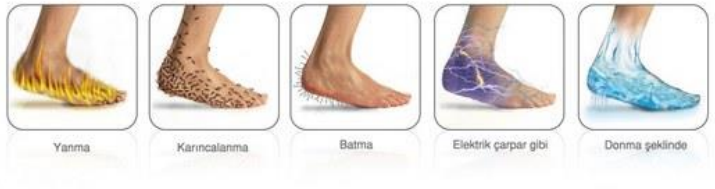


NÖROPATİK AĞRI TEDAVİSİNDE FARMAKOLOJİK AJANLAR

Doç. Dr. Yüksel Erkin

DEÜTF Anesteziyoloji ve Reanimasyon Anabilim Dalı

Algoloji Bilim Dalı

5. Ulusal Diyabetik Ayak İnfeksiyonları Simpozyumu – 2018 – İzmir

Nöropatik ağrı

- Sinir sisteminin bir hastalığına, yaralanmasına ya da disfonksiyonuna bağlı anormal nöronal aktiviteden kaynaklanan ağrı (IASP – 1994)

- **Somatosensoriyel sistemi etkileyen bir hastalık veya lezyon sonucu ortaya çıkan ağrı** (Treede ve Ark. – 2008)

Nöropatik ağrıda

Periferal sensitizasyon

Fenotipik depişim

Santral sensitizasyon

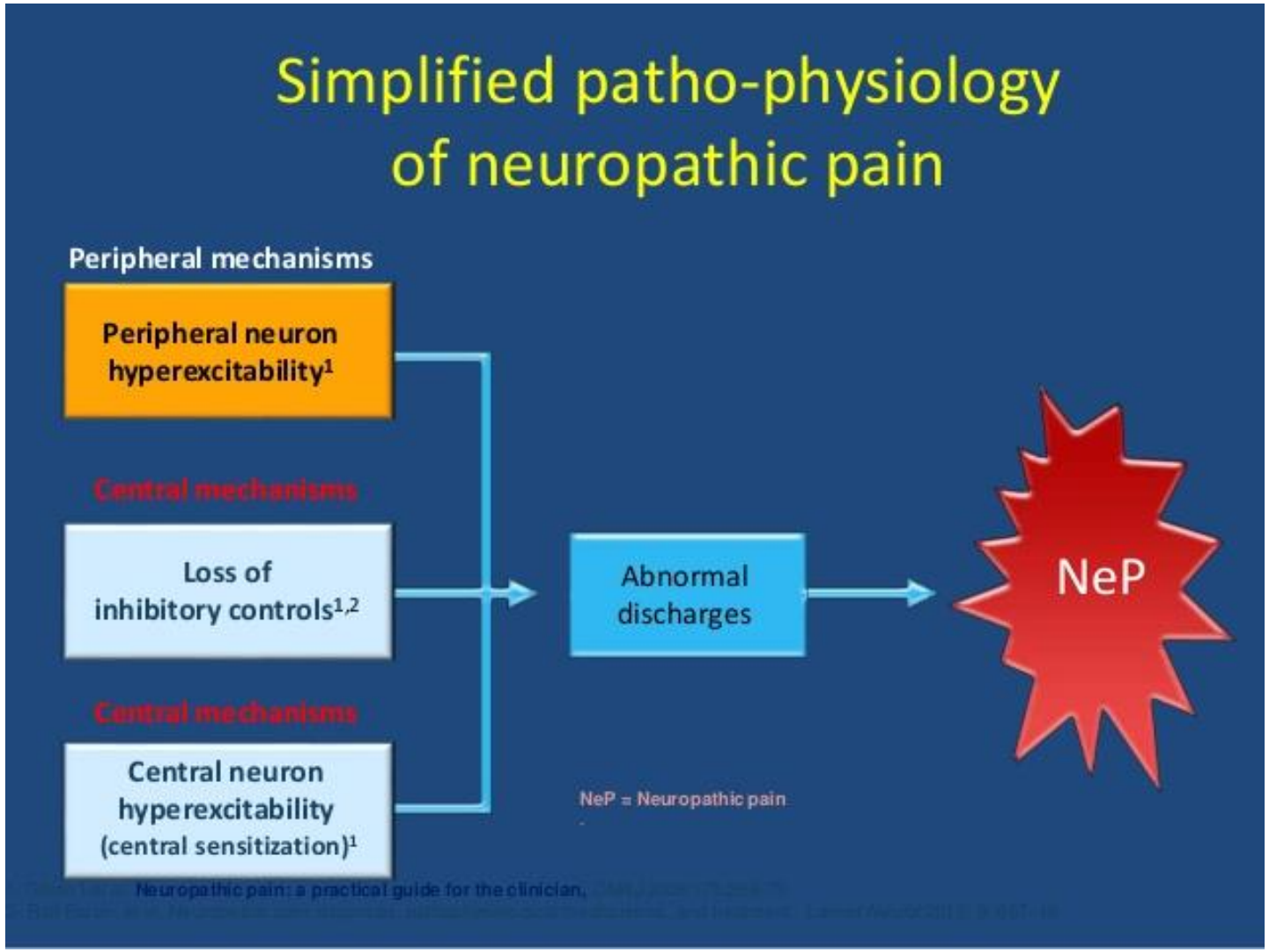
Nöron-glia etkileşimi

Azalmış disinhibisyon

Artmış fasilitasyon

Yapısal reorganizasyon

söz konusudur



Nöropatik ağrı

Genel popülasyonda % 7-9

Kronik ağrısı olan her 5 hastanın 1‘inde nöropatik özellikler mevcut

Hastaların % 80’i orta ve şiddetli ağrıdan yakınır

Basit ağrı kesiciler, NSAİİ’lar etkili değil

Uluslararası Diyabet Federasyonu (IDF) Diyabet Atlasına (2017) göre **dünyada erişkin** (20-79 yaş) **nüfusta diyabet prevelansı % 8,8'dir**

IDF dünyada 425 milyon olan diyabetli nüfusun 2045 yılında 693 milyon olacağını bildirmektedir

IDF (2017) verilerine göre Türkiye'de diyabet prevelansının %12,8 olduğu ve 6.700.000 diyabetli hasta bulunduğu rapor edilmektedir (IDF 2017)

Nöropatik ağrı Avrupa'da genel populasyonda: %8-9

(Torrance N,et al 2006, Bouhassira D, 2008)

Türkiye Diyabet Epidemiyolojisi TURDEP-I (1995)

Diyabet prevalansı:%7.2

Glukoz intoleransı: %6.7

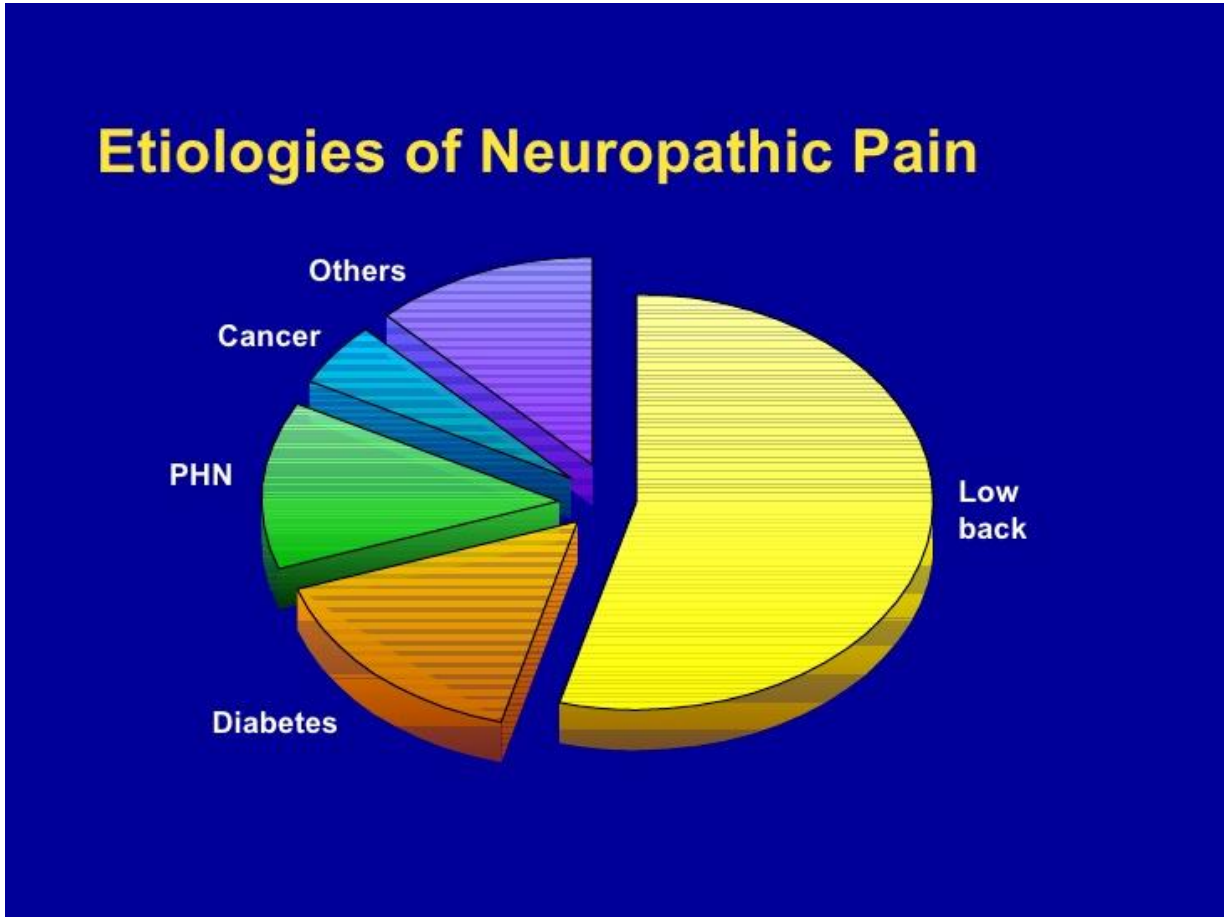
Diyabetik nöropati: Diyabetlilerde ~%50

TURDEP-II çalışmasına göre:

Türk erişkinlerde tip 2 diyabet sıklığının geçen yıllarda önemli derecede arttığı ve %7,2'den %13,7'ye ulaştığı görülmüştür

(Satman, 2009, Sivrikaya ve Çınar 2016)

Nöropatik ağrı



En sık

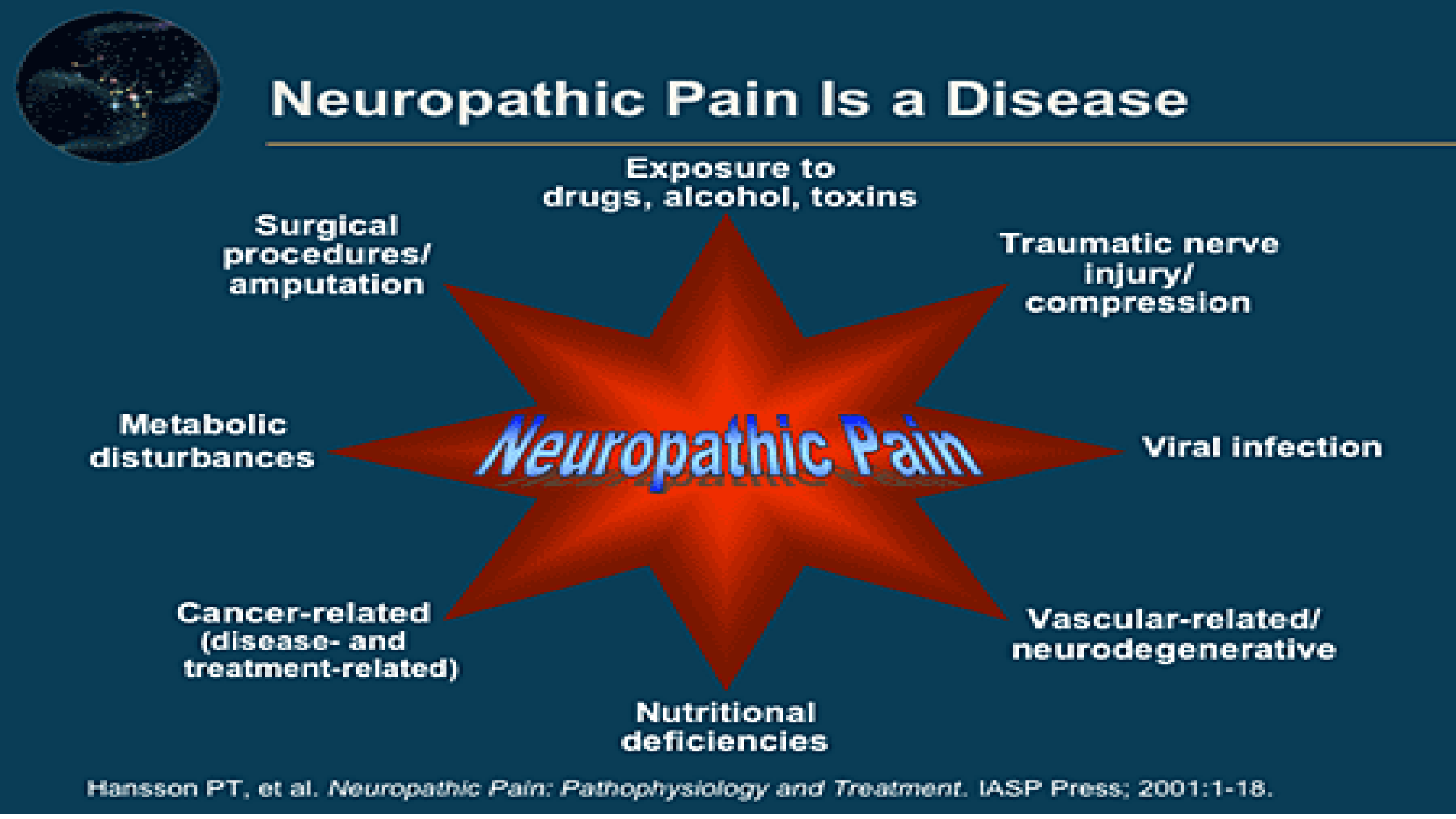
kronik bel ağrısı olan hastalarda

ve

diyabetlilerde

görülür

Neuropathic Pain Is a Disease



Hansson PT, et al. *Neuropathic Pain: Pathophysiology and Treatment*. IASP Press; 2001:1-18.

