Opioids for Pain

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Objectives

- Contrast the usual causes and natural history of chronic pain of malignant or non-malignant origin.
- Identify treatment goals for a patient being treated for acute vs chronic pain.
- Describe the clinical data describing the utility of opioids vs non-opioids for the treatment of non-malignant pain
- Describe non-drug therapies that may be included into an integrated plan for treating chronic non-malignant pain

Required Reading

- Herndon, C, et al. Pain Management in Chapter 77 of DiPiro's Pharmacotherapy (11th ed) (or Chapter 60 in the 10th ed.)

What is “Acute Pain”

- Previously defined as pain lasting less than 6 months
- Pain associated with tissue injury:
  - An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. (IASP)
- Expected to resolve
  - Other expectations can impact perception of severity of pain

Should Patients Tough it Out?

- Inadequately controlled acute pain can lead to central sensitization and a higher risk of long term (chronic) pain
  - Delayed ambulation, participation with PT
  - Also associated with an increased long-term use of opioids
- Should opioids be routinely used for the treatment of acute pain?

Using Pain Scores

- NRS (Numerical Rating Scale): 0 – 10
  - Make sure patient knows which end is what
- VAS (Visual Analog Scale): 0-100 mm
  - Requires dexterity by patient to place a mark
- Faces / FLACC for children
  - Face
  - Legs
  - Activity
  - Cry
  - Consolability

Numerical Rating Scale

- 0 – 10 scale based largely on the work of Cleeland and the Brief Pain Inventory
- Primarily based upon interference with function:

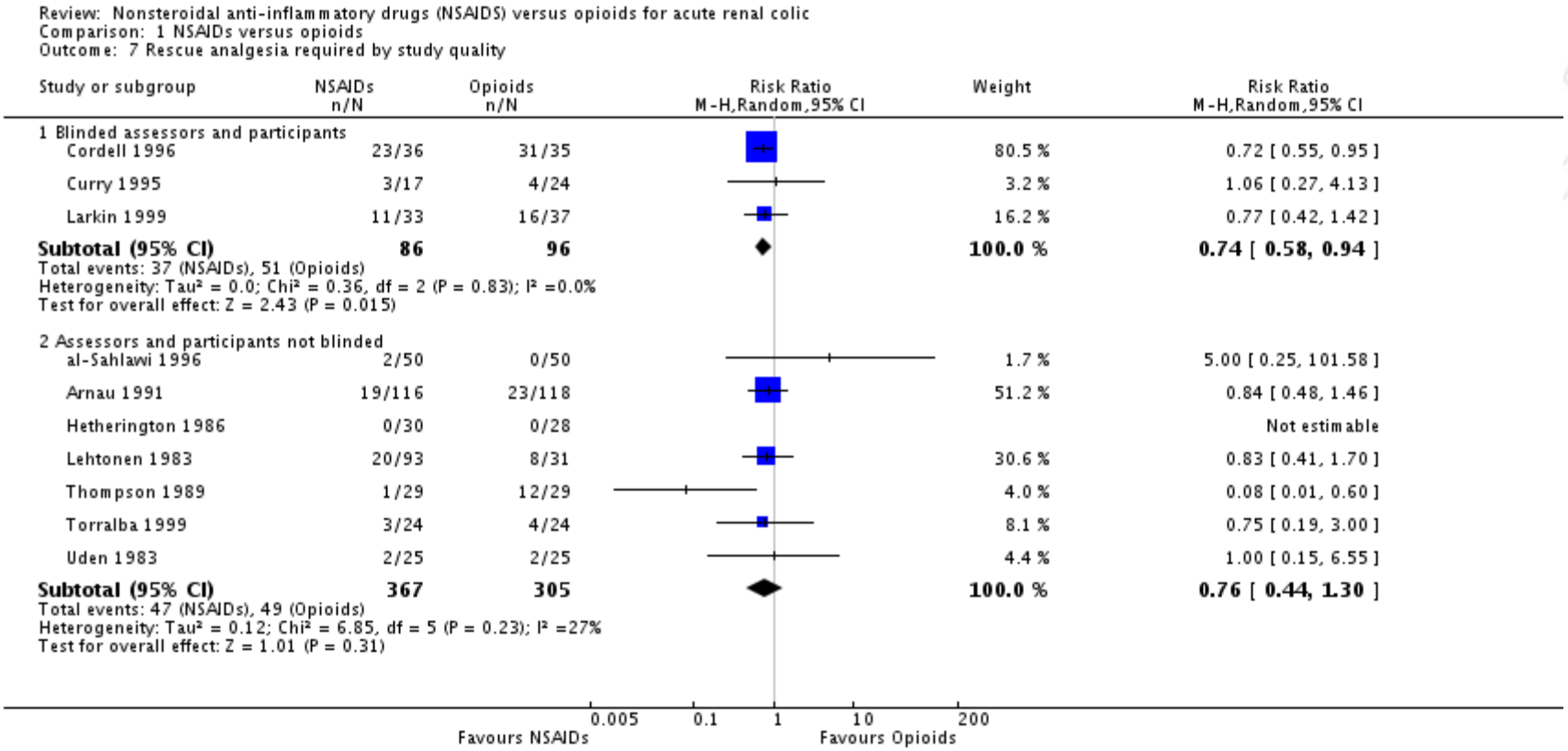
0:	No pain
1 – 4:	Mild pain; no interference with activity
5 – 6:	Moderate pain; some interference
≥ 7:	Severe pain; greatly impairing ADLs

