

The Oral Pharmacotherapy of Peripheral Neuropathic Pain

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- *The Food and Drug Administration should require that new drugs be **compared** not just with placebo, but **with old drugs** for the same condition". Marcia Angell 2004*
- *"Between measurements based on RCTs and benefit in the community, there is a gulf which has been much underestimated". Archie L. Cochrane 1971*
- *"All....randomized controlled trials and systematic reviews should contain a section entitled "**To whom do these results apply?**" Peter Rothwell 2005*

Is this trial relevant to my clinical practice?

- 50 + good RCTs of oral analgesics in neuropathic pain
- External validity? (generalizability to clinical practice)
 - ◆ Comparative trials of different analgesics? (6/50 trials!)
 - ◆ Clinical meaningfulness? (number needed to treat) (20/50)

Methods

- Systematic review
- Quality assessment tool (Jadad)
- All trials at least randomized, controlled, double blind with withdrawals accounted for = 3/5
- + method of blinding and randomization in most = 5/5

Neuropathic Pain: Definition(IASP)

- Pain initiated or caused by a primary lesion or dysfunction in the nervous system.
 - ◆ “Peripheral neuropathic” if peripheral nerve lesion
 - ◆ “Central pain” if central nervous system lesion

Not discuss

- Central neuropathic pain
 - ◆ more difficult to treat
- Trigeminal neuralgia
 - ◆ a different type of neuropathic pain
 - ◆ a mechanism-based Rx?
- Complex regional pain syndrome I and II
- Topical agents, some anticonvulsants, etc

Peripheral Neuropathic Pain: Some Examples

- Postherpetic neuralgia
- Painful diabetic neuropathy
- Nerve root pain
(Disc herniation at L5,S1
or C5,C6)
- Other painful neuropathies:
- Carpal tunnel syndrome
- Incisional neuralgia
(mastectomy,
thoracotomy, post ACB)
- Nerve trauma
- Phantom limb pain

JC

- Male, age 27, shot in left upper arm
- Median and ulnar nerve injury
- Day 2 “burning and darting” pain/median n.
- “the pain was so severe that a touch ... or shaking the bed or a heavy step caused it to increase”

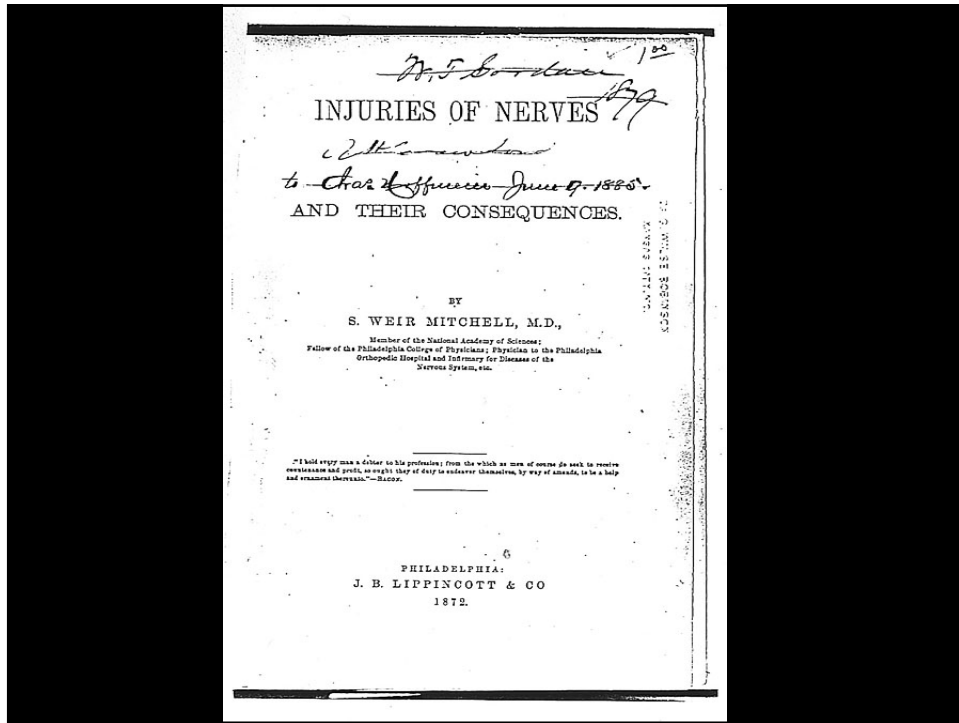
Case JC. Silas Weir Mitchell 1864

“Gunshot wounds and other injuries of nerves” p 109

- Joseph Corless, private, Co B, 14th NYSM,
- April 1861, 1st battle of Bull Run
- Dx “causalgia” burning pain after peripheral nerve injury
- 1) All pain components described 140 years ago!
 - ◆ (steady burning, electric shocks, allodynia)
- 2) relief with “heavy doses of morphia”

