NEUROPATSKA BOL

Dr Ljiljana Radulović
Klinika za neurologiju, Klinički centar Crne Gore
Medicinski fakultet, Univerzitet Crne Gore

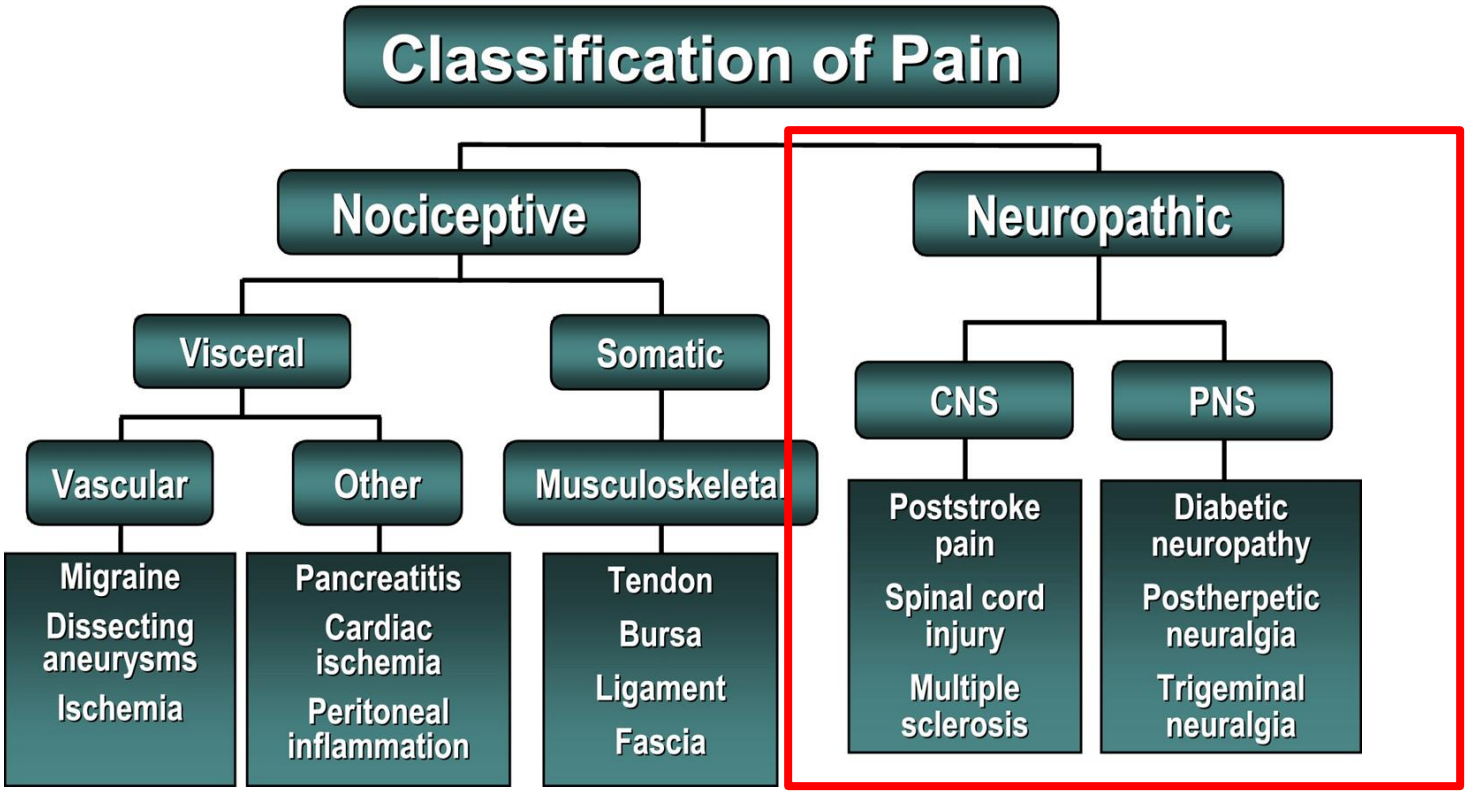
BOL – PETI VITALNI ZNAK / 21.12.2020.

