

**Pharmacologic
management of chronic neuropathic pain.
Is it effectively managed at all?**

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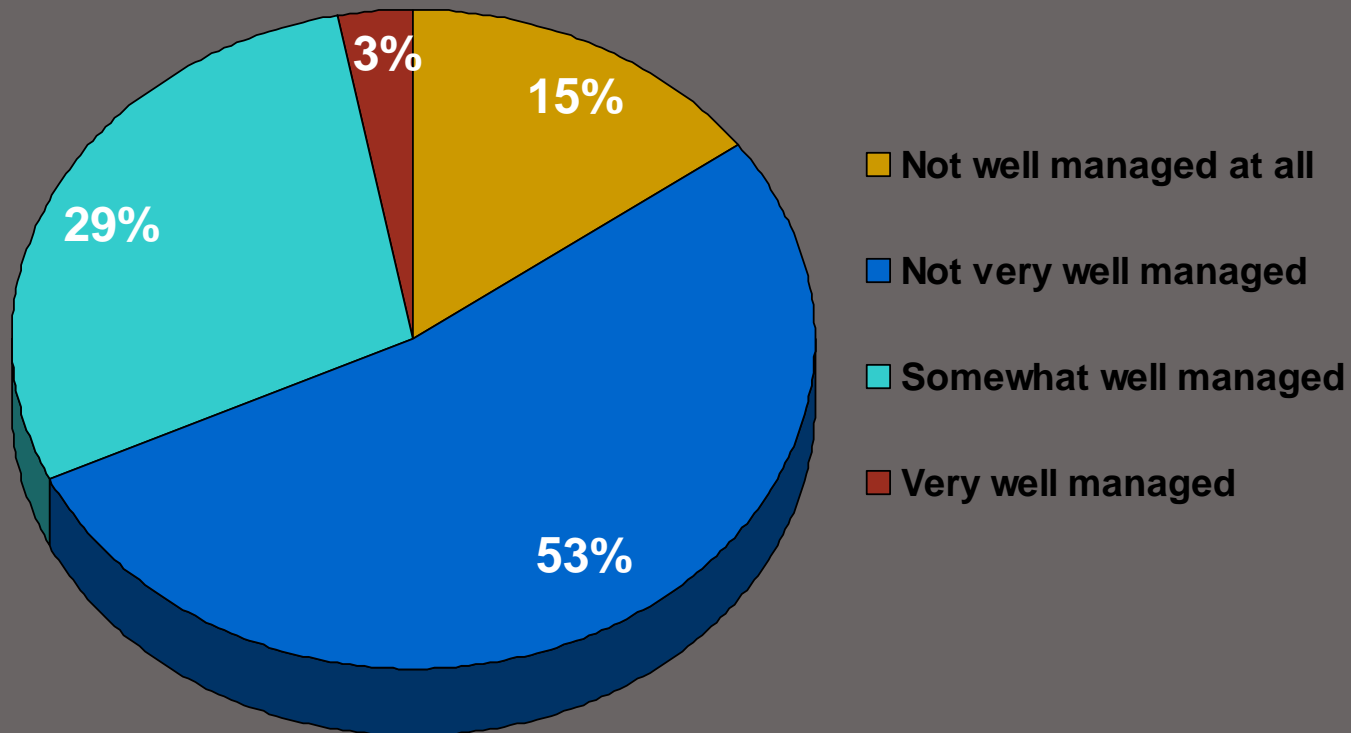
An ambitious task for 8 minutes



Introduction

- NP is estimated to afflict millions of people worldwide
- Many common diseases, injuries, and interventions cause NP

Chronic pain management



Is chronic pain under-treated?

- 64% of patients say it is under-treated
- 68% of physicians say it is under-treated.

**What is the impact
of undertreated
pain?**

Consequences of Poor Pain Management

- Poor quality of life - 30%
- Economic costs or loss of productivity - 37%
- Emotional problems or depression - 18%
- Need for frequent physician visits - 15%
- Increase caregiver burden - 85%

The Economic Impact of Pain

- 13% of workers lose a mean of 4.6 hrs/week of productive work time
- Costs to industry est. \$61.2 billion / year (U.S.)