All modern literature begins with
one book: Huckleberry Finn

Hemingway



Neuropathic Pain: History

- Silas Weir Mitchell and the American civil war
- Causalgia: (the burning pain after nerve injury)
- Phantom limb pain (pain after amputation in missing limb)

Silas Weir Mitchell

Injuries of Nerves and Their Consequences 1872

- “For the easing of neuro-traumatic pain we tried, in turn, the whole range of medicines,....None of them save morphia, seemed... to be of the slightest value and one by one they were laid aside until in the vast mass of cases ,the salts of morphia alone were employed... The morphia salts are invaluable....”p. 270

Neuropathic pain qualities

- Steady (burning)
- Jabs
- Skin sensitivity (pain to touch = allodynia)

Neuropathic pain Outline

- **Clinical problems:**
 - ◆ different or the same?
 - ◆ different drugs for different problems?
- **Pathophysiological mechanisms** as targets for drugs
 - ◆ Is mechanism-based treatment possible?
- **Oral pharmacological options**

Peripheral Neuropathic Pain: Some Examples

- | | |
|---|--|
| ■ Postherpetic neuralgia | ■ Carpal tunnel syndrome |
| ■ Painful diabetic neuropathy | ■ Incisional neuralgia
(mastectomy,
thoracotomy, post ACB) |
| ■ Nerve root pain
(Disc herniation at L5,S1
or C5,C6) | ■ Nerve trauma |
| ■ Other painful neuropathies: | ■ Phantom limb pain |

Are these NP conditions really similar and treated in the same way?

- Most trials done in PHN and PDN:
 - ◆ Are these data applicable to other NP?
 - ◆ Certainly they are not to TN

Neuropathic pain: clinical research models

- Postherpetic neuralgia
- Diabetic neuropathy

Trigeminal Neuralgia

Oral Pharmacotherapy of Peripheral Neuropathic Pain

Can we tailor Rx to pathophysiology?

- Peripheral sensitization:
 - ◆ NSAIDS
- Ectopic foci in nerves:
 - ◆ local anaesthetics, anticonvulsants (block Na channels)
- Central sensitization:
 - ◆ prevention, antidepressants, opioids

Oral Pharmacological Rx: Peripheral Neuropathic Pain OUTLINE

Pharmacotherapy

- Antidepressants
 - nortriptyline, duloxetine
- Anticonvulsants
 - gabapentin, pregabalin, carbamazepine
- Opioids
 - oxycodone, morphine, fentanyl patch, hydromorphone
- Cannabinoids

Neuropathic pain: pharmacotherapy

- 1. We do **not** yet have a **mechanism-based** Rx (except carbamazepine?)
- 2. All pharmacotherapeutic approaches to neuropathic pain have at best **a modest effect**
- 3. It is reasonable to aim to take pain from **severe/moderate to mild in one half** to two-thirds of patients
- 4. **Adverse effects** should be expected and dealt with if possible

Neuropathic Pain: Treatment

- **1. Antidepressants**
- **2. Anticonvulsants**
- **3. Opioids**
- **4. Cannabinoids**
- **-----**
- **Other (topicals etc)**

1. Antidepressant drugs

- A standard therapy
- Evidence-based (controlled trials+++)
- The older, tricyclic antidepressants
 - ◆ nortriptyline*
 - ◆ amitriptyline
 - ◆ imipramine
 - ◆ desipramine
 - ◆ (maprotiline)

ANTIDEPRESSANTS AND ANALGESIA

Antidepressant Analgesia

- *serotonin/NORADRENALINE re-uptake blockade
- Other effects
 - ✓ Peripheral sodium channel blockade
 - ✓ NMDA antagonism

