

Painful Diabetic Neuropathy – Effective Management

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Neuropathic Pain

- Prevalence varies between 10 and 90% depending on classification
- Accounts for 50-75% of non-traumatic amputations
 - 1.7 fold increase in the risk of amputation; 12 fold, if there is deformity; 36 fold, if there is a history of previous ulceration
- Mortality rate approximates 25-50% within 5-10 years of diagnosis

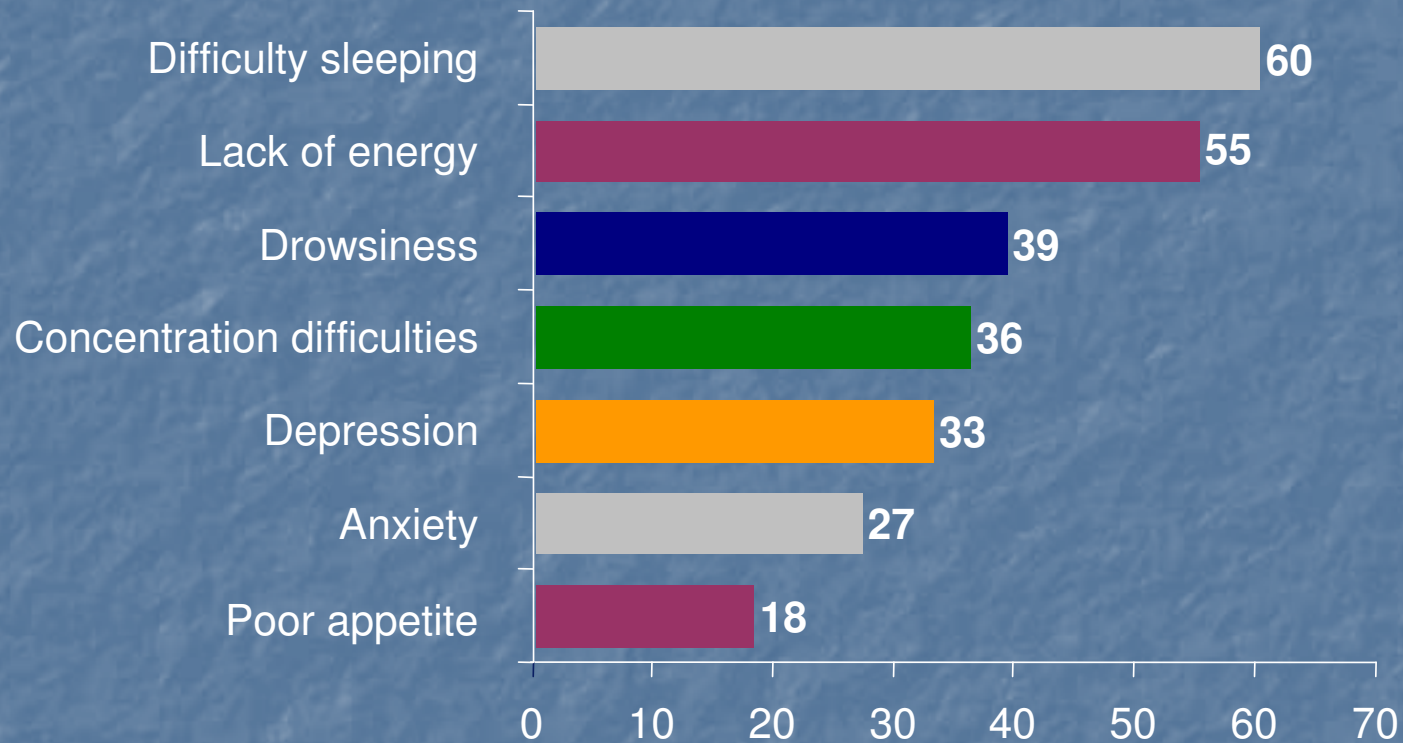
Neuropathic Pain

- Neuropathic pain is also often associated with:
 - Sleep interference
 - Emotional disturbance
 - Reductions in quality of life and functioning
 - Reduced employment status

Symptoms of Neuropathic Pain

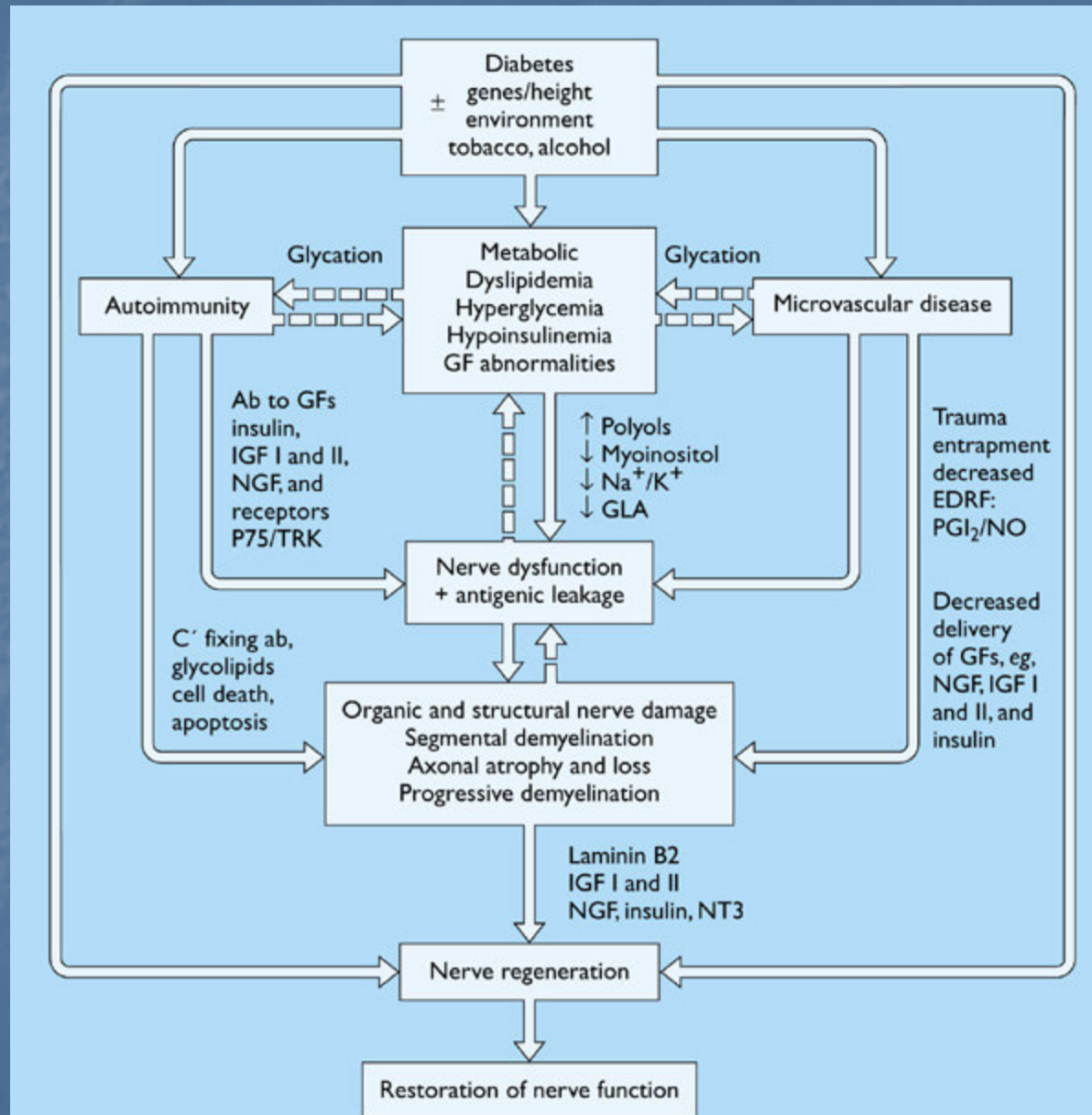
- Spontaneous pain
 - Shooting, burning or electric shock-like
 - Numbness, pins and needles
- Hyperalgesia
 - Increased sensation of pain in response to normally painful stimuli
- Allodynia
 - Pain in response to normally non-painful stimuli

