SERTIFIKAT

KALBE ACADEMIA

Diberikan Kepada

dr. Putu Eka Widyadharma, SpS(K)

Telah Berpartisipasi Dalam

Symposium & Workshop
"Type-2 Diabetes Mellitus & Its Neurological Complications"

Minggu, 8 Juli 2018 - Swiss-belHotel Mangga Besar, Jakarta

Sebagai

SPEAKER

Ketua IDI Cabang Jakarta

IKATAN DOKTER INDONESIA CAB. JAKARTA PUSAT

Dr. H. Kemas Abdurrohim, MARS., M.Kes., Sp.Ak.

No SKP : 131 /IDIWILJKT/SKP/VI/2018

Simposium : Peserta : 2 SKP, Pembicara : 8 SKP, Moderator : 2 SKP, Panitia : 1 SKP

Workshop : Peserta : 6 SKP, Instruktur : 2 SKP, Panitia : 2 SKP

CURICULUM VITAE

dr. I Putu Eka Widyadharma, M.Sc, Sp.S(K)

Pendidikan :

S1	: Universitas Udayana Denpasar Tahun 1997
Profesi	: Universitas Udayana Denpasar Tahun 1999
S2 –Clinical Medicine	: Universitas Gadjah Mada Yogyakarta Tahun 2009
Spesialis Saraf	: Universitas Gadjah Mada Yogyakarta Tahun 2009
Konsultan Nyeri	: Kolegium Neurologi Indonesia Tahun 2014
Pendidikan Doktor	: S3 Ilmu Kedokteran Universitas Udayana sejak 2015-sekarang

Pelatihan/Workshop :

- Neuropathic pain Management, Manila, Philippine, 2011
- Pain Management, Mumbai, India, 2012
- Diabetic Neuropathy Workshop, , Manila, Philippine, 2012
- USG for Neurologist, Jakarta, 2012
- Neuropathic pain workshop, Milan, Italy 2012
- USG Guidance for Interventional Pain management, Bandung 2012
- Pain Management Camp, Singapore 2013
- Interventional Pain Management, Medan 2013
- USG Guidance In Pain management, Yogyakarta 2014
- Asia Facific Pain Summit, Denpasar 2016
- Neuropathic Pain, Yokohama, Jepang 2016
- Dry Needling, Perth, Australia, 2017

Towards an Understanding of Pain in Diabetic Neuropathy

I Putu Eka Widyadharma

Departemen Neurologi, Fakultas Kedokteran
Universitas Udayana, Denpasar-Bali

What is pain?

An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

International Association for the Study of Pain (IASP) 2011

International Association for the Study of Pain. *IASP Taxonomy.* Available at: http://www.iasp-pain.org/AM/Template.cfm?Section=Pain_Definitions. Accessed: July 15, 2013.

Pain Is the 5th Vital Sign

Respiration

Pulse

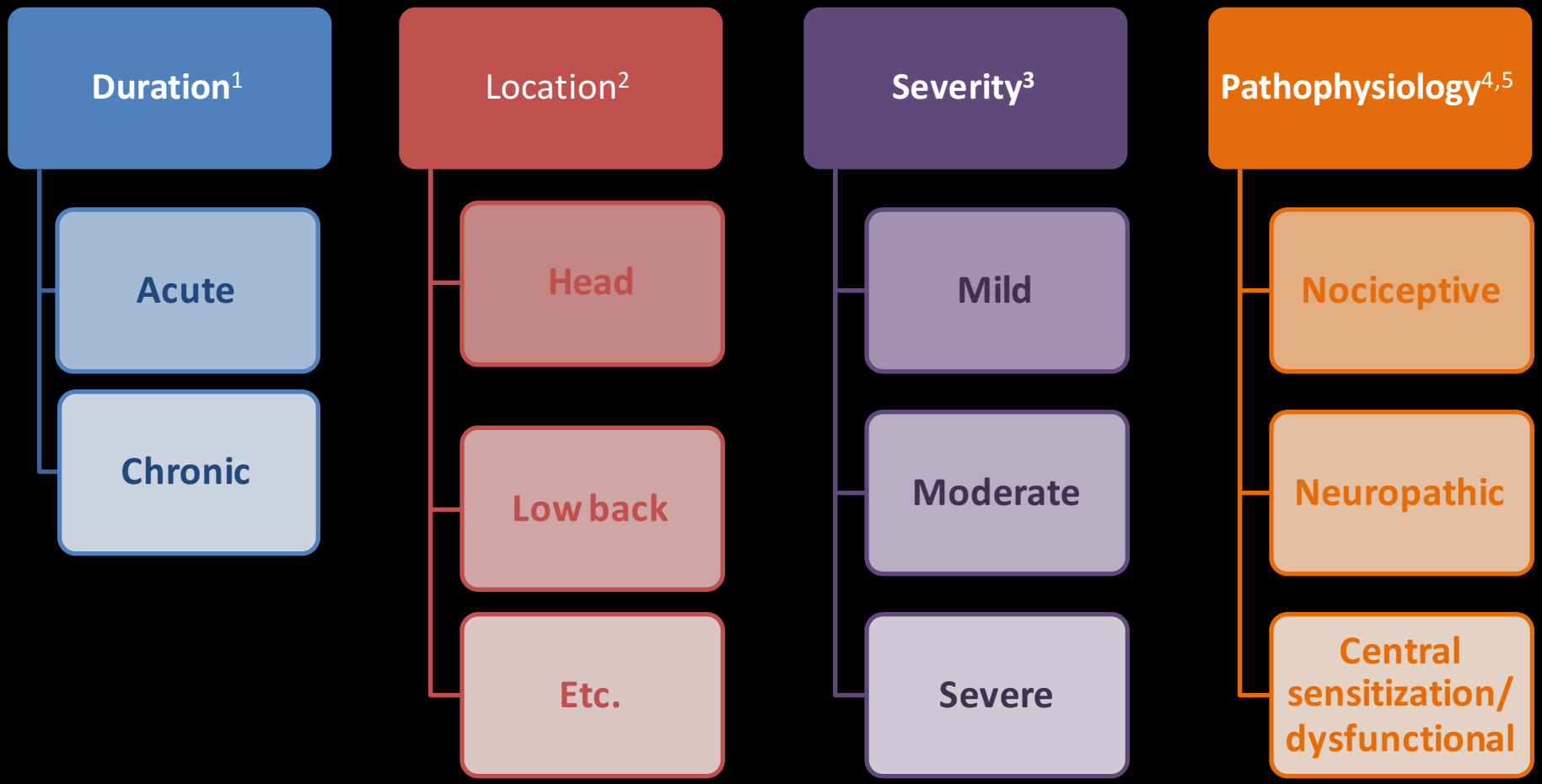
Blood pressure

Temperature

Pain

Phillips DM. *JAMA* 2000; 284(4):428-9.

Pain Classification



1. McMahon SB, Koltzenburg M. In: McMahon SB, Koltzenburg M (eds). *Wall and Melzack's Textbook of Pain.* 5th ed. Elsevier; London, UK: 2006;
2. Loeser D *et al* (eds). *Bonica's Management of Pain*. 3rd ed. Lippincott Williams & Wilkins; Hagerstown, MD: 2001;
3. Hanley MA *et al. J Pain* 2006; 7(2):129-33; 4. Jensen TS *et al. Pain* 2011; 152(10):2204-5; 5. Woolf CJ. *Pain* 2011; 152(3 Suppl):S2-15.

The Pain Continuum

Normal, time-limited response to 'noxious' experience (less than 3 months)

- Usually obvious tissue damage
- Serves a protective function
- Pain resolves upon healing

Pain that has persisted beyond normal tissue healing time (usually more than 3 months)

- Usually has no protective function
- Degrades health and function

Acute pain may become chronic

Chapman CR, Stillman M. In: Kruger L (ed). *Pain and Touch*. Academic Press; New York, NY: 1996; Cole BE. *Hosp Physician* 2002; 38(6):23-30;
International Association for the Study of Pain. *Unrelieved Pain Is a Major Global Healthcare Problem.*
Available at: http://www.iasp-pain.org/AM/Template.cfm?Section=Press_Release&Template=/CM/ContentDisplay.cfm&ContentID=2908. Accessed: July 24: 2013;
National Pain Summit Initiative. *National Pain Strategy: Pain Management for All Australians.*
Available at: http://www.iasp-pain.org/PainSummit/Australia_2010PainStrategy.pdf. Accessed: July 24, 2013;
Turk DC, Okifuji A. In: Loeser D *et al* (eds.). *Bonica's Management of Pain*. 3rd ed. Lippincott Williams & Wilkins; Hagerstown, MD: 2001.

Prevalence of Acute Pain

- **Lifetime** prevalence in general population:
  - Approaches **100%** for acute pain leading to use of analgesics[1]
- **Emergency room** patients:
  - Pain accounts for **>2/3** of emergency room visits[2]
- **Hospitalized** patients:
  - **>50%** report pain[3]

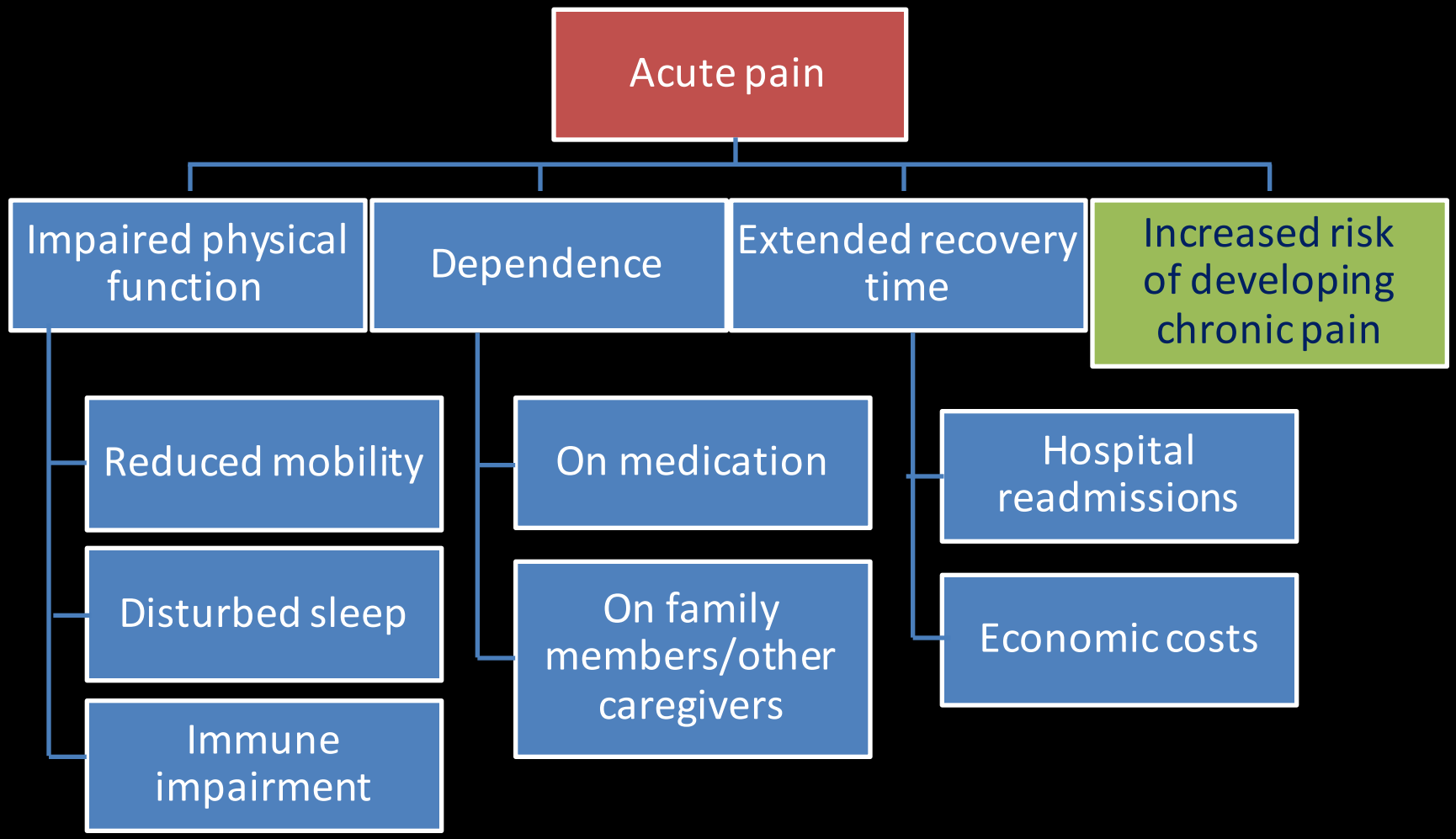
1. Diener HC *et al. J Headache Pain* 2008; 9(4):225-31; 2. Todd KH, Miner JR. In: Fishman SM *et al* (eds). *Bonica's Management of Pain.* 4th ed. Lippincott, Williams and Wilkins; Philadelphia, PA: 2010; 3. Dix P *et al. Br J Anaesth* 2004; 92(2):235-7.