Project number: 585927-EPP-1-2017-1-RS-EPPKA2-CBHE-JP (2017 – 3109 / 001 – 001)

Neuropatska bol
-veliki klinički problem-

Project number: 585927-EPP-1-2017-1-RS-EPPKA2-CBHE-JP (2017 – 3109 / 001 – 001)

Bol



Siddall PJ, Taylor DA, Cousins MJ. Classification of pain following spinal cord injury. Spinal Cord 1997;35(2):69 e75.

Project number: 585927-EPP-1-2017-1-RS-EPPKA2-CBHE-JP (2017 – 3109 / 001 – 001)

"This project has been funded with support from the European Commission. This publication reflects the views only of the author, and the Commission cannot be held responsible for any use which may be made of the information contained therein"

Table 2 – Prevalence of neuropathic pain or painful neuropathy in the general population and in various neurological conditions, based on results obtained with screening tools (studies published since 2011 or landmark studies before 2011, with at least 50% return rate for studies in the general population; $n \geq 100$ patients).

Condition explored	Author, year	Nature of the study	Geographic origin	Sample size	Screening tool	Prevalence
Neuropathic pain in the general population	Bouhassira 2008	Cross sectional	France	30155	DN4 interview	6.9%
	Harifi 2013		Morocco	5328		10.3%
	DeMoraes 2012		Brazil	1597	DN4	10%
	Adounokou 2014		Benin	2314	S LANSS	6.3%
	Torrance 2006		UK	6000	PainDetect	8%
	Torrance 2013		UK	8000		8.9%
	Elzahaf 2016		Lybia	1212		3.9%
	Inoue 2017		Japan	10000		3.20%
Painful diabetic neuropathy in type I or II diabetes	Bouhassira 2013	Cross-sectional	France	855	DN4	17.9%
	Van Acker 2009		Belgium	1111		14.1%
	Jacovides 2014		South Africa	1046		30.3%
	Halawa 2010		Saudi Arabia	1039		65.3%
	Jambart 2011		Middle East	3989		53.7%
Neuropathic pain in type I or II diabetes	Celik 2016	Cross-sectional	Turkey	1357	DN4	23.0% (90% type 2)
	Aslam 2015		UK	204	S LANSS	30.3%
	Liberman 2014		Israel	342		46.5% (100% type 2)
Postherpetic neuralgia after herpes zoster	Bouhassira 2012	Prospective	France	1032	DN4	6.4% at 12 months
	Cho 2014		UK	305	S LANSS	6.2% at 12 months
Poststroke neuropathic pain	Aprile 2015	Cross-sectional	Italy	106	DN4	10.5% at rehabilitation
	Harno 2014	Prospective	Finland	824	PainDetect	5.9%
Neuropathic pain in multiple sclerosis	Truini 2012	Prospective	Italy	302	DN4	14%
	Heitmann 2016		Germany	377	PainDetect	4.2% at early stage
Neuropathic pain in Parkinson disease	Buhman 2017	Cross-sectional	Germany	181	PainDetect	15.3%

Bouhassira D. Neuropathic pain: Definition, assessment and epidemiology. Rev Neurol (Paris). 2019 Jan-Feb;175(1-2):16-25.

Project number: 585927-EPP-1-2017-1-RS-EPPKA2-CBHE-JP (2017 – 3109 / 001 – 001)

Neuropatski bol javno-zdravstveni problem

- Prevalencija u kliničkoj praksi iznosi **7-10%**.[1]
- **Trećina** pacijenata sa DM2 ima neuropatski bol.[2]
- Ostali uzročnici neuropatskog bola:

Periferni neuropatski bol	Centralni neuropatski bol
HIV-neuropatija	Povrede kičmene moždine
Neuropatija usljed primene hemoterapije	Bol nakon moždanog udara
Postherpetična neuralgia; Trigeminalna neuralgia	Kompresivne mijelopatije
Kompresivne mononeuropatije; Radikulopatije	Bol u multiploj sklerozi
Inflamatorne neuropatije (AIDP i CIDP)	Siringomijelija
Posttraumatske neuropatije	Talamički bolni sindrom

1 van Hecke O, Austin SK, Khan RA, et al. Neuropathic pain in the general population: a systematic review of epidemiological studies. Pain 2014;155(4):654 Y 662.
2 Abbott CA, Malik RA, van Ross ER, et al. Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the U.K. Diabetes Care 2011;34(10):2220 Y 2224.