Co-morbidity Associated with Peripheral Neuropathic Pain

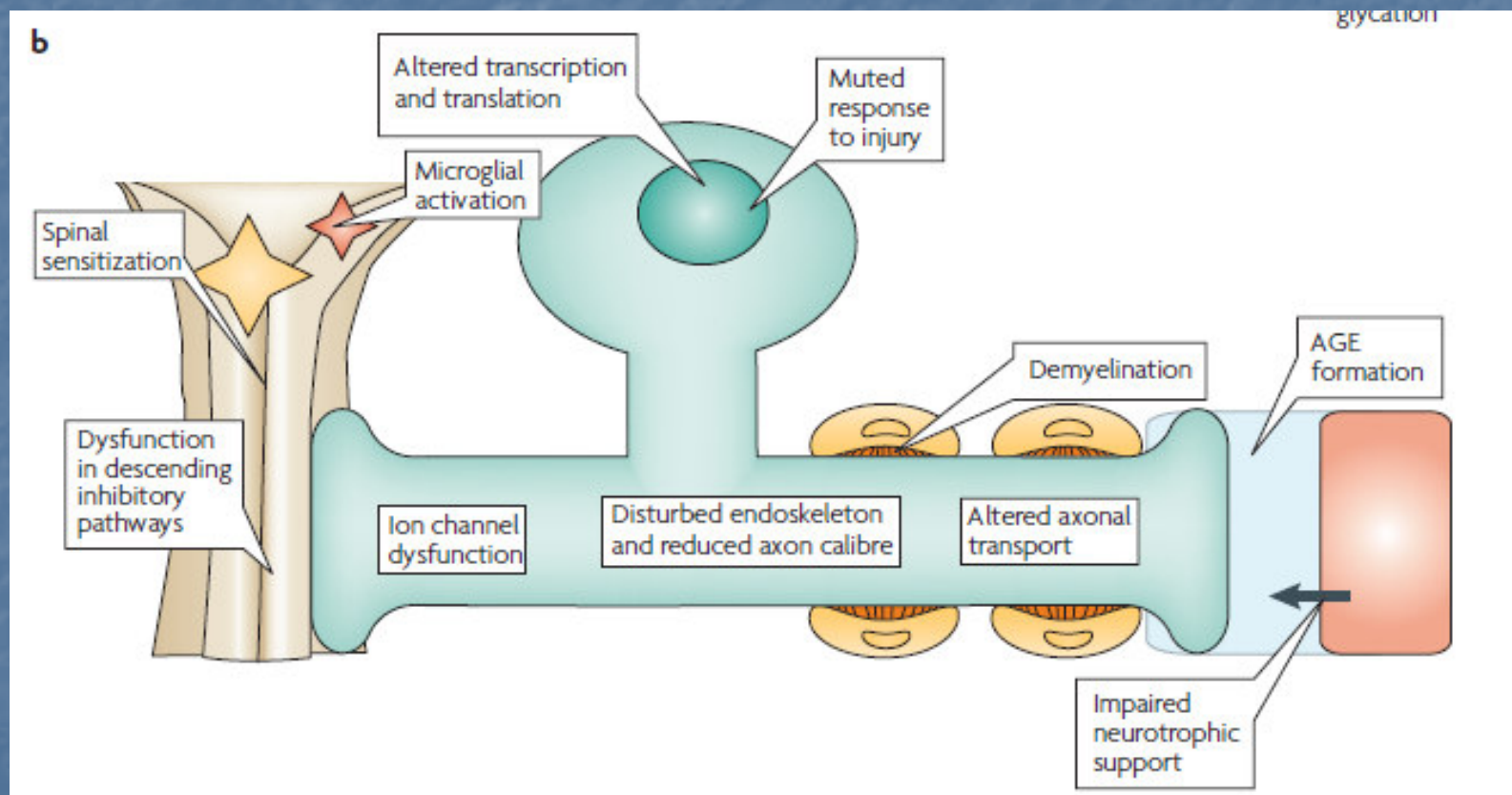


% patients with moderate to very severe discomfort due to symptoms (n=126)