Multimodal Treatment

- (Nerve Blocks and Peri (Pre) procedural Tx)
- Cold packs
- NSAID
- Acetaminophen
- Glucocorticoid
- PT / Ambulation (or rest)
- Opioids

NSAIDs vs Opioids for Renal Colic

Need for Rescue Analgesia

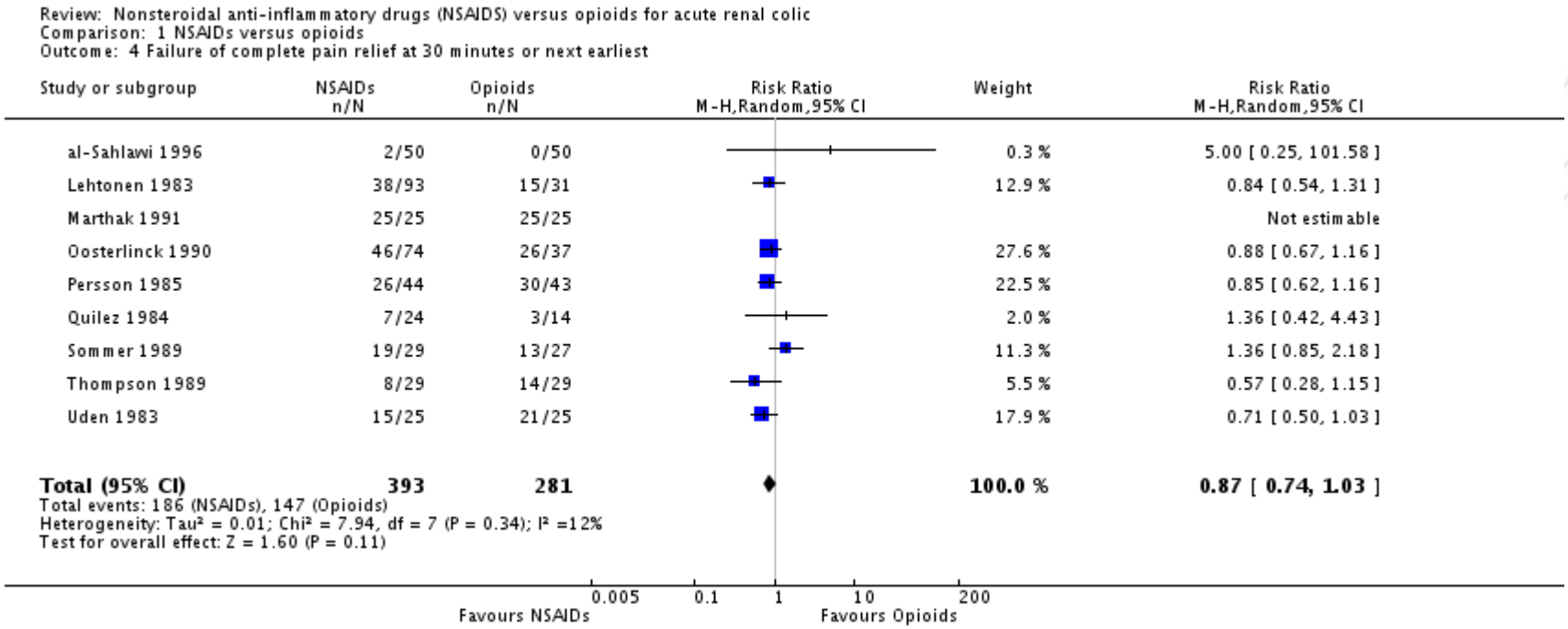


Favors NSAIDs Favors Opioids

Holdgate A, Pollock T. Nonsteroidal anti-inflammatory drugs (NSAIDS) versus opioids for acute renal colic. Cochrane Database of Systematic Reviews 2004, Issue 1. Art. No.: CD004137. DOI: 10.1002/14651858.CD004137.pub3.

NSAIDs vs Opioids for Renal Colic

Complete Pain Relief at 30 min



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Chronic Pain

- Longer than 3 months
- Many categories possible
  - Cancer (malignant) pain
  - Musculoskeletal pain
  - Postsurgical and posttraumatic pain
  - Neuropathic pain
  - Headache and/or orofacial pain
  - Visceral pain
  - Primary pain (eg, fibromyalgia, diffuse pain)

Treede RD, et al. Pain 2015; 156: 1003-7

Lower Back Pain

- About 25% of US adults reported LBP at least one full day in last 3 months
  - 7.6% gave report of severe, acute LBP in last year
- Approximately 2% of US work force is compensated for LBP
  - Cost to US economy is greater than $28 billion
- About 33% of adults with an acute pain injury report some persistent pain at up to a year
  - 20% report substantial limitations in activity

Chou R, et al. Ann Int Med 2007; 147: 478-91.

