 635-645.

COMMON CONCERNS WITH METHADONE*

QTc Prolongation

- 3 levels of vigilance based off goals of care
  - If Methadone being used for comfort measures on NOT curative therapy, ECG monitoring is not recommended

Liver Disease

- If advanced liver disease is present the dose may need to be lowered and/or extra time needs to be allowed before titration
  - 10-14 days instead of 5-7

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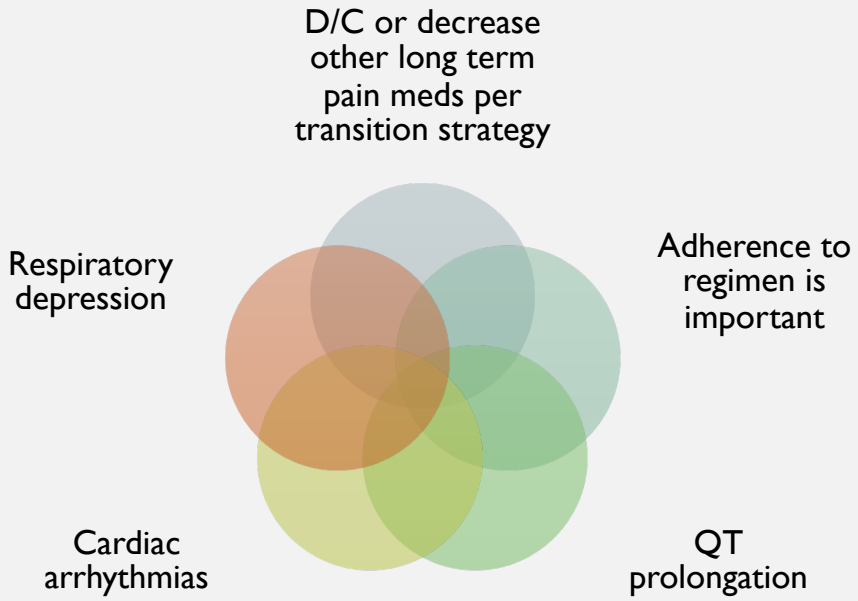
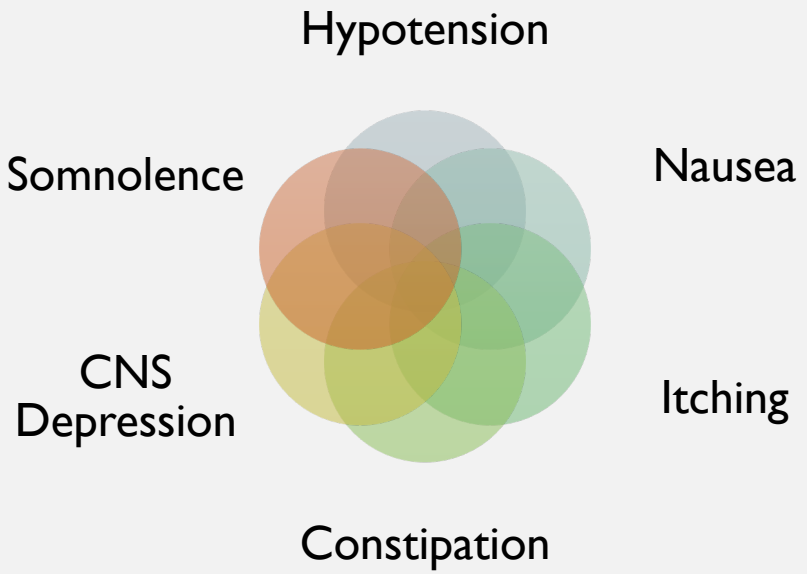
PATIENT'S ELIGIBILITY

- Clinician should perform and assess risks and benefits through:
  - An individualized medical evaluation
  - Behavioral risk evaluation
  - Thorough history
  - Review of records
  - Physical evaluation

COUNSELING POINTS





INITIATION OF METHADONE*

Opioid naive patients / Adults on low doses of other opioids

- Start methadone at 2.5mg TID
- Dose increase should ≤ 5mg/day every 5 to 7 days

*McPherson, Mary Lynn, Kathryn A. Walker, Mellar P. Davis, Eduardo Bruera, Akhila Reddy, Judith Paice, Kasey Malotte et al. Safe and appropriate use of methadone in hospice and palliative care: Expert consensus white paper. Journal of Pain and Symptom Management 57, no. 3 (2019): 635-645.