Nöropatik ağrı tedavisi

1. Fizik tedavi ve rehabilitasyon uygulamaları, bilişsel ve davranışsal tedavi

2. Medikal

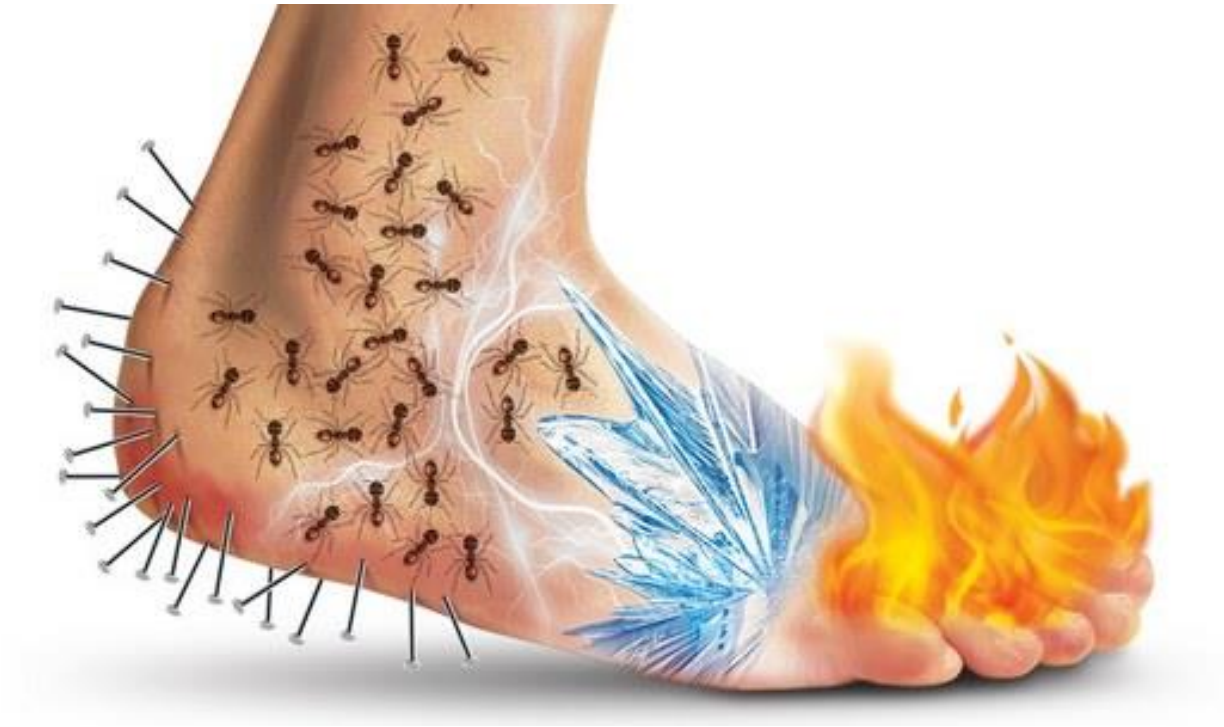
3. Girişimsel ve cerrahi

- Klasik ağrı kesicilere (analjezik, antenflamatuar ilaçlar ya da opioidlere) yanıt vermez
- **Nöropatik ağrıya özel tedavi gerektirir**

“Nosiseptif ağrı” mekanizmaları ile

“nöropatik ağrı”

mekanizmaları farklıdır



Nöropatik ağrıda medikal tedavi

SANTRAL SENSİTİZASYON	**Ca^+**	- PGB
		GBT
DESANDAN MODÜLASYON	**Na^+, 5HT**	- TSA
		SNRI
PERİFERİK SENSİTİZASYON	**Na^+**	- Karbamazepin
		Lamotrigin
		Lidokain
	TRPV	- Kapsaisin

Nöropatik ağrıda medikal tedavi

Antiepileptikler

Gabapentinoidler, CBZ, LTG…

Antidepresanlar

TSA, SNRI…

Topikal Ajanlar

Kapsaisin, Lidokain, Btx…

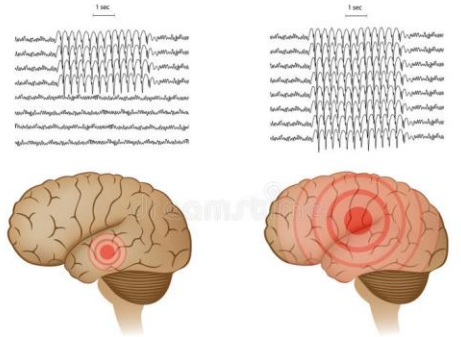
Opioidler

Tramadol, Opioidler (Kontrollü salınımlı oksikodon ve morfin …)

İLAÇ	ETKİ	DİKKAT	NA +	DOZAJ			TİTRASYON	GRADE
				Başlangıç	Max.	Etkin		
AMİTRİPTİLİN	Na, MARI	KVS, GLOKOM, NÖBET, TRAMADOL	UYKU DEPRESYON	10-25	150		3-7 GÜNDE 10-25 MG	1. BASAMAK TÜM NA TİPLERİ
VENLAFAKSİN	SNRI	KARDİYAK TRAMADOL HT	DEPRESYON ANKSİYETE	37.5	225	150	HAFTALIK 37,5 / 75	1. BASAMAK PERİFERİK
DULOKSETİN	SNRI	KC HAST. TRAMADOL HT	DEPRESYON ANKSİYETE	30	120	60	HAFTALIK 30	1. BASAMAK PERİFERİK
GABAPENTİN	VGCa	RENAL	İLAÇ ETKİLEŞİMİ ANKSİYETE UYKU	300	3 X 1200	1200	3-7 GÜNDE 300	1. BASAMAK TÜM NA TİPLERİ
PREGABALİN	VGCa	RENAL	İLAÇ ETKİLEŞİMİ ANKSİYETE UYKU	75	2 X 300	150	3-7 GÜNDE 75 - 150	1. BASAMAK TÜM NA TİPLERİ

İLAÇ	ETKİ	DİKKAT	NA +	DOZAJ		TİTRASYON	GRADE
				Başlangıç	Max.		
TRAMADOL	Mü Monoamin	BAĞIMLILIK İNTİHAR DEPRESYON	İnfl. HIZLI ETKİ	50	400	3-7 GÜNDE 50 - 100 MG	ZAYIF 2. BASAMAK
MORFİN	Mü Monoamin	BAĞIMLILIK İNTİHAR DEPRESYON	İnfl. HIZLI ETKİ	3 X 15			ZAYIF 3. BASAMAK
LİDOKAİN	Na	YOK	YAN ETKİ AZ	1 – 3			ZAYIF 2. BASAMAK
KAPSAİSİN	TRPV 1	YOK	YAN ETKİ AZ	1 - 4			ZAYIF 2. BASAMAK
BTX - A	Ach Rsptr	LOKAL	YAN ETKİ AZ			3 AYDA BİR	ZAYIF 3. BASAMAK

Antiepileptikler



- Karbamazepin (≤ 1800 mg)
- Okskarbazepin (≤ 2400 mg)
- Lamotrijin (≤ 400 mg)
- Gabapentin (≤ 3600 mg)
- Pregabalin (≤ 600 mg)

Karbamazepin

- Voltaj kapılı Na kanalı inaktivasyonunu artırır
- Eksitatör nörotransmiter salınımını azaltır
- Trigeminel Nevralji ++++
- Yan etkileri fazla

Okskarbazepin

- Karbamazepin analoğu, Voltaj kapılı Na kanalı inaktivasyonunu artırır,

  Eksitatör nörotransmiter salınımını azaltır

- N tipi Ca^{++} kanalları, Voltaj kapılı K kanalları
- Diayabetik nöropati, Postherpetik nevralji, Trigeminal Nevralji
- Yan etkileri daha az, yüksek tolarabilite

Gabapentinoidler

Pregabalin Biyoyaralanımı - %90

Farmakokinetik – Lineer

Kullanım 2x1

Atılım - % 98 böbrek

Gabapentin Biyoyaralanımı % 60

Farmakokinetik – Non-Lineer

Kullanım 3x1

Atılım - % 80 böbrek

Duloksetin

- 30 mg ----- 120 mg
- 1 x 1
- Karaciğer , Böbrek (eliminasyon)
- Çekilme semptomlarını yaşamamak için kademeli kesim
- Tramadol, MAO inhibitörleri, Antipisikotikler, İNH, Makrolitler ile birlikte kullanımından kaçınılmalı
- Antiagregan kullananlarda kanama riskini artırabilir

Kapsaisin

- TRPV reseptörlerini uyararak etki eder. Yüksek dozlarda (%8) desensitizasyon ve dejenerasyona yol açarak ağrı kesici etki gösterir
- 30 – 60 Dk
- 3 ayda bir uygulanabilir
- 1-5 gün buz ve analjezikler kullanılarak lokal yan etkileri önlenebilir
- Duysal nöronlardan substans P yi açığa çıkarıp tüketerek etkili

Lidokain

- Nonspesifik bir Na^+ Kanal blokeridir
- %5'lik flaster günde 1-3 kez, 3 hafta uygulanır
- Allerjik reaksiyon, lokal eritem …
- Lidokainin oral analoğu **meksiletinin** etkisi tartışmalı

Opioidler - Tramadol

- Sürekli ağrı ve allodinide etkili
- Orta derece etkinliğe sahip
- Tramadolün yan etkileri diğer opioidlere göre daha az ve dual etkili
- Bazı opioidlerin kontrollü salınımlı formları mevcut (2 x 1)

Botilinum Toksini

- Btx A
- SC
- 2.5 – 7.5 IU/cm^2 (max 200 IU)

Fabregat G. ark. Subcutaneous and perineural botulinum toxin type a for neuropathic pain: a descriptive review. Clin J Pain. 2013 Nov;29(11):1006-12.

İlaçları neye göre seçelim?

Hastaya,

Hastalığa,

Ülkenin koşullarına ve ilaca ulaşabilme imkanlarına

KLAVUZLARA

IASP 2007

Tanı , değerlendir, komorbiteleri

Mümkünse hastalığı tedavi et

Hastalığı tedavi edemiyorsan

1. Basamak ilaçları başla **TCA, SNRI, GBP/PGB**

Topikal ajan kullanmak gerekli ise **Lidokain**

Ağrıda azalma %30 dan az ise ilacı değiştir

Ağrıda azalma %30 dan fazla ise; ağrı <3/10 tedaviye devam

>4/10 2. ilacı ekle

2. Basamak tedavi **Tramadol , Opioidler**

Table 1 Stepwise Pharmacologic Management of Neuropathic Pain

Step 1
- Assess pain and establish the diagnosis of NP (Dworkin et al., 2003; Cruccu et al., 2004); if uncertain about the diagnosis, refer to a pain specialist or neurologist
- Establish and treat the cause of NP; if uncertain about availability of treatments addressing NP etiology, refer to appropriate specialist
- Identify relevant comorbidities (e.g., cardiac, renal, or hepatic disease, depression, gait instability) that might be relieved or exacerbated by NP treatment, or that might require dosage adjustment or additional monitoring of therapy
- Explain the diagnosis and treatment plan to the patient, and establish realistic expectations

Step 2
- Initiate therapy of the disease causing NP, if applicable
- Initiate symptom treatment with one or more of the following:
  - Antidepressant medication: either secondary amine TCA (nortriptyline, desipramine) or SSNRI (duloxetine, venlafaxine)
  - Calcium channel α_2-δ ligand: either gabapentin or pregabalin
  - For patients with localized peripheral NP: topical lidocaine used alone or in combination with 1 of the other first-line therapies
  - For patients with acute NP, neuropathic cancer pain, or episodic exacerbations of severe pain, and when prompt pain relief during titration of a first-line medication to an efficacious dosage is required, opioid analgesics or tramadol may be used alone or in combination with 1 of the first-line therapies
- Evaluate patient for nonpharmacologic treatments, and initiate if appropriate

Step 3
- Reassess pain and health-related quality of life frequently
- If substantial pain relief (e.g., average pain reduced to NRS $\leq$3/10) and tolerable side effects, continue treatment.
- If partial pain relief (e.g., average pain remains NRS $\geq$4/10) after an adequate trial (see Table 3), add 1 of the other first-line medications
- If no or inadequate pain relief (e.g., $<$30% reduction) at target dosage after an adequate trial (see Table 3), switch to an alternative first-line medication

Step 4
- If trials of first-line medications alone and in combination fail, consider second-line medications or referral to a pain specialist or multidisciplinary pain center

NP = neuropathic pain; NRS = numeric rating scale; SSNRI = selective serotonin and norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant.
Reprinted with permission from *Pain*.[13]

Treatment of Neuropathic Pain: An Overview of Recent Guidelines

Alec B. O'Connor, MD, MPH,[a] Robert H. Dworkin, PhD[b]

NICE 2013

Issued: November 2013

NICE clinical guideline 173
http://guidance.nice.org.uk/CG173

Neuropathic pain – pharmacological management

The pharmacological management of neuropathic pain in adults in non-specialist settings

NICE National Institute for Health and Care Excellence

Nöropatik ağrı:

Amitiriptilin, Duloksetin, GBP/PGB ile başla

Ağrı şiddetli, günlük yaşamı etkiliyor, nedeni net değil

Trigeminal Nevraljide CBZ yanıt yok ise Ağrı uzmanına yönlendir

Ağrı uzmanınca önerilmedikçe;

LTG, Kannabinoid, Kapsaisin, TPM, OXC, Venlafaksin başlama

NeuPSIG - 2015

NeuP SIG NEUROPATHIC PAIN

1. Basamak ilaçlar

TCA, SNRI, GBP/PGB, **GBP ER**

2. Basamak ilaçlar

Tramadol, Lidokain, Kapsaisin

3. Basamak ilaçlar

Güçlü Opioidler, **Btx A**

Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis

NeuPSIG of the International Association for the Study of Pain.

