OPIOID-INDUCED TOLERANCE AND HYPERALGESIA

WHAT TO DO WHEN IT STILL HURTS

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Central AR Veterans Healthcare System
OBJECTIVES

- Discuss common terminology
- Discuss prevalence
- Discuss mechanisms of tolerance and hyperalgesia
- Discuss strategies for prevention & treatment
Pain Medications in the U.S. - 2012

Painkiller prescriptions per person differ among states in 2012

Source: CDC Vital Signs, July 2014
BACKGROUND

- Opioids most prescribed class of medication in the United States (2015)
- Chronic opioid therapy → paradoxically induce or sensitize patients to acute pain
- Long-term effectiveness
- Misuse/Abuse is a growing problem
- Adverse effects with long-term use
BACKGROUND

- Morphine → (increased pain)
  - Albutt 1870

- “When dependence on opioids finally becomes an illness of itself, opposite effects like restlessness, sleep disturbance, hyperesthesia, neuralgia, and irritability become manifest.”
  - Rossback 1880

- Hyperalgesia has been described in former opioid addicts
  - Maintained on methadone vs. controls
**TERMINOLOGY**

- **Dependence**
  - A physiologic and biochemical adaptation of neurons such that removing a drug precipitates withdrawal or an abstinence syndrome

- **Addiction**
  - A chronic, relapsing *syndrome* of psychological dependence and *craving* a drug for its psychedelic, sedative, or euphoric effects; characterized by compulsion, loss of control, and continued use of a substance despite harmful effects
**TERMINOLOGY**

- **Opioid-Induced Tolerance**
  - Progressive *lack of response* to a drug
  - Increases in dosing → **decreases** in pain
  - May develop to adverse effects
  - *Decreased sensitivity to opioids*

- **Opioid-Induced Hyperalgesia**
  - Paradoxical *increase in sensitivity* to painful stimuli
  - Increases in dosing → **increases** in pain
  - Same pain OR different pain
  - *Increased sensitivity to pain*
**Terminology**

- **Opioid-Induced Tolerance**
  - **Innate** – predisposition - (pharmacogenetic)
  - **Acquired** – repeated exposure
    - Pharmacokinetic – inhibitor/inducer (metabolism)
    - Pharmacodynamics – decreased response of receptor system
    - Learned – i.e. alcoholics

- **Opioid-Induced Hyperalgesia**
  - **Hyperesthesia** – dramatically increased sensitivity to painful stimuli
  - **Allodynia** – pain elicited by a normally non-painful stimulus
TOLERANCE VS HYPERALGESIA

Graph showing the relationship between pain tolerance, pain threshold, opioid dose, and different conditions:

1. Opioid naive
2. Opioid tolerance
3. Opioid-induced hyperalgesia

Source: Nat Rev Rheumatol © 2010 Nature Publishing Group
PATIENT CASE 1

- A.B. is a 61 y/o with pancreatic islet cell cancer with liver metastases, presenting today with chronic malignant pain (abdominal).
- Current medications:
  - Morphine 60mg q8h long-acting
  - Morphine 15mg immediate release q4h prn breakthrough pain
- He has been on the above regimen for 3 months.
- He complains of increased abdominal pain today.
- Morphine 15mg is no longer effective. 30mg is effective but causes significant n/v.
PATIENT CASE 2

- A.B. is a 61 y/o with pancreatic islet cell cancer with liver metastases, presenting today with chronic malignant pain (abdominal).
- Current medications:
  - Morphine 60mg q8h long-acting
  - Morphine 15mg immediate release q4h prn breakthrough pain
- He has been on the above regimen for 3 months.
- He complains of increased pain (all over) today. It is unrelieved with his immediate release morphine. He has tried up to 30mg per dose without improvement.
PATIENT CASE 3

- A.B. is a 61 y/o with pancreatic islet cell cancer with liver metastases, presenting today with chronic malignant pain (abdominal).

