Opioid Therapy for Chronic Non-cancer Pain: Evidence from randomized trials

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Chronic Pain States

Nociceptive/ Inflammatory Pain

Neuropathic Pain

Mixed Type

(Cancer Pain)

Dysfunctional

(central sensitization)

Pain

Opioids for Chronic Non-cancer Pain: The Evidence

Will restrict discussion to:

- Evidence of efficacy from peer-reviewed publications of randomized controlled trials (RCTs) in nociceptive and neuropathic pains
- Meta-analysis and Critical reviews

Not Included …

- RCTs in Cancer and Dysfunctional pain
- Breakthrough pain
- Adverse effects
- Observational non-randomized studies (Ballantyne)
- Limitations of studies (Turk)
- Alternative therapies in light of limitations (Rowbotham)

Opioids for Chronic Non-cancer pain: Clinical Models

Chronic nociceptive pain

- Osteoarthritis
- Low back pain
- Musculoskeletal pain
- Rheumatoid arthritis

Chronic neuropathic pain

- Post-herpetic neuralgia
- Diabetic neuropathy
- Post-amputation pain
- Peripheral and central pain states

Randomized Controlled Trials (RCTs)

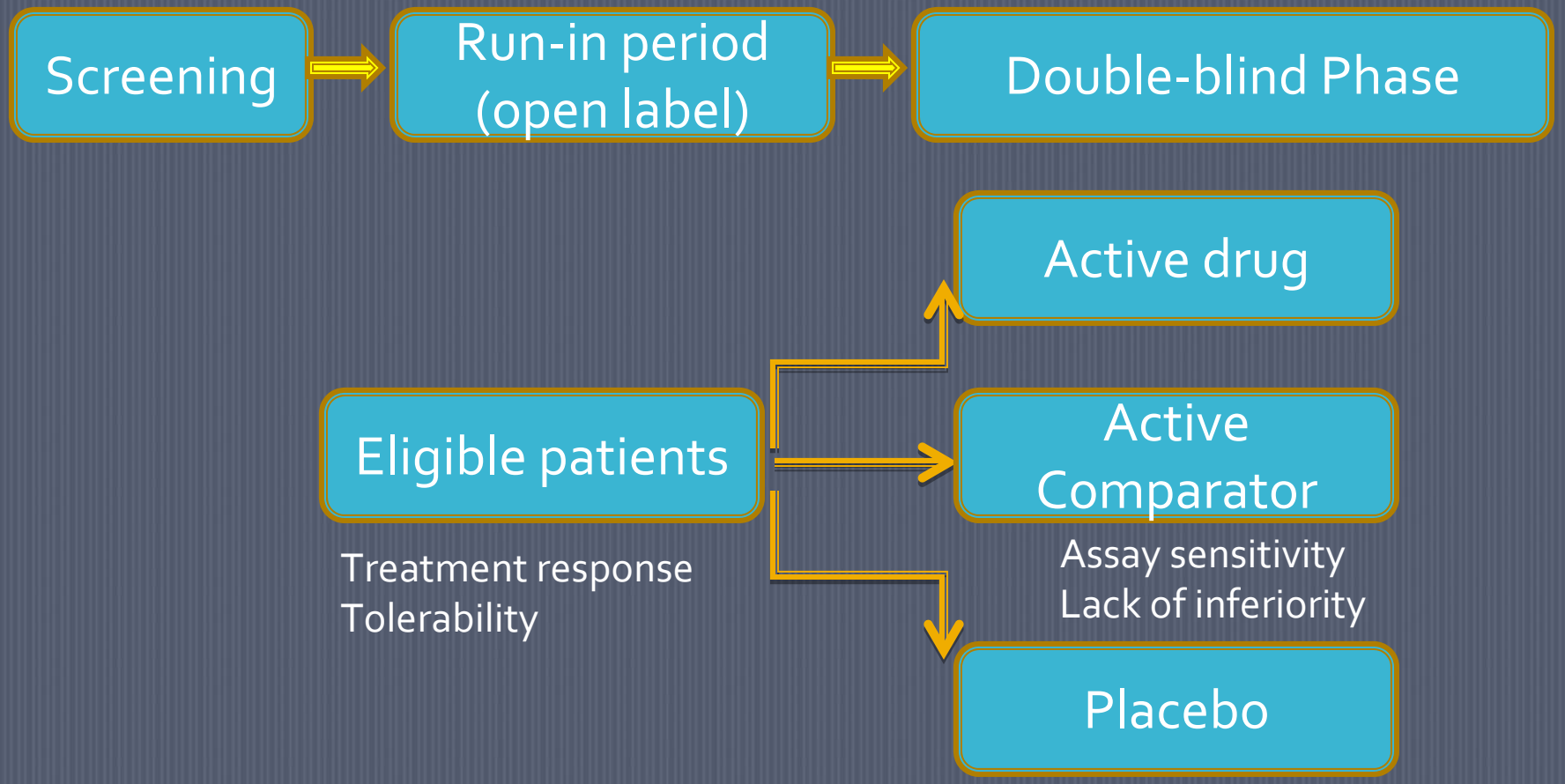
INCLUSION CRITERIA

- Adults ≥ 18yr
- Pain ≥ 4 on a 0-10 scale
- Moderate or severe pain
- Pain not adequately controlled by NSAIDs or COX-2 inhibitors

STUDY DESIGNS

- Parallel double-blind
- Cross-over
- Enriched enrollment
  - Placebo and/or active comparator
- Usually 4-12 wk treatment periods

Enriched enrollment designs



Opioids for Chronic Non-cancer pain: Drugs studied with RCTs

- Morphine
- Oxycodone
- Fentanyl
- Levorphanol
- Hydromorphone
- Oxymorphone

- Tramadol
- Tapentadol
- Buprenorphine

Mu-opioid receptor agonists

Mu-agonist + reuptake inhibition (NE/5-HT, NE)

