1968-2018
50 Years of Challenge, Hope for Diabetes Cure

icdm
International Congress of Diabetes & Metabolism 2018
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전북대학교병원
CHONBUK NATIONAL UNIVERSITY HOSPITAL

New hope in management of diabetic peripheral neuropathy

Chonbuk National University Medical School
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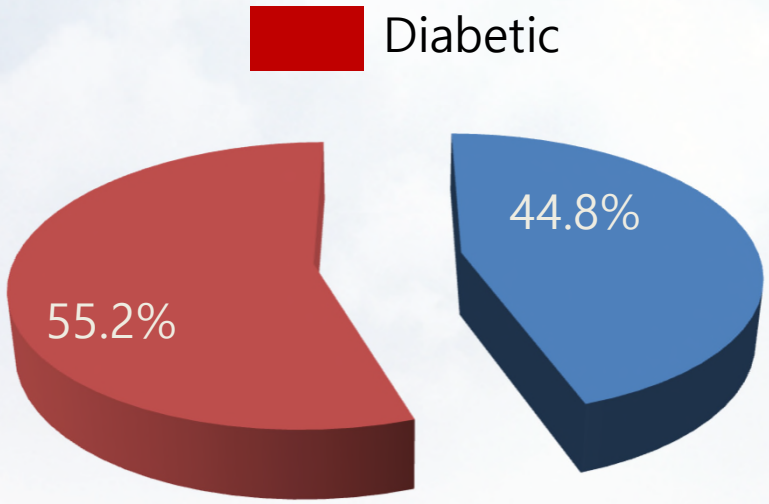
Contents

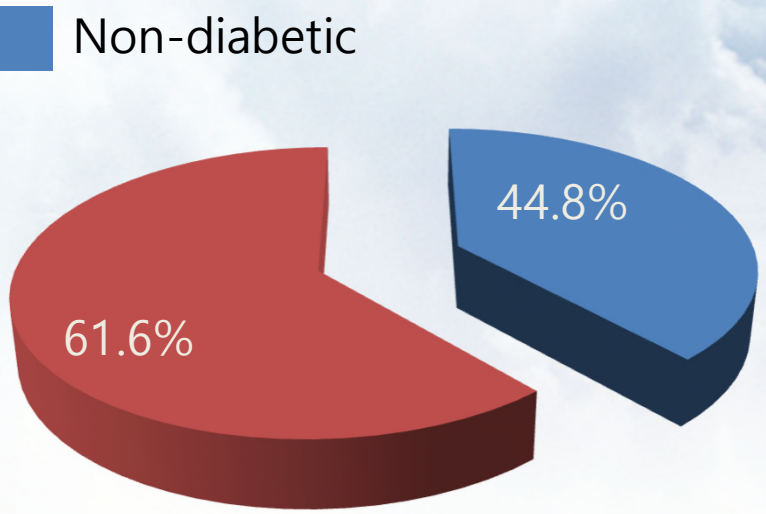
1. Epidemiology of DPN in Korea
2. Characteristics of DPNP
3. Current management of DPNP
4. Paradigm shift to future management of DPNP
5. Conclusion

Diabetes in Korea, 2007

Foot amputation (*N*= 3,829, 2003)

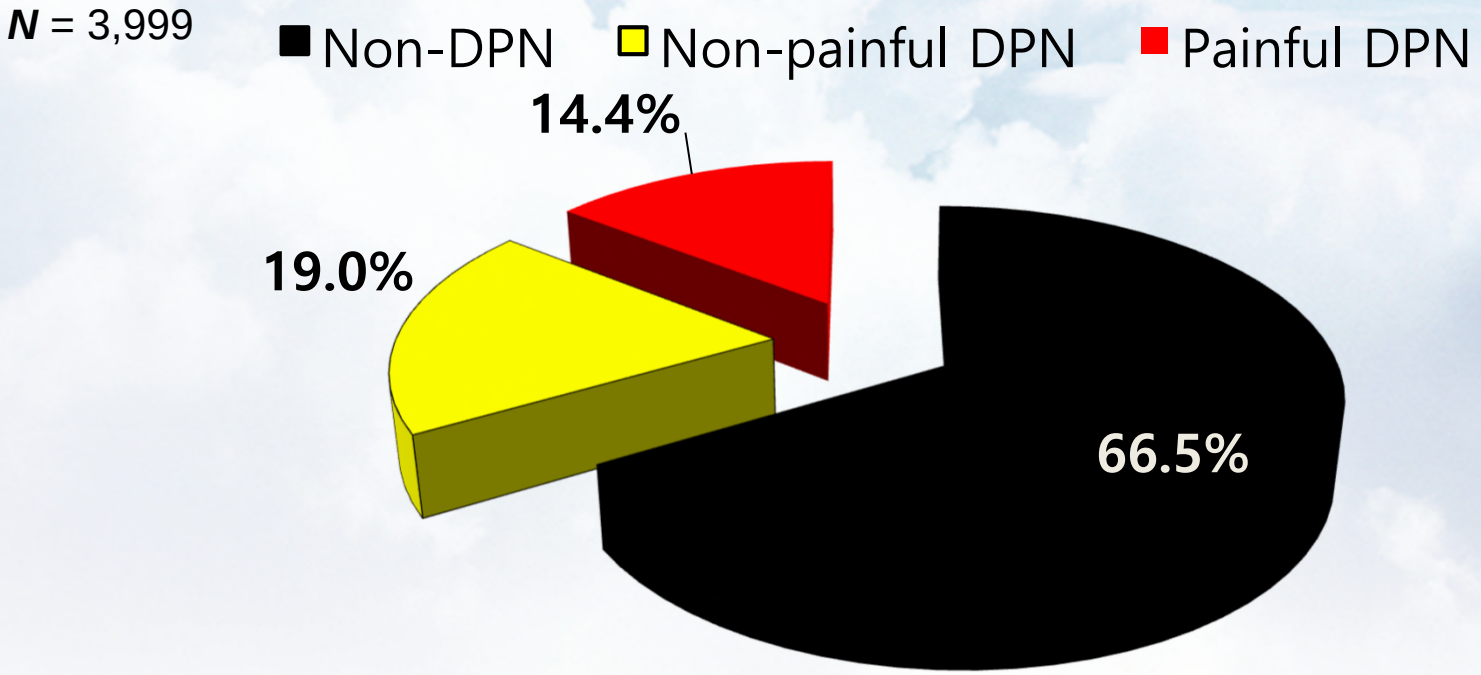


Foot ulcer (*N*= 8,495, 2003)



KDA. Diabetes in Korea, 2007

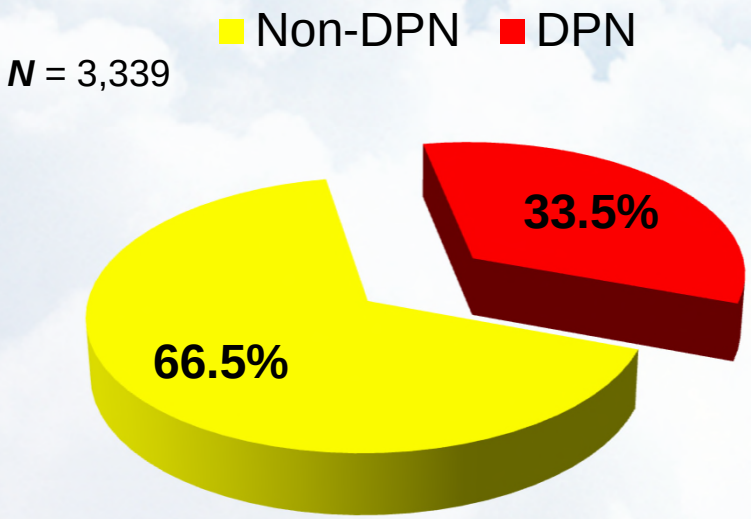
Prevalence of DPN in Korea

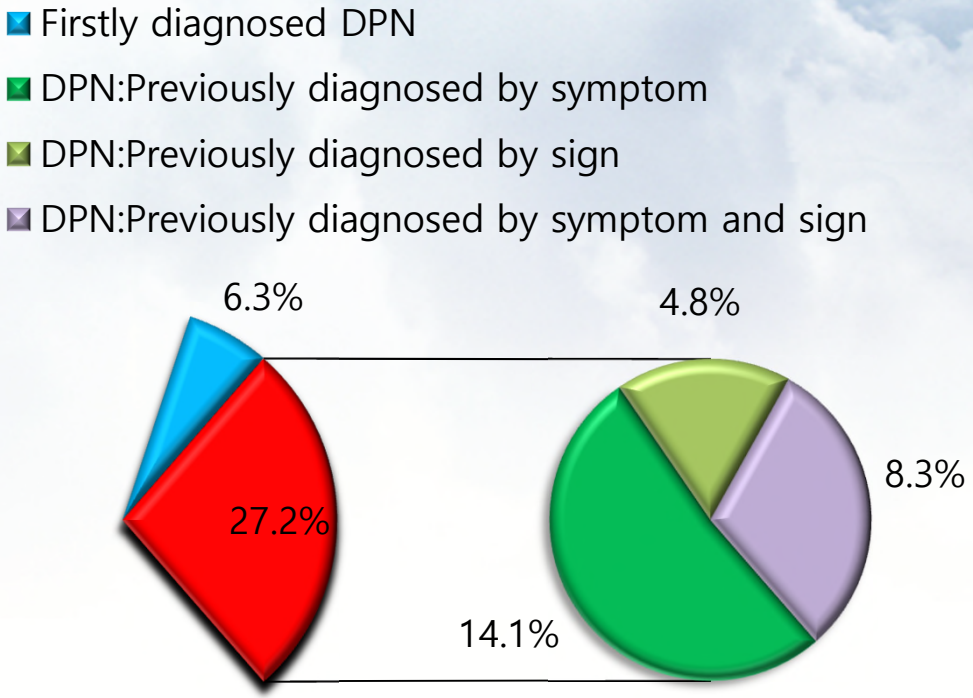


Nearly one third to half of patients with diabetes may have DPN.