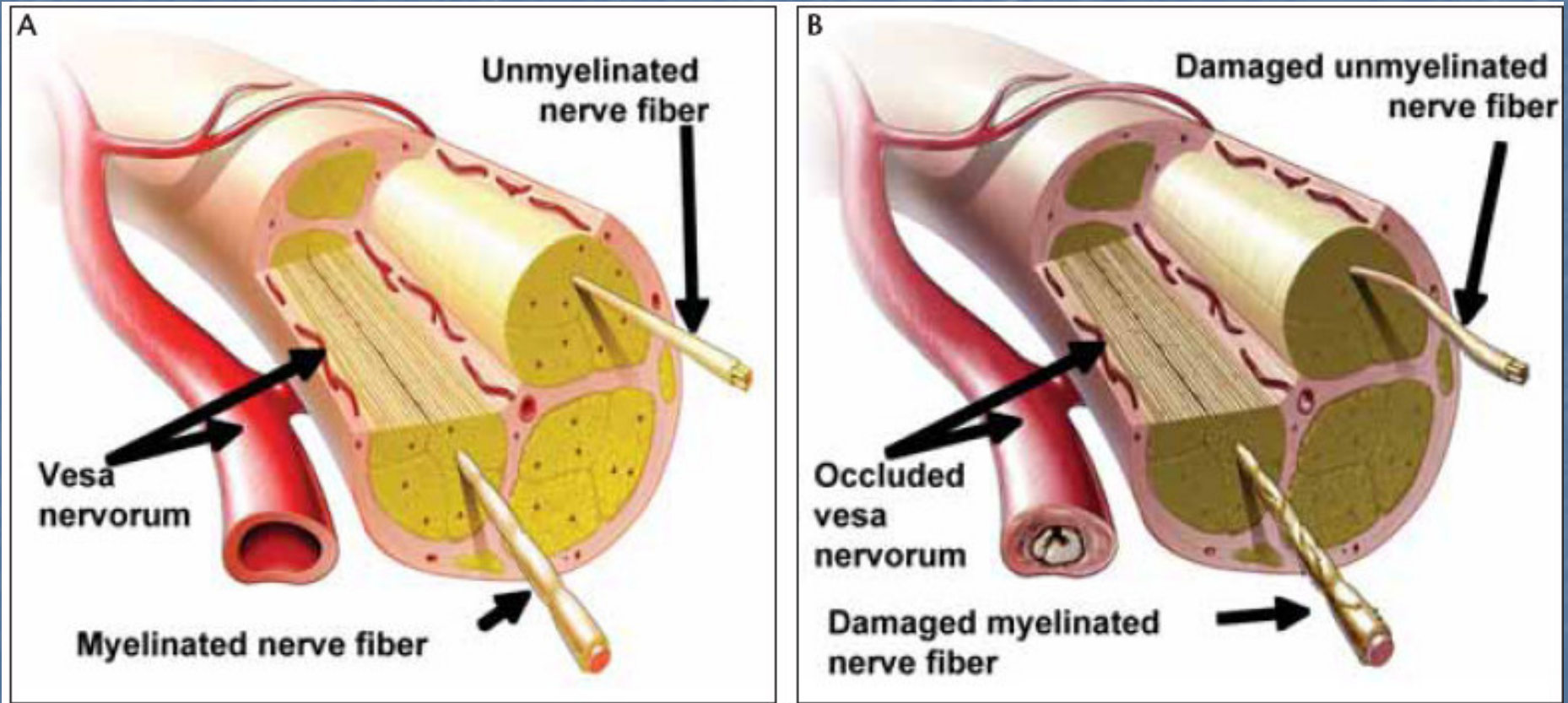
Pathogenesis



Mechanism of Damage



Damaged Nerves



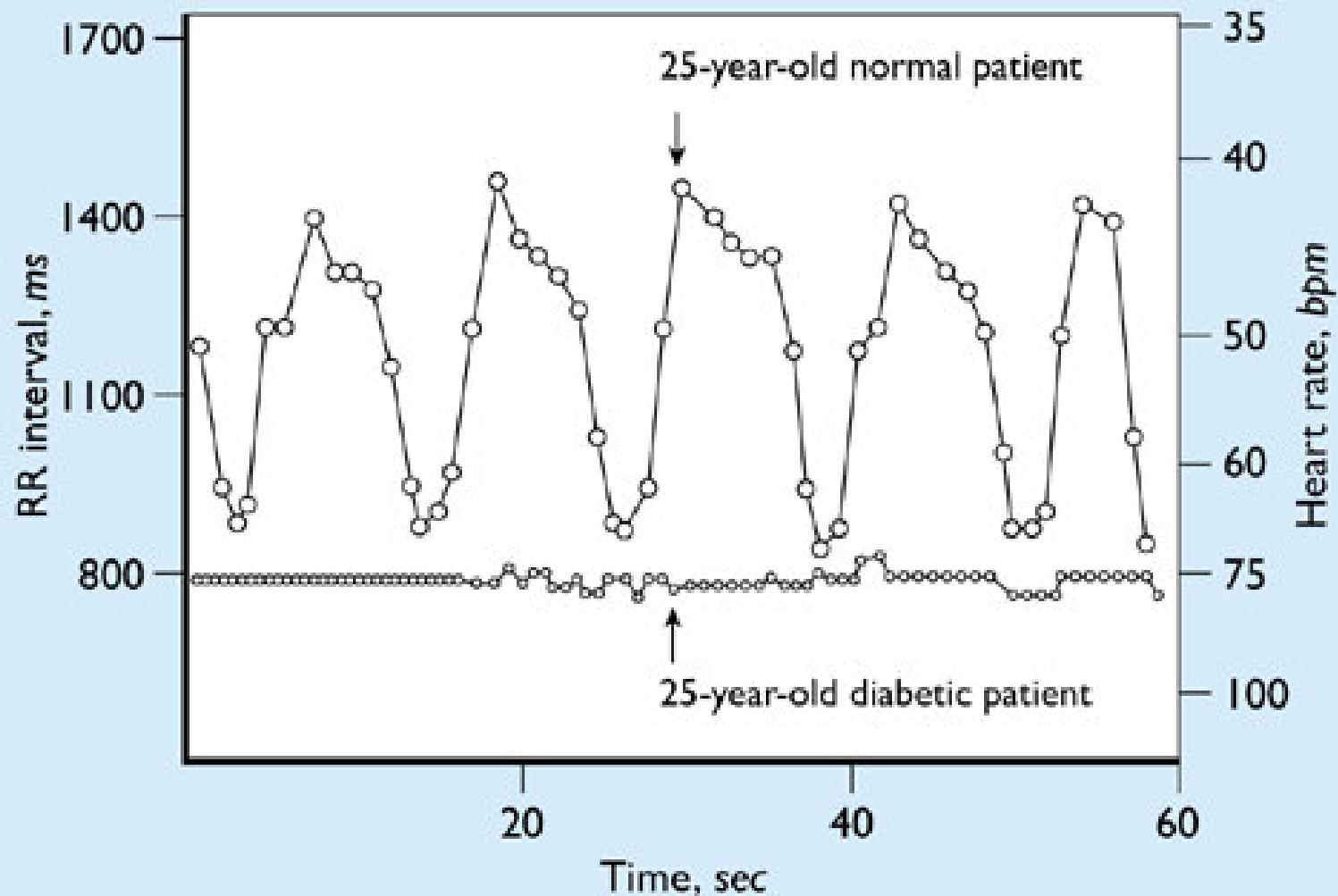
Classification

- Subclinical neuropathy
 - Abnormalities in electro-diagnostic and quantitative sensory testing
- Diffuse clinical neuropathy
 - Distal symmetric sensorimotor and autonomic syndromes
- Focal syndromes

Subclinical Neuropathy

- Diagnosed by
 - Abnormal electro-diagnostic tests with decreased nerve conduction velocity or decreased amplitudes
 - Abnormal quantitative sensory tests for vibration, tactile, thermal thresholds
 - Autonomic function tests with diminished heart rate variation with deep breathing, Valsalva manoeuvre, and postural testing

Autonomic Neuropathy



Diffuse Peripheral Neuropathy

- Diabetes may damage small fibres, large fibres, or both
- These can lead to dysfunction of almost any segment of the somatic peripheral and autonomic nervous systems
- The size of the fibres involved often determines the order in which they are affected

Fibre Size and Symptoms

- Small fibres are affected earliest, manifested first in the lower limbs by pain and hyperalgesia
- Loss of thermal sensitivity follows, with reduced light touch and pinprick sensation
- Large fibre neuropathies may involve sensory or motor nerves, or both

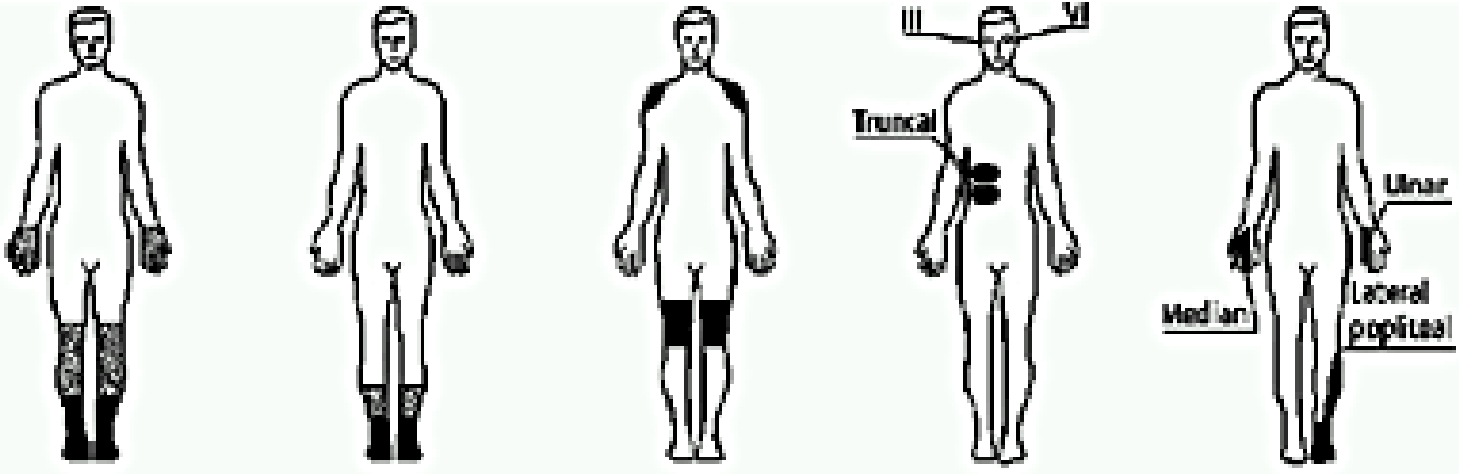
Clinical Presentation of Large Fibre Neuropathy

- Presentation
 - Impaired vibration perception
 - Pain of A- type: deep-seated, gnawing
 - Ataxia
 - Wasting of small muscles, intrinsic muscles feet with hammer toes
 - Weakness
 - Increased blood flow (the hot foot)
 - Risk of Charcot neuroarthropathy

However

- Most patients with distal sensory polyneuropathy have a mixed variety, with both large and small nerve fibre involvement
- With a distal sensory polyneuropathy, a "glove and stocking" distribution of sensory loss is very common