Non-Drug Therapies

- Moderate Strength of Evidence
  - Gentle exercise / Motor Control Exercise
  - Multidisciplinary rehabilitation
  - Local heat packs
  - Mindfulness Stress Reduction
- Low Strength of Evidence
  - Spinal manipulation
  - Acupuncture
  - Massage

Chou R, et al. Ann Int Med 2017; 166: 493-505

Drug Treatment of Lower Back Pain

- Acetaminophen
  - Not better than placebo for acute back pain
  - No studies for chronic back pain
- NSAIDs
  - Better than placebo for acute and chronic LBP, but chronic effect was small
- Skeletal Muscle Relaxants
  - Evidence of benefit in first week
  - Little evidence of benefit chronically

Chou R, et al. Ann Int Med 2017; 166: 480-92

Drug Treatment of Lower Back Pain

- Benzodiazepines
  - Failure to improve by Day 14
- Antidepressants (TCA/SSRI)
  - No effect on chronic LBP for most trials
  - Small benefit by duloxetine
- Antiseizure (gabapentin/pregabalin)
  - Unevaluable
- Systemic Corticosteroids
  - Little effect on pain; possible improved function

Chou R, et al. Ann Int Med 2017; 166: 480-92

Drug Treatment of Lower Back Pain

- Opioids
  - Tramadol and strong opioids were better than placebo in reducing pain, improving function
  - Improvement in function is small
  - Studies are short, usually 3 months or less
  - None longer than 4 months
  - Most all opioid studies were industry-funded
    - Many were enriched with responders
    - At risk patients were excluded (SUD, depression)

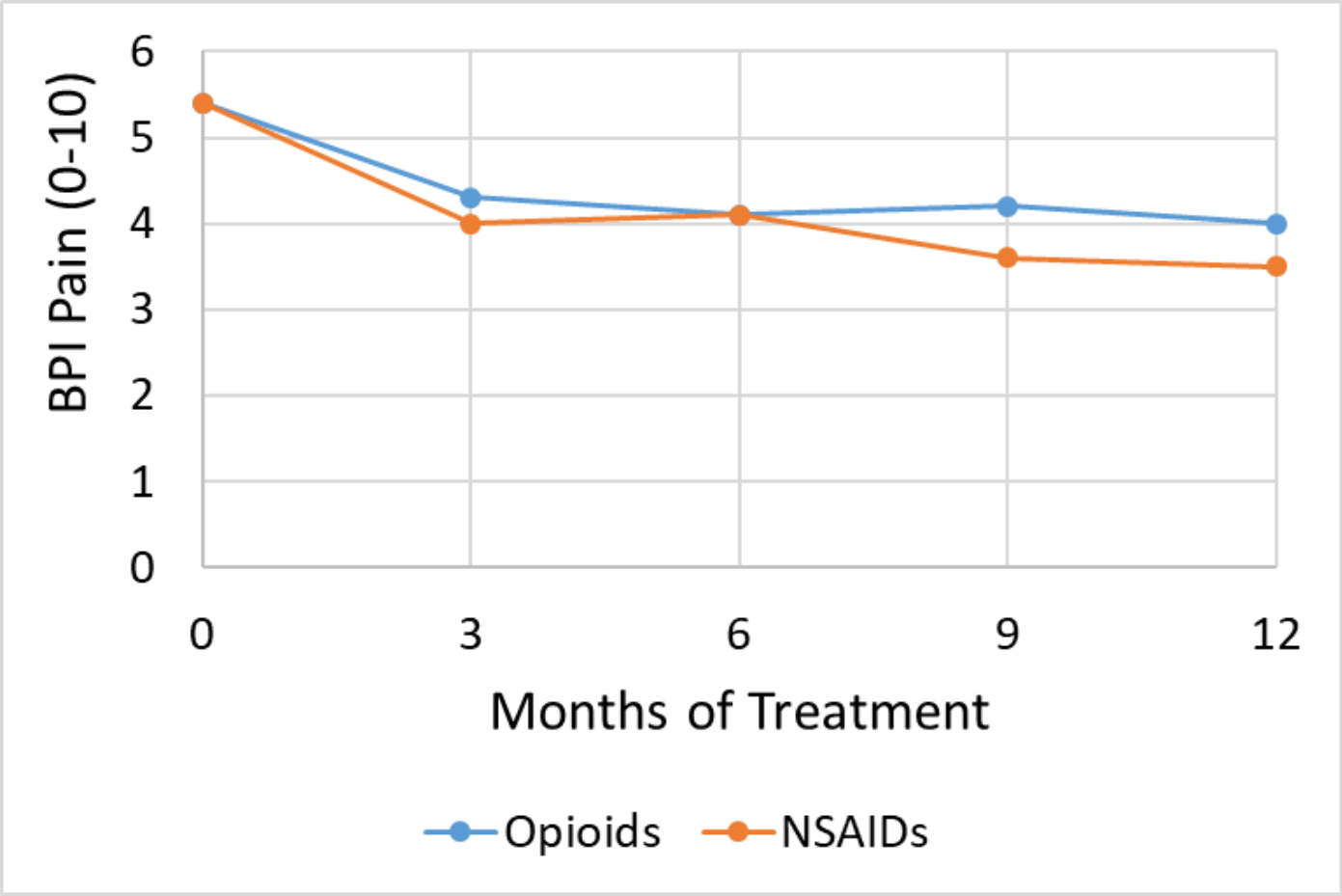
Chou R, et al. Ann Int Med 2017; 166: 480-92

Opioids vs NSAIDs for Low Back Pain and Osteoarthritis

- N= 240 VA pts with LBP or knee/hip pain
- Randomized to stepped treatment arms:
  - Opioids (morphine, oxycodone, hydrocodone)
    - Switched to other opioid if MEDD reached 60
  - NSAIDs step 1
    - Other NSAIDs or doses used not specified
    - Step 2: TCA, gabapentin, topical capsaicin, lidocaine
    - Step 3: duloxetine, pregabalin
  - Assessed over 12 months