Won JC, Diabetic Medicine, 2012
KIM SS and Won JC, DRCP, 2014
Won JC, DMJ, 2014

Prevalence of DPN in Korean

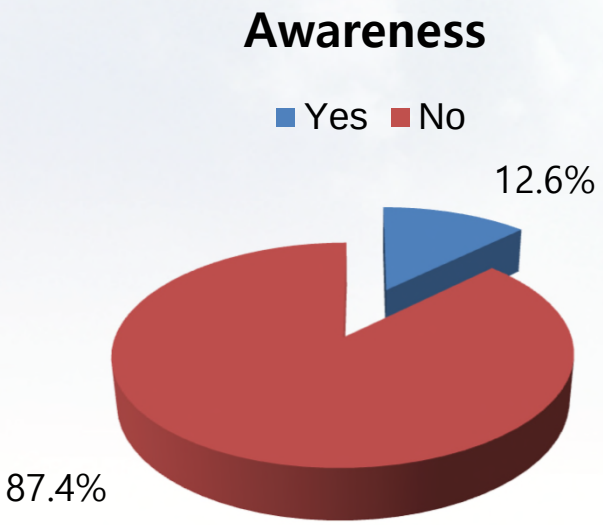


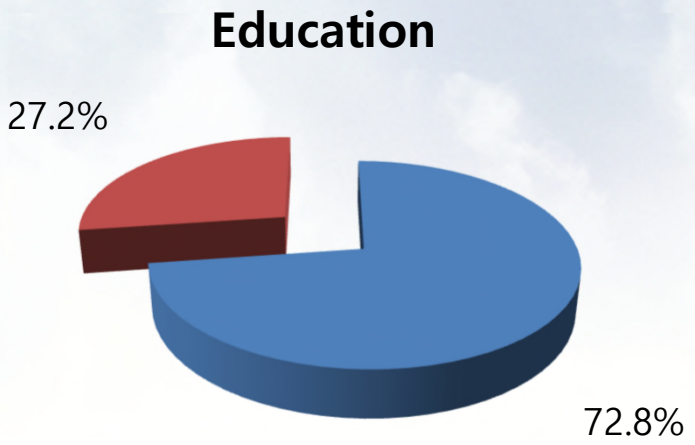


Won JC et al, DMJ, 2014;38:25-31.

Unawareness for DPN in Korean

- Despite the high prevalence or available education program in each hospital, only 1 among the eight patients with DPN know about their foot problem.
- High rate of education, but low level of awareness their having DPN





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Characteristics of DPN

- DPN is the most common Cx in diabetic patients
- Neurobiological mechanisms outnumber clinical manifestations
- DPN combined co-morbidities such as depression, insomnia etc.
- DPN must be diagnosed by **exclusion of other causes** **of peripheral neuropathy**

Pathophysiology of DPNP

- Neuropathic pain is initiated or caused by a primary lesion or dysfunction in the nervous system
  - Peripheral or central in origin
- Characterized by positive and negative symptoms and signs
  - Shared across neuropathic pain states
- Peripheral neuropathic pain may often co-exist with neuropathic and nociceptive pain
- Peripheral and central mechanisms mediate neuropathic pain independent of etiology.

Current perception status about DPNP

- Pain does not equal pain –numerous, different, spontaneous, and evoked pain-related symptoms.
- Patients' complaints are summarized under an umbrella diagnosis of "neuropathic pain syndrome"
- Treated according to the underlying disease entity and the overall pain intensity.
- Mechanism-based classification of DPNP is recommended.
- Mechanism-based individualized Tx is not performed yet.

Clin Pharmacol Ther. 2015 Feb;97(2):135-42

Problems of Disease-based approach in DPNP

- No clear indications that specific diseases should be treated with specific Txs
- Symptoms and signs overlap in various neuropathic pain conditions
- Current drugs act unspecific neurodepressant rather than pivotal pathophysiological mechanisms
- No good rationale for Tx algorithm that discriminates between underlying etiologies

Finnerup NB. et al. Pain 2010;150:573–581(578)

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Current management principles for DPNP

- Set the realistic Tx goals and expectations.
- Medication dosing must be tailored for the individual patient.
- Although drug combination Tx in DPNP is recommended, the use of multiple agents should be avoided whenever possible.
- Pharmacologic and nonpharmacologic intervention should consider
- Multidisciplinary approach is recommended

Current problems of DPNP management

- Disease-modifying Tx is partially effective
- DPNP symptom not completely improved by current therapy
- Effective dosage use often limited by the side effects
- New agents/new uses for existing agents offer additional Tx options
- ‘Rational’ polypharmacy is frequently necessary

Current therapies for DPNP

1. Glycemic control
2. Mechanism based therapy
   1) Aldose reductase inhibitors
   2) PKC inhibitors
   3) Agents acting on hexosamine pathway
   4) Agents acting on AGE pathway
   5) ROS inhibitors
3. Symptomatic treatment
   1) TCA and tetracyclic agents
   2) Selective serotonin reuptake inhibitors (SSRI)
   3) Serotonin–norepinephrine reuptake inhibitors (SNRI)
   4) Anticonvulsants
   5) Opioids
4. Non Pharmacological therapy
   – Exercise, biofeedback, cognitive behavioral therapy , TENS etc

Symptomatic treatment

1) TCA and tetracyclic agents
    1) Amitryptline
    2) Imipramine
    3) Clomipramine
    4) Nortriptyline
    5) Desipramine
2) Selective serotonin reuptake inhibitors (SSRI)

    specifically inhibiting presynaptic reuptake of serotonin
    1) Fluoxetine
    2) Paroxetine
    3) Citalopram

Symptomatic treatment

3) Serotonin–norepinephrine reuptake inhibitors (SNRI)
   - Dual inhibitory action :serotonin and Nep reuptake inhibition
   1. Duloxetine: approved by FDA for DPN Tx
   2. venlafaxine
4) Anticonvulsants
   1. Carbamazepine
   2. Lamotrigine
   3. Oxcarbazapine
   4. Topiramate
   5. Lacosamide
   6. Gabapentin and pregabalin
5) Opioids
   1. Tapentadol

Future directions for management of DPN

1. Potential targets for management of DPN
   1) DPP-IV inhibitors: alogliptin, vildagliptin
   2) Hsp90 inhibitors: KU-32
   3) NMDA antogonists
   4) Cannabinoid CB1 receptor agonist and antagonist
   5) μ-opioid receptor agonist-norepinephrine reuptake inhibitors (MOR-NRI)
   6) Topical agents
   7) Vasopeptidase inhibition
   8) α4 ß2 neuronal nicotinic acetylcholine receptor agonist
   9) PDE-5 inhibitor
   10) IκB phosphorylation inhibitor
   11) P13K/Akt signaling pathway
   12) Galanin receptor-1

Exercise as therapy for DPN

- Exercise Improves Epidermal Nerve Regeneration Capacity in the Setting of Non-diabetic Metabolic Syndrome.
- Exercise May Reduce Risk or Slow Progression of Diabetic Neuropathy
- Exercise Is Safe in Patients With Diabetic Neuropathy
- How Much Exercise Is Enough?
  - Strategies to Reduce Sedentary Behavior May Be More Effective Than Brief Periods of Intensive Exercise