Lancet Neurol 2015; 162–73

Nanna B Finnerup, Nadine Attal*, Simon Haroutounian, Ewan McNicol, Ralf Baron, Robert H Dworkin, Ian Gilron, Maija Haanpää, Per Hansson, Troels S Jensen, Peter R Kamerman, Karen Lund, Andrew Moore, Srinivasa N Raja, Andrew S C Rice, Michael Rowbotham, Emily Sena, Philip Siddall, Blair H Smith, Mark Wallace*

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	Total daily dose and dose regimen	Recommendations
Strong recommendations for use		
Gapabentin	1200–3600 mg, in three divided doses	First line
Gabapentin extended release or enacarbil	1200–3600 mg, in two divided doses	First line
Pregabalin	300–600 mg, in two divided doses	First line
Serotonin-noradrenaline reuptake inhibitors duloxetine or venlafaxine*	60–120 mg, once a day (duloxetine); 150–225 mg, once a day (venlafaxine extended release)	First line
Tricyclic antidepressants	25–150 mg, once a day or in two divided doses	First line†
Weak recommendations for use		
Capsaicin 8% patches	One to four patches to the painful area for 30-60 min every 3 months	Second line (peripheral neuropathic pain)‡
Lidocaine patches	One to three patches to the region of pain once a day for up to 12 h	Second line (peripheral neuropathic pain)
Tramadol	200–400 mg, in two (tramadol extended release) or three divided doses	Second line
Botulinum toxin A (subcutaneously)	50–200 units to the painful area every 3 months	Third line; specialist use (peripheral neuropathic pain)
Strong opioids	Individual titration	Third line§

GRADE=Grading of Recommendations Assessment, Development, and Evaluation (see appendix for details about the GRADE classification). *Duloxetine is the most studied, and therefore recommended, of the serotonin-noradrenaline reuptake inhibitors. †Tricyclic antidepressants generally have similar efficacy (appendix); tertiary amine tricyclic antidepressants (amitriptyline, imipramine, and clomipramine) are not recommended at doses greater than 75 mg/day in adults aged 65 years and older because of major anticholinergic and sedative side-effects and potential risk of falls;[33] an increased risk of sudden cardiac death has been reported with tricyclic antidepressants at doses greater than 100 mg daily.[34] ‡The long-term safety of repeated applications of high-concentration capsaicin patches in patients has not been clearly established, particularly with respect to degeneration of epidermal nerve fibres, which might be a cause for concern in progressive neuropathy. §Sustained release oxycodone and morphine have been the most studied opioids (maximum doses of 120 mg/day and 240 mg/day, respectively, in clinical trials; appendix); long-term opioid use might be associated with abuse, particularly at high doses, cognitive impairment, and endocrine and immunological changes.[35–37]

European Journal of Neurology 2006, **13:** 1153–1169 doi:10.1111/j.1468-1331.2006.01511.x

EFNS TASK FORCE/CME ARTICLE

EFNS guidelines on pharmacological treatment of neuropathic pain

N. Attal[a,b], G. Cruccu[a,c], M. Haanpää[a,d], P. Hansson[a,e], T. S. Jensen[a,f], T. Nurmikko[g], C. Sampaio[h], S. Sindrup[i] and P. Wiffen[j]

European Journal of Neurology 2010, **17:** 1113–1123 doi:10.1111/j.1468-1331.2010.02999.x

EFNS GUIDELINES

EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision

N. Attal[a,b], G. Cruccu[a,c], R. Baron[a,d], M. Haanpää[a,e], P. Hansson[a,f], T. S. Jensen[a,g] and T. Nurmikko[a,h]

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Aetiology	Level A rating for efficacy	Level B rating for efficacy	Level C rating for efficacy	Level A/B rating for inefficacy or discrepant results	Recommendations for first line	Recommendations for second or third line
Diabetic NP[a]	Duloxetine Gabapentin-morphine TCA Gabapentin Nicotine agonist** Nitrate derivatives** Oxycodone Pregabalin TCA[b] Tramadol alone or with acetaminophen Venlafaxine ER	Botulinum toxin* Dextromethorphan Gabapentin/venlafaxine* Levodopa*	Carbamazepine Phenytoin	Capsaicin cream Lacosamide Lamotrigine Memantine Mexiletine Mianserin NK1 antagonist** Oxcarbazepine SSRI Topical clonidine Topiramate Valproate Zonisamide	Duloxetine Gabapentin Pregabalin TCA Venlafaxine ER	Opioids Tramadol[c]

European Journal of Neurology 2010, 17: 1113–1123 doi:10.1111/j.1468-1331.2010.02999.x

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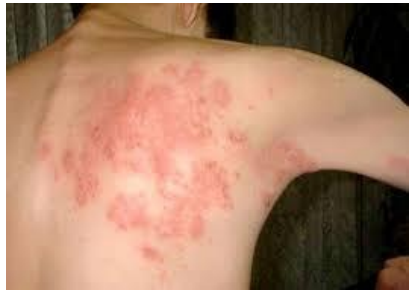
Aetiology	Level A rating for efficacy	Level B rating for efficacy	Level C rating for efficacy	Level A/B rating for inefficacy or discrepant results	Recommendations for first line	Recommendations for second or third line
PHN	Capsaicin 8% patch** Gabapentin Gabapentin ER** Lidocaine plasters Opioids (morphine, oxycodone, methadone) Pregabalin TCA[b]	Capsaicin cream Valproate*		Benzydamide topical Dextromethorphan Fluphenazine Memantine Lorazepam Mexiletine COX-2 inhibitor** Tramadol	Gabapentin Pregabalin TCA Lidocaine plasters[d]	Capsaicin Opioids



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Aetiology	Level A rating for efficacy	Level B rating for efficacy	Level C rating for efficacy	Level A/B rating for inefficacy or discrepant results	Recommendations for first line	Recommendations for second or third line
Classical trigeminal neuralgia	Carbamazepine	Oxcarbazepine	Baclofen* Lamotrigine* Pimozide* Tizanidine*		Carbamazepine Oxcarbazepine	Surgery
Central pain[e]	Cannabinoids (oro-mucosal **, oral) (MS) Pregabalin (SCI)	Lamotrigine (CPSP) TCA (SCI, CPSP) Tramadol (SCI)* Opioids		Carbamazepine Gabapentin Lamotrigine (SCI) Levetiracetam Mexiletine S-ketamine iont. Valproate	Gabapentin Pregabalin TCA	Cannabinoids (MS) Lamotrigine Opioids Tramadol (SCI)

Guidelines for the Pharmacological Treatment of Neuropathic Pain

Therapeutic Options		Notes
Peripheral neuropathy (e.g. postherpetic neuralgia (PHN), painful peripheral diabetic neuropathy) and central sensitisation pain syndromes (CRPS, CVPS, CWPS - see glossary on page 6 for definitions)		
First-line in localised peripheral neuropathic pain (e.g. PHN)	Topical lignocaine 5% patch (Versatis®)	• Use on area of pain and allodynia for 12 hours per day • Trial for 3 to 4 weeks, if no clinical benefit then cease • Ideal in elderly or frail due to few systemic side effects and interactions • Not covered by PBS and may be costly
First-line in all other conditions	Tricyclic antidepressants (TCAs): - amitriptyline - nortriptyline or - imipramine	• Start at low dose (5-10 mg) and increase slowly to optimise acceptability • Effective doses vary widely between 10 and 100 mg in individual patients • Slow onset of effect and should be trialed for at least 2 weeks (ideally 6-8 weeks) • Amitriptyline given at night is superior if sleep disturbance also needs treatment • Nortriptyline is less sedating and may have fewer adverse effects • TCAs have significant adverse effects including: dry mouth, constipation, sweating, dizziness, sedation, drowsiness, palpitation, orthostatic dysregulation and urinary retention • Use in elderly patients and those with cardiovascular risk factors should be avoided
	Serotonin/noradrenaline reuptake inhibitors (SNRIs): - duloxetine or - venlafaxine	• Start duloxetine at 30 mg daily, increase as tolerated to 60 mg (maximum 120 mg daily) • Start venlafaxine at 37.5 mg, increase as tolerated to 75 mg (maximum 225 mg daily) • Precaution in hepatic, renal and cardiac co-morbidity • Venlafaxine can cause withdrawal reactions with rapid discontinuation; titrate down carefully

Second-line	Alpha-2-delta subunit modulators: pregabalin or gabapentin	• Use is indicated if TCAs are contraindicated, not tolerated, ineffective or if a rapid onset of effect is needed in acute neuropathic pain states • Pregabalin is preferable to gabapentin due to more predictable dose-response relationship, twice daily dosing and ability to titrate quickly at comparable prices (and being PBS listed) • Starting dose for pregabalin is 75 mg bd, (25-50 mg in the elderly and frail), maximum dose 300 mg bd • Reduce dose in renal insufficiency
Third-line	Tramadol	• Start at 50 mg slow release twice daily; increase as needed and tolerated up to 400 mg/day • Rapid onset of effect • Precaution in seizure disorder and potential interaction with TCAs/SNRIs/SSRIs Contraindicated with MAOIs
	Tapentadol	• Start at 50 mg slow release twice daily; increase as needed and tolerated up to 500 mg/day • Rapid onset of effect • Less GI adverse effects (nausea and vomiting) than tramadol • Controlled medication (S8)

Fourth-line	Opioids (e.g. buprenorphine, oxycodone, morphine or methadone)	• Rapid onset of effect • Only fourth-line treatment in view of limited long-term data on efficacy and safety • Consider usual precautions with regard to prescribing long-term opioids (i.e. endocrine and immunological effects, risk of addiction, abuse and diversion)
Fifth-line	Sodium valproate	
	Sublingual ketamine	• Use in highly selected patients by pain medicine and palliative care specialists only • Currently not a registered drug, requires individual patient consent (see hospital protocol) • Limited data on safety with long-term use (i.e. cognitive or hepatic effect) • Consider risk of abuse and diversion
General comment: Combinations of gabapentin or pregabalin with opioids, antidepressants and lignocaine medicated plasters have been documented in clinical trials; these studies suggest that combination therapies maybe effective, enable dose reductions and/or reduce adverse effects.		