Different Presentations of Diabetic Neuropathy



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: +-+++

Natural History

- Sensory and autonomic neuropathies are generally progressive and irreversible
 - Progression is related to glycaemic control
- Mononeuropathies, radiculopathies, and acute painful neuropathies, although symptoms are severe, are short-lived and tend to recover
 - Recovery is dependent on restoration of good glycaemic control

Examples



Mononeuritis vs Entrapment

■ Mononeuritis

- Sudden onset
- Usually single nerve, but maybe more
- Common nerves C3, 6, 7, ulnar, peroneal
- Not progressive and resolves spontaneously
- Treatment symptomatic

■ Entrapment

- Gradual onset
- Single nerve exposed to trauma
- Common nerves Median, ulnar, peroneal, medial and lateral plantar
- Progressive
- Treatment rest, splints, diuretics, steroids, surgery

Proximal Motor Neuropathy

- Amyotrophy
 - Primarily affects the elderly
 - Gradual or abrupt onset
 - Begins with pain in the thighs and hips or buttocks
 - Followed by significant weakness of the proximal muscles of the lower limbs with inability to rise from the sitting position
 - Begins unilaterally and spreads bilaterally,
 - Coexists with distal symmetric polyneuropathy, and
 - Spontaneous muscle fasciculation, or provoked by percussion

Proximal Motor Neuropathy

- Secondary causes may be more common and not related to diabetes
 - Chronic inflammatory demyelinating polyneuropathy (CIDP),
 - Monoclonal gammopathy,
 - Circulating GM1 antibodies and
 - Antibodies to neuronal cells and inflammatory vasculitis

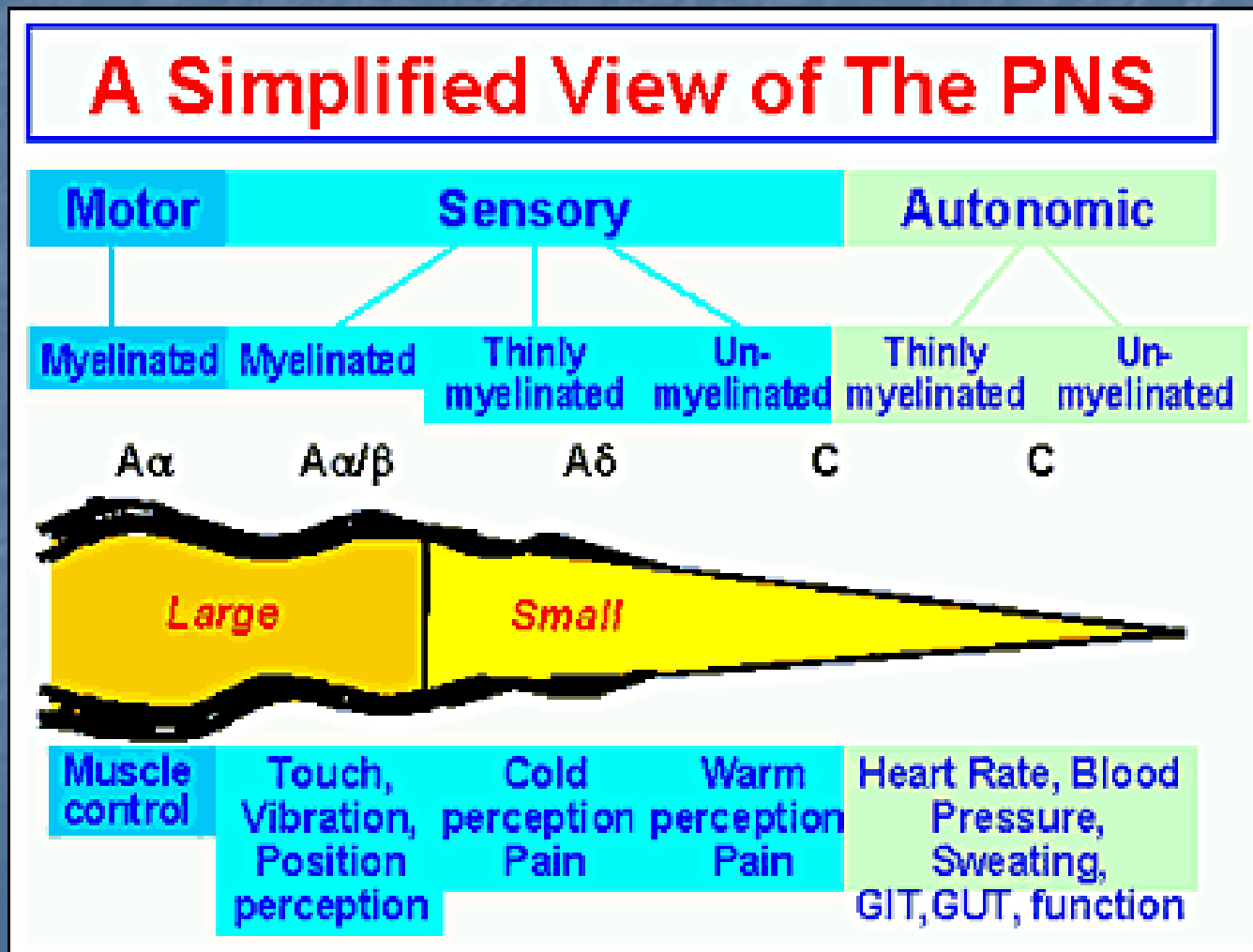
Proximal Motor Neuropathy

- Clinical features
 - Weakness of the iliopsoas, obturator, and adductor muscles, together with relative preservation of the gluteus maximus and minimus and hamstrings. Great difficulty rising out of chairs unaided and often use their arms to assist themselves
 - Heel or toe standing is preserved

