



# MANAGEMENT OF DIABETIC NEUROPATHY

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## ◆ The Diabetic neuropathy cannot be reversed

- ▣ Not to restore function to damaged nerve
- ▣ Slowly progress
- ▣ no initial symptom or sign

# Contents



- Disease-modifying treatment
- Treatment of neuropathic pain
- To prevent complications of neuropathy



# **Disease-modifying treatment**

# Tight glucose control

- DCCT (5 yrs, type I with insulin), 1993
  - ▣ A relative risk reduction after 5yrs of 53%
  - ▣ The beneficial effect on cardiac autonomic neuropathy

	Trial size	Length of study (years)	Clinical outcome	Other outcomes	Enhanced glycaemic control
Type 1 diabetes					
Holman et al <sup>56</sup>	74	2.0	No	QST	Yes
Lauritzen et al <sup>57</sup>	30	2.0	No	QST	No
Dahl-Jorgensen et al <sup>58</sup>	45	2.0	No	NCS	Yes
Jakobsen et al <sup>59</sup>	24	2.0	No	QST	Yes
DCCT <sup>42</sup>	1441	5.0	Yes	NCS	Yes
Reichard et al <sup>60</sup>	102	7.5	No	NCS, QST	Yes
Linn et al <sup>61</sup>	49	5.0	Yes	None	Yes

# Clinical trials of enhanced control on neuropathy(type II)

	Trial size	Length of study (years)	Clinical outcome	Other outcomes	Enhanced glycaemic control superior?
Type 2 diabetes					
Kawamori et al <sup>62</sup>	50	4.0	No	NCS	Yes
UKPDS <sup>43</sup>	3867	10.0	No	QST	Yes
Tovi et al <sup>63</sup>	38	1.0	Yes	None	No
Azad et al <sup>64</sup>	153	2.0	Yes	None	No
Shichiri et al <sup>65</sup>	110	8.0	No	NCS, QST	Yes
Gaede et al <sup>66</sup>	160	8.0	No	QST	No
Duckworth et al <sup>67</sup>	1791	5.6	Yes	None	No
Ismail-Beigi et al <sup>68</sup>	10 251	3.7	Yes	None	No

# Enhanced glucose control for preventing and treating diabetic neuropathy

- 17 randomized studies
- Types of outcome measures
  - ▣ 1' outcome : annual development of clinical neuropathy
  - ▣ 2' outcome : motor NCV, quantitative vibration
- **Conclusions**
  - ▣ Type 1 : prevent the clinical neuropathy and reduce NCV/Vibration threshold (significantly)
  - ▣ Type 2 : reduce the incidence of clinical neuropathy (not significantly) and reduce NCV/Vibration threshold
  - ▣ Significantly increase the risk of severe hypoglycemia