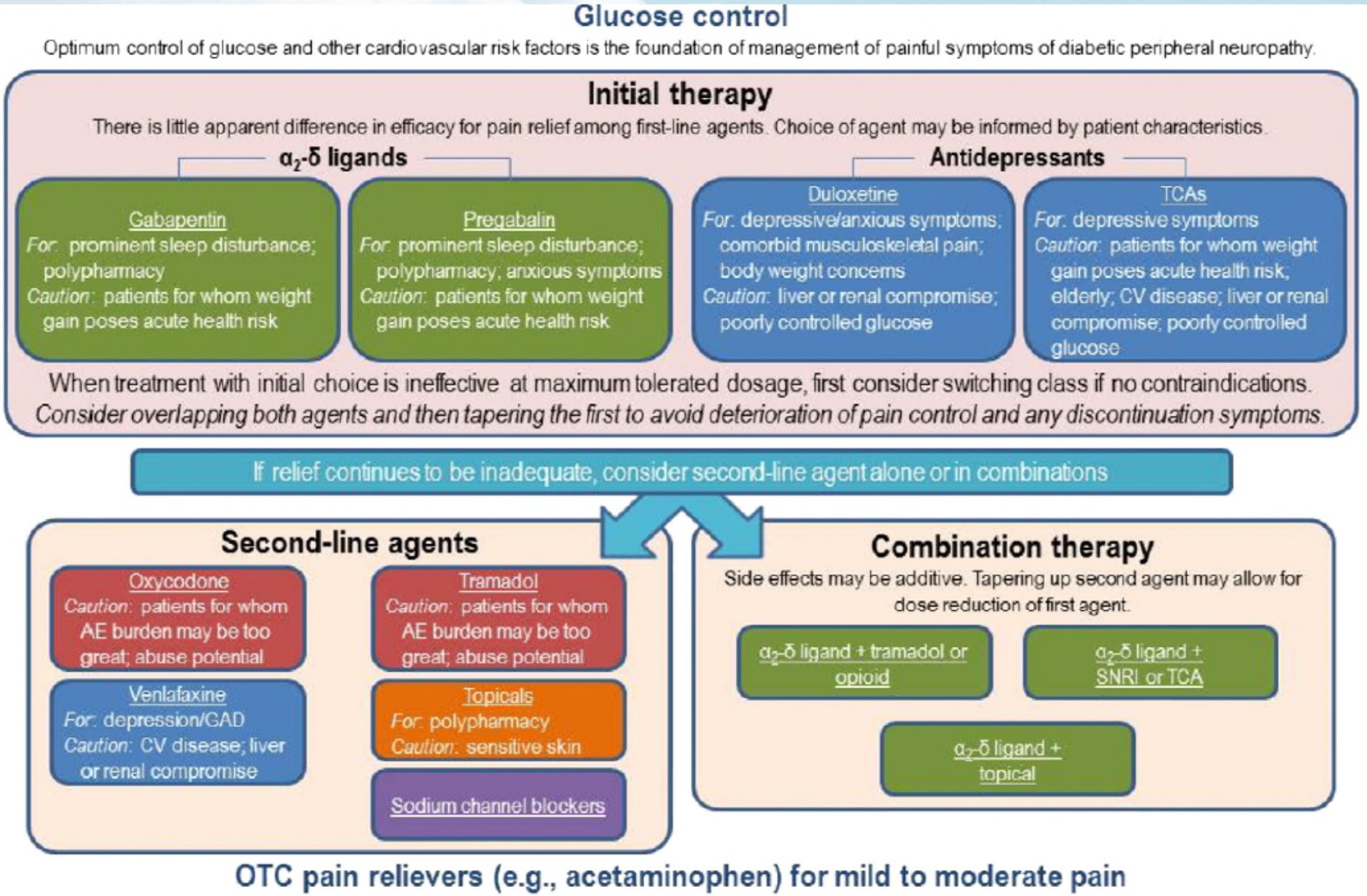
Singleton JR et al. Curr Diab Rep (2015) 15: 120

Barriers of exercise as therapy for DPN

- Neuropathic pain often limits ambulation for DPN patients
- For DPN patients, exercise is uncomfortable or make worse
- Exercise requires time, planning and motivation for patients
- Insurance does not cover exercise counseling
- Exercise promotion infrastructure is not geared to patients
- Additional validation studies are required

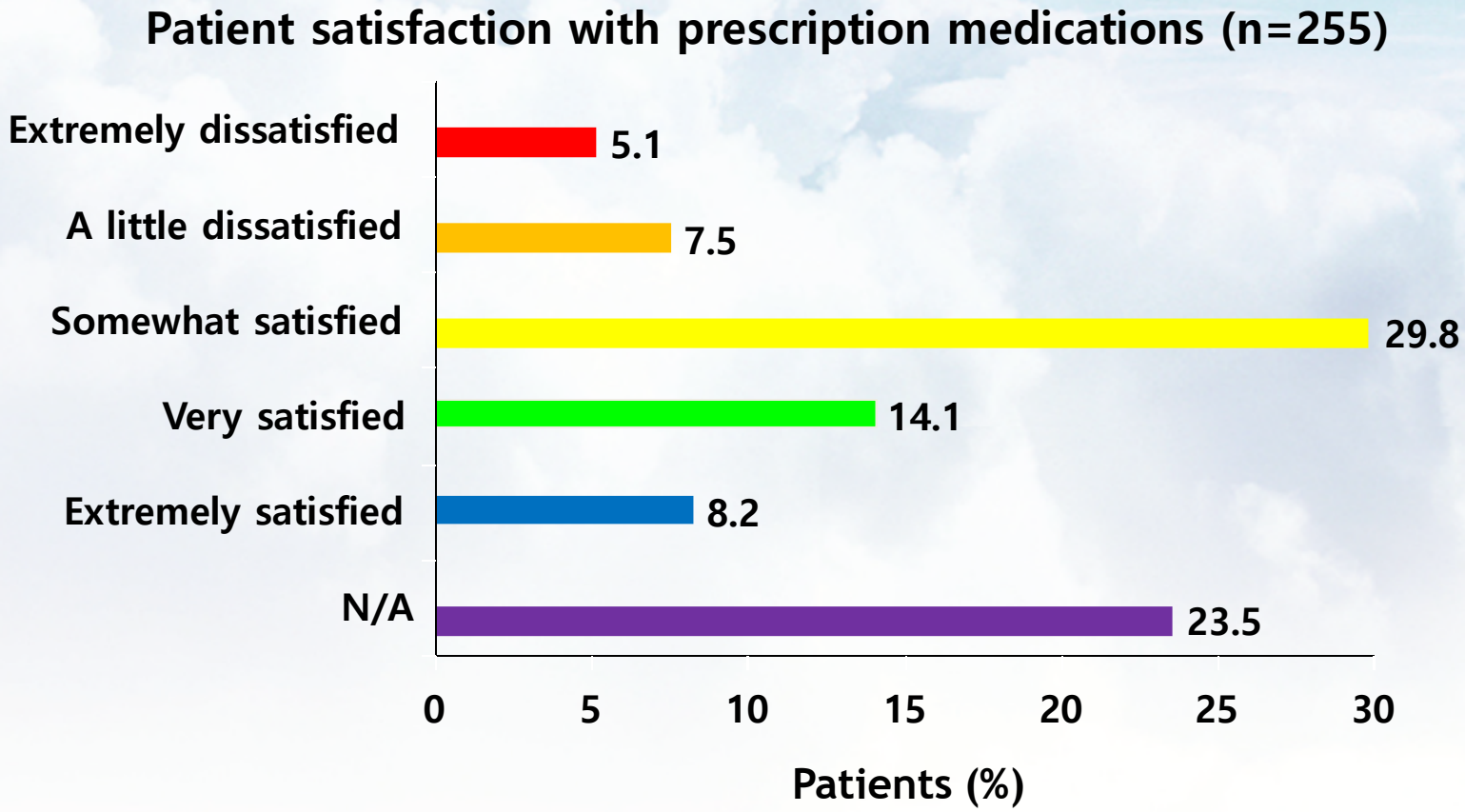
Singleton JR et al. Curr Diab Rep (2015) 15: 120

Tx algorithm for DPNP



D. Ziegler, V. Fonseca / J Diabetes Complications 29 (2015) 146–156

Treatment of DPNP: Satisfaction with medication is inadequate



Only 22.3% of patients surveyed were extremely or very satisfied with their prescription medications

Gore M, et al. *J Pain*. 2006;7:892–900.

Issues in the combination therapy for DPNP(1)

- There is no magic bullet for pain management
  - The frequent need for two or more drugs to control chronic pain
- The frequent need for at least one more drug therapy for psychological non-pain suffering
- The frequent need for at least one drug therapy for side effects of core therapies

Issues in the combination therapy for DPNP(2)

- The need for a sound PD/ PK basis for more than one drug from a particular class
- The need for critical review of the use of three or more drugs for any single indication
- The need to beware of additive and synergic effects and drug interaction

Benefits of combination therapy for DPNP

- Greater analgesic activity (due to complimentary or mutually reinforcing effects of the drugs)
- More favorable tolerability profile
- Improvement in other symptoms such as anxiety, depression and sleep disturbance

Gilron I et al. Lancet Neurol. 2013;12:1084–95.
Pain Ther (2017) 6 (Suppl 1):S35–S42

Current limitations for DPNP management drug trial

(1) Limited number of trials on new drugs and lesser studied diseases.

(2) Use of a disease-based classification in all trials.

