



OPIOID

RESISTANT

PAIN

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IS MORE ALWAYS BETTER?





ADVANTAGES

- 1. Efficacy**
- 2. Dose based response**
- 3. Dose related side effects**
- 4. Treatable, manageable side effects**
- 5. No cumulative end organ damage**
- 6. Versatile**
- 7. Cost**



QUESTIONS TO PONDER?

- **Do Opioids relieve all types of pain?**
- **Do all patients get pain relief from Opioids?**
- **Does increasing the Opioid always relieve pain since there is no ceiling effect?**
- **What about patients who do not get relief?**
- **What about patients who get worse?**

DEFINITION

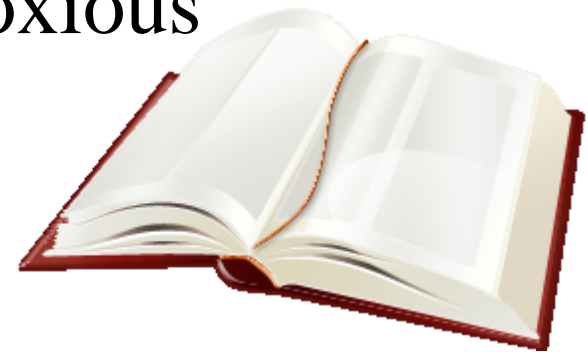
Hyperalgesia is an increased sensitivity to pain, which may be caused by damage to nociceptors or peripheral nerves.

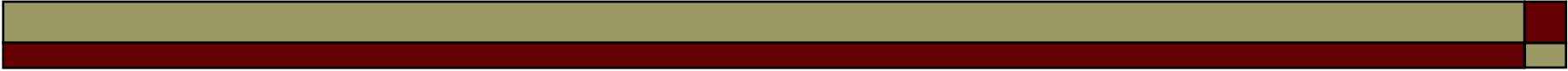
Temporary increased sensitivity to pain also occurs as part of sickness behavior, the evolved response to infection.



DEFINITION

Opioid-induced hyperalgesia or **opioid-induced abnormal pain sensitivity** is a phenomenon associated with the long term use of opioids. Over time, individuals taking opioids can develop an increasing sensitivity to noxious stimuli, even evolving a painful response to previously non-noxious stimuli (allodynia).





TYPES OF PAIN

1. Nociceptive

2. Neuropathic



NOCICEPTIVE

1. Somatic

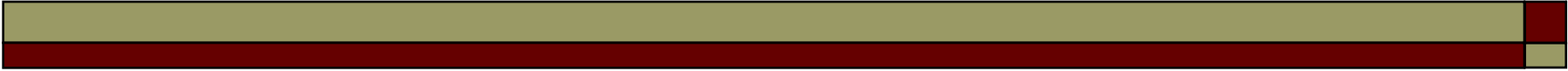
2. Visceral



NEUROPATHIC

1. Central

2. Peripheral



CAUSES

- 1. Tolerance**
- 2. Psuedotolerance**
- 3. Neuropathic pain**
- 4. Psychological pain**
- 5. Opioid induced pain**



TOLERANCE

- **Reduced effectiveness to a given dose over time**
- **Not clinically significant with chronic dosing**
- **If dose is increasing, suspect disease progression**



PSUEDOTOLERANCE

- **Patient has more pain with a previously adequate dose of analgesics**
- **Need to look for a new cause for increasing pain**
- **In cancer patients think new metastases**