CONSENSUS STATEMENT

Pharmacological management of chronic neuropathic pain: Revised consensus statement from the Canadian Pain Society

DE Moulin MD, A Boulanger MD, AJ Clark MD, H Clarke MD PhD, T Dao DMD PhD, GA Finley MD, A Furlan MD PhD, I Gilron MD MSc, A Gordon MD, PK Morley-Forster MD, BJ Sessle MDS PhD, P Squire MD, J Stinson RN PhD, P Taenzer PhD, A Velly DDS PhD, MA Ware MD, EL Weinberg MD, OD Williamson MBBS

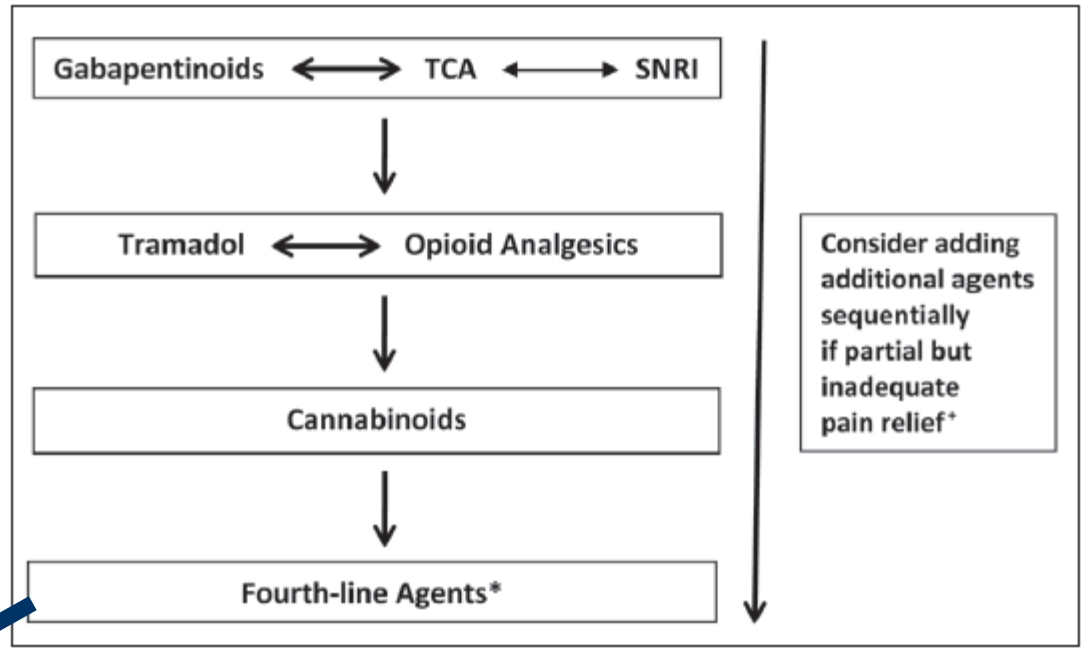


Figure 1) *Algorithm for the pharmacological management of neuropathic pain. *Topical lidocaine (second line for postherpetic neuralgia), methadone, lamotrigine, lacosamide, tapentadol, botulinum toxin; +Limited randomized controlled trial evidence to support add-on combination therapy. TCA Tricyclic antidepressants; SNRI Serotonin noradrenaline reuptake inhibitor*

SSRI
Lamotrijin Lokasomid
Metadon
Topikal lidokain
Tapentadol

Pain Res Manag Vol 19 No 6 November/December 2014

Pain Ther (2017) 6 (Suppl 1):S35–S42
DOI 10.1007/s40122-017-0087-0

REVIEW

A review of Neuropathic Pain: From Guidelines to Clinical Practice

Giorgio Cruccu · Andrea Truini

Table 1 Summary of recommendations for pharmacological management of neuropathic pain

	EFNS [7]				NICE [10]		CPS [2]		NeuPSIG [4]
	Diabetic neuropathy	Post-herpetic neuralgia	Trigeminal neuralgia	Central neuropathic pain	All neuropathic pain	Trigeminal neuralgia	All neuropathic pain	Trigeminal neuralgia	All neuropathic pain
First-line therapy	Duloxetine Gabapentin Pregabalin TCA Venlafaxine[d]	Gabapentin Pregabalin TCA Lidocaine plasters[a]	Carbamazepine Oxcarbazepine	Gabapentin Pregabalin TCA	Amitriptyline Duloxetine Gabapentin Pregabalin Capsaicin cream[b] (localized pain in patients who wish to avoid or who cannot tolerate oral treatments)	Carbamazepine	Gabapentin Pregabalin Duloxetine Venlafaxine[d] TCA	Carbamazepine	Gapabentin Gabapentin ER/ enacarbil Pregabalin Duloxetine Venlafaxine[d] TCAs
Second-line therapy	Tramadol	Strong opioids Capsaicin cream		Tramadol Strong opioids	One of the remaining 3 oral drugs of the First-line therapy		Tramadol Strong opioids Lidocaine cream[c] Lidocaine patches[c]		Capsaicin patches[b] Lidocaine patches[b] Tramadol

Pain Ther (2017) 6 (Suppl 1):S35–S42
DOI 10.1007/s40122-017-0087-0

REVIEW

A review of Neuropathic Pain: From Guidelines to Clinical Practice

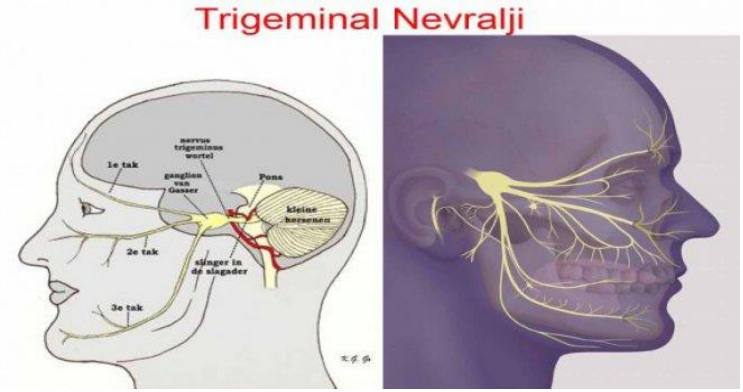
Giorgio Cruccu · Andrea Truini

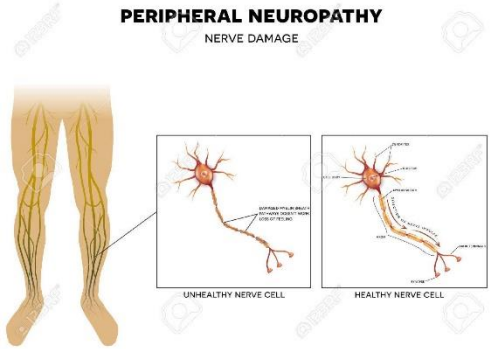
Table 1 continued

	EFNS [7]				NICE [10]		CPS [2]		NeuPSIG [4]
	Diabetic neuropathy	Post-herpetic neuralgia	Trigeminal neuralgia	Central neuropathic pain	All neuropathic pain	Trigeminal neuralgia	All neuropathic pain	Trigeminal neuralgia	All neuropathic pain
Third-line therapy	Strong opioids			Strong opioids	One of the remaining 3 oral drugs of the First-line therapy		Cannabinoids		Botulinum toxin type A Strong opioids
Fourth-line therapy				Lamotrigine (in central post-stroke pain) Cannabinoids (in multiple sclerosis)			Other opioids Lacosamide Lamotrigine Botulinum toxin Lidocaine cream Lidocaine patches		

CPS Canadian Pain Society, *EFNS* European Federation of Neurological Societies, *ER* extended release, *NeuPSIG* Neuropathic Pain Special Interest Group, *NICE* National Institute for Health and Care Excellence

[a] For use in the elderly; [b]for use in localized pain; [c]for use in post-herpetic neuralgia; [d]in most European countries, including Italy, venlafaxine is not approved for the indication of 'neuropathic pain', and therefore any such use should be considered off-label

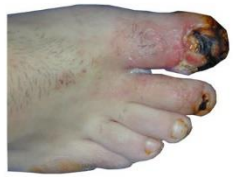


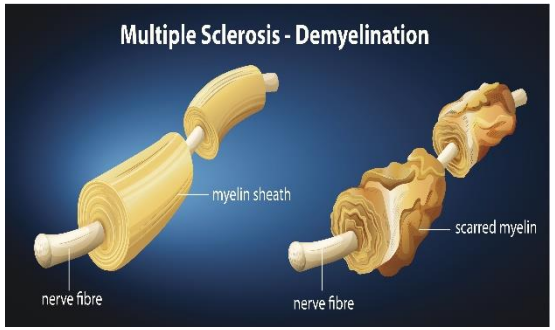


İLAÇLARIMIZI HASTALIĞA GÖRE NASIL VERELİM?

Diyabetik Nöropati

- Diabet, pankreasın yeterli miktarda insülin hormonu üretmemesi ya da ürettiği insülin hormonunun etkili bir şekilde kullanılamaması durumunda gelişen ve ömür boyu süren bir hastalıktır.





Periferik Nöropatik Ağrı (Trigeminal Nevralji Hariç): TSA, Gabapentinoidler

Ağrılı periferik nöropati : Duloksetin
Kapsaisin , Venlafaksin, Lidokain

PHN : Lidokain, Kapsaisin

Trigeminal Nevralji : CBZ /OXC, LTG, Baklofen, Gabapentinoidler, DPH...

Santral Nöropatik Ağrı: TSA, Gabapentinoidler
LTG, Duloksetin, Kannabinoidler (MS)

Ülkemizin koşullarına ve ilaca ulaşabilme imkanlarına

Topikal ajanlar ülkemizde yok (versatis, qutenza), fiyatları çok yüksek

Bazı ajanlar renkli reçete sistemine girdi

Bazı ajanlarla ilgili kötüye kullanım

Her ilacı her uzman yazamıyor

Alfa Lipoik Asit ?

Antioksidan mekanizmaları ve

bilinmeyen mekanizmalarla

Nöropatik süreçlerde etkili olduğu …

Nöropatik ağrıda etkisi ????

J Obstet Gynaecol Can 2017;39(3):131–137

Alpha Lipoic Acid Plus Omega-3 Fatty Acids for Vestibulodynia Associated With Painful Bladder Syndrome

Filippo Murina, MD;[1] Alessandra Graziottin, MD;[2] Raffaele Felice, MD;[1]
Dania Gambini, MD[2]

Journal of Brachial Plexus and Peripheral Nerve Injury 2009, **4**:22

Intraperitoneal Alpha-Lipoic Acid to prevent neural damage after crush injury to the rat sciatic nerve

Mehmet Senoglu*[1], Vedat Nacitarhan[2], Ergul Belge Kurutas[3],
Nimet Senoglu[4], Idris Altun[1], Yalcin Atli[3] and Davut Ozbag[5]

Acta Cirúrgica Brasileira - Vol. 30 (4) 2015 - 247

Does alfa lipoic acid prevent liver from methotrexate induced oxidative injury in rats?[1]

Tuğrul Çakır[I], Ahmet Baştürk[II], Cemal Polat[III], Arif Aslaner[IV], Himmet Durgut[V], Ahmet Özer Şehirli[VI], Mehmet Gül[VII], Ayliz Velioğlu Öğünç[VIII], Semir Gül[IX], Mehmet Zafer Sabuncuoglu[X], Mehmet Tahir Oruç[XI]

Vitamin verelim mi?

Eksiklik varsa - Evet

Kombine Preparat Kullanalım mı?

???????

Tedavimiz gerçekten etkili mi?

%30-40 azalma

Tedaviye başlamadan ağrı şiddeti mutlaka ölçülmeli

İlacı Keselim mi?

Nöropatik ağrıya neden olan hastalık ortadan kalktı mı?

Nöropatik Ağrı Tedavisinde Yeni Ufuklar ???

- **Mirogabalin** : The next pregabalin?

Special Populations

Pharmacokinetics and Safety of a Single Oral Dose of Mirogabalin in Japanese Subjects With Varying Degrees of Renal Impairment

The Journal of Clinical Pharmacology
2018, 58(1) 57–63

DOI: 10.1002/jcph.974

Manabu Kato, MSc[1], Naoyuki Tajima, PhD[1], Takako Shimizu, PhD[1], Masahiro Sugihara, PhD[2], Kenichi Furihata, MD, PhD[3], Kazuhiro Harada, MD, PhD[4], and Hitoshi Ishizuka, PhD[1]

Original Manuscript

A Randomized, Placebo-Controlled, Double-Blind Study of the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single and Repeated Doses of Mirogabalin in Healthy Asian Volunteers

Clinical Pharmacology in Drug Development
2018, 00(0) 1–9

DOI: 10.1002/cpdd.448

Mendel Jansen[1,*], Steven Warrington[2], Victor Dishy[3,*], Shoichi Ohwada[4], Lisa Johnson[1,*], Karen Brown[3,*], and Hitoshi Ishizuka[4]

Binding characteristics and analgesic effects of mirogabalin, a novel ligand for the $\alpha_2\delta$ subunit of voltage-gated calcium channels

Yuki Domon, Naohisa Arakawa, Tatsuya Inoue, Fumihiko Matsuda, Makoto Takahashi, Naotoshi Yamamura, Kiyonori Kai, Yutaka Kitano

Pharmacometrics

Exposure–Response Modeling of Average Daily Pain Score, and Dizziness and Somnolence, for Mirogabalin (DS-5565) in Patients With Diabetic Peripheral Neuropathic Pain

The Journal of Clinical Pharmacology
2016, 56(1) 67–77

DOI: 10.1002/jcph.567

Matthew M. Hutmacher, MS[1], Bill Frame, BS[2], Raymond Miller, DSc[3], Kenneth Truitt, MD[3], and Domenico Merante, MD[4]

Nöropatik Ağrı Tedavisinde Yeni Ufuklar ???