Prevalence of Chronic Pain in the General Population

17–46%

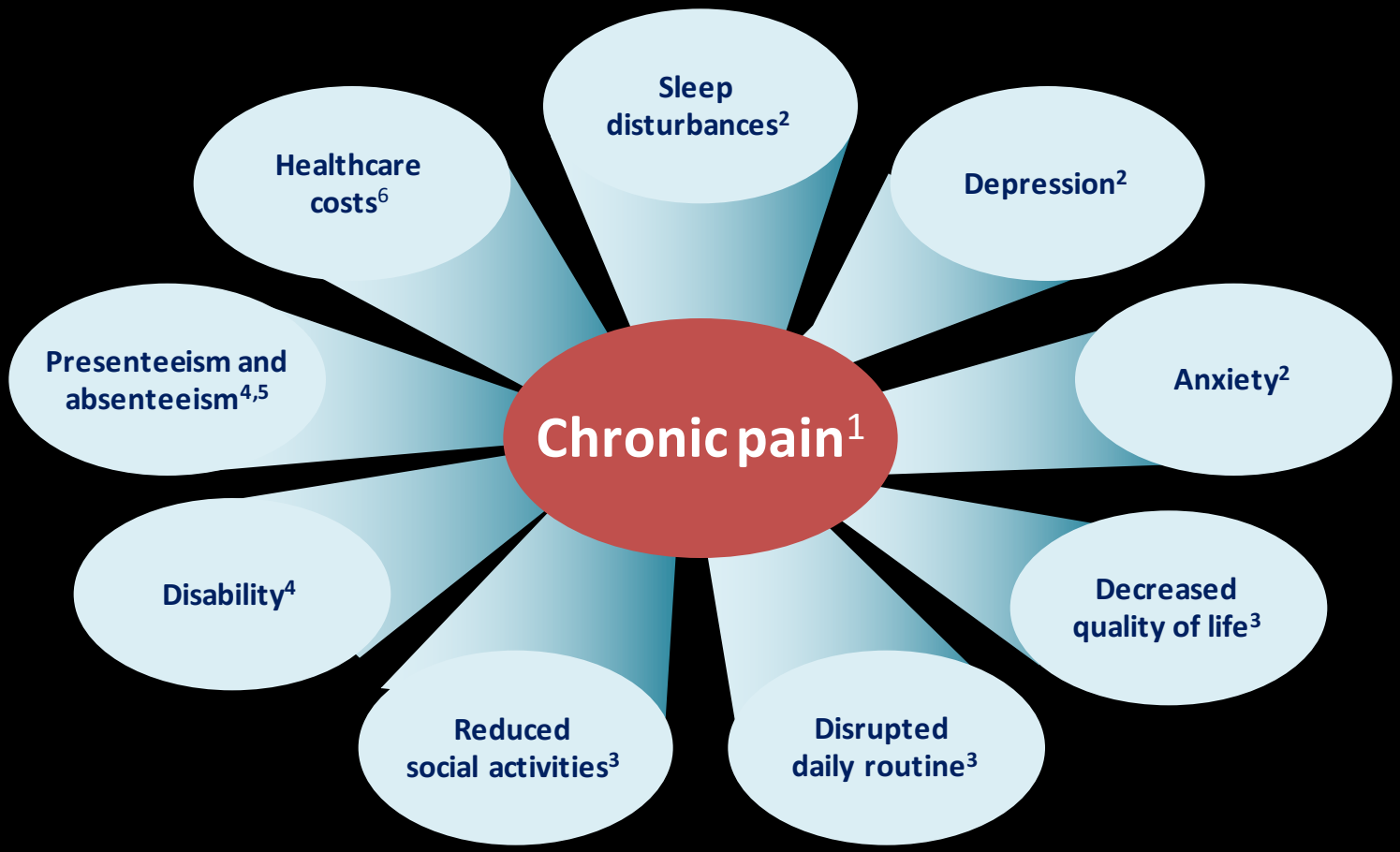
Blyth FM *et al. Pain* 2001; 89(2-3):127-34; ; Breivik H *et al. Eur J Pain* 2006; 10(4):287-333;
Elliott AM *et al. Lancet* 1999; 354(9186):1248-52; Eriksen J *et al. Pain* 2003; 106(3):221-8

Consequences of Unrelieved Pain



Institute of Medicine. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research.* The National Academies Press; Washington, DC: 2011.

Impact of Chronic Pain



1. Douglas C *et al. J Neurosci Nurs* 2008; 40(3):158-68; 2. Tang NKY *et al. J Sleep Res* 2007; 16(1):85-95;
3. Hawker GA *et al. Osteoarth Cartil* 2008; 16(4):415-22; 4. Munce SE *et al. J Occup Environ Med* 2007; 49(11):1206-1211;
5. Stewart WF *et al. JAMA* 2003; 290(18):2443-54; 6. Ritzwoller DP *et al. BMC Musculoskelet Disord* 2006; 7:72-81.

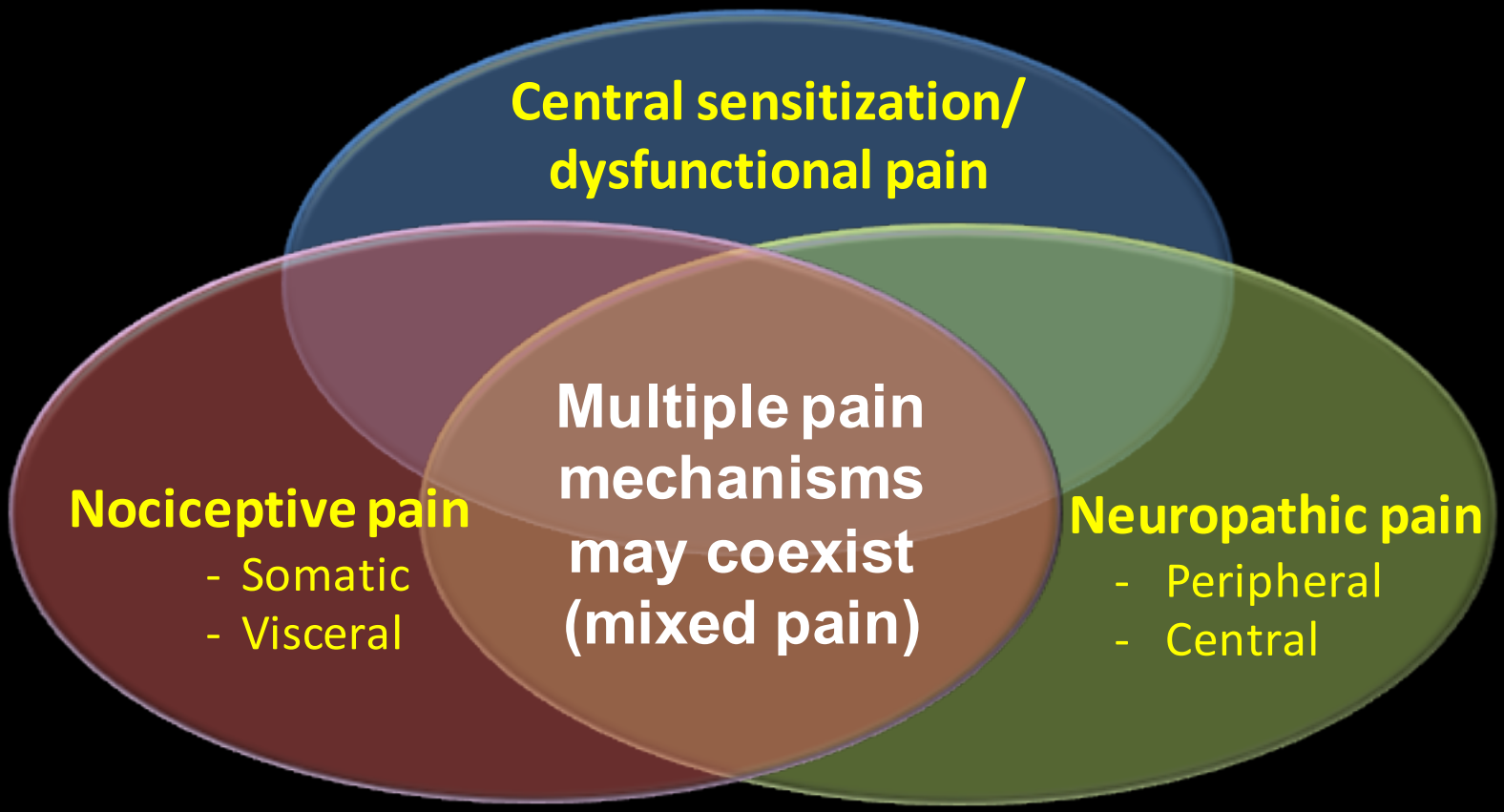
Many Common Conditions are Painful

- Headache, migraine
- Trauma
- Musculoskeletal injury
- Muscle spasm
- Carpal tunnel syndrome
- Low back pain
- Osteoporosis
- Arthritis*
- Systemic lupus erythematosus
- Gout
- Herpes zoster
- Postherpetic neuralgia
- Peripheral neuropathy
- Fibromyalgia
- Cancer
- Surgery

***Includes osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis**

Merskey H *et al* (eds). *Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms.* 2nd ed. IASP Press; Seattle, WA: 1994.

Pathophysiological Classification of Pain



Freynhagen R, Baron R. *Curr Pain Headache Rep* 2009; 13(3):185-90; Jensen TS *et al*. *Pain* 2011; 152(10):2204-5;
Julius D *et al*. In: McMahon SB, Koltzenburg M (eds). *Wall and Melzack's Textbook of Pain*. 5th ed. Elsevier; London, UK: 2006;
Ross E. *Expert Opin Pharmacother* 2001; 2(1):1529-30; Webster LR. *Am J Manag Care* 2008; 14(5 Suppl 1):S116-22; Woolf CJ. *Pain* 2011; 152(3 Suppl):S2-15.

What is nociceptive pain?

Definition

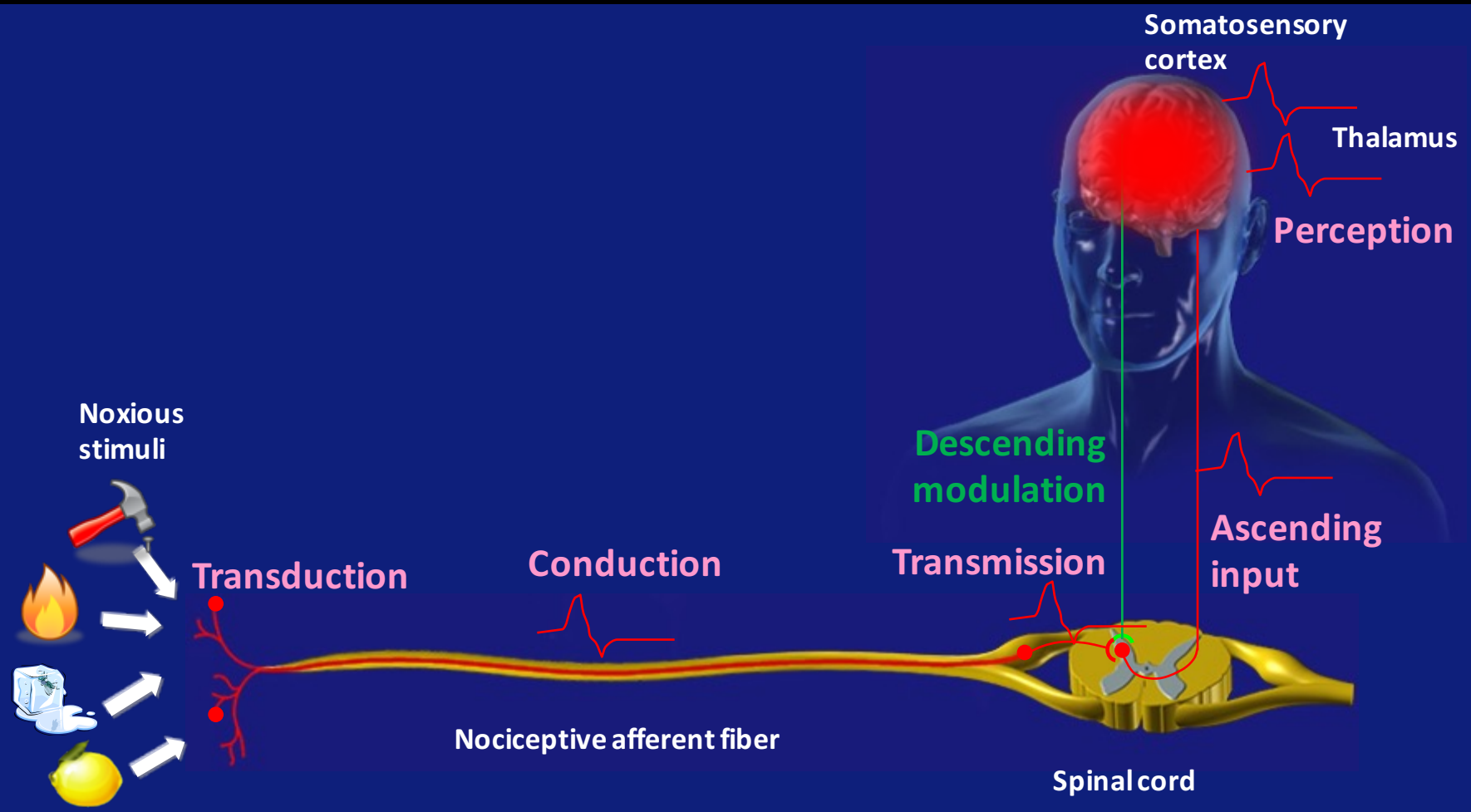
- Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors
- Can be somatic or visceral

Pain Quality

- Usually aching or throbbing
- Usually time-limited (resolves when damaged tissue heals)
- Usually well localized if somatic
- May be referred if visceral
- Can become chronic

Felson DT. *Arthritis Res Ther* 2009; 11(1):203; International Association for the Study of Pain. *IASP Taxonomy.* Available at: http://www.iasp-pain.org/AM/Template.cfm?Section=Pain_Definitions. Accessed: July 15, 2013; McMahon SB, Koltzenburg M (eds). *Wall and Melzack's Textbook of Pain.* 5th ed. Elsevier; London, UK: 2006; Woolf CJ. *Pain* 2011;152(3 Suppl):S2-15.

