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Painful Neuropathies: a few tips on diagnosis and management

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Disclosure

- **Off label use of various drugs will be mentioned**
- **Non FDA approved procedures for pain will be discussed**

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Introduction

- **Chronic pain, often of uncertain causes, is a challenge for all medical specialties. Its impact on patients' quality of life and its socioeconomic burden are astronomical.**
- **Although pain can have different etiologies, many symptoms and manifestations are common to all chronic pain syndromes.**
- **Chronic pain syndromes can be grossly divided in to 3 subgroups:**
  - **Myofascial pain syndromes**
  - **Visceral pain syndromes**
  - **Neuropathic pain: maybe visceral pain should be considered a variant of it**

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Introduction (cont.)

- **Data is not clear cut: some studies are of questionable quality and difficult interpretation**
- **Patients may not be homogeneous: same is true for many pain studies when no clear organic basis is present**
- **Chronic pain affects the person as a whole, in what is represents the pain complex experience. The pain origin/localization is various, but central integration and sensitization occur in all chronic pain cases, thus resulting in the emotional and cognitive changes that are easily recognized in any chronic pain sufferer**

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Neuropathic pain definition

- **Neuropathic pain is defined as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system**

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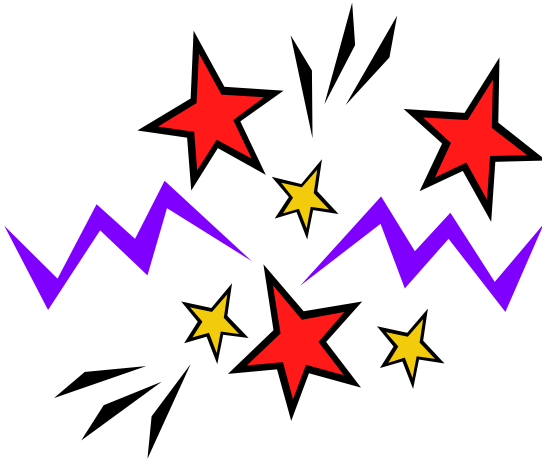
Does the patient have neuropathic pain?

- **intensity doesn't help**
- **quality:**
  - -continuous pain: burning, icy, intense tightness
  - -pins-needles
  - -Paroxysmal pain: lancinating, jabbing or shooting
  - -Itching
  - -Allodynia: aberrant sensation of pain in response to a normally nonpainful stimulus



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Is there a peripheral neuropathy?

- **Associate symptoms:**
  - **numbness**
  - **paresthesia/dysesthesia**
  - **allodynia**
  - **weakness**
  - **imbalance**
  - **altered autonomic function (vaso-sudomotor or trophic changes)**

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Caveat

- paresthesia/dysesthesia can be seen also in myofascial pain
- Patient can have pain and a normal neuro exam

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Neuropathy

Disease of peripheral nerve resulting from loss of function or abnormality of function of its fiber components

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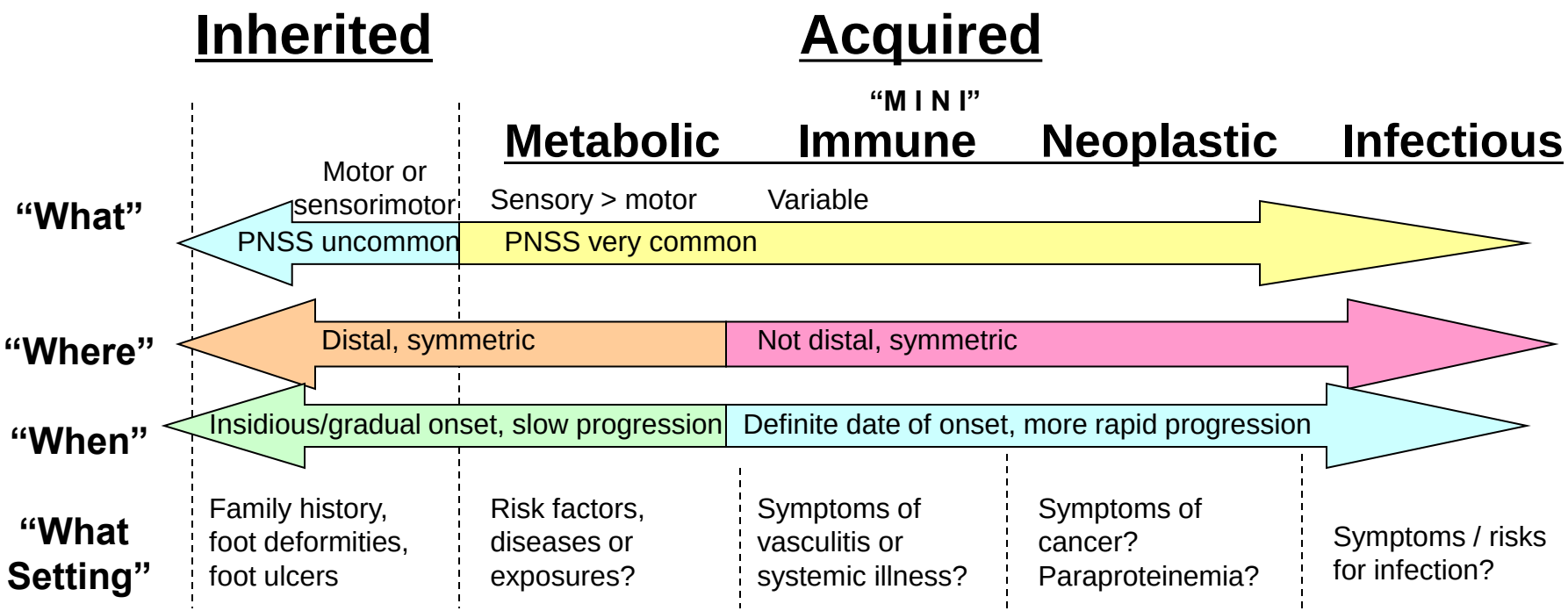
Background

- **Peripheral neuropathy has an estimated prevalence of 2-3% in the general population.**
- **As high as 8% in people older than 55 yrs.**
- **Evaluation for etiology important as it may identify a treatment and prevent progression to disability.**

England, JD Lancet 2004

Hughes, RA. BMJ 2002.