- (Uzun etkili) **Gabapentin ER**

JOURNAL OF DERMATOLOGICAL TREATMENT, 2017
VOL. 28, NO. 1, 65–77
http://dx.doi.org/10.3109/09546634.2016.1163315

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

Different doses of gabapentin formulations for postherpetic neuralgia: A systematical review and meta-analysis of randomized controlled trials

Juan Wang[a]* and Yuyou Zhu[b]*

[a]Department of Dermatology, the Affiliated Provincial Hospital of Anhui Medical University, Hefei, China; [b]Department of Neurology, the Affiliated Provincial Hospital of Anhui Medical University, Hefei, China

Assessment of Pain Quality in a Clinical Trial of Gabapentin Extended Release for Postherpetic Neuralgia

Mark P. Jensen, PhD, Yu-Kun Chiang, PhD,† and Jacqueline Wu, PhD‡*

Clin J Pain • Volume 25, Number 4, May 2009

ORIGINAL RESEARCH ARTICLE

Clin Drug Investig 2010; 30 (11): 765-776
1173-2563/10/0011-0765/$49.95/0

Gabapentin Extended-Release Tablets for the Treatment of Patients with Postherpetic Neuralgia

A Randomized, Double-Blind, Placebo-Controlled, Multicentre Study

Mark S. Wallace,[1] Gordon Irving[2] and Verne E. Cowles[3]

Clin Drug Investig. 2012 Sep 1;32(9):593-601. doi: 10.2165/11634520-000000000-00000.

Steady-state pharmacokinetics of gabapentin after administration of a novel gastroretentive extended-release formulation in postmenopausal women with vasomotor symptoms.

Cowles VE[1], Gordi T, Hou SY

Nöropatik Ağrı Tedavisinde Yeni Ufuklar ???

- Transient receptor potential vanilloid 1 **(TRPV1) antagonistleri**

Contents lists available at ScienceDirect

Journal of Pharmacological Sciences

journal homepage: www.elsevier.com/locate/jphs

Full paper

Vincristine-induced peripheral neuropathic pain and expression of transient receptor potential vanilloid 1 in rat

Terumasa Chiba [a], Yusuke Oka [b], Hiroya Sashida [c], Toshie Kanbe [d], Kenji Abe [a], Iku Utsunomiya [e], Kyoji Taguchi [f, *]

Clin Drug Investig (2015) 35:353–363
DOI 10.1007/s40261-015-0285-7

ORIGINAL RESEARCH ARTICLE

Safety, Tolerability and Pharmacokinetic and Pharmacodynamic Learnings from a Double-Blind, Randomized, Placebo-Controlled, Sequential Group First-in-Human Study of the TRPV1 Antagonist, JNJ-38893777, in Healthy Men

Prasarn Manitpisitkul[1] · Arthur Mayorga[1] · Kevin Shalayda[1] · Marc De Meulder[2] · Gary Romano[1] · Chen Jun[1] · John A. Moyer[1]

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

TRPV1 receptor inhibition decreases CCL2-induced hyperalgesia

Diana Spicarova, Pavel Adamek, Nataliia Kalynovska, Petra Mrozkova, Jiri Palecek*

Department of Functional Morphology, Institute of Physiology vvi, Academy of Sciences of the Czech Republic, Videnska 1083, 142 20 Prague 4, Czech Republic

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Blocking PAR2 attenuates oxaliplatin-induced neuropathic pain via TRPV1 and releases of substance P and CGRP in superficial dorsal horn of spinal cord

Kun Chen, Zhi-Fa Zhang, Ming-Feng Liao, Wen-Long Yao, Juan Wang, Xue-Ren Wang *

Nöropatik Ağrı Tedavisinde Yeni Ufuklar ???

❑ NMDA receptor antagonistleri

JOURNAL OF PAIN & PALLIATIVE CARE PHARMACOTHERAPY
2016, VOL. 30, NO. 4, 276–283
http://dx.doi.org/10.1080/15360288.2016.1241334

Taylor & Francis
Taylor & Francis Group

REPORT

Memantine for the Treatment of Phantom Limb Pain: A Systematic Review

Brittany M. Loy, Rachel B. Britt, and Jamie N. Brown

Delage et al. Trials (2017) 18:517
DOI 10.1186/s13063-017-2254-3

Trials

STUDY PROTOCOL Open Access

Effect of ketamine combined with magnesium sulfate in neuropathic pain patients (KETAPAIN): study protocol for a randomized controlled trial

Noémie Delage[1], Véronique Morel[2*], Pascale Picard[1], Fabienne Marcaillou[1], Bruno Pereira[3] and Gisèle Pickering[2,4]

KJP The Korean Journal of Pain | Original Article |

Korean J Pain 2015 April; Vol. 28, No. 2: 96-104
pISSN 2005-9159 eISSN 2093-0569
http://dx.doi.org/10.3344/kjp.2015.28.2.96

Anti-allodynic Efficacy of NMDA Antagonist Peptide and Noradrenaline Alone and in Combination in Rodent Neuropathic Pain Model

Physiology Research Center, Department of Physiology, Iran University of Medical Sciences, Tehran, *Department of Physiology, Ilam University of Medical Sciences, Ilam, Iran

Farinaz Nasirinezhad, Marjan Hosseini, and Sajad Salari*

Clin J Pain • Volume 34, Number 5, May 2018

A Systematic Review of NMDA Receptor Antagonists for Treatment of Neuropathic Pain in Clinical Practice

Rohit Aiyer, MD, Neel Mehta, MD,† Semih Gungor, MD,‡ and Amitabh Gulati, MD§*

act on the NMDARs. This systematic review will investigate the following 8 NMDA receptors antagonists and their role in treatment of NeuP: MEM, methadone, phenytoin, AMAN, CBZ, KET, phenytoin, and VPA. Consequently,

Contents lists available at ScienceDirect

Brain Research

journal homepage: www.elsevier.com/locate/bres

ELSEVIER

Research report

Inhibition of the NMDA and AMPA receptor channels by antidepressants and antipsychotics

CrossMark

Oleg I. Barygin *, Elina I. Nagaeva, Denis B. Tikhonov, Darya A. Belinskaya, Nina P. Vanchakova [1], Natalia N. Shestakova

Nöropatik Ağrı Tedavisinde Yeni Ufuklar ???

- Nerve growth factor **(NGF) antagonists**

0022-3565/07/3221-282–287$20.00
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
Copyright © 2007 by The American Society for Pharmacology and Experimental Therapeutics
JPET 322:282–287, 2007
Vol. 322, No. 1
116236/3219807
Printed in U.S.A.

Antibodies to Nerve Growth Factor Reverse Established Tactile Allodynia in Rodent Models of Neuropathic Pain without Tolerance

Kenneth D. Wild, Di Bian,[1] Dawn Zhu, James Davis, Anthony W. Bannon,[2] Tie J. Zhang, and Jean-Claude Louis

Drugs (2014) 74:619–626
DOI 10.1007/s40265-014-0208-6

CURRENT OPINION

Targeting Nerve Growth Factor (NGF) for Pain Management: What Does the Future Hold for NGF Antagonists?

Bernard Bannwarth · Marie Kostine

frontiers in Molecular Neuroscience
ORIGINAL RESEARCH
published: 21 November 2017
doi: 10.3389/fnmol.2017.00389

Attenuation of the Infiltration of Angiotensin II Expressing CD3+ T-Cells and the Modulation of Nerve Growth Factor in Lumbar Dorsal Root Ganglia – A Possible Mechanism Underpinning Analgesia Produced by EMA300, An Angiotensin II Type 2 (AT_2) Receptor Antagonist

Nemat Khan[1], Arjun Muralidharan[1] and Maree T. Smith[1,2]*

Drugs (2017) 77:1377–1387
DOI 10.1007/s40265-017-0781-6

CrossMark

CURRENT OPINION

Nerve Growth Factor Antagonists: Is the Future of Monoclonal Antibodies Becoming Clearer?

Bernard Bannwarth[1,2] · Marie Kostine[1]

Nerve growth factor induces facial heat hyperalgesia and plays a role in trigeminal neuropathic pain in rats

Renata C. dos Reis, Caroline M. Kopruszinski, Carina F.M. Nones and Juliana G. Chichorro

Behavioural Pharmacology 2016, **27**:528–535

Nöropatik Ağrı Tedavisinde Yeni Ufuklar ???

- **Cannabis** (multiple sklerozda sadece Kanada ve birkaç avrupa ülkesinde izinlidir)

Cochrane Library
Cochrane Database of Systematic Reviews

Cannabis-based medicines for chronic neuropathic pain in adults (Review)

Mücke M, Phillips T, Radbruch L, Petzke F, Häuser W

Eur Rev Med Pharmacol Sci. 2018 Feb;22(4):1161-1167. doi: 10.26355/eurrev_201802_14405.

Medical use of cannabis: Italian and European legislation.

Zaami S[1], Di Luca A, Di Luca NM, Montanari Vergallo G.

Current Pain and Headache Reports (2018) 22: 8
https://doi.org/10.1007/s11916-018-0658-8

NEUROPATHIC PAIN (E EISENBERG, SECTION EDITOR)

Medical Cannabis for Neuropathic Pain

Gemayel Lee[1] · Brittany Grovey[1] · Tim Furnish[1] · Mark Wallace[1]

Journal of Pain Research 2016:9 735–744

Medical cannabis – the Canadian perspective

Gordon D Ko

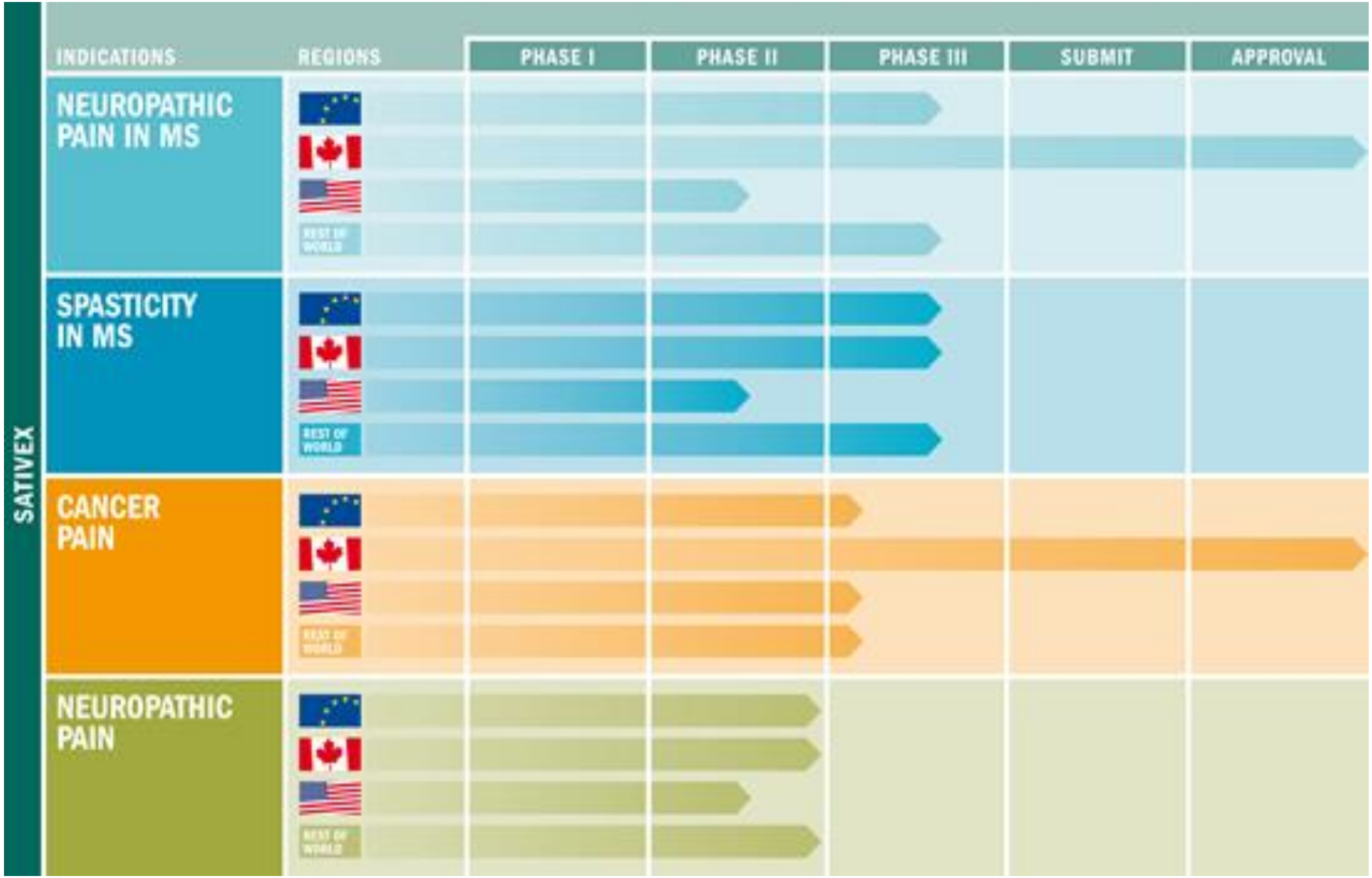
PLOS ONE | DOI:10.1371/journal.pone.0155113 May 12, 2016

The Role of Medicinal Cannabis in Clinical Therapy: Pharmacists' Perspectives

Sami Isaac, Bandana Saini, Betty B. Chaar*

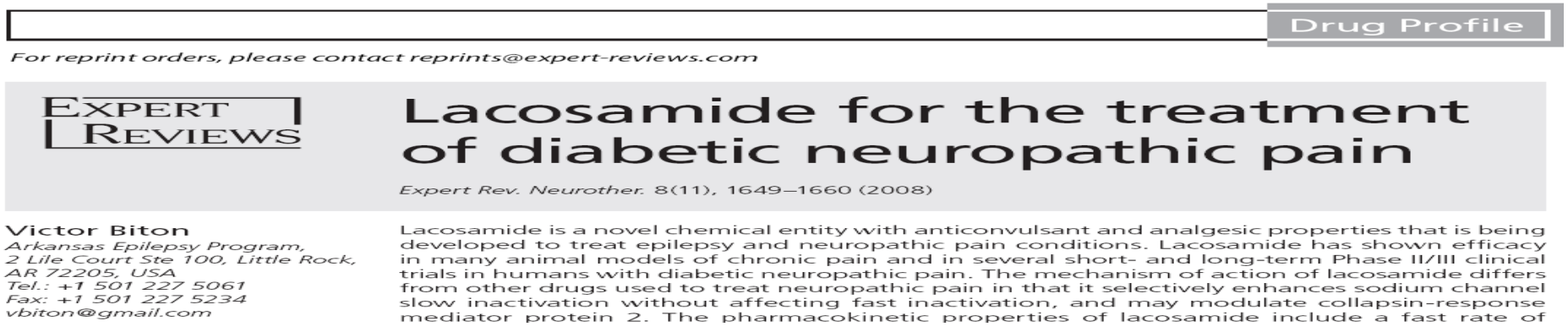
Cannabinoid Buccal Spray for Chronic Non-Cancer or Neuropathic Pain: A Review of Clinical Effectiveness, Safety, and Guidelines

21 September 2016


SATIVEX
INDICATIONS
REGIONS
PHASE I
PHASE II
PHASE III
SUBMIT
APPROVAL
NEUROPATHIC PAIN IN MS
SPASTICITY IN MS
CANCER PAIN
NEUROPATHIC PAIN
REST OF WORLD

Nöropatik Ağrı Tedavisinde Yeni Ufuklar ???