Nociception:
Neural Process of Encoding Noxious Stimuli



Consequences of encoding may be autonomic (e.g., elevated blood pressure) or behavioral (motor withdrawal reflex or more complex nocifensive behavior). Pain perception is not necessarily implied.

Scholz J, Woolf CJ. *Nat Neurosci* 2002; 5(Suppl):1062-7.

What is neuropathic pain?

Neuropathic Pain

Pain caused by a lesion or disease of the ***somatosensory nervous system***

Peripheral Neuropathic Pain

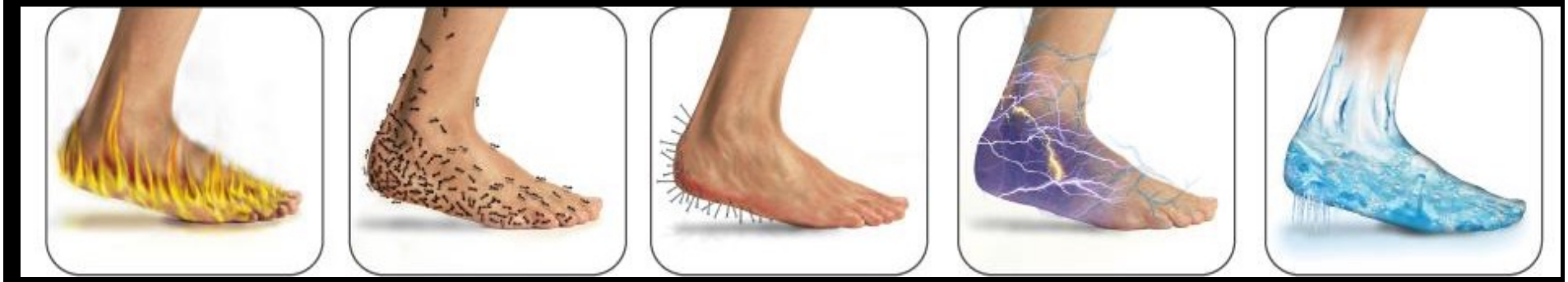
Pain caused by a lesion or disease of the ***peripheral somatosensory nervous system***

Central Neuropathic Pain

Pain caused by a lesion or disease of the ***central somatosensory nervous system***

International Association for the Study of Pain. *IASP Taxonomy, Changes in the 2011 List.* Available at: http://www.iasp-pain.org/AM/Template.cfm?Section=Pain_Definitions. Accessed: July 15, 2013.

Common Descriptors of Neuropathic Pain



Burning ***Tingling*** ***Pins and needles*** ***Electric shock-like*** ***Numbness***

Baron R *et al. Lancet Neurol* 2010; 9(8):807-19; Gilron I *et al. CMAJ* 2006; 175(3):265-75.

Painful Diabetic Neuropathy (PDN)

- In the literature, the prevalence of PDN ranges from[1]
  - 10% to 20% of patients with diabetes
  - 40% to 50% of those with diabetic neuropathies

- In a survey from Augsburg, Germany, the prevalence of painful polyneuropathy was found to be
  - 13.3% in diabetic subjects,
  - 8.7% in individuals with impaired glucose tolerance,
  - 4.2% in individuals with impaired fasting glucose, and
  - 1.2% in individuals with normal glucose tolerance

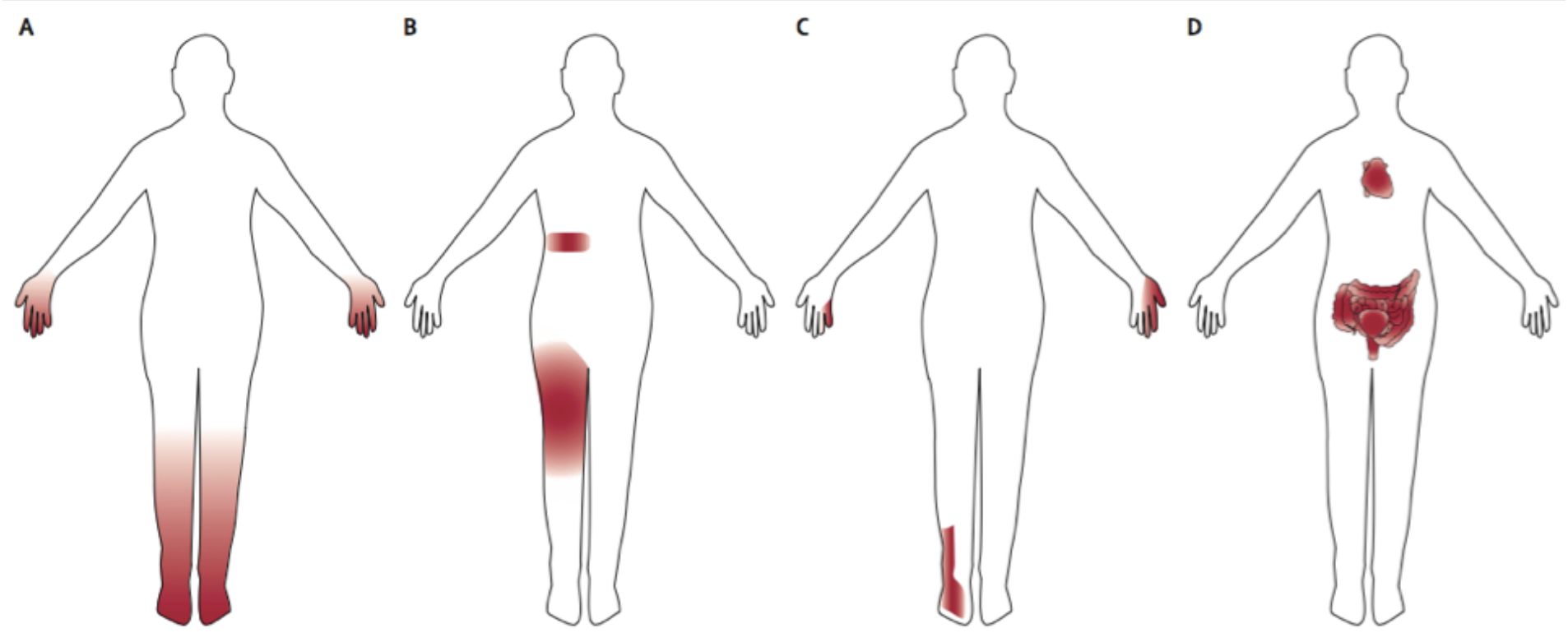
1. Veves A, et al. American Academy of Pain Medicine 2008;9(6):660-674.
2. 2. Ziegler D. Diabetes Care 2009;32(suppl2):S414-419

Neuropathies associated with Diabetes Mellitus

- Distal symmetric sensorimotor polyneuropathy
- Small fiber neuropathy
- Acute severe distal sensory polyneuropathy
- Diabetic neuropathic cachexia
- Hypoglycemia neuropathy
- Treatment induced neuritis (Insulin Neuritis)
- Polyradiculopathy
- Diabetic radiculoplexopaththy
- Mononeuropathies
- Cranial neuropathy (in particular oculomotor)

Russel JW et al, 2014. Diabetic Neuropathies. Continuum lifelong learning neurology;20(5):1226-1240

Pattern of nerve injury in diabetic patients



(A) distal symmetrical polyneuropathy (DSP), small-fibre predominant neuropathy, and treatment-induced neuropathy (B) radiculoplexopathy and radiculopathy; (C)mononeuropathy and mononeuritis multiplex; and (D) autonomic neuropathy and treatment-induced neuropathy. Small-fibre predominant neuropathy has the same pattern as DSP but neurological examination and electrodiagnostic studies give quite different results, which can help the clinician to distinguish between these types of neuropathy.

Mechanisms of Neuropathic Pain in Diabetic Peripheral Neuropathy

Peripheral Mechanisms

- Changes in sodium channel distribution and expression
- Changes in calcium channel distribution and expression
- Altered neuro-peptide expression
- Sympathetic sprouting
- Loss of spinal inhibitory control
- Altered peripheral blood flow
- Axonal atrophy, degeneration or regeneration
- Damage to small fibers
- Increased glycemic flux

Central Mechanisms

- Central sensitization
- Changes in the balance of facilitation/inhibition with descending pathways
- Increased thalamic vascularity

Tesfaye S *et al. Diabetes Care* 2013; 36(9):2456-65.

Positive sensory symptoms:
Chronic or Acute/Remitting:
Spontaneous:
Painless paresthesias:
numbness, tingling, pricking, burning, or
creeping
Pain/dysesthesia: burning,
electric, sharp, or dull/aching
Evoked pain/dysesthesia: allodynia or
hyperalgesia, mechanical/
tactile or thermal

Negative sensory signs/symptoms:
Decrease in sensory nerve amplitude/conduction velocity
Decrease or loss of perception:
Vibratory stimuli
Thermal stimuli (warming or cooling)
Tactile perception (light touch)
Nociception (hypoalgesia):
Thermal (heat or cold)
Mechanical (pin-prick)
Loss of tendon reflexes

Motor signs/symptoms
Decrease in motor nerve amplitude/conduction velocity
Muscle wasting

Figure 3 Signs and symptoms of distal peripheral neuropathy. Categories of

PO Box 2345, Beijing 100023, China
www.wjgnet.com
wjg@wjgnet.com

World J Gastroenterol 2007 January 14; 13(2): 175-191
World Journal of Gastroenterology ISSN 1007-9327

TOPIC HIGHLIGHT

Parimal Chowdhury, Professor, *Series Editors*

Early diabetic neuropathy: Triggers and mechanisms

Maxim Dobretsov, Dmitry Romanovsky, Joseph R Stimers

Topical Review

PAIN

OPEN

Risk factors for neuropathic pain in diabetes mellitus

Harry L. Hébert*, Abirami Veluchamy, Nicola Torrance, Blair H. Smith

PAIN;158 (2017) 560–568

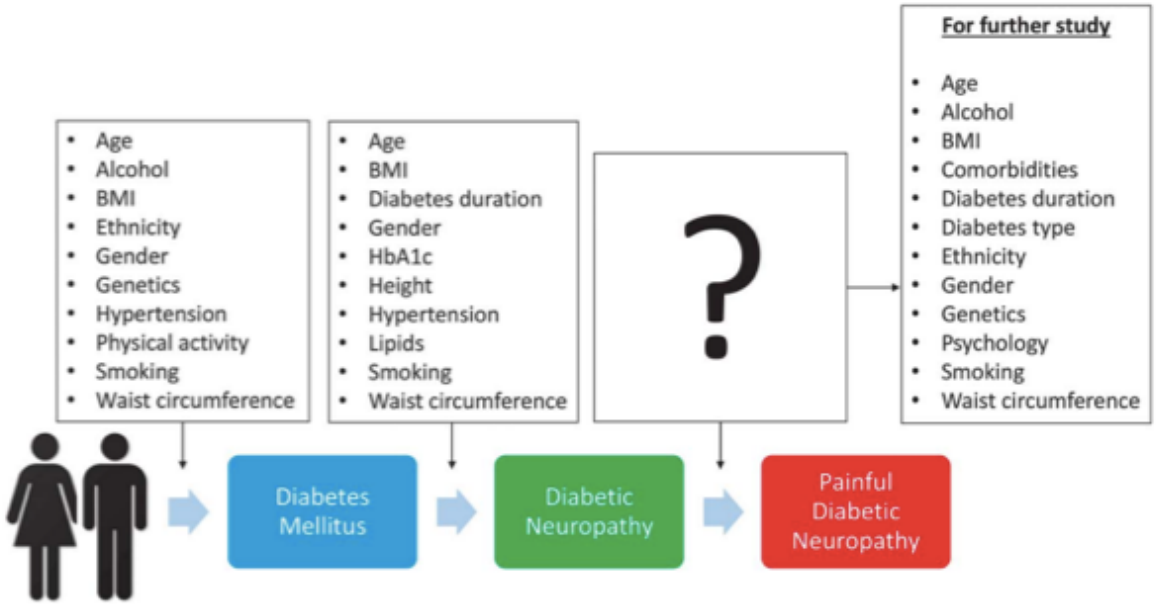


Figure 1. Schematic of the process from diabetes mellitus to diabetic neuropathy and finally painful diabetic neuropathy. Both diabetes mellitus and diabetic neuropathy have their own set of risk factors, both of which could provide important clues as to the risk factors that contribute to painful diabetic neuropathy.