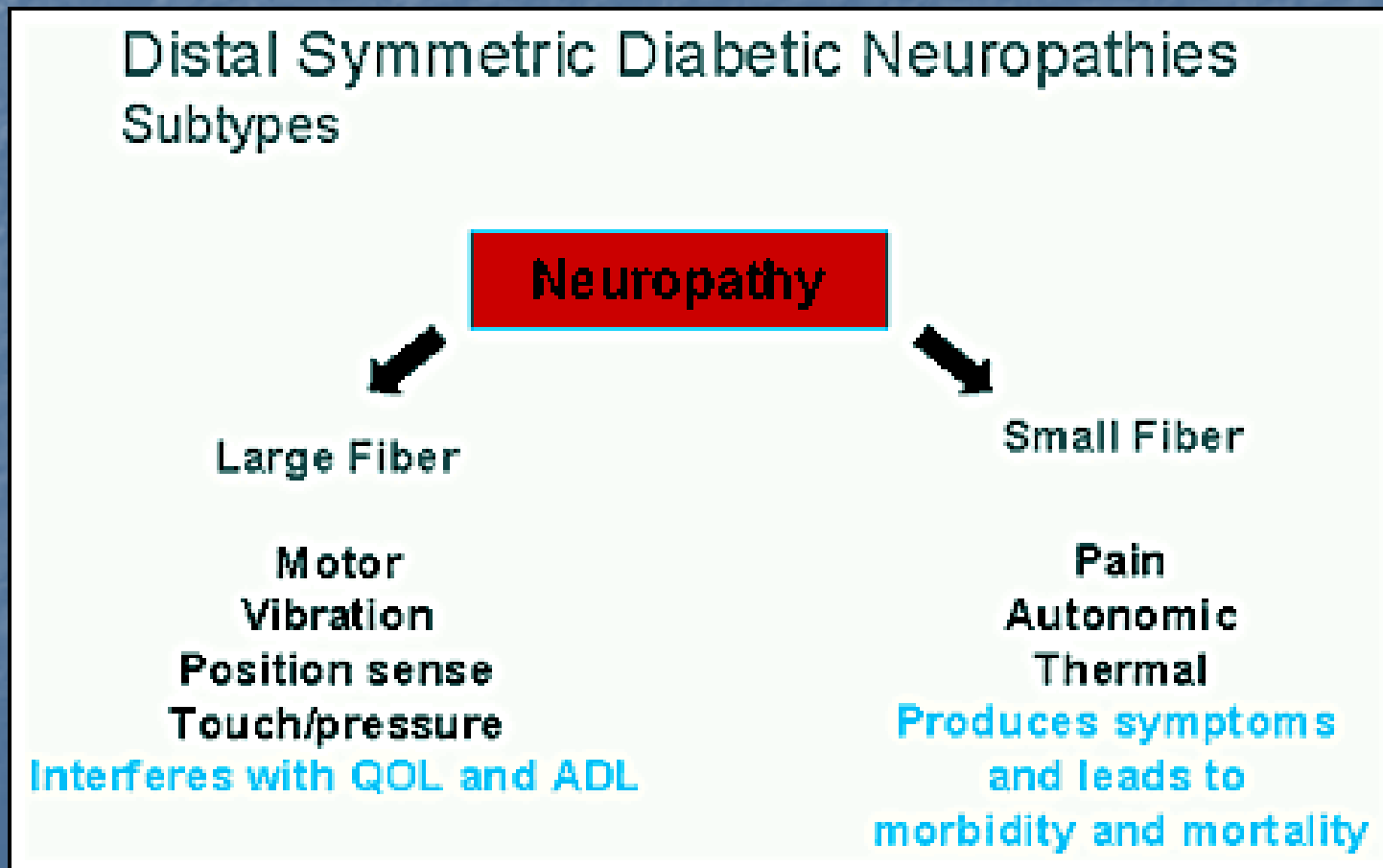
Proximal Motor Neuropathy

- Treatment
 - Formerly thought to resolve spontaneously in 1.5 to 2 years, but now, if found to be immune-mediated, can resolve within days on immunotherapy

Distal Symmetric Polyneuropathy



Distal Symmetric Polyneuropathy



Small Fibre Neuropathies

- Can be acute or chronic
- Pain (variable character) and parasthesae
- May be disabling
- Can be difficult to treat

Large Fibre Neuropathies

- Impaired vibration perception (often the first objective evidence) and position sense
- Depressed tendon reflexes
- Aδ type deep-seated gnawing, dull, like a toothache in the bones of the feet, or even crushing or cramp-like pain
- Sensory ataxia (waddling gait)
- Wasting of small muscles of feet with hammertoes with weakness of hands and feet
- Shortening of the Achilles tendon with pes equinus
- Increased blood flow (hot foot)

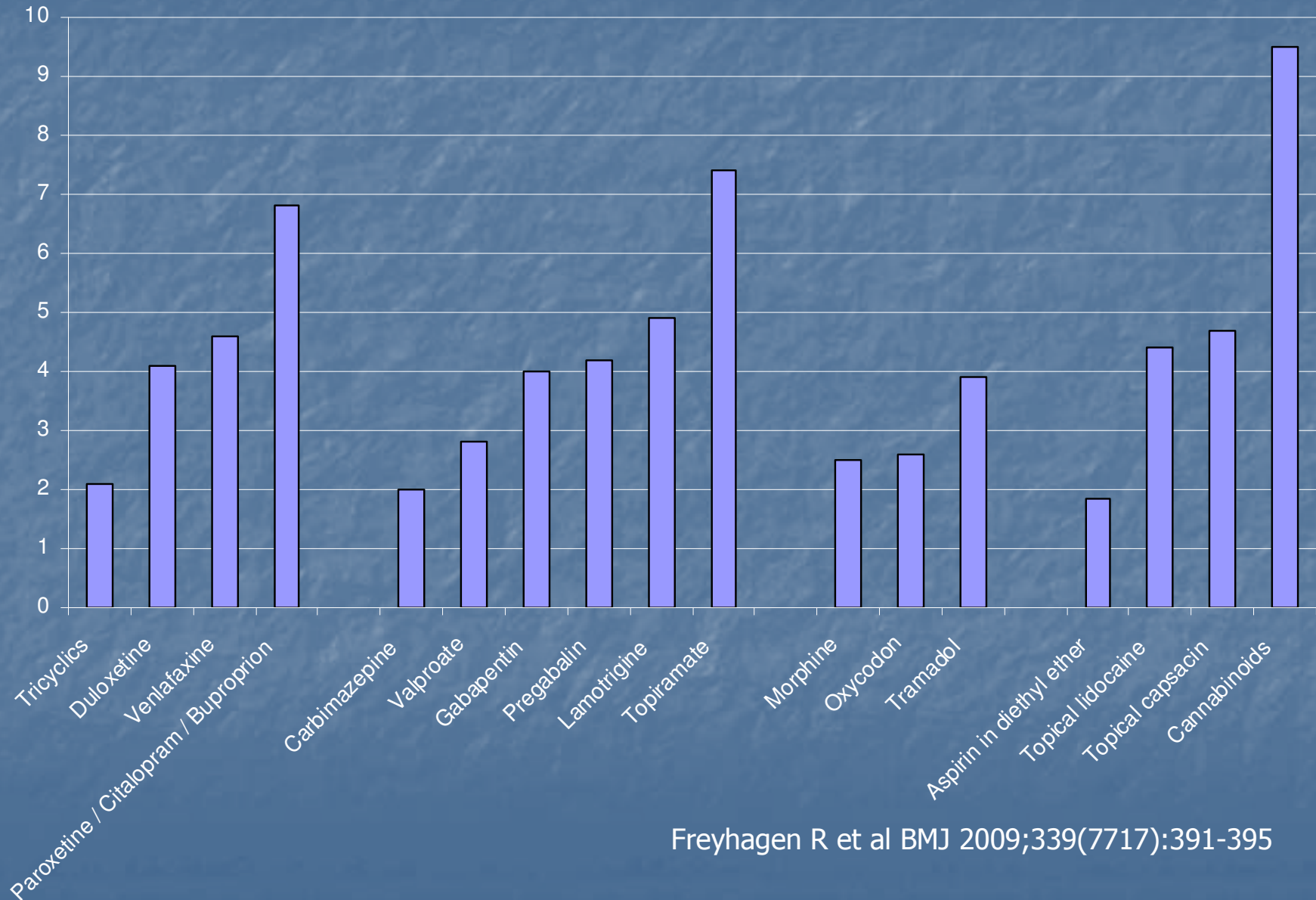
Treatment

- Good glycaemic control underlies all treatments
- BP control is also important
- Increasing evidence that statins and ACE inhibitors help to prevent the progression of established disease

