Sunu Akışı

- Genel bilgiler
- Tedavi seçenekleri
- Patogeneze yönelik tedaviler
- Kanıta dayalı tıpta alfa-lipoik asid tedavisinin yeri
- Son sözler..

Diyabetik nöropati

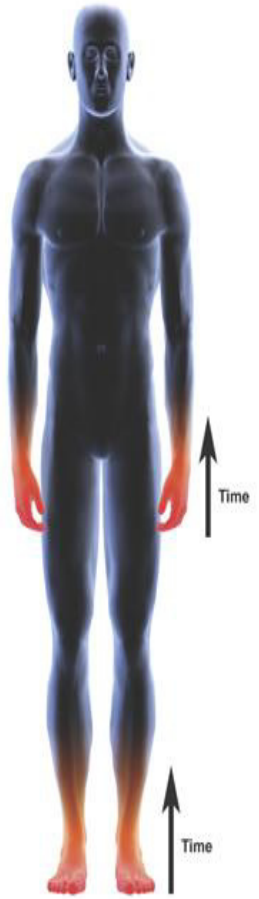
- Genel olarak:

Diyabetli hastalarda periferik sinir sisteminde oluşan yapısal ve fonksiyonel bozukluklar

diğer etiyolojik faktörler ekarte edilmek koşulu ile Diyabetik Nöropati olarak tanımlanmaktadır.

Diyabetik nöropati

- Periferal sinir sistemin yanında
  otonom SS ve
  MSS'de etkilenmek·
- Morbidite ve mortalitesi yüksek,
- Yaşam kalitesini olumsuz yönde etkilemekte



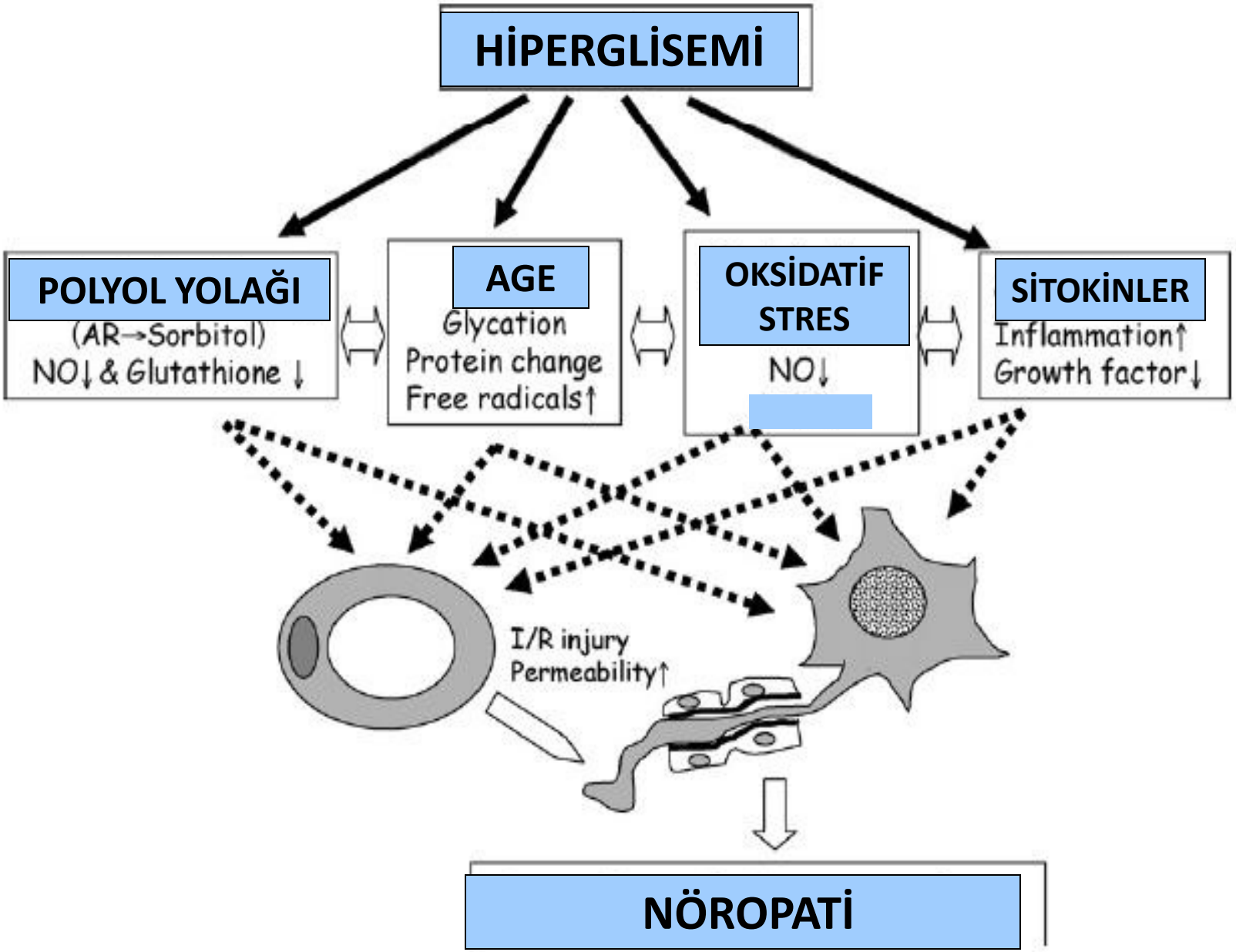
Pain 2010:149:338-334

Subklinik DNP

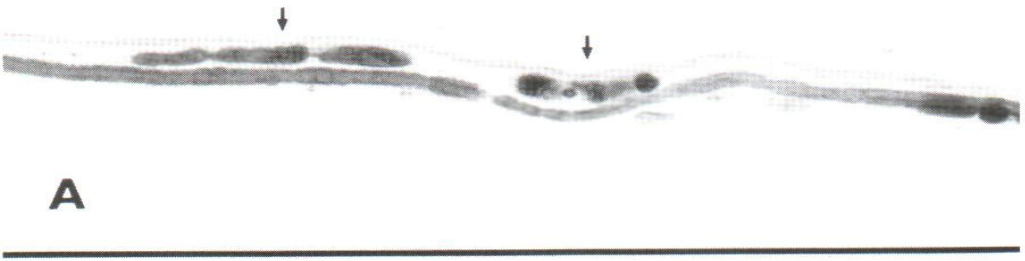
- **Anormal elektrofizyolojik testler**
  - Sinir ileti hızında azalma
  - Uyarılmış kas veya sinir aksiyon potansiyellerinin amplitüdünde azalma
- **Anormal kantitatif duyusal testler**
  - Vibrasyon/dokunma
  - Termal ısıtma/soğutma
  - Diğer
- **Anormal otonom fonksiyon testleri**
  - Kalp hızı değişkenliği
  - Sudomotor disfonksiyon
  - Pupil latansında artma

Klinik DNP

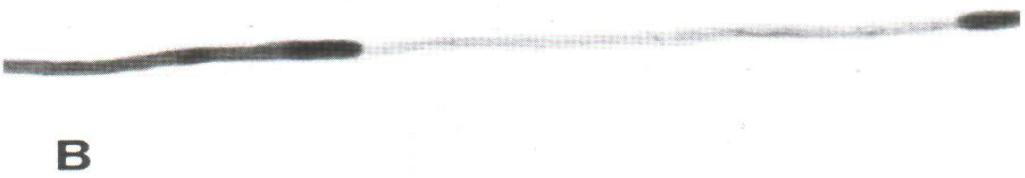
- Difüz Nöropati
  - Distal simetrik sensörimotor PNP
    - Küçük lif
    - Büyük lif
    - Mikst
- Fokal Nöropati
  - Mononöropati (üst ve alt ekstremite)
  - Mononöritis multipleks
  - Pleksopati
  - Poliradikülopati
  - Kraniyal mononöropati
- Otonom Nöropati
  - Anormal pupil fonksiyonu
  - Sudomotor disfonksiyon
  - Genitoüriner otonom nöropati
    - Mesane disfonksiyonu
    - Seksüel disfonksiyon
  - Gastrointestinal otonom nöropati
    - Gastrik atoni
    - Safra kesesi atonisi
    - Diyabetik diyare
  - Kardiyovasküler otonom nöropati
  - Hipoglisemiyi farkedememe



Adapted from Yasigashi et al. Diab Res Clin Pract 2007

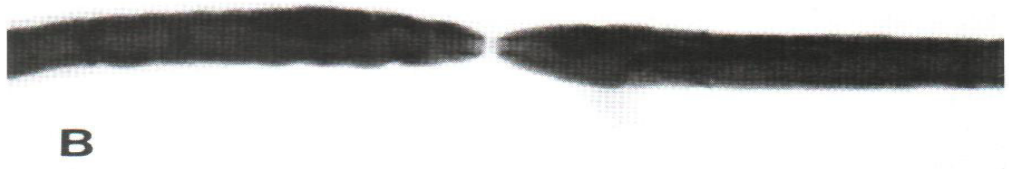


Wallerian Degenerasyonu:
Sinir liflerinde kabarma,bozulma ve myelin yumrularının oluşması



İleri düzeyde myelin kaybı,
Segmental demiyelinizasyon

Paranodal demiyelinizasyon:
Kabarmış myelin kılıfı
Bütünlüğü bozulmuş Ranvier nodu

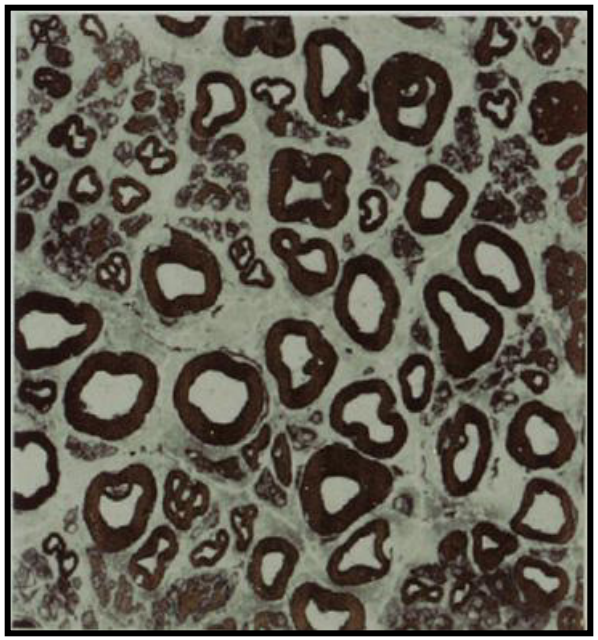


Normal Ranvier nodu

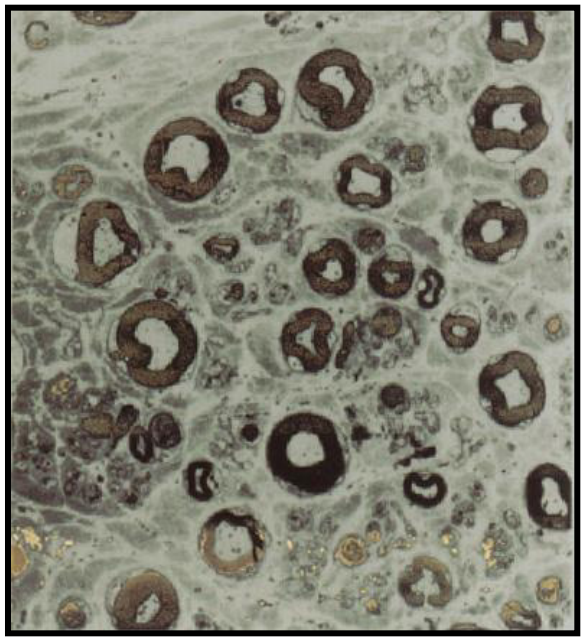
Textbook of Diabetic Neuropathy' den uyarlanmıştır

Sural Sinir Morfolojisi

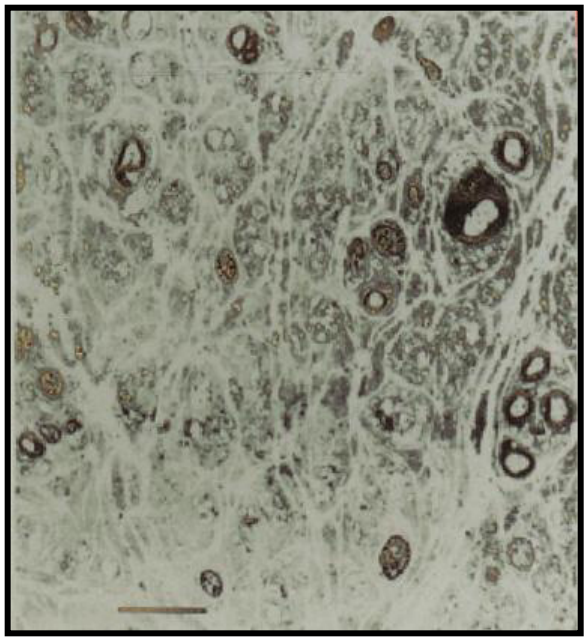
Non-diabetik



Hafif diabetik PNP



İlerlemiş diabetik PNP



SYDNEY Study Group

NeuroDiab 2001

Epidemiyoloji

- DNP Batı toplumlarında en sık nöropati nedeni
- Tanı için seçilen yöntem ve kriterlere bağlı olarak klinik ve subklinik DNP prevalansı **%10-90** arası bildirilmekte
- Hastaların **en az yarısında** seyir sırasında DNP gelişir

Prevalence of Peripheral Neuropathy and Painful Peripheral Neuropathy in Turkish Diabetic Patients

Tomris Erbas, Mustafa Ertas,† Aysen Yucel,‡ Abdulkadir Keskinaslan,§ Mustafa Senocak,‖ and TURNEP Study Group*

TURNEP Çalışması

- 14 üniversite hastanesi, 1113 hasta
- Klinik DPNP **%40.4**
- Elektrofizyolojik çalışma ile ---- **%62.2**
- Ağrılı nöropati **%16** --- LANSS

J Clin Neurophysiol, 2011

Diabetik Nöropatide Semptomlar

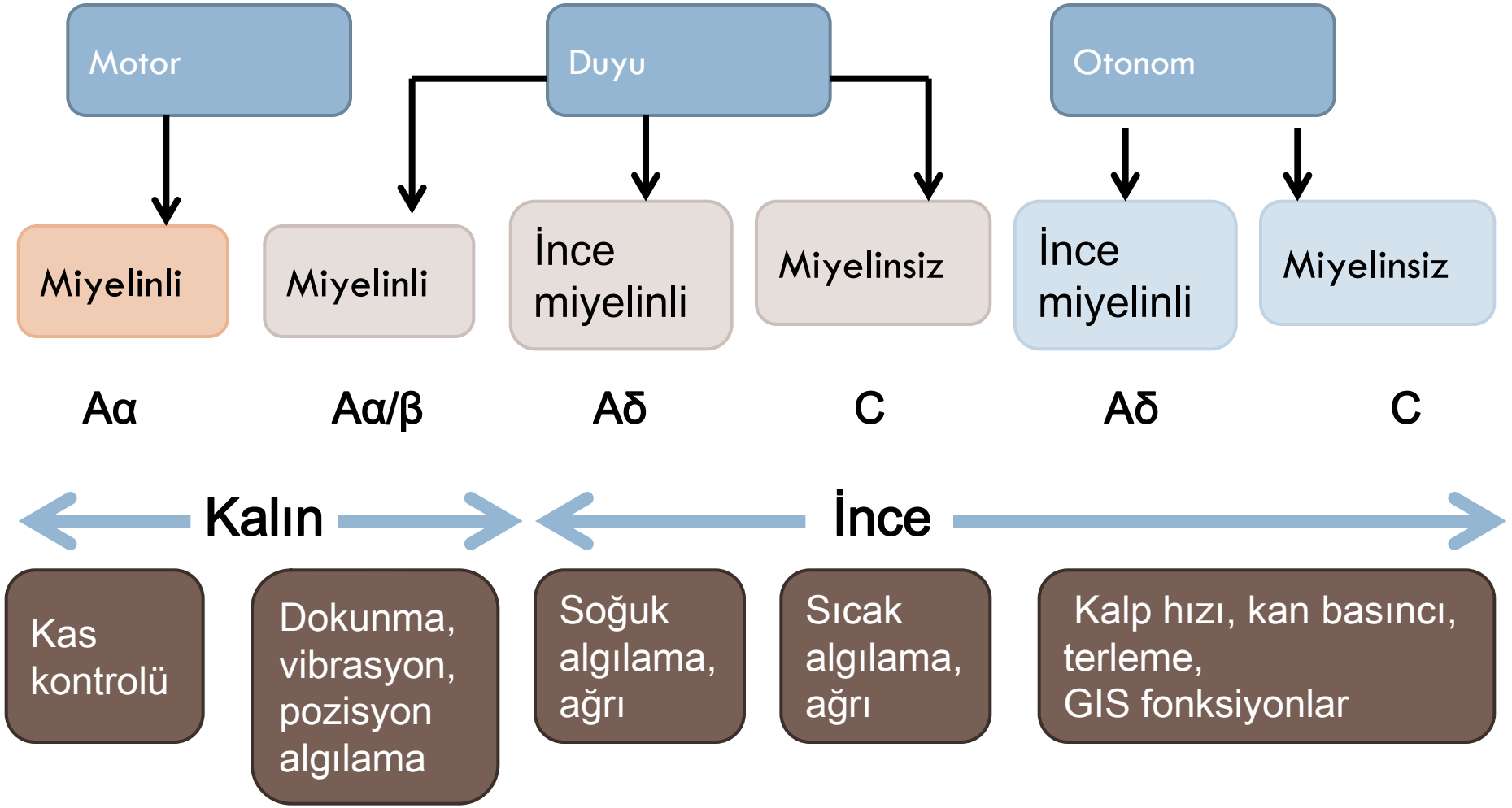
- **“Pozitif” Semptomlar:**

  Sürekli yanıcı veya künt ağrı
  Paroksismal patlayıcı, batıcı ağrı
  Dizesteziler
  Uyarılmış ağrı (hiperaljezi, allodini)
  Uyuşukluk