(3) Available drugs do not target the various mechanisms underlying the pain
   - many of these drugs act mainly by reducing neuronal hyperexcitability, but not the more distinct pain-generating mechanisms.

(4) The primary outcome measure in most pain trials is based on a one -dimensional recording of pain intensity
   - does not encapsulate the complex spectrum of the pain experience such as the emotional and socioeconomic aspects of long-lasting pain.

(5) Trials have not looked at agents attempting to prevent the maladaptive changes in the pain process
   - those processes where the underlying disease or the long-standing pain cause irreversible changes in the nervous system that are beyond any type of modulation.

Finnerup NB. et al. Pain 2010;150:573–581(578)

Further clinical trial for DPNP management

- Drugs combination type
  - Pathogenic + symptomatic, symptomatic + symptomatic, pathogenic + pathogenic
  - Synergistic or additive effects
- Patients characteristics
  - Sex, genetic profile, underlying mechanism
- Trial duration for efficacy
- Effective doses with tolerable adverse effects

Solutions for current drug's limitation to DPNP

Cause

- Inadequate response to drug therapy constitutes a substantial unmet needs in patients with neuropathic pain.
- Modest efficacy, large placebo responses, heterogeneous diagnostic criteria, and poor phenotypic profiling probably account for moderate trial outcomes.

Solution

- Individuals' sensory profiles should be used to select patients.
- Sensory profiling of patients with neuropathic pain lead to personalized treatment.

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Tx target order of DPNP

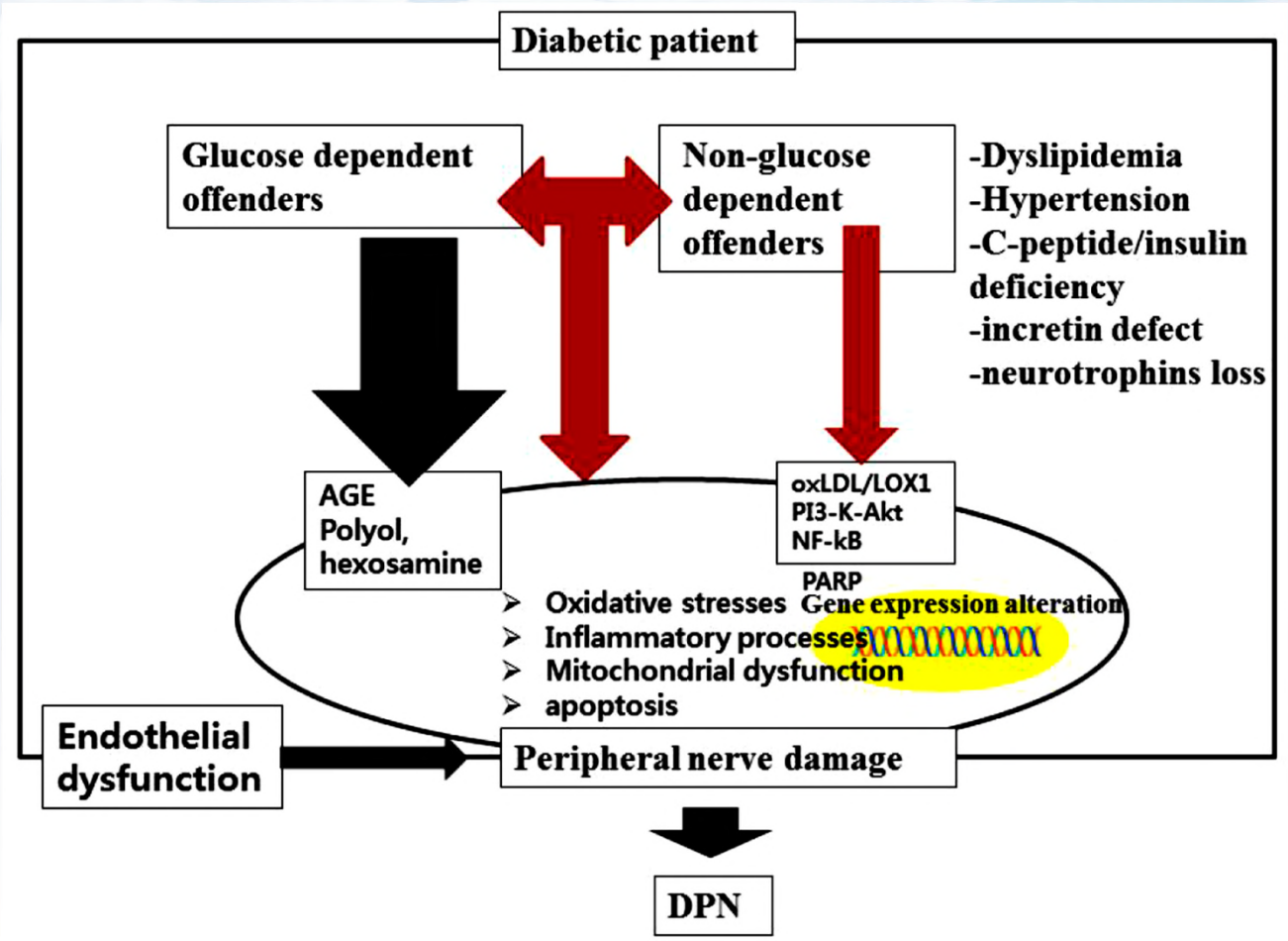
1. Underlying pathogenic mechanisms
2. Symptoms and improvement in QOL
3. The complications of neuropathy and their progression

Tx for delay and progression of diabetic microvascular complications

1. *Eliminate hyperglycemia*
2. *Inhibit the major mechanisms that hyperglycemia activates to induce vascular dysfunction*
3. *Neutralize accelerants such as inflammation and oxidative stress*
4. *Activate tissue specific protective factors*

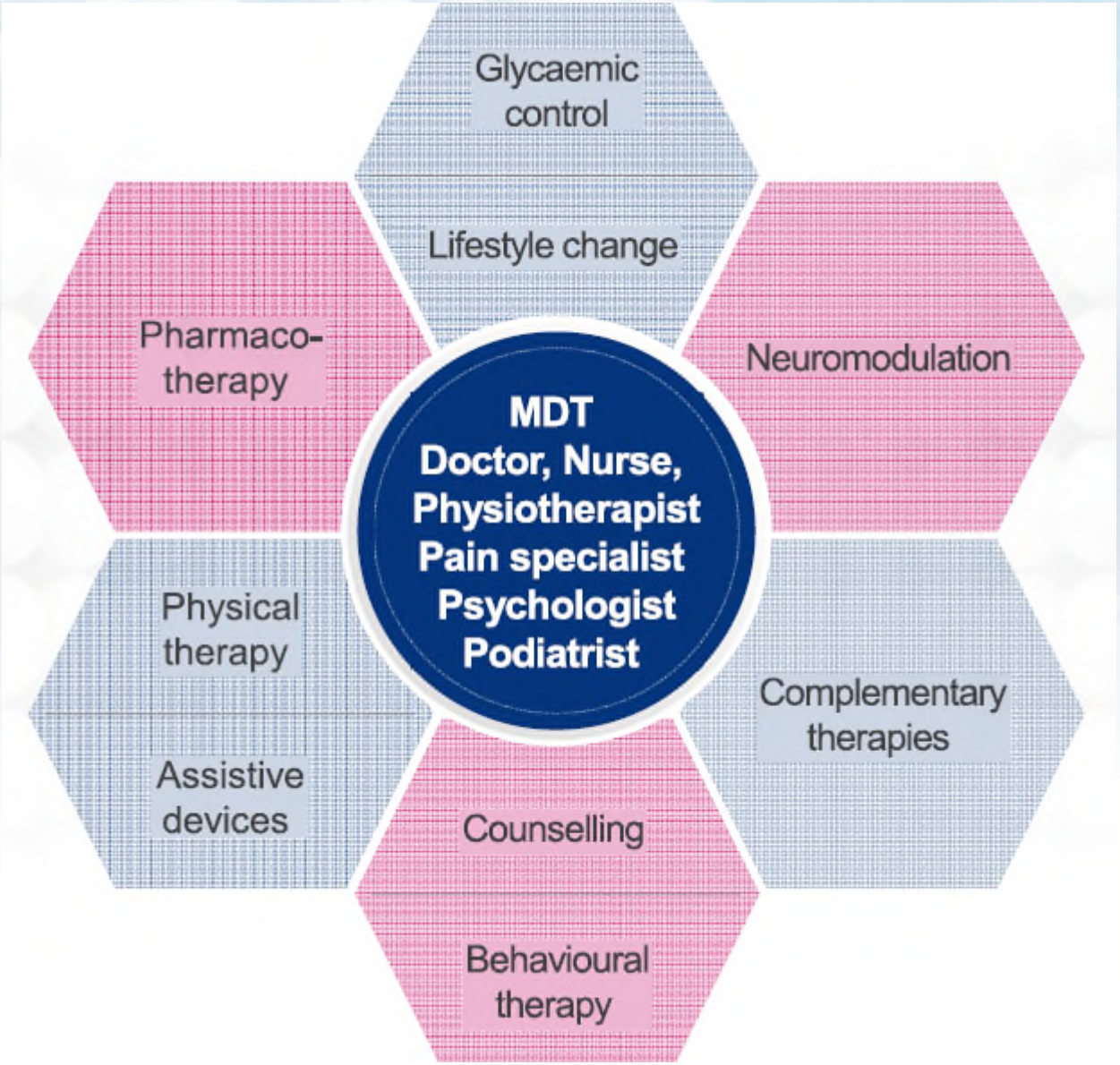
Barrett EJ ea al. J Clin Endocrinol Metab 102: 4343–4410, 2017 (4355).