- Cochrane review 2012-

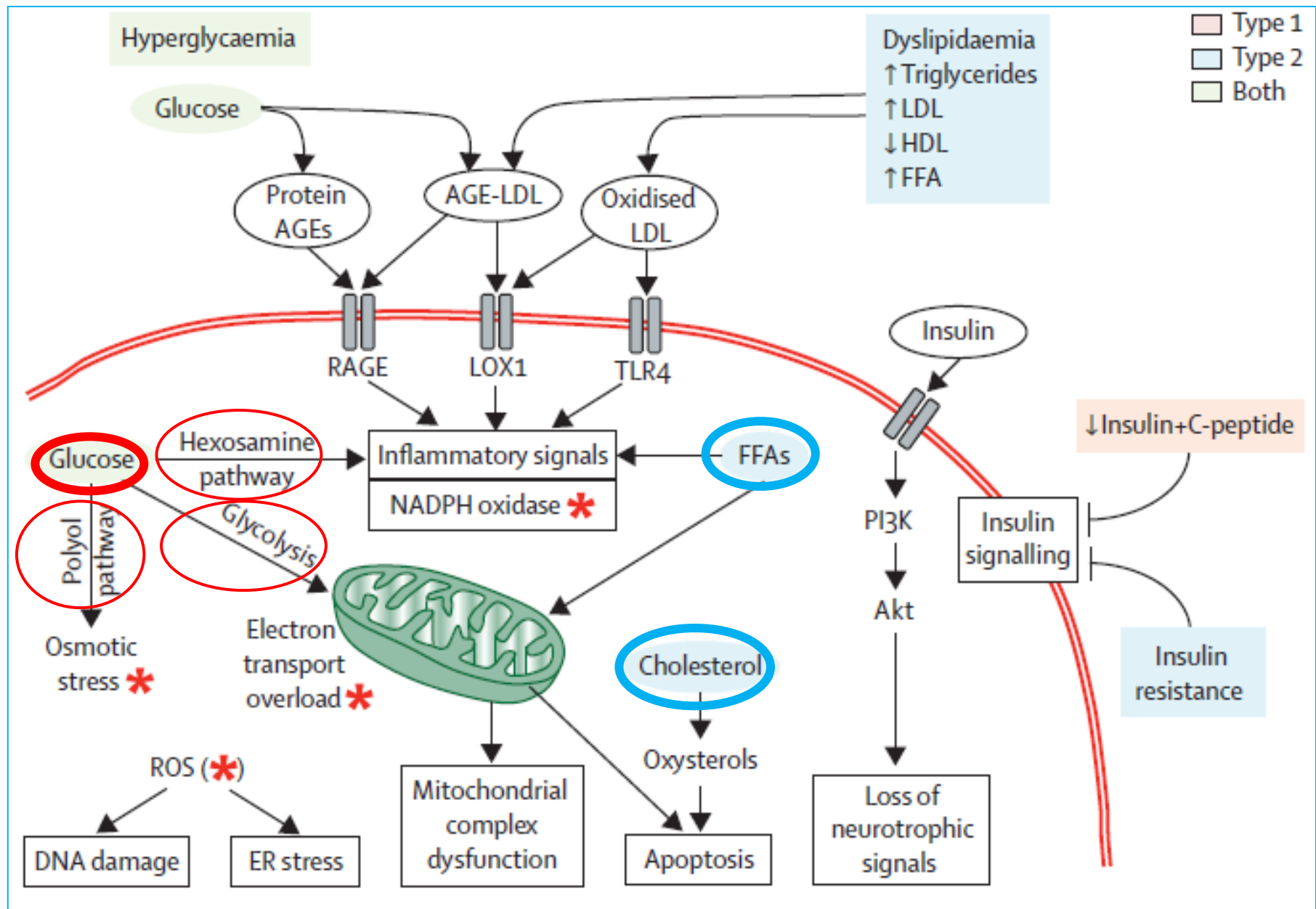
# Tight glucose control



- The cornerstone of therapy
  - ▣ Effectively slow the progression of diabetic neuropathy
  - ▣ Delay the onset of neuropathy in Type I
  - ▣ Significantly more effective in early diabetes



# <Mechanisms of diabetic neuropathy>



# Control of the Dyslipidemia

- High in type II diabetes
- Underlying mechanism
  - ▣ FFA : inflammatory signals
  - ▣ Modified LDL : oxidative stress
  - ▣ Cholesterol : apoptosis
- Type II neuropathy
  - ▣ Not typically develop rapidly, after many years of obesity
  - ▣ linked to dyslipidemia
  - ▣ A combination of Hyperglycemia, dyslipidemia and insulin resistance

# Treatment of hypertension

- Thiazide diuretics
  - ▣ Decreased sensitivity to glucose of pancreatic beta cell
  - ▣ Aggravate abnormal glucose metabolism
- ACE inhibitor or ARB
  - ▣ Some protective effect against microvascular complication and organ damage from diabetes
  - ▣ Reduce the risk of diabetes or severity of diabetic neuropathy

# Alpha lipoic acid (ALA)

- An orally bioavailable antioxidant (Thiotic acid<sup>®</sup>)
- SYDNEY 2 study, 2006
  - : randomized, double-blind, placebo-controlled
  - : 600mg, 1200mg, 1800mg for 5 weeks
  - : outcomes – TSS, NIS, NSC
  - : ALA groups improved neuropathic symptoms and deficits
- Intravenous infusion of 600mg of ALA for 3wks
- Effects
  - : to influence the pathophysiology of neuropathy
  - : to improve the endothelial dysfunction and blood flow
  - : Caution - hypoglycemic pt, thiamine deficiency