Project number: 585927-EPP-1-2017-1-RS-EPPKA2-CBHE-JP (2017 – 3109 / 001 – 001)

"This project has been funded with support from the European Commission. This publication reflects the views only of the author, and the Commission cannot be held responsible for any use which may be made of the information contained therein"

Neuropatski bol javno-zdravstveni problem

TABLE 1. Classification of Neuropathic Pain According to Site of Major Pathology

Pathology	Peripheral	Spinal	Brain
Genetic	Fabry neuropathy	Syringomyelia	Syringobulbia
Metabolic	Painful diabetic neuropathy	B_{12} myelopathy	
Traumatic	Nerve injury	Spinal cord injury	Multiple sclerosis
Vascular	Vasculitic neuropathy	Spinal cord stroke	Brain stroke
Neoplastic	Tumor compression neuropathy	Tumor compression	Tumor compression
Immunological	Guillain-Barré syndrome	Multiple sclerosis	Multiple sclerosis
Infectious	HIV, Borreliosis	Infectious myelitis	Encephalitis
Toxic	Chemotherapy neuropathy		

Gilron I, Jensen TS, Dickenson AH. Combination pharmacotherapy for management of chronic pain: from bench to bedside. Lancet Neurol. 2013;12(11):1084-1095

Project number: 585927-EPP-1-2017-1-RS-EPPKA2-CBHE-JP (2017 – 3109 / 001 – 001)

"This project has been funded with support from the European Commission. This publication reflects the views only of the author, and the Commission cannot be held responsible for any use which may be made of the information contained therein"

Neuropatski bol javno-zdravstveni problem

- Najveći broj pacijenata je nezadovoljan liječenjem
  - Neuropatski bol je refraktaran na liječenje
  - Ljekovi imaju neželjene efekte
  - Pacijenti nekada imaju nerealna očekivanja od liječenja
  - Neuropatski bol pogađa mnoge segmente života (spavanje, kvalitet života...)
- Postavljanje dijagnoze neuropatskog bola je ponekad teško
  - Psihološki komorbiditeti
  - Poremećaji spavanja
  - Socijalna podrška

Project number: 585927-EPP-1-2017-1-RS-EPPKA2-CBHE-JP (2017 – 3109 / 001 – 001)

"This project has been funded with support from the European Commission. This publication reflects the views only of the author, and the Commission cannot be held responsible for any use which may be made of the information contained therein"

Bol je subjektivni doživljaj pacijenta! (različiti opisi kod različitih pacijenata)

Pozitivni simptomi neuropatskog bola	Negativni simptomi neuropatskog bola
Trnjenje (osjećaj bockanja iglicama)	Utrnulost
Peckanje	Umrtvljenost
Strujanje	
Bockanje	
Žarenje, paljenje	
Probodi	

ANAMNEZA

NEUROLOŠKI PREGLED!

EMNG

Project number: 585927-EPP-1-2017-1-RS-EPPKA2-CBHE-JP (2017 – 3109 / 001 – 001)

"This project has been funded with support from the European Commission. This publication reflects the views only of the author, and the Commission cannot be held responsible for any use which may be made of the information contained therein"

Zašto nastaje neuropatska bol?

- **ABERANTNA** obrada signala u centralnom i perifernom nervnom sistemu!
- Prateći oštećenje perifernog nerva, dolazi do **senzitizacije** koju karakteriše spontana aktivnost nerva, sniženi prag za aktivaciju bola i povećanje odgovora na stimuluse. Oštećenje nerva rezultira povišenjem frekvencije izbijanja impulsa nociceptora, te posledično povećanjem bolova. Prateći nervno oštećenje, nociceptori **C-vlakana** mogu razviti nove adrenergičke receptore i senzitivnost koja može pomoći u ispoljavanju mehanizma simpatičkog održavanja bola. Periferna senzitizacija ima ulogu u nastanku **centralne senzitizacije**, pri čemu samo povrede s oštećenjem perifernog nerva indukuju promene u CNS sa centralnom senzitizacijom, koja može trajati neograničeno dugo[1]

1 Covington EC. The biological basis of pain. Int Rev Psychiatry. 2000;12:128-47

Project number: 585927-EPP-1-2017-1-RS-EPPKA2-CBHE-JP (2017 – 3109 / 001 – 001)