- **“Negatif” Semptomlar (Defisitler):**

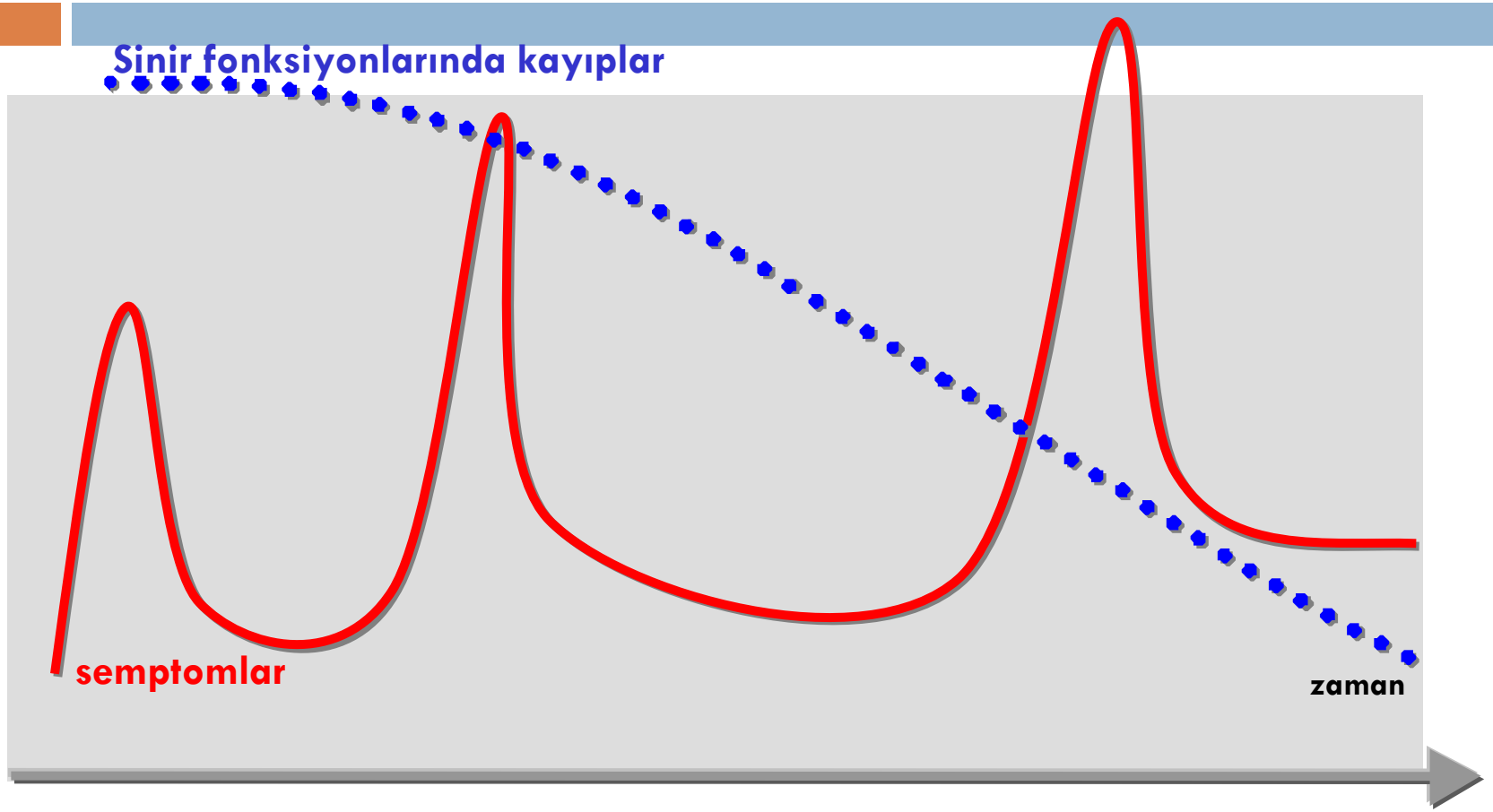
  Hipoaljezi, analjezi
  Hipoestezi, anestezi
  Termal, vibrasyon, basınç duyumu, refleksler ↓

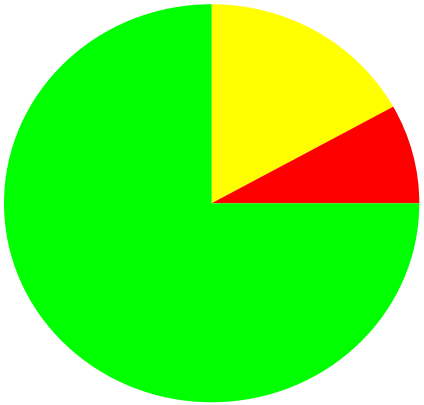
Farklılığın nedenini



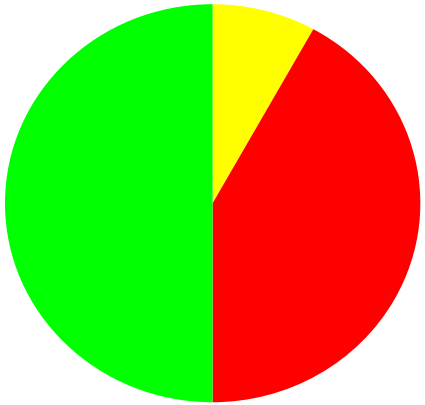
Feldman ve ark, Textbook of Diabetic Neuropathy, 2002

Diabetik Nöropatinin Kliniği:

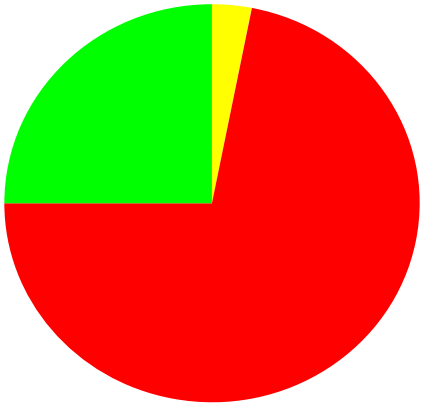




75% Normal Fonksiyon



50% Normal Fonksiyon



25% Normal Fonksiyon

Diyabetin süresi

Geri dönüşümsüz

Geri dönüşümlü

Normal

Modified after Pfeifer & Schumer, Diabetes, 1995

Distal simetrik polinöropatinin klinik sonuçları

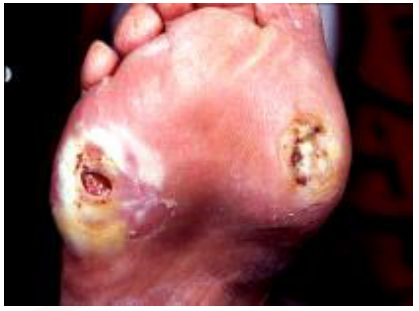
DPN

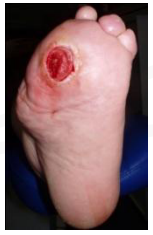
Nöropatik semptomlar

Sakatlık

Nöröpatik defisit

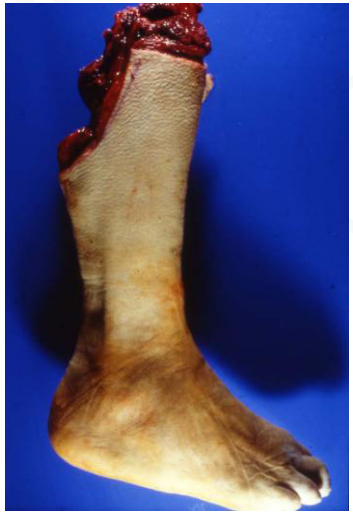
Yaşam kalitesi↓





Mortalite ↑

Maliyet↑

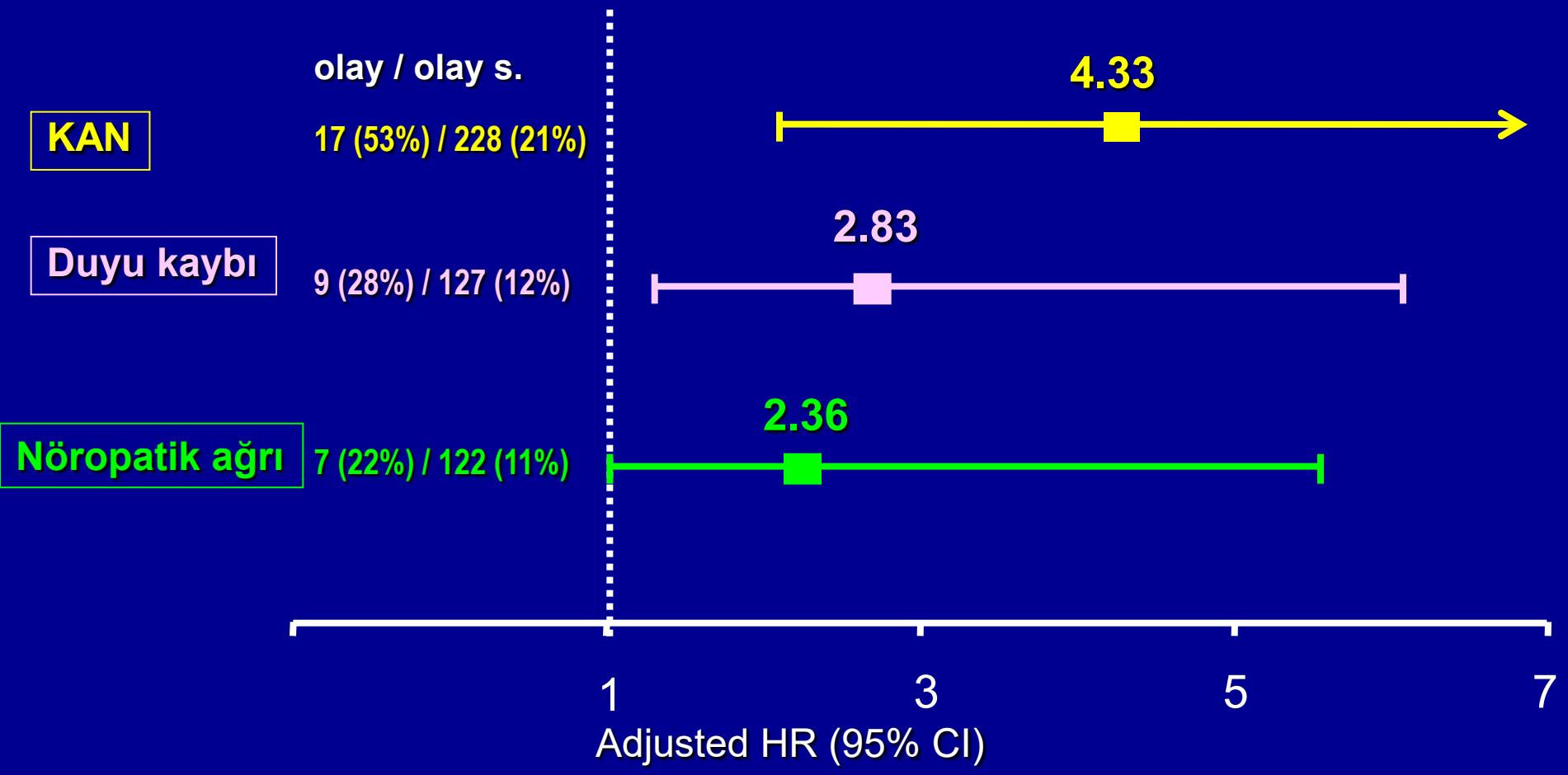


Ayak ülserleri

Charcot ayağı

Cerrahi Amputasyon

DIAD Çalışması: Nöröpatik ağrı ve kardiyak otonom nöropati (KAN) nin 5 yıllık izlemde kardiyak ölüm ve MI riskine etkisi



Young et al., JAMA 2009; 301: 1547-55

Tedavi seçenekleri

Treatment of Diabetic Neuropathy and Neuropathic Pain

How far have we come?

DAN ZIEGLER, MD, FRCPE

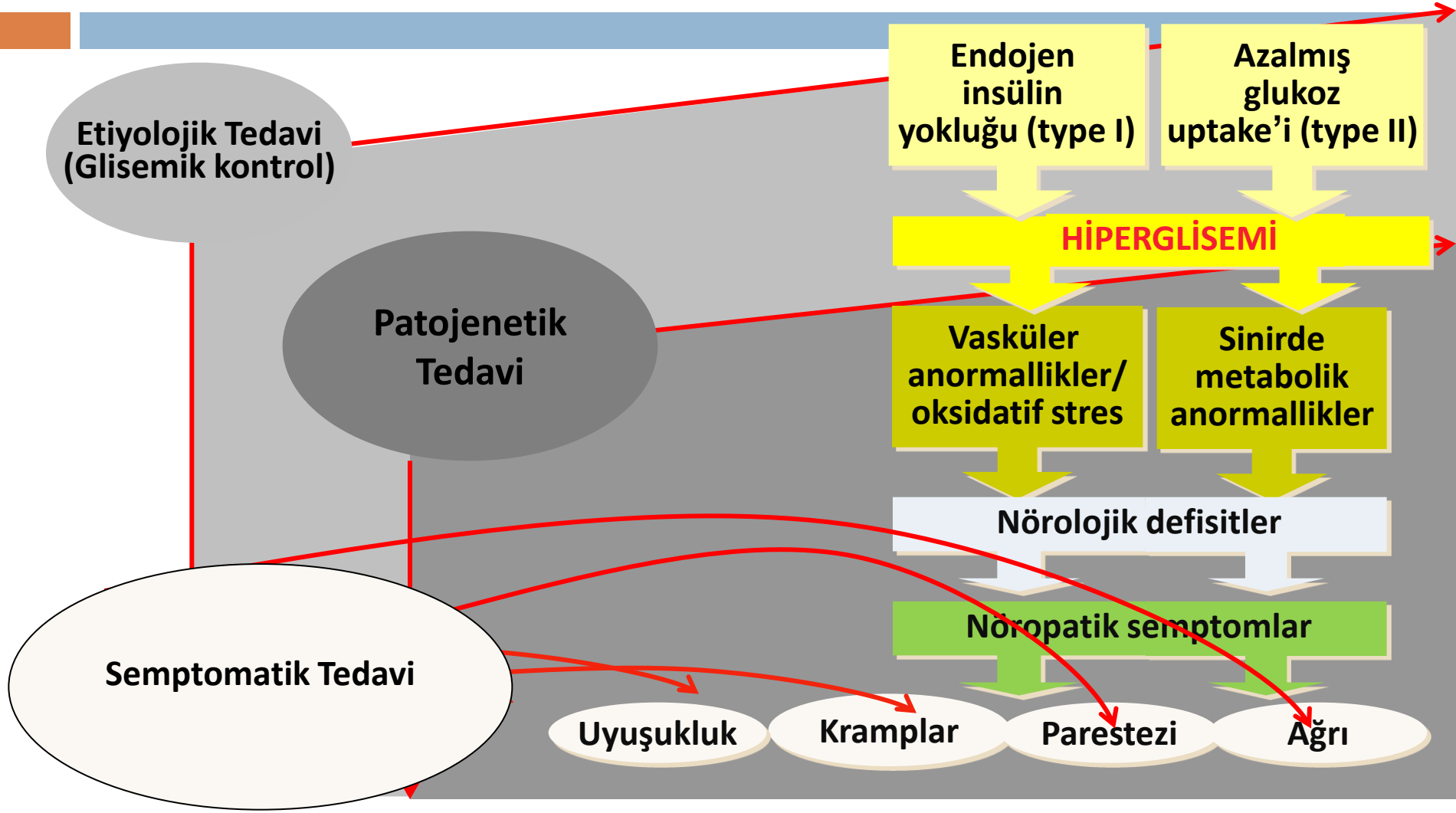
At least one of four diabetic patients is affected by distal symmetric polyneuropathy, which represents a major health problem, since it may present with partly excruciating neuropathic pain and is responsible for substantial morbidity, increased mortality, and impaired quality of life. Treatment is based on four cornerstones: *1)* causal treatment aimed at (near)-normoglycemia, *2)* treatment based on pathogenetic mechanisms, *3)* symptomatic treatment, and *4)* avoidance of risk factors and complications. Recent experimental studies suggest a multifactorial pathogenesis of diabetic neuropathy. From the clinical point of view, it is important to note that, based on these pathogenetic mechanisms, therapeutic approaches could be derived, some of which are currently being evaluated in clinical trials. Among these agents, only α-lipoic acid is available for treatment in several countries and epalrestat in Japan. Although several novel analgesic drugs such as duloxetine and pregabalin have recently been introduced into clinical practice, the pharmacologic treatment of chronic painful diabetic neuropathy remains a challenge for the physician. Individual tolerability remains a major aspect in any treatment decision. Epidemiological data indicate that not only increased alcohol consumption but also the traditional cardiovascular risk factors such as hypertension, smoking, and cholesterol play a role in development and progression of diabetic neuropathy and hence need to be prevented or treated.

Diabetes Care 31 (Suppl. 2):S255–S261, 2008

threshold also predicts the development of neuropathic foot ulceration, one of the most common causes for hospital admission and lower-limb amputations among diabetic patients (6). Pain is a subjective symptom of major clinical importance, since it is often this complaint that motivates patients to seek health care. Chronic neuropathic pain is present in 16–26% of diabetic patients (7). Pain associated with diabetic neuropathy exerts a substantial impact on the quality of life, particularly by causing considerable interference in sleep and enjoyment of life (8). Despite this significant impact, 25 and 39% of the diabetic patients, respectively, had no treatment for their pain in two surveys (7,9).

