Treatment of neuropathic pain – current guidelines.
Лікування невропатичного болю - сучасні керівні принципи.

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Taxonomy 2008

Neuropathic pain – the pain arising as a direct consequence of a lesion or disease affecting the somatosensory system.

Treede 2008

Neuropathic pain = non-nociceptive, pathological, chronic, severe, devastating

Neuropathic pain

- **Resistant to conventional and OTC analgesics ie. NSAIDs, paracetamol**
- **Affecting the health-related quality of life – physical, emotional.**
- **Associated with social costs and high financial burden on health care systems**

Jensen MP et al.. The impact of neuropathic pain on health-related quality of life: review and implications. Neurology 2007.

In USA costs associated with neuropathic pain have been estimated at 30% of total costs associated with all chronic pain syndromes, although the prevalence of neuropathic pain is about 17% of chronic pain conditions.

Turk DC 2002

Patients with neuropathic pain

- **higher pain scores**
- **lower quality of life**
- **require more medications**
- **less pain relief with treatment**
- **higher incidence of treatment related side effects**

Smith 2007, Torrance 2007, Dworkin 2007

- **less than 50% of patients obtain satisfactory, but only partial symptom relief**
- **significant incidence of treatment related side effects**
- **in the therapy aren't used drugs of proven effectiveness in this type of pain**
- **the medication dose is too low to obtain a therapeutic effect**
- **patients despite the use of recommended drugs of proven effectiveness are still suffering from moderate pain.**

McDermott 2006, O'Connor 2009

Therapeutic goals

- Pain relief – patients' expectations, achievable goals, realistic treatment options, individualization
- Risk-benefit profile of proposed treatment
- Treatment of concomitant symptoms:
  - Sleep disturbances
  - Depression
- Improvement of HRQoL – physical and emotional functioning, possible treatment related side effects

Treatment plan and expected results discussed with patient.

Management of neuropathic pain

1. Prophylaxis
2. Causal treatment
3. Treatment based on underlying mechanism
4. Symptomatic treatment

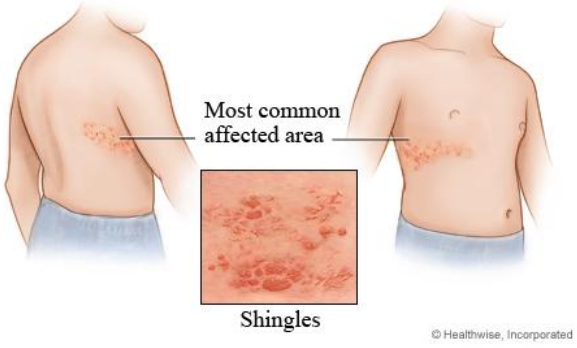
Prophylaxis?

Multicenter RCT - 38 500 patients > 60 years old.

50% of them – vaccination with Zostavax – vaccine containing attenuated Varicella zoster virus.

Observation time - 3 years.

Herpes zoster



Incidence of shingles:

In placebo group - 11,1 /1000

In vaccinated group - **5,4/1000**.

Reduction in incidence of shingles 61,1%.

Reduction in incidence of postherpetic neuralgia 66,5%.

Oxman MN et al. N Engl J Med. 2005.
Hornberger J, Robertus K. Ann Int Med. 2006.

Prophylaxis?

Painful diabetic neuropathy

Several studies indicate, that tight glycemic control and aggressive insulin therapy can reduce the risk of developing neuropathy.