Boulanger A. Pain Res Mgt Vol 12 Nol 1 2007 2. Stewart et al. JAMA 2003; 290:2443-54. 3. Stewart et al. JAMA 2003; 289:3135-44.

Management problems

- Complex
- Response to existing treatments is often inadequate
- Effectiveness is unpredictable
- Dosing can be complicated, analgesic onset is delayed, and side effects are common



- IASP evaluated relevant literatures according to the Oxford Centre for Evidence-based Medicine levels of evidence and a treatment recommendation has been made

First-line Medications (Grade A recommendation)

TCA



- 2° amine - nortriptyline and desipramine
- Tertiary amine – amitriptyline & imipramine

SSNRI



- Duloxetine
- Venlafaxine

**Ca channel $\alpha 2-\delta$
ligand**



- Gabapentin
- Pregabalin

Topical lidocaine



- Lidocaine patch 5%

TCA_s

- Secondary amine TCAs are preferred because they are better tolerated than tertiary amine TCAs
- Amitriptyline should be avoided in elderly patients.
- TCAs should be avoided in patients who have IHD or an increased risk of sudden cardiac death
- A screening ECG is recommended before beginning treatment with TCAs in patients over 40 years of age

*Finnerup NB, et al. Pain 2005;118:289–305.

*Max MB, et al. N Engl J Med 1992;326:1250–6.

*Watson CPN, et al. Neurology 1998;51:1166–71.

SSNRIs

- Duloxetine – effective in patients with painful DPN but it has not been studied in other types of NP
- Venlafaxine
 - RCTs in patients with painful DPN and painful polyneuropathies of various types demonstrated efficacy

*Raskin J, et al. Pain Med 2005;6:346–56.

*Wernicke JF, et al. Neurology 2006;67:1411–20.

*Rowbotham MC, Goli V, Kunz NR, Lei D. Pain 2004;100:697–706.

Calcium channel $\alpha 2$ - δ ligands

- Gabapentin and pregabalin both bind to the $\alpha 2$ - δ subunit of voltage-gated calcium channels, decreasing the release of glutamate, norepinephrine, and substance P
- RCTs demonstrated that gabapentin reduces pain greater than placebo in various types of NP
- Gabapentin is generally safe, has no clinically important drug interactions

*Backonja M, et al. JAMA 1998;280:1831–6.

*Caraceni A, et al. J Clin Oncol 2004;22:2909–17.

*Gorson KC, et al. J Neurol Neurosurg Psychiatry 1999;66:251–2.

*Serpell MG. Pain 2002;99:557–66.



- Pregabalin has demonstrated efficacy in several RCTs in PHN & painful DPN
- Because it is a new medication, long-term safety of pregabalin is not as well established as it is for gabapentin

*Dworkin RH, et al. Neurology 2003;60:1274–83.

*Lesser H, et al. Neurology 2004;63:2104–10.

*Richter RW, et al. Pain 2005;6:253–60.

*Rosenstock J, et al. Pain 2004;110:628–38.

Topical lidocaine

- Lidocaine patch 5% is recommended for patients with localized peripheral NP but not for patients with central NP

*Galer BS, et al. Pain 1999;80:533–8.

*Meier T, et al. Pain 2003;106:151–8.

*Rowbotham MC, et al. Pain 1996;65:39–44.

Second-line Medications

Opioid analgesics

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graph LR; A[Opioid analgesics] --> B["▪ Oxycodone  
▪ Morphine  
▪ Methadone  
▪ levorphanol"]; C[Tramadol]
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- Oxycodone
- Morphine
- Methadone
- levorphanol

Tramadol

Second-line Medications That Can Be Used for First-line Treatment in Select Clinical Circumstances

- Grade A recommendation
 - When prompt pain relief is required during titration of first line drugs.
 - Episodic exacerbations of severe pain
 - Acute neuropathic pain
 - Neuropathic cancer pain

*Gimbel JS, Richards P, Portenoy RK. *Neurology* 2003;60:927–34.

*Morley JS, et al. *Palliat Med* 2003;17:576–87.