DISTAL SYMMETRIC POLYNEUROPATHY — The term

DNP Tedavi Yaklaşımları:



Semptomatik DNP tedavi seçenekleri

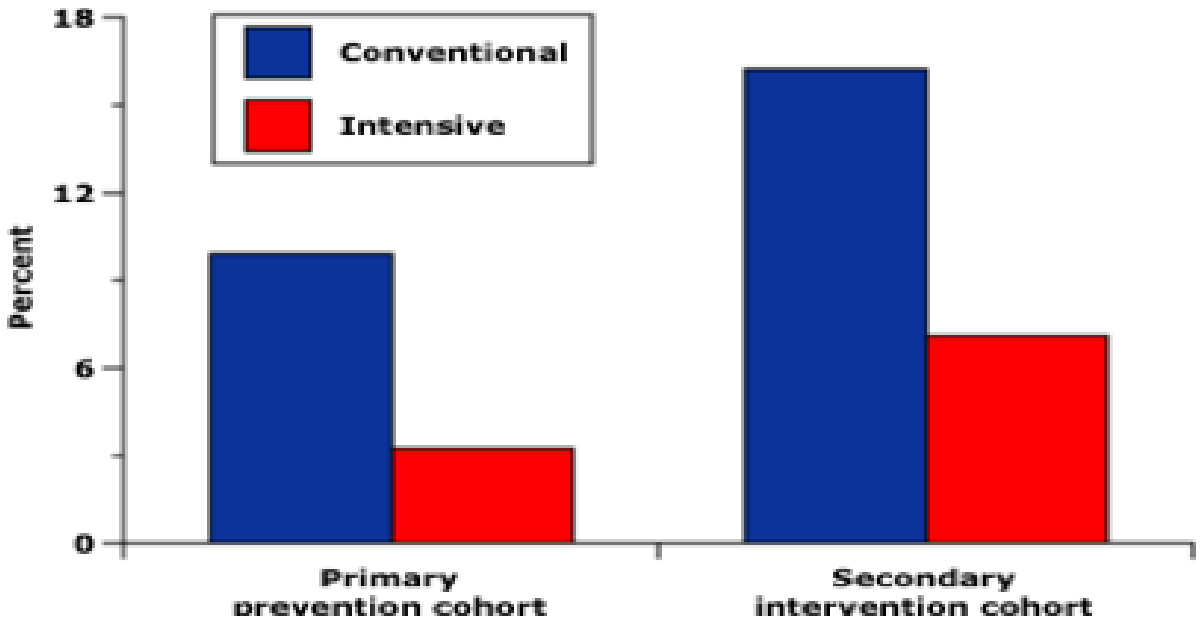
1. Normogliseminin sağlanması.
2. Bulunan risk faktörlerinin tedavisi
   a. TA regülsayonu,
   b. Dislipideminin tedavisi,
   c. Obezite ile mücadele,
   d. Sigaranın kesilmesi,
   e. Aşırı alkolden kaçınma
3. Semptomların giderilmesi
4. Patogeneze yönelik tedavi

Cur Opin Support Palliot Care 2009;3:136-143

Cur Op End Diab Obes . 2007:14;141-145

D.Care 2008;31(Supl2)S255-S261

Glisemik kontrol nöröpatiyi önlüyor

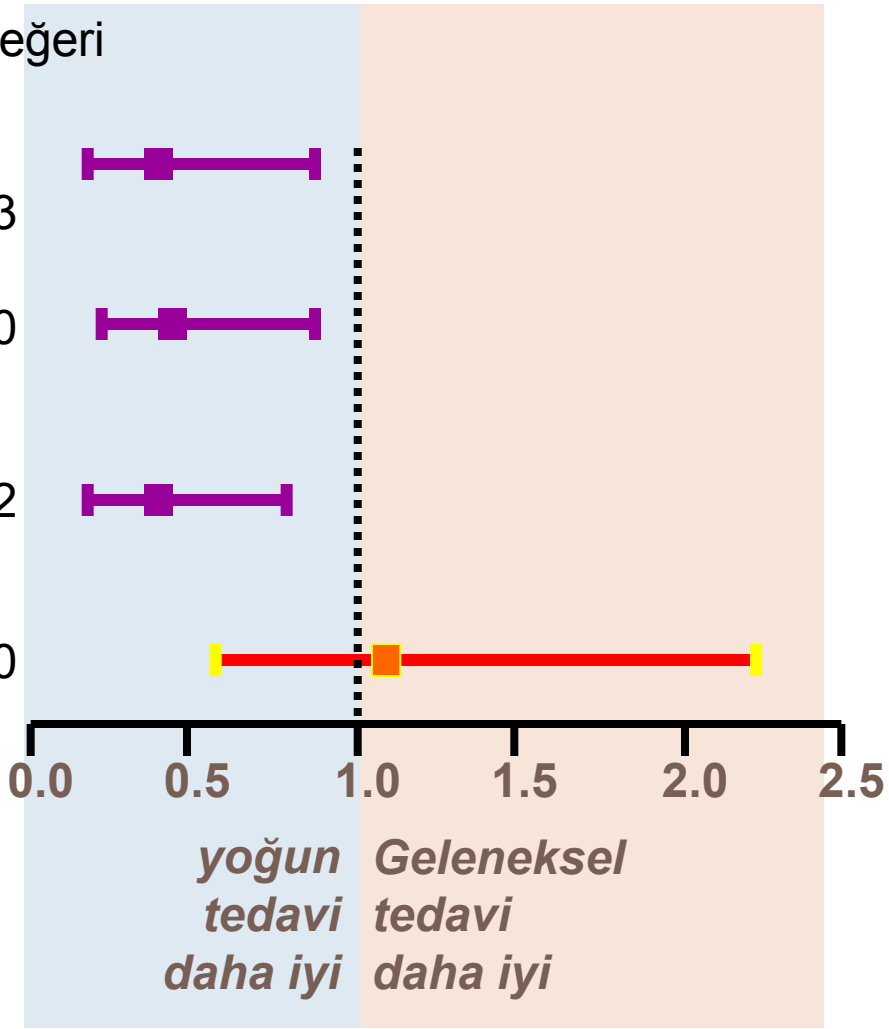


DCCT, N Eng J Med 1993

Steno 2 Çalışması 13.3 yıllık sonuçları:

Diyabetin geç dönem komplikasyonlarının progresyonu üzerine çok yönlü tedavilerin etkileri değerlendirilmiştir.

Değişken	Rölatif Risk (95% CI)	P-değeri
Nefropati	0.39 (0.17-0.87)	0.003
Retinopati	0.42 (0.21-0.86)	0.020
Otonomik Nöropati	0.37 (0.18-0.79)	0.002
Periferik Nöropati	1.09 (0.54-2.22)	0.660



Gaede et al., *N Engl J Med* 2003; 348: 383-93

VADT- Effect of intensive glucose lowering on microvascular complications of type 2 diabetic patients

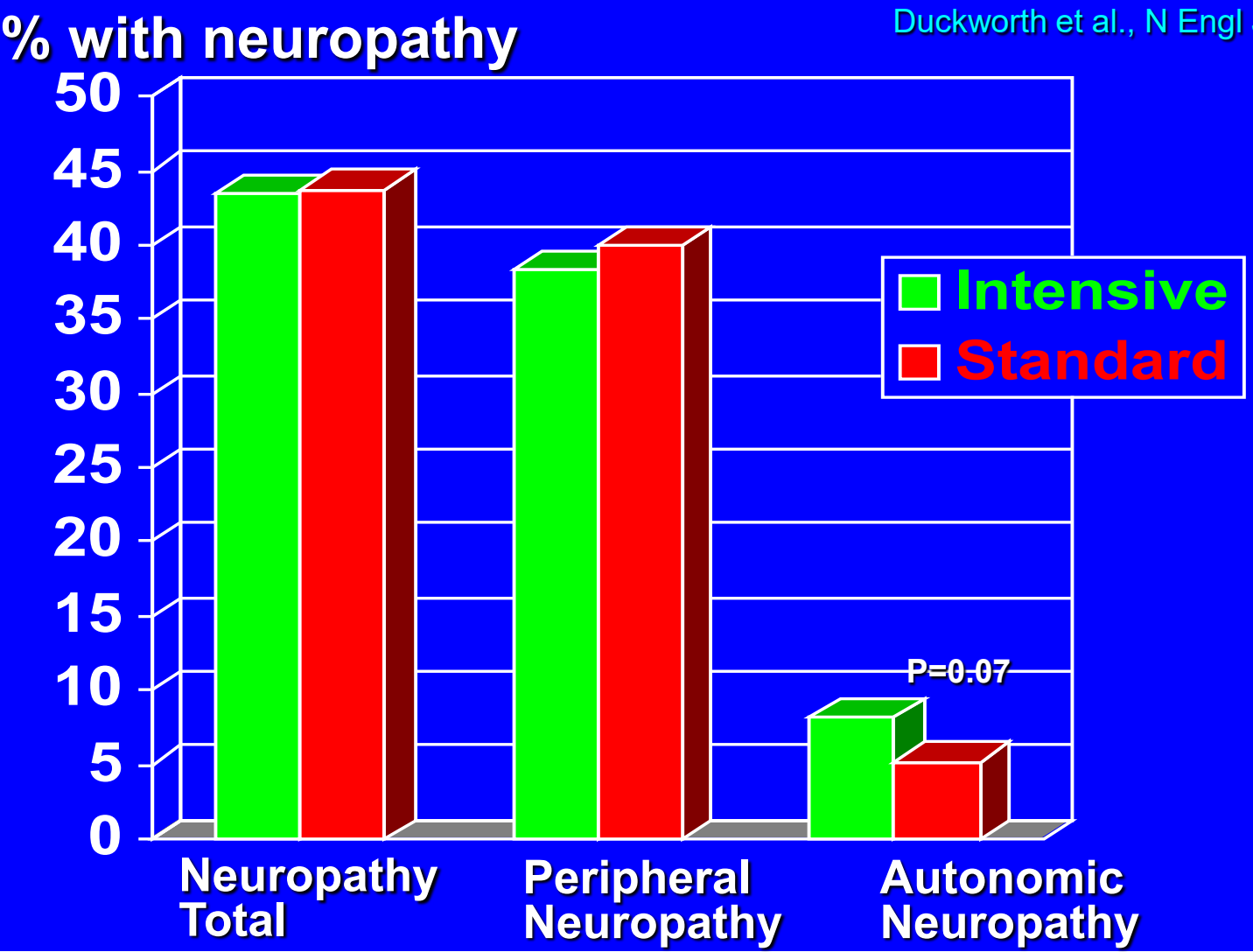
DIABETIC RETINOPATHY	•Eye procedures	No difference
	•Proliferative retinopathy	No difference
	•Macular edema	No difference
	•New onset retinopathy	No difference
	•2 step progression	*P*=0.07
DIABETIC NEPHROPATHY	•Doubling of serum creatinine	No difference
	•Serum creatinine > 3mg/dl	No difference
	•End-stage renal disease	No difference
	•Micro to macroalbuminuria	No difference
	•Normal to micro/macroalbuminuria	*P*=0.02
	•Renal function decline	No difference
DIABETIC NEUROPATHY	•Mononeuropathy	No difference
	•Peripheral neuropathy	No difference
	•Autonomic neuropathy	*P*=0.07

Duckworth et al., N Engl J Med 2009; 360: 129-39

Veterans Affairs Diabetes Trial (VADT)

No effect of intensive diabetes therapy on DPN and trend toward increased incidence of autonomic neuropathy over 5,6 years in type 2 DM

Duckworth et al., N Engl J Med 2009; 360: 129-39



HbA1c (Median):
6,9% vs 8,4%

Semptomatik DNP tedavi seçenekleri

1. Normogliseminin sağlanması.
2. Risk faktörlerinin tedavisi
   a. Kan basıncı regülasyonu,
   b. Dislipideminin tedavisi,
   c. Obezite ile mücadele,
   d. Sigaranın kesilmesi,
   e. Aşırı alkolden kaçınma
3. Semptomların giderilmesi
4. Patogeneze yönelik tedavi

	TİP 1 DM	TİP 2 DM
Yaş	+	+
Cinsiyet	-	-
Boy	+	+?
Ağırlık	-	+?
Hiperglisemi	++	++
Hipoinsülinemi		+
Diyabet süresi	++	++
Sigara	+	+?
Alkol	+?	+?
Hiperlipidemi	+?	+?
Hipertansiyon	++	+?
Nefropati	++	+
Retinopati	++	+

Cur Opin Support Palliot Care 2009;3:136-143

Cur Op End Diab Obes . 2007:14;141-145

D.Care 2008;31(Supl2)S255-S261

Semptomatik DNP tedavi seçenekleri

1. Normogliseminin sağlanması.
2. Bulunan risk faktörlerinin tedavisi
   a. TA regülsayonu,
   b. Dislipideminin tedavisi,
   c. Obezite ile mücadele,
   d. Sigaranın kesilmesi,
   e. Aşırı alkolden kaçınma
3. **Semptomların giderilmesi**
4. Patogeneze yönelik tedavi

Cur Opin Support Palliot Care 2009;3:136-143

Cur Op End Diab Obes . 2007:14;141-145

D.Care 2008;31(Supl2)S255-S261

Ağrı tedavisi

ELSEVIER

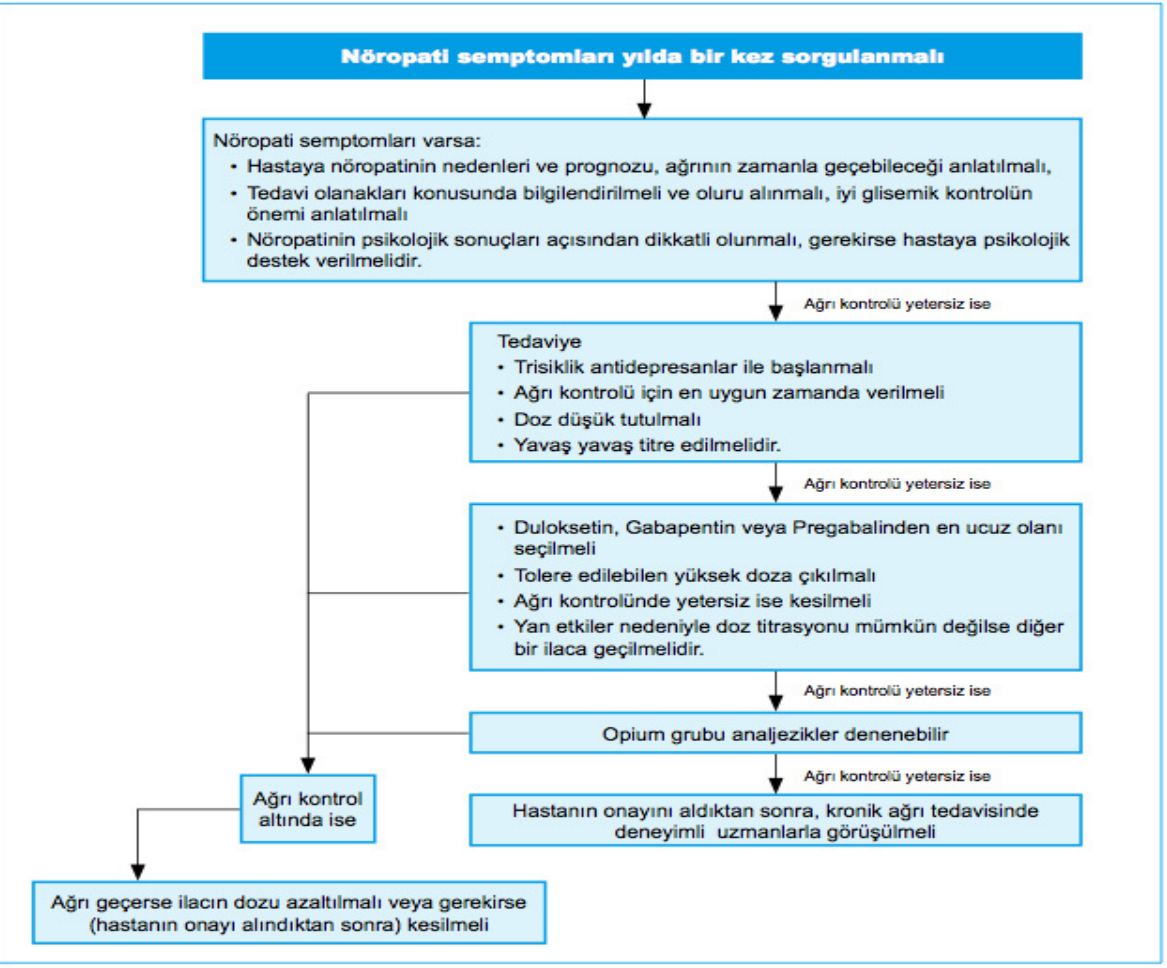
Seminars in VASCULAR SURGERY

Diabetic Neuropathy: Is Pain God's Greatest Gift to Mankind?

Dr Paul W Brand,

Andrew J.M. Boulton, MD, DSc, FRCP

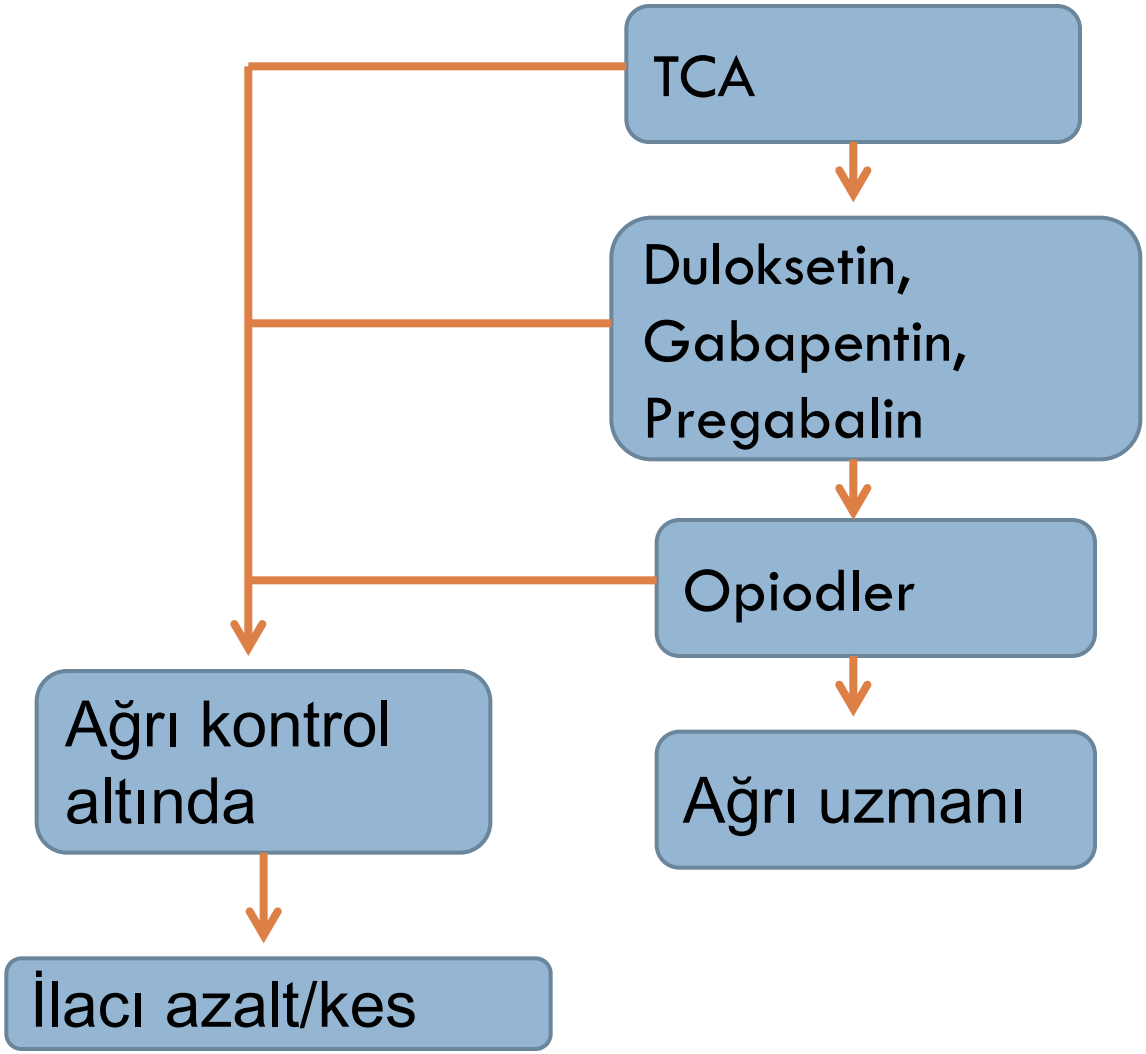
TEMD Önerileri



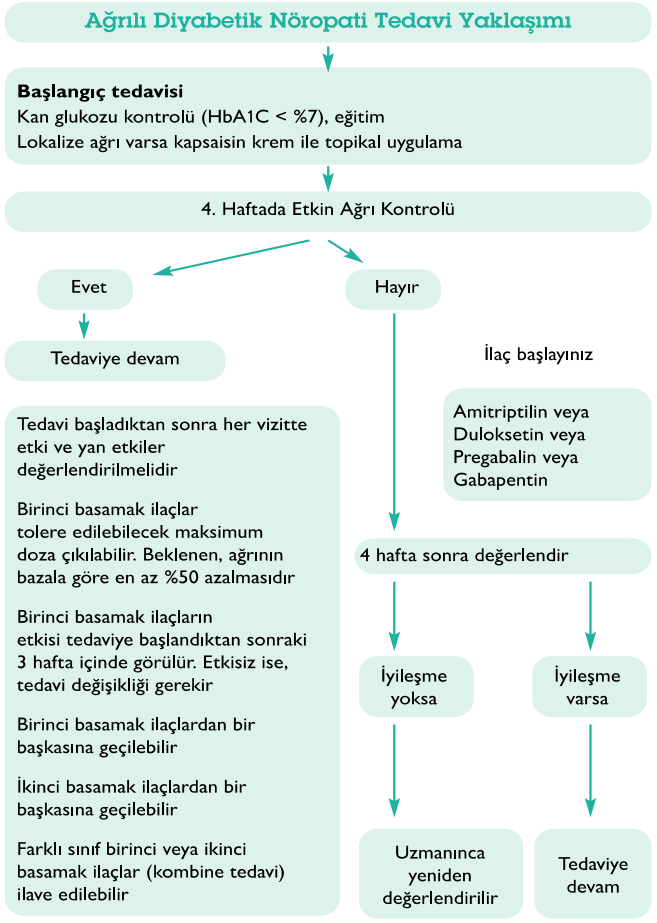
TABLO 13.2 | **Diyabetik nöropatide ağrı tedavisi**