Intensive insulin therapy with insulin pump or three or more insulin injections per day is more effective than conventional therapy in preventing neuropathy:

5% vs 13% conventional therapy

Diabetic peripheral neuropathic pain. Consensus guidelines for treatment. J Fam Pract June 2006

Causal treatment

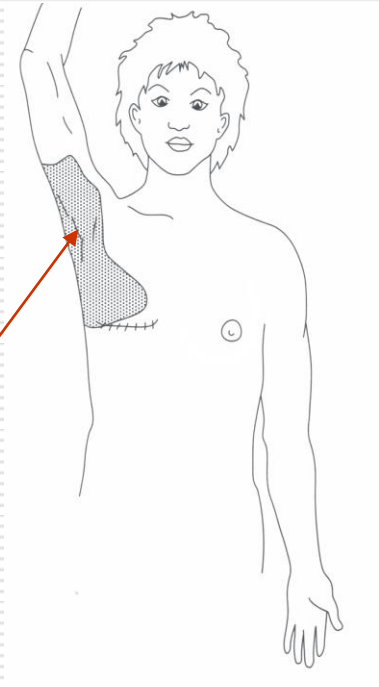
1. **Microsurgical *microvascular decompression* (MVD) of trigeminal nerve – the only method of TN causal treatment**
2. **CTS – surgical decompression of the median nerve**
3. **Discectomy – surgical decompression of spinal nerve root**

An example of treatment based on underlying mechanism

57 years old female patient with a history of breast cancer
3 years ago underwent mastectomy and excision of axillary lymph nodes
She complains of severe pain (NRS 8 –9) localized in thoracic wall and inner part of the arm on the operated side.

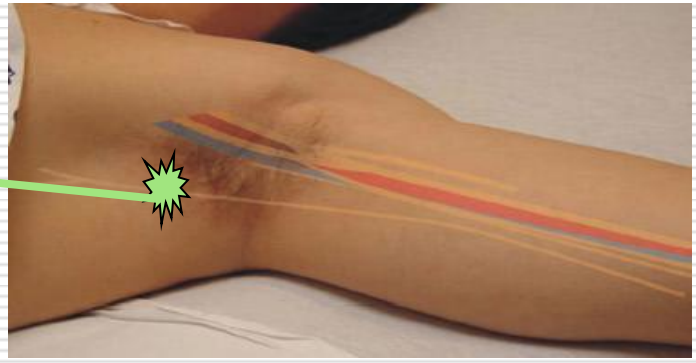
Diagnosis: persistent postoperative pain

Treatment: tramadol, amitryptyline, gabapentin, peripheral infiltration blocks.



Treatment unsuccessful.

Radiofrequency lesioning of neuroma localized in intercostobrachial nerve



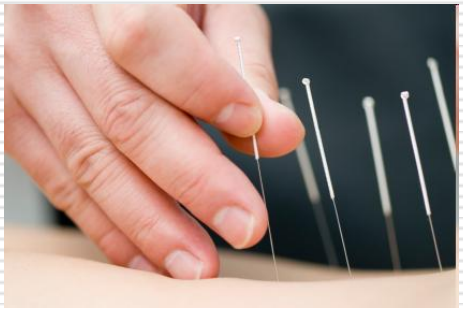
pain relief > 50%, satisfactory for the patient

Symptomatic treatment

1. Pharmacological therapies

2. Invasive methods

3. Non-pharmacologic treatment:



- **TENS, acupuncture**
- **psychological interventions**

Algorithms of pharmacological neuropathic pain treatment

- *Finnerup NB et al. Algorithm for neuropathic pain treatment: An evidence based proposal. Pain 2005.*
- *Stępień A, Dobrogowski J, Wordliczek J: Leczenie bólu neuropatycznego – propozycje terapeutyczne oparte na kontrolowanych badaniach klinicznych. Ból 2006.*
- *Attal N et al.. EFNS guidelines on pharmacological treatment of neuropathic pain. Eu J Neu 2006*
- *Moulin DE et al. Pharmacological management of chronic neuropathic pain – Consensus statement and guidelines from the Canadian Pain Society. Pain Res Manage 2007.*
- *Dworkin RH et al.. Pharmacological management of neuropathic pain: Evidence based recommendations. Pain 2007*
- *O'Connor AB, Dworkin RH. Treatment of neuropathic pain: An Overview of Recent Guidelines. Am J Med 2009*
- *Dworkin RH et al.. Recommendations for the Pharmacological Management of Neuropathic Pain: An Overview and Literature Update. Mayo Clin Proc March 2010.*

Algorithms of pharmacological neuropathic pain treatment

Created on the basis of available randomized controlled trials on pharmacotherapy of neuropathic pain syndromes:

- degree of evidence of analgesic efficacy
- ease of use
- adverse effects, safety
- impact on quality of life
- cost-effectiveness of pharmacological agents

Recommend the individual choice of a particular drug for each patient taking into account its efficacy, concomitant diseases, the risk of side effects, drug interactions, risk of addiction, the cost and availability of treatment.