MU RECEPTORS

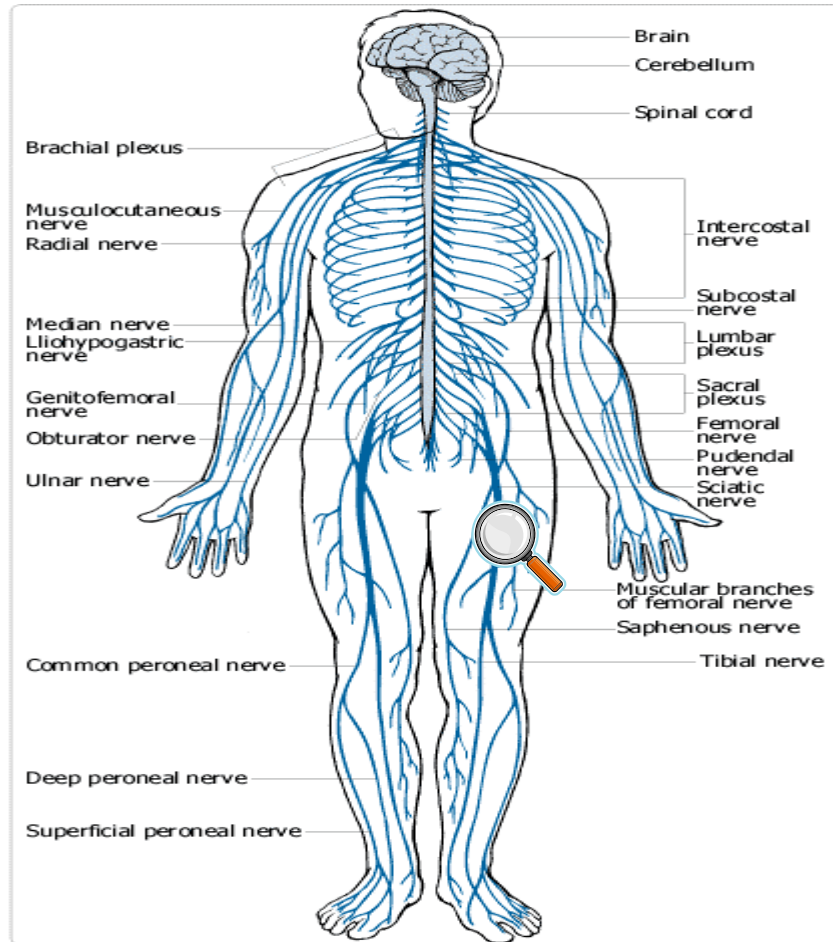


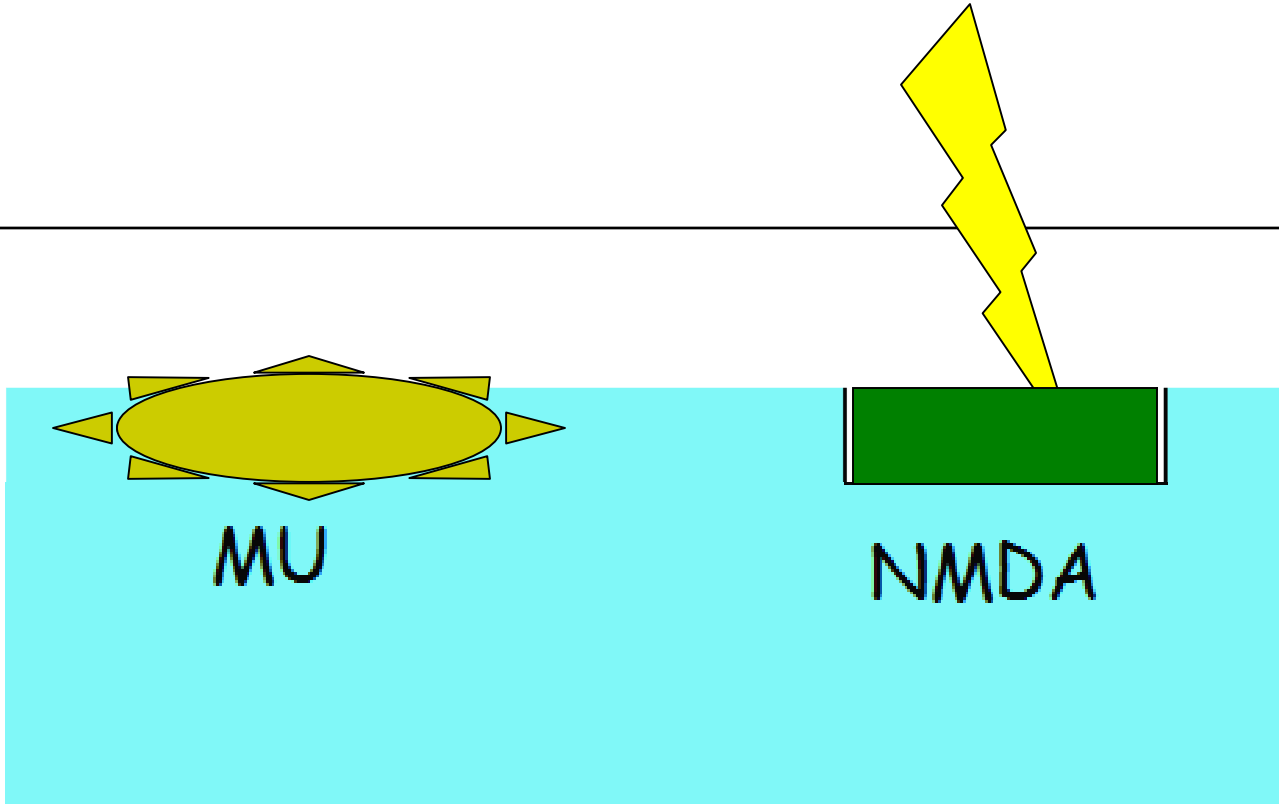
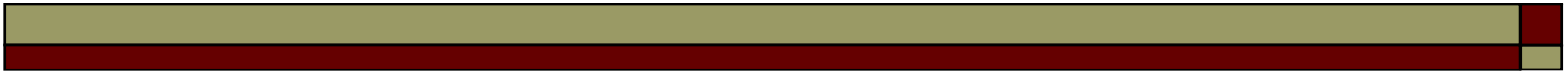