Glucose and Non-glucose factors that can cause DN



HY Jin et al. submitted

Multimodal approach to managing DPN



Paradigm shift of neuropathic pain management

- **Historically,** neuropathic pain classified and treated on the basis of the underlying etiology.
- **Currently,** pain is differentiated by the underlying mechanism and treated by mechanisms rather than diseases.
  - The expression of some sensory sign can be related to mechanisms and pathophysiological dysfunction of afferent processing.

Baron R et al. Pain 158 (2017) 261–272

Needs of individualized Tx for DPNP

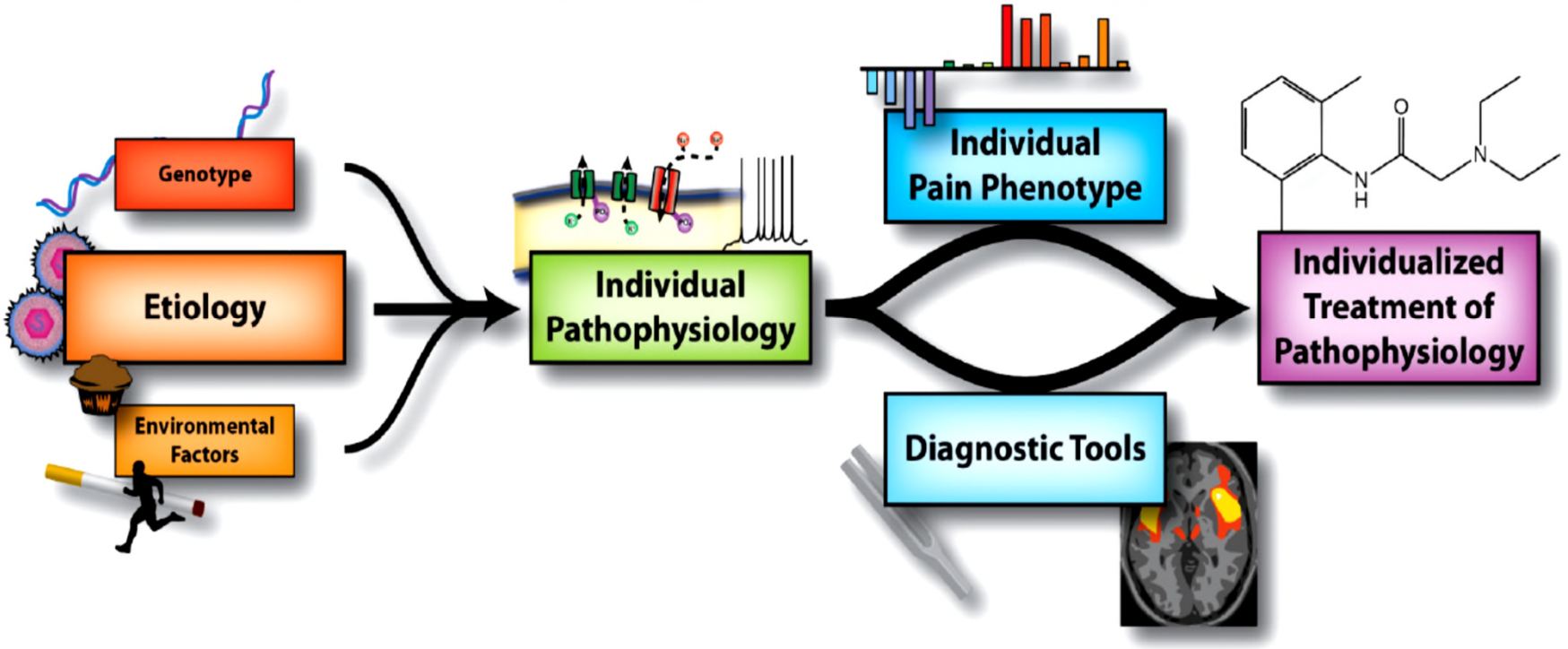


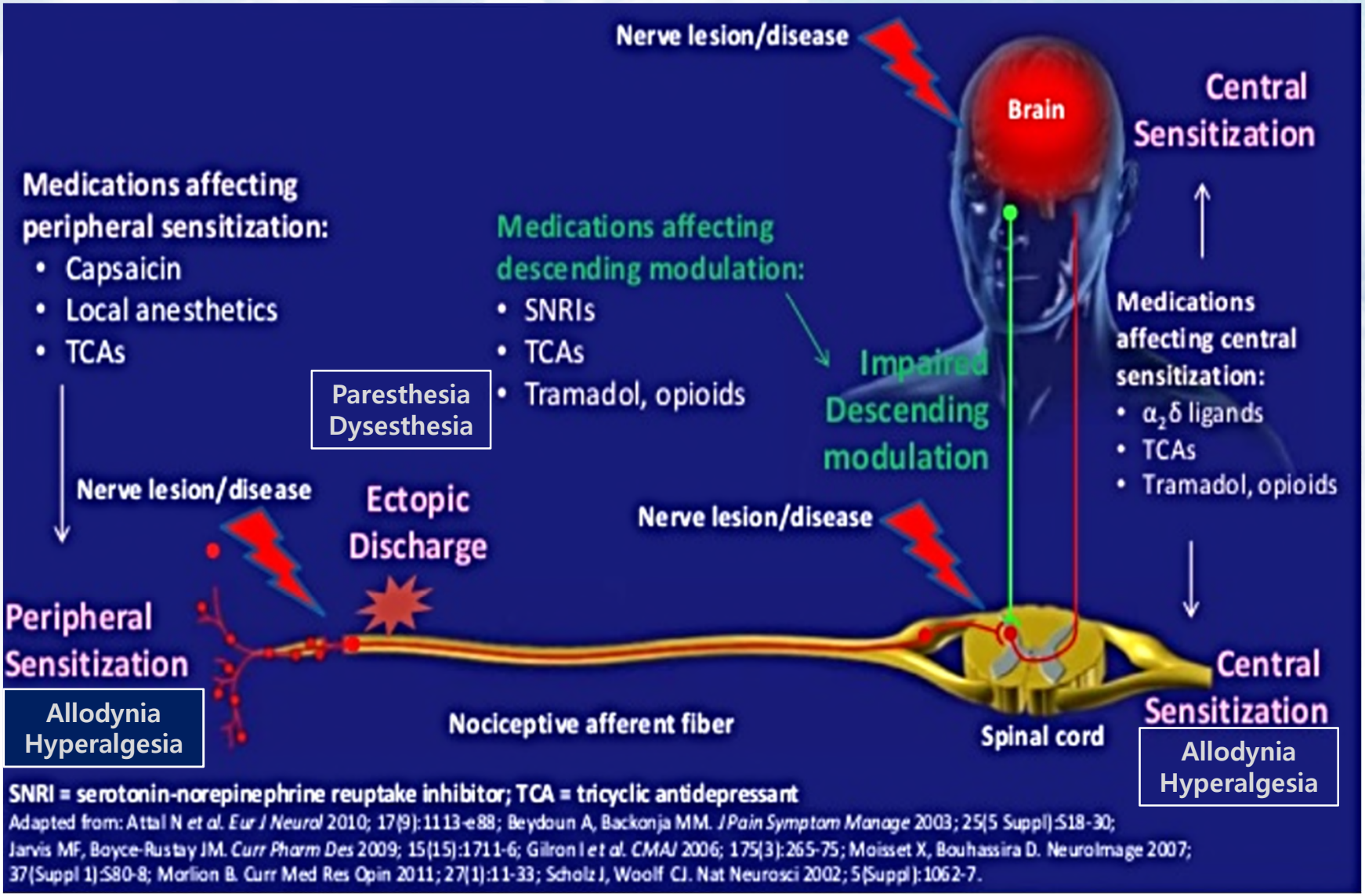
Figure 7. Individual pathophysiology requires personalized treatment
Etiology, genotype and environmental factors lead to individual pathophysiological changes and individual neuropathic pain profiles. Precise clinical examination and diagnostic tools are a prerequisite to define the pain phenotype and then to use this to identify personalized treatment options.

von Hehn CA et al. Neuron. 2012; 73: 638–652.