Mu-agonist + κ and δ antagonist

Efficacy: Outcome measures

- **Pain intensity**
- Responder rates
- $NNT_{30\%}$ and $NNT_{50\%}$
- Pain relief
- Patient Global Impression of Change (PGIC)
- Quality of sleep
- Physical function
- Quality of Life

Pain Assessment: Outcome measures

- NRS-11: pain intensity on a 0-10 scale (11 point,)=no pain, 10= worst pain you can imagine)
- 5-point categorical scale: 0= none to 4= excruciating
- VAS 100: 100 mm line from no pain to excruciating pain
- WOMAC OA index: pain subscale that includes 5 items each rated on a 0-4 range (during walking, using stairs, in bed, sitting/lying, standing)

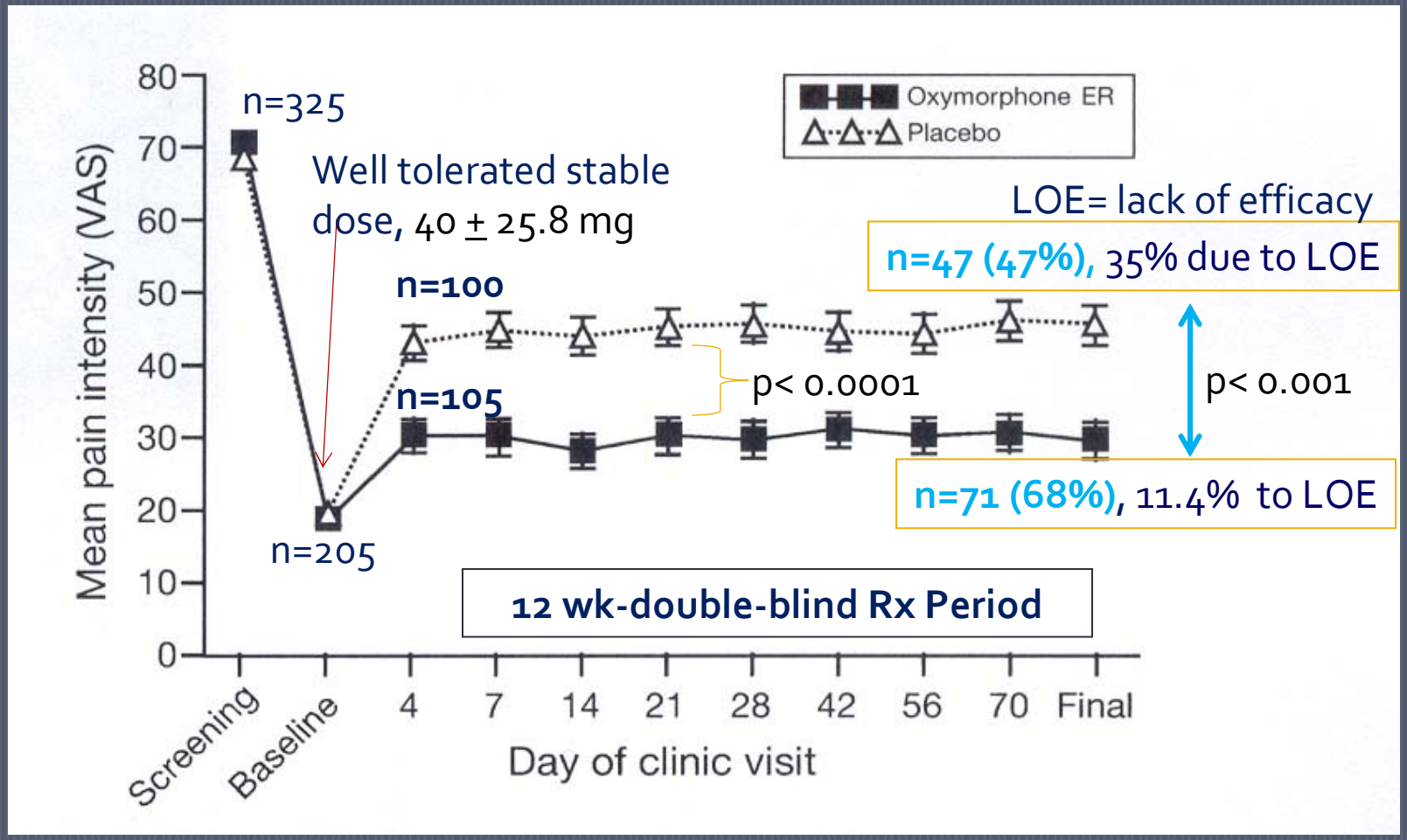
Nociceptive Pain: Oral morphine for musculo-skeletal pain

- Double-blind, 2-period cross-over RCT (3+ 6 wk))
- Soft tissue, musculo-skeletal, rheumatic
- Pain >6 m, ≥ 5 on VAS
- Failure to respond to NSAID, TCA
- Pain, drug liking, psychological features, functional status, cognition

"In patients with treatment-resistant chronic regional pain of soft-tissue or musculoskeletal origin, 9 weeks of oral morphine in doses up to 120 mg daily may confer analgesic benefit with a low risk of addiction ...."