Dworkin 2010

Symptomatic treatment

O'Connor AB, Dworkin RH. Treatment of Neuropathic Pain: An Overwiev of Recent Guidelines. Am J Med 2009

	Recommendations	**Medication class**
„first line"	Multiple RCTs on NP	secondary amine TCAs SSNRIs, pregabalin, gabapentin, topical lidocaine
„second line"	Multiple RCTs on NP, additional guidelines, authors' experience	Opioids, tramadol
„third line"	1 positive RCT or inconsistent >2 RCTs	carbamazepine, valproic acid, lamotrigine, bupropion, citalopram, paroxetine, topiramat, oxcarbazepine
Other	Inconsistent or negative	Mexiletine, NMDA antagonists, capsaicine

Pain assessment, diagnosis of neuropathic pain, identifying of concomitant diseases, causal treatment, non-pharm. methods

Diagnosis, treatment plan and expectations discussed with patient

Localized peripheral neuropathic pain: **topical lidocaine**

First-line medication:

TCA or SSNRI
nortriptyline, desipramine
duloxetine, venlafaxine

calcium channel α2δ ligand
gabapentin, pregabalin

No pain relief or side effects

Partial pain relief > 4 NRS

Switch to another first-line medication

Add another first-line medication

No pain relief or side effects

Multidisciplinary pain center

third-line drugs, invasive methods, rehabilitation programmes

Dworkin RH 2010

Symptomatic pharmacological treatment of neuropathic pain effective in 40 – 60% of patients

Mechanisms of action

TCA (tricyclic antidepressants)
(amitryptyline, desipramine, nortriptyline, imipramine)

SSNRI (Selective Serotonine Norepinephrine Reuptake Inhibitors)
(duloxetine, venlafaxine)

calcium channels α2δ ligands
(**pregabalin, gabapentin**)

opioids
(**tramadol, oxycodone CR, morphine, methadon, buprenorphine**)

topically applied drugs
(**lidocaine**)

Symptomatic treatment

Secondary amine TCAs desipramine, nortriptyline
Tertiary amine TCAs (only if secondary amine TCA not available) amitriptyline, imipramine
Starting dosage 25 mg at bedtime, increase by 25 mg/day every 3 – 7 days as tolerated. Maximum dosage 150mg/d

Duration of adequate trial 6-8 weeks, at least 2 weeks at maximum tolerated dosage

Side effects: sedation, dry mouth, constipation, urinary retention, gain weight, cardiotoxicity, risk of sudden cardiac death. Secondary amine TCAs better tolerated. Screening ECG in patients older than 40 years

Contraindications – patients older than 65 years, ischemic heart disease, glaucoma, risk of suicide, serotonin syndrome with tramadol, SSRI

Benefits: decrease of depression symptoms, sleep improvement

American Geriatrics Society Panel on the Pharmacological Management of Persistent Pain in Older Persons 2009
Dworkin 2010

Symptomatic treatment

TCAs – negative trials:

- Painful HIV neuropathy
- Chemotherapy-induced peripheral neuropathy
- Lumbosacral radiculopathy

Refractory pain?

Dworkin RH et al.. Recommendations for the Pharmacological Management of Neuropathic Pain: An Overview and Literature Update. Mayo Clin Proc March 2010

Symptomatic treatment

Selective Serotonin Noradrenaline Reuptake Inhibitors

Duloxetine

Starting dosage 30 mg once daily, increase to 60 mg/d after one week.
Maximum dosage 60 mg twice daily.
Duration of adequate trial 4 weeks.
Side effects: nausea, somnolence, sweating, ataxia, dry mouth
Contraindications: renal and hepatic failure, alcohol abuse
Benefits: decrease of depression symptoms

Goldstein DJ et al. Duloxetine vs. placebo in patients with painful diabetic neuropathy. Pain.2005;16:109-118.