Challenges in mechanism based Tx in DPNP

- What are the neurobiological mechanisms responsible for the pain?
- How can we identify which mechanism operates in patients to produce their pain?
- How to develop pharmacological tools that are targeted specifically at the mechanisms and enable their disruption?

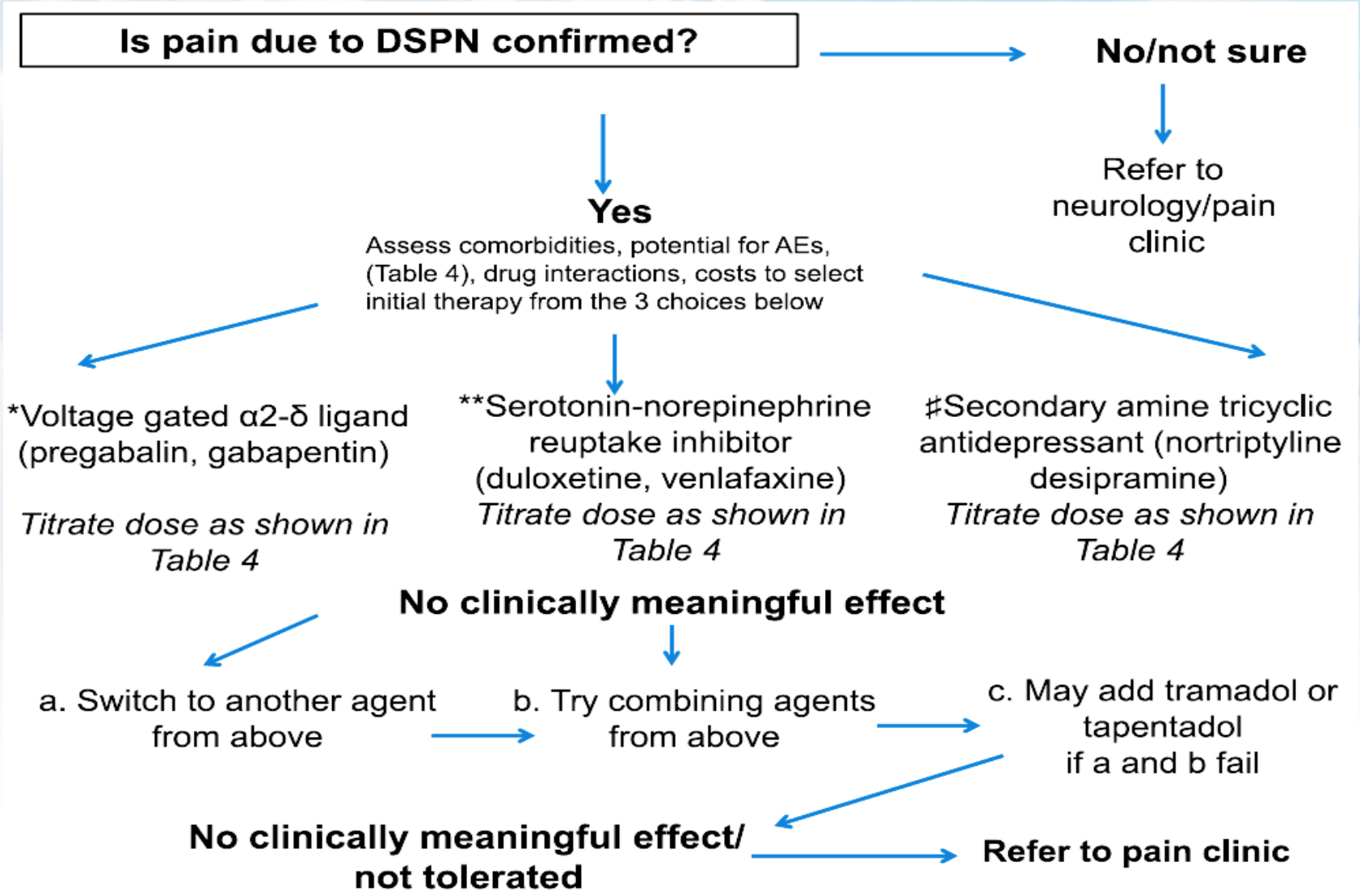
Mechanism-based pharmacological treatment of DPNP



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; Marlion B. Curr Med Res Opin 2011; 27(1):11-33; Scholz J, Woolf CJ. Nat Neurosci 2002; 5(Suppl):1062-7.

Algorithm for management of the patient with pain because of painful DN



Pop-Busui R et al. Diabetes Care 2017;40:136–154

Table 3: Summary of GRADE recommendations

	First-line drugs			Second-line drugs			Third-line drugs	
	Serotonin-noradrenaline reuptake inhibitors duloxetine and venlafaxine	Tricyclic antidepressants	Pregabalin, gabapentin, gabapentin extended release or enacarbil	Tramadol	Capsaicin 8% patches	Lidocaine patches	Strong opioids	Botulinum toxin A
Quality of evidence	High	Moderate	High	Moderate	High	Low	Moderate	Moderate
Balance between desirable and undesirable effects								
Effect size	Moderate	Moderate	Moderate	Moderate	Low	Unknown	Moderate	Moderate
Tolerability and safety*	Moderate	Low-moderate	Moderate-high	Low-moderate	Moderate-high	High	Low-moderate	High
Values and preferences	Low-moderate	Low-moderate	Low-moderate	Low-moderate	High	High	Low-moderate	High
Cost and resource allocation	Low-moderate	Low	Low-moderate	Low	Moderate-high	Moderate-high	Low-moderate	Moderate-high
Strength of recommendation	Strong	Strong	Strong	Weak	Weak	Weak	Weak	Weak
Neuropathic pain conditions	All	All	All	All	Peripheral	Peripheral	All	Peripheral

GRADE=Grading of Recommendations Assessment, Development, and Evaluation (see appendix for details about the GRADE classification). *Common side-effects: antidepressants: somnolence, constipation, dry mouth (particularly with tricyclic antidepressants), and nausea (particularly duloxetine); pregabalin or gabapentin: somnolence, dizziness, and weight gain; opioids (including tramadol): constipation, nausea, vomiting, tiredness, somnolence, dizziness, dry mouth, and itch; lidocaine patches: local irritation; capsaicin patches: local pain, oedema, and erythema; botulinum toxin A: local pain; see the appendix for further information about safety issues.

Finnerup et al. Lancet Neurol 2015; 162–73

NeuPSIG recommendations for implementation of future clinical trials in neuropathic pain

Limitations of clinical trials in neuropathic pain	NeuPSIG recommendation for future trials in neuropathic pain
Patient population (appendix)	
All randomised controlled trials were in adults	Do more studies in the paediatric population
Absence of validated diagnostic criteria and algorithms for neuropathic pain	Use NeuPSIG diagnostic criteria for probable or definite neuropathic pain and validated screening tools to confirm diagnosis*
Classification of patients is generally based on the cause of the pain	Classification should be based on sensory phenotypes rather than merely on the cause of the pain†
Characteristics of the trials (appendix)	
Trial duration is 12 weeks or less in 81% of the trials	Consider longer trial duration
High placebo response, particularly in recent trials	Exclude patients with low pain intensity and high variability of pain at baseline[44]

Finnerup et al. Lancet Neurol 2015;14:162-73

NeuPSIG recommendations for implementation of future clinical trials in neuropathic pain

- Inadequate response to drug treatments constitutes a substantial unmet need in patients with neuropathic pain.
- Modest efficacy, large placebo responses, heterogeneous diagnostic criteria, and poor phenotypic profiling probably account for moderate trial outcomes
- Should be taken into account in future studies.

Finnerup et al. Lancet Neurol 2015;14:162-73

Hindawi
Journal of Diabetes Research
Volume 2017, Article ID 5751687, 9 pages
https://doi.org/10.1155/2017/5751687

Research Article

Clinical Phenotype of Diabetic Peripheral Neuropathy and Relation to Symptom Patterns: Cluster and Factor Analysis in Patients with Type 2 Diabetes in Korea

Jong Chul Won,[1] Yong-Jin Im,[2] Ji-Hyun Lee,[3] Chong Hwa Kim,[4] Hyuk Sang Kwon,[5] Bong-Yun Cha,[5] and Tae Sun Park[6]

OBJECTIVES: Patients with diabetic peripheral neuropathy (DPN) is the most common complication. However, patients are usually suffering from not only diverse sensory deficit but also neuropathy-related discomforts. The aim of this study is to identify distinct groups of patients with DPN with respect to its clinical impacts on symptom patterns and comorbidities.

METHODS: A hierarchical cluster analysis and factor analysis were performed to identify relevant subgroups of patients with DPN (n = 1338) and symptom patterns.