## □ Acetyl-L-carnitine

- ▣ Another antioxidant
- ▣ Inhibit lipid peroxidation and increase nitric oxide synthase and nitric oxide in experimental models
- ▣ Randomized, blinded control study
  - : improved sural morphology and VAS
- ▣ Nutritional supplement, 500 mg daily

## □ Benfotiamine

- ▣ Vitamin B1 derivative, antioxidant

## □ Increasing vascular or microvascular blood flow

- ▣ Decompressive surgery

# Pre-diabetes and neuropathy

- NCV tests at the time of diabetes diagnosis
  - ▣ 10-18% : neuropathy
  - ▣ Subclinical neuropathy
  - ▣ The nerve injury occurs at the earliest stages of diabetes
- IGT or IFG
  - ▣ One-third of adult Americans
  - ▣ The effects of pre-diabetes on neuropathy – uncertainty
- The diabetes Prevention Program (DPP) study
  - ▣ Intensive diet and exercise / metformin treatment in IGT
  - ▣ Metformin : less effective



(사진 : 복사태, 발가락도 있는 '무'의 모습 / 일본 독자가 언론에 제보한 사진 / 마이니치 신문 보도 화면 (C) Tadashi Fukuda)

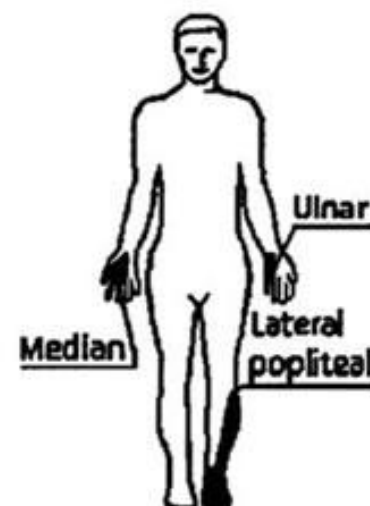
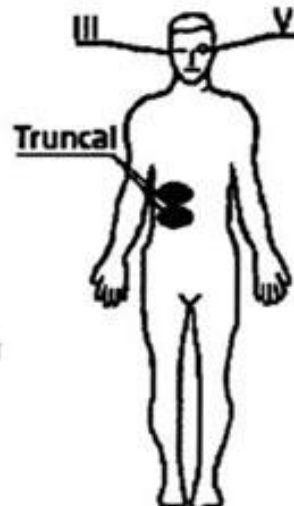
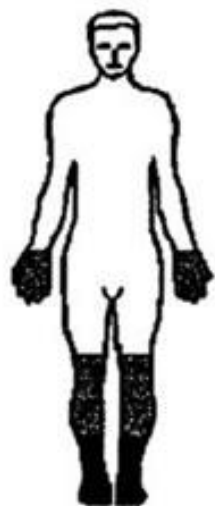
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# Treatment of neuropathic pain







Large fiber Neuropathy	Small fiber Neuropathy	Proximal motor Neuropathy	Acute mono Neuropathies	Pressure Palsies
Sensory loss: 0 → +++ (Touch, vibration) Pain: + → +++ Tendon reflex: N → ↓↓↓ Motor deficit 0 → +++	Sensory loss: 0 → + (thermal, allodynia) Pain: + → +++ Tendon reflex: N → ↓ Motor deficit: 0	Sensory loss: 0 → + Pain: + → +++ Tendon reflex: ↓↓ Proximal Motor deficit: + → +++	Sensory loss: 0 → + Pain: + → +++ Tendon reflex: N Motor deficit: + → +++	Sensory loss in Nerve distribution: + → +++ Pain: + → ++ Tendon reflex: N Motor deficit: + → +++

<Diabetic Neuropathic pain>

- 40-60% of neuropathy
- Distal symmetric, small fibers (C- and A  $\delta$  fiber)
- a negative impact of QOL