Neuropathic pain: clinical research models

- Postherpetic neuralgia
- Diabetic neuropathy

Antidepressants: Postherpetic Neuralgia

RCTs

- Amitriptyline:1982:Watson et al
- Amitriptyline:1988:Max et al
- Desipramine:1990:Kishore-Kumar et al
- Maprotiline:1992: Watson et al
- Nortriptyline:1998:Watson et al

Antidepressants (+RCTs) Diabetic Neuropathy

- imipramine (1984):Kvinesdal
- amitriptyline(1987):Max
- imipramine(1989):Sindrup
- desipramine(1991):Max
- desipramine vs. amitriptyline (1992): Max
- maprotiline(1997): Vrethem

Antidepressants

Mixed(S+N)

amitriptyline

imipramine
doxepin
venlafaxine
duloxetine

Serotonin

clomipramine
trazosone
nefasodone
fluoxetine
fluvoxamine
sertraline
paroxetine
zimeclidine

Noradrenaline

nortriptyline*

desipramine
bupropion

Antidepressants: New kids on the block (all either S or S+N)

- bupropion (N), NNT=?
- duloxetine (S+N) in PDN, (FDA-approved), NNT=5
- venlafaxine (S+N), (NNTs = 4.5, 5.2)
vs. imipramine (S+N), (NNT =2.7)

Antidepressants: Summary

- nortriptyline*
- amitriptyline
- desipramine
- Other = imipramine, venlafaxine, duloxetine, bupropion

- Analgesic/not antidepressant effect
- Relief of different pain qualities
- Low doses (75 mg)
- Mechanism: ? serotonin/noradrenaline

Practical Guidelines for nortriptyline & amitriptyline

- Dose: <65 yr =25mgm qhs, >65 yr=10mgm qhs
- Increase q 1- 2 weeks by 10-25 mgm
- Endpoint=analgesia or adverse event
- Trials of different agents
- Adverse events

2. Anticonvulsants

- most block sodium channels
- carbamazepine (trigeminal neuralgia)
- gabapentin, pregabalin (modulate calcium channels)

carbamazepine

- works best in trigeminal neuralgia (also known as tic douloureux), a unique type of neuropathic facial pain, or sometimes in other neuropathic conditions (especially multiple sclerosis) when the predominant pain is electric shock-like

Carbamazepine

- Perhaps the only clinical example of a mechanism-based treatment for neuropathic pain
- Relieves electric shock-like triggered neuropathic pain
- Other drugs (antidepressants, opioids) relieve all aspects of neuropathic pain (steady pain, shocks, allodynia) except the shocks of trigeminal neuralgia

gabapentin

- Anticonvulsant
- Several RCTs / relieves neuropathic pain
- Mode of action:
 - ◆ calcium channel modulation/ presynaptic /inhibits excitatory neurotransmitter release
- About 30% more relief than placebo
- “Good adverse event profile”
- Few head to head trials with other drugs (Morello, Gilron)

Gabapentin/ neuropathic pain: +RCTs

- Postherpetic neuralgia
 - ◆ Rowbotham et al., JAMA 280 (1998) 1837-1842
 - ◆ Rice et al., Pain 94 (2001) 215-224
- Diabetic neuropathy
 - ◆ Backonja et al., JAMA 280 (1998) 1831-1836
 - ◆ Morello et al., gabapentin v. amitriptyline, Arch Int Med 159 (1999) 1931-1937
- PHN + PDN
 - ◆ Gilron, morphine/gabapentin, NEJM, March 31/05

Pregabalin

Pregabalin

- Anticonvulsant
- Pre-synaptic calcium channel modulation, reduced release of excitatory neurotransmitters
- 30% have 50%+ relief more than placebo
- NNT =3.4
- Problems: external validity (generalizability)
- ? A “me too” drug

Pregabalin : advertising claims

- Rapid pain relief –week 1
 - Relief sustained-3 months
 - Sleep improved- week 1
 - No drug interactions
 - Simple dosing
 - No claim as better than TCAs or gabapentin
- Adverse effects(150-600 mg/day)
- ◆ Dizziness 9-37%
 - ◆ Somnolence 6-25%
 - ◆ Peripheral edema 6-16%
 - ◆ Dry mouth 2-15%