RESULTS: Patients with DPN were divided into three clusters: asymptomatic (cluster 1, n = 448, 33.5%), moderate symptoms with disturbed sleep (cluster 2, n = 562, 42.0%), and severe symptoms with decreased quality of life (cluster 3, n = 328, 24.5%). Patients in cluster 3, compared with clusters 1 and 2, were characterized by higher levels of HbA1c and more severe pain and physical impairments. Patients in cluster 2 had moderate pain levels but disturbed sleep patterns comparable to those in cluster 3. The frequency of symptoms on each item of MNSI by "painful" symptom pattern showed a similar distribution pattern with increasing intensities along the three clusters.

CONCLUSIONS: Cluster and factor analysis endorsed the use of comprehensive and symptomatic subgrouping to individualize the evaluation of patients with DPN.

Cluster Analysis of Clinical Profiles in Korean DPNP patients

Cluster (n)	1 (448)	2 (562)	3 (328)
Age (yr)	61.66±9.86	62.57±11.52	62.68±10.47
BMI (kg/m^2)	24.88±3.41	24.88±3.46	25.48±4.08
MNSI	1.6±1.24	3.06±1.73	5.35±2.05
BPI	0.59±1.53	6.32±5.96	17.31±7.26
EQ-5D VAS	81.82±9.64	65.86±16.14	51.37±19.27
EQ-5D index	5.3±0.74	6.46±1.42	8.84±1.79
MOS-SS	32.97±3.13	26.01±6.26	26.03±7.2

BMI, body mass index; MNSI, Michigan Neuropathy Screening Instrument questionnaire; EQ-5D, EuroQol, 5-dimensions; VAS, visual analogue scale; MOS-SS, medical outcomes study sleep scale

Cluster 1: asymptomatic, Cluster 2: moderate symptoms with disturbed sleep, Cluster 3: severe symptoms with decreased QOL

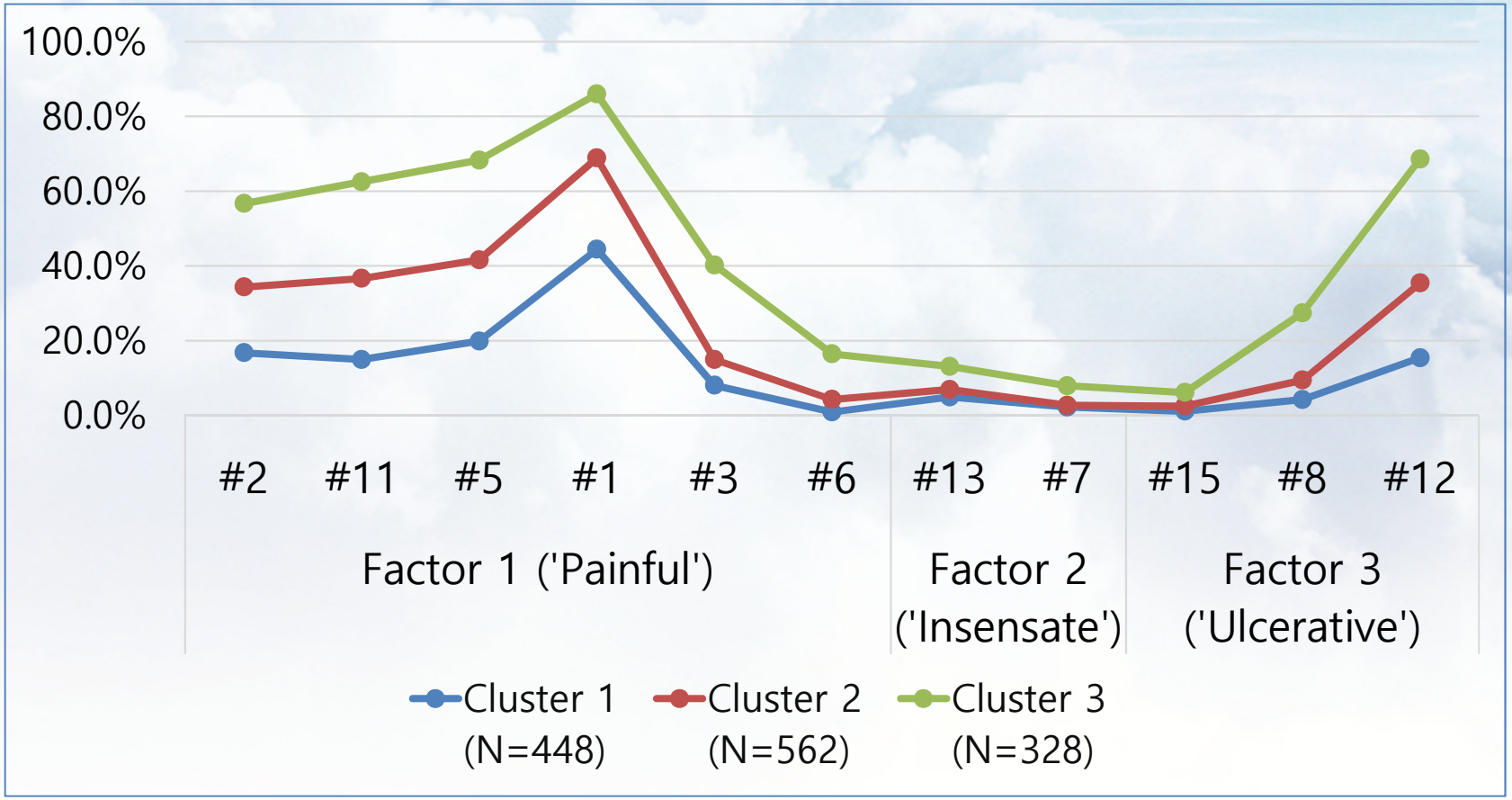
Won JC, Park TS. Journal of Diabetes Research 2017, Article ID 5751687

Common symptoms according to factor by the MNSI

Factor	MNSI Symptom question
1 painful	2. Do you ever have any burning pain in your legs and/or feet? 11. Are your symptoms worse at night? 5. Do you ever have any prickling feelings in your legs or feet? 1. Are your legs and/or feet numb? 3. Are your feet too sensitive to touch? 6. Does it hurt when the bed covers touch your skin?
2 insensate	13. Are you able to sense your feet when you walk? 7. When you get into the tub or shower, are you able to tell the hot water from the cold water?
3 ulcerative	15. Have you ever had an amputation? 8. Have you ever had an open sore on your foot? 12. Do your legs hurt when you walk ?

Won JC, Park TS. Journal of Diabetes Research Volume 2017, Article ID 5751687

The frequency of symptoms by the MNSI among clusters according to subgroups symptom pattern



Cluster 1: asymptomatic, cluster 2: moderate symptoms with disturbed sleep, cluster 3: severe symptoms with decreased QOL

Won JC, Park TS. Journal of Diabetes Research Volume 2017, Article ID 5751687

J Diabetes Res. 2017;2017:5751687. doi: 10.1155/2017/5751687. Epub 2017 Dec 13.

Clinical Phenotype of Diabetic Peripheral Neuropathy and Relation to Symptom Patterns: Cluster and Factor Analysis in Patients with Type 2 Diabetes in Korea.

Won JC[1], Im YJ[2], Lee JH[3], Kim CH[4], Kwon HS[5], Cha BY[5], Park TS[6].

Author information

Abstract

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Conclusions:

Cluster and factor analysis endorsed the use of comprehensive and symptomatic subgrouping to individualize the evaluation of patients with DPN.

Research Paper

PAIN

OPEN

Peripheral neuropathic pain: a mechanism-related organizing principle based on sensory profiles

Ralf Baron[a,*], Christoph Maier[b], Nadine Attal[c,d], Andreas Binder[a], Didier Bouhassira[c,d], Giorgio Cruccu[e], Nanna B. Finnerup[f], Maija Haanpää[g,h], Per Hansson[i,j], Philipp Hüllemann[a], Troels S. Jensen[f], Rainer Freynhagen[k], Jeffrey D. Kennedy[l], Walter Magerl[m], Tina Mainka[b,n], Maren Reimer[a], Andrew S.C. Rice[o], Märta Segerdahl[p,q], Jordi Serra[r], Sören Sindrup[s], Claudia Sommer[t], Thomas Tölle[u], Jan Vollert[b,m], Rolf-Detlef Treede[m], on behalf of the German Neuropathic Pain Research Network (DFNS), and the EUROPAIN, and NEUROPAIN consortia

Abstract

Patients with neuropathic pain are heterogeneous in etiology, pathophysiology, and clinical appearance. They exhibit a variety of pain-related sensory symptoms and signs (sensory profile). Different sensory profiles might indicate different classes of neurobiological mechanisms, and hence subgroups with different sensory profiles might respond differently to treatment. The aim of the investigation was to identify subgroups in a large sample of patients with neuropathic pain using hypothesis-free statistical methods on the database of 3 large multinational research networks (German Research Network on Neuropathic Pain (DFNS), IMI-Europain, and Neuropain). Standardized quantitative sensory testing was used in 902 (test cohort) and 233 (validation cohort) patients with peripheral neuropathic pain of different etiologies. For subgrouping, we performed a cluster analysis using 13 quantitative sensory testing parameters. Three distinct subgroups with characteristic sensory profiles were identified and replicated. Cluster 1 (sensory loss, 42%) showed a loss of small and large fiber function in combination with paradoxical heat sensations. Cluster 2 (thermal hyperalgesia, 33%) was characterized by preserved sensory functions in combination with heat and cold hyperalgesia and mild dynamic mechanical allodynia. Cluster 3 (mechanical hyperalgesia, 24%) was characterized by a loss of small fiber function in combination with pinprick hyperalgesia and dynamic mechanical allodynia. All clusters occurred across etiologies but frequencies differed. We present a new approach of subgrouping patients with peripheral neuropathic pain of different etiologies according to intrinsic sensory profiles. These 3 profiles may be related to pathophysiological mechanisms and may be useful in clinical trial design to enrich the study population for treatment responders.