Clinical Approach to Peripheral Neuropathy



Mauermann ML, Burns TM. The Evaluation of Chronic Axonal Polyneuropathies. Semin Neurol 2008;28:133-151.

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Algorithm for approach to PN

- ***What?*** **Which nerve fibers are involved**

- ***Where?*** **The distribution of nerve involvement**

- ***When?*** **The onset and progression of neuropathy**

- ***What setting?*** **Clues from the patient**

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Components of the nerve and clinical manifestations

Component	Fiber type	Function	Clinical manifestation
Sensory - Small fiber	Small myelinated (Ad) Unmyelinated (C)	Pain and temperature	**Burning pain** Hyperalgesia **Anesthesia** Thermanesthesia
-Large fiber	Large myelinated (Aa, Ab, Ia, Ib)	Touch, vibration proprioception	**Numbness** **Paresthesia** **Sensory ataxia** Areflexia
Motor	Large myelinated (A)	Final common motor pathway	**Weakness** **Atrophy** **Fasciculations** **Areflexia**
Autonomic Preganglionic Postganglionic	Small myelinated (B) Unmyelinated (C)	Vasomotor Sudomotor Visceromotor	Cold or warm limb Hyper or anhidrosis Orthostatic hypotension Bladder, bowel and sexual dysfunction

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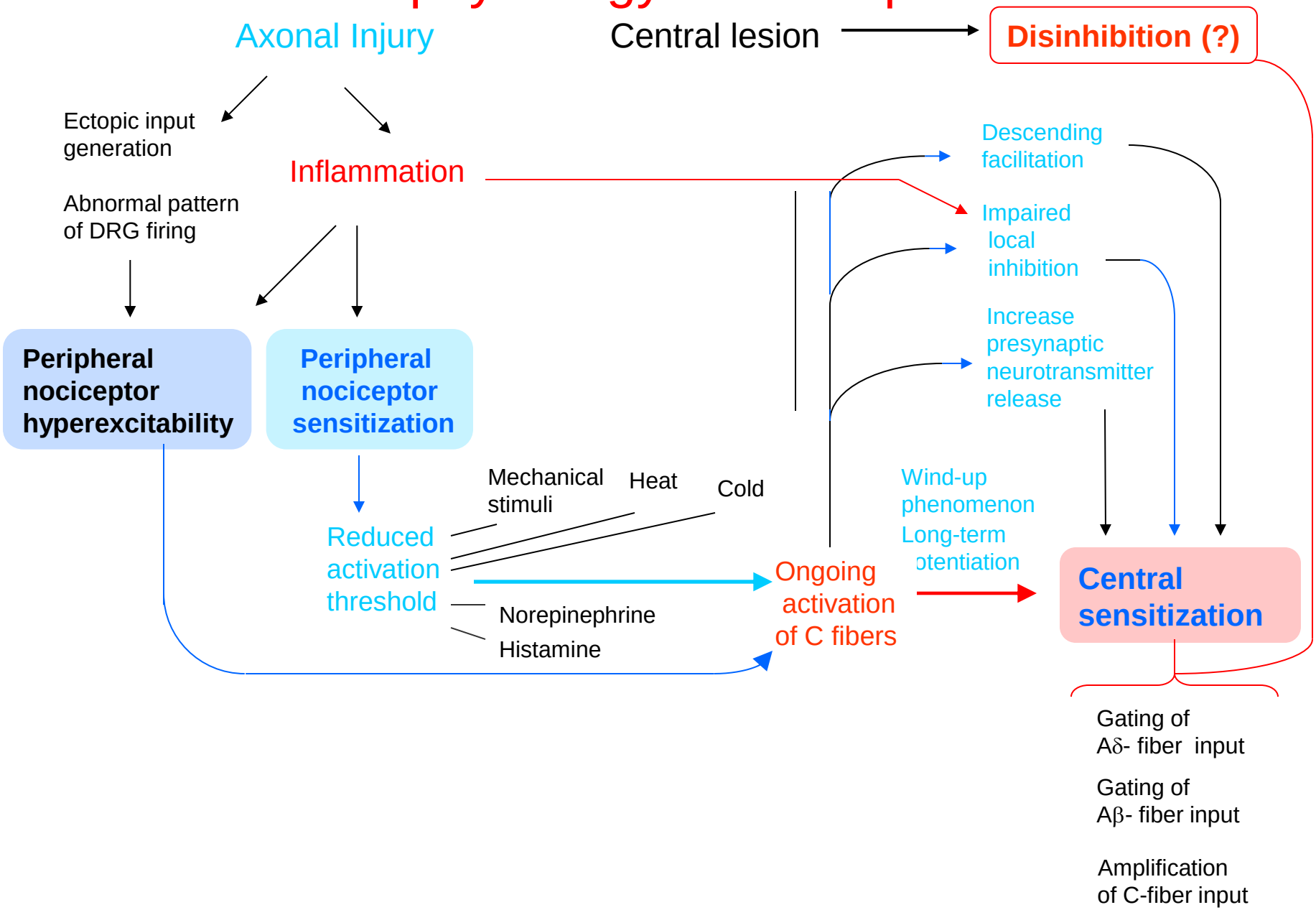
Pathophysiology of Neuropathic Pain



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