Pregabalin in neuropathic pain

1. pregabalin (300/600 mg) > placebo (PHN)
Dworkin et al., 2003
2. pregabalin (150, 300 mg) > placebo (PHN)
Sabatowski et al., 2004
3. pregabalin (300, 600 but not 75 mg) > placebo (painful DPN)
Lesser et al., 2004
4. pregabalin (300 mg) > placebo (painful DPN)
Rosenstock et al., 2004
5. pregabalin (150, 300 mg) > placebo (painful DPN)
Richter et al., 2005
6. pregabalin (150-600, 600 mg) > placebo (PHN + painful DPN)
Freyenhagen et al., 2005

Unpublished studies:

- 1 positive and 1 negative study in PHN
- 1 positive and 1 negative study in painful DPN
- 1 positive study in spinal cord injury pain

Pregabalin:adverse effects (most mild/moderate)

- Dizziness (up to 30%)
- Somnolence (up to 18%)
- Dry mouth
- Blurred vision
- Peripheral edema (?cause)
- Weight gain
- Abnormal thinking
- Euphoria(controlled substance in US)

Pregabalin: Clinical meaningfulness

- No published comparative trials with standard therapy (TCAs)
- To whom do these results apply?
 - ◆ External validity
 - ◆ Clinical meaningfulness

Pregabalin: RCTs: Clinical meaningfulness

Author/disease	Pregabalin dose	50% relief - placebo
Lesser PDN	75-600 mg/day	48% - 18% = 30%
Rosenstock PDN	300 mg/day	40% - 14.5% = 25.5%
Richter PDN	150-600 mg/day	39% - 15% = 24%
Dworkin PHN	300-600 mg/day	50% - 20% = 30% NNT=3.4, NNH=4.3
Sabatowski PHN	150-300mg/day	28% - 10% = 18%
Freyenhagen NP	150-600mg/day	52% - 24.% = 28.1%

Pregabalin

- Dose range = 150-300mg/day for NP
- Approved for PDN and PHN
- Cost for 30 days supply
 - ◆ Pregabalin 75 bid = 91.07
 - ◆ Gabapentin 1800 mg/day = 110.34
 - ◆ Duloxetine 60mg/day = 106.49

Pregabalin: summary

- No published comparative trials
- NNT = 3.4, NNH = 4.3 (Dworkin)
- Linear pharmacokinetics
- Bid dosing, no titration
- No drug interactions
- Excreted unchanged in urine
- Taper over 1 week (withdrawal)
- Long term effects unknown

Anticonvulsants not discussed (not effective, weak effect, no NNT)

- Carbamazepine + PDN
- Lamotrigine + HIV, PDN, CPSP
- Topiramate – PDN
- Oxcarbazepine + PDN
- Zonisamide – PDN

3. Neuropathic Pain: Opioids

“Diseases desperate grown
By desperate measures are relieved
Or not at all”

Hamlet IV, iii, 9

Opioids/Neuropathic Pain: RCTs

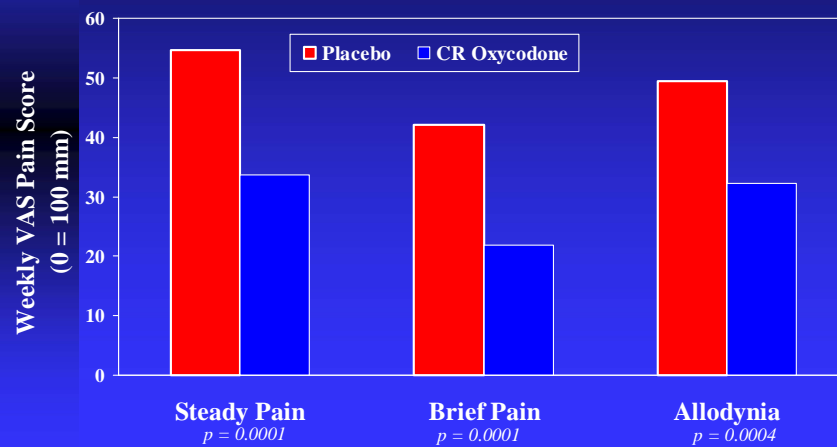
ORAL OPIOIDS: RCTs

- Watson and Babul 1998 oxycodone PHN
- Raja et al 2002 morphine/methadone PHN
- Gimbel et al 2003 oxycodone PDN
- Rowbotham et al 2003 levorphanol PNP + CNP
- Watson et al 2003 oxycodone PDN