Raskin J et al. A double-blind, randomized multicenter trial comparing duloxetine with placebo in the management of diabetic peripheral neurophatic pain. Pain Med. 2005;6:346-356.

Venlafaxine

Starting dose 37,5 mg once or twice daily, increase by 75 mg each week.
Maximum dosage 225 mg/d. Duration of trial 4-6 weeks.
Side effects: nausea (>10%), sleep disturbances (>10%), dyspepsia, sweating, dizziness, dry mouth, ECG changes, risk of discontinuation syndrome
Contraindications: cardiac diseases, concomitant use of tramadol

Sindrup SH et al. Venlafaxine versus imipramine in painful polyneuropathy: a randomized, controlled trial. Neurology. 2003;60:1284-1289

Symptomatic treatment

Calcium channels α2δ ligands

Pregabalin

Starting dosage 50 mg 3 times daily or 75 mg twice daily as tolerated, increase to 300mg/d after 3-7 days, maximum dosage 600mg/d

Duration of trial 4 weeks

Side effects: dizziness (27,2%), somnolence (23,5%), peripheral oedema (7,4%), gain weight. Dose reduction in renal failure.

Benefits– low risk of DDI, sleep improvement, decrease anxiety

Richter RW et al. Relief of painful diabetic peripheral neuropathy with pregabalin: a randomized placebo-controlled trial. J Pain. 2005.

Lesser H et al. Pregabalin relieves symptoms of painful diabetic neuropathy: a randomized controlled trial. Neurology. 2004.

Gabapentin

Starting dose 100-300mg at bedtime or 100-300 mg 3 times daily.

Increase by 100-300mg every 1-7days as tolerated. Maximum dosage 3600 mg/d,

dose reduction in renal failure. Duration of trial 3-8 weeks of titration, 2 weeks at max. dose.

Side effects: dizziness, somnolence, peripheral oedema.

Benefits – minimal risk of DDI, sleep improvement

Backonja M et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. JAMA. 1998.

Symptomatic treatment

Calcium channels α2δ ligands– negative trials:

- Painful HIV neuropathy
- Chemotherapy-induced peripheral neuropathy
- Lumbosacral radiculopathy
- CRPS

Dworkin RH et al.. Recommendations for the Pharmacological Management of Neuropathic Pain: An Overview and Literature Update. Mayo Clin Proc March 2010

Symptomatic treatment

Topical drugs

5% lidocaine patch containing 700 mg

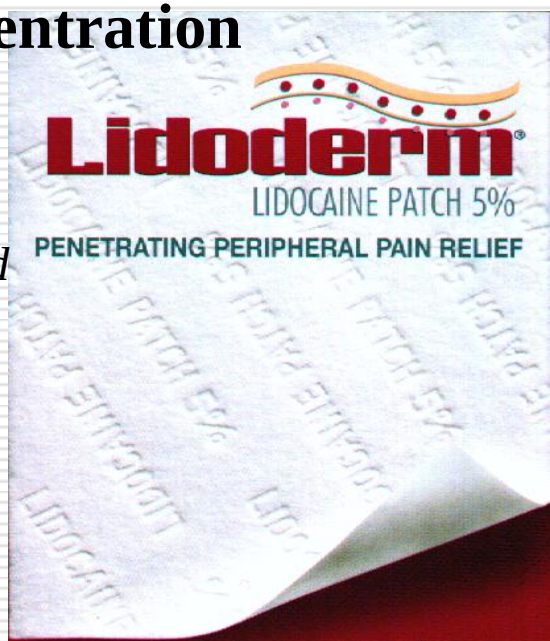
Maximum 3 patches daily for a maximum of 12h

No titration needed

Duration of trial – 3 weeks

Side effects – erythema and skin irritation, alergic reactions

Systemic side effects unlikely – low plasma concentration



Hans G et al.. Efficacy and tolerability of a 5% lidocaine medicated plaster for the topical treatment of post-herpetic neuralgia: results of a long-term study. Curr Med Res Op 2009.