INITIATION OF METHADONE*

Patients on higher dose of opioids

- Calculate current opioid 24-hour total and convert to OME (Oral morphine equivalents)
- Must not be higher than 30-40mg/day
- Dose increase less than or equal to 10mg/day every 5 to 7 days

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TITRATING METHADONE

Slow titration

- Reduces the risk of unintended accumulation
- Can cause compliance issues due to mismanaged pain

Rapid titration

- Can manage pain issues faster
- May cause delayed toxicity
- Higher risk of adverse events

METHADONE EQUIANALGESIC TABLES

AYANDORIDE TABLE

Daily Oral Morphine	Conversion (morphine to methadone)
≤ 100mg	3:1
101-300mg	5:1
301-600mg	10:1
601-800mg	12:1
801-1000mg	15:1
≥ 1001mg	20:1

LAWLOR STUDY*

Study Design	Methods	Results/ Comments

• Retrospective
• 19 patients with cancer
	• Done over a 3-day period:
	  • Day 1: ⬇️ morphine dose by 30% and replace with methadone
	  • Day 2: ⬇️ morphine by additional 30% and replace with methadone
	  • Day 3: morphine is DC & replaced with methadone
	• Methadone given every 8h
		• Author concluded: Morphine must be carefully converted to methadone, especially when higher doses of morphine are used

* Lawlor PG, Turner KS, Hanson J, et al. Dose ratio between morphine and methadone in patients with cancer pain: a retrospective study. Cancer. 1998;82:1167-1173.

MERCADANTE

Daily oral morphine	Conversion (morphine to methadone)
30-90mg	4:1
91-300mg	8:1
≥ 301	12:1

MERCADANTE STUDY*

Study Design	Methods	Results/ Comments

• Prospective cohort
• 50 cancer patients with uncontrolled pain
• Converted from oral morphine to oral methadone
	• <90 mg morphine= 1:4 ration
	• 90-300 mg morphine = 1:8 ratio
	• >300 mg morphine = 1:12 ratio
	• Administered every 8 hours
	• 1/6 of the daily dose available for breath through pain
	  • Up to 3 doses per day were allowed
		• Switching was effective in 80% of pop
		  • Results achieved in about 3.65 days
		• Pts receiving <90 mg of morphine or 90-300 mg improved pain intensity
		  • Needed higher methadone doses

*Mercadante, S., Casuccio, A., Fulfaro, F., Groff, L., Boffi, R., Villari, P., et al. (2001). Switching from morphine to methadone to improve analgesia and tolerability in cancer patients: a prospective study. *J.*

RIPAMONTI

Daily Oral Morphine	Conversion (Morphine to Methadone)
30-90 mg	4:1
91-300 mg	6:1
≥ 301 mg	8:1

RIPAMONTI STUDY*

Study Design	Methods	Results/ Comments

• Cross sectional
• 38 cancer patients
	• Done over a 3-day period
	  • Day 1: ⬇ morphine dose by 30% and replace with methadone
	  • Day 2: ⬇ morphine; methadone only ⬆ if moderate to severe pain
	  • Day 3: morphine is DC & replaced with methadone
	• Methadone to morphine ratios:
	  • 30 -90 mg = 1:4
	  • 90-300 mg= 1:6
	  • ≥ 300mg= 1:8
	• Methadone given every 8 h
	• 10% of methadone was available for
		• Prior to switch
		  • patients receiving 30 -800mg/d of morphine
		• After switch
		  • Methadone range from 9 to 60mg/d
		• Median dose ration achieved after switch:
		  • 30 -90 mg = 1:3.7
		  • 90-300 mg= 1:7.75
		  • ≥ 300mg= 1:12.25

Ripamonti C, Groff L, Brunelli C, Polastri D, Stavrakis A, De Conno F, et al. Switching from morphine to oral methadone in treating cancer pain: What is the equianalgesic dose ratio? J Clin Oncol 1998;16:3216-2

FRIEDMAN

≤1000mg daily oral Morphine equivalent AND less than 65 years old	≤1000mg daily BUT 65 or older	≥1000mg but less than 2000 mg daily	≥ than 2000mg
• 10:1 Ratio	• 20:1 Ratio	• 20:1	• Consider higher ratio such as 30:1

EXPERT CONSENSUS CONVERSION RECOMMENDATIONS*

- <60mg oral OME refer to opioid-naïve dosing
- 60-199mg of OME and patient is <65 years of age use a 10:1 conversion
  - 10mg of OME to 1mg oral methadone
- ≥200mg OME and or patient is >65 years of age use a 20:1 conversion
  - 20mg of OME to 1mg of oral methadone
- Initial dose no greater than 30-40mg of methadone per day

*McPherson, Mary Lynn, Kathryn A. Walker, Mellar P. Davis, Eduardo Bruera, Akhila Reddy, Judith Paice, Kasey Malotte et al. Safe and appropriate use of methadone in hospice and palliative care: Expert consensus white paper. Journal of Pain and Symptom Management 57, no. 3 (2019): 635-645.