High TNF-alpha plasma levels and macrophages iNOS and TNF-alpha expression as riskfactors for painful diabetic neuropathy

Purwata, TE,

Journal of Pain Research 2011:4 169–175

Table 1 Characteristics of diabetic neuropathy patients

Variable	N	Range	Mean ± SD
Age (years)	110	37–65	54.11 ± 7.64
Gender			
Women	61		
Men	49		
Duration of DM (years)	110	2–10	5.30 ± 3.05
PDN			
Yes	59		
No	51		
Fasting blood sugar (mg %)	110	65–363	167 ± 70
Blood sugar 2 hours pp (mg %)	110	102–588	255 ± 105
HbA_{1C} (%)	110	3.30–18.60	9.69 ± 3.49
Plasma TNF-α (pg/mL)	110	5.40–56.64	15.06 ± 7.01
TNF-α expression (%)	110	0–40	12.43 ± 10.36
iNOS expression (%)	110	0–38	9.22 ± 9.33

Abbreviations: DM, type 2 diabetes; HbA_{1c}, glycosylated hemoglobin; iNOS, inducible nitric oxide synthase; pp, post prandial; SD, standard deviation; TNF-α, tumor necrosis factor alpha.

High TNF-alpha plasma levels and macrophages iNOS and TNF-alpha expression as risk factors for painful diabetic neuropathy

Purwata, TE,

Journal of Pain Research 2011:4 169–175

Table 2 Comparison of clinical data of painful DN (cases) and painless DN (controls)

Characteristics	Case mean ± SD	Control mean ± SD	*P*
Age (years)	53.97 ± 8.26	54.27 ± 6.94	0.834
Duration of diabetes (years)	5.31 ± 3.13	5.29 ± 2.99	0.985
Fasting blood sugar (mg %)	168.96 ± 73.02	165.31 ± 69.14	0.789
Blood sugar 2 hours pp (mg %)	259.37 ± 109.51	251.96 ± 100.77	0.714
HbA_{1C} (%)	10.40 ± 3.61	8.88 ± 3.18	0.023[a]
Plasma TNF-α (pg/mL)	17.44 ± 8.23	12.30 ± 3.76	<0.001[a]
iNOS expression (%)	12.18 ± 10.27	5.80 ± 6.41	<0.001[a]
TNF-α expression (%)	16.15 ± 11.05	8.13 ± 7.56	<0.001[a]

Note: [a]Statistically significant.

Abbreviations: DN, diabetic neuropathy; HbA_{1C}, glycosylated hemoglobin; iNOS, inducible nitric oxide synthase; pp, post prandial; SD, standard deviation; TNF-α, tumor necrosis factor alpha.

Examining a diabetic patient with pain: Taking a pain history

- Question the patient about his/her pain[1]
  - Duration
  - Frequency
  - Quality
  - Intensity
- Be alert and ask for ***common verbal descriptors*** of neuropathic pain (eg, tingling, electric shock-like, numbness, burning, shooting)[2,3]
- Use analogue or numerical scales to quantify the pain[2]

1. Haanpää ML et al. *Am J Medicine* 2009;122(10 Suppl):S13-21.
2. Gilron I *et al. Can Med Assoc J* 2006;175:265-275.
3. Baron R, et al. *Lancet Neurol* 2010;9:807-819.

Pain Assessment Tools

Unidimensional Tools

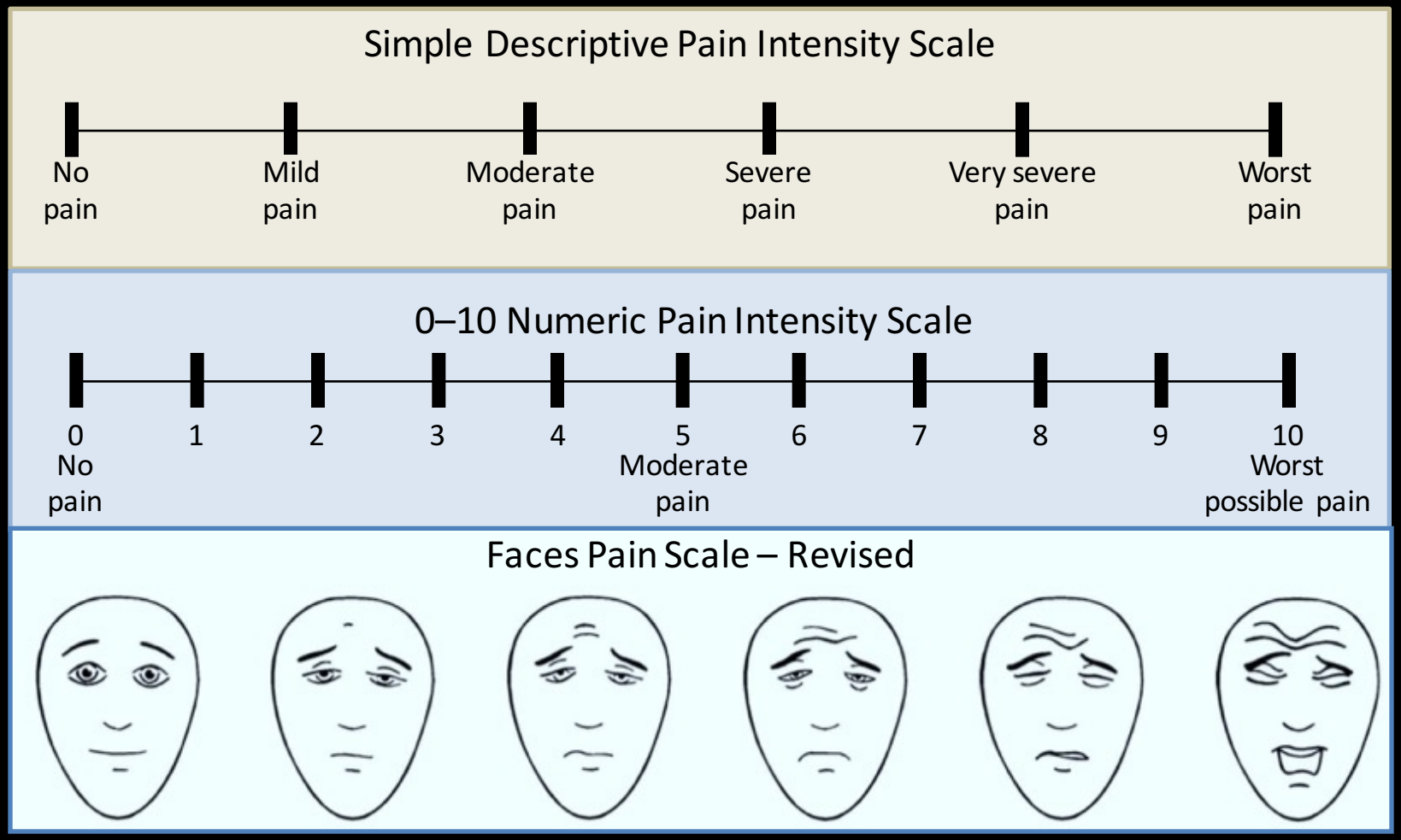
- Visual Analog Scale
- Verbal Pain Intensity Scale
- Faces Pain Scale
- 0–10 Numeric Pain Intensity Scale

Multidimensional Tools

- Brief Pain Inventory
- McGill Pain Questionnaire

Bieri D *et al*. *Pain* 1990; 41(2):139-59; Cleeland CS, Ryan KM. *Ann Acad Med Singapore* 1994; 23(2):129-38; International Association for the Study of Pain. Faces Pain Scale – Revised. Available at: http://www.iasp-pain.org/Content/NavigationMenu/GeneralResourceLinks/FacesPainScaleRevised/default.htm. Accessed: July 15, 2013; Farrar JT *et al*. *Pain* 2001; 94(2):149-58; Kremer E *et al*. *Pain* 1981; 10(2):241-8; Melzack R. *Pain* 1975; 1(3):277-99.

Determine Pain Intensity



International Association for the Study of Pain. *Faces Pain Scale – Revised.* Available at: http://www.iasp-pain.org/Content/NavigationMenu/GeneralResourceLinks/FacesPainScaleRevised/default.htm. Accessed: July 15, 2013;
Iverson RE *et al. Plast Reconstr Surg* 2006; 118(4):1060-9.

Neuropathic pain screening tools

Name	*Description*	*Sensitivity**	*Specificity**	*Author & year*
LANSS	5 symptom items and 2 clinical examination items	82-91%	80-94%	Bennett, 2001
NPQ	10 sensory-related items and 2 affect items	66%	74%	Krause, 2003
DN4	7 symptom items and 3 clinical examination items	83%	90%	Bouhassira, 2005
painDETECT	7 sensory items and 2 spatial characteristics items	85%	80%	Freynhagen, 2006
ID-Pain	5 sensory items and 1 pain location	NR	NR	Portenoy, 2006

*Compared with clinical diagnosis.
LANSS, Leeds Assessment of Neuropathic Symptoms and Signs; NPQ, Neuropathic Pain Questionnaire; DN4, Douleur neuropathic en 4 questions; NR, not reported

Bennett MI et al. *Pain* 2007;127:199-203.

Recognition of NeP: Symptomatology

	Non Neuropathic Pain (%)	Neuropathic Pain (%)	P value
"burning"	30.4	68.3	<0.001
"squeezing"	37.7	48.8	0.171
"painful cold"	10.1	25.6	0.015
"Electric shock"	17.4	64.6	<0.001
"lancinating"	65.2	75.6	0.162
"pins and needles"	17.4	65.9	<0.001
"itching"	5.8	29.3	<0.001
"numbness"	30.4	65.9	<0.001

Bouhashira, D., Attal., N., 2011. Diagnosis and assessment of neuropathic pain: The Saga of clinical tools. *Pain*;152:574-583.

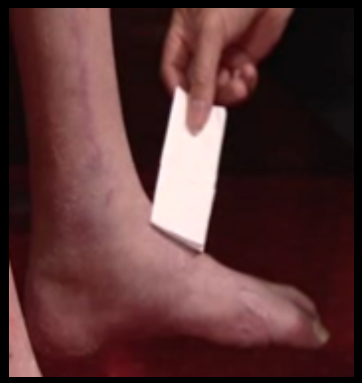
Recognizing NeP: Clinical examination

Tools assessing sensory functions			
Fiber type	**Sensation**	**Clinical testing instrument**	**Quantitative Sensory Testing**
Aβ	Touch	Fingers, a piece of cotton wool, or a soft brush	Von Frey filaments
	Vibration	Tuning fork (128 Hz)	Vibrameter
Aδ	Pinprick, sharp pain	Wooden cocktail sticks	Weighted needles
	Cold	Cold object (20°C)/thermorollers	Thermotest
C	Warmth	Warm object (40°C)	Thermotest

Crucu P, et al. EFNS Guidelines on neuropathic pain assessment, *European Journal Of Neurology, 2004;11:153-162*

Look: Simple Bedside Tests

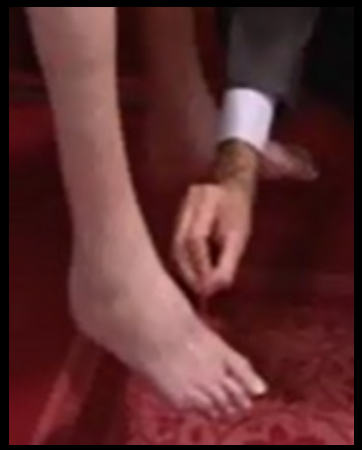
Stroke skin with brush, cotton or apply acetone



Sharp, burning superficial pain

ALLODYNIA

Light manual pinprick with safety pin or sharp stick



Very sharp, superficial pain

HYPERALGESIA

Baron R. *Clin J Pain* 2000; 16(2 Suppl):S12-20; Jensen TS, Baron R. *Pain* 2003; 102(1-2):1-8.