Treatment Aimed at Pathogenesis

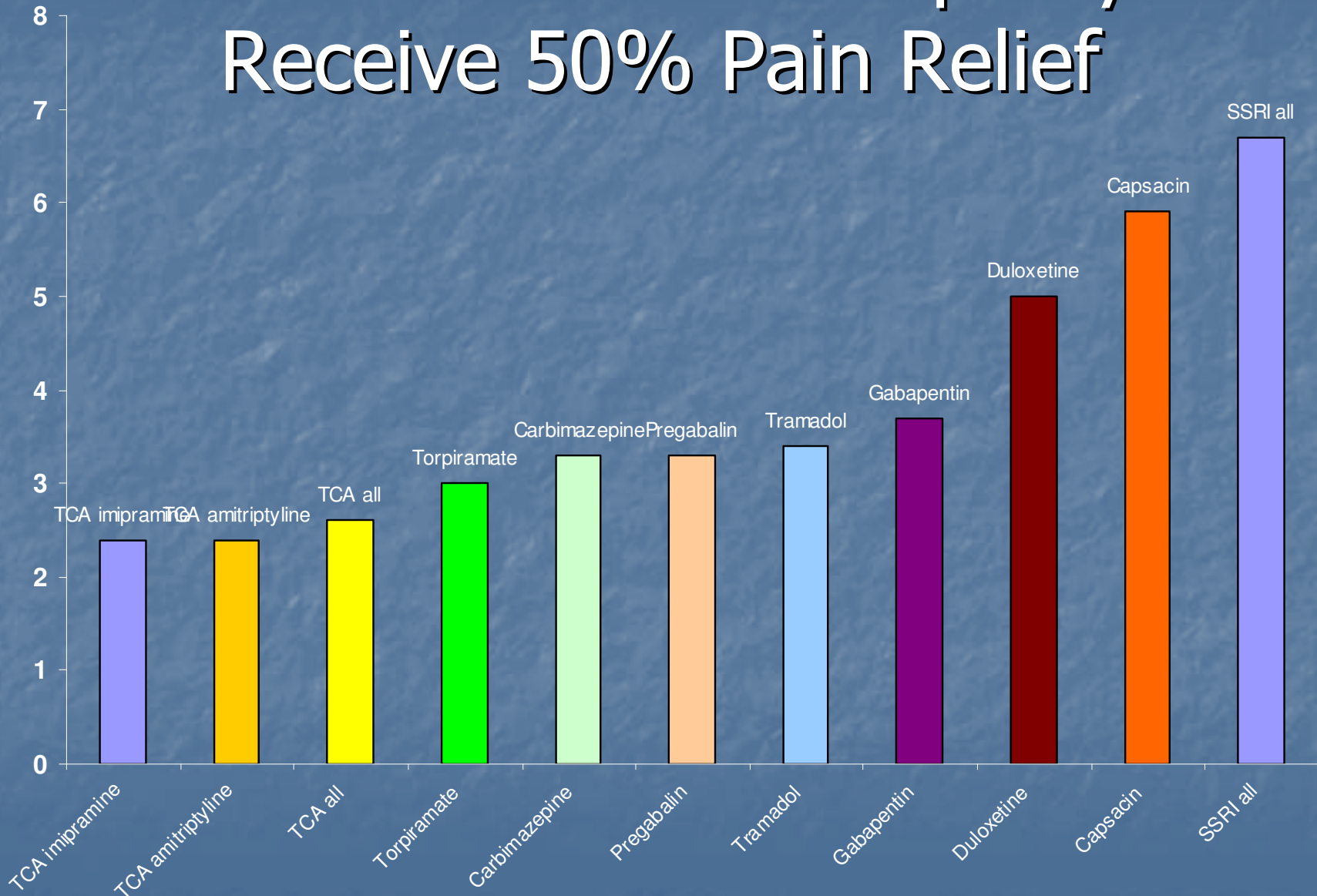
- Aldose reductase inhibitors
 - inhibiting tissue accumulation of sorbitol and fructose preventing reduction of redox potentials
- Alpha-lipoic acid
 - A thiol replenishing and redox modulating agent
- Gamma-linolenic acid
 - Important for preservation of nerve blood flow
- Aminoguanidine
 - An inhibitor of the formation of advanced glycosylation end products
- IVIg