Opioids are considered as a second-line medication

1. Side effects more frequent than TCA or α2δ ligands
2. No studies on the safety of a long-term use – hypogonadism, immunological changes
3. Opioid induced hyperalgesia
4. Risk of addiction (5 – 50%)

Certain circumstances, in which opioids and tramadol can be considered as a first-line medication:

1. During titration of a first-line medication for a prompt pain relief
2. Episodic exacerbations of severe pain
3. Acute neuropathic pain
4. Neuropathic cancer pain

Dworkin RH et al.. Recommendations for the Pharmacological Management of Neuropathic Pain: An Overview and Literature Update. Mayo Clin Proc March 2010

Symptomatic treatment

Opioid agonists **Opioids**

Starting dosage 10-15mg of morphine IR every 4 hours as needed or equianalgesic dosages of other opioid

After 1 weeks switch to a long-acting form of drug, IR medication as needed

Maximum dosage limited by side effects typical for opioids – constipation, nausea, sedation.

Duration of trial 4-6 weeks.

Treatment according to special guidelines, careful evaluation by pain treatment specialist.

Dworkin RH et al.. Recommendations for the Pharmacological Management of Neuropathic Pain: An Overview and Literature Update. Mayo Clin Proc March 2010

Tramadol

Starting dosage 50 mg once or twice daily, increase by 50-100 mg every 3-7 days as tolerated

Maximum dosage 400mg/d. Duration of trial 4 weeks.

Side effects: nausea (23,1%), constipation (21,5%), headache (16,9%), somnolence (12,3%), sweating, risk of serotonin syndrome

Finnerup NB et al.. Algorithm for neuropathic pain treatment an evidence base proposal. Pain 2005.

Symptomatic treatment

Third-line medications 1 positive RCT or inconsistent results in >2 RCTs
Reserved for patient who don't respond to first- and second-line medications or who cannot tolerate them.

SSRI - bupropion, citalopram, paroxetine, escitalopram:

•Better safety profile compared with TCAs
•Lack of a need for titration
•Less adverse effects

Dworkin 2007

In future – trials comparing with first-line treatments
reevaluation of the role of SSRIs in neuropathic pain treatment.

Anticonvulsants - carbamazepine, valproic acid, lamotrigine, topiramat, oxcarbazepine

Other - mexiletine, NMDA antagonists, cannabinoids, topical capsaicine

Trials in different neuropathic pain syndromes, but still lack of many positive RCTs

Symptomatic treatment

<u>Combination therapies</u> – single RCTs only, but recommended

SSNRI + α2δ CCM + opioids + topical medication
TCA + α2δ CCM + opioids + topical medication
- an additive beneficial effect
- better pain relief
- better tolerability

<u>Recent studies</u>

- **Botulinum toxin**
- **High-concentration capsaicin patch**
- **Lacosamide**
- **Bicifadine**

Dworkin RH et al.. Recommendations for the Pharmacological Management of Neuropathic Pain: An Overview and Literature Update. Mayo Clin Proc March 2010

Issues concerning pharmacological treatment

- **Cost effectiveness of recommended drugs**
- **Lack of reimbursement**
- **Off-label prescription – legal issues**
- **Availability in different countries:**