- Current medications:
  - Morphine 60mg q8h long-acting
  - Morphine 15mg immediate release q4h prn breakthrough pain

- He has been on the above regimen for 3 months.

- He complains of increased abdominal pain today, is eating less and is less active. He is requiring the morphine immediate release several doses per day more than at the last visit.
Acute Opioid Tolerance: Intraoperative Remifentanil Increases Postoperative Pain and Morphine Requirement.
Guignard, Bruno; Bossard, Anne; Coste, Carole; Sessler, Daniel; Lebrault, Claude; Alfonsi, Pascal; Fletcher, Dominique; Chauvin, Marcel

Fig. 6. Cumulative postoperative morphine consumption in the two groups during 24 h after tracheal intubation. Values are mean +/- 95% confidence interval. Open circles = desflurane group, filled squares = remifentanil group. Area under the curve differed significantly in the two groups (P < 0.05).
CLINICAL EVIDENCE

- Methadone & Buprenorphine

- Fig. 1. Cold-pressor withdrawal latency in long-acting opioid-maintained former opioid addicts and matched controls. Each bar (and bracket) represents the mean value (and SD) for the subjects derived from three testing sessions. Asterisk indicates significant.

Long-acting morphine in chronic LOW BACK hyperalgesia with one month of therapy.

Figure 1. The experimental pain threshold (time to first pain) and pain tolerance (time to intolerable pain) were assessed with aid of the cold pressor test before and 1 month after initiating chronic morphine therapy in 6 patients with chronic low back pain.

RECEPTOR OCCUPANCY THEORY

- A pharmacologic response is proportional to the fraction of the target receptor population occupied at a particular drug concentration.

  - Drug concentration (receptor) ↑ = Drug binding ↑ = ↑ Drug effects

Diminished opioid analgesic effects

Opioid tolerance
- Receptor desensitization
- Superactivation of cAMP pathway

**Mechanisms:**
- Opioid dose escalation
- Use longer-acting opioids
- Add nonopioid analgesics
- Add drugs that prevent or delay tolerance

**Therapeutic approaches:**

Opioid-induced hyperalgesia
- Sensitization of primary afferent neurons
- Activation of dynorphin and central glutamatergic systems

**Mechanisms:**
- Tapering opioid doses
- Add NMDA antagonists
- Try longer-acting opioids
- Attempt rotation of opioids

**Therapeutic approaches:**

Worsening pain state
- Disease progression
- Neuropathic pain mechanisms
- Enhanced opioid metabolism

**Mechanisms:**
- Opioid dose escalation
- Add nonopioid analgesics
- Treat for neuropathic pain or other pain mechanisms

**Therapeutic approaches:**
**Mechanisms**

- **CYP enzyme responsible for Phase I, II biotransformation**
  - Ex. Poor-metabolizer phenotype will not convert codeine to morphine efficiently with reduced effect.

- **P-glycoprotein – barrier transporter**
  - Limits absorption from intestines or penetration into organs

MECHANISMS

- Production of metabolites that accumulate and interfere by competing for receptor binding OR down-regulation the response of receptor system.
  - M3G (morphine-3-glucuronide)

- Opioid Receptor-Mediated Changes – Mu, Delta, Kappa
  - First step is receptor phosphorylation – ADP → ATP
  - This leads to desensitization of the opioid receptor

MECHANISMS

- NMDA-sensitive glutamate receptor
- Nitrous Oxide mediates conversion of GTP → cGMP a mediator of tolerance
- Increased in chronic use
- NMDA antagonists potential
WHAT TO DO WHEN IT STILL HURTS?
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Opioid tolerance
- Mechanisms: Receptor desensitization, Superactivation of cAMP pathway
  - Therapeutic approaches: Opioid dose escalation, Use longer-acting opioids, Add nonopioid analgesics, Add drugs that prevent or delay tolerance

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- Mechanisms: Sensitization of primary afferent neurons, Activation of dynorphin and central glutamatergic systems
  - Therapeutic approaches: Tapering opioid doses, Add NMDA antagonists, Try longer-acting opioids, Attempt rotation of opioids