"This project has been funded with support from the European Commission. This publication reflects the views only of the author, and the Commission cannot be held responsible for any use which may be made of the information contained therein"

Vjerovatnoća postojanja neuropatskog bola

1. Jasna i tačna neuroanatomska distribucija bola (periferni nerv, dermatom, polineuropatija...)

2. Vremensko poklapanje bola sa odgovarajućom lezijom ili oboljenjem somatosenzornog sistema (anamneza)

3. Najmanje jedan neurološki znak koji potvrđuje jasnu i tačnu neuroanatomsku distribuciju bola (neurološki pregled).

4. Najmanje jedan test kojim se potvrđuje odgovarajuća lezija ili oboljenje somatosenzornog sistema (laboratorija, EMNG, CT, MRI,...).

Zadovoljena sva 4 kriterijuma – DEFINITIVNI NEUROPATSKI BOL

1 i 2 + 3 ili 4 – VJEROVATNI NEUROPATSKI BOL

1 i 2 – MOGUĆI NEUROPATSKI BOL

Project number: 585927-EPP-1-2017-1-RS-EPPKA2-CBHE-JP (2017 – 3109 / 001 – 001)

"This project has been funded with support from the European Commission. This publication reflects the views only of the author, and the Commission cannot be held responsible for any use which may be made of the information contained therein"

Kako objasniti pacijentu?

Preuzeto sa: southwestspineandpain.com

Project number: 585927-EPP-1-2017-1-RS-EPPKA2-CBHE-JP (2017 – 3109 / 001 – 001)

"This project has been funded with support from the European Commission. This publication reflects the views only of the author, and the Commission cannot be held responsible for any use which may be made of the information contained therein"

Šta realno možemo očekivati od liječenja?[1]

- Smanjenje bola za > 30–50%
- Poboljšan kvalitet spavanja
- Poboljšan kvalitet života
- Održavanje socijalnih aktivnosti
- Povratak i održavanje radnih aktivnosti

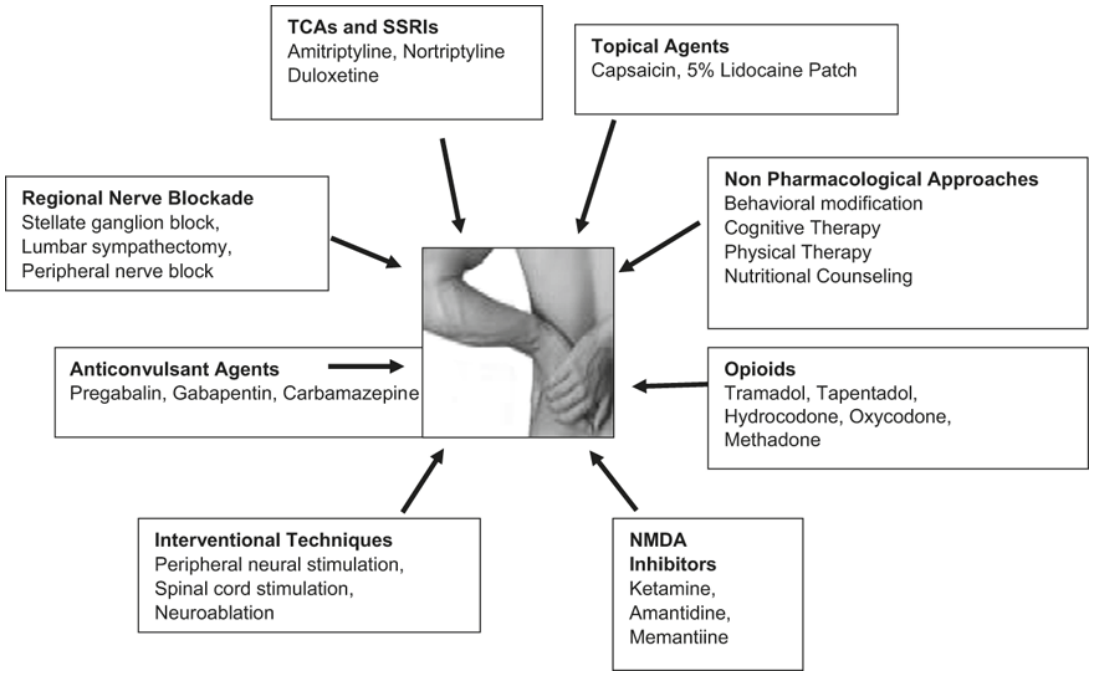
1 Binder A, Baron R. The Pharmacological Therapy of Chronic Neuropathic Pain. Dtsch Arztebl Int. 2016;113(37):616-625.