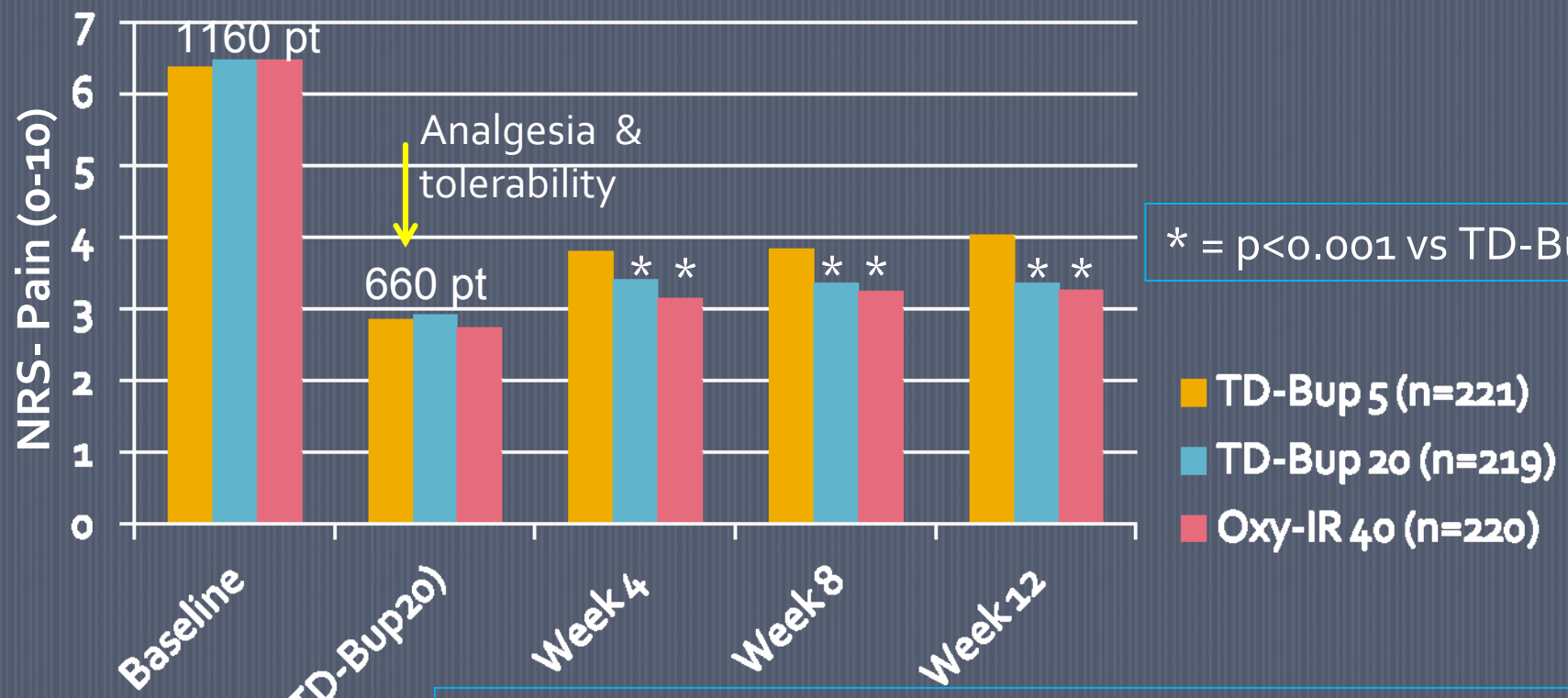
Moulin DE et al.
Lancet 347; 143–146:1996

Oxymorphone ER in Chronic Low Back Pain: Enriched enrollment withdrawal trial



Katz et al. Curr Med Res Opin 2007;23:117

Transdermal Buprenorphine for Chronic Low Back Pain: Enriched enrollment comparator trial



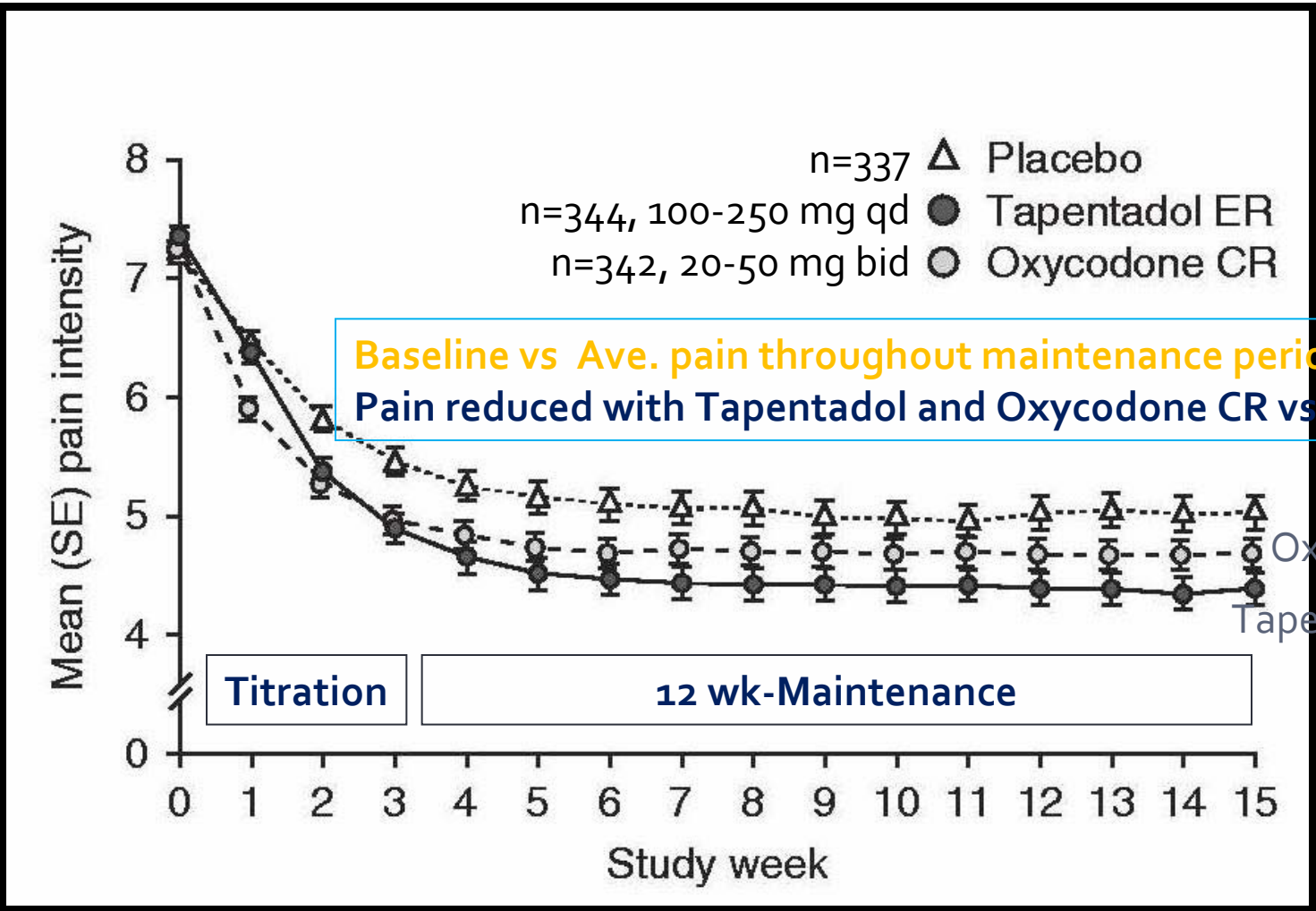
Mean difference (95% CI) from TD-Bup5 over 4,8, 12 wk