Symptoms related to neuropathic pain

Spontaneous pain

- Continuos
  - Superficial
    - →Burning
  - Deep
    - → compression
- Paroxysmal
  - Electric shock
  - Shooting – like
  - Sharp

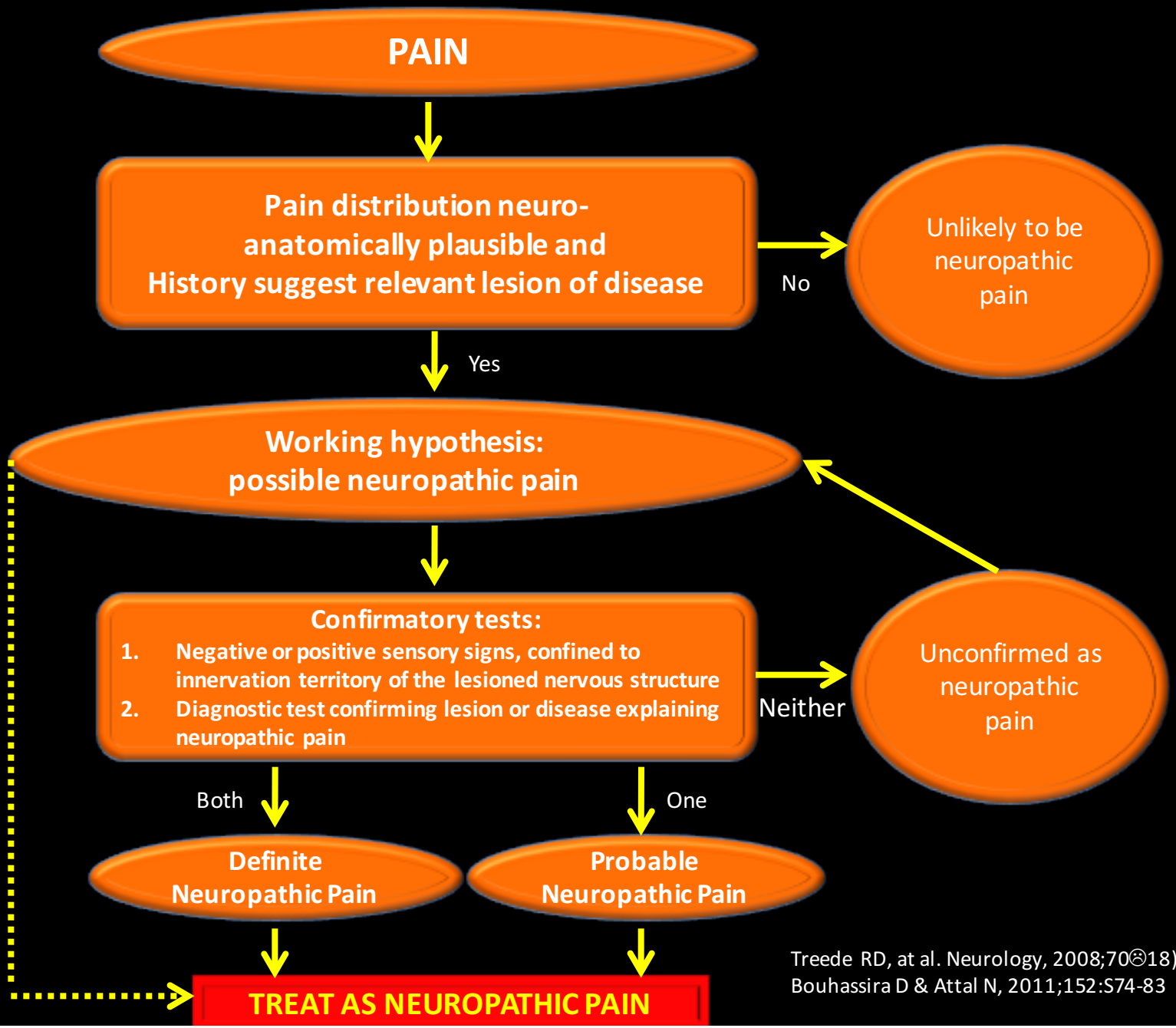
Evoked pain

- Allodynia
  - Dynamic
    - (soft skin brushing)
  - Static
    - (ligth pressure)
  - Thermal
    - (warm/cold)
- Hyperalgesia
  - Hot
  - Cold
  - Pinprick

Frequent association with paresthesia and dysesthesia

Guastella & Mick, 2009. Strategies for the diagnosis and treatment of neuropathic pain secondary to diabetic peripheral sensory polyneuropathy, Diabetes and Metabolism;35:12-19

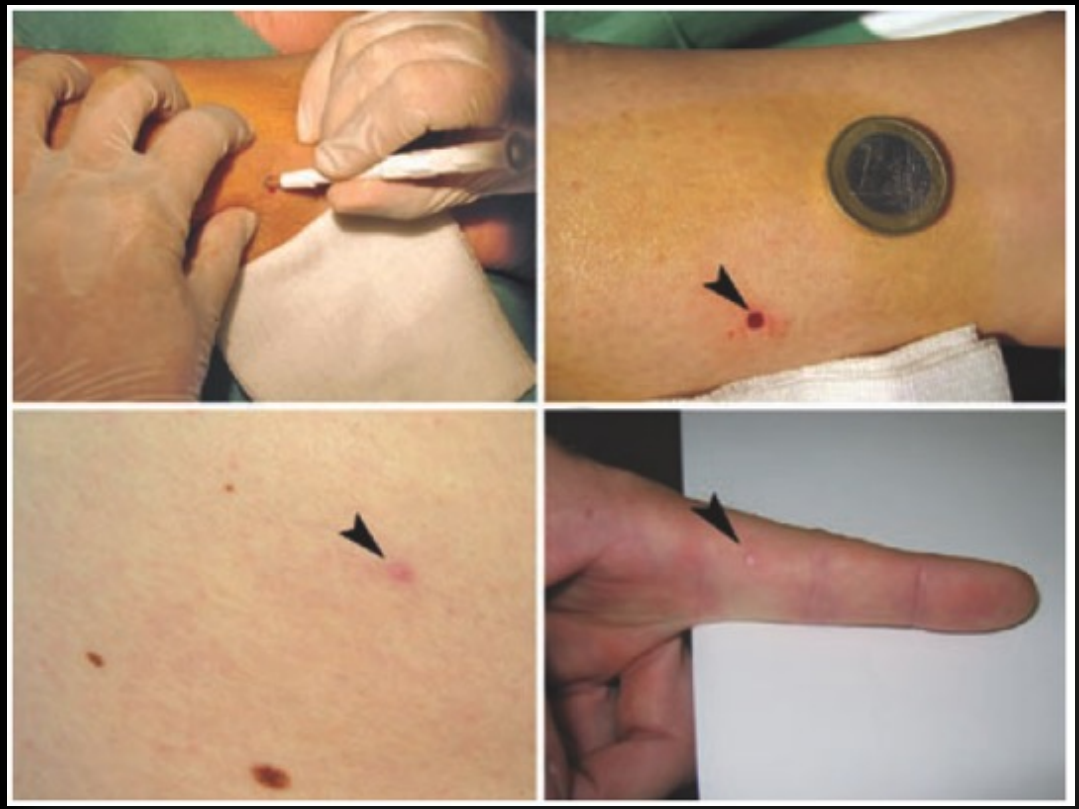
Flowchart for the grading system for neuropathic pain based on level of diagnostic certainty



Treede RD, at al. Neurology, 2008;70☹18):1630-5
Bouhassira D & Attal N, 2011;152:S74-83

Skin Biopsy

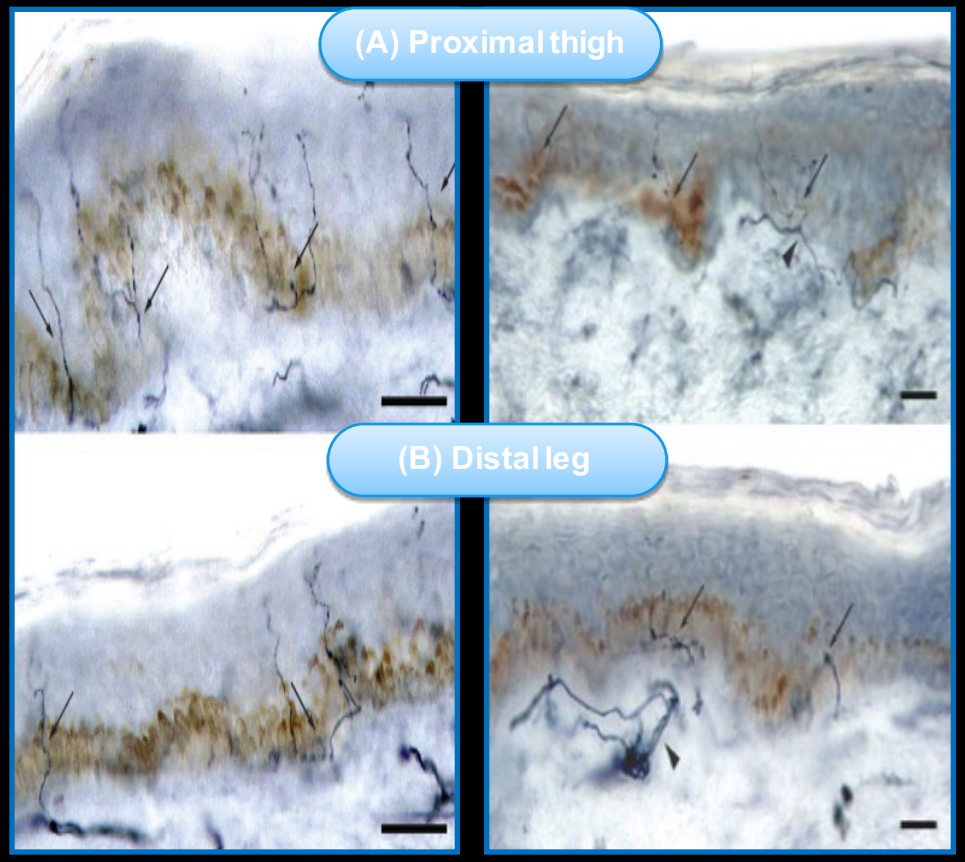
- Circular punch is used to excise a hairy skin sample, usually from distal part of the leg
- Lidocaine used as a topical anesthetic
- No sutures are required
- No side effects
- Wound heals quickly



Lauria G *et al. Eur J Neurol* 2005; 12(10):747-58; Lauria G, Devigili G. *Nature Clin Practice Neurol* 2007; 3(10):546-57; Lauria G, Lombardi R. *BMJ* 2007; 334(7604):1159-62.

Small-fiber neuropathy in PDN

- Loss of small fibers are characterized by reduced density of intraepidermal nerve fibers (IENF) as shown by arrows[1]
  - Arrowheads indicate dermal nerve bundles
- Length-dependent denervation of skin is particularly seen in distal leg
- Typical clinical presentation[2]
  - Burning and superficial pain; allodynia and hyperalgesia
  - May have normal strength, reflexes and conduction velocity
  - Abnormal thresholds for warm thermal perception and pain
- Patients with prediabetes glucose intolerance and normal HbA_{1c} levels may have small-fiber neuropathy and experience pain[3]



Normal epidermis ***Diabetic patient with small-fiber neuropathy***

PDN, painful diabetic neuropathy; HbA_{1C}, glycated hemoglobin

1. 1. Lauria G, Devigili G. *Nat Clin Pract Neurol* 2007;3:546–557.
2. 2. Tavee J, Zhou L. *Cleve Clin J Med* 2009;76(5):297–305.
3. Tesfaye S, Selvarajah D. *Current Diabetes Reports* 2009;9:432–434.

Neuropathic pain of PDN negatively affects quality of life

- Pain may significantly **interfere with a patient's ability to exercise or walk**[1]
  - Walking has been shown to improve HbA_{1C} in patients with diabetes regardless of change in body mass[2,3]
- Pain often intensifies at night and may significantly **interfere with sleep**[4]
  - Sleep debt has been shown to have a negative impact on metabolic and endocrine control[5-7]
- Pain is significantly correlated with **depression** in diabetic patients[8]

PDN, painful diabetic neuropathy; HbA_{1C}, glycated hemoglobin

1. Novak P, et al. *J Rehabil Med* 2004;36:249–252.
2. Boule NG, et al. *JAMA* 2001;286:1218–1227.
3. American Diabetes Association. *Diabetes Care* 2011;34(Suppl1):S11–S61.
4. Quattrini C, et al. *Diabetes Metab Res Rev* 2003;19:S2–S8.
5. Zelman DC, et al. *Clin J Pain* 2006;22:681–685.
6. Spiegel K, et al. *Lancet* 1999;354:1435–1339.
7. Åkerstedt T, Nilsson PM. *J Intern Med* 2003;254:6–12.
8. Raval A, et al. *Indian J Med Res* 2010;132:195-200.

Treatment of Diabetic Neuropathy: Risk Factor Control –PDN????

- Glucose Control
- Vascular risk factors control
  - Dyslipidemia
  - Obesity
  - Hypertension?
  - etc
- NeuroProtection
  - B Vitamins?
  - Alpha lipoic Acid
- Pain Medication for PDN