  ***in Poland* – lidocaine 5% patch**

  and secondary amine TCAs not available

Invasive methods in neuropathic pain treatment

Nerve blocks

Intrathecal drug administration

Neurodestruction techniques

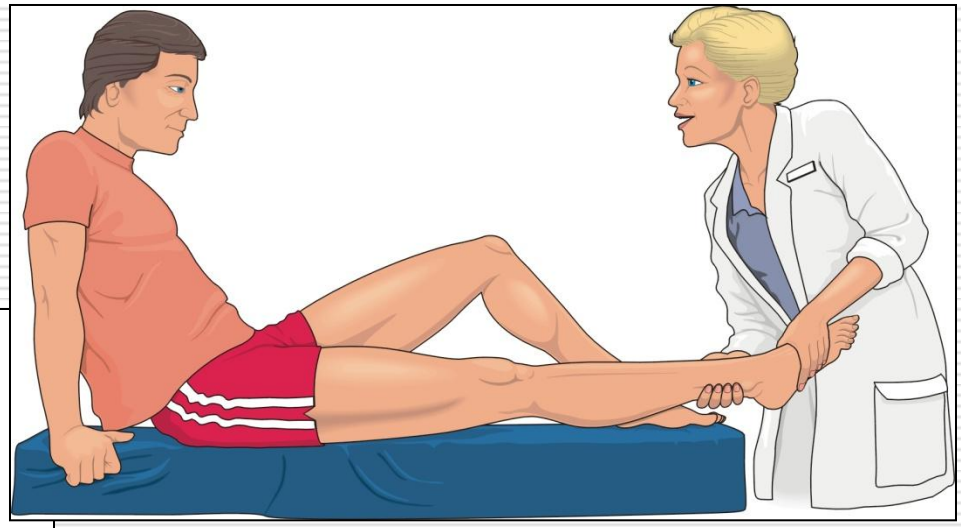
Spinal cord and peripheral nerve stimulation

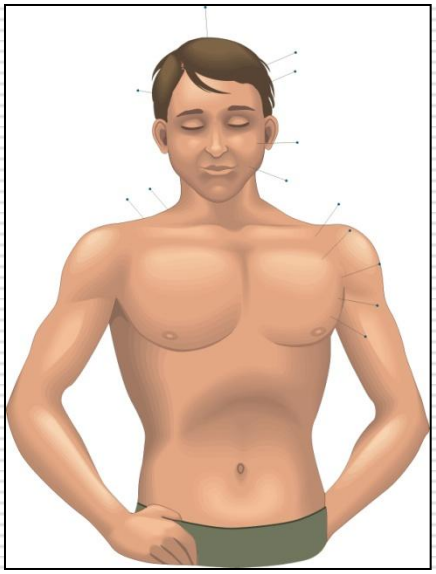
Lack of supportive evidence of efficacy

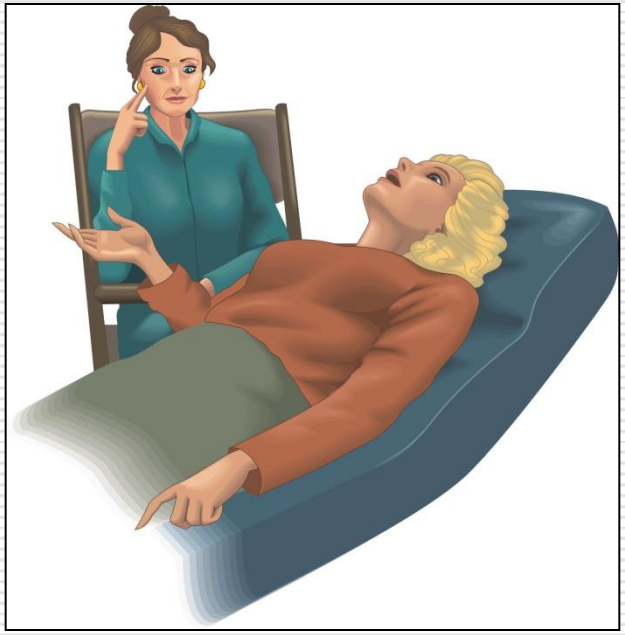
Neurodestruction techniques
Radiofrequency lesioning - indications

- TN
- Cluster headache
- Back pain
- Occiptal neuralgia
- Stump pain
- CRPS
- AO

Multimodal chronic pain treatment








Thank you for your attention
Have a nice evening!
Дякую за увагу.
Бажаю приємно провести вечір.