Krebs E, et al. JAMA 2018; 319: 872-882

Opioids vs NSAIDs for Low Back Pain and Osteoarthritis



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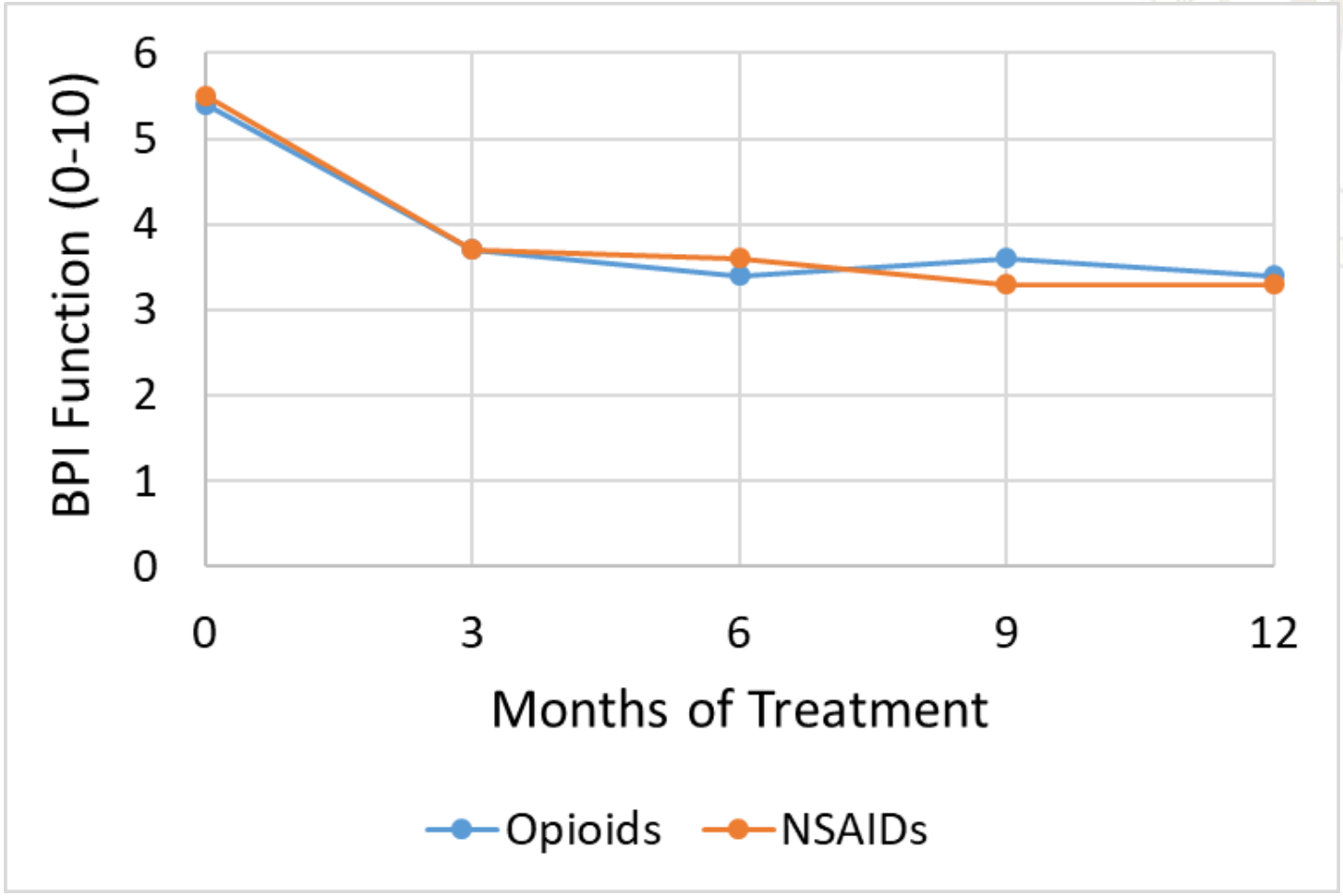