TD-Bup20 mcg/hr = 0.67 (0.99, 0.35)

Oxy-IR 40 mg/day = 0.75 (1.07, 0.44)

Steiner et al. J Pain 2011;12:1163

Tapentadol ER for Knee Osteoarthritis: Active and placebo-controlled parallel study



Baseline vs Ave. pain throughout maintenance period

Pain reduced with Tapentadol and Oxycodone CR vs placebo

Cochrane review: Oral or Transdermal Opioids for OA Knee or Hip

- 10 controlled trials with 2268 subjects included
- Codeine, oral morphine, TD fentanyl, oxycodone, oxymorphone (51 mg MS equivalent)
- Pain: Placebo (29% decrease) vs Opioid (44% decrease, Δ=0.9, CI: -1.2 to -0.7)
- Function (WOMAC): Improvement larger in opioid vs placebo (Δ=0.7, 13% difference in improvement)

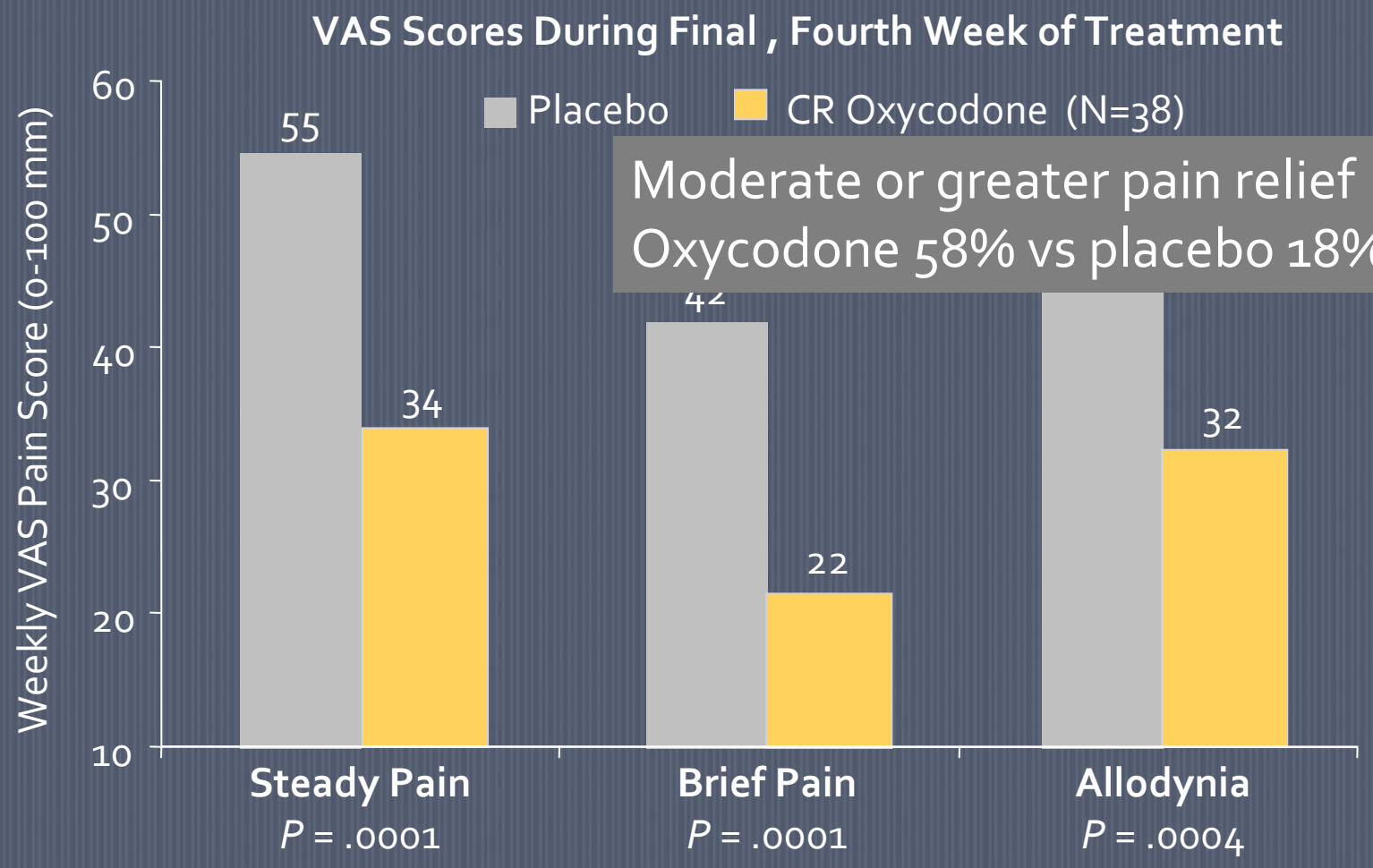
Nuesch E et al. Cochrane Database Systematic Review2009

Cochrane review: Oral or Transdermal Opioids for OA Knee or Hip

- "Overall opioids more effective than control interventions in terms of pain relief and improvement of function."
- No substantial difference: type of opioid, analgesic potency (strong/weak), trial methodological quality, type of funding ..