OTHER OPIOID RECEPTORS

- κ - analgesia, respiratory depression, miosis
- δ - analgesia

AFFERENT NERVE

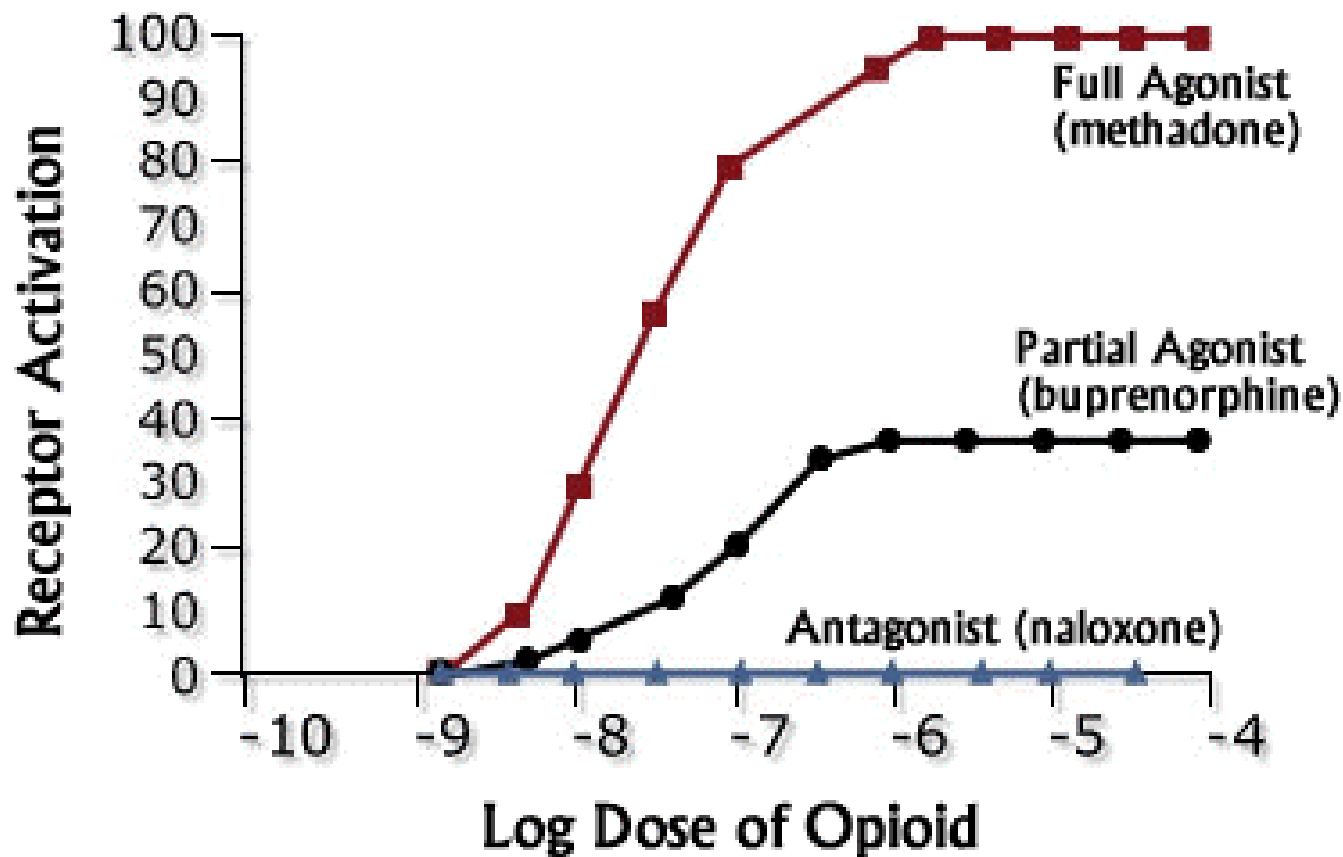




AFFERENT NERVE FIBER

AGONIST vs. ANTAGONIST

RECEPTOR ACTIVATION





NEUROEXCITATORY EFFECTS

- 1. Myoclonus**
- 2. Agitation**
- 3. Hallucinations**
- 4. Seizures**
- 5. Hyperalgesia ?**

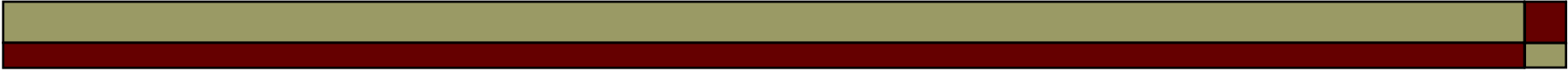


TREATMENT

- **Stop the opioid**
- **Reduce the opioid**
- **Change the opioid**
- **Methadone**
- **Ketamine**
- **Others?**

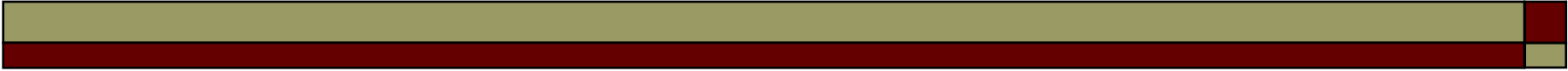
**Mrs. Dancer is a 53 year old with
metastatic breast cancer...**





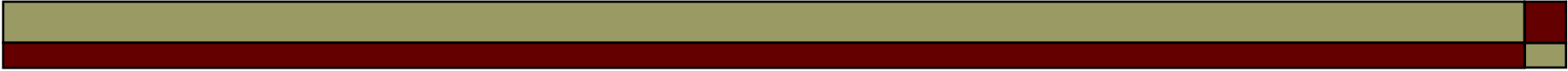
Mrs. Dancer is a 53 year old with metastatic breast cancer...

- **Palliative care consult-pt was known to us from previous admission, 4 pain meds: Morphine IV, Ultram, Cymbalta, and Neurontin.**
- **Pain score: 7/10 - a large part of her pain was believed to be neuropathic in nature**
- **Spasticity/twitching/jerking, pain precipitated admission which contributed to interrupted sleep**



Mrs. Dancer is a 53 year old with metastatic breast cancer...

- **Stopped Ultram, increased Neurontin (titrated to maximum dose over next week), changed Cymbalta dosing into once daily**
- **Morphine was changed to IV Hydromorphone**
- **Offered music distraction, discussed positioning strategies, radiation tx to be used if mass is found via CT, aggressive bowel regimen was put in place**



Mrs. Dancer is a 53 year old with metastatic breast cancer...