	EFNS <sup>72</sup>	AAN <sup>74</sup>
Pregabalin (300–600 mg a day)	A	A
Gabapentin	A	B
Lamotrigine	A/B*	B†
Oxcarbazepine	A/B*	B†
Lacosamide	A/B*	B†
Sodium valproate	A/B*	B
Tricyclic antidepressants	A	B (amitriptyline)
Serotonin-norepinephrine reuptake inhibitor	A	B (venlafaxine, duloxetine)
Opioids	A (oxycodone)	B (morphine, oxycodone)
Tramadol	A	B
Dextromethorphan	B	B
Topical capsaicin	A/B*	B
Isosorbide spray	A	B
ABT-594	A	..
Botulinum toxin	B	..
Levodopa	B	..
Lidocaine patch	..	C

<A: established, B: probably, C: possibly, \*ineffective or discrepant, †: not recommended>

# Anticonvulsant (I)

## □ Pregabalin

- ▣ Level A evidence both EFNS and AAN
- ▣ Binds to the  $\alpha_2$ - $\delta$  subunit of voltage-gated calcium channels
  - > reduces calcium influx at presynaptic terminals
  - > inhibit the release of excitatory neurotransmitters
- ▣ Anticonvulsant, anxiolytic activity, fibromyalgia
- ▣ 150mg -> 300-600 mg a day (Linear pharmacokinetics)
- ▣ half-life : 12hr

# Anticonvulsant (II)

## □ Gabapentin

### ▣ Pain-modulating neurotransmitter

- Alteration of the synthesis and release of GABA
- Alteration of monoamine neurotransmitter release and blood serotonin levels

### ▣ Renal excretion

### ▣ 900mg -> 2400-3600 mg a day

## □ Sodium valproate (trigeminal neuralgia and migraine), Oxcarbazepine, Lamotrigine : not recommended

# Antidepressants (I)

## □ TCA (amitriptyline)

- A first-line treatment

- Mechanism

- Inhibition of norepinephrine serotonin reuptake within CNS
- Alpha-adrenergic blockade, sodium channel block, NMDA-receptor antagonism

- Inexpensive, sleep initiation, hypotension,

- 25-100 mg (beginning at 10mg)

- Caution

- Partial or complete heart block (esp old pts), MI

- Nortriptylin – reduced side effect

# Antidepressants (II)

## □ SNRI

### ▣ Duloxetine (Cymbalta®)

- Balanced selective serotonin /norepinephrine reuptake inhibitor
- 60-120 mg
- FDA-indicated
- Depression, anxiety, fibromyalgia
- Not recommended in ESRD, hepatic impairment

### ▣ Venlafaxine

- More effective in high dose(150-225mg)
- Combination with gabapentin : improvement in mood and QOL