Nuesch E et al. Cochrane Database Systematic Review2009

Opioids for Neuropathic Pain: Efficacy of CR Oxycodone in Postherpetic Neuralgia

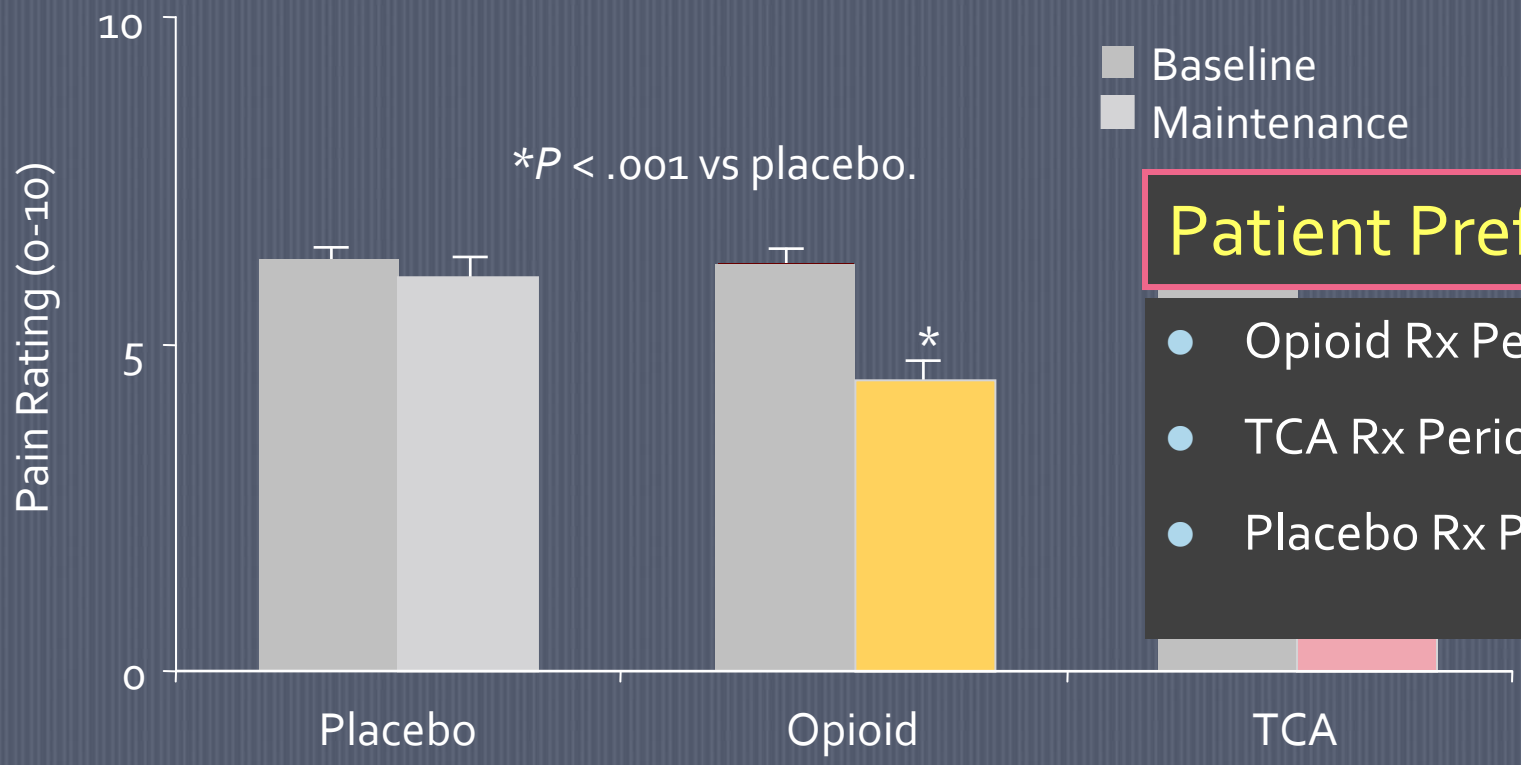


Moderate or greater pain relief
Oxycodone 58% vs placebo 18%

Watson CPN, Babul N. *Neurology*. 1998;50:1837-1841.

Opioids for Neuropathic Pain: Opioid vs Tricyclic Antidepressant in Postherpetic neuralgia

VAS Pain Scores During Final Week of Treatment

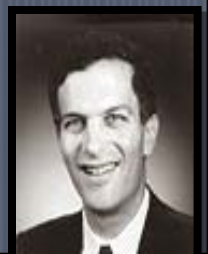


Patient Preference

- Opioid Rx Period - 54%
- TCA Rx Period- 30%
- Placebo Rx Period- 16%

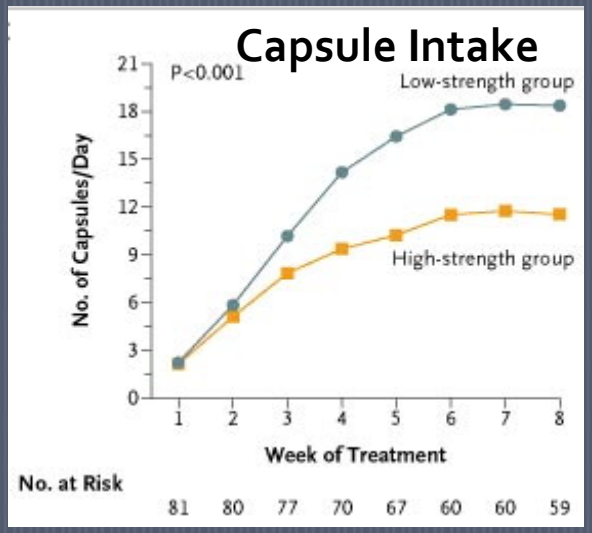
Randomized, double-blind, placebo-controlled, three-period crossover trial- antidepressant (TCA), opioid, placebo