Project number: 585927-EPP-1-2017-1-RS-EPPKA2-CBHE-JP (2017 – 3109 / 001 – 001)

"This project has been funded with support from the European Commission. This publication reflects the views only of the author, and the Commission cannot be held responsible for any use which may be made of the information contained therein"

Kako pomoći pacijentu?

- **Farmakoterapija**
- Psihoterapija
- Fizikalna terapija
- Podrška sredine



Project number: 585927-EPP-1-2017-1-RS-EPPKA2-CBHE-JP (2017 – 3109 / 001 – 001)

Farmakoterapija (1)

Table 1. Pharmacotherapy for neuropathic pain.

		Drugs	Dose range	Adverse effect
First-line therapy	Gabapentinoids	Gabapentin	150–600 mg/day	Lethargy, vertigo, peripheral swelling, blurred vision
		Pregabalin	300–3600 mg/day	Lethargy, vertigo, peripheral swelling, increased body weight
	Tricyclic antidepressants (TCAs)	Amitriptyline	10–150 mg/day	Anticholinergic effects, QT prolongation (arrhythmia), suicide risk, urinary retention
	Serotonin–norepinephrine reuptake inhibitors (SNRI)	Duloxetine	20–120 mg/day	Nausea, lethargy, constipation, ataxia, dry mouth
		Venlafaxine	150–225 mg/day	Nausea, vertigo, lethargy, hyperhidrosis, hypertension
Second-line therapy	Opioids	Tramadol	25–400 mg/day	Nausea/vomiting, constipation, lethargy, seizures, ataxia
		Tapentadol	50–600 mg/day	Nausea/vomiting, constipation, lethargy, seizures, ataxia
	Topical treatment	Lidocaine	5% patches or gel	Local erythema, itching and rash
		Capsaicin	8% patches	Pain, erythema, itching; rare cases of high blood pressure
Third-line therapy	Strong opioids	Morphine	10–120 mg/day	Nausea, vomiting, constipation, dizziness and lethargy
		Oxycodone	10–120 mg/day	Nausea/vomiting, constipation, lethargy, respiratory control
	Neurotoxin	Botulinum toxin	25–300 U BTX-A 0.9% saline	Pain at injection site

Project number: 585927-EPP-1-2017-1-RS-EPPKA2-CBHE-JP (2017 – 3109 / 001 – 001)

Farmakoterapija (2)

Medication	Dose	Adequate Trial	Side Effects	Comments
Tricyclic antidepressants				
Amitriptyline, nortriptyline	10–25 mg at bedtime, titrate up to a maximum of 150 mg/d	6–8 weeks (2 weeks at maximum dose)	Sedation, anticholinergic effects (eg, dry mouth, blurred vision, urinary retention), cardiac conduction abnormalities	Use with caution in patients with cardiac disease, risk of serotonin syndrome
Serotonin norepinephrine reuptake inhibitors (SNRIs)				
Duloxetine	30 mg once a day, titrate up to 60 mg twice a day	4 weeks	Nausea, increased sweating, increased blood pressure	Risk of serotonin syndrome, risk of hepatic dysfunction; venlafaxine immediate release in particular is associated with a withdrawal syndrome if the patient forgets to take a dose on time
Venlafaxine	Venlafaxine immediate release: 75 mg/d in 2 or 3 divided doses, titrate up to total daily dose of 225 mg/d Venlafaxine extended release: 37.5 mg or 75 mg once daily, titrate up to 225 mg once daily	4–6 weeks		

Project number: 585927-EPP-1-2017-1-RS-EPPKA2-CBHE-JP (2017 – 3109 / 001 – 001)

"This project has been funded with support from the European Commission. This publication reflects the views only of the author, and the Commission cannot be held responsible for any use which may be made of the information contained therein"