Sınıf	Örnek	Önerilen dozlar (*)
Trisiklik antidepresan ilaçlar	Amitriptilin Nortriptilin İmipramin	Gece 10-75 mg Gece 25-75 mg Gece 25-75 mg
Antikonvulsif ilaçlar	Gabapentin Karbamazepin Pregabalin	3 x 300-1200 mg 3 x 200-400 mg 3 x 100 mg(**)
5-hidroksitriptamin ve norepinefrin re-uptake inhibitörleri	Duloksetin	1 x 60-120 mg
Alfa-lipoik asit(**)	Thioctacid ampul	600-1200 mg i.v. infuzyon
Substans-P inhibitörü	Kapsaisin krem	%0.025-0.075 Haricen günde 1-3 kez
İsosorbid dinitrat(**)	İsosorbid topikal krem	Haricen günde 1-2 kez

TEMD Önerileri



Diyabet Tanı ve Tedavi Rehberi



Diyabet
Tanı ve Tedavi
Rehberi

Diyabetik Ağrılı Nöropati Tedavisinde Kullanılan İlaçlar

Sınıf	İlaç	Dozlar
Trisiklik ilaçlar	Amitriptilin[1]	10-75 mg / uyku zamanı / gün
	Nortriptilin	25-75 mg / uyku zamanı / gün
	İmipramin	25-75 mg / uyku zamanı / gün
Antikonvülzanlar	Gabapentin[2]	300-1200 mg / 3 kez / gün
	Karbamazepin[2]	200-400 mg / 3 kez / gün
	Pregabalin[1]	75 - 150 mg / 2 kez / gün
5-hidroksitriptamin ve norepinefrin geri alım inhibitörü	Duloksetin[1]	60-120 mg / gün
Substans P inhibitörü	Kapsaisin krem	%0.025-0.075 / 3-4 kez / gün
Alfa-lipoik asit[3]	Alfa-lipoik asit	600 mg / gün

(1) Birinci basamak
(2) İkinci basamak
(3) Ağrı kesici olarak değil nöropatiyi önlemek amacıyla kullanılmalıdır

EFNS ADNP tedavisi için 2010 kılavuzu

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	Recommendation 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]

Europ J Neurology 2010;17:1113-1123

ADNP tedavisinde kullanılan ilaçların yan etkileri, kontrendikasyonları ve izlemlerindeki öneriler

İlaç	Yan etkileri	En sık görülen yan etki	K.Endik.	İzlem ve dikkat
TCA		Sedasyon, bulanık görme, ağız kuruluğu, idrar retansiyon,	Yaşlı ve/veya Kardiyak hast. aritmi, blok, post.hipotansiy.	Kalp hast. ve yaşlılar
Amitriptilin	Ağız kuruluğu, sedasyon, baş dönmesi, aritmi, ortostatik hipotansiyon, bulanık görme, idrar retansiyonu,	Ağız kuruluğu baş dönmesi sersemlik	KVS hast. **MAOI ile birlikte kullanım**	KB,EKG,Kilo , kalp hızı, mental durum (tedavi öncesi tedavi başlangıcında)
İmipramine	Ağız kuruluğu, sedasyon,,baş dönmesi, aritmi, ort. hipotansiyon bulanık görme, idrar retansiyonu		Akut MI iyileşme dönemi, MAOI	KB ve kalp hızı (tedavi öncesi ve tedavi başlangıcı)
Desipramine	Ağız kuruluğu, sedasyon,,baş dönmesi, aritmi, ort. hipotansiyon bulanık görme, idrar retansiyonu		Akut MI iyileşme dönemi, MAOI	KB,EKG,Kilo , kalp hızı, mental durum (tedavi öncesi tedavi başlangıcında)

Clinical Diabetes 2007;1:6-15
D.Care 2009;32(suppl.2):S414-419
JAMA 2010;303(5):420:1451-1458

ADNP tedavisinde kullanılan ilaçların yan etkileri, kontrendikasyonları ve izlemlerindeki öneriler

İlaç	Yan etkileri	En Sık görülen yan etki	K.Endik.	İzlem
Antiepileptikler				
Gabapentin	Somnolans, baş dönmesi, ataksi, bulantı, tremor, diplopi, bulanık görme	Baş dönmesi, ödem, kilo artışı, somnolans	Ciddi renal yetmezlik	
Pregabalin	Periferal ödem, baş dönmesi, somnolans, ataksi, bulanık görme, diplopi, EKG:RR mesafesinde uzama, aritmi,	Baş dönmesi, somnolans, periferal ödem, ılımlı kilo artışı,	Renal yetmezlik KKY, hipertansiyon, TZD ile birlikte kullanım,	Sedasyon, miyopati, serum CPK,, ödem
Topiramate	Baş dönmesi, ataksi, psikomotor sistemde yavaşlama, bulantı, kilo kaybı, onoreksi, nefrolithiasis, hipertermi, glokom,		Kc. Ve renal yetmezlik, MAOI , gebelik	Hidrasyo, tedavi öncesi ve başlangıcında elektrolit, nefrolitihiasis, osteomalazi

Clinical Diabetes 2007;1:6-15
D.Care 2009;32(suppl.2):S414-419
JAMA 2010;303(5):420:1451-1458

DNP tedavisinde kullanılan ilaçların yan etkileri, kontrendikasyonları ve izlemlerindeki öneriler

İlaç	Yan etkileri	En Sık görülen yan etki	K.Endik.	İzlem
Antiepileptikler				
Karbamazepine	Ajitasyon, ağız kuruluğu, bulanık görme, bulantı kusma, nistagmus nadiren Apl. anemi	KCFT yükseklik baş dönmesi, somnolans	Kİ depresyonu, MAOI , gebelik	Hemogram, retikulosit, serum Fe, lipid paneli, KCFT, BUN, R.idrar, TFT,
Lamotrijin	Baş dönmesi, ataksi, sedasyon, baş ağrısı, diplopi, bulantı, rinit, konfüzyon, nistagmus		Valporik asid ile birlikte kullanım,	Rash,
Valproate	Baş dönmesi, somnolans, diyare allopesi, bulantı, kusma, tremor, trombositopeni, nadiren apl. anemi			

Clinical Diabetes 2007;1:6-15
D.Care 2009;32(suppl.2):S414-419
JAMA 2010;303(5):420:1451-1458

ADNP tedavisinde kullanılan ilaçların yan etkileri, kontrendikasyonları ve izlemlerindeki öneriler

İlaç	Yan etkileri	En Sık görülen yan etki	K.Endik.	İzlem
SSNRI				
Duloxetine	Bulantı, somnolans baş dönmesi, baş ağrısı, halsizlik, ağız kuruluğu,	Bulantı, kan şekeri yükselmesi	Kc.yetm., CrCl<30 ml/dk, kr. Alkolik, MAOI ,	KCFT, Plazma glukoz , mental durum
Venlafaxine	Baş ağrısı,bulantı, sedasyon, konstip. Ağız kuruluğu, seks.disf., diyare hipertansiyon	Bulantı, somnolans	MAOI	KB, kalp hızı, kolesterol

Clinical Diabetes 2007;1:6-15
D.Care 2009;32(suppl.2):S414-419
JAMA 2010;303(5):420:1451-1458

Sözü edilen ilaçların özellikle

- ADNP'de ağrının giderilmesindeki yetersizliği ve yan etkilerinin fazla olması,

- Hastalığa yönelik patolojiyi düzeltici etkilerinin olmaması ve dolayısı ile hastalığın ilerlemesini önlemede yetersiz kalması

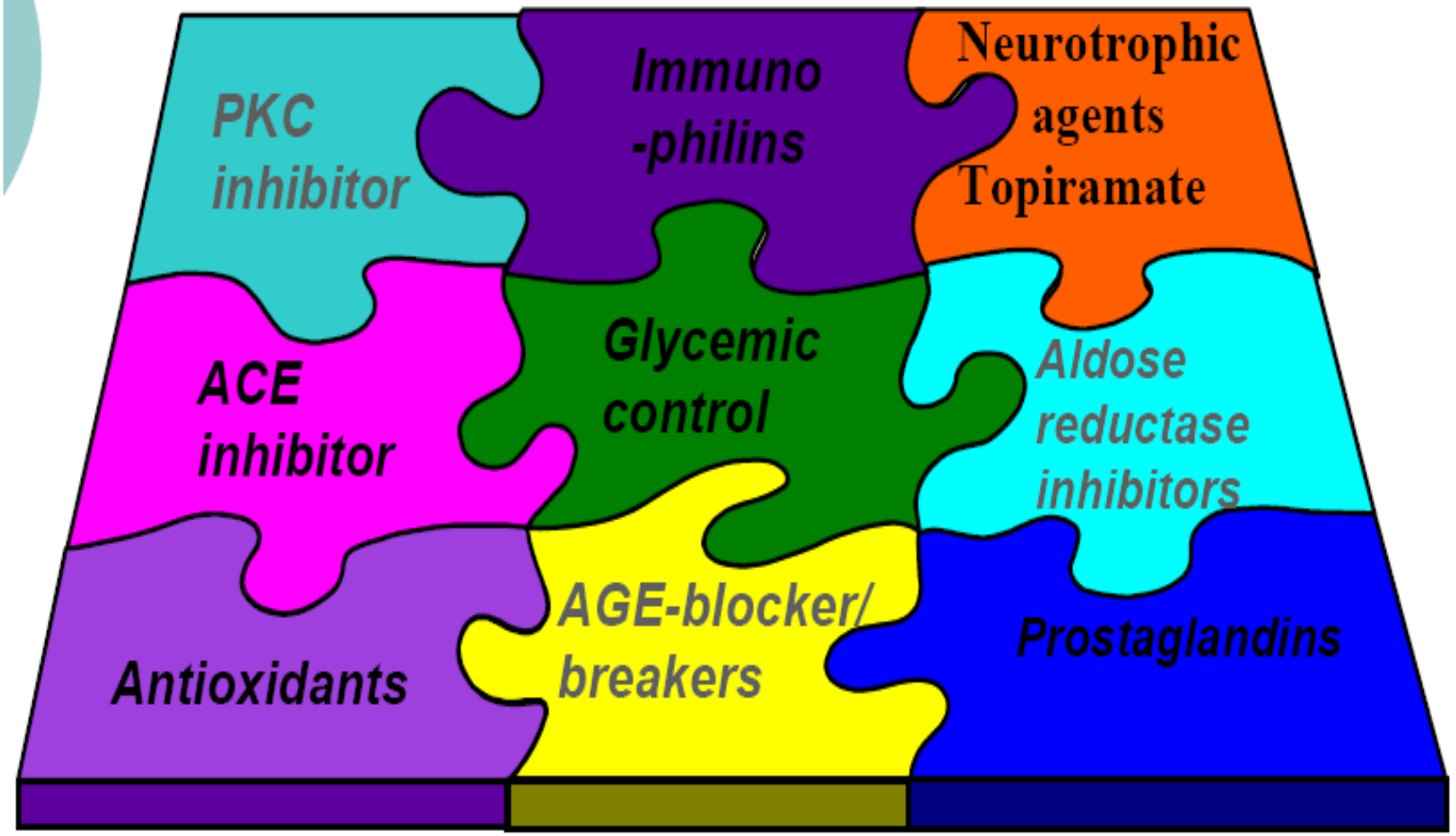
PATOGENEZE YÖNELİK TEDAVİ ARAYIŞLARINI GÜNDEME GETİRMİŞTİR

Diabetologia 2000;43:957-73

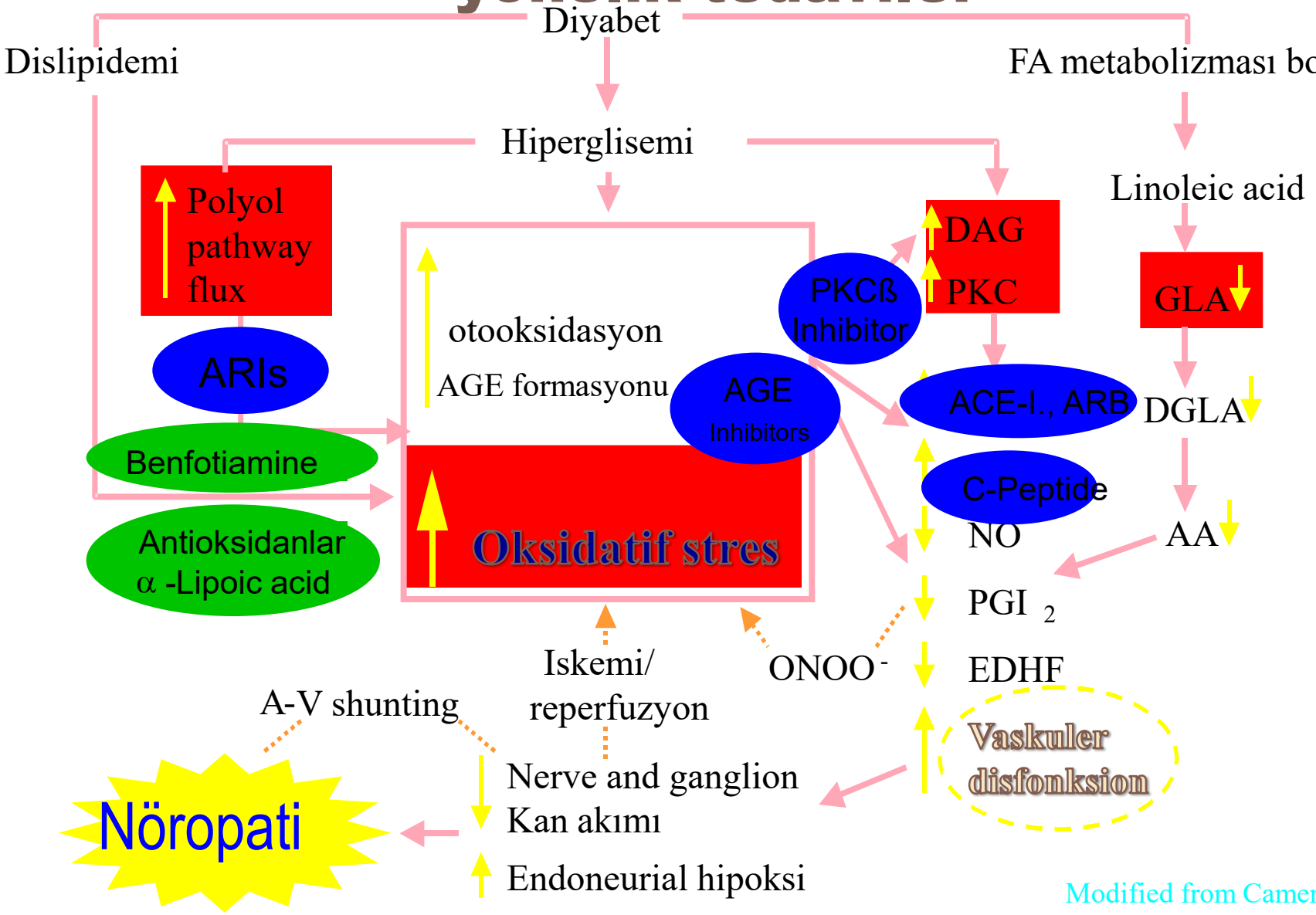
Am J Health-Syst Pharm 2004;61:160-76.