Keywords: Neuropathic pain, Sensory signs, Clinical trials, QST, Epidemiology

Baron R et al. Pain. 2017; 158:261–272.

Subgrouping patients with peripheral neuropathic pain based on sensory signs

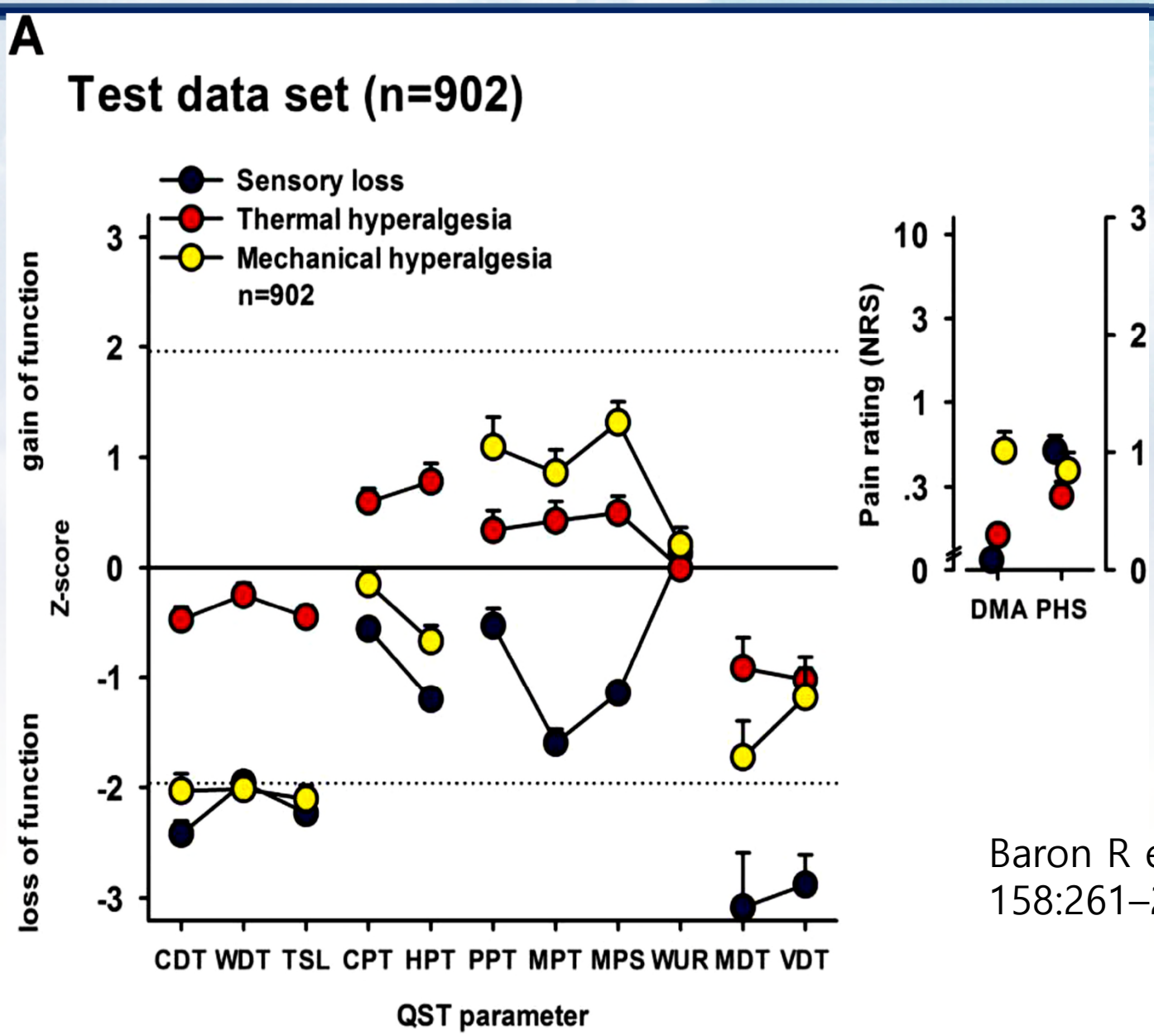

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Table 4

Cluster characteristics, hypotheses on underlying pathophysiology, and rational pharmaceutical treatment.

	Sensory loss	Thermal hyperalgesia	Mechanical hyperalgesia
Original data set, n (%)	381 (42)	302 (33)	219 (24)
Validation data set, n (%)	124 (53)	77 (33)	32 (14)
Sensory profile			
Sensory loss	Touch, thermal, pain	None	Mostly thermal
Hyperalgesia	None	Mostly cold and heat	Mostly pressure and pin
DMA	Little	Little	Much
PHS	Much	Little	Little
Pathophysiology			
Sensory loss	Small and large fibres	—	Mostly small fibres
Hyperalgesia	—	Mostly peripheral sensitization	Mostly central sensitization
Ongoing pain	Ectopic activity in damaged nociceptors or in CNS neurons	Spontaneous activity in surviving nociceptors	(Ectopic?) activity in nociceptors
Predicted findings			
IENFD	Loss	None	Mild loss
CCM	Loss	None	Mild loss
Peripheral MRI	Damage	None	Mild damage
LEP	Reduction	Normal or gain	Mild reduction
RIII	Reduction	Normal or gain	Gain
μENG	Denervation	Sensitization	Little denervation
Predicted efficacy			
NSAIDS	—	(+)	—
Botox		+	
Topical capsaicin		+	
NMDA-antagonist			+
Antidepressant	++	+	+
Gabapentinoid	+	+	++
Na-channel blocker	+	++	++
Opioid	++	+	+

CCM, confocal corneal microscopy; CNS, central nervous system; DMA, dynamical mechanical allodynia; IENFD, intraepidermal nerve fiber density; LEP, laser evoked potential; NMDA, *N*-methyl-D-aspartate; PHS, paradoxical heat sensation; RIII, flexor reflex; μENG, microneurography.
MRI, magnetic resonance imaging.

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Predicted efficacy of treatment response and rational pharmaceutical treatment.

Predicted efficacy

	Cluster 1	Cluster 2	Cluster 3
NSAIDs	−	(+)	−
Botox		+	
Topical capsaicin		+	
NMDA-antagonist			+
Antidepressant	++	+	+
Gabapentinoid	+	+	++
Na-channel blocker	+	++	++
Opioid	++	+	+

Predicted efficacy in clusters 1 to 3, based on studies identifying predictors of treatment response in subgroups. "++" very efficient, "+" moderate efficient, "−" not efficient. NMDA, *N*-methyl-D-aspartate; NSAIDs, nonsteroidal anti-inflammatory drugs.

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Peripheral neuropathic pain: a mechanism-related organizing principle based on sensory profiles

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Abstract

Patients with neuropathic pain are heterogeneous in etiology, pathophysiology, and clinical appearance. They exhibit a variety of pain-related sensory symptoms and signs (sensory profile). Different sensory profiles might indicate different classes of neurobiological mechanisms, and hence subgroups with different sensory profiles might respond differently to treatment. The aim of the investigation was to identify subgroups in a large sample of patients with neuropathic pain using hypothesis-free statistical methods on the database of 3 large multinational research networks (German Research Network on Neuropathic Pain (DFNS), IMI-Europain, and Neuropain). Standardized quantitative sensory testing was used in 902 (test cohort) and 233 (validation cohort) patients with peripheral neuropathic

We present **a new approach of subgrouping patients with peripheral neuropathic pain** of different etiologies according to intrinsic sensory profiles. These 3 profiles may be related to pathophysiological mechanisms and may be useful in clinical trial design to enrich the study population for treatment responders.

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Keywords: Neuropathic pain, Sensory signs, Clinical trials, QST, Epidemiology

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Conclusion

- Better stratify patients to individualize treatment to block key pathophysiological driver(s) in each patient.
- Mechanism based research will yield new treatments for DPNP and, potentially, also provide disease-modifying improvements.
- Ongoing advances in sensory phenotyping, genotyping, electrophysiology, and imaging outcomes should aid in this translation of current and future preclinical advances to improved patient outcomes in DN.


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