- **Lacosamid**, 2008 Ekim'de FDA tarafından parsiyel epilepsi vakalarında kullanım için onay almış
- İn vitro çalışmalarda voltaj kapılı sodyum kanalları üzerinden etkili olduğu bildirilmiştir



Drug Profile

EXPERT REVIEWS

Lacosamide for the treatment of diabetic neuropathic pain

Expert Rev. Neurother. 8(11), 1649–1660 (2008)

Victor Biton
Arkansas Epilepsy Program,
2 Lile Court Ste 100, Little Rock,
AR 72205, USA
Tel.: +1 501 227 5061
Fax: +1 501 227 5234
vbiton@gmail.com

Lacosamide is a novel chemical entity with anticonvulsant and analgesic properties that is being developed to treat epilepsy and neuropathic pain conditions. Lacosamide has shown efficacy in many animal models of chronic pain and in several short- and long-term Phase II/III clinical trials in humans with diabetic neuropathic pain. The mechanism of action of lacosamide differs from other drugs used to treat neuropathic pain in that it selectively enhances sodium channel slow inactivation without affecting fast inactivation, and may modulate collapsin-response mediator protein 2. The pharmacokinetic properties of lacosamide include a fast rate of

Nöropatik Ağrı Tedavisinde Yeni Ufuklar ???

- **Orfenadrin** ; Daha önce bu molekülün Histaminerjik, Muskarinik ve NMDA reseptörleri üzerindeki etkinliği gösterilmiş

Bazı çalışmalar da da Nav1.8 ve Nav1.9 kanallarını da bloke ettiği gösterilmiş

Aminoamid derivesi olup, etki mekanizması nedeniyle umut vaat eden bir ilaç

Rat DRG 'da hem Sodyum kanallarına (Nav 1.8 ve Nav 1.7) hemde kalsiyum (Cav 2.2) inhibe eden bir molekül olduğu bildirilmiştir

PAIN 142 (2009) 225–235

PAIN

www.elsevier.com/locate/pain

Involvement of voltage-gated sodium channels blockade in the analgesic effects of orphenadrine

Jean-François Desaphy [a,*,1], Antonella Dipalma [a,1], Michela De Bellis [a], Teresa Costanza [a], Christelle Gaudioso [b], Patrick Delmas [b], Alfred L. George Jr. [c], Diana Conte Camerino [a]

[a] Sezione di Farmacologia, Dipartimento FarmacoBiologico, Facoltà di Farmacia, Università di Bari, Bari, Italy
[b] CRN2M, CNRS UMR 6231, Université de la Méditerranée, CS80011.Bd Pierre Dramard, 13344 Marseille Cedex 15, France
[c] Division of Genetic Medicine, Department of Medicine, Vanderbilt University, 529 Light Hall, Nashville, TN 37232-0275, USA

ARTICLE INFO

Article history:
Received 7 July 2008
Received in revised form 18 December 2008
Accepted 9 January 2009

ABSTRACT

Orphenadrine is a drug acting on multiple targets, including muscarinic, histaminic, and NMDA receptors. It is used in the treatment of Parkinson's disease and in musculoskeletal disorders. It is also used as an analgesic, although its mechanism of action is still unknown. Both physiological and pharmacological results have demonstrated a critical role for voltage-gated sodium channels in many types of chronic pain

Nöropatik Ağrı Tedavisinde Yeni Ufuklar ???

- Spinal cord N-type Ca $^{2+}$ kanal blokajı yapan intratekal tedavi **ziconotide**

(Deniz salyangozu biyotoksini) ZİKONOTİD, nöropatik ağrı yaşayan hastaları kapsayan Faz III çalışmalarda intratekal uygulamayı takiben etkinlik göstermiştir

Ancak, bazı hastalarda zikonotid kullanımı anlamlı yan etkilerle ilişkili bulunmuştur

Neurol Ther (2015) 4:159–168
DOI 10.1007/s40120-015-0035-z

CrossMark

CASE SERIES

Intrathecal Ziconotide and Morphine for Pain Relief: A Case Series of Eight Patients with Refractory Cancer Pain, Including Five Cases of Neuropathic Pain

Ana Bella de la Calle Gil · Isaac Peña Vergara · María Auxiliadora Cormane Bornacelly · Antonio Pajuelo Gallego

Nöropatik Ağrı Tedavisinde Yeni Ufuklar ???

Nöropatik ağrıda yeni tedaviler geliştirilmesinde hedefler

- Glial hücreler
- Sitokinler
- Kemokin reseptörleri

Nöronal hasarı takiben, mikroglia ve astrositlerin ATP, glutamat, Substans P ve fraktalkin gibi nöronal sinyaller tarafından aktivasyonu, proinflamatuar sitokinlerin (IL-1, IL-6, TNF-α), kemokinlerin (monosit kemoatraktan protein 1, kemokin CCL5) üretimine yol açar

Nöropatik Ağrı Tedavisinde Yeni Ufuklar ???

- Nöropatik ağrıda rutinde kullandığımız ilaçlar aktive olmuş glial hücreler tarafından salınan, nöronal hipereksitabilitenin yaratılmasından sorumlu olabilen proenflamatuvar sitokinleri değil, nosiseptif bilgileri ileten nöronlar üzerinden etkili olduğundan allodini ve hiperaljeziyi tedavi etmeleri yetersizdir

Nöropatik Ağrı Tedavisinde Yeni Ufuklar ???

- **Minosiklin** Bir mikroglial aktivasyon inhibitörü, antimikrobiyel etkilerinden bağımsız olan antienflamatuvar etkilere sahiptir ve glial hücrelere dayalı allodini ve hiperaljezinin kontrolü için bir potansiyele sahiptir

Iran J Basic Med Sci, Vol. 21, No. 2, Feb 2018

Minocycline through attenuation of oxidative stress and inflammatory response reduces the neuropathic pain in a rat model of chronic constriction injury

Abolfazl Abbaszadeh [1], Saeideh Darabi [2, 3], Amin Hasanvand [2, 3*], Hossein Amini-khoei [4], Amir Abbasnezhad [5], Razieh Choghakhori [5], Asghar Aaliehpour [6]

C. Yang et al. / Biomedicine & Pharmacotherapy 94 (2017) 380–385

Minocycline attenuates the development of diabetic neuropathy by inhibiting spinal cord Notch signaling in rat

Nöropatik Ağrı Tedavisinde Yeni Ufuklar ???

Kemotaktik sitokin= KEMOKİN

- Kemokinler, mikroglialara bağlanıp aktive ederek nöropatik ağrıya yol açar.
- Periferik sinir zedelenmesinden sonra nöron ile glial hücreler arasındaki iletişimde kritik bir rol oynar
- **Kemokinleri nötralize eden antikorlar allodini ve hiperaljeziyi geçirebilirler!!!!!**

- **MAPK** (Mitogen-Activated Protein Kinases) aktivasyonunu önleyen yenilikçi terapötik ajanların nöropatik ağrı tedavisinde etkili olacağı düşünülmektedir. Hayvan modeli çalışmaları MAPK yolunun inhibisyonunun nöropatik ağrıda azalmaya yolaçtığını göstermiştir
- **MAPK** ailesi sadece nöronlarda değil nonnöronal hücelerde de bulunur ve **blokajları mikroglial aktivasyonu bloke eder**

MAP kinase and pain BRAIN RESEARCH REVIEWS 60 (2009) 135–148

Ru-Rong Ji[a,], Robert W. Gereau IV [b], Marzia Malcangio[c], Gary R. Strichartz[a]*

Nöropatik Ağrı Tedavisinde Yeni Ufuklar ???

- Kronik nöropatik ağrıda merkezi adenozine A1 reseptör uyarımının ağrıyı dindirici etkisi gözlenmiştir
- Adenozin eklenmesi, allodiniyi ve hiperaljeziyi azaltmaktadır

Neuroscience 338 (2016) 1–18

ADENOSINE RECEPTOR TARGETS FOR PAIN☆

J. SAWYNOK *

Department of Pharmacology, Dalhousie University, Halifax, Nova Scotia B3H 4R2, Canada

PAIN Publish Ahead of Print
DOI: 10.1097/j.pain.0000000000001246

Title: Downregulation of adenosine and adenosine 1 receptor contributes to neuropathic pain in resiniferatoxin neuropathy

Hung-Wei Kan[a#], Chin-Hong Chang[b#], Chih-Lung Lin[c,d], Yi-Chen Lee[e,f], Sung-Tsang Hsieh[a,g,h], Yu-Lin Hsieh[e,f,*]

EXPERT OPINION ON THERAPEUTIC PATENTS, 2017
VOL. 27, NO. 8, 967
https://doi.org/10.1080/13543776.2017.1341018

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LETTER TO THE EDITOR

Highly selective A3 adenosine receptor agonists relieve chronic neuropathic pain

Daniela Salvemini[a] and Kenneth A. Jacobson [b]

Nöropatik Ağrı Tedavisinde Yeni Ufuklar ???

- Şu an mevcut olan ilaçlar nöropatik ağrının oluşması ve yayılmasının altında yatan çoklu kompleks mekanizmaları çoğunlukla hedeflemediğinden, yeni arayışlar ağrı için hücre ve gen tedavileri gibi yeni moleküler yöntemlere yönelmektedir

- Son Hedef ise kişiselleştirilmiş ilaçlar geliştirerek nöropatik ağrı tedavisidir


TEŞEKKÜRLER


TEŞEKKÜRLER

Ağrı

Vücudun belirli bir bölgesinden kaynaklanan, doku hasarına bağlı olan veya olmayan, kişinin geçmişteki deneyimleri ile ilgili, hoş olmayan, emosyonel ve sensoryal bir duyum ve Davranış şeklidir

IASP "International Association for the Study of Pain, 1979"

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		

From *Lancet Neurol*,[3] with permission.