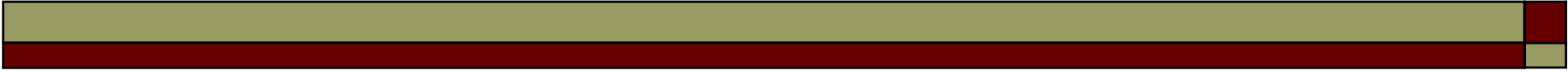
- **Hydromorphone was titrated (non-standard concentration) twitching decreased initially, pain scored remained high**
- **10 days – new pain site: in addition to R thigh and back pain, now has shoulder pain, (tight, squeezing) Twitching- variable, but generally increasing in frequency and intensity. Hydromorphone requirements (85 mg/hr, or over 2000mg /day)**

**Mrs. Dancer is a 53 year old with
metastatic breast cancer...**

How Much Is That???

- **85mg per hour of hydromorphone is 2 grams per day.**
- **Parental morphine dosage is 12 grams per day.**
- **Oral morphine dosage is 36 grams per day**
- **Is this just tolerance?**



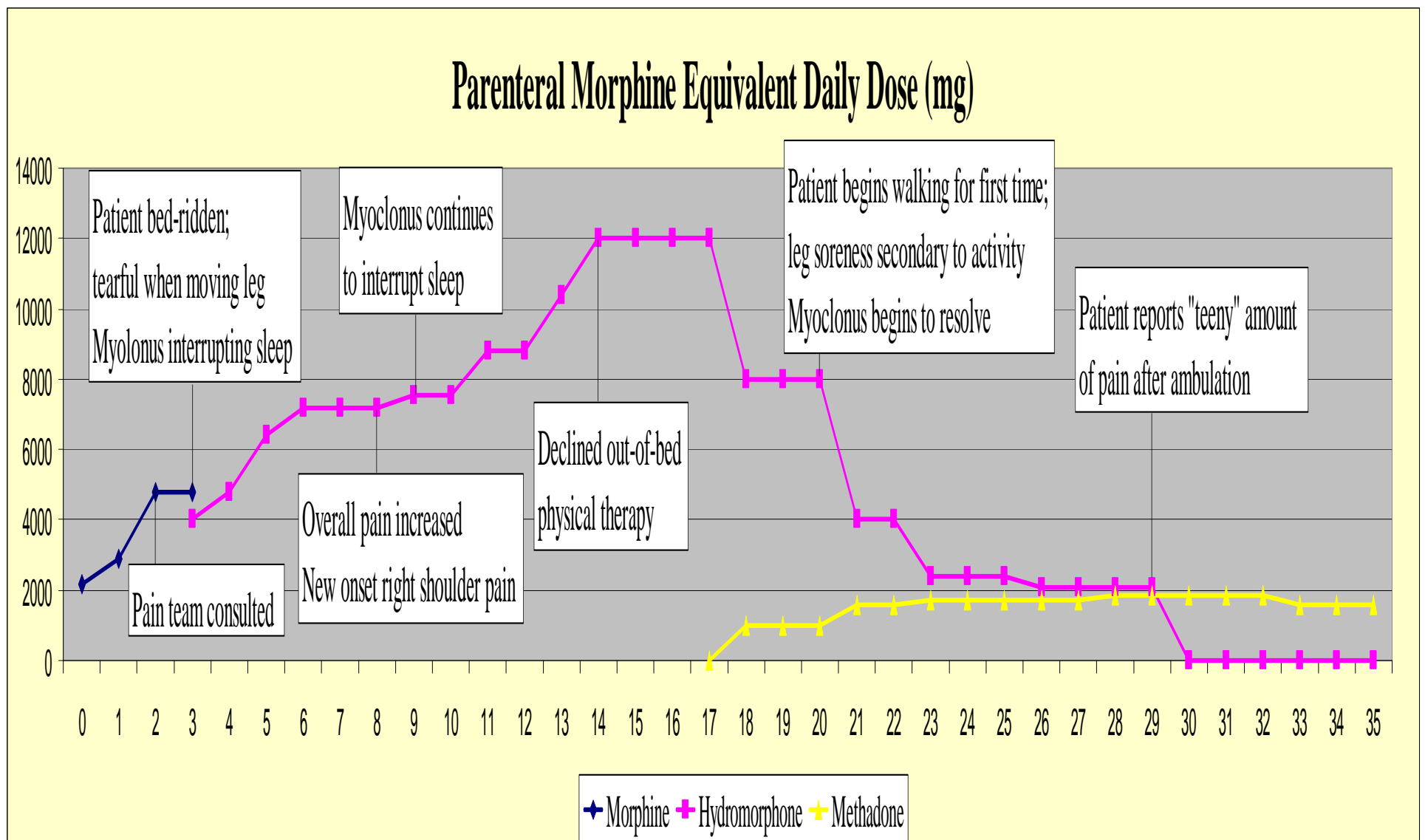


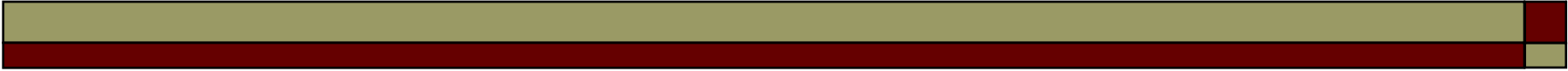
**Mrs. Dancer is a 53 year old with
metastatic breast cancer...**

Methadone conversion plan is implemented.

**After 3 days of tx pain worse due to
overexertion! Pt commented, this is good
pain. After 5 days twitching disappears.
Pt regularly walking in hallway and
sleeping well. Actiq (fentanyl lolly-pops) is
used (for break-through pain) successfully
for transportation to RT**

Opioid-Induced Hyperalgesia





Mrs. Dancer is a 53 year old with metastatic breast cancer...

- **Prior to discharge: IV pain meds are discontinued. Pain is treated with Methadone, Pain scores are 2-5/10, pt is ambulating well, no adverse drug reactions being reported.**
- **Hydromorphone 2200mg/day - \$700/day or \$21,000/month**