Controlled-Release Oxycodone in the Treatment of Postherpetic Neuralgia

Watson CPN, Babul N., Neurology 1998

Mean Weekly Visual Analog Scale (VAS) Scores for Steady Pain, Brief Pain and Allodynia (Final Week of Treatment)

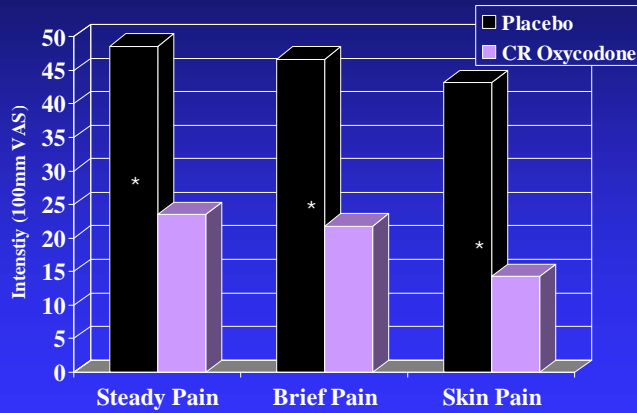


Oxycodone in Diabetic Neuropathy: A Randomized Controlled Trial

Pain 105 (2003) 71-78

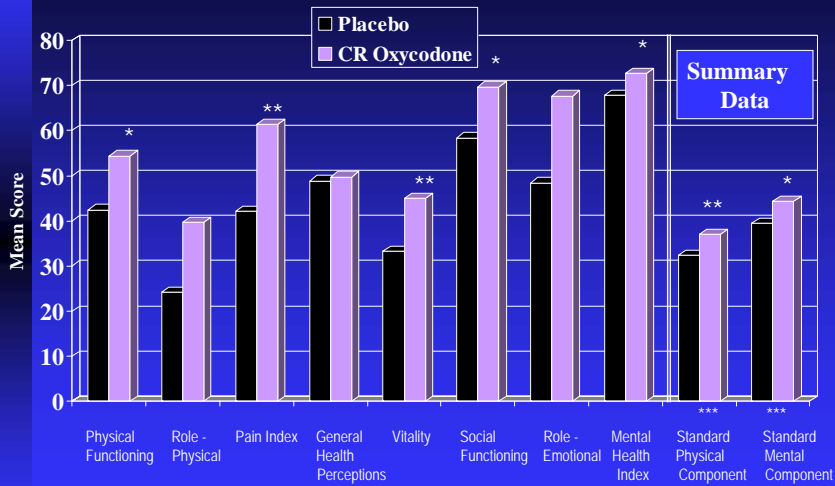
- Peter Watson
- Dwight Moulin
- Judy Watt-Watson
- Allan Gordon
- John Eisenhoffer

Figure 2.



* p = 0.0001

Figure 3.



N.B. Higher scores indicate a better health state

* p ≤ 0.05, ** p ≤ 0.0005, *** data normalized to Canadian Standard

Neuropathic pain/opioids:summary

- RCTs + for levorphanol, **morphine**, methadone, **oxycodone**
- **methadone** requires special knowledge but is now in pill form
- morphine, oxycodone available as **controlled release**
- Also hydromorphone, **transdermal fentanyl** (no RCTs)

Psychological dependency
(**addiction**) is **uncommon** when
opioids are taken for chronic pain

Are opioids safe and effective in the longterm?

- Chronic non-cancer pain and the longterm effects of opioids Watson CPN, Watt-Watson JH, Chipman ML, Pain Research and Management (in press 2003)
 - ◆ 102 patients
 - ◆ Neuropathic pain
 - ◆ Median 8 years (range 1 – 21 years)
 - ◆ Variety of opioids/doses, polypharmacy
 - ◆ Tolerance a non-issue, addiction not major issue
 - ◆ 47/78 had improved function

4. Cannabinoids

- Cannabinoid receptors
 - ◆ 1988 CB1 (10x number vs. mu opioid receptors)
 - ◆ 1991 CB2
 - ◆ PAG, RVM, dorsal horn, DRG
- Endocannabinoids
- Canada:
 - ◆ Nabilone, dronabinol (both oral and off-label for pain)
 - ◆ delta THC/cannabidiol (oromucosal for pain in MS)