Mayo Clin Proc. 2015 Apr;90(4):532-545.Neuropathic Pain: Principles of Diagnosis and Treatment. Gilron I et al

Nöropatik ağrı tedavisinde kullanılan ilaçlar (EFNS 2010 rev)

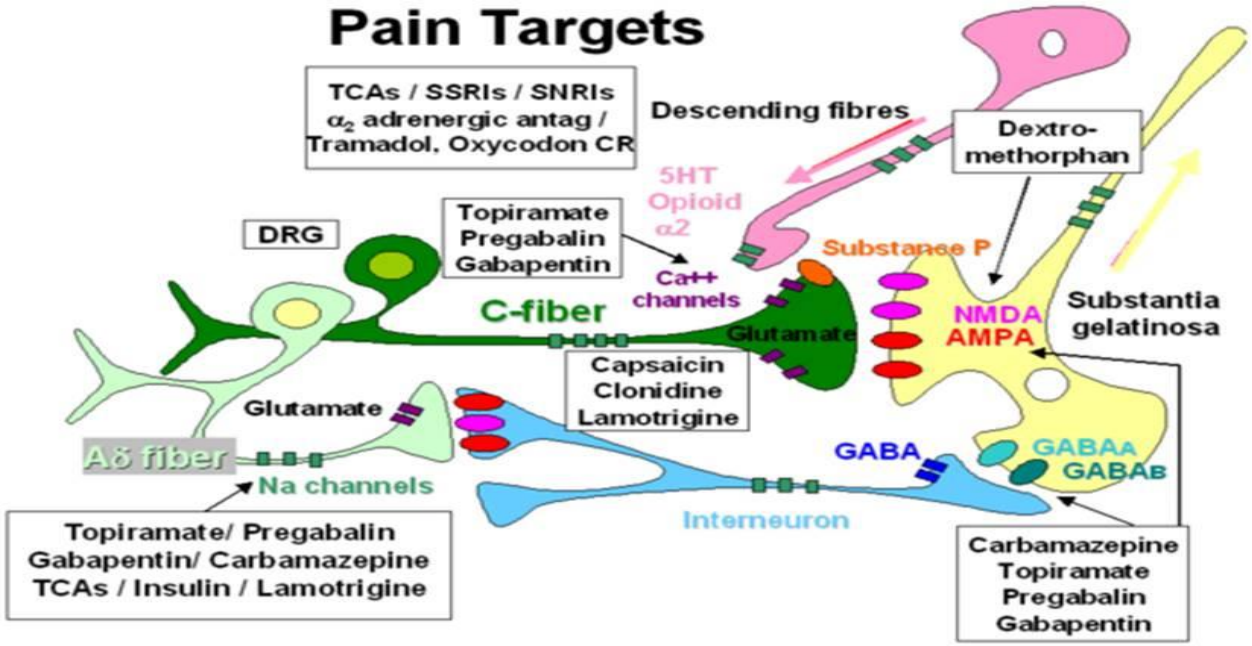
Gabapentin (1200-3600mg/g)

Pregabalin (150-600mg/g)

TCA (25-150mg/g

Duloksetin (60-120mg/g)

Venlafaksin (150-225mg/g)



TN ve PHN hariç birçok ağrılı nöropatilerde ilk seçenek olabilir

Nöropatik Ağrıda Medikal Tedavi

Santral sensitizasyon

Ca^{+} — PGB, GBP

Desandan modülasyon

TCAs, SNRI — NA, SHT

Periferik sensitizasyon

Karbamazepin, Lamotrigin, Lidokain — Na^{+}

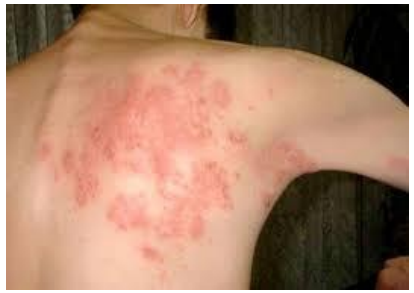
Kapsaisin — TRPV

European Journal of Neurology 2010, 17: 1113–1123 doi:10.1111/j.1468-1331.2010.02999.x

EFNS GUIDELINES

EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision

N. Attal[a,b], G. Cruccu[a,c], R. Baron[a,d], M. Haanpää[a,e], P. Hansson[a,f], T. S. Jensen[a,g] and T. Nurmikko[a,h]

Aetiology	Level A rating for efficacy	Level B rating for efficacy	Level C rating for efficacy	Level A/B rating for inefficacy or discrepant results	Recommendations for first line	Recommendations for second or third line
Diabetic NP[a]	Duloxetine Gabapentin-morphine TCA Gabapentin Nicotine agonist** Nitrate derivatives** Oxycodone Pregabalin TCA[b] Tramadol alone or with acetaminophen Venlafaxine ER	Botulinum toxin* Dextromethorphan Gabapentin/venlafaxine* Levodopa* 	Carbamazepine Phenytoin	Capsaicin cream Lacosamide Lamotrigine Memantine Mexiletine Mianserin NK1 antagonist** Oxcarbazepine SSRI Topical clonidine Topiramate Valproate Zonisamide	Duloxetine Gabapentin Pregabalin TCA Venlafaxine ER	Opioids Tramadol[c]
PHN	Capsaicin 8% patch** Gabapentin Gabapentin ER** Lidocaine plasters Opioids (morphine, oxycodone, methadone) Pregabalin TCA[b]	Capsaicin cream Valproate* 		Benzydamide topical Dextromethorphan Fluphenazine Memantine Lorazepam Mexiletine COX-2 inhibitor** Tramadol	Gabapentin Pregabalin TCA Lidocaine plasters[d]	Capsaicin Opioids

European Journal of Neurology 2010, 17: 1113–1123 doi:10.1111/j.1468-1331.2010.02999.x

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Classical trigeminal neuralgia	Carbamazepine	Oxcarbazepine	Baclofen* Lamotrigine* Pimozide* Tizanidine*	Carbamazepine Oxcarbazepine	Surgery
Central pain[e]	Cannabinoids (oro-mucosal **, oral) (MS) Pregabalin (SCI)	Lamotrigine (CPSP) TCA (SCI, CPSP) Tramadol (SCI)* Opioids	Carbamazepine Gabapentin Lamotrigine (SCI) Levetiracetam Mexiletine S-ketamine iont. Valproate	Gabapentin Pregabalin TCA	Cannabinoids (MS) Lamotrigine Opioids Tramadol (SCI)

[a]Diabetic neuropathy was the most studied. Only TCA, tramadol and venlafaxine were studied in non-diabetic neuropathies. [b]Amitriptyline, clomipramine (diabetic neuropathy), nortriptyline, desipramine, imipramine. [c]Tramadol may be considered first line in patients with acute exacerbations of pain especially for the tramadol/acetaminophen combination. [d]Lidocaine is recommended in elderly patients (see section 2). [e]Cannabinoids (positive effects in MS) and lamotrigine (positive effects in CPSP but negative results in MS and SCI except in patients with incomplete lesion and brush-induced allodynia in one study based on post hoc analysis) are proposed for refractory cases. iont., iontophoresis; CPSP, central post-stroke pain; ER, extended release; MS, multiple sclerosis; PHN, post-herpetic neuralgia; SCI, spinal cord injury; TCA, tricyclic antidepressants; SSRI, Selective serotonin reuptake inhibitor.

European Journal of Neurology 2010, 17: 1113–1123 doi:10.1111/j.1468-1331.2010.02999.x

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Table 2 Classification of evidence for drug treatments in less commonly studied neuropathic pain (NP) conditions. Treatments are presented in alphabetical order. Drugs marked with an asterisk were found effective in single class II studies

Aetiology of NP	Level A rating for efficacy	Level B rating for efficacy	Level A/B rating for inefficacy/poor efficacy or discrepant results
HIV neuropathy	Capsaicin 8% patch Smoked cannabis	Lamotrigine	Amitriptyline Capsaicin cream Gabapentin Lidocaine plasters Memantine
Post-traumatic or post-surgical NP		Amitriptyline* Botulinum toxin-A*	Cannabinoids Capsaicin Gabapentin Levetiracetam Propranolol Venlafaxine ER
Chronic radiculo-pathy			Morphine* Nortriptyline* Nortriptyline-morphine * Pregabalin (unpublished) Topiramate
Cancer NP	Gabapentin	Amitriptyline* Tramadol*	Valproate

European Journal of Neurology 2010, **17:** 1113–1123 doi:10.1111/j.1468-1331.2010.02999.x

EFNS GUIDELINES

EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision

N. Attal[a,b], G. Cruccu[a,c], R. Baron[a,d], M. Haanpää[a,e], P. Hansson[a,f], T. S. Jensen[a,g] and T. Nurmikko[a,h]

		Tramadol	
Phantom pain	Morphine Tramadol		Amitriptyline Gabapentin Memantine Mexiletine
Multi-aetiology NP	Bupropion Cannabinoids (oromucosal, synthetic analogue) Levorphanol	Methadone TCA (nortriptyline, clomipramine)	Amitriptyline/ketamine topical CCK2 antagonists Dextromethorphan Dihydrocodeine Gabapentin[a] Venlafaxine ER[a] Lidocaine plasters Lamotrigine Lidocaine plasters Mexiletine[a] Nabilone Riluzole

[a]These drugs were found effective in some spontaneous NP symptoms (gabapentin) or only on brush-induced or static mechanical allodynia (mexiletine, venlafaxine) in single trials. ER, extended release; TCA, tricyclic antidepressants.

Trigeminal neuralgia		
First-line	Carbamazepine	• Should be started at low dose and titrated according to effect/adverse effects in a range of 200-1200 mg • Has several adverse effects, but is highly effective • Enzyme inducer; may interact with other drugs
Second-line	Procedural pain management, neurosurgery or radiosurgery (gamma knife)	
Third-line (if surgery is contraindicated)	Pregabalin/gabapentin	• Baclofen may be used as add-on therapy with carbamazepine • For each medication, commence at a low dose twice daily and increase every 3 days according to effect/adverse effects
	Baclofen	
	Clonazepam	

Spinal cord injury (SCI) pain at and below lesion	
First-line	Alpha-2-delta subunit modulators (see notes above): - pregabalin or gabapentin
Second-line	TCAs (possibly combined with first line treatment)
	Tramadol/tapentadol (possibly combined with first-line treatment) Baclofen (if associated with muscle spasms)

Central post-stroke pain (CPSP)	
First-line	TCAs
	Alpha-2-delta subunit modulators (see notes above): - pregabalin or gabapentin
Second-line	Lamotrigine

Acute neuropathic pain conditions requiring parenteral treatment (Acute SCI, acute plexus injury, Guillain-Barré Syndrome, severe CRPS)		
First-line	IV/SC ketamine	• Use initial bolus titration in 5 mg steps to effect or adverse effects • Maintain effect by continuous IV or SC infusion at an average rate of 0.1 mg/kg/hr • Adverse effects are rare at these rates and special monitoring is not required (see local protocol) • If rare psychomimetic adverse events are experienced by patient the addition of low dose midazolam may be effective
Second-line	IV lignocaine	• Use initial slow bolus of 1-1.5 mg/kg • Maintain effect by infusion of 1-2 mg/minute

Phantom limb pain		
First-line	IV/SC calcitonin	• Use 100 IU daily as SC injection or IV infusion (in 100 mL saline over 1 hr) • Give metoclopramide 20mg prior as prophylactic anti-emetic • Repeat daily for at least 3 days
Second-line	All other neuropathic pain treatment options including tramadol, tapentadol or opioids	
General comments: Calcitonin may also be considered by specialist Pain Medicine Services in selected cases of CRPS, CVPS and CWPS (and pain caused by vertebral body fractures)		

DIAGNOSIS	TREATMENTS BASED ON RANDOMIZED TRIALS WITH POSITIVE RESULTS	CLINICAL TRIALS WITH NEGATIVE RESULTS
Post-herpetic neuralgia (PHN)	Nortriptyline Gabapentin, pregabalin Oxycodone Lidocaine—topical High-concentration capsaicin patch	Carbamazepine
Painful diabetic neuropathy (PDN)	Gabapentin, pregabalin Duloxetine Amitriptyline, nortriptyline Divalproex Oxycodone Tramadol	
Trigeminal neuralgia (TN)	Carbamazepine Lamotrigine	
Central post-stroke pain (CPSP)	Nortriptyline	Carbamazepine
HIV polyneuropathy	Lamotrigine Smoked cannabis	Mexiletine
Pain after spinal cord injury, including pain in MS patients	Amitriptyline Lamotrigine Cannabis	Divalproex

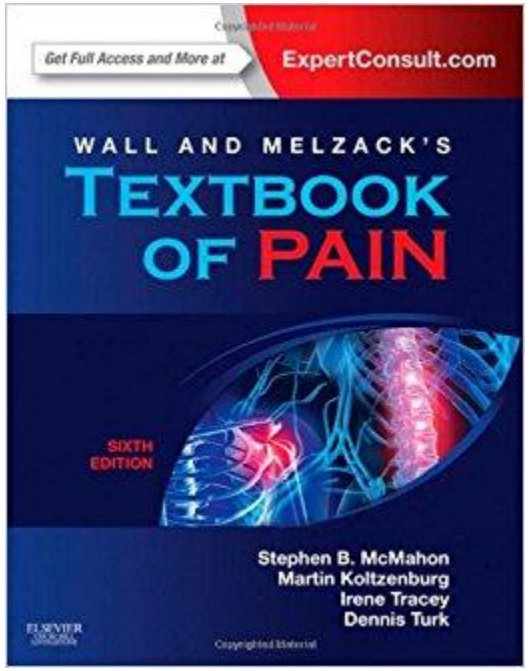


TABLE 1
Dosing regimens for selected agents for neuropathic pain

Agent	Starting dose and titration	Usual maintenance dose	Adverse effects	Comments
Tricyclic antidepressants				
Amitriptyline Nortriptyline Desipramine	10–25 mg/day; increase weekly by 10 mg/day	10–100 mg/day	Drowsiness, confusion, orthostatic hypotension, dry mouth, constipation, urinary retention, weight gain, arrhythmia	Amitriptyline more likely to produce drowsiness and anticholinergic side effects; contraindicated in patients with glaucoma, symptomatic prostatism and significant cardiovascular disease
Serotonin noradrenaline reuptake inhibitors				
Venlafaxine	37.5 mg/day; increase weekly by 37.5 mg/day	150–225 mg/day	Nausea, dizziness, drowsiness, hyperhidrosis, hypertension	Dosage adjustments required in renal failure
Duloxetine	30 mg/day; increase weekly by 30 mg/day	60–120 mg/day	Sedation, nausea, constipation, ataxia, dry mouth	Contraindicated in patients with glaucoma
Anticonvulsants				
Gabapentin	100–300 mg/day; increase weekly by 100–300 mg/day	300–1200 mg three times daily	Drowsiness, dizziness, peripheral edema, visual blurring	Dosage adjustments required in renal failure and in elderly patients
Pregabalin	25–150 mg/day; increase weekly by 25–150 mg/day	150–300 mg twice daily	Drowsiness, dizziness, peripheral edema, visual blurring	Similar adjustments in renal failure
Carbamazepine	100 mg once daily; increase weekly by 100–200 mg/day	200–400 mg three times daily	Drowsiness, dizziness, blurred vision, ataxia, headache, nausea, rash	Drug of first choice for tic douloureux (idiopathic trigeminal neuralgia); as an enzyme inducer, may interfere with activity of other drugs such as warfarin; monitoring of blood counts and liver function tests recommended