Max



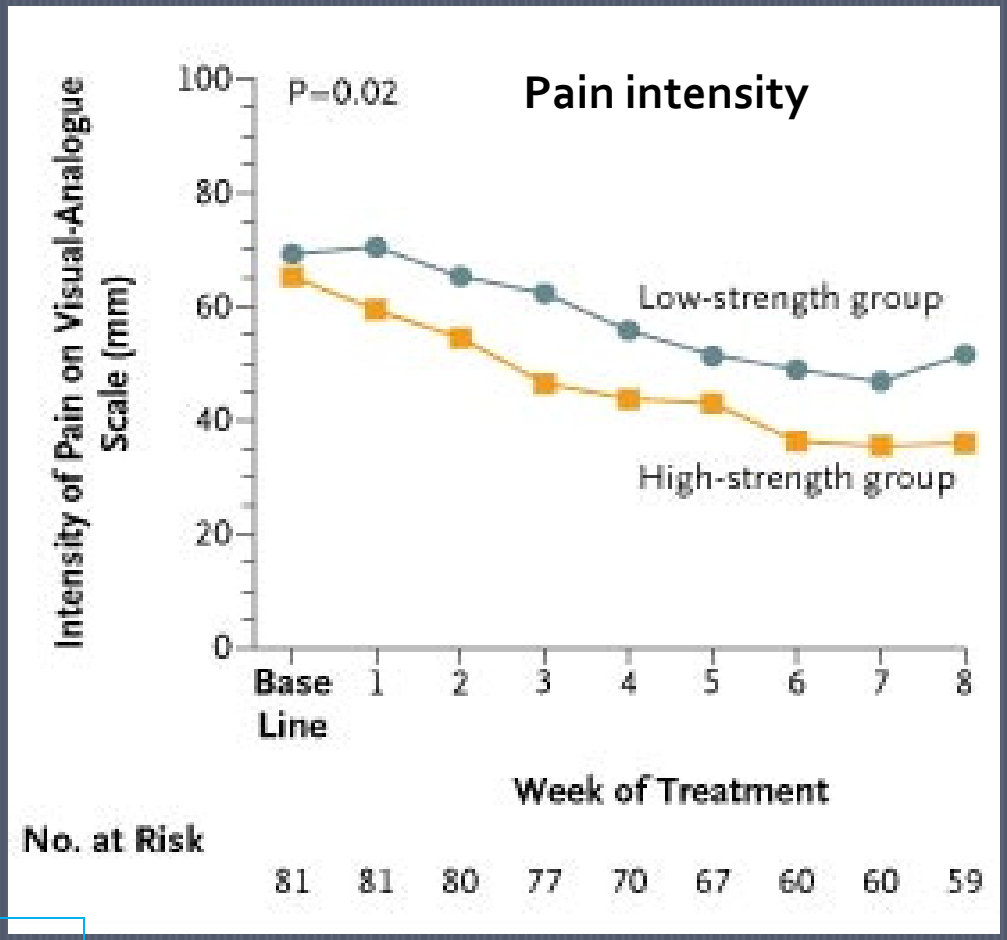
Raja SN et al. *Neurology*. 2002

Levorphanol for chronic peripheral and central neuropathic pains



Ave. dose 2.7 mg/d

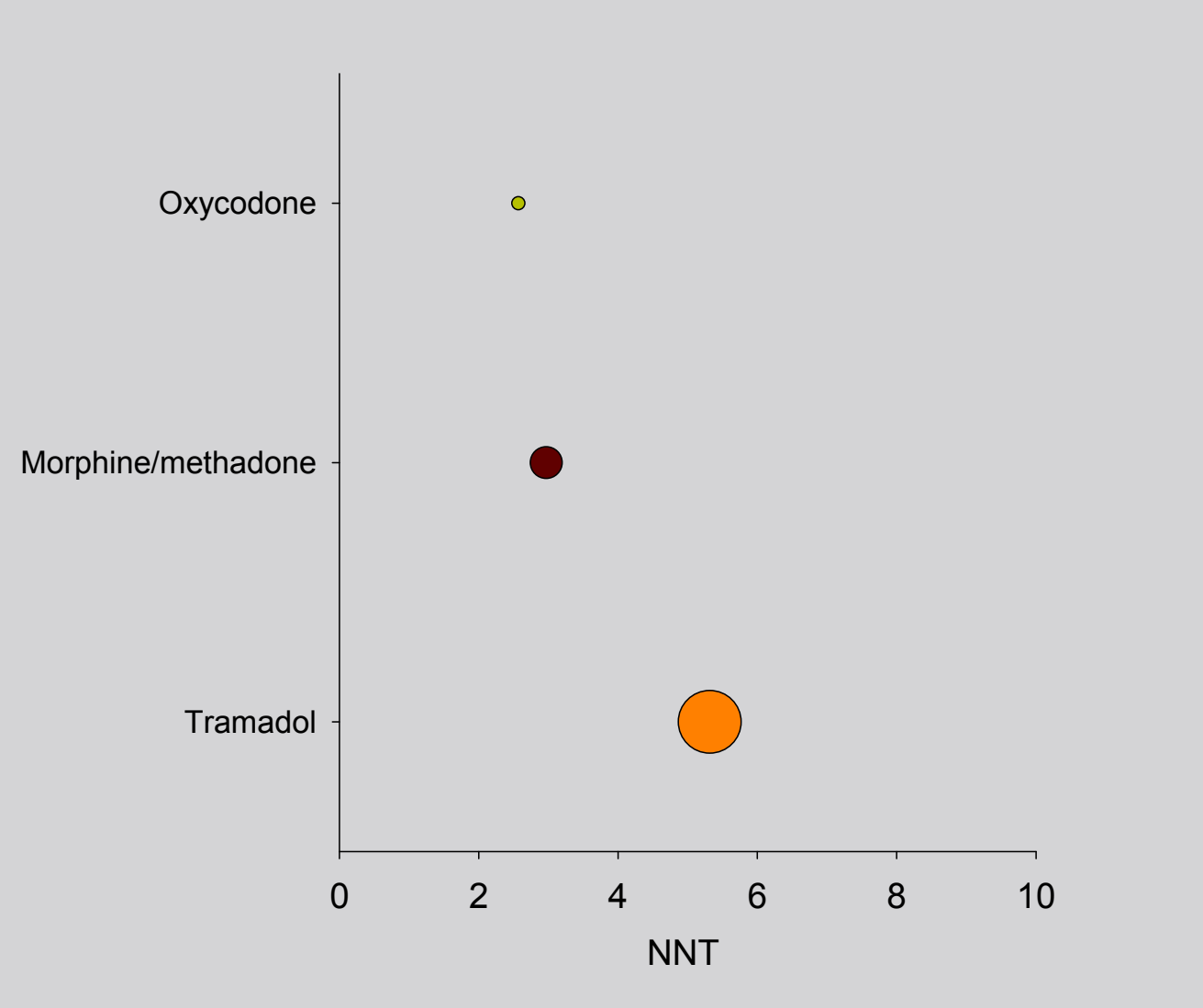
Ave. dose 8.9 mg/d



Parallel design
Both peripheral and central NP

Rowbotham MC et al. N EJM 2003;348:1223-1232.

Efficacy of Opioids for neuropathic pain: Number needed to treat (NNT)



Finnerup NB et al
Pain 2010 ;150:573

Opioids and Chronic non-cancer pain in older adults: Systematic review & meta-analysis