# Opioids

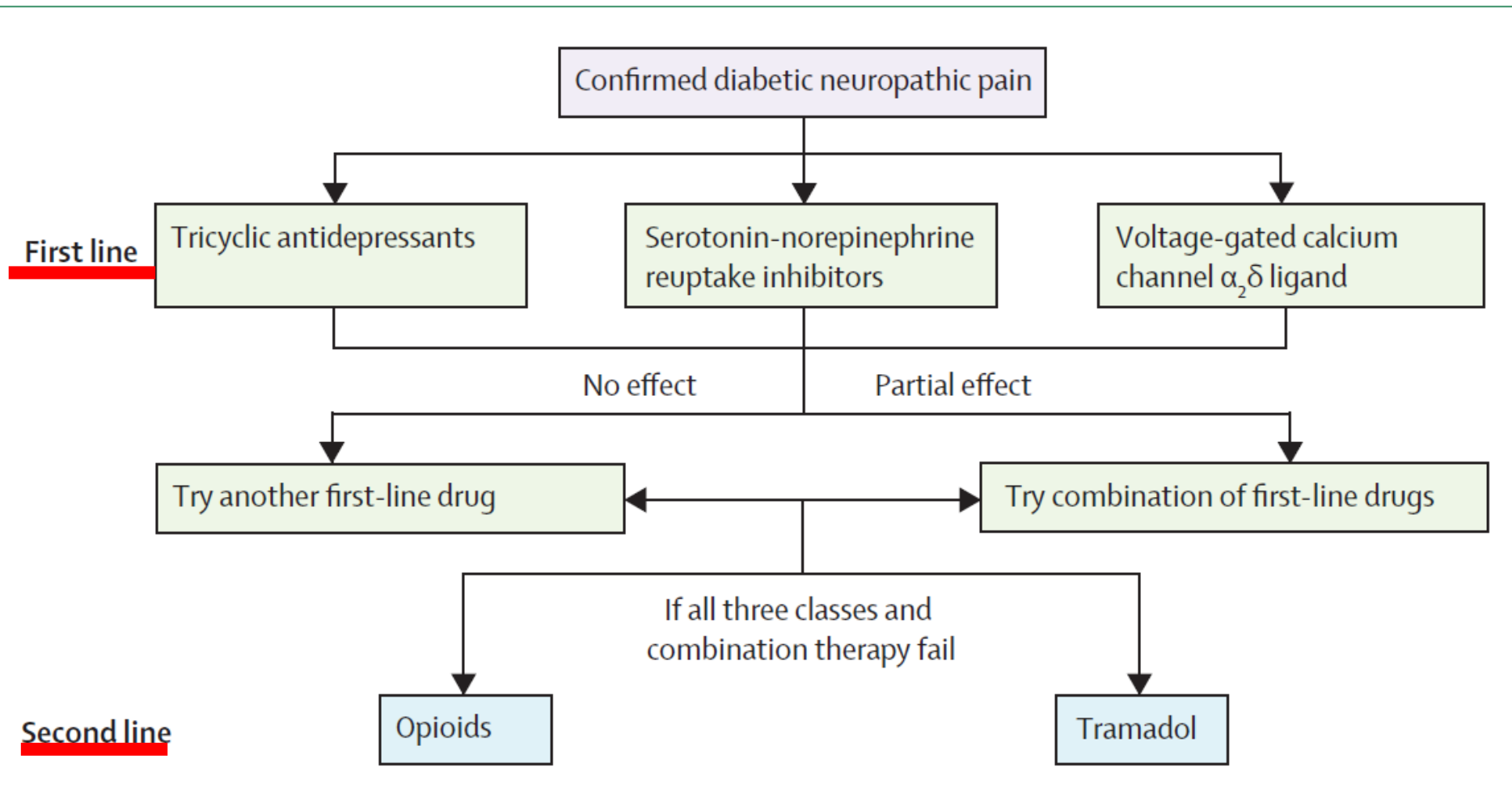
## □ Oxycodone

- ▣ Adjunct treatment in poorly controlled neuropathic pain
- ▣ Combination of gabapentin
  - More pain relief
  - Constipation, dry mouth

## □ Tramadol

- ▣ Binds to opiate receptors and block reuptake of serotonin and norepinephrine
- ▣ A low potential for abuse
- ▣ 50-100mg -> 200-400 mg a day

# <Algorithm for the treatment of diabetic painful neuropathy>





# To prevent complications of neuropathy



# Complication of diabetic neuropathy

- The primary cause of the majority of diabetic foot
- Foot ulceration and amputation
  - ▣ Increase the risk of ulcer sevenfold
  - ▣ Over 60% of L/E amputation
  - ▣ Related to duration of neuropathy and severity of hyperglycemia
- Diabetic charcot's neuroarthropathy
- Falls
  - ▣ At higher risk of falling (Diabetic pt over 55 yrs : 1/3)
  - ▣ Sensory loss, distal weakness, diabetic retinopathy