Patogeneze yönelik DNP tedavisi

Zemindeki patojenik bozuklukların giderilmesi

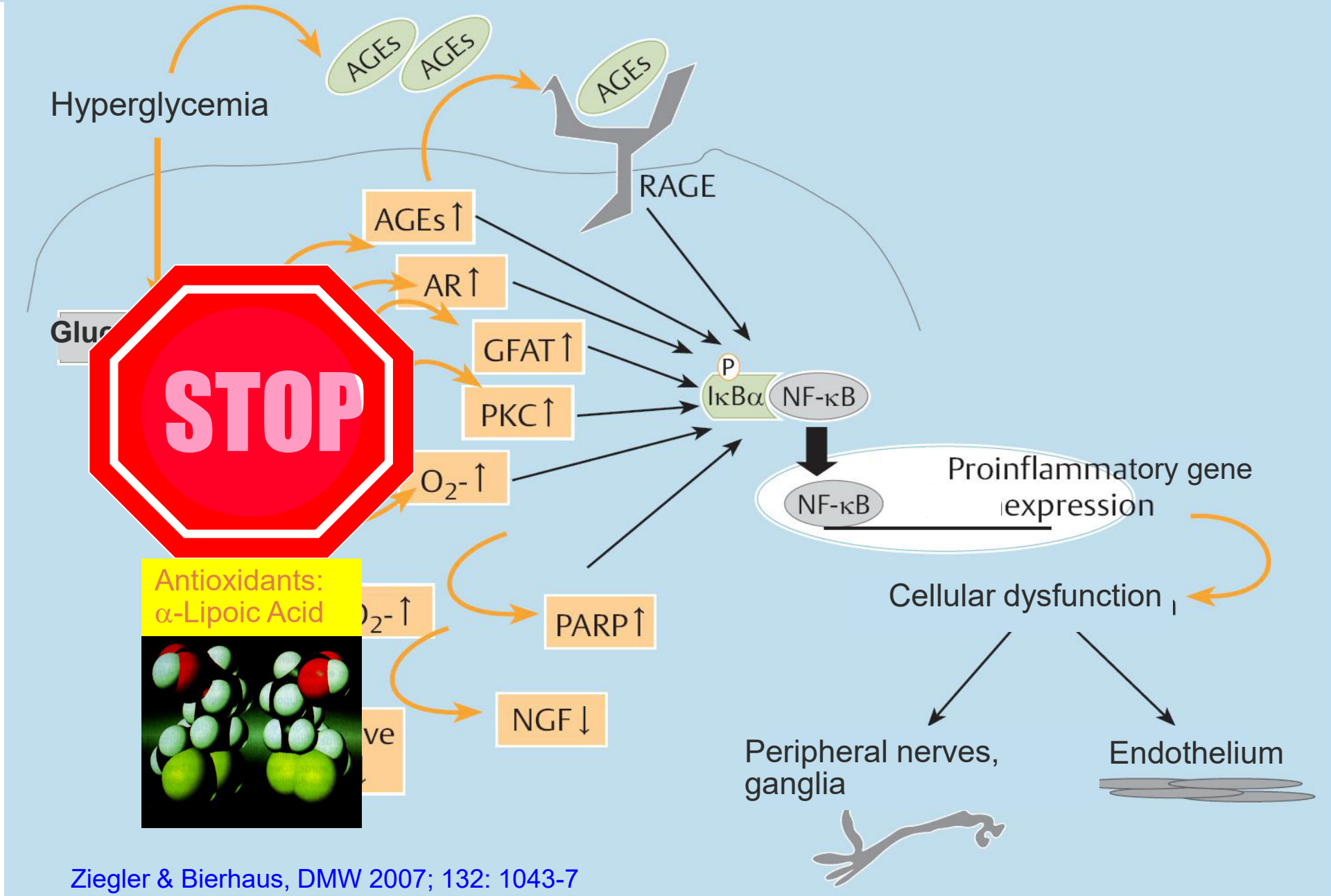


Diyabetik Nöropatinin patogenezine yönelik tedaviler



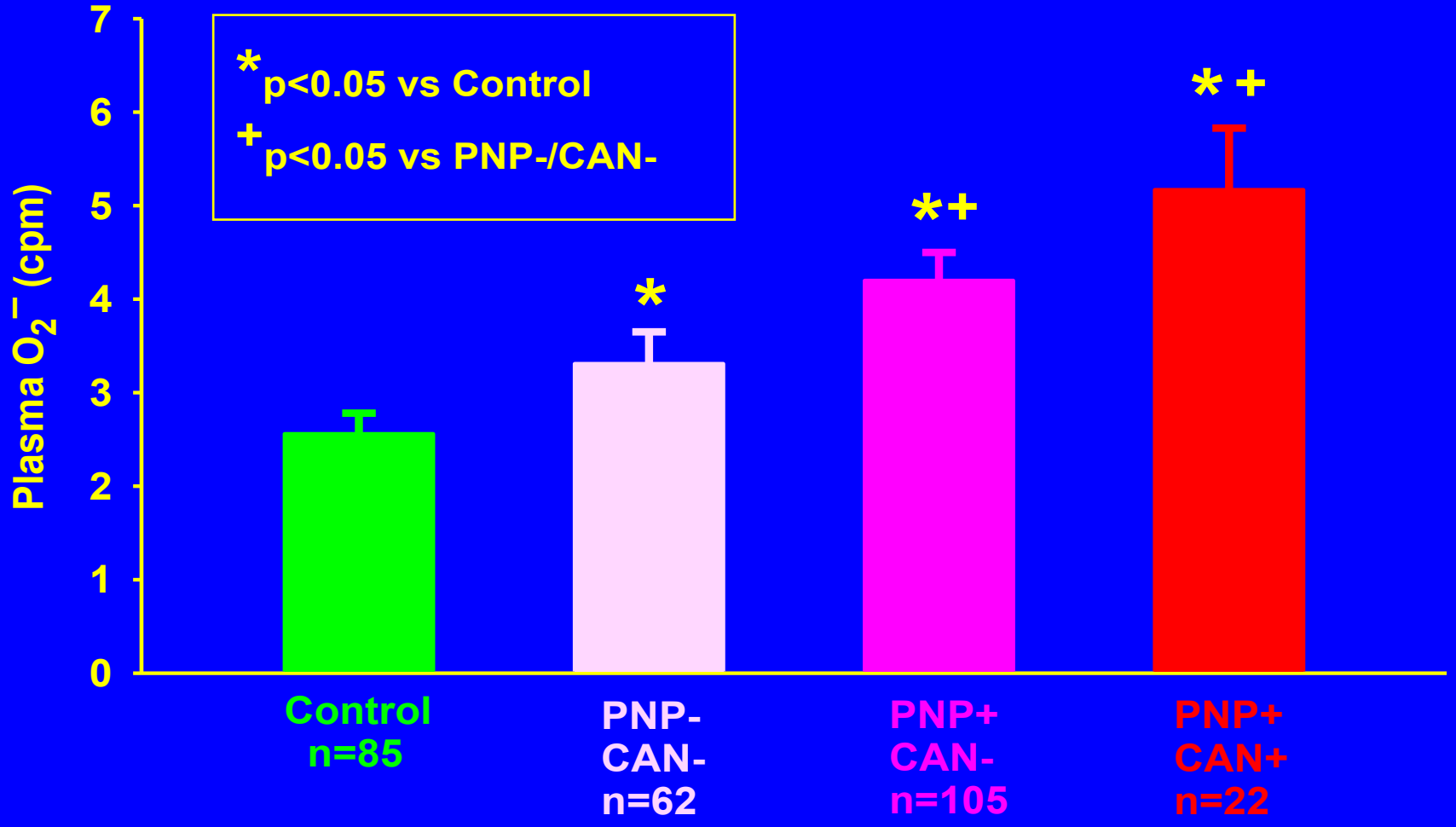
Modified from Cameron et al., Diabetologia 2001; 44: 1973-88

Superoksid anyon (O_2-) fazla üretimine bağlı oluşan oksidatif stres diyabetik nöropatinin patogenezindeki yeri



Ziegler & Bierhaus, DMW 2007; 132: 1043-7

Plazma superoksid anyon üretimindeki artışı ile diyabetik polinöropatinin şiddeti arasındaki ilişki



CAN = Cardiovascular autonomic neuropathy

Ziegler et al., *Diabetes Care* 2004; 27: 2178-83

Superoksid anyon düzeyi median sinir ileti hızının diyabetik hastalarda 6 yıllık takipte en iyi belirleyicisi

	ß	P value
Superoxide anion (mV)	-0.997	0.036
Age (years)	0.018	0.864
Sex	-0.899	0.716
BMI (kg/m²)	0.553	0.075
Diabetes duration (years)	0.197	0.194
Change in HbA1c (%)	-0.692	0.420
Change in albuminuria (μg/min)	-0.009	0.184
Hypertension	3.290	0.252

Multiple linear regression analysis

$R^2 = 0.272$; p=0.068 for model

Ziegler et al., ADA, 2010

"Patogeneze yönelik tedavide ilk tercih olarak alfa-lipoik asit…."

REVIEW ARTICLE

doi: 10.1111/j.1463-1326.2007.00741.x

Diabetic neuropathy: new strategies for treatment

Tamás Várkonyi[1] and Peter Kempler[2]

[1]First Department of Medicine, University of Szeged, Szeged, Hungary
[2]First Department of Medicine, Semmelweis University, Budapest, Hungary

Current therapeutic possibilities can be divided into two groups: the pathogenetically oriented and the symptomatic therapy. One of the most important component of etiology-based treatment is the stabilization of glycemic control. Based on efficacy and safety data benfotiamine and alpha-lipoic acid should be considered as first choices among pathogenetically oriented treatments of diabetic neuropathy. Promising data were published about the aldose reductase inhibitor ranirestat. The symptomatic effect of antiepileptic drugs in diabetic painful neuropathy (DPN) is originated from several possible pharmacological properties. Pregabalin and gabapentin have the highest efficacy and the lowest frequency of adverse events among these drugs. Antidepressants also extensively used for symptomatic treatment in DPN. In the last years several studies were published about the benefial effect of duloxetine. Most likely combination therapy will be frequently applied in the future for the treatment of DPN, the optimal choice could be to combine pathogenetically oriented and symptomatic treatment.

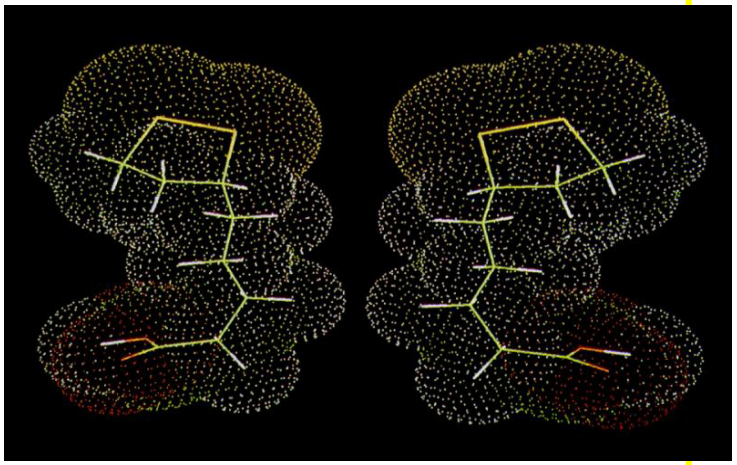
Keywords: alpha-lipoic acid, benfotiamine, duloxetine, gabapentin, pathogenetically oriented therapy, pregabalin, symptomatic therapy, treatment of diabetic neuropathy

Received 21 December 2006; returned for revision 7 May 2007; revised version accepted 9 May 2007

Alfa-lipoik asit tedavisinin klinik dayanakları

ALADIN
ALADIN 2
ALADIN 3
ORPIL
DEKAN
SYDNEY
SYDNEY 2
NATHAN 1

- i.v.
- oral



Randomized Placebo-Controlled Trials

Toplam Semptom Skoru (TSS) AYAK

1.) Batıcı ağrı
2.) Yanma
3.) Parestezi
4.) Karıncalanma

	Semtom şiddeti			
Semptom Sıklığı	*yok*	*hafif*	*orta*	*şiddetli*
arasıra	0	1.00	2.00	3.00
sık	0	1.33	2.33	3.33
sürekli	0	1.66	2.66	3.66

Neuropathy Impairment Score (NIS)

Kas Gücü

- Baş 5 muscle groups
- Üst gövde 11 muscle groups
- Alt Gövde: 8 muscle groups

Refleksler

- Biceps, triceps, radial, knee, ankle

Duyu

- İşaret parmağı: Touch, pain, vibration, position
- Ayak başparmağı: Touch, pain, vibration, position

Scoring for muscle strength:
0 = Defisit yok
1 = hafif defisit
2 = Orta defisit
3 = Ciddi defisit
4 = Çok ciddi defisit/Fonksiyon kaybı

Scoring for reflexes and sensation:
0 = Defisit yok
1 = hafif orta defisit
2 = Ciddi defisitits/
Fonksiyon kaybı

Dyck et al., Ann Neurol, 1980

ALADIN 1 (Alfa Lipoik Asid in DIabetic Neuropathy) IV

Diabetologia (1995) 38: 1425–1433

Diabetologia
© Springer-Verlag 1995

Treatment of symptomatic diabetic peripheral neuropathy with the anti-oxidant α-lipoic acid

A 3-week multicentre randomized controlled trial (ALADIN Study)

D. Ziegler[1], M. Hanefeld[2], K. J. Ruhnau[3], H. P. Meißner[3], M. Lobisch[4], K. Schütte[4], F. A. Gries[1], The ALADIN Study Group*

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[2] Abteilung Klinische Stoffwechselforschung, Universitätsklinikum "Carl Gustav Carus" der Technischen Universität, Dresden, Germany
[3] Diabetologische Schwerpunktpraxen, Berlin, Germany
[4] Medizinische Forschung, ASTA Medica AG, Frankfurt am Main, Germany

328 Tip2 DM ve semptomatik DNP hasta
100, 600,1200mg ALA(İV) ve plasebo (randomize)
Tedavi süresi 3 hafta
- Semptom skoru
- Toplam semptom skoru (TSS)
- NöropatiK disabilite skoru (NDS)

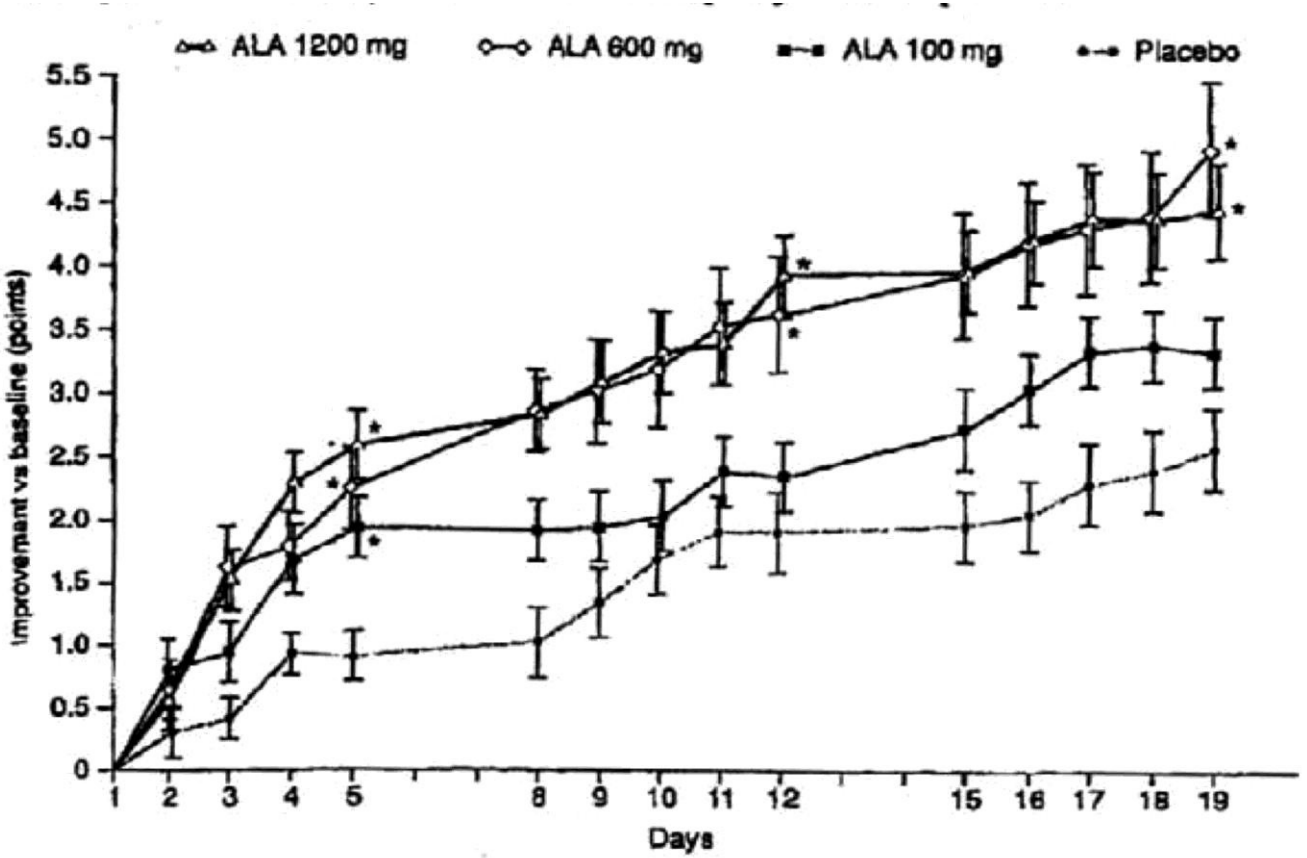
Başlangıç özellikleri

Table 1. Clinical characteristics of the patients at entry into the study

	α-Lipoic acid 1200 mg	α-Lipoic acid 600 mg	α-Lipoic acid 100 mg	Placebo
Number	65	63	66	66
Sex (male/female)	40/60	37/63	51/49	35/65
Age (years)	59.2 ± 7.7	57.5 ± 8.7	58.7 ± 7.9	60.2 ± 7.7
Body mass index (kg/m^2)	29.2 ± 4.8	27.7 ± 4.9	27.8 ± 4.4	29.7 ± 4.9
Systolic blood pressure (mm Hg)	144 ± 16	143 ± 16	145 ± 15	144 ± 14
Diastolic blood pressure (mm Hg)	85 ± 9	85 ± 6	84 ± 8	84 ± 9
Smokers[a]	11	13	14	14
Duration of diabetes (years)	11.0 ± 7.3	10.4 ± 7.1	11.7 ± 7.0	12.3 ± 7.7
Insulin treatment[a]	57	67	68	65
Blood glucose (mmol/l)	11.1 ± 4.1	11.2 ± 4.1	11.4 ± 4.3	11.0 ± 3.6
HbA_1 (%)	8.8 ± 1.9	9.2 ± 2.5	9.0 ± 2.1	9.4 ± 2.6
Retinopathy[a]	34	30	27	38
Duration of neuropathy (years)	3.3 ± 4.1	2.8 ± 2.6	2.8 ± 2.6	3.4 ± 3.7
Symptom score: Pain	2.02 ± 1.18	2.08 ± 1.15	1.82 ± 1.24	1.70 ± 1.24
Burning	1.51 ± 1.32	1.63 ± 1.29	1.77 ± 1.32	1.24 ± 1.31
Paraesthesiae	2.06 ± 1.08	1.93 ± 1.23	2.04 ± 1.30	1.98 ± 1.12
Numbness	2.04 ± 1.24	2.17 ± 1.28	1.95 ± 1.34	1.89 ± 1.32
Neuropathy Symptom Score	5.3 ± 1.8	5.6 ± 2.0	5.0 ± 1.9	5.3 ± 1.7
Neuropathy Disability Score	6.1 ± 2.7	6.0 ± 2.5	6.2 ± 2.6	6.2 ± 2.4
Pain Adjective List (total scale)	2.01 ± 1.44	2.14 ± 1.51	2.17 ± 1.40	2.06 ± 1.41

Values are mean ± SD or [a] percentage of patients

Semptom Skorunda İV 1200-600 mg ALA alan gruplarda plaseboya göre anlamlı düzelme



Diabetologia 1995

IV+oral

ALADIN 2 (Alfa Lipoik Asid in DIabetic Neuropathy)

Treatment of Diabetic Polyneuropathy with the Antioxidant Thioctic Acid (α-Lipoic Acid): A Two Year Multicenter Randomized Double-blind Placebo-controlled Trial (ALADIN II)

M. RELJANOVIC[a], G. REICHEL[b], K. RETT[c], M. LOBISCH[d], K. SCHUETTE[d], W. MÖLLER[d], H.-J. TRITSCHLER[d], H. MEHNERT[e]* and THE ALADIN II STUDY GROUP[f]

[a]*University Clinic for Diabetes, Endocrinology and Metabolic Diseases "Vuk Vrhovac", Medical faculty, University of Zagreb, Dugi dol 4a, 10000 Zagreb, Croatia;* [b]*Paracelsus Clinic, Werdauer Str. 68, 08060 Zwickau, Germany;* [c]*Eberhard-Karls University Clinic, Geissweg 3, 72076 Tübingen, Germany;* [d]*ASTA Medica AG, Weismüllerstr. 45, 60314 Frankfurt am Main, Germany;* [e]*Institute for Diabetes Research, City Hospital Munich, Kölner Platz 1, 80804 München, Germany*

- Semptomatik DNP olan hastalara
- ALA 600, 1200 (IV+idame Oral) ve plasebo
- 2 yıl boyunca tedavinin
- Sinir ileti hızları ve
- Aksiyon potansiye üzerine etkisi araştırılıyor

F R Res. 1999

ALADIN 2: Başlangıçtaki klinik özellikler

	Placebo	TA 600	TA 1200
Number	20	27	18
Sex (Male/Female)[a]	10/10	11/16	7/11
Age (Years)	57.3 ± 6.4	58.1 ± 17.3	58.0 ± 5.5
Body mass index (kg/m^2)	28.3 ± 3.4	29.2 ± 3.5	29.9 ± 4.0
Systolic blood pressure (mmHg)	137.7 ± 10.5	141.3 ± 17.8	140.6 ± 18.6
Diastolic blood pressure (mmHg)	82.0 ± 7.6	82.4 ± 11.3	83.0 ± 8.9
Smokers[a]	3	7	1
HbA_{1c} (%) at baseline	93 ± 2.2	88 ± 1.5	9.1 ± 2.2
HbA_{1c} (%) after 24 months	9.1 ± 2.4	9.2 ± 2.2	8.0 ± 1.5

Values are mean ± SD or [a]number of patients.