Summary of AAN recommendations

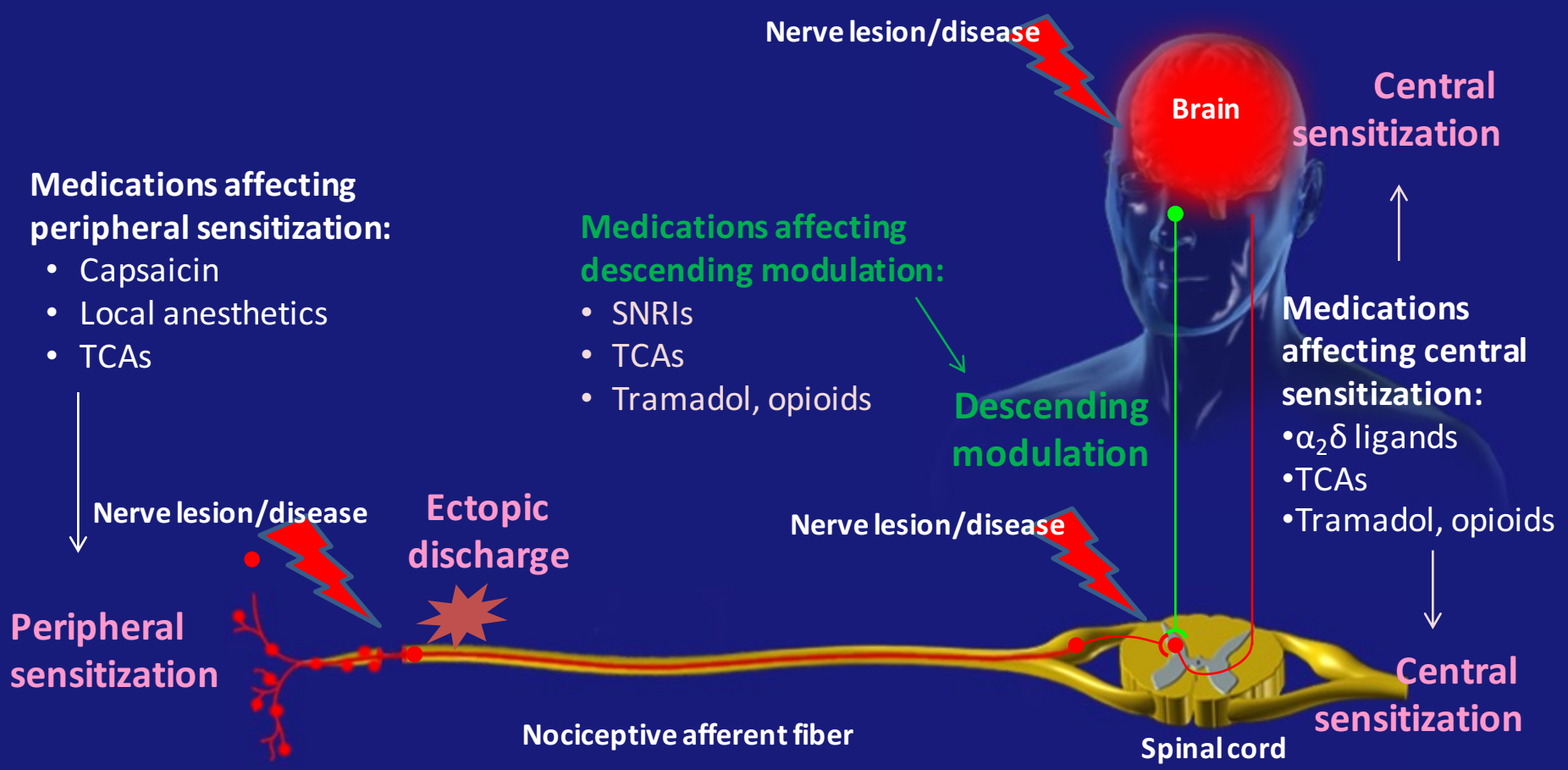
	Recommended drug and dose	*Not recommended*
Level A	• Pregabalin 300–600 mg/day	
Level B	• Gabapentin 900–3,600 mg/day • Valproate 500–1,200 mg/day • Venlafaxine 75–225 mg/day • Duloxetine 60–120 mg/day • Amitriptyline 25–100 mg/day • Dextromethorphan 400 mg/day • Morphine sulfate, titrated to 120 mg/day • Tramadol 210 mg/day • Oxycodone, mean 37 mg/day, maximum 120 mg/day • Capsaicin 0.075% four times per day • Isosorbide dinitrate spray • Electrical stimulation, percutaneous nerve stimulation for 3–4 weeks	• Oxcarbazepine • Lamotrigine • Lacosamide • Clonidine • Pentoxifylline • Mexiletine • Magnetic field treatment • Low-intensity laser therapy • Reiki therapy

"Based on consistent Class I evidence, pregabalin is established as effective in lessening the pain of PDN. If clinically appropriate, pregabalin should be offered for the treatment of PDN (Level A)."

The AAN recognizes that specific care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved. Venlafaxine is not approved for the treatment of neuropathic pain. PDN, painful diabetic neuropathy; AAN, American Academy of Neurology

Bril V, et al. *Neurology* 2011;76:1758-1765.

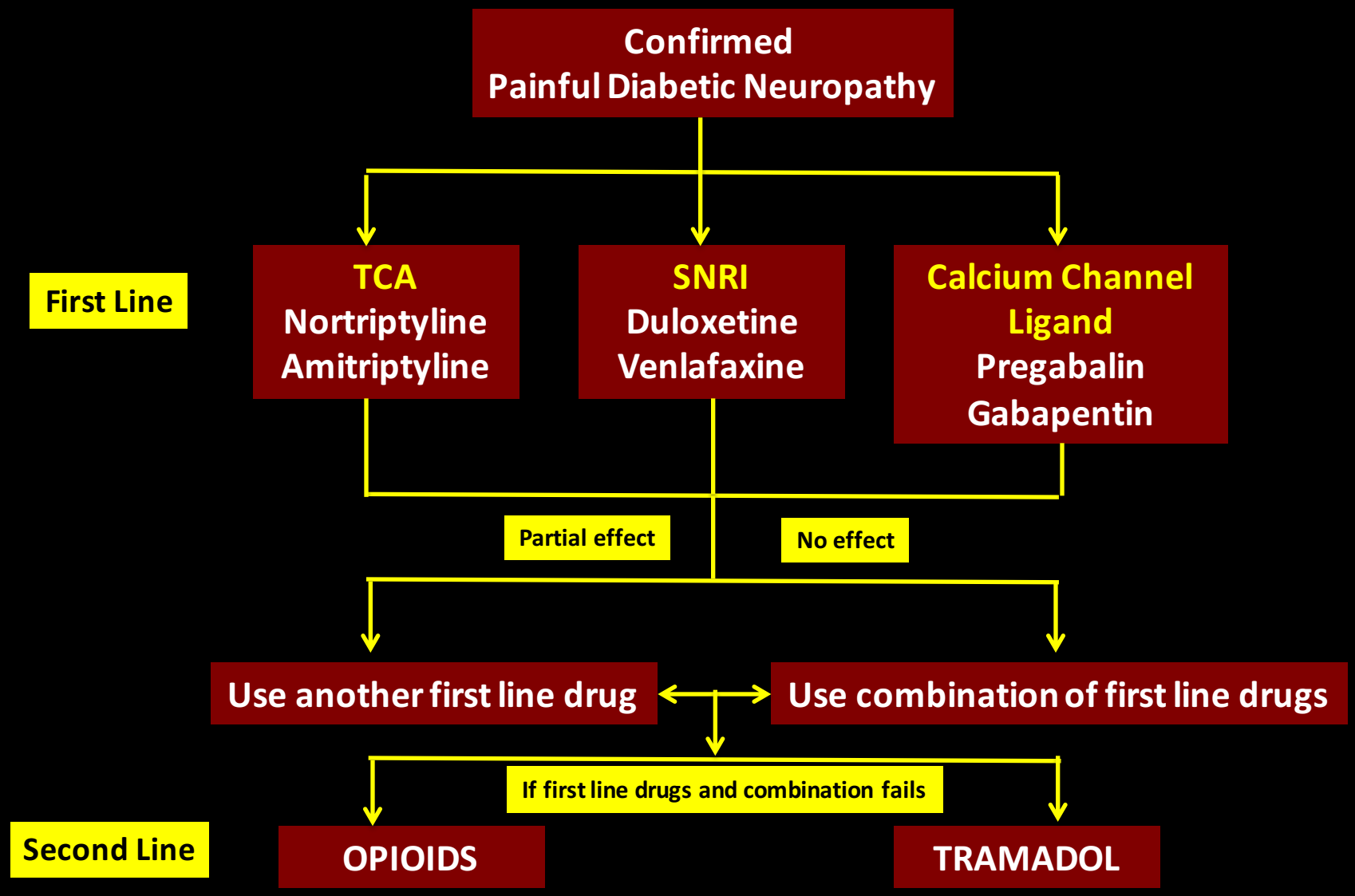
Mechanism-Based Pharmacological Treatment of Neuropathic Pain



SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant

Adapted from: Attal N *et al. Eur J Neurol* 2010; 17(9):1113-e88; Beydoun A, Backonja MM. *J Pain Symptom Manage* 2003; 25(5 Suppl):S18-30; Jarvis MF, Boyce-Rustay JM. *Curr Pharm Des* 2009; 15(15):1711-6; Gilron I *et al. CMAJ* 2006; 175(3):265-75; Moisset X, Bouhassira D. NeuroImage 2007; 37(Suppl 1):S80-8; Morlion B. Curr Med Res Opin 2011; 27(1):11-33; Scholz J, Woolf CJ. Nat Neurosci 2002; 5(Suppl):1062-7.

Algorithm for treatment strategy of PDN

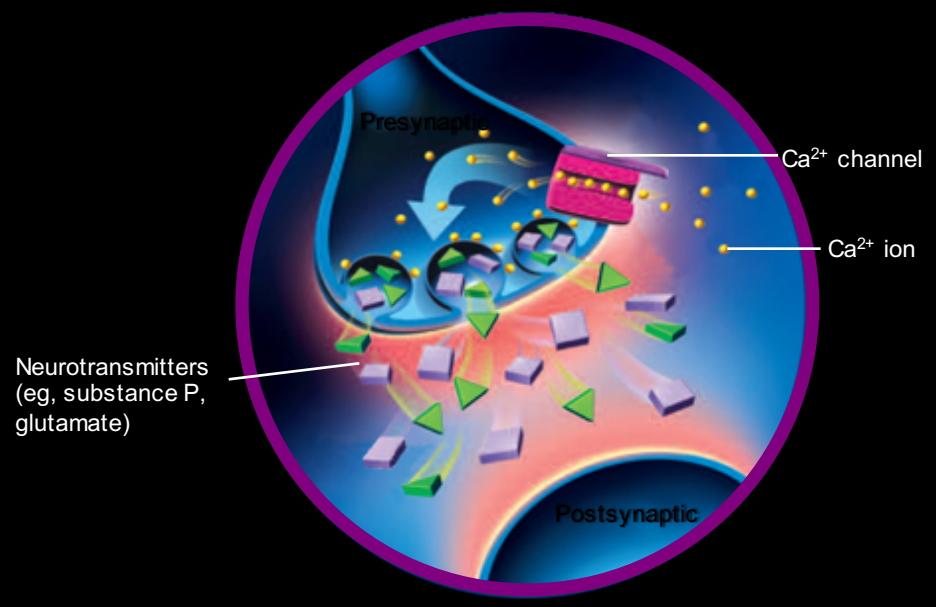


Pharmacological Research 80 (2014) 21–35

Central sensitization: Underlying cause of amplified pain perception associated with PDN

- Central sensitization is believed to be the underlying cause of amplified pain perception that results from dysfunction in the CNS[1,2]
- This is believed to result from excessive release of two important neurotransmitters, **substance P** and **glutamate**[3]

Excessive neurotransmitter release in hyperexcited neuron



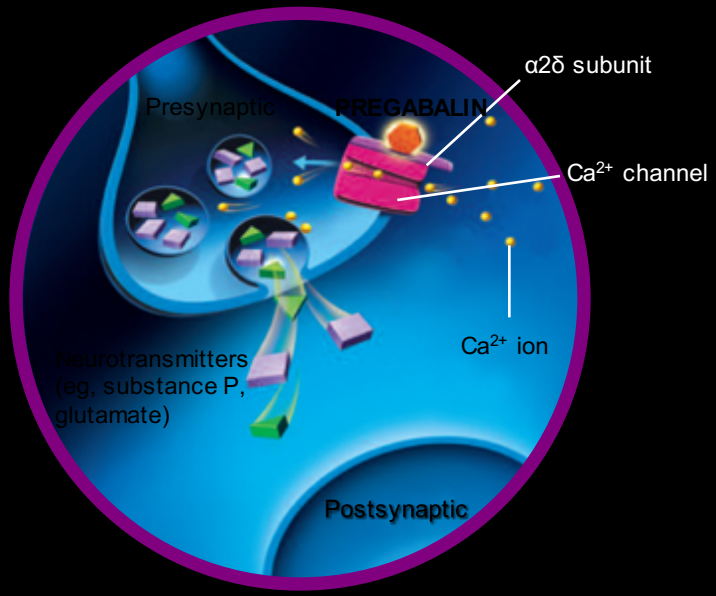
PDN, painful diabetic neuropathy; CNS, central nervous system

1. Costigan M, et al. *Annu Rev Neurosci* 2009;32:1–32.
2. Staud R. *Arthritis Res Ther* [serialonline] 2006;8:208–214.
3. Costigan M, et al. In: Siegel GJ, et al, eds. Basic Neurochemistry: Molecular, Cellular and Medical Aspects. 7th ed. Burlington, MA: Elsevier Academic Press;2006:927–938.

Pregabalin is believed to impact central sensitization

- Binds with high affinity to α2δ subunit of voltage-gated calcium channels at dorsal horn
- Reduces excessive calcium-dependent release of **substance P** and **glutamate**
- Although exact mechanism of action of pregabalin is unknown, results from animal models suggest binding to α2δ subunit may be associated with anti-hyperalgesic and anti-allodynic effects of pregabalin

Pregabalin reduces excessive neurotransmitter release



The clinical significance of these observations in humans is currently unknown

Costigan M, et al. In: Siegel GJ, et al, eds. Basic Neurochemistry: Molecular, Cellular and Medical Aspects. 7th ed. Burlington, MA: Elsevier Academic Press;2006:927–938.