# Prevention of Diabetic foot

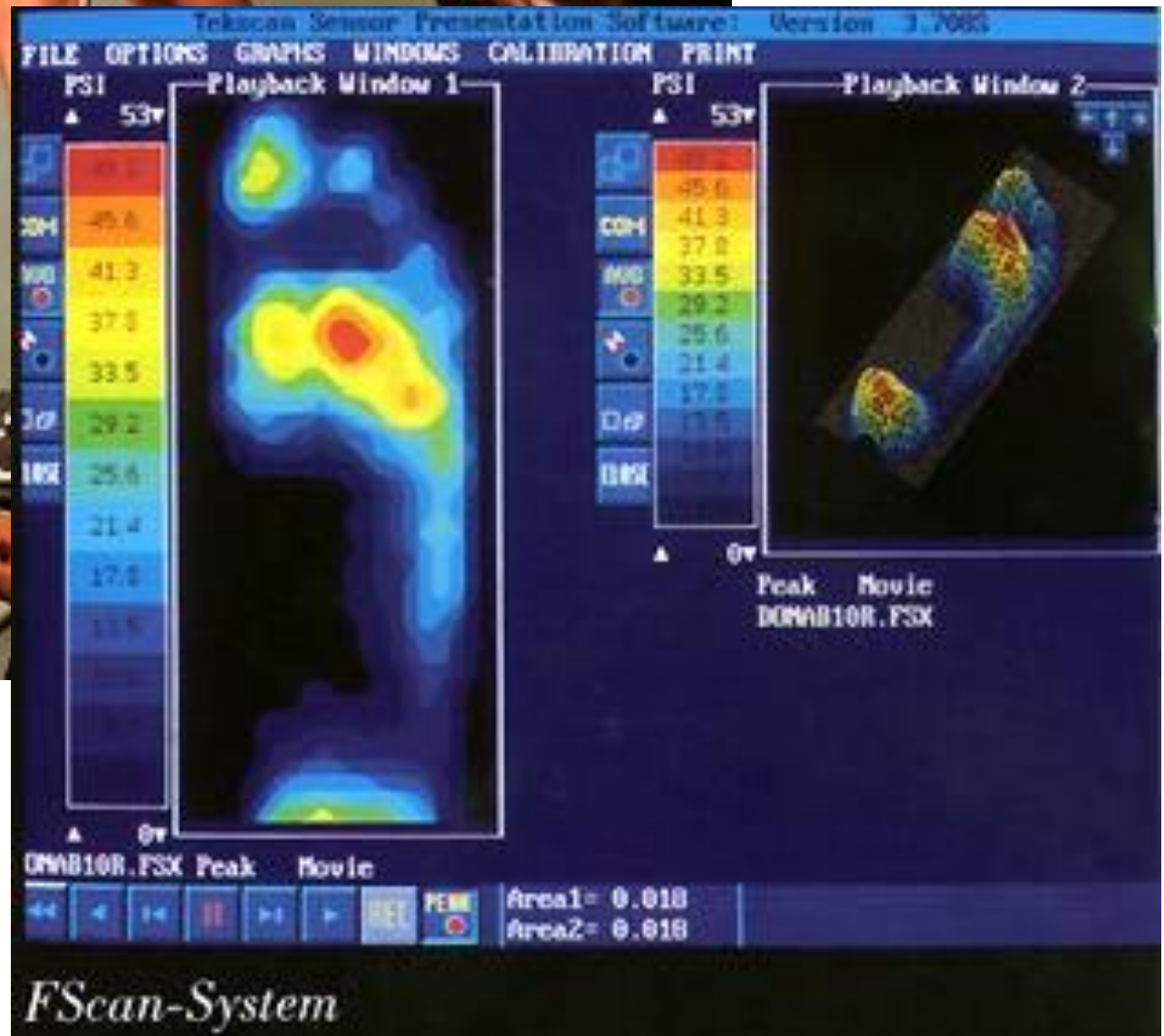
- Patient's education
- Daily self examination
- Good shoes for diabetic foot
- Visit to diabetic specialist (foot care)
  - ▣ Toenail
  - ▣ Corn and callus