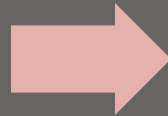
*Rowbotham MC, et al. *N Engl J Med* 2003;348:1223–32.

*Harati Y, et al. *Neurology* 1998;50:1842–6.

*Hollingshead J, Du`hmke RM, Cornblath DR. *Cochrane Database Syst Rev* 2005. [Art. No.:CD003726].

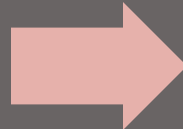
Third-line Medications (Grade B recommendation)

Anti epileptic



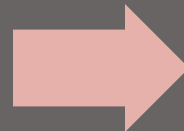
- Carbamazepine
- Lamotrigine
- Oxcarbazepine
- Topiramate
- Valproic acid

Antidepressant



- Bupropion
- Citalopram
- Paroxetine

Others



- Mexiletine
- NMDA receptor antagonists
- Topical capsaicin

Central NP (Grade B recommendation)

TCA_s



Central post stroke pain

GBP & PGB

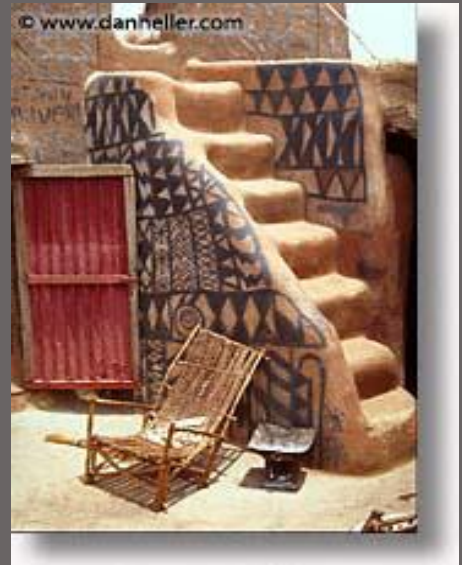


Spinal cord injury pain

Cannabinoids



NP associated with MS



Stepwise Pharmacologic Management of NP

Step 1

Assess pain and establish the diagnosis of NP



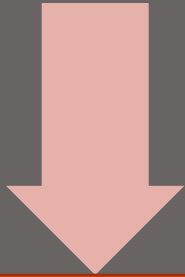
Identify co morbidities that might be affected by medications



Explain the diagnosis and treatment plan to the patient

Step 2

Initiate therapy of the disease causing NP



Initiate symptom treatment

- 2° amine TCA
- SSNRI
- Gabapentin or pregabalin



- Topical lidocaine
- Opioid analgesics or tramadol

Evaluate patient for non-pharmacologic treatments, and initiate if appropriate

Step 3

Reassess pain and health-related quality of life frequently



If substantial pain relief and tolerable side effects, continue treatment



If partial pain relief after an adequate trial, add one of the other first-line medications.



If no or inadequate pain relief at target dosage after an adequate trial, switch to an alternative first-line medication

Step 4

If trials of first-line medications
alone and in combination fail



Consider second- and third-line
medications



Referral to a pain specialist or
multidisciplinary pain center

----- we are getting too much
under water



Summary

- Management of NP should focus on identifying and treating the underlying disease processes
- Coexisting depression, anxiety, sleep disturbances, and other adverse impacts of NP should be properly addressed
- Patient education and support are critical components of the successful management of NP



- Non-pharmacologic methods of coping with pain should be discussed
- Clinicians must consider several other factors when selecting a specific medication for a patient with NP
 - Medication-related side effects
 - Drug interactions



- Comorbidities
- Costs associated with therapy
- Risks of medication abuse
- Risks of intentional and unintentional overdose

Conclusion

- For better management of NP
 - Continued development of new medications
 - Additional trials involving existing medications alone and in combination to identify characteristics of treatment responders
 - Identification of efficacious non-pharmacologic treatments
 - Development of strategies to prevent NP are therefore needed to advance the management of NP

A scenic landscape at sunrise or sunset. The sun is low on the horizon, casting a warm glow over a vast sea of clouds that fills the valley. The sky is a deep blue, and the foreground shows the dark silhouette of a hillside with some trees. The text "Thank you" is overlaid in the center in a serif font.

Thank you