- Opioid vs Placebo or add-on Rx (Mean age≥60yr)
  - 18 RCTs, 78% excellent methodology score
  - Significant reductions in pain intensity and physical disability, non-significant changes in sleep and QOL

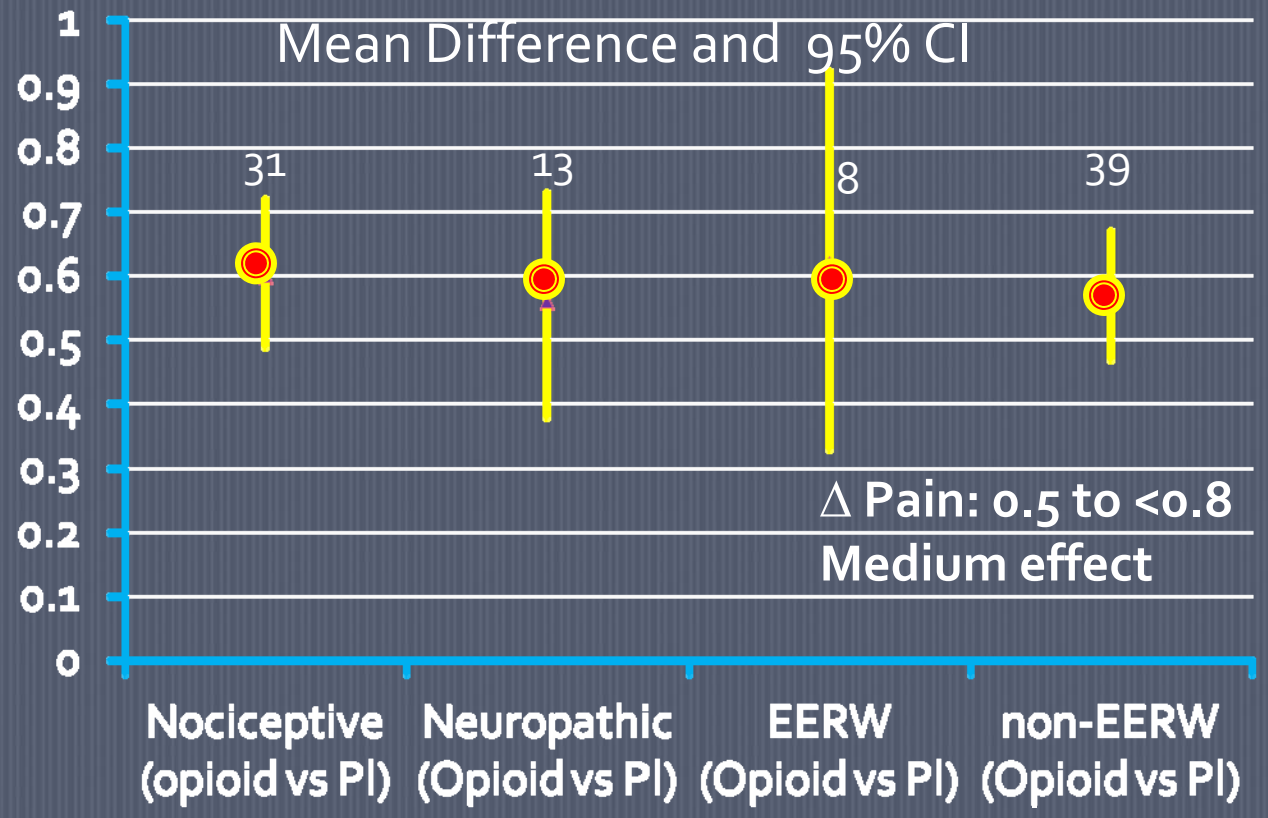
Outcome	Studies	Subjects Opioid / Placebo	Placebo mean change	Opioid Mean change	Mean ΔEffect (ES) (P-value)
PAIN	18	3005 / 1865	- 0.68	-1.25	-0.55 (<0.001)
PHYSICAL FUNCTION	9	1822 / 935	-0.57	-1.0	-0.43 (0.001)