- **Methadone 240mg/day - \$1.25 or \$37.50/month**
- **Monthly difference in cost, greater than \$20,000.**



METHADONE

is a synthetic opioid, used medically as an analgesic and in the treatment of narcotic addiction. It was developed in Germany in 1937, and in the USA was first brought to market by the pharmaceutical company Eli Lilly and Company

METHADONE

- **In the USA, can be prescribed by *ANY* clinician who has a DEA license to prescribe schedule II medications**
- **In most states must write “*for pain*”**
- **Special license only required for the treatment of addiction**



METHADONE

Pharmacology

- **Racemic mixture of L and D isomers**
- **Highly lipophilic**
- **Rapid distribution phase**
- **Slow tissue release into bloodstream**

METHADONE

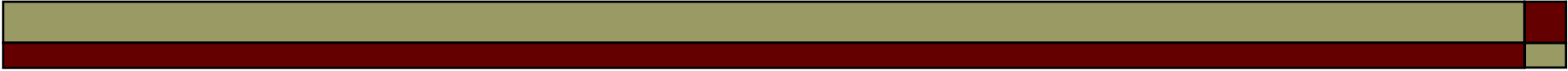
Mechanism of Action

- **Mu and kappa receptors – similar affinity to morphine**
- **Delta receptors – possibly greater affinity than morphine**
- **NMDA – receptor thought to be involved in neuropathic pain**

METHADONE

Unique Properties

- **Long and variable half-life of elimination**
- **No known active metabolites**
- **Duration of analgesic effect is shorter than elimination half-life**
- **only oral pain medicine to antagonize NMDA receptors**



QUESTIONS ???

- **What opioids are likely to cause hyperalgesia?**
- **At what doses?**
- **By what delivery system?**
- **Are there warning signs?**
- **What treatments are the most beneficial?**