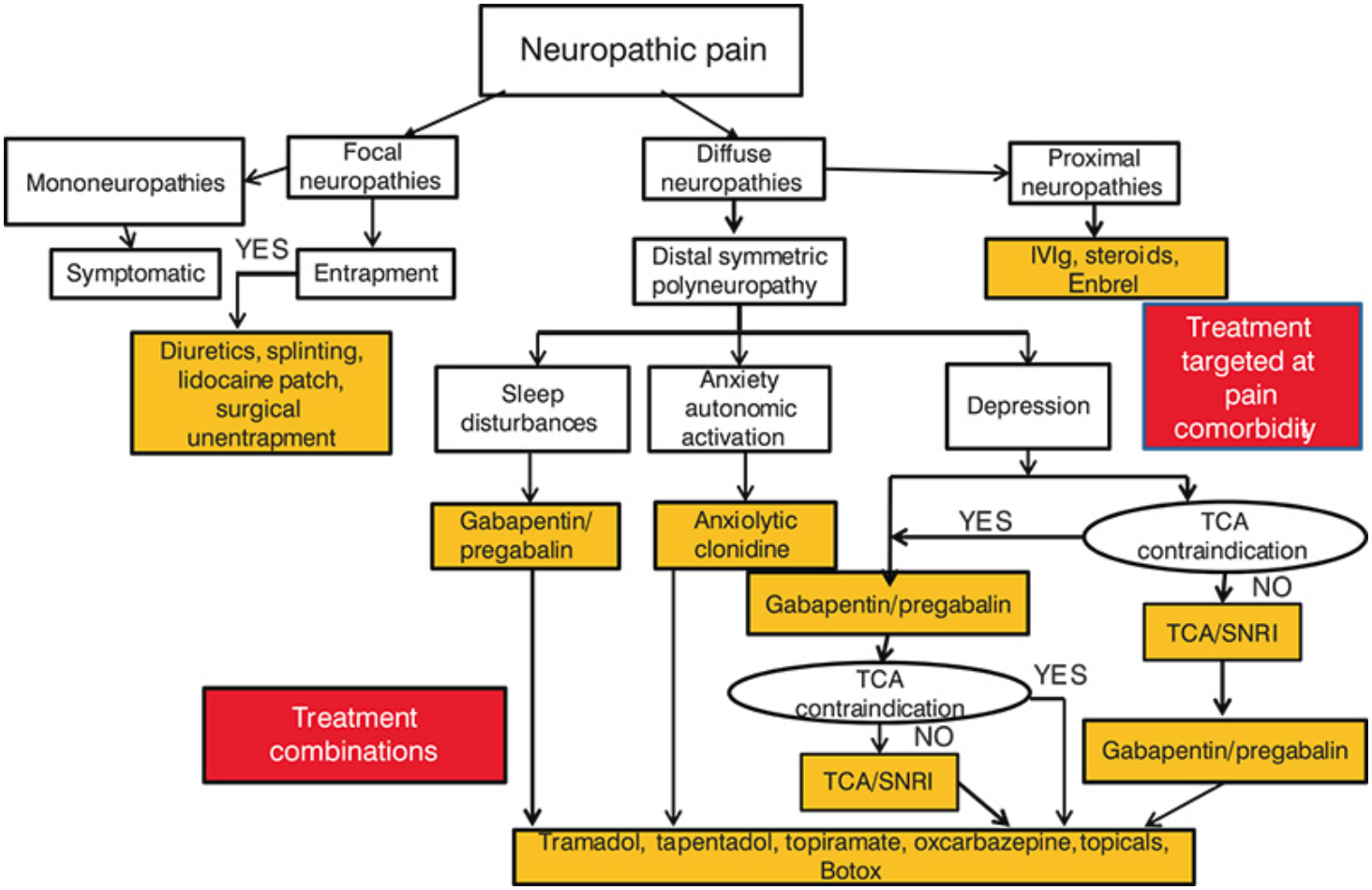
Farmakoterapija (3)