Worsening pain state
- Mechanisms: Disease progression, Neuropathic pain mechanisms, Enhanced opioid metabolism
  - Therapeutic approaches: Opioid dose escalation, Add nonopioid analgesics, Treat for neuropathic pain or other pain mechanisms
PATIENT CASE 1

- A) A.B. is experiencing progression of disease. The morphine dose should be increased.
- B) A.B. is experiencing opioid induced hyperalgesia. The morphine dose should be decreased.
- C) A.B. is experiencing opioid induced tolerance. The morphine should be rotated to a different opioid.
- D) A.B. is taking too much medication and should be educated on the potential for addiction with opioids.
Patient Case 2

- A.B. is a 61 y/o with pancreatic islet cell cancer with liver metastases, presenting today with chronic malignant pain (abdominal).

- Current medications:
  - Morphine 60mg q8h long-acting
  - Morphine 15mg immediate release q4h prn breakthrough pain

- He has been on the above regimen for 3 months.

- He complains of increased pain (all over) today. It is unrelieved with his immediate release morphine. He has tried up to 30mg per dose without improvement.
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- Use longer-acting opioids
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- Sensitization of primary afferent neurons
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**Therapeutic approaches:**
- Tapering opioid doses
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Worsening pain state
- Disease progression
- Neuropathic pain mechanisms
- Enhanced opioid metabolism

**Therapeutic approaches:**
- Opioid dose escalation
- Add nonopioid analgesics
- Treat for neuropathic pain or other pain mechanisms
PATIENT CASE 2

- A) A.B. is experiencing progression of disease. The morphine dose should be increased.
- B) A.B. is experiencing opioid induced hyperalgesia. The morphine dose should be decreased.
- C) A.B. is experiencing opioid induced tolerance. The morphine should be rotated to a different opioid.
- D) A.B. is taking too much medication and should be educated on the potential for addiction with opioids.
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A.B. is a 61 y/o with pancreatic islet cell cancer with liver metastases, presenting today with chronic malignant pain (abdominal).

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A) A.B. is experiencing progression of disease. The morphine dose should be increased.

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D) A.B. is taking too much medication and should be educated on the potential for addiction with opioids.
PAIN MANAGEMENT STRATEGIES

- Opioid-sparing/rotation (evidence lacking)
- NMDA receptor antagonists
- Adjuvant drug therapies (i.e. anticonvulsants, antidepressants)
- Combining opioids with low-dose opioid antagonists (i.e. naltrexone)

Wang et al. (2005)
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Wang et al. (2005)
PATIENT CASE 1 - ROTATION

- A.B. is a 61 y/o with pancreatic islet cell cancer with liver metastases, presenting today with chronic malignant pain (abdominal).

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  - Morphine 15mg immediate release q4h prn breakthrough pain

- He has been on the above regimen for 3 months.
- He complains of increased abdominal pain today.
- Morphine 15mg is no longer effective. 30mg is effective but causes significant n/v.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Equianalgesic Dose (mg)</th>
<th>Starting Dose (Adult&gt;50kg)</th>
<th>Pharmacokinetics</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Parenteral</td>
<td>Oral/Other</td>
<td>Parenteral</td>
<td>Oral/Other</td>
</tr>
<tr>
<td>Morphine</td>
<td>10</td>
<td>30</td>
<td>2.5-5mg q4h</td>
<td>5-10mg q4h</td>
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<tr>
<td>Hydromorphone</td>
<td>1.4</td>
<td>7.5</td>
<td>0.5-1mg q4h</td>
<td>1-2mg q4h</td>
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<tr>
<td>Oxycodeone</td>
<td>-</td>
<td>20-30</td>
<td>-</td>
<td>5mg q4h</td>
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<td>Hydrocodone</td>
<td>-</td>
<td>30</td>
<td>-</td>
<td>10mg q4h</td>
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<tr>
<td>Oxymorphone</td>
<td>1</td>
<td>15</td>
<td>0.5mg q4h</td>
<td>5-10mg q4h</td>
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<tr>
<td>Tapentadol</td>
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<td>75</td>
<td>-</td>
<td>50-100mg q6h</td>
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<tr>
<td>Tramadol</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>50-100mg q4h</td>
</tr>
<tr>
<td>Methadone</td>
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<td>2-20</td>
<td>1-5mg q4-8h</td>
<td>2.5-10mg q4-8h</td>
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<tr>
<td>Fentanyl</td>
<td>0.1*</td>
<td>7.5-15*</td>
<td>25-50mcg/hr</td>
<td>12-25mcg/hr</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>0.3-0.4</td>
<td>5-10*</td>
<td>0.3mg q6h</td>
<td>5mcg/hr q7days TD</td>
</tr>
</tbody>
</table>