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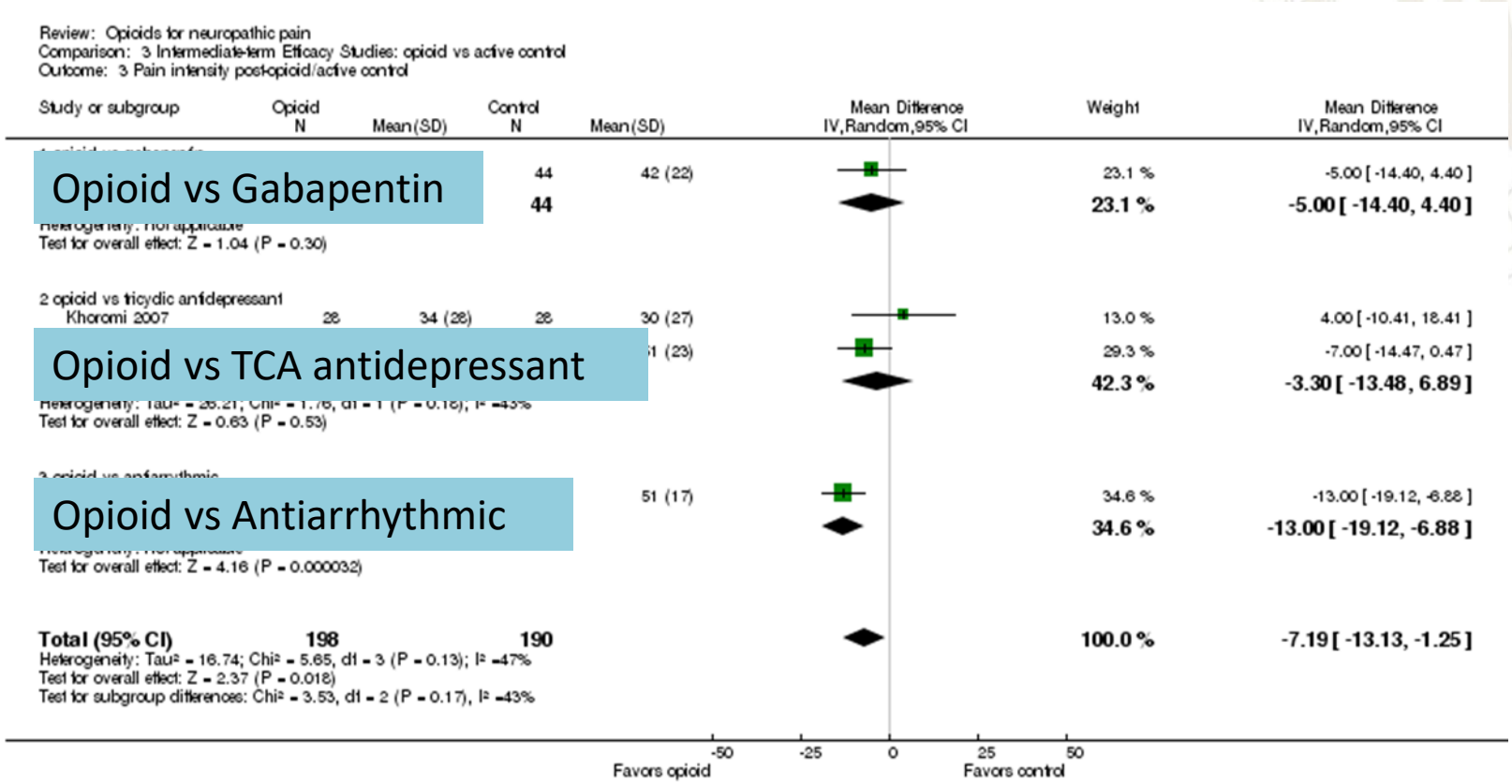
Opioids for Neuropathic Pain?



Favors opioid Favors active control

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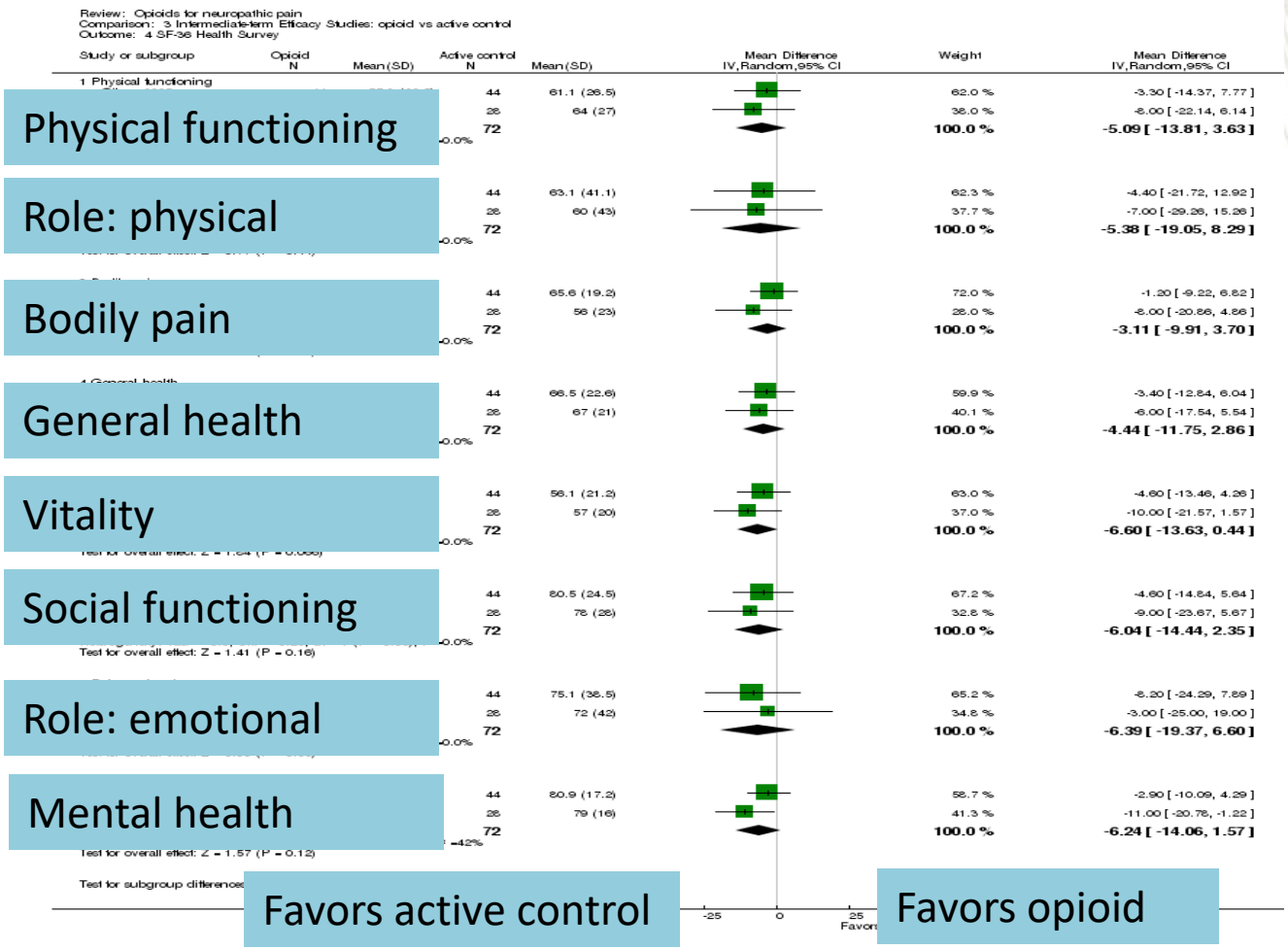
McNicol ED, et al. Cochrane Database Syst Review 2013, DOI: 10.1002/14651858.CD006146.pub2.