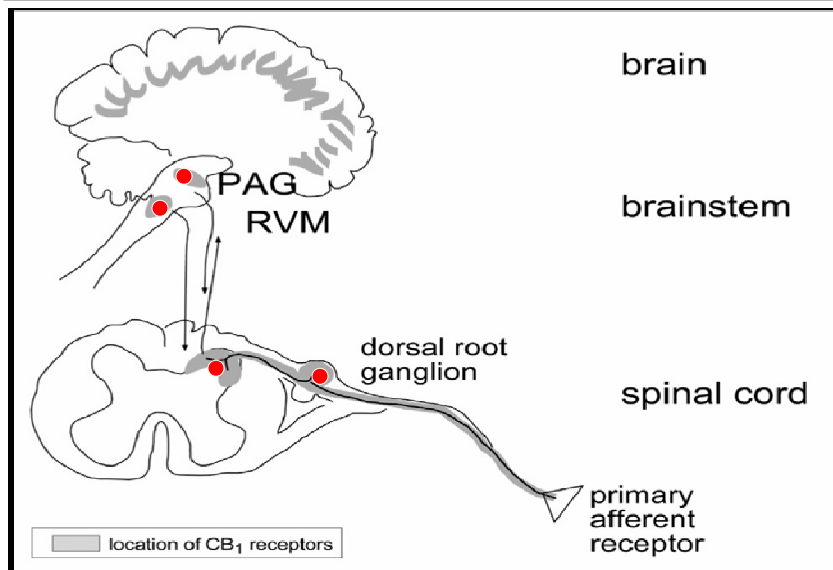


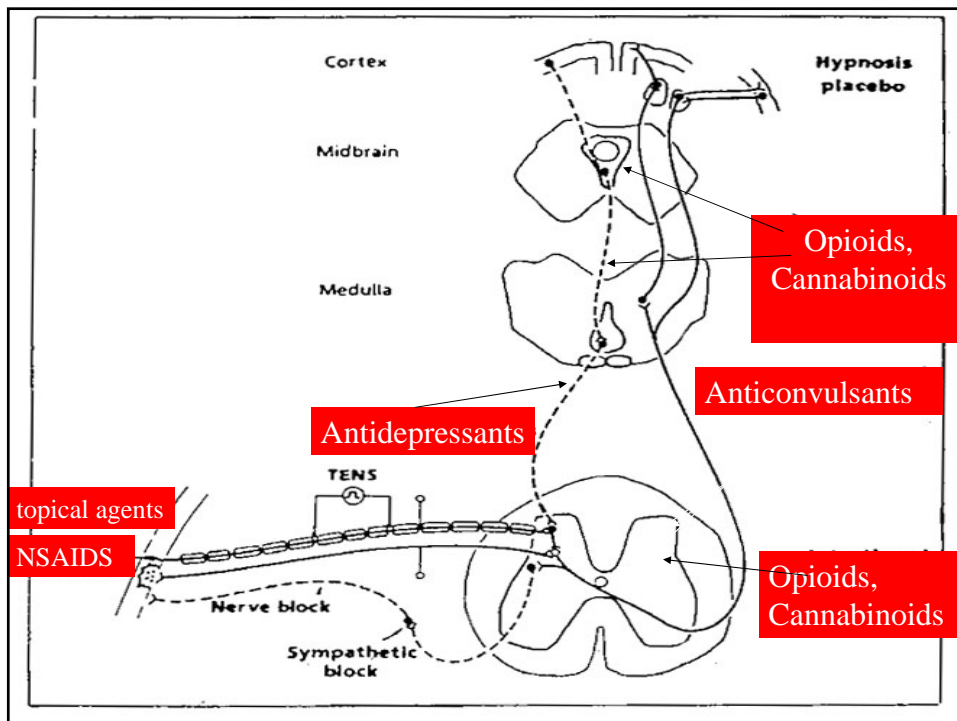
Figure 2) Location of cannabinoid receptors (CB_1) in the areas of the nervous system that are important for pain transmission and modulation. PAG Periaqueductal gray; RVM Rostral ventrolateral medulla