*Titrate slowly.*
### EQUIANALGESIC DOSING

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone</td>
<td>30</td>
</tr>
<tr>
<td>Morphine</td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>7.5</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20</td>
</tr>
<tr>
<td>Fentanyl transdermal</td>
<td>7.5 (mcg)</td>
</tr>
</tbody>
</table>
How to Rotate Opioids?

Patient Case 1

- Calculate 24 hour dose of opioid
  - Morphine 60mg q8h = 180mg
    +
  - Morphine 15mg q4h prn = 90mg

- Total morphine per 24 hours = 270mg
HOW TO ROTATE OPIOIDS?

PATIENT CASE 1

- Convert 24 hour dose to new opioid
  - Morphine 270mg PO x (20/30) = 180mg oxycodone

- Consider adjusting for cross-tolerance
  - ↓ 25-50% = 120mg oxycodone

- Choose dose/dosing interval
  - Oxycodone SA 60mg q12h

- Choose breakthrough opioid and dose
  (10% of 24 hour dose)
  - Oxycodone IR 10-15mg q4h prn
PATIENT CASE 2

- A.B. is a 61 y/o with pancreatic islet cell cancer with liver metastases, presenting today with chronic malignant pain (abdominal).

- Current medications:
  - Morphine 60mg q8h long-acting
  - Morphine 15mg immediate release q4h prn breakthrough pain

- He has been on the above regimen for 3 months.

- He complains of increased pain (all over) today. It is unrelieved with his immediate release morphine. He has tried up to 30mg per dose without improvement.
**How to Taper Off Opioid?**

- **Morphine, Oxycodone, Hydrocodone, Hydromorphone, Fentanyl**
  - Decrease by **25-50%** every **3-5 days**
  - May go faster if pain severe and patient has not been on opioids long-term at current dose

- **Methadone**
  - Decrease by **25-50%** every **7-10 days**
  - Taper could take weeks to months depending on dose

- **Variability**
  - Different for each patient/situation
Pain Management Strategies

- Opioid-sparing/rotation (evidence lacking)
- NMDA receptor antagonists
- Adjuvant drug therapies (i.e. anticonvulsants, antidepressants)
- Combining opioids with low-dose opioid antagonists (i.e. naltrexone)

Wang et al. (2005)
Clinical Evidence

- Blockade of NMDA receptors ↓ Opioid-Induced Hyperalgesia and slow Tolerance

- Rotation to methadone enhances analgesia.

- No reduction in hyperalgesia or tolerance after 3 months of concurrent treatment with morphine and NMDA receptor antagonist (dextromethorphan).
  - Galer et al., 2005.

- Increased pain sensitivity in opioid addicts on methadone maintenance, well documented.
CLINICAL POTENTIAL - NMDA

- May delay onset and extent of tolerance
- Intolerable central side effects limit use
- Target non-centrally located NMDA receptors (i.e. peripheral)
  - Large/small intestines
  - Kidney, lung, spleen, testis, ovaries, uterus

Fig. 6a. Non-NMDA receptors are selectively agonized by kainate, AMPA and quisqualate. The associated ion channels are more permeable to Na+ and K+ ions than Ca+2 (from Kandel et al., 1991).