## <corn and callus>











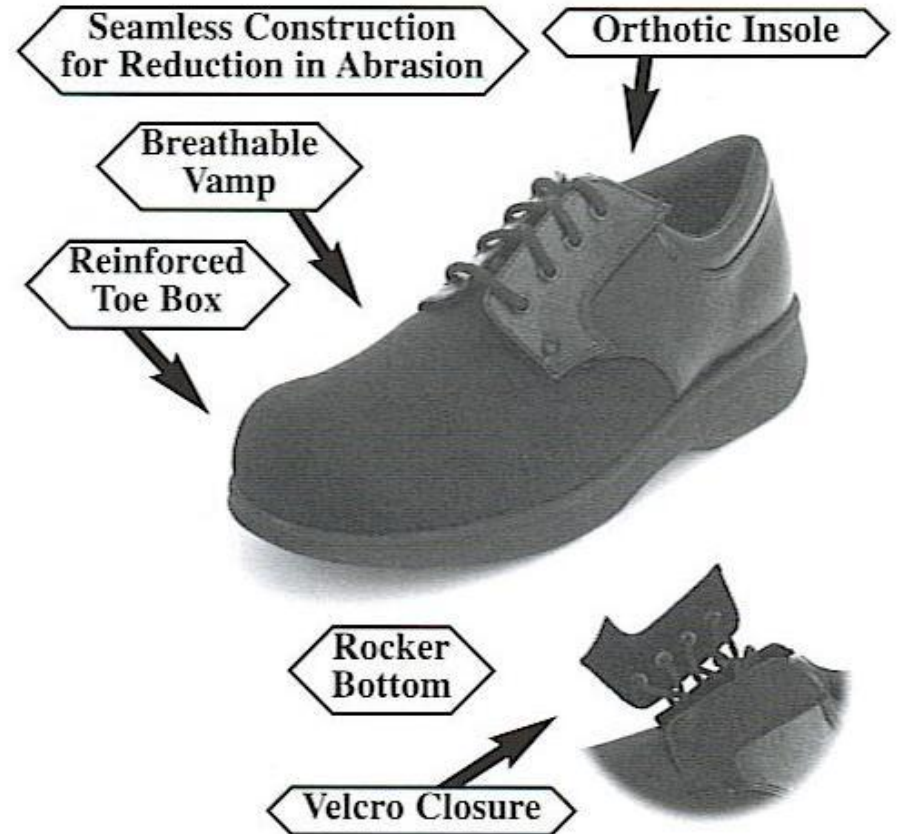




# Shoe

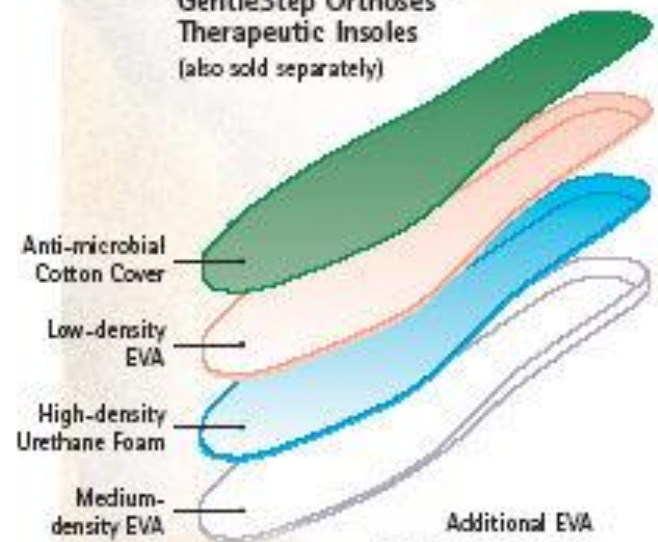
- Length / width
- Toe box
- Confirm heel counter
- Soft upper part
- Seamless inner surface
- Rocker bottom
- To confirm the foreign body in shoe

## Designed for the Diabetic foot





GentleStep Orthoses™  
Therapeutic Insoles  
(also sold separately)



Additional EVA  
material provided for  
customizing orthoses



# Take home message

- Diabetic neuropathy
  - ▣ Tight glucose control
  - ▣ Treatment of neuropathic pain
- Neuropathic pain
  - ▣ 1<sup>st</sup> line : pregabalin, TCA, SSRI
  - ▣ 2<sup>nd</sup> line : tramadol, opioid
- Prevention of the diabetic foot
  - ▣ Good shoes
  - ▣ Regular exam and foot care





*Thank you for your attention !!*