ALA 600 ve1200mg sinir ileti ve AP etkisi

TABLE II Changes of peripheral nerve function indices from baseline to 24 month

	Placebo	TA 600	TA 1200
Sural SNCV (m/s)			
Baseline	41.6 ± 4.1	41.0 ± 7.1	38.9 ± 95
Change (month 24)	−0.1 ± 4.8	3.0 ± 3.0[a]	3.8 ± 4.2[a]
Sural SNAP (μV)			
Baseline	33 ± 3.2	3.1 ± 2.4	25 ± 2.0
Change (month 24)	−0.7 ± 1.5	0.3 ± 1.4[a]	0.6 ± 2.5[b]
Tibial MNCV (m/s)			
Baseline	48.2 ± 6.2	46.6 ± 6.2	47.1 ± 5.1
Change (month 24)	−1.5 ± 2.9	−0.3 ± 5.2	1.2 ± 3.8[a]
Tibial nerve DML (ms)			
Baseline	5.4 ± 1.3	5.1 ± 1.2	5.2 ± 0.9
Change (month 24)	0.0 ± 1.1	−0.03 ± 1.1	−0.17 ± 1.3

Values are mean ± SD, [a]$p < 0.05$ vs PLA, [b]$p = 0.076$ vs PLA.
SNCV: sensory nerve conduction velocity; MNCV: motor nerve conduction velocity; SNAP: sensory nerve action potential; DML: distal motor latency.

o 24

Sinir ileti hızlarında ve aksiyon potansiyelde plaseboda azalma varken ALA kullananlarda artış

ALADIN III

IV+oral

Treatment of Symptomatic Diabetic Polyneuropathy With the Antioxidant α-Lipoic Acid

A 7-month multicenter randomized controlled trial (ALADIN III Study)

DAN ZIEGLER, MD
MARKOLF HANEFELD, MD
KLAUS-JÜRGEN RUHNAU, MD
HELMUT HASCHE, MD
MICHAEL LOBISCH, MD
KLEMENS SCHÜTTE, PHD
GORAZD KERUM, MD, PHD
ROLF MALESSA, MD
THE ALADIN III STUDY GROUP

points in A-A, −5.76 ± 0.69 points in A-P, and −4.37 ± 0.83 points in P-P ($P = 0.09$ for A-A vs. P-P). The rates of adverse events were not different between the groups throughout the study.

Semptomatik DNP olan hastalar,
3 hafta IV ardından 6 ay oral 600 ALA
plasebo karşılaştırılıyor
TSS ve NIS

ALADIN III

Başlangıç özellikleri

Table 1—*Clinical characteristics at baseline of the three groups studied*

	A-A	A-P	P-P
n	165	173	165
Sex (%)			
Male	45.5	54.3	50.3
Female	54.5	45.7	49.7
Age (years)	56.5 ± 7.1	57.0 ± 6.2	57.3 ± 5.5
BMI (kg/m²)	29.0 ± 4.8	28.8 ± 4.2	29.5 ± 4.8
Heart rate (bpm)	78.4 ± 8.8	78.1 ± 9.5	77.3 ± 9.6
Systolic blood pressure (mmHg)	141 ± 17	142 ± 14	140 ± 15
Diastolic blood pressure (mmHg)	82.7 ± 8.9	83.4 ± 8.0	81.5 ± 9.2
Duration of diabetes (years)	11.5 ± 8.4	11.7 ± 7.9	11.3 ± 7.7
Duration of neuropathy (months)	37.7 ± 38.5	35.1 ± 31.3	38.0 ± 36.7
HbA_{1c} (%)	8.5 ± 1.9	8.7 ± 1.8	8.7 ± 1.8
Insulin treatment	62.4	63.6	61.2
Smokers	15.2	16.8	13.3
Retinopathy	28.2	30.4	33.5
TSS	8.1 ± 3.0	8.3 ± 2.9	8.4 ± 3.2
NIS	14.0 ± 10.5	14.3 ± 10.5	14.0 ± 10.4
NIS(LL)	11.0 ± 7.0	11.3 ± 7.4	11.0 ± 7.3

Data are *n*, means ± SD, or % of patients.

7.Ayda toplam semptom skoru(TTS), Noropati impairment skoru(NIS) sonuçları

1-19.gün IV tedavi sonrası karşılaştırma

	α-Lipoic acid	*n*	Placebo	*n*	P value
TSS (Day 19 vs. 1)	−3.7 (−12.6 to 5.0)	338	3.0 (−12.3 to 8.0)	165	0.447
TSS (AUC)	85.6 (0 to 219)	338	95.9 (5.5 to 220)	165	0.033
NIS (Day 19 vs. 1)	−4.34 ± 0.35	314	−3.49 ± 0.58	154	0.016
NIS(LL) (Day 19 vs. 1)	−3.32 ± 0.26	314	−2.79 ± 0.42	154	0.055

Data are medians (range), *n*, or means ± SEM.

7.Ay sonuçları

Table 3—*Changes in the TSS, NIS, and the NIS(LL) after 7 months versus baseline in the three groups*

	A-A	*n*	A-P	*n*	P-P	*n*
TSS	−3.98 (−12.64 to 5.66)	165	−3.99 (−12.31 to 5.33)	173	−3.98 (−12.32 to 8.32)	165
NIS	−5.82 ± 0.73*	119	−5.76 ± 0.69	121	−4.37 ± 0.83	124
NIS(LL)	−4.39 ± 0.51*	120	−4.20 ± 0.52	123	−3.37 ± 0.54	125

Data are medians (range), *n*, or means ± SEM. *P = 0.09 vs. P-P.

4 yıl sürecek NATHAM ' Neurologic Assesment of Thioctic acid in Neuropaty Study' kararı alınıyot

DEKAN çalışması

ORIGINAL ARTICLE

Effects of Treatment With the Antioxidant α-Lipoic Acid on Cardiac Autonomic Neuropathy in NIDDM Patients

A 4-month randomized controlled multicenter trial (DEKAN Study)

DAN ZIEGLER, MD
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FRANK CONRAD, PHD
F. ARNOLD GRIES, MD
HEINZ ULRICH, MD
THE DEKAN STUDY GROUP
GERHARD REICHEL, MD

CAN (5). However, the Diabetes Control and Complications Trial has shown that heart rate variability (HRV) abnormalities were not completely prevented by intensive insulin treatment (7), and studies in

DIABETES CARE, VOLUME 20, NUMBER 3, MARCH 1997

DEKAN çalışması

Çalışma dizaynı

- Kardiyak otonom nöropatiye etkisinin araştırıldığı plasebo kontrollü çift kör çok merkezli bir çalışma
- Tip2 DM'li hastalara 800 mg oral ALA tedavisini uygulanıyor
- Çalışma süresi 4 ay
- Kardiyak otonom nöropati HRV ile değerlendiriliyor

Sonuçlar

Table 3—*Parameters of cardiac autonomic nerve function at entry*

	ALA	Placebo
LF band (bpm²)	0.071 (0.017–0.352)†	0.122 (0.011–0.549)
HF band (bpm²)	0.085 (0.014–2.080)	0.124 (0.010–0.904)
CV (%)	1.42 (0.75–4.80)*	1.89 (0.69–3.31)
RMSSD (ms)	4.8 (2.0–46.7)‡	8.1 (1.6–25.2)

Data are medians (ranges). *$P < 0.05$ vs. placebo; †$P = 0.064$ vs. placebo; ‡$P = 0.078$ vs. placebo.

Kardiyak otonam nöröpatide düzelme

DIABETES CARE, VOLUME 20, NUMBER 3, MARCH 1997

SYDNEY I

Emerging Treatments and Technologies
ORIGINAL ARTICLE

The Sensory Symptoms of Diabetic Polyneuropathy Are Improved With α-Lipoic Acid

The SYDNEY Trial

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PETER C. O'BRIEN, PHD[3]
MIROSLAV RELJANOVIC, MD[6]
RUSTEM SAMIGULLIN, MD[4]
KLEMENS SCHUETTE, BSC[3]
IGOR STROKOV, MD[1]
HANS J. TRITSCHLER, PHD[4]
KLAUS WESSEL, PHD[4]
NIKOLAI YAKHNO, MD[2]
DAN ZIEGLER, MD[7]

several other neuropathic end points. This improvement of symptoms was attributed to improved nerve pathophysiology, not to increased nerve fiber degeneration. Because of its safety profile and its effect on positive neuropathic sensory symptoms and other neuropathic end points, this drug appears to be a useful ancillary treatment for the symptoms of diabetic polyneuropathy.

Diabetes Care 26:770–776, 2003

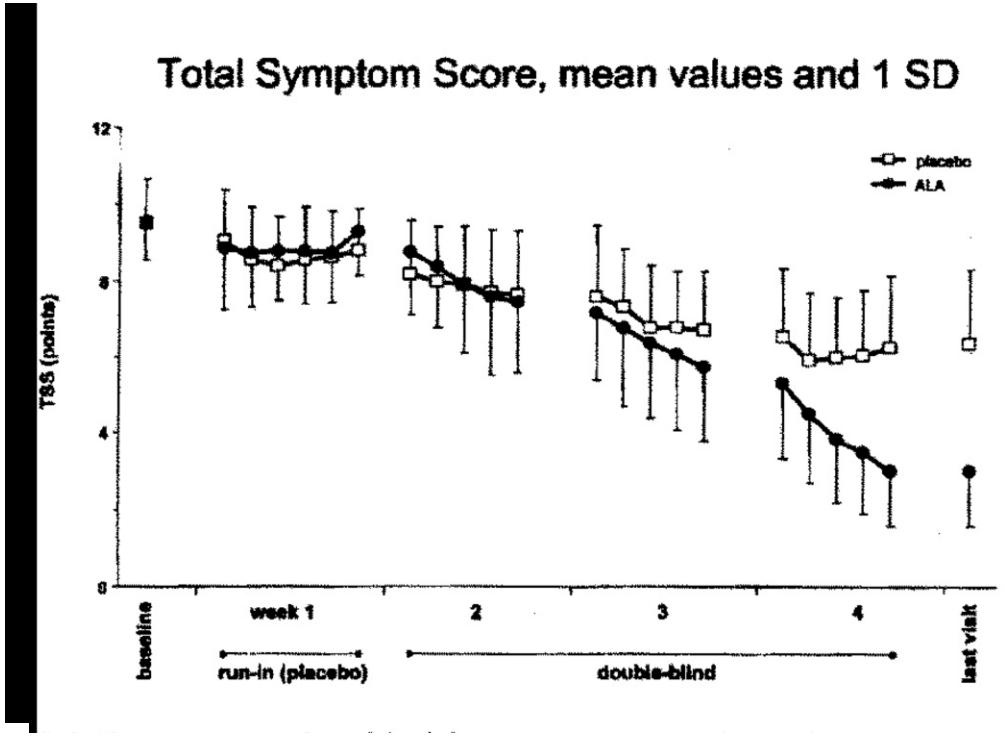
SYDNEY I

(İV)

Çalışma dizaynı

- Kısa süreli İV ALA tedavisinin TSS'na etkisini karşılaştıran Randomize çift kör plasebo kontrollu çalışma

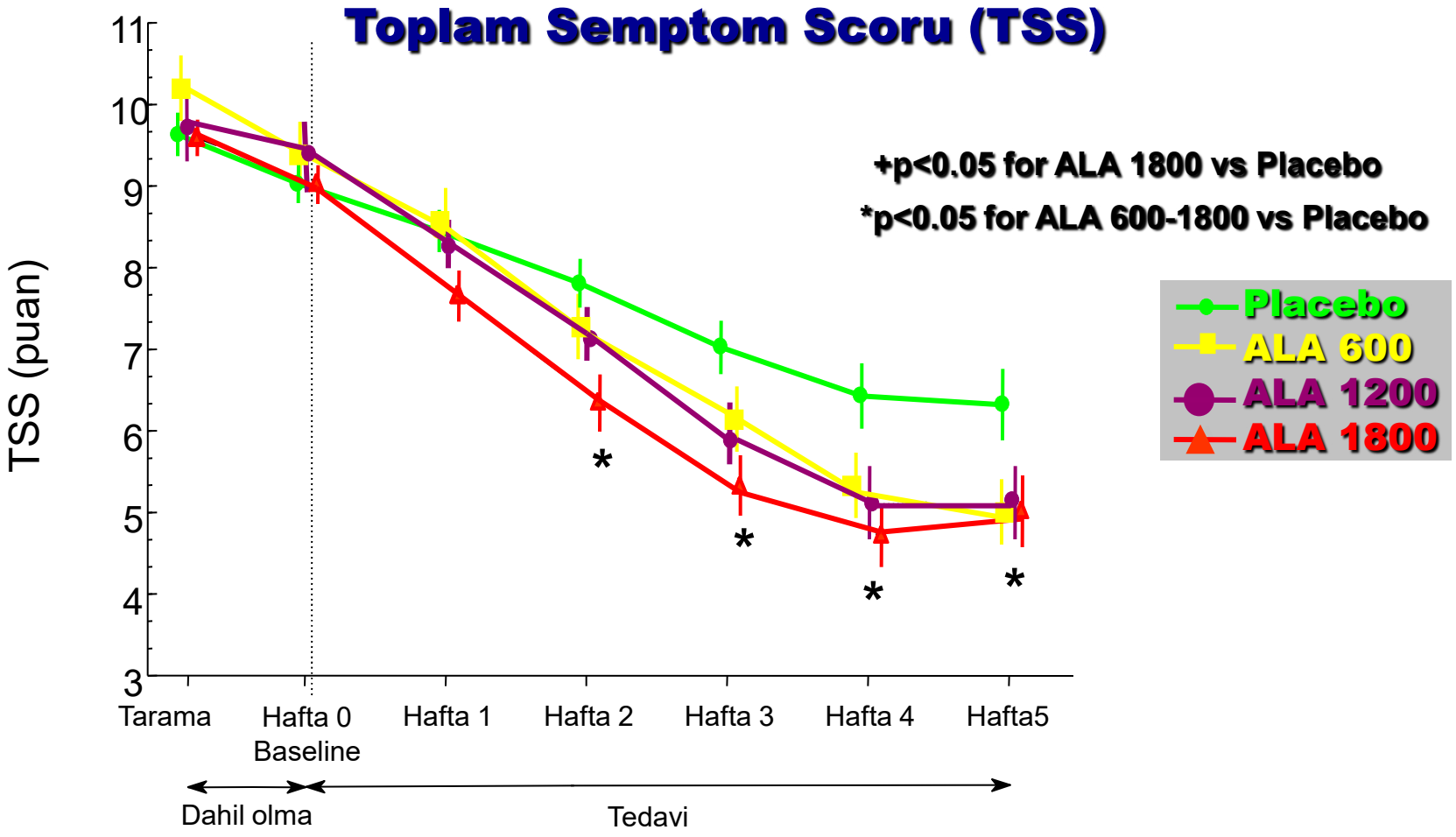
Sonuçlar



Diabetes Care 26:770–776, 2003

Sydney 2

5 haftalık oral α-lipoik asid tedavisi



Mean± SEM

Ziegler et al., Diabetes Care, 2006

NATHAN1 (The Neurological Assessment of Thioctic Acid in diabetic Neuropathy)

Efficacy and Safety of Antioxidant Treatment With α-Lipoic Acid Over 4 Years in Diabetic Polyneuropathy

The NATHAN 1 Trial

Dan Ziegler, md, frcpe[1]
Phillip A. Low, md[2]
William J. Litchy, md[2]
Andrew J.M. Boulton, md, frcp[3]
Aaron I. Vinik, md, macp[4]
Roy Freeman, md[5]
Rustem Samigullin, md[6]
Hans Tritschler, phd[7]
Ullrich Munzel, phd[7]
Joachim Maus, md[7]
Klemens Schütte, bsc[8]
Peter J. Dyck, md[2]

Diabetic distal symmetric
motor polyneuropathy (D
chronic progressive disease
around one-third of the diabeti
tion and accounts for considera
bidity, increased mortality, and
quality of life (1,2). Recent k

Diabetes Care 34:1–7, 2011

Nathan 1

Çalışma Dizaynı

- ABD, Kanada ve Avrupadan 36 merkez
- 460 diyabetik ve hafif-orta nöropatisi olan hasta
- Plasebo kontrollü randomize çift-kör parellel çalışma
- 4 yıl süreyle ALA 600 mg oral veya plasebo
- Primer ölçek NIS(LL)+7 (Mayo Klinik)