Fig. 6b. NMDA receptors are structurally complex, with separate binding sites for glutamate, glycine MG+2, Zn+2 and polyamines. NMDA-gated channels are more permeable to Ca+2 than Na+ ions (from Kandel et al., 1991).
**Clinical Evidence - Ketamine**

- **NMDA antagonist** – anesthetic & neuropathic pain effects

- **Meta-analysis of studies examining perioperative low-dose ketamine with opioids** – opposing results
  - Systematic review failed to show benefit of ketamine in addition to opioids for cancer pain
  - Shown to be significantly beneficial in patients who:
    - Require large amounts of opioid medications
    - Display some degree of opioid tolerance

- **Abolishes opioid-induced post-infusion secondary hyperalgesia.**


Clinical Evidence - Ketamine

- Human experimental pain studies show that administration of ketamine abolishes remifentanil-induced aggravation of hyperalgesia included by electrical stimulation.

- These findings were duplicated in post-surgical patient population.


**Clinical Evidence - Dextromethorphan**

- NMDA receptor antagonist – used as a cough suppressant
- In 3 large randomized, double-blinded, placebo controlled multicenter trials of MorphiDex (morphine and dextromethorphan mixture in a 1:1 ratio) in chronic non-cancer patients – unable to find any significant difference between MorphiDex and morphine alone in the outcome measures.

Clinical Evidence - Methadone

- Methadone is effective in reducing high-dose opioid OIH (multiple studies)

- In a case report, OIH was aggravated with methadone rather than reversing it.
CLINICAL EVIDENCE - METHADONE

- Advantages for switching/rotation:
  - Incomplete cross-tolerance with opioid receptors
  - NMDA receptor antagonism

- Disadvantages:
  - Complex conversion (sample next slide)
  - Torsades de Points – QTc prolongation
  - Linked with increased pain in former opioid addicts

- Add low dose to current opioid
  - Avoids toxicity of high dose methadone
## Methadone Dosing

<table>
<thead>
<tr>
<th>Morphine equivalent dose</th>
<th>Conversion ratio (morphine to methadone)</th>
<th>Conversion factor (approximate percentage of morphine dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 100 mg</td>
<td>3 to 1</td>
<td>33.3</td>
</tr>
<tr>
<td>101 to 300 mg</td>
<td>5 to 1</td>
<td>20.0</td>
</tr>
<tr>
<td>301 to 600 mg</td>
<td>10 to 1</td>
<td>10.0</td>
</tr>
<tr>
<td>601 to 800 mg</td>
<td>12 to 1</td>
<td>8.3</td>
</tr>
<tr>
<td>801 to 1,000 mg</td>
<td>15 to 1</td>
<td>6.7</td>
</tr>
<tr>
<td>≥ 1,001 mg</td>
<td>20 to 1</td>
<td>5.0</td>
</tr>
</tbody>
</table>
PAIN MANAGEMENT STRATEGIES

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Wang et al. (2005)
ADJUVANT DRUG THERAPIES

- Antidepressants
- Anticonvulsants
- Topical local anesthetics
**Multimodal Analgesia**

- **Perception:** opioids, alpha₂-agonists, TCAs, SSRIs, SNRIs
- **Modulation:** TCAs, SSRIs, SNRIs
- **Transmission:** LAs, alpha₂-agonists
- **Transmission:** LAs, opioids
- **Transduction:** LAs, capsaicin, anticonvulsants, NSAIDs, ASA, acetaminophen, nitrate

Pain pathways include:
- Ascending input
- Descending modulation
- Spinothalamic tract
- Dorsal horn
- Dorsal root ganglion
- Peripheral nerve
- Trauma
- Peripheral nociceptors
ANTIDEPRESSANTS

- Tricyclics (TCAs)
  - Amitriptyline (25mg - 50mg bedtime)
  - Nortriptyline (25mg - 150mg bedtime)