Opioids vs Active Controls for Neuropathic Pain: SF-36 Outcome



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Opioids for Neuropathic Pain?

- Some benefit noted in placebo-controlled trials
- Small difference in active-control trials
- No benefit in SF-36 domains
- Consider instead:
  - TCA, duloxetine
  - Lidocaine (topical and/or systemic)
  - Ketamine, other NMDA antagonists

McNicol ED, et al. Cochrane Database Syst Review 2013, DOI: 10.1002/14651858.CD006146.pub2.

Opioids for Chronic Pain

- Non-malignant chronic pain
  - Studies are typically short
  - While benefit may be seen vs placebo, opioids are commonly no better than NSAIDs ± other adjuvants
- Cancer-related pain
  - More likely to respond to opioids
  - Caution still needed in initiation and titration
  - Adjuvants are still appropriate

Chronic Opioids: Adverse Effects

- Overdose, death
- Sleep-disordered breathing
- Sedation, delirium
- Falls, fractures
- Nausea, vomiting
- Chronic constipation, intestinal obstruction
- Hyperalgesia
- Sexual dysfunction
- Urinary retention
- Depression, anxiety, fatigue
- Dry mouth (dental consequences)
- Opioid use disorder
- Pruritus, urticaria
- Myoclonus, seizures (high doses of certain opioids)
- ↓Testosterone
- ↓Estradiol
- Osteoporosis

Vuong C *et al., Endocr Rev* 2010;31(1):98-132.

Von Korff MR. *Best Pract Res Clin Rheumatol* 27 (2013) 663–672.

Opioid Abuse Epidemic in the US

- The number of prescribed opioids has quadrupled since 1999, **but** reports of pain have not declined
- In 2015, opioids were associated with the death of over 33,000 Americans, approximately 90 every day
  - Half of overdose deaths involve prescription opioids
  - Co-prescribing of benzodiazepines greatly increases overdose risk
- In 2014, almost 2 million Americans abused or were dependent on prescription opioids
- Non-medical use: 10-18% of 12-18 year olds
- **Opioid use disorder**: up to 25% of patients treated with long-term opioids for chronic non-cancer pain

CDC: https://www.cdc.gov/drugoverdose/index.html

How Long Does it Take to Become Physically Dependent on Opioids?

- Physical dependence will result in symptoms of withdrawal if dosage is substantially, quickly reduced
- Physical dependence can be presumed to occur when one has developed some tolerance to opioids (no longer “naive”)
  - Tolerance and dependence occur on similar time frames but are not necessarily concurrent
  - Faster onset with opioids with shorter T1/2

FDA Opioid Tolerance Definition

- Patients who are taking, for 1 week or longer, at least:
  - 60 mg oral morphine (hydrocodone)/day
  - 30 mg oral oxycodone/day
  - 8 mg oral hydromorphone/day
  - 25 µg transdermal fentanyl/hour
  - 25 mg oral oxymorphone/day; or
  - An equianalgesic dose of any other opioid.

Increasing Pressure to Limit Initial Dose

MME	Odds of Overdose	Absolute Risk Difference
< 20 mg/day	1 (comparator)	0
20 To 49 mg/day	1.3 – 1.9	
50 to 99 mg/day	1.9 – 4.6	1.4% (0.15% fatal)
≥ 100 mg/day	2.0 – 8.9	4.04% (0.25% fatal)

Dowell D, Haegerich TM, Chou R. MMWR 2016; 65: 1-50.

CMS Part D Opioid Safety Edits

- Limits initial opioid prescription to a 7-day supply
  - 3-day supply is recommended
  - Cancer and end-of-life patients are exempt (in theory)
- Limits opioid daily dose (in Morphine equivalents, MME or MEDD) to 90mg/day
  - 90 MME is aggregate from all current Rx
  - **Oxycodone 5mg i-ii tabs Q4-6hrs PRN = 90MME**
  - Hydrocodone/APAP 5mg/325 i-ii tabs Q4-6hrs PRN = 60MME
    - Some chain pharmacies will refuse Rx for > 50 MME

https://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNMattersArticles/Downloads/SE18016.pdf

CDC 2016 Opioid Guideline

The Guideline is not intended for patients who are in active cancer treatment, palliative care, or end-of-life care.

IMPROVING PRACTICE THROUGH RECOMMENDATIONS

CDC's *Guideline for Prescribing Opioids for Chronic Pain* is intended to improve communication between providers and patients about the risks and benefits of opioid therapy for chronic pain, improve the safety and effectiveness of pain treatment, and reduce the risks associated with long-term opioid therapy, including opioid use disorder and overdose.