CONVERSION METHODS

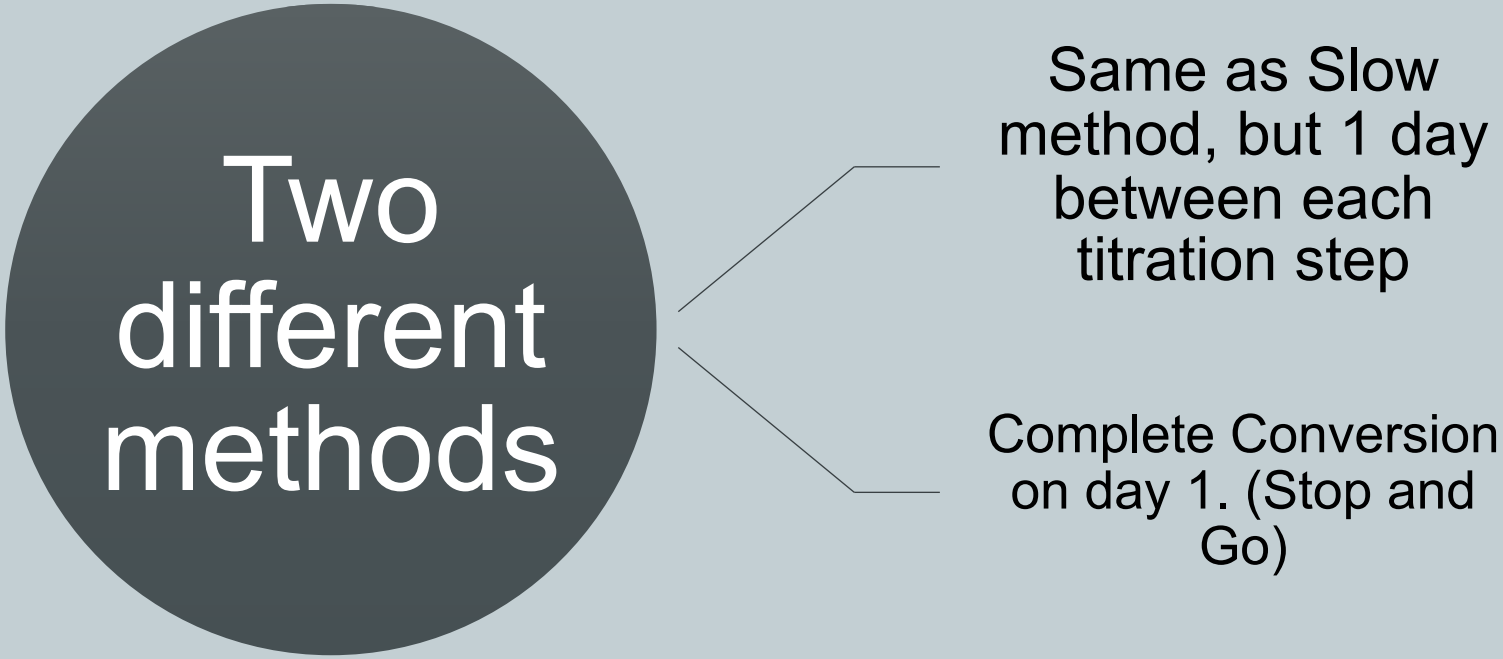
MORLEY- MAKIN METHOD (UK MODEL)

- D/C previous opioid
- Initiate methadone at 10% of TDD morphine q 3 h as needed
  - Do NOT give more than 30mg/dose
- Day 6:
  - Give average TDD methadone used on days 4 &5 (administer as divided doses q 12 h)
  - Use 10-15% of new methadone TDD as breakthrough offered q 3h prn

SLOW METHOD

- Slowly decrease previous ER opioid while slowly increasing methadone
- Wait 5-7 days between each dose adjustment
- Can take 2-4 weeks to fully convert over

RAPID METHADONE



PATIENT MANAGEMENT

INDIVIDUALIZED FOR THE PATIENT*

Conservative approach with patients older than 65	Debilitated or malnourished patients	After the initial titration period, don't increase daily dose more often than 5-7 days
	• Require lower doses due to lower plasma proteins	• Plasma levels may take up to 14 days to stabilize

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INDIVIDUALIZED FOR THE PATIENT

Maintain PRN meds, especially during the initial titration period

- Prior short acting opioid may need to be scheduled for the first few days

Loss of analgesic effect may result if another medication is affecting methadone metabolism

METHADONE AS AN ADJUVANT ANALGESIC*

- May be particularly useful in cases where the patient's life expectancy is shorter than the time to reach steady state
- Studies show that an added dose of methadone as low as 3mg showed improvement of pain symptoms

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MANAGEMENT OF AE'S

Monitor

- Signs of respiratory depression
  - Daily for 5 to 7 days after initiation or dose increase
- Opioid adverse effects