(NIS + 5 elekrofizyolojik parametre+kalp frekan değişimi +vibrasyon duyusu)

- Ayrıca Sinir ileti hızları Nöropati semptomları vb. değerlendiriliyor

Başlangıç verileri

	ALA	Placebo	*P*
n	230	224	
Age (years)	53.3 ± 8.3	53.9 ± 7.6	0.3607
Sex (% male)	66.1	67.0	0.8430
BMI (kg/m^2)	29.7 ± 6.1	29.8 ± 6.1	0.9226
Heart rate (bpm)	76.3 ± 12.3	74.6 ± 12.6	0.1603
Type 1/type 2 diabetes	27.4 / 72.6	21.0 / 79.0	0.1111
Diabetes duration (years)	13.3 (0.8–56.1)	13.5 (0.9–46.7)	0.4190
Neuropathy duration (years)	3.0 (0.0–25.4)	3.2 (0.0–21.1)	0.2588
Insulin treatment	58.9	55.1	0.4170
HbA_{1c}	8.9 ± 1.8	8.8 ± 1.9	0.6354
Fasting blood glucose (mmol/L)	11.1 ± 4.68	10.9 ± 4.26	0.6529
Nephropathy	11.7	12.0	0.5935
Retinopathy	45.5	43.6	0.6833
Neuropathy stage 1/stage 2a	11.3 / 88.7	9.8 / 90.2	0.6074
NIS-LL+7 (nds)	17.1 ± 8.4	16.8 ± 8.0	0.6740
NIS (points)	12.7 ± 8.6	12.2 ± 7.8	0.5062
NIS-LL (points)	9.8 ± 5.6	9.5 ± 5.3	0.6087
Peroneal MNCV (m/s)	38.5 ± 5.03	38.1 ± 6.48	0.4957
Sural SNAP (μV)	2.49 ± 3.38	2.43 ± 3.21	0.8387
Vibration perception threshold (JND)	21.27 ± 3.18	21.21 ± 3.52	0.8393
Cold detection threshold (JND)	17.86 ± 5.14	17.58 ± 5.33	0.5765
Heart rate deep breathing (bpm)	7.26 ± 5.44	8.59 ± 6.59	0.0193
NSC weakness (number)	0.06 ± 0.30	0.03 ± 0.23	0.2353
NSC weakness (severity)	0.10 ± 0.56	0.04 ± 0.31	0.1613
TSS (points)	2.4 ± 1.9	2.6 ± 1.8	0.2752

Data are means ± SD, median (range), or %. *P* values derived from χ^2 test for binary data and from *t* tests otherwise. JND, just noticeable difference; SNAP, sensory nerve action potential

Diabetes Care 34:1–7, 2011

Nathan 1

2. ve 4.yıl sonuçları NIS(LL)+7

	2 Years		4 Years	
	ALA	Placebo	ALA	Placebo
n	214	207	215	207
Composite score				
NIS-LL+7 (nds)	−0.40 ± 4.92	0.19 ± 4.74	−0.37 ± 5.59*	0.29 ± 5.37
NIS and subscores				
NIS	−0.54 ± 6.62	0.12 ± 6.13	−0.68 ± 6.44†	0.61 ± 6.61
NIS pinprick	−0.06 ± 1.48	−0.05 ± 1.44	−0.07 ± 1.60‡	0.05 ± 1.43
NIS-LL	−0.38 ± 4.52	0.03 ± 4.22	−0.34 ± 4.48§	0.43 ± 4.49
NIS-LL sensory function	−0.34 ± 3.02	−0.09 ± 2.92	−0.12 ± 3.01	0.10 ± 2.89
NIS-LL muscular weakness	−0.15 ± 1.66	0.05 ± 1.85	−0.21 ± 1.57†	0.17 ± 2.12
NIS-LL reflexes	0.10 ± 1.63	0.07 ± 1.57	0.03 ± 1.75	0.16 ± 1.80
NIS responders	37.9	35.2	41.1†	30.0
NIS unchanged	35.6	32.4	29.7†	31.9
NIS progressors	26.5	32.4	29.2†	38.1
NIS-LL responders	34.7	34.8	35.6†	29.0
NIS-LL unchanged	42.0	35.2	40.2†	36.2
NIS-LL progressors	23.3	30.0	24.2†	34.8
Nerve function tests				
Peroneal MNCV (m/s)	0.04 ± 3.89	0.18 ± 3.99	−0.35 ± 4.23	−0.06 ± 4.07
Sural SNAP (μV)	−0.00 ± 2.17	−0.07 ± 1.96	−0.20 ± 2.34	−0.15 ± 2.43
Foot VPT (JND)	0.47 ± 2.12	0.58 ± 2.11	0.87 ± 2.35	0.76 ± 2.38
Cold detection threshold (JND)	0.65 ± 3.56	0.87 ± 3.33	1.12 ± 3.96	1.28 ± 3.43
Heart rate deep breathing (bpm)	−0.68 ± 3.39	−1.06 ± 3.23	−0.67 ± 4.44¶	−1.35 ± 3.72
Neuropathic symptoms				
NSC weakness (number)	−0.02 ± 0.30	0.04 ± 0.42	−0.04 ± 0.26†	0.04 ± 0.42
NSC weakness (severity)	−0.03 ± 0.40	0.03 ± 0.48	−0.05 ± 0.39†	0.04 ± 0.50
TSS	−0.27 ± 2.46	−0.04 ± 2.16	−0.22 ± 2.42	−0.21 ± 2.45

Data are means ± SD or %. All *P* values calculated vs. placebo, with two-way ANOVA for NIS-LL+7 and Wilcoxon Mann-Whitney tests otherwise. JND, just noticeable difference; SNAP, sensory nerve action potential; VPT, vibration perception threshold. *$P = 0.105$. †$P < 0.05$. ‡$P = 0.074$. §$P = 0.0505$. ¶$P = 0.087$.

Nathan 1

2. ve 4.yıl sonuçları NIS(LL)

	2 Years		4 Years	
	ALA	Placebo	ALA	Placebo
n	214	207	215	207
Composite score				
NIS-LL+7 (nds)	−0.40 ± 4.92	0.19 ± 4.74	−0.37 ± 5.59*	0.29 ± 5.37
NIS and subscores				
NIS	−0.54 ± 6.62	0.12 ± 6.13	−0.68 ± 6.44†	0.61 ± 6.61
NIS pinprick	−0.06 ± 1.48	−0.05 ± 1.44	−0.07 ± 1.60‡	0.05 ± 1.43
NIS-LL	−0.38 ± 4.52	0.03 ± 4.22	−0.34 ± 4.48§	0.43 ± 4.49
NIS-LL sensory function	−0.34 ± 3.02	−0.09 ± 2.92	−0.12 ± 3.01	0.10 ± 2.89
NIS-LL muscular weakness	−0.15 ± 1.66	0.05 ± 1.85	−0.21 ± 1.57†	0.17 ± 2.12
NIS-LL reflexes	0.10 ± 1.63	0.07 ± 1.57	0.03 ± 1.75	0.16 ± 1.80
NIS responders	37.9	35.2	41.1†	30.0
NIS unchanged	35.6	32.4	29.7†	31.9
NIS progressors	26.5	32.4	29.2†	38.1
NIS-LL responders	34.7	34.8	35.6†	29.0
NIS-LL unchanged	42.0	35.2	40.2†	36.2
NIS-LL progressors	23.3	30.0	24.2†	34.8
Nerve function tests				
Peroneal MNCV (m/s)	0.04 ± 3.89	0.18 ± 3.99	−0.35 ± 4.23	−0.06 ± 4.07
Sural SNAP (μV)	−0.00 ± 2.17	−0.07 ± 1.96	−0.20 ± 2.34	−0.15 ± 2.43
Foot VPT (JND)	0.47 ± 2.12	0.58 ± 2.11	0.87 ± 2.35	0.76 ± 2.38
Cold detection threshold (JND)	0.65 ± 3.56	0.87 ± 3.33	1.12 ± 3.96	1.28 ± 3.43
Heart rate deep breathing (bpm)	−0.68 ± 3.39	−1.06 ± 3.23	−0.67 ± 4.44¶	−1.35 ± 3.72
Neuropathic symptoms				
NSC weakness (number)	−0.02 ± 0.30	0.04 ± 0.42	−0.04 ± 0.26†	0.04 ± 0.42
NSC weakness (severity)	−0.03 ± 0.40	0.03 ± 0.48	−0.05 ± 0.39†	0.04 ± 0.50
TSS	−0.27 ± 2.46	−0.04 ± 2.16	−0.22 ± 2.42	−0.21 ± 2.45

Data are means ± SD or %. All *P* values calculated vs. placebo, with two-way ANOVA for NIS-LL+7 and Wilcoxon Mann-Whitney tests otherwise. JND, just noticeable difference; SNAP, sensory nerve action potential; VPT, vibration perception threshold. *$P = 0.105$. †$P < 0.05$. ‡$P = 0.074$. §$P = 0.0505$. ¶$P = 0.087$.

Nathan 1

2. ve 4.yıl sonuçları: Nöröpati semptomları

	2 Years		4 Years	
	ALA	Placebo	ALA	Placebo
n	214	207	215	207
Composite score				
NIS-LL+7 (nds)	−0.40 ± 4.92	0.19 ± 4.74	−0.37 ± 5.59*	0.29 ± 5.37
NIS and subscores				
NIS	−0.54 ± 6.62	0.12 ± 6.13	−0.68 ± 6.44†	0.61 ± 6.61
NIS pinprick	−0.06 ± 1.48	−0.05 ± 1.44	−0.07 ± 1.60‡	0.05 ± 1.43
NIS-LL	−0.38 ± 4.52	0.03 ± 4.22	−0.34 ± 4.48§	0.43 ± 4.49
NIS-LL sensory function	−0.34 ± 3.02	−0.09 ± 2.92	−0.12 ± 3.01	0.10 ± 2.89
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NIS-LL reflexes	0.10 ± 1.63	0.07 ± 1.57	0.03 ± 1.75	0.16 ± 1.80
NIS responders	37.9	35.2	41.1†	30.0
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Nerve function tests				
Peroneal MNCV (m/s)	0.04 ± 3.89	0.18 ± 3.99	−0.35 ± 4.23	−0.06 ± 4.07
Sural SNAP (μV)	−0.00 ± 2.17	−0.07 ± 1.96	−0.20 ± 2.34	−0.15 ± 2.43
Foot VPT (JND)	0.47 ± 2.12	0.58 ± 2.11	0.87 ± 2.35	0.76 ± 2.38
Cold detection threshold (JND)	0.65 ± 3.56	0.87 ± 3.33	1.12 ± 3.96	1.28 ± 3.43
Heart rate deep breathing (bpm)	−0.68 ± 3.39	−1.06 ± 3.23	−0.67 ± 4.44¶	−1.35 ± 3.72
Neuropathic symptoms				
NSC weakness (number)	−0.02 ± 0.30	0.04 ± 0.42	−0.04 ± 0.26†	0.04 ± 0.42
NSC weakness (severity)	−0.03 ± 0.40	0.03 ± 0.48	−0.05 ± 0.39†	0.04 ± 0.50
TSS	−0.27 ± 2.46	−0.04 ± 2.16	−0.22 ± 2.42	−0.21 ± 2.45

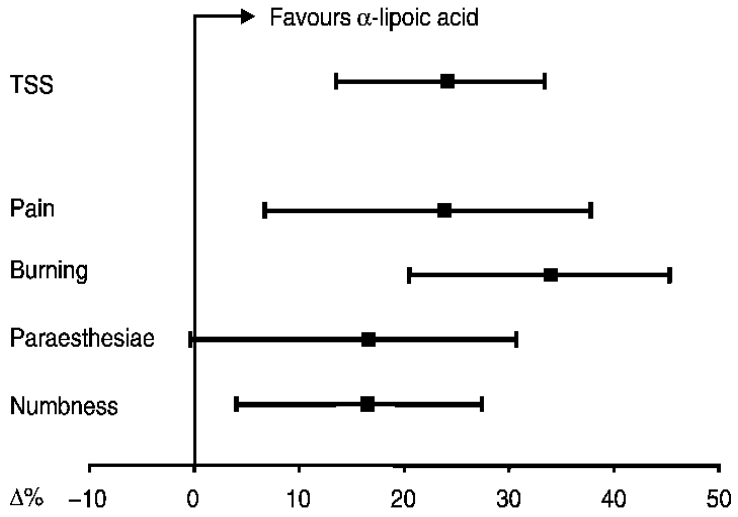
Data are means ± SD or %. All *P* values calculated vs. placebo, with two-way ANOVA for NIS-LL+7 and Wilcoxon Mann-Whitney tests otherwise. JND, just noticeable difference; SNAP, sensory nerve action potential; VPT, vibration perception threshold. *$P = 0.105$. †$P < 0.05$. ‡$P = 0.074$. §$P = 0.0505$. ¶$P = 0.087$.

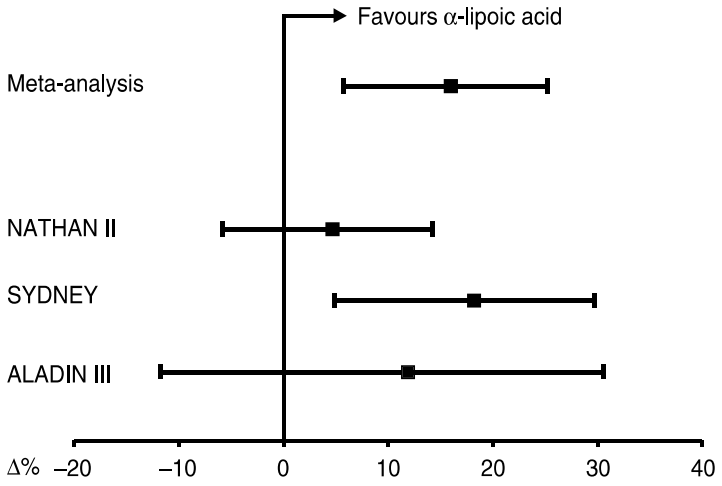
Treatment of symptomatic diabetic polyneuropathy with the antioxidant α-lipoic acid: a meta-analysis

D. Ziegler, H. Nowak*, P. Kemplert†, P. Vargha‡ and P. A. Low§

ALADIN I, ALADIN III, SYDNEY, NATHAN II)
n **= 1258 patients (α-lipoic acid)** ***n*** **= 716; placebo =542**

NIS (LL) skoru





Ziegler et al., *Diabetic Med* 2004;21:114-21

Review Article

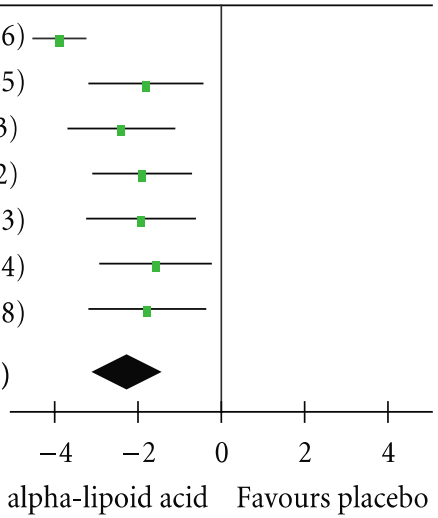
Alpha Lipoic Acid for Symptomatic Peripheral Neuropathy in Patients with Diabetes: A Meta-Analysis of Randomized Controlled Trials

TSS bakılan randomize plasebo konrollü çalışmaların meta analizi

Study or subgroup	Alpha-lipoic acid Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean difference IV, random, 95% CI
Ametov et al. 2003	−5.72	1.53	60	−1.83	1.97	60	18.1%	−3.89 (−4.52, −3.26)
Ruhnau et al. 1999	−3.75	1.88	12	−1.94	1.5	12	13.3%	−1.81 (−3.17, −0.45)
Ziegler et al.1995b	−5	4.1	63	−2.6	3.2	66	13.9%	−2.40 (−3.67, −1.13)
Ziegler et al. 1995c	−4.5	3.7	66	−2.6	3.2	66	14.5%	−1.90 (−3.08, −0.72)
Ziegler et al. 2006a	−4.85	3.03	45	−2.92	3.18	43	13.7%	−1.93 (−3.23, −0.63)
Ziegler et al. 2006b	−4.5	3.28	47	−2.92	3.18	43	13.5%	−1.58 (−2.92, −0.24)
Ziegler et al. 2006c	−4.7	3.54	46	−2.92	3.18	43	13.1%	−1.78 (−3.18, −0.38)
Total (95% CI)			**339**			**333**	**100%**	**−2.26 (−3.12, −1.41)**

Heterogeneity: $\tau^2 = 0.95$; $\chi^2 = 22.98$, $df = 6$ ($P = 0.0008$); $I^2 = 74\%$

Test for over all effect: $Z = 5.19$ ($P < 0.00001$)



Mijnhout et al, International Journal Endocrinology 2012

A systematic review and meta-analysis of α-lipoic acid in the treatment of diabetic peripheral neuropathy

Tingting Han, Jiefei Bai, Wei Liu and Yaomin Hu

Department of Endocrinology, Renji Hospital, Shanghai Jiaotong University, 200127 Shanghai, China

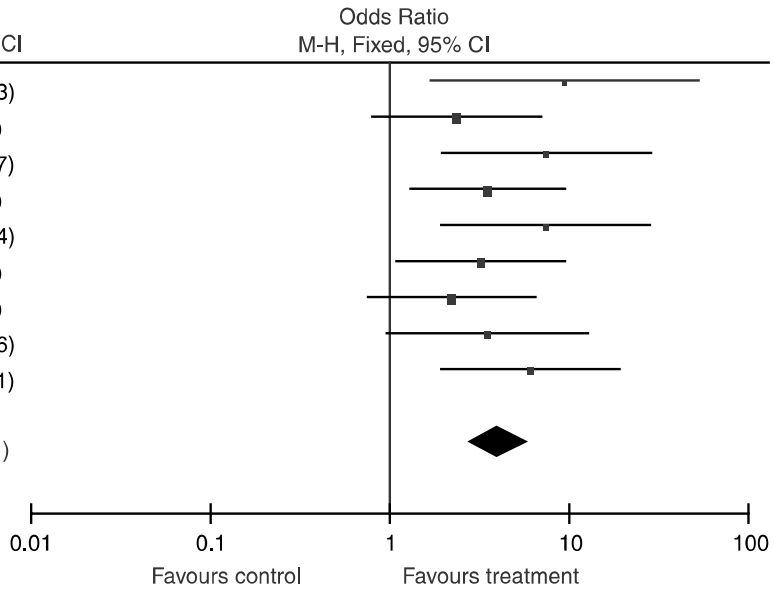
(Correspondence should be addressed to Y Hu; Email: amin1031@hotmail.com)