Diabetic Neuropathy - NNT

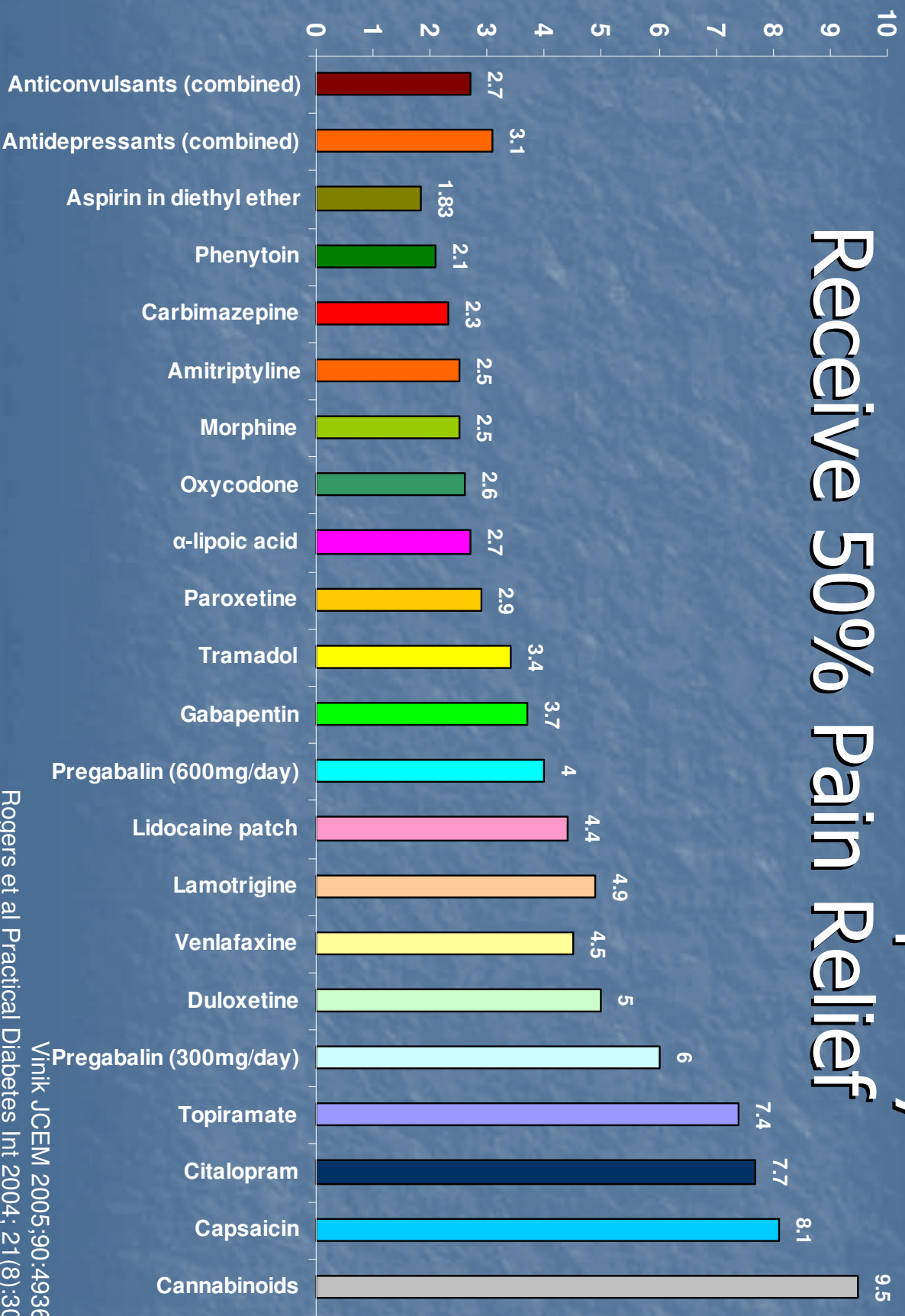


Freyhagen R et al BMJ 2009;339(7717):391-395

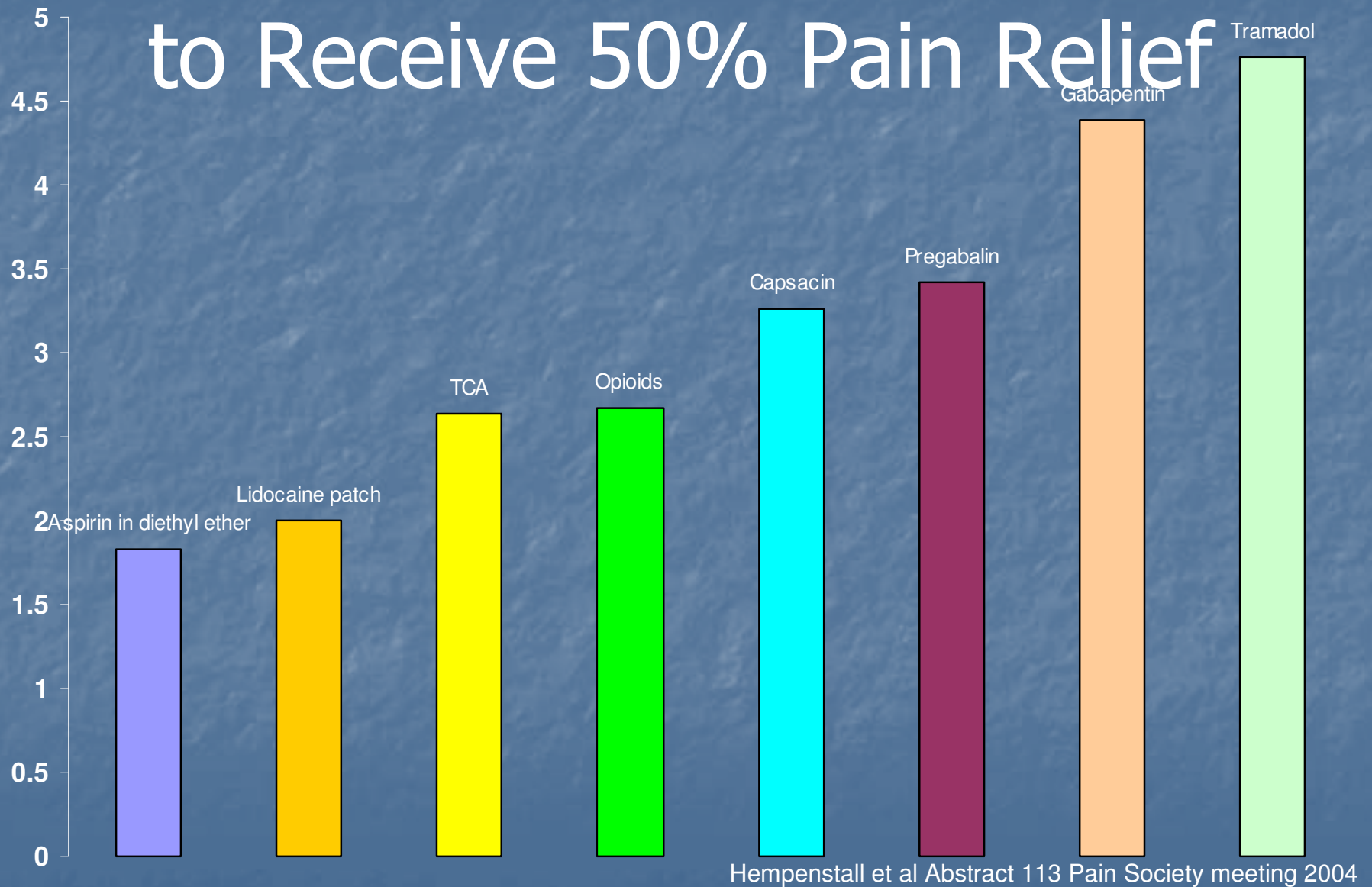
NNT for Diabetic Neuropathy to Receive 50% Pain Relief



NNT for Diabetic Neuropathy to Receive 50% Pain Relief



NNT for Post Herpetic Neuralgia to Receive 50% Pain Relief



Very Recent Data

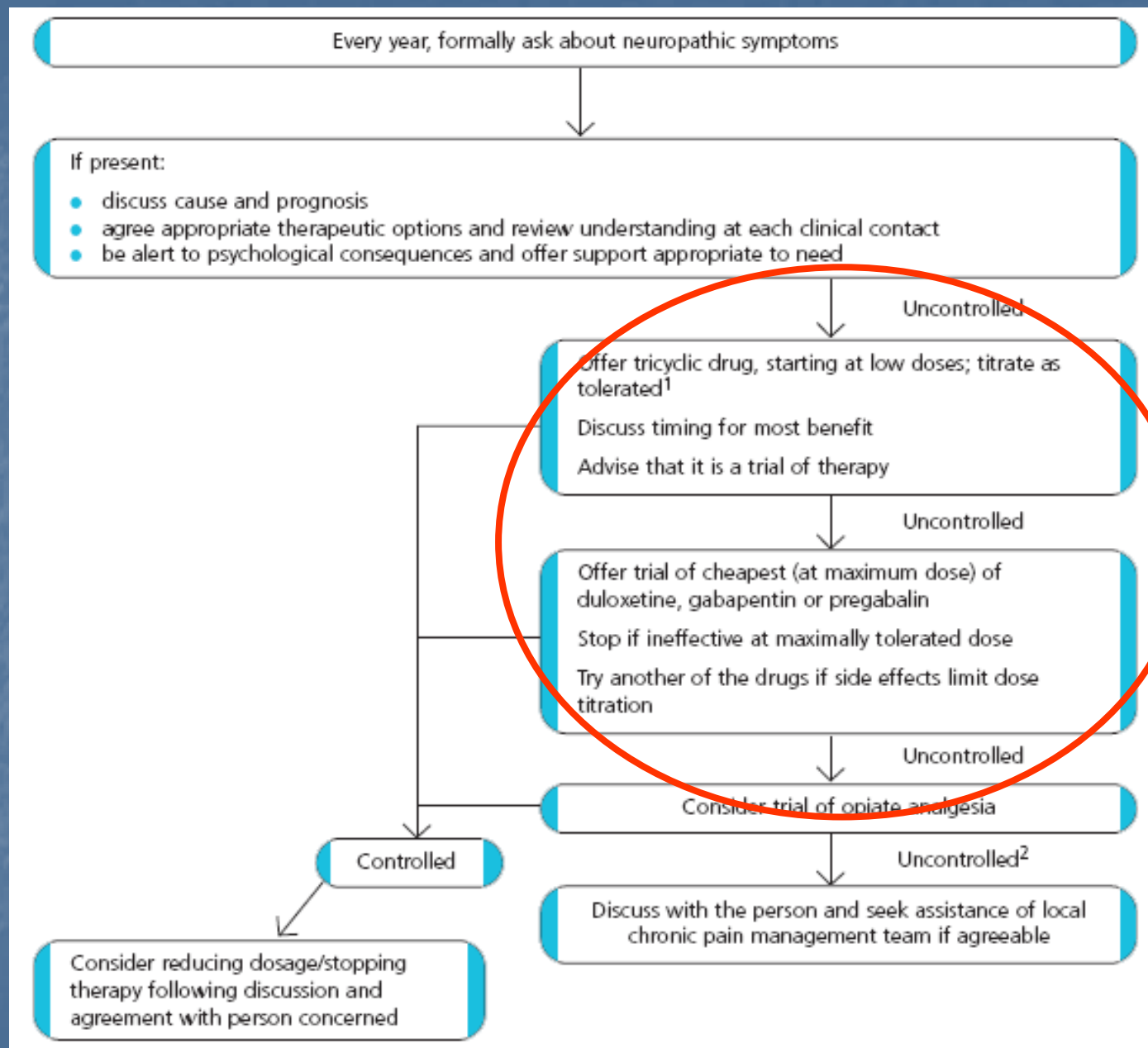
- A meta-analysis of pregabalin use in 7 trials
- 1,510 patients – 953 on the drug, 557 on placebo
- Pain assessed using a visual analogue scale
- Conclusions
 - Pain was relieved in a dose dependent manner
 - A >1 point reduction in pain was achieved in 60 days for those on placebo, 13 days for those on 150 mg/d, 5 days for those on 300 mg/d and 4 days for those on 600mg/d