Constipation

- Considered bowel regiment

Anti-emetics

MEDICATION INTERACTIONS

CYP inducers

- Carbamazepine, phenytoin, prednisone
  - May need higher doses due to faster metabolism

CYP inhibitors

- Clarithromycin, amlodipine, fluoxetine, sertraline
  - May need to decrease dose due to slower metabolism

Potential QT prolonging drugs

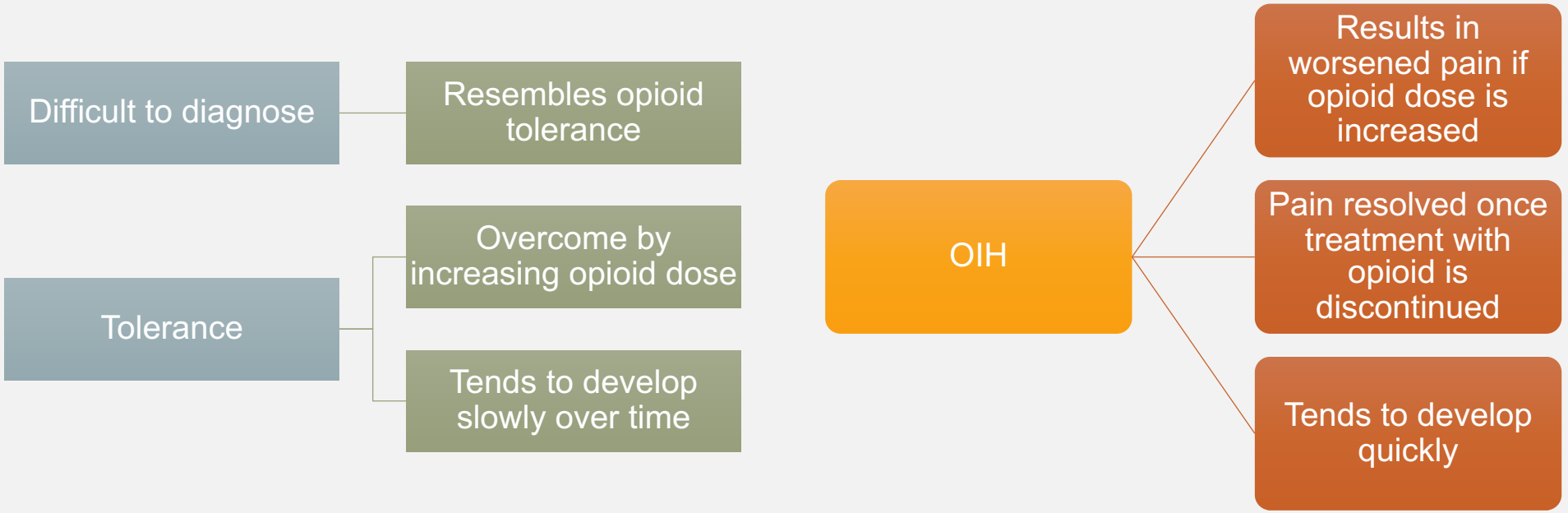
- Amiodarone, macrolide antibiotics (erythromycin, clarithromycin, azithromycin), amitriptyline

OPIOID INDUCED HYPERALGESIA

OPIOID INDUCED HYPERALGESIA (OIH)

- Phenomenon that could explain loss of opioid efficacy in some patients
- State of nociceptive sensitization caused by exposure to opioids
- Patients on opioids can become more sensitive to certain painful stimuli
  - Pain could be the same as the underlying pain or might be different pain
- Thought to happen from neuroplastic changes in the peripheral and central nervous system

DIAGNOSING


Difficult to diagnose
Resembles opioid tolerance
Tolerance
Overcome by increasing opioid dose
Tends to develop slowly over time
OIH
Results in worsened pain if opioid dose is increased
Pain resolved once treatment with opioid is discontinued
Tends to develop quickly

OIH COMMON CHARACTERISTICS

- Worsening pain over time despite increased opioid dose
- Nociceptive sensitization
- Area of pain more diffuse
- Pain of lesser quality and harder to pinpoint
- Opioid treatment continues, pain will get worse

TREATMENT OPTIONS

- Discontinue previous extended-release opioid
  - Should be titrated down to minimize withdrawal effect
- Switch from one structural class of opioids to another
- Currently studies have shown that OIH is associated with phenathrene opioids
  - Codeine, hydrocodone, hydromorphone, morphine, oxycodone, and oxymorphone

TREATMENT OPTIONS

- Methadone
  - Weak NMDA antagonist
- Reported that the addition of low dose methadone has been effective at reducing hyperalgesia
  - Study showed 10mg BID and reduction in total opioid dose of about 50% reduced pain

QUESTIONS?

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