Pregabalin Dosage Adjustment Based on Renal Function

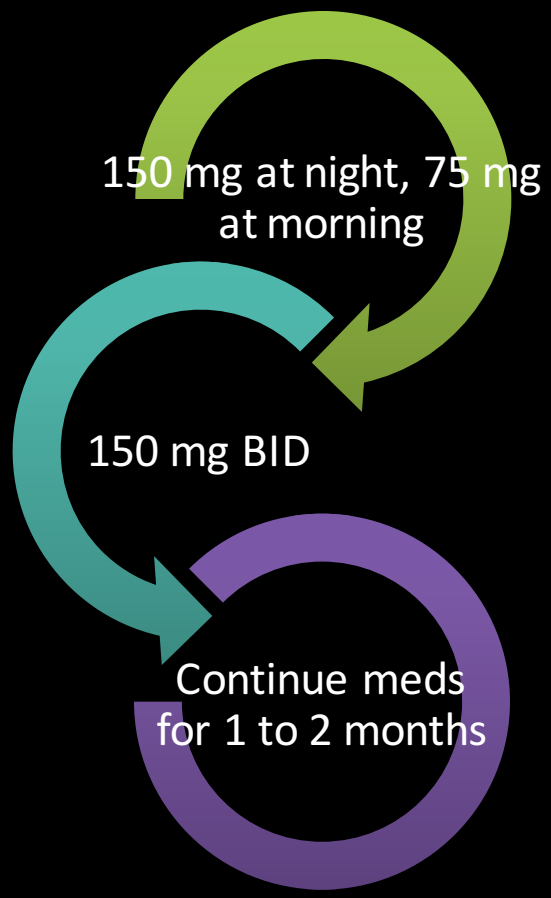
Creatinine clearance (mL/min)	Total pregabalin daily dose*		Dose regimen
	Starting dose (mg/day)	Maximum dose (mg/day)	
≥60	150	600	BID or TID
≥30 - <60	75	300	BID or TID
≥15 - <30	25-50	150	OD or BID
<15	25	75	OD
Supplementary dose following hemodialysis (mg)	25	100	Single additional dose

TID = three divided doses; BID = two divided doses; OD = once daily dose

* Total daily dose should be divided as indicated by dose regimen to provide mg/dose

Summary of Product Characteristics

How to increase the dose



Adverse Effects of $\alpha_2\delta$ Ligands

System	Adverse effects
Digestive system	Dry mouth
CNS	Dizziness, somnolence
Other	Asthenia, headache, peripheral edema, weight gain

$\alpha_2\delta$ ligands include gabapentin and pregabalin
CNS = central nervous system
Attal N, Finnerup NB. *Pain Clinical Updates* 2010; 18(9):1-8.

Cara mengatasi Efek Samping

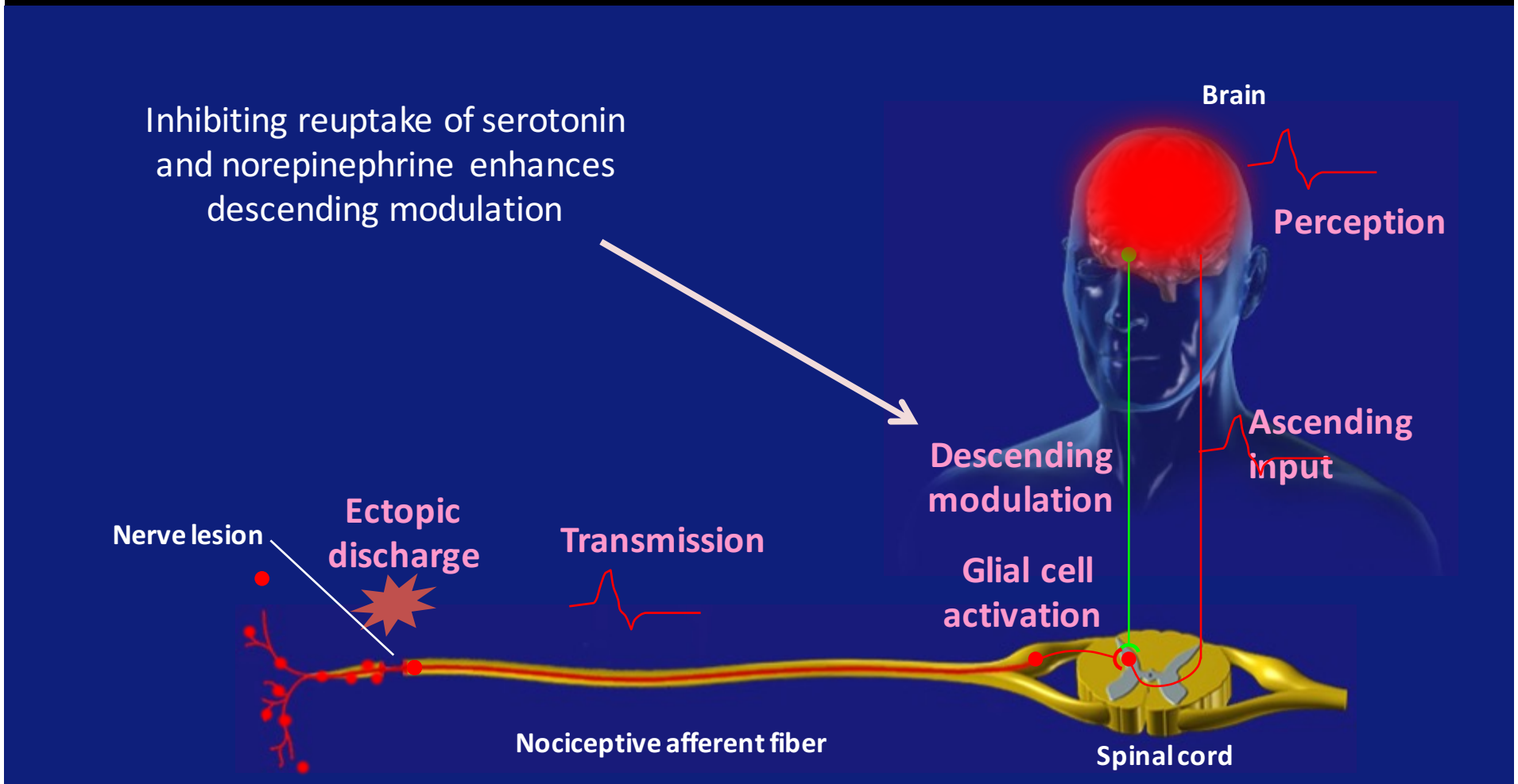
Resep per 10 hari , dengan pembagian sbb :

1 x 50 mg (malam hari)	3 Hari Pertama
1 x 75 mg (malam hari)	3 Hari Kedua
2 x 75 mg (Pagi – Malam)	4 Hari Ketiga

1. Sebelum diresepkan, pasien dikomunikasikan mengenai adanya efek samping (ES) ini
2. Jika efek samping terjadi (biasa setelah bangun tidur, disarankan untuk tidak langsung segera bangun)
3. ES akan berlangsung selama 3-5 hari, setelah itu ES akan ditoleransi dengan baik

1. Jika setelah 10 hari, pasien masih merasakan nyeri, maka dosis dititrasi menjadi 150 mg malam dan 75 mg pagi hari, selama 10 hari berikutnya
2. Jika setelah 10 hari, pasien masih terasa nyeri tapi terjad ES, maka dosis diturunkan menjadi 1x75 mg dan monitoring 10 hari
3. Jika setelah 10 hari pasien tidak lagi merasakan nyeri, maka teruskan pemakaian hingga 2-3 bulan

How Antidepressants Modulate Pain



Verdu B *et al. Drugs* 2008; 68(18):2611-2632.

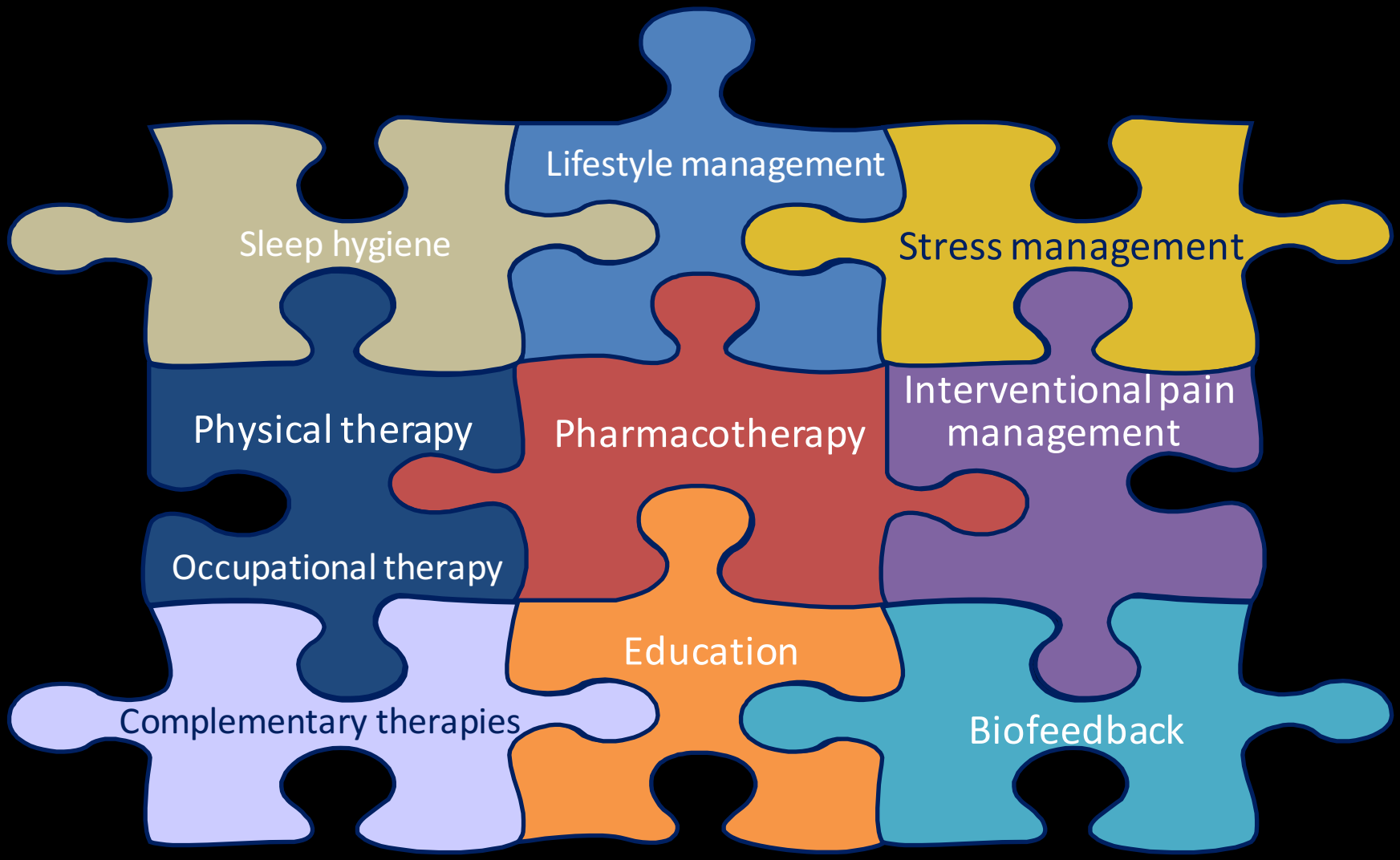
Adverse Effects of Antidepressants

System	TCAs	SNRIs
Digestive system	Constipation, dry mouth, urinary retention	Constipation, diarrhea, dry mouth, nausea, reduced appetite
CNS	Cognitive disorders, dizziness, drowsiness, sedation	Dizziness, somnolence
Cardiovascular	Orthostatic hypotension, palpitations	Hypertension
Other	Blurred vision, falls, gait disturbance, sweating	Elevated liver enzymes, elevated plasma glucose, sweating

CNS = central nervous system; TCA = tricyclic antidepressant; SNRI = serotonin-norepinephrine reuptake inhibitor

Attal N, Finnerup NB. Pain Clinical Updates 2010; 18(9):1-8.

Penanganan Multimodal Untuk Nyeri



Gatchel RJ *et al. Psychol Bull* 2007; 133(4):581-624; Institute of Medicine. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research.*; National Academies Press; Washington, DC: 2011; Mayo Foundation for Medical Education and Research. *Comprehensive Pain Rehabilitation Center Program Guide.* Mayo Clinic; Rochester, MN: 2006.

Conclusions

- Diabetic Neuropathy is the most common microvascular complication of DM
  - Painful diabetic neuropathy affects more than 20% of patients with Diabetic Neuropathy
  - Correlated with significant impairment of QoL
- Proper diagnosis of the two conditions brings to a proper treatment
- Glucose control as well as vascular risk factors such as dyslipidemia, obesity, hypertension play important role in controlling DN and PDN
- Mechanism based and symptomatic treatment should be given simultaneously

Thank you

RESEARCH ARTICLE Open Access

Musculoskeletal pain in people with and without type 2 diabetes in Taiwan: a population-based, retrospective cohort study

Lee-Wen Pai[1,2], Chin-Tun Hung[3], Shu-Fen Li[3], Li-Li Chen[4,5*], Yueh- Chin Chung[2] and Hsin-Li Liu[2]

Abstract

Background: Musculoskeletal pain in people with type 2 diabetes is a common issue even to this day. The study aimed to explore the 10-year cumulative incidence of musculoskeletal pain, the mean number of doctor visits for musculoskeletal pain, and the mean number of doctor visits for musculoskeletal pain by location in people with type 2 diabetes, compared with respective values for people without diabetes.