Controlled-release opioid analgesics				
Morphine	15 mg every 12 h	30–120 mg every 12 h	Nausea, vomiting, sedation, dizziness, urinary retention, constipation	Constipation requires concurrent bowel regimen; monitor for addiction
Oxycodone	10 mg every 12 h	20–60 mg every 12 h		
Fentanyl	12–25 µg/h patch	25–100 µg/h patch		
Hydromorphone	3 mg every 12h	6–24 mg every 12 h		
Others				
Tramadol	50 mg/day; increase weekly by 50 mg/day	50–100 mg four times daily or 100–400 mg daily (controlled release)	Ataxia, sedation, constipation, seizures, orthostatic hypotension	May lower seizure threshold; use with caution in patients with epilepsy
Lidocaine		5% patches or gel applied to painful areas for 12 h in a 24 h period		Most useful for postherpetic neuralgia; has virtually no systemic side effects; lidocaine patches not available in Canada
Tetrahydro-cannabinol/ cannabidiol (nabiximols)	1–2 sprays every 4 h, maximum 4 sprays on day 1, titrate slowly	Two sprays four times daily	Dizziness, fatigue, nausea, euphoria	Approved in Canada for neuropathic pain associated with multiple sclerosis; causes positive urine drug testing for cannabinoids; monitor application site (oral mucosa)
Nabilone	0.25–0.5 mg at night; increase weekly by 0.5 mg/day	3 mg twice daily	Dizziness, drowsiness, dry mouth	Approved in Canada for nausea and vomiting associated with chemotherapy. Does not test positive for cannabinoids on routine urine drug testing

Etyolojiye göre nöropatik ağrı tedavisinde farklı öneriler

- **2011 AAN'in diyabetik PNP** için A düzeyi kanıtta olan tek ilaç pregabalindir

- Yaygın vücut ağrısı ile seyreden **fibromyalji sendromunda** da 1. sınıf ilaçlar; pregabalin, duloksetin, milnasipran ve amitriptilin olarak geçmektedir

- **Radiküler ağrıda** multidisipliner yaklaşılmalı, akutta NSAİİ, nöropatik komponentli subakut ve kronik formda gabapentin/pregabalin ve antidepresan grup verilir. Gerekirse opioidler verilebilir

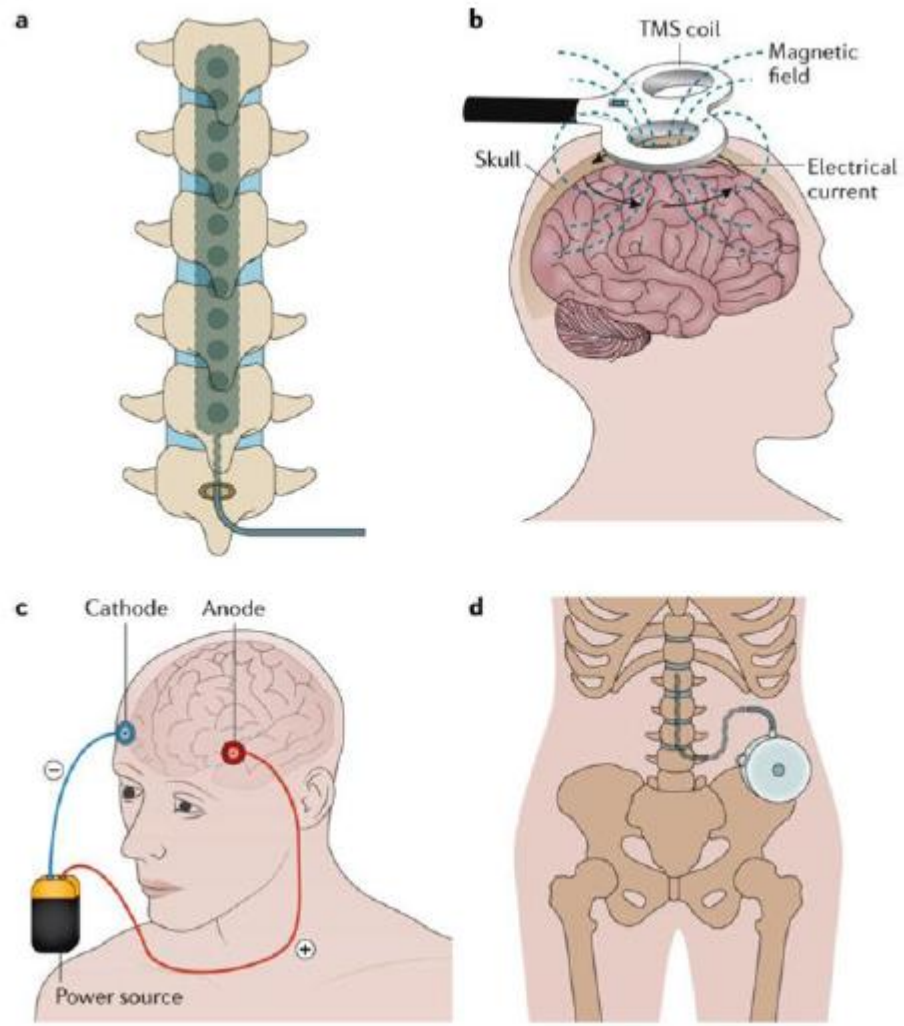
Nöropatik ağrıda girişimsel tedaviler (Colloca et all)

A- SCS (spinal kord stimulatörü)

B- TMS (transkranial manyetik stimülasyon)

C- DBS (derin beyin stimülasyonu)

D-İntratekal pompa sistemleri

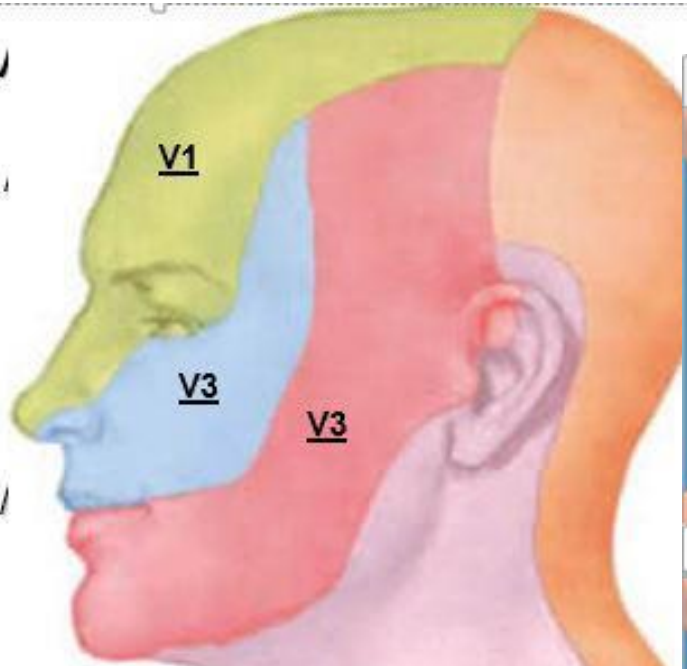


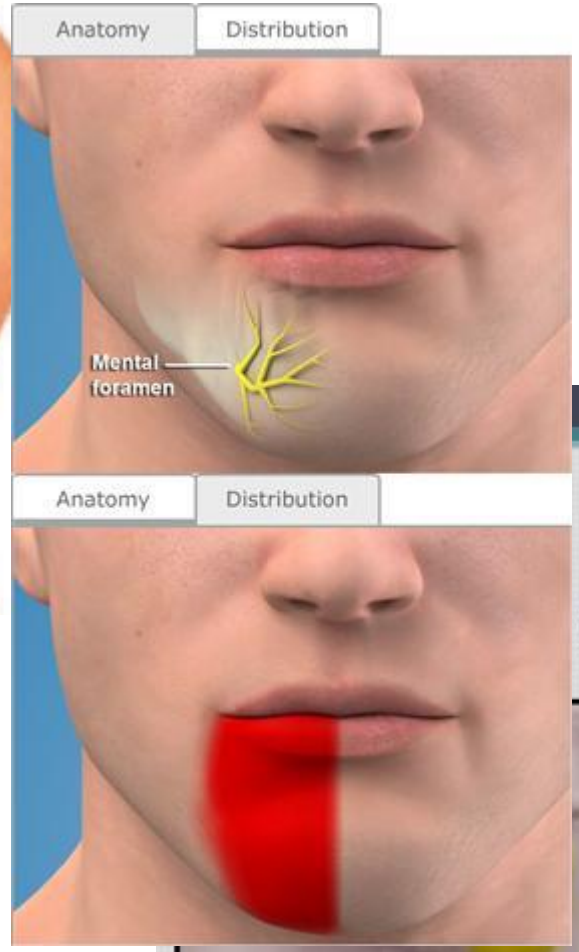

Y
B
K
D
E
yanma
batma
kanıncalanma
donma
elektrik çarpması

Trigeminal Nerve /CN V

Branches:

1. Ophthalmic Division / Nerve (V1)
2. Maxillary Division / Nerve(V2)
2. Mandibular Division / Nerve(V3)





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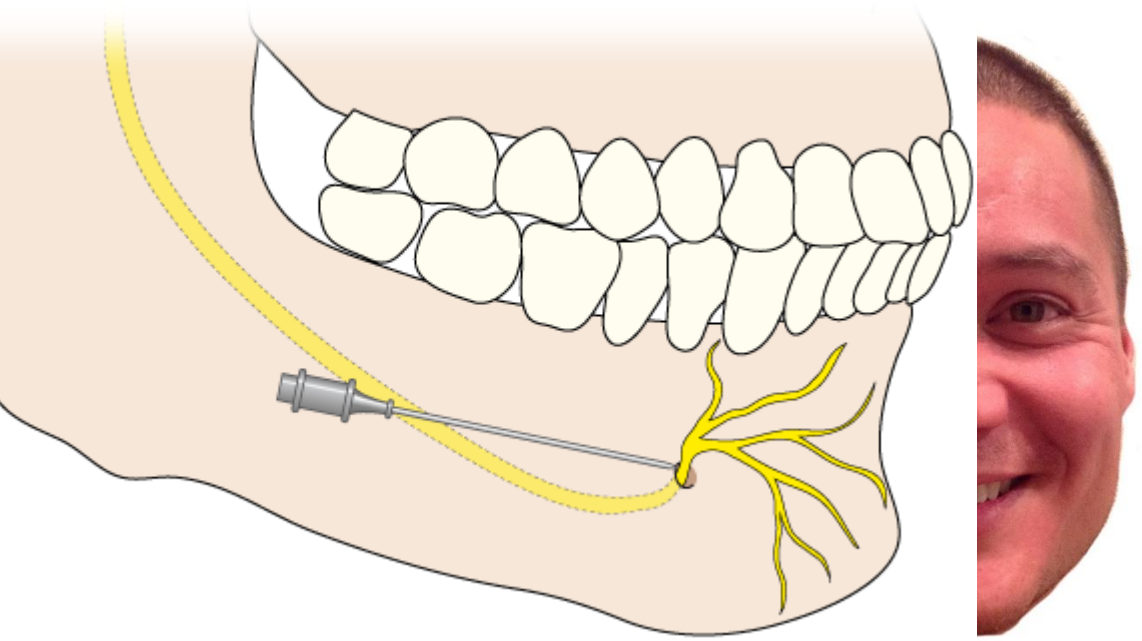

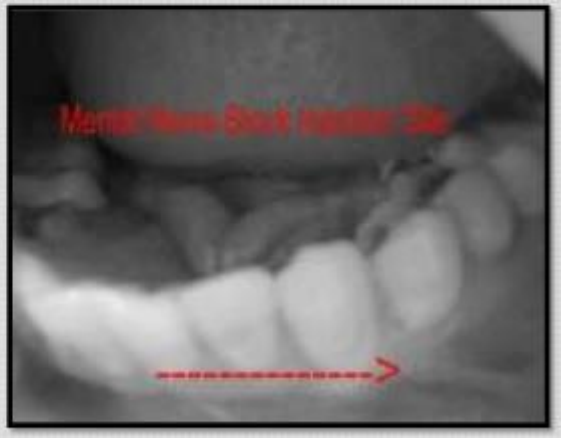

Nöropatik ağrı Avrupa'da genel populasyonda: %8-9

(Torrance N,et al 2006, Bouhassira D, 2008)

Türkiye-TURDEP (1995) verisi:

Diyabet prevalansı:%7.2

Glukoz intoleransı: %6.7

Diyabetik nöropati: Diyabetlilerde ~%50