Medication	Dose	Adequate Trial	Side Effects	Comments
Calcium channel α2δ ligands				
Gabapentin	100–300 mg once or 3 times a day, titrate up to total daily dose of 3600 mg/d	5–10 weeks (2 weeks at maximum dose)	Sedation, dizziness, weight gain, edema	Reduce dose in patients with renal impairment
Pregabalin	50 mg 3 times a day or 75 mg 2 times a day, titrate up to 300–600 mg/d	4 weeks	Sedation, dizziness, weight gain, edema	Reduce dose in patients with renal impairment; risk of dependence and tolerance (schedule V controlled substance)
Topical lidocaine	1–3 patches for a maximum of 12 hours	3 weeks	Local erythema or rash	Not effective in central neuropathic pain

Zilliox LA. Neuropathic Pain. Continuum (Minneap Minn). 2017 Apr;23(2, Selected Topics in Outpatient Neurology):512-532.

Project number: 585927-EPP-1-2017-1-RS-EPPKA2-CBHE-JP (2017 – 3109 / 001 – 001)

"This project has been funded with support from the European Commission. This publication reflects the views only of the author, and the Commission cannot be held responsible for any use which may be made of the information contained therein"



Vinik A, Casellini C, Nevoret ML. Diabetic Neuropathies. [Updated 2018 Feb 5]. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279175/

Project number: 585927-EPP-1-2017-1-RS-EPPKA2-CBHE-JP (2017 – 3109 / 001 – 001)

"This project has been funded with support from the European Commission. This publication reflects the views only of the author, and the Commission cannot be held responsible for any use which may be made of the information contained therein"

Šta dalje?

Targeting cytokines for treatment of neuropathic pain

Alice L. Hung[a], **Michael Lim**[a], and **Tina L. Doshi**[b,*]

[a]Department of Neurosurgery, Johns Hopkins University School of Medicine, Baltimore, MD, USA

[b]Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Table 2. Phase III Clinical Trials.

NCT number	Study title	Drug	Results
NCT01536314	Prophylaxis of neuropathic pain by memantine	*Memantine EBIXA®* *Placebo: lactose*	*Memantine prevented post-mastectomy pain and diminished chemotherapy-induced pain symptoms*
NCT00313378	Effects of perioperative systemic ketamine on development of long-term neuropathic pain after thoracotomy	*Ketamine*	*Ketamine did not prevent chronic pain after thoracotomy*
NCT00224588	KETOR: Effects of peri-operative administration of ketamine on long-term post thoracotomy pain	*Ketamine*	*Data not available*
NCT00872144	Sativex for the treatment of chemotherapy-induced neuropathic pain	*Sativex®*	*Sativex reduced chemotherapy-induced neuropathic pain in five participants that trended toward statistical significance*
NCT01604265	A study of Sativex in the treatment of central neuropathic pain due to multiple sclerosis	*Sativex®*	*Sativex reduced pain and sleep disturbance in patients with multiple sclerosis*
NCT01606202	A study of cannabis-based medicine extracts and placebo in patients with pain due to spinal cord injury	*GW-1000-02* *Placebo*	*GW-1000-02 improved pain score*
NCT00713817	A study to determine the maintenance of effect after long-term treatment of Sativex® in subjects with neuropathic pain	*Sativex®* *Placebo*	*Sativex showed no effect*
NCT00713323	A study to compare the safety and tolerability of Sativex® in patients with neuropathic pain	*Sativex®* *Placebo*	*Sativex improved pain score*

Cavalli E, Mammana S, Nicoletti F, Bramanti P, Mazzon E. The neuropathic pain: An overview of the current treatment and future therapeutic approaches. Int J Immunopathol Pharmacol. 2019;33:2058738419838383.

Project number: 585927-EPP-1-2017-1-RS-EPPKA2-CBHE-JP (2017 – 3109 / 001 – 001)

"This project has been funded with support from the European Commission. This publication reflects the views only of the author, and the Commission cannot be held responsible for any use which may be made of the information contained therein"

Zaključak

- Veliki javno-zdravstveni problem
- Dijagnostički i terapijski izazov
- Dalja edukacija, istraživanja i usavršavanja
- Donošenje nacionalnih terapijskih protokola

Project number: 585927-EPP-1-2017-1-RS-EPPKA2-CBHE-JP (2017 – 3109 / 001 – 001)

"This project has been funded with support from the European Commission. This publication reflects the views only of the author, and the Commission cannot be held responsible for any use which may be made of the information contained therein"