Methods: The study utilized a population-based retrospective cohort study design. The subjects were randomly obtained from the Taiwan National Health Insurance Research Database. The diabetic group included 6586 people with type 2 diabetes aged 18–50 years, while the non-diabetic group consisted of 32,930 age- and sex-matched people. Based on the medical records of individuals with musculoskeletal pain in the two groups from 2001 to 2010, the 10-year cumulative incidence of musculoskeletal pain, the mean number of doctor visits for musculoskeletal pain, and the mean number of doctor visits for musculoskeletal pain by location were calculated and compared, with the aim of identifying differences between the two groups.

Results: Showed that people in the diabetic group had a higher 10-year cumulative incidence of and a higher mean number of doctor visits for musculoskeletal pain than the non-diabetic group ($p < 0.05$). The relative risk (RR) of the 10-year cumulative incidence of musculoskeletal pain in the two groups was the highest (RR = 1.39) for people between 30 and 39 years of age. The mean number of doctor visits for musculoskeletal pain by location was significantly different between the two groups. However, the mean number of doctor visits for limb pain registered the largest difference between the two groups.

Conclusion: People with type 2 diabetes aged 18–50 years had a higher 10-year cumulative incidence of and a higher mean number of doctor visits for musculoskeletal pain than the non-diabetic group. Musculoskeletal pain might directly or indirectly interfere with or decrease the physical activity levels of people with diabetes. Therefore, it is important to detect and treat musculoskeletal pain early in order to promote physical activity and optimize blood sugar control.

Keywords: Type 2 diabetes, Musculoskeletal pain, Incidence

Triceps

REFERRAL

The long head usually refers pain into the posterior shoulder and sometimes down into the posterior forearm (skipping the elbow). Trigger points in the center of the medial head refer into the olecranon process (the elbow). Trigger points in the lateral part of the medial head refer to the lateral epicondyle, and are a common component of "tennis elbow".

ACTION

Extends the elbow.

ORIGIN

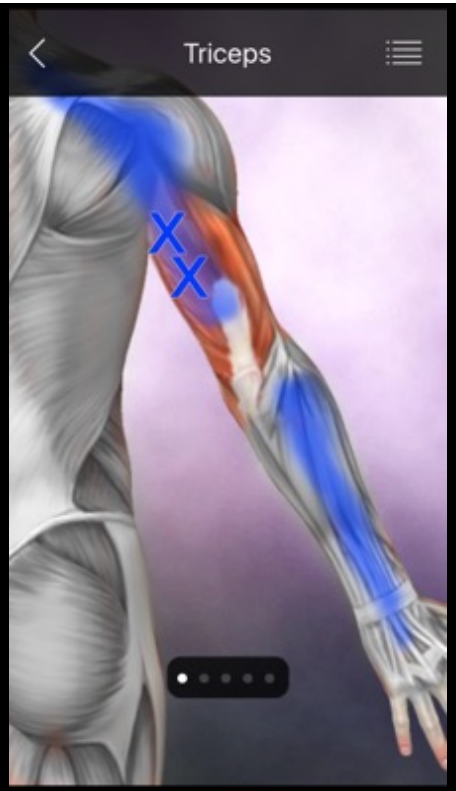
Long head: infraglenoid tubercle of scapula. Lateral head: posterior humerus. Medial head: posterior humerus

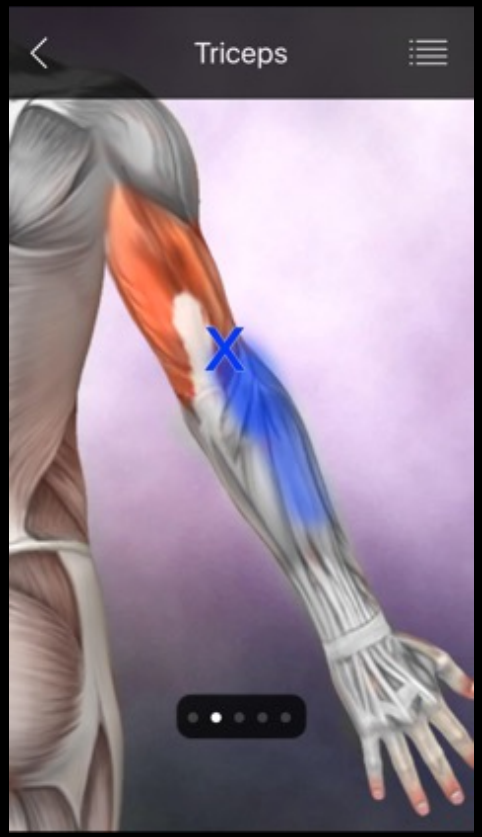
INSERTION

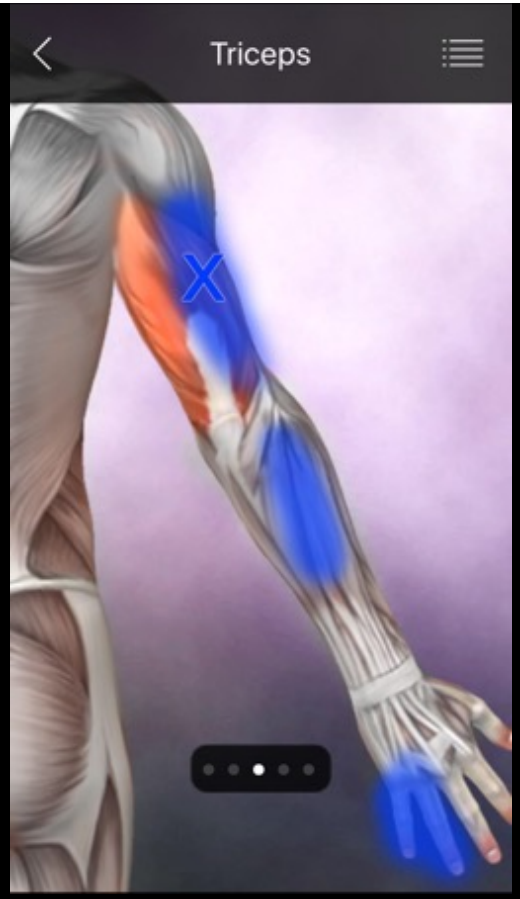
Olecranon process of ulna

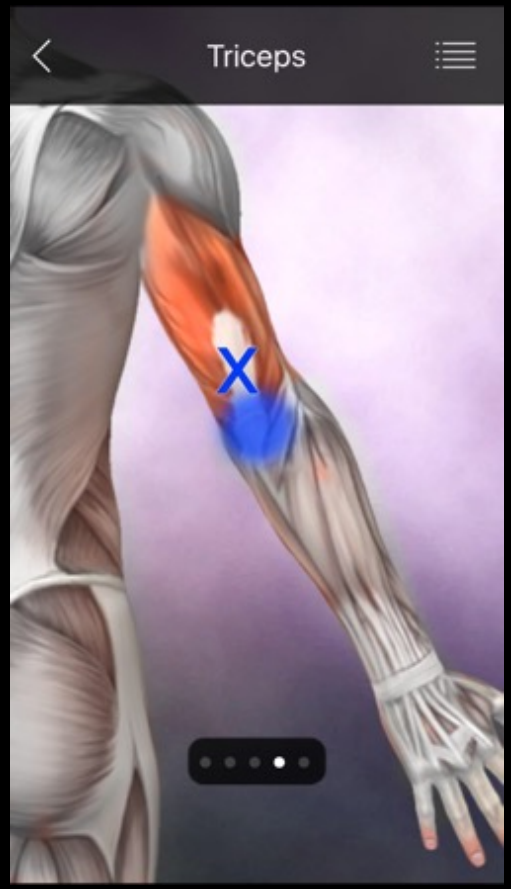
NERVE

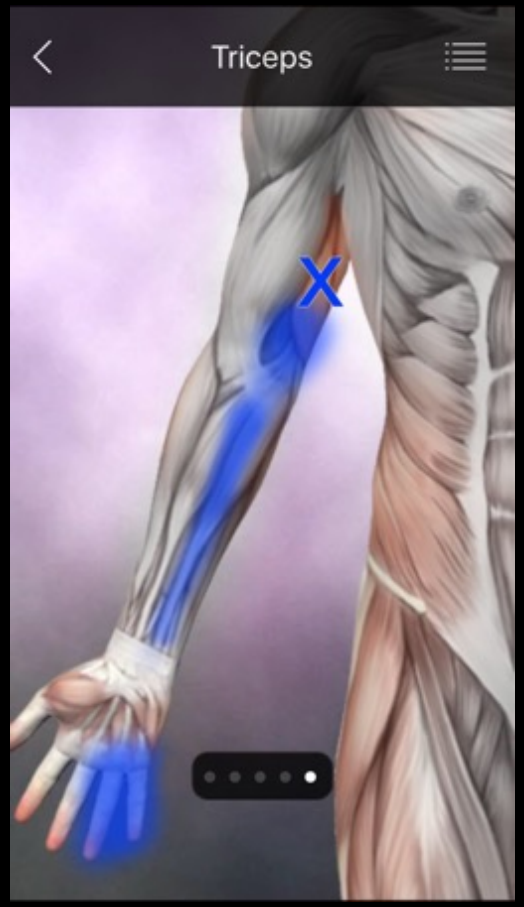
Radial nerve

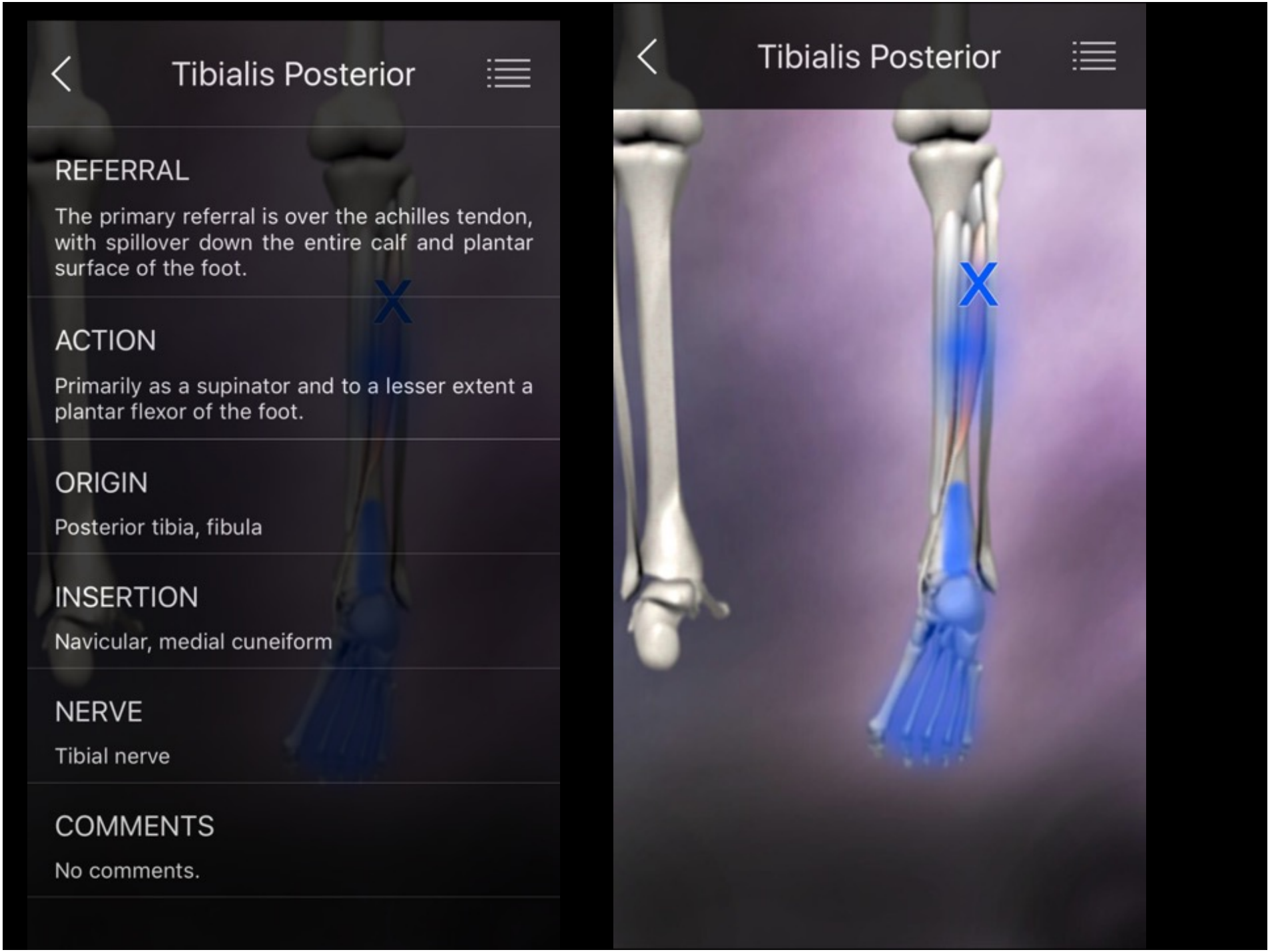





Triceps


Triceps


Triceps


Tibialis Posterior
REFERRAL
The primary referral is over the achilles tendon, with spillover down the entire calf and plantar surface of the foot.
X
ACTION
Primarily as a supinator and to a lesser extent a plantar flexor of the foot.
ORIGIN
Posterior tibia, fibula
INSERTION
Navicular, medial cuneiform
NERVE
Tibial nerve
COMMENTS
No comments.
Tibialis Posterior
X