15 randomize plasebon konrollü çalışmaların meta analizi Semptomlardaki iyileşmeye göre

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Chen *et al.* (2008)	17	19	9	19	3.6%	9.44 (1.69, 52.73)
Li & Xu (2008)	39	45	33	45	16.5%	2.36 (0.80, 6.99)
Lu (2009)	23	27	10	23	6.0%	7.47 (1.95, 28.67)
Qiao (2009)	41	48	30	48	16.4%	3.51 (1.30, 9.48)
Wang (2009)	37	40	25	40	7.0%	7.40 (1.94, 28.24)
Wu *et al.* (2008)	40	46	27	40	14.2%	3.21 (1.09, 9.49)
Xia *et al.* (2008)	31	38	24	36	17.1%	2.21 (0.76, 6.48)
Zhang *et al.* (2009)	28	32	20	30	9.7%	3.50 (0.96, 12.76)
Zhao (2008)	34	39	19	36	9.5%	6.08 (1.94, 19.11)
Total (95% CI)		334		317	100.0%	4.03 (2.73, 5.94)
Total events	290		197			

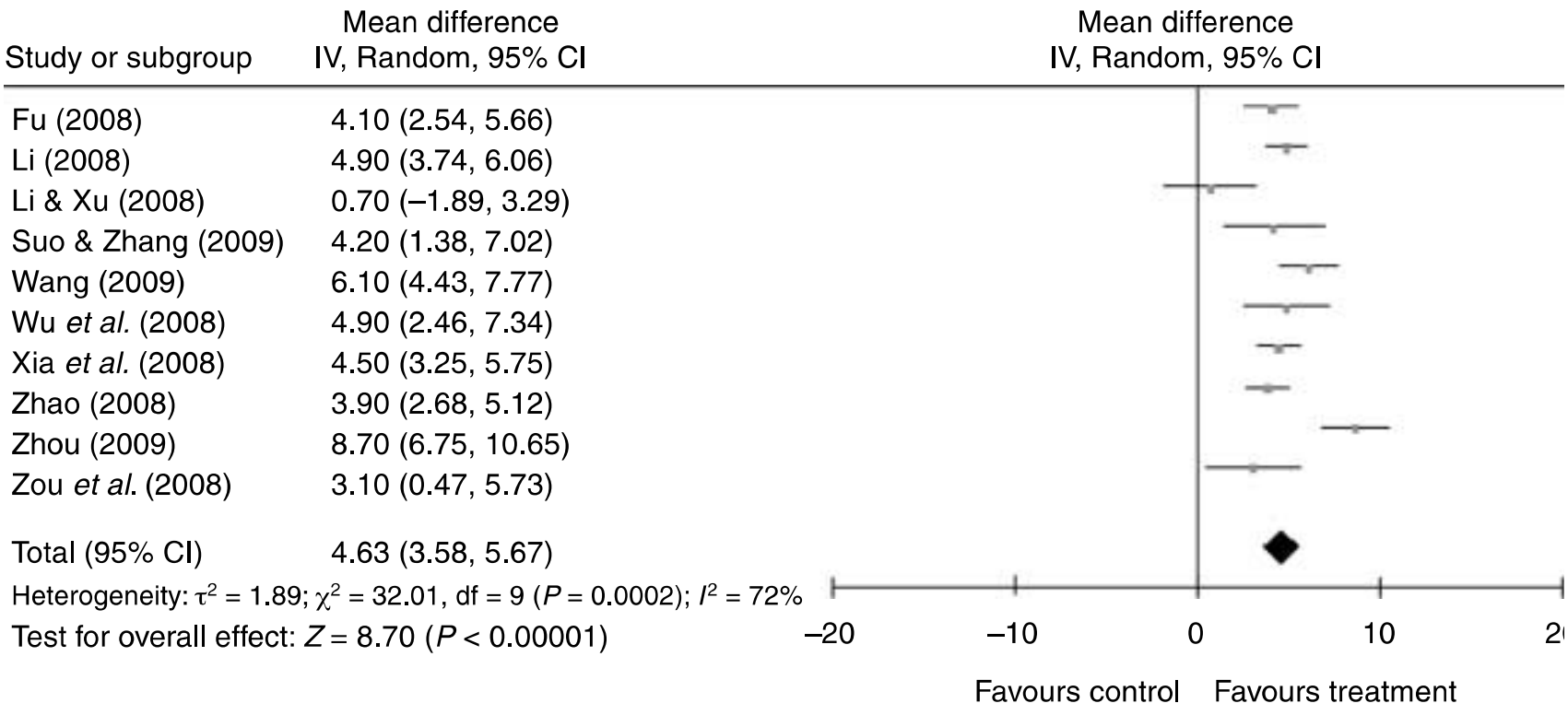
Heterogeneity: $\chi^2 = 5.45$, df = 8 ($P = 0.71$); $I^2 = 0\%$

Test for overall effect: $Z = 7.00$ ($P < 0.00001$)



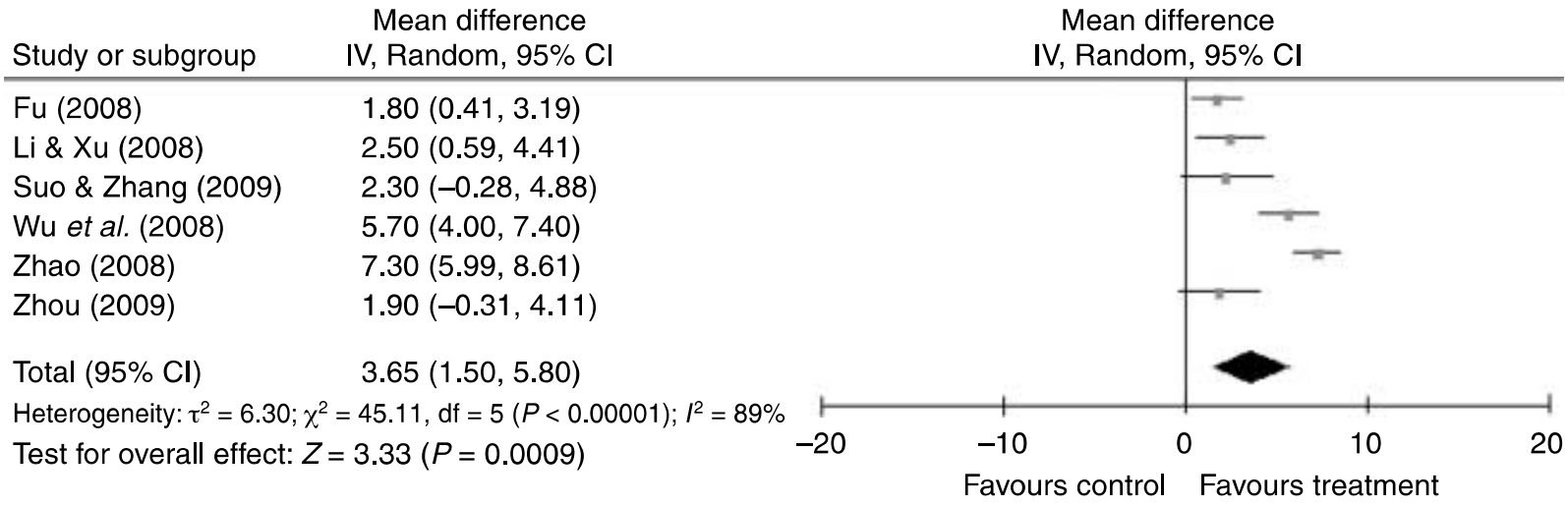
European Journal of Endocrinology 2012

Sinir ileti hızlarının ALA verilen grup ile plasebo verilen grupların meta analizi (median Sensori NCV)



Sinir ileti hızlarının ALA verilen grup ile plasebo verilen grupların meta analizi (median Motor NCV)

EUROPEAN JOURNAL OF ENDOCRINOLOGY (2012) **167**



European Journal of Endocrinology 2012

α –lipoik asit

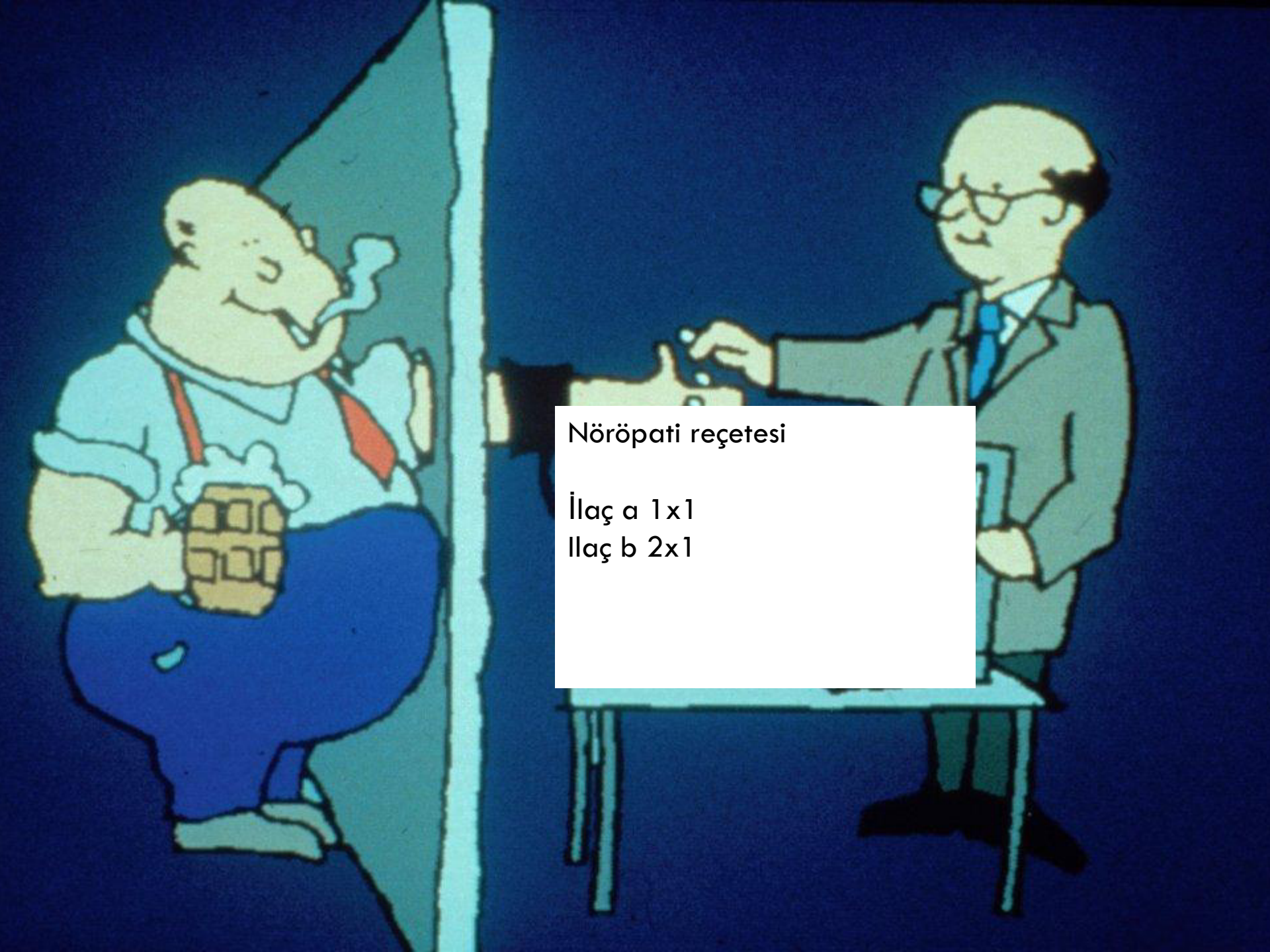
ETKİLERİ

Sinir içi kan akımını ve aksonal transportta iyileşme,
NGF stimülasyonu,
Oksidatif stresi azaltır (antioksidan)
AGE inhibisyonu

İlaç	Optimal Doz (mg/g)	NNT	NNH	Etki başlaması
α –lipoik asit	600 IV 600-1800 PO	6.3 2.8-4.2		3 hafta

NNT= Ağrı yakınmasında %50'lik azalma elde etmek için tedavi edilmesi gerekli hasta sayısı
NNH= Bir hastanın yan etkileri nedeniyle ilacı kesmesi için gerekli hasta sayısı

* Pharmacist June 2010
The Cochrane Collaboration 2010
Mayo Clin Pract 2010;85(Sup:3)S3-S14
D.Care 2009;32(suppl.2):S414-419
JAMA 2010;303(5):420:1451-1458

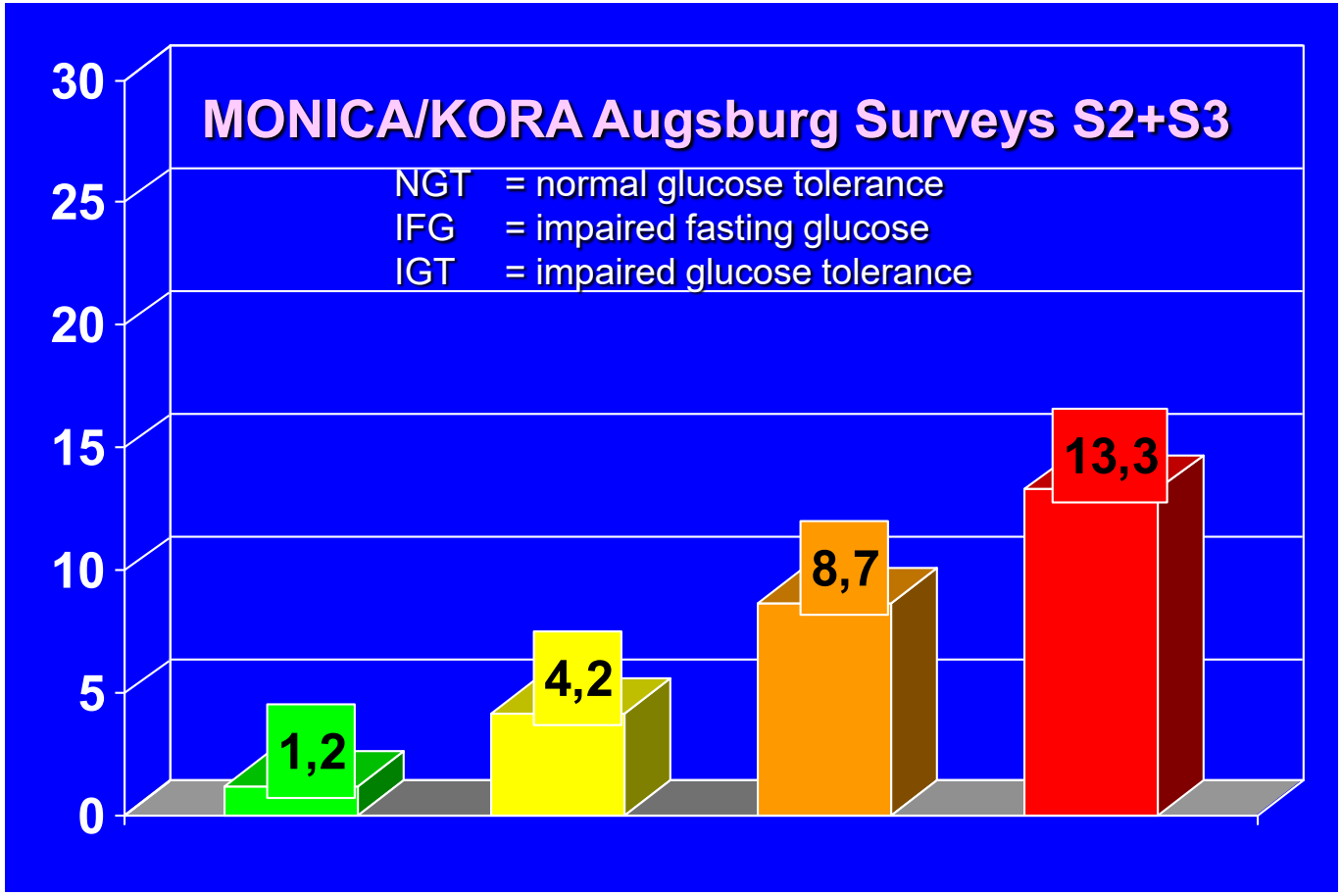

Nöröpati reçetesi
İlaç a 1x1
Ilaç b 2x1

Potential mechanisms linking metbolic, vascular, and neural defects in diabetic neuropathy

Initiator	Metabolic defect	Metabolic mediator	Functional mediator	Consequence
↑ Glucose	Glycation/AGE	Protein cross-linking	Matrix defects	Endoneurial fibrosis ↓ Neurotrophic SAM
		Protein inactivation	Receptor-ligand defects	↓ Neurotrophism
		NO quenching	Vasoconstriction	Ischemia/hypoxia
		Macrophage activation	Cytokines, ↑ TGF	Cytotoxicity* Endoneurial fibrosis
		Free radical formation	Oxidative stress	Cytotoxicity
	Autooxidation	Free radical formation	Oxidative stress	Cytotoxicity*
	↑ Sorbitol pathway	↓ NADPH	Oxidative stress↓ NO synthesis	Cytotoxicity* Ischemia/hypoxia
		NADH/lactate	Pseudohypoxia	Cytotoxicity*
		↑ Glycation	(see above)	(see above)
		↓ Taurine	Oxidative stress	Cytotoxicity*
		↓ MI/↓ PI/↓ PKC	Signal transduction Eicosinoid defects	↓ Neurotrophism Ischemia/hypoxia
	↑ DAG	↑ PKC	Signal transduction	Ischemia
FA defects	↑ free FA	↑ long-chain acyl-Co's	Mitochondrial defects	Cytotoxicity
	↓ 3-β-dehydrog.	↓ GLA	Eicosinoid defects	Ischemia/hypoxia
↓ Insulin	?↓ GF expression	?IGF/NGF/BDNF/NT3	Neurotrophic factors	↓ Neurotrophism

AGE: advanced glycosylation end-products; BDNF: brain-derived neurotrophic factor; DAG: diacylglycerol; FA: fatty acid; GLA: gamma linoleic acid; IGF: insulin-like growth factors; MI: myoinositol; NO: nitric oxide; PI: phosphoinositides; PKC: protein kinase C; NT3: neurotrophin-3; SAM: substrate adhesion molecules; TGF: transforming growth factor.
* Cytotoxicity of neural, glial, and vascular components of peripheral nerve.
Adapted from: Stevens, MJ, Feldman, EL, Greene, DA, Diabet Med 1995; 12:566.

Diyabet ve Prediyabetiklerde ağrılı nöröpati sıklığı



Ziegler et al., Pain Med 2009; 10: 393-400