- Effective
- Dry Mouth
- Confusion (Not Recommended > 65 y/o)
- Urinary Retention
- Constipation
ANTIDEPRESSANTS

- Serotonin/Norepinephrine Reuptake Inhibitors (SNRI’s)
  - Venlafaxine (ER 150 - 225mg daily)
  - Duloxetine (60mg – 120mg daily)
  - Milnacipran (50mg – 100mg twice daily)

- Not as effective
- More expensive
- Better tolerated
- Monitor Blood Pressure
ANTICONVULSANTS

- **Gabapentin** (1800mg – 3600mg daily)
  - Long Dose titration
  - Effective

- **Pregabalin** (75 – 150mg twice daily)
  - Sedation
  - Short Dose titration

- **Carbamazepine** (200mg – 600mg twice daily)
  - Therapeutic Range (4 – 12 mg/L)
TOPICALS

- **Lidocaine** 5% patch
- **Lidocaine** 2% topical gel

- First line for post-herpetic neuralgia
- Effective
- 12 hours on/off

- **Capsaicin** cream 0.075% (four times daily)

- Cough
- Skin Irritation
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Wang et al. (2005)
OPIOIDS + LOW-DOSE OPIOID ANTAGONISTS

- **Morphine + Naltrexone** (100mg/4mg)
- **Oxycodone + Naloxone** (40mg/20mg)

- Not to be used PRN
- When other options not effective or **tolerance** develops (i.e. non-opioids, immediate-release opioids)
- Ceiling dose – decreased analgesia or withdrawal

**tolerance** - defined as 60mg PO Morphine Equivalents
OTHER OPTIONS

- Buprenorphine
- Propofol
- Cox-2 Inhibitors
- Alpha-receptor agonists
BUPRENORPHINE

- Partial opioid agonist (Mu) with antagonist (Kappa) properties
  - Kappa receptor agonists are known to induce OIH
  - Used for decades in anesthesia and treatment of pain

- PO film/buccal (opioid dependence)
- Transdermal patch (chronic pain)
Clinical Evidence - Buprenorphine

- Induced pain sensitivity in patients maintained on methadone

- Enhanced ability to treat OIH vs fentanyl
PROPOFOL

- Modulatory effect on OIH?
- Possibly through interactions with Gamma-aminobutyric acid (GABA) receptors at the spinal level?
- Clinical significance in chronic pain unknown

COX-2 Inhibitors - Celecoxib

- Sensitizes the NMDA nociceptive system before activation

- Shown to attenuate development of opioid tolerance in animals

- Less important role than the NMDA receptor system?
- Compared to other NSAIDs?
**Alpha-Receptor Agonists**

- **Clonidine**
  - Shown to attenuate opioid-induced post-infusion antianalgesia and abolish secondary hyperalgesia.

- **Dexmedetomidine**
  - Sedative in ICU
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Wang et al. (2005)
CLINICAL STRATEGIES

- **Early identification**
  - Repeated dose escalations fail
  - Unexplained pain exacerbation after increasing opioid
  - Disease progression is ruled out
  - Acute insult ruled out

- **Hyperalgesia**
  - Decrease or eliminate offending opioid
  - Supplement with NMDA receptor modulators

- **Tolerance**
  - Rotate – no RCTs exist demonstrating superiority of one opioid over another
TREATMENT STRATEGIES

- Weaning from high dose opioid
  - Time/patience of patient/family
  - Transient increases in pain
  - Mild withdrawal
  - Hyperalgesia might not improve initially (specific dose?)

- Multiple Office Visits
- Utilize Non-opioid medications
- Interventional pain management
- Behavioral management
REFERENCES

- Angst MS, Clark JD. Opioid-induced hyperalgesia: A qualitative systematic review. Anesthesiology 2006; 104:570-587
- Fig. 6. Cumulative postoperative morphine consumption in the two groups during 24 h after tracheal intubation. Values are mean +/- 95% confidence interval. Open circles = desflurane group, filled squares = remifentanil group. Area under the curve differed significantly in the two groups (P < 0.05).
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