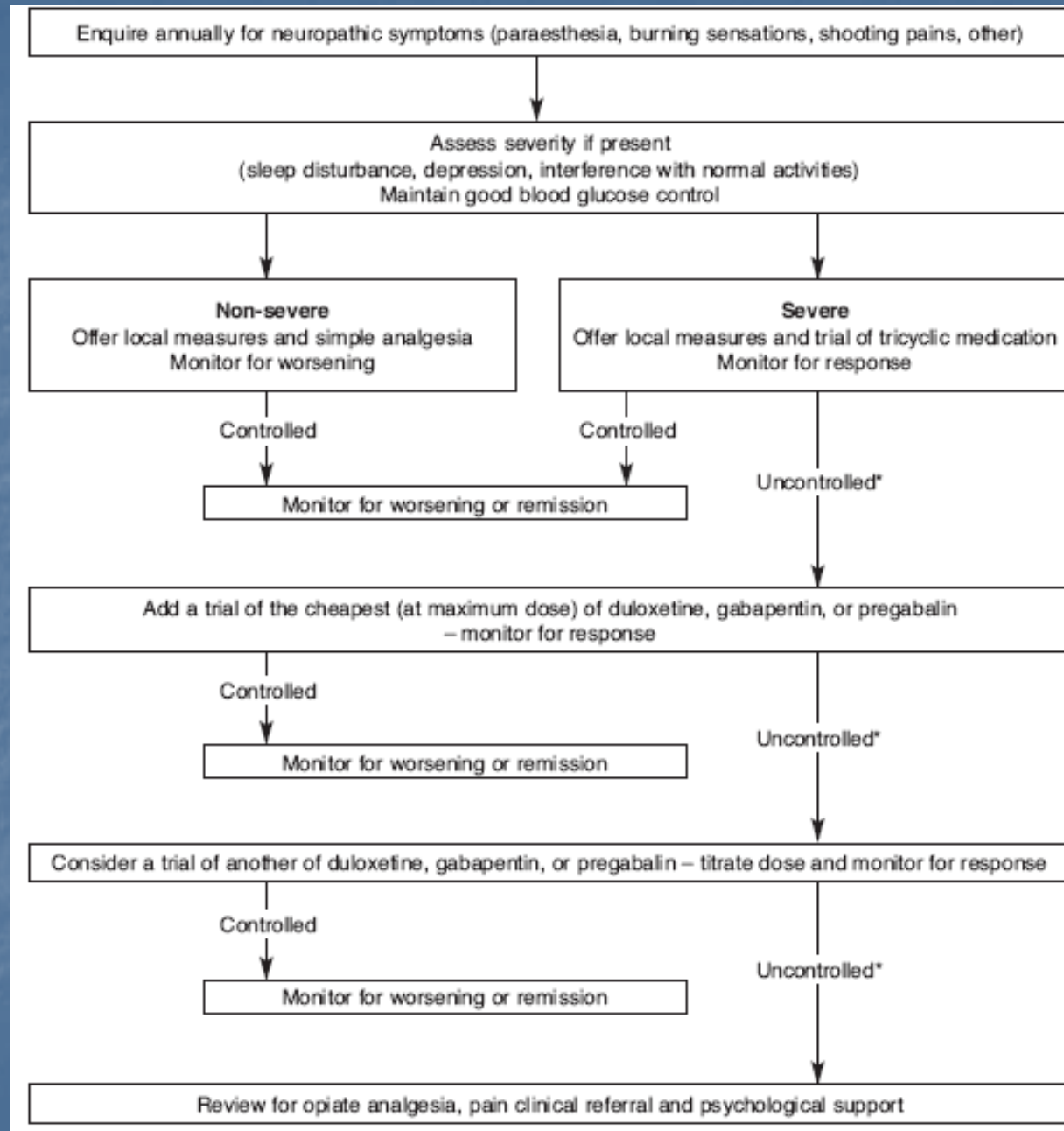
Neuropathy

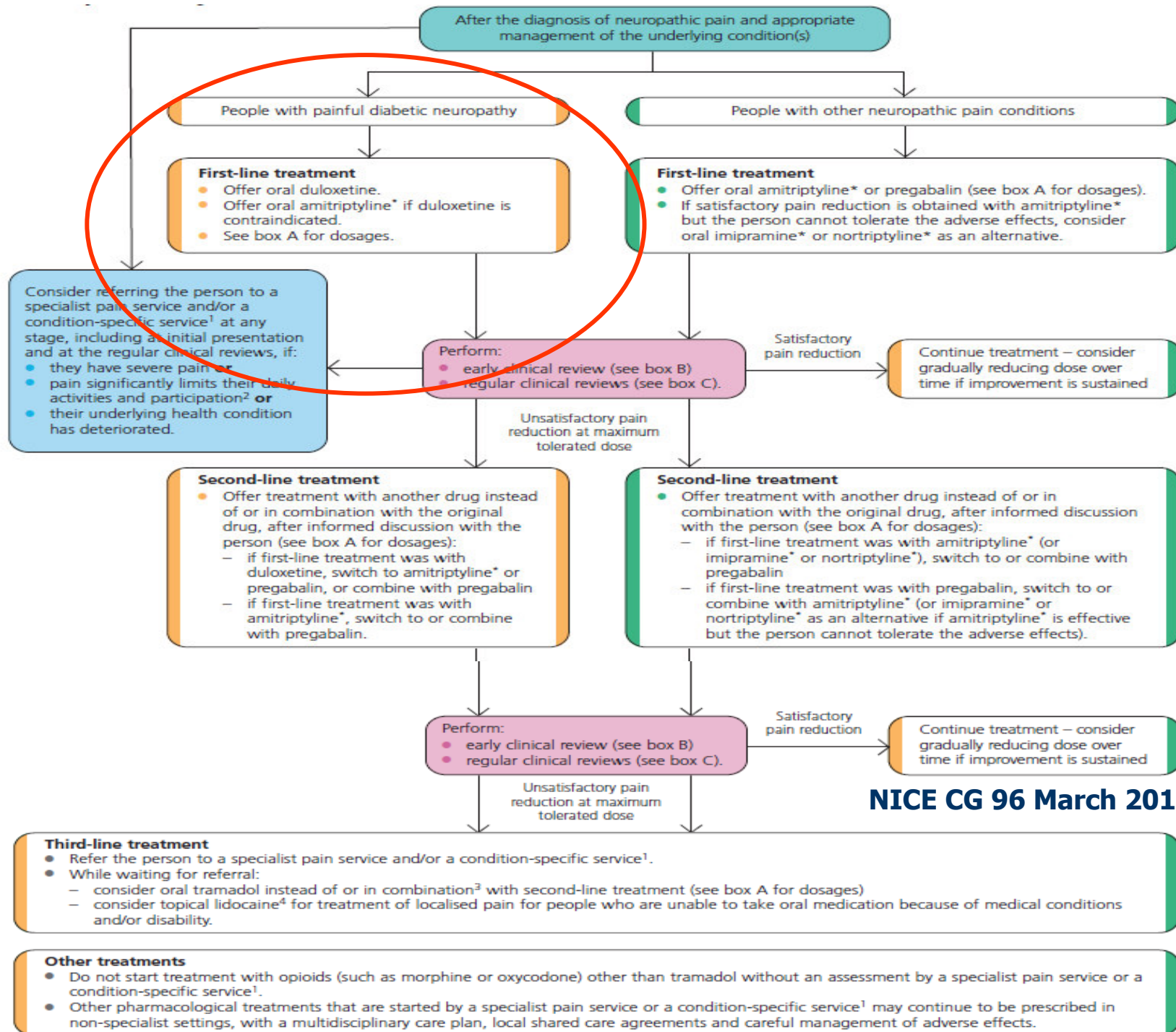
- Ask annually about symptoms
- Be alert to the psychological consequences of chronic, painful diabetic neuropathy and offer psychological support according to their individual needs

Neuropathy

- Start with simple analgesia
- Then low dose tricyclics and titrate the dose up
- Then chose from duloxetine, gabapentin or pregabalin (which drug depends on price). Get to top dose, if one does not work, try another
- Try an opioid if anticonvulsants do not work







Any Questions?