Papaleontiou M. J Am Geriatr Soc 58;1353:2010

ES= Active- Placebo

Opioids for Nociceptive versus Neuropathic Non-cancer Pains

- A review of 62 RCTs (enriched and non-enriched enrollment)
- Study design and pain etiology did not alter the efficacy and functional outcomes



Furlan et al.
Pain Res Manage
16;337:2011

Long-term opioid for chronic non-cancer pain: a Cochrane review

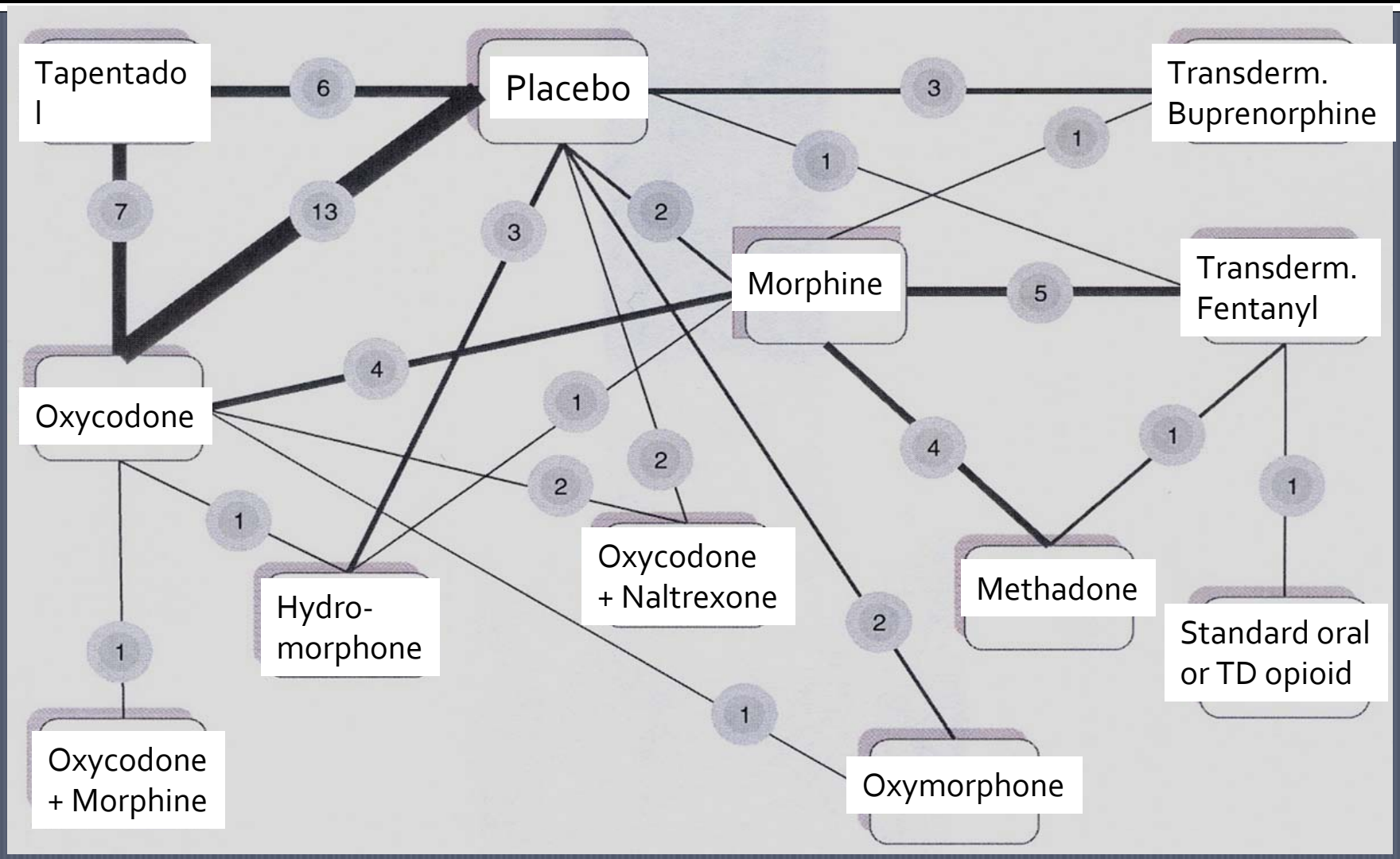
- Open-label extension studies of RCTs-oral opioids
- Osteoarthritis, low back & diabetic neuropathic pain
- Follow-up 6 -18 m, pooled data from 4 studies (6-7.5 m)

..we conclude that pain relief that appears to be clinically important is achieved long-term for patients able to remain on oral opioids for six months.
Strength of evidence .. weak

- Harati *J Diabetes Complications 2000;14:65–70*; Roth *Archive Internal Med 2000;160:853–60*, McIlwain *Am J Therapeutics 2005;12:106–12*; Rauck *Pain Medicine* 9:777–84.2008

Noble M et al. The Cochrane Library 2010:11

Opioids for chronic moderate to severe pain: Network Analysis



Riemsma R et al. Current Medical Research & Opinion 27,, 2011, 1907

Summary: Opioids for Non-cancer Pain

- Randomized short duration efficacy studies using various trial designs show that, compared to placebo, opioids significantly decrease nociceptive and neuropathic pains
- The efficacy of opioids in nociceptive and neuropathic pain is similar
- No clear difference in efficacy of the different opioids has been shown in comparative trials

THANK YOU