Cannabinoid RCTs

Rog et al 2005	Brachial plexus avulsion oromucosal	N=48 X-over 2 doses	+ NNT=9 and 7.7 for 30%
Berman et al 2004	Multiple sclerosis pain oromucosal	64/66 parallel	+NNT=3.7 for 50%
Svendsen et al 2004	MS central pain/oral	N=24 X-over	+NNT=3.5 for 50%
Karst et al 2003	“Chronic neuropathic pain” THC	N=21 X-over	+ but ? clinical meaningfulness

Topical agents

- NSAIDS
- Capsaicin
- Local anaesthetics (lidocaine patch)
- Antidepressants (doxepin)



How clinically meaningful is the relief with these drugs?

How do the drugs compare?

- Comparative trials of different antidepressants? (5)
- Comparative trials of different analgesics? (6)
- Numbers needed to treat?

Comparative trials: Antidepressants

1. amitriptyline (S+N) > fluoxetine (S)
2. amitriptyline (S+N) > maprotiline (N)
3. nortriptyline (N) > amitriptyline re AEs
4. imipramine (S+N) > venlafaxine (S, S+N)

Comparative trials: different analgesics N=6 (all non-industry)

- Trend opioid > tricyclics, different mechanisms
- Fluphenazine ineffective (not additive to amitriptyline)
- Carbamazepine ineffective v amitriptyline in central pain
- Gabapentin = amitriptyline (analgesia, AEs)
- Gabapentin adds 20% to morphine analgesia but no difference vs. placebo

How then can we assess relative efficacy of different drugs?

**Neuropathic Pain:
Number Needed to Treat (NNT)**

No. of patients treated for moderate (50%) or better relief vs. placebo

- antidepressants, opioids: 2-3 patients
- gabapentin, pregabalin: 3-5 patients

Numbers needed to treat: neuropathic pain

	PHN	PDN	OTHER
all tricyclics	2.3*2.3*2.1*	3.0* 2.4* 3.4*	
● venlafaxine	4.5		5.2
imipramine			2.7
● duloxetine	5.0		
gabapentin	3.2, 5.0	3.7	
● pregabalin	3.4		
oxycodone	2.5	2.6	
tramadol	4.76	4.3	

External validity

- Major problems with generalizability of these trials
- Very selected subjects, enrichment
- Most trials in PHN, PDN (80%)
- Most published trials are favourable (90%)
- NNTs less than clinical practice (derived from selected pts)
- Satisfaction with pain relief and AE tolerability not studied
- Few comparative trials

Practical general advice

Respect Individual Variability

- Tailor the treatment to the individual
- Start low, go slow and titrate
- Try different drugs and approaches

Mono vs. polytherapy?

- “The bad news is that using highly targeted drugs for selective removal of small subsets of nociceptors may not be enough to reduce nociceptive input to the spinal cord. “The long sought **magic bullet** may not be found.”

Alan Basbaum 2004

Polypharmacy

- A tricyclic antidepressant and an opioid
- Gilron et al., morphine and gabapentin
 - ◆ NEJM;352; 1324-1334 (March 31/05)
- An oral and a topical agent

Polypharmacy

- Tricyclic antidepressant and an opioid
- Anticonvulsant + opioid
- An oral and a topical agent
- All of the above!

Neuropathic pain Outline

- **Clinical problems:**
 - ◆ different or the same? similar, severity varies
 - ◆ different drugs for different problems? No (except tic douloureux)
- **Pathophysiological mechanisms** as targets for drugs
 - ◆ Is mechanism-based treatment possible? Not now
- **Oral pharmacological options**

Pharmacological Rx: Peripheral Neuropathic Pain OUTLINE

Oral Pharmacotherapy

- 1. Antidepressants
 - nortriptyline, **duloxetine**
- 2. Anticonvulsants
 - gabapentin, **pregabalin**, carbamazepine
- 3. Opioids
 - oxycodone, morphine, fentanyl patch,
– hydromorphone
- **4. Cannabinoids**

Neuropathic pain: pharmacotherapy

- 1. We do **not** yet have a **mechanism-based** Rx (except carbamazepine?)
- 2. All pharmacotherapeutic approaches to neuropathic pain have at best **a modest effect**
- 3. It is reasonable to aim to take pain from **severe/moderate to mild in one half** to two-thirds of patients
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