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

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International Symposium
"Pain Medicine: Present and Future"
27-29 May 2010 Kyiv, Ukraine
Neuropathic pain – the pain arising as a direct consequence of a lesion or disease affecting the somatosensory system.

Taxonomy 2008

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

Treede 2008
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


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


• 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.

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%.

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

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


• Attal N et al.. EFNS guidelines on pharmacological treatment of neuropathic pain. Eu J Neu 2006


• Dworkin RH et al.. Pharmacological management of neuropathic pain: Evidence based recommendations. Pain 2007


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


<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Medication class</th>
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<tbody>
<tr>
<td>„first line“ Multiple RCTs on NP</td>
<td>secondary amine TCAs</td>
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<td>SSNRIs, pregabalin, gabapentin, topical lidocaine</td>
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<td>„second line“ Multiple RCTs on NP,</td>
<td>Opioids, tramadol</td>
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<td>additional guidelines, authors’</td>
<td></td>
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<tr>
<td>experience</td>
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<td>„third line“ 1 positive RCT or</td>
<td>carbamazepine, valproic acid, lamotrigine, bupropion,</td>
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<tr>
<td>inconsistent &gt;2 RCTs</td>
<td>citalopram, paroxetine, topiramat, oxcarbazepine</td>
</tr>
<tr>
<td>Other</td>
<td>Mexiletine, NMDA antagonists, capsaicine</td>
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</tbody>
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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:
- Switch to another first-line medication

Partial pain relief > 4 NRS:
- 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)
(amitriptyline, desipramine, nortriptyline, imipramine)

SSNRI (Selective Serotonin 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?

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

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
Symptomatic treatment

Calcium channels $\alpha_2\delta$ 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

**Gabapentin**
Starting dose 100-300mg at bedtime or 100-300 mg 3 times daily.
Increase by 100-300mg every 1-7 days 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
Symptomatic treatment

**Calcium channels α2δ ligands**—negative trials:

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

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, allergic reactions
Systemic side effects unlikely – low plasma concentration

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

Symptomatic treatment

**Opioid agonists**
Starting dosage 10-15mg of morphine IR every 4 hours as needed or equianalgesic dosages of other opioid
After 1 week 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.


**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

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

Dworkin 2007
Symptomatic treatment

Combination therapies – 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

Recent studies
• Botulinum toxin
• High-concentration capsaicin patch
• Lacosamide
• Bicifadine

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
- Occipital 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.