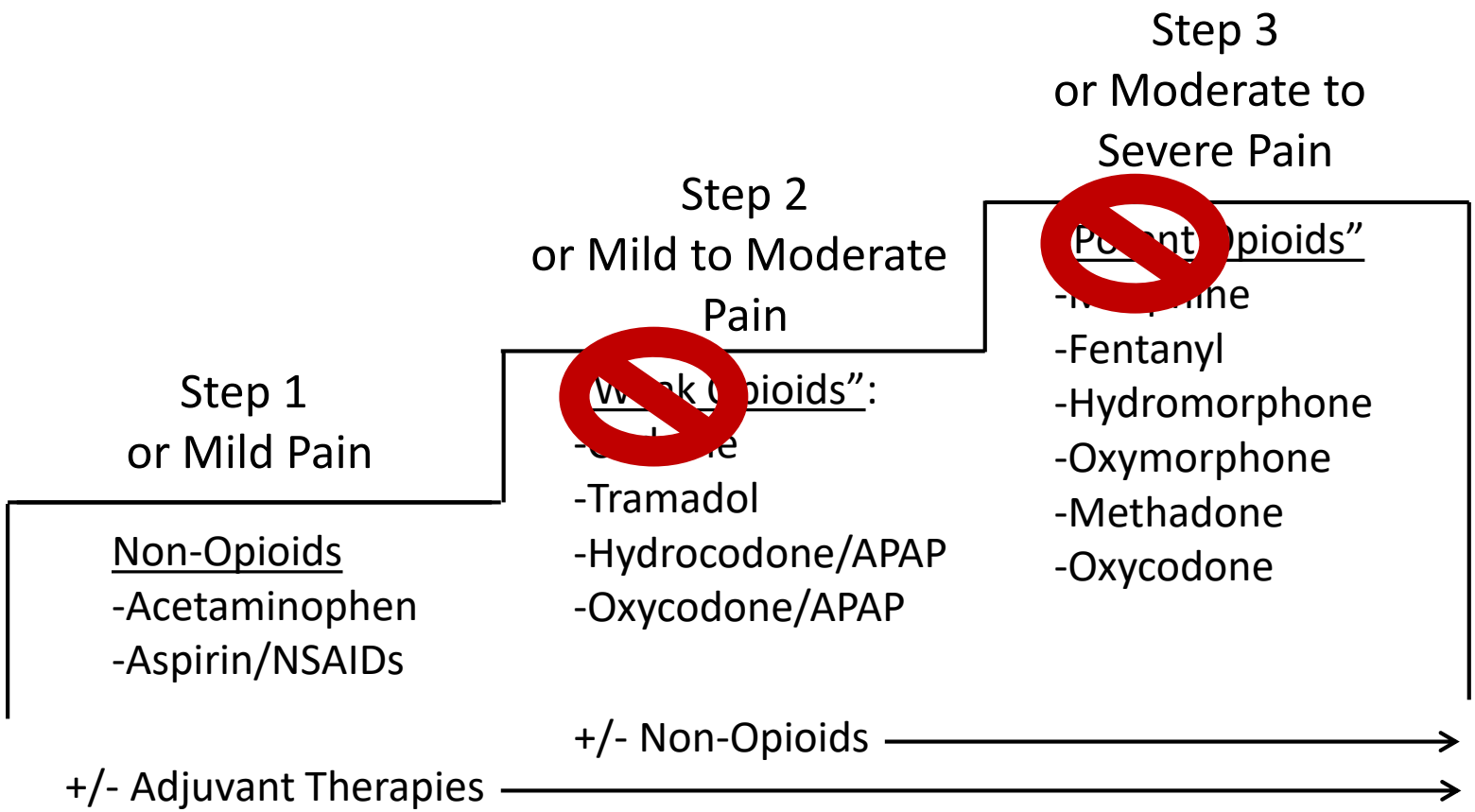
The Guideline is not intended for patients who are in active cancer treatment, palliative care, or end-of-life care.

*www.**cdc**.gov/drugoverdose/prescribing/**guideline**.html*

Components of a Rational Approach to Treating Pain

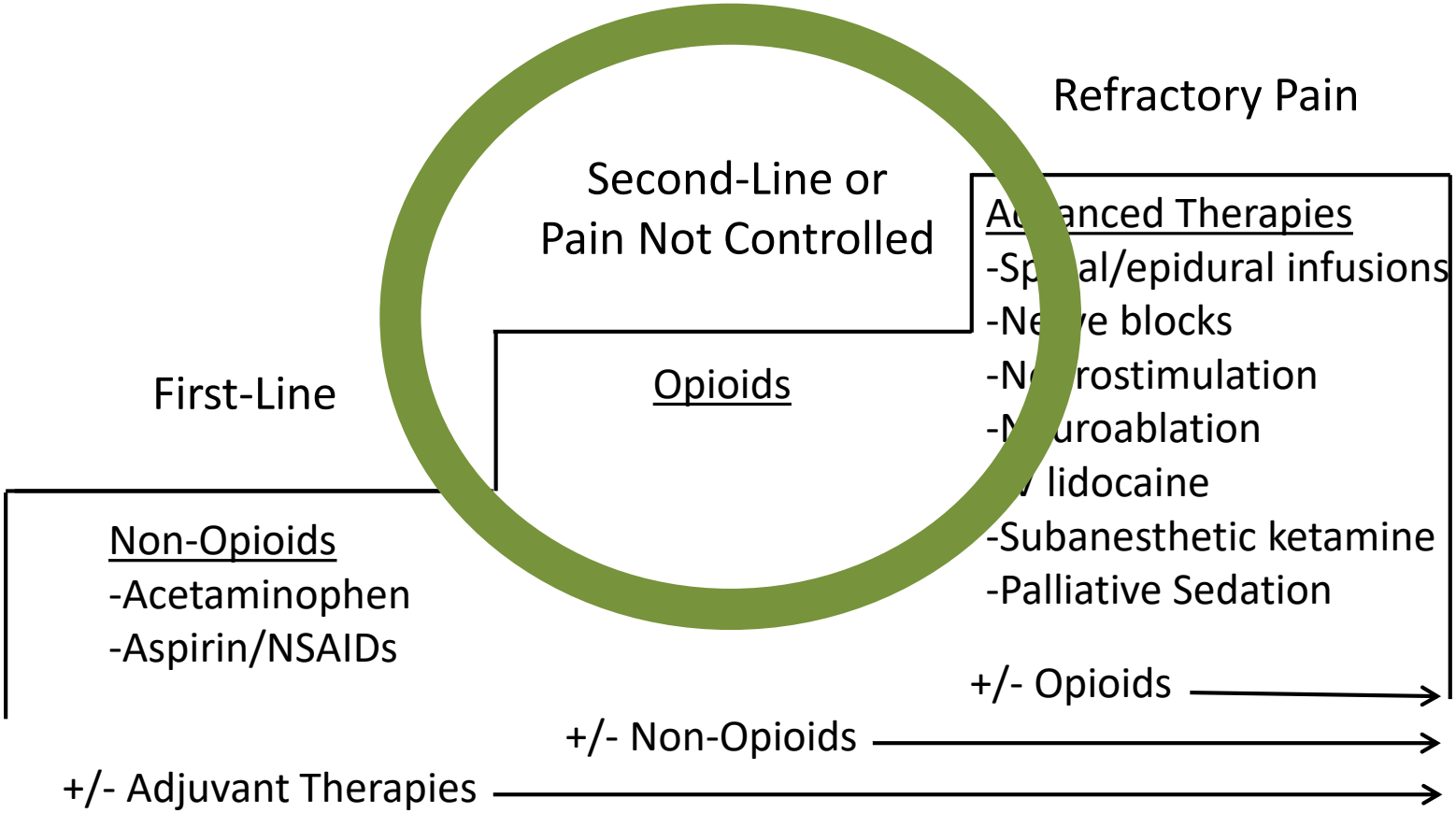
- Careful assessment
- Clear diagnosis
- Goal-oriented treatment plan
- Maximize non-drug therapies
- Maximize non-opioid medications
- Screen for risk factors
- Monitor efficacy (function and pain)
- Stop ineffective treatments
- Use opioids in the lowest effective dose for the shortest appropriate duration

WHO Analgesic Step-Ladder Approach to Cancer Pain Management: **Outdated**



Adaptation of WHO Analgesic Ladder, 1990

Revised WHO Step-Ladder



Adapted from Fine PG. *Anesth Analg*. 2005; 100: 183-8.

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Cancer ("Malignant") Pain

- Accompanies disease progression
- Malignant pain is not expected to resolve or heal
- Frequently responds to medication
- Disease progression may cause pain to "break through" an established analgesic regimen
- CDC and Wisconsin MEB Opioid Prescribing Guidelines *do not* apply to the treatment of cancer-related pain
  - 50mg/day morphine equivalent limit on initial opioid prescription is inappropriate for this population with what can be expected to be chronic, progressive cancer pain.
  - Co-Rx of naloxone is reasonable for other safety considerations

Wisconsin ePDMP

- Prescribers must check ePDMP prior to issuing a prescription for any controlled substance, not just opioids
  - https://docs.legis.wisconsin.gov/statutes/statutes/961/III/385
- Exceptions include:
  - The patient is receiving hospice care
  - The prescription is not refillable and is prescribed for 3 or fewer days
  - The drug is administered directly to the patient
  - Emergency does not allow review of the PDMP
  - The ePDMP platform is down
  - Document exceptions, document, document …
  - https://pdmp.wi.gov

Wisconsin ePDMP

- Dispensers (pharmacists) must submit dispensing information on scheduled drugs to the ePDMP by the end of the business day
- Exceptions include:
  - The monitored prescription drug is administered directly to a patient
  - The monitored prescription drug is compounded, packaged, or labeled in preparation for delivery but is not delivered
  - The prescription order is for a monitored prescription drug that is a substance listed in State Controlled Substances Schedule V and is not a narcotic drug, and the prescription order is for a number of doses that is intended to last the patient 7 days or less (e.g., pseudoephedrine)
  - https://pdmp.wi.gov

ePDMP: What To Look For

- What scheduled drugs are prescribed? (Are they consistent with your record?)
- Are scheduled drugs prescribed by different prescribers or dispensed from different pharmacies, especially over the same time period?
- For patients treated for chronic pain, how consistent is their filling of prescriptions? (e.g., early refills)
- What notes have been added to the ePDMP by other prescribers and/or pharmacies regarding unusual or mitigating events?

Response To Unusual PDMP Findings

- Consider meeting with your practice partners to establish a common set of expectations and responses
- Possible scenarios and training are available, e.g., Brandeis University's website (http://www.pdmpassist.org/)

PDMP TTAC
Prescription Drug Monitoring Program Training and Technical Assistance Center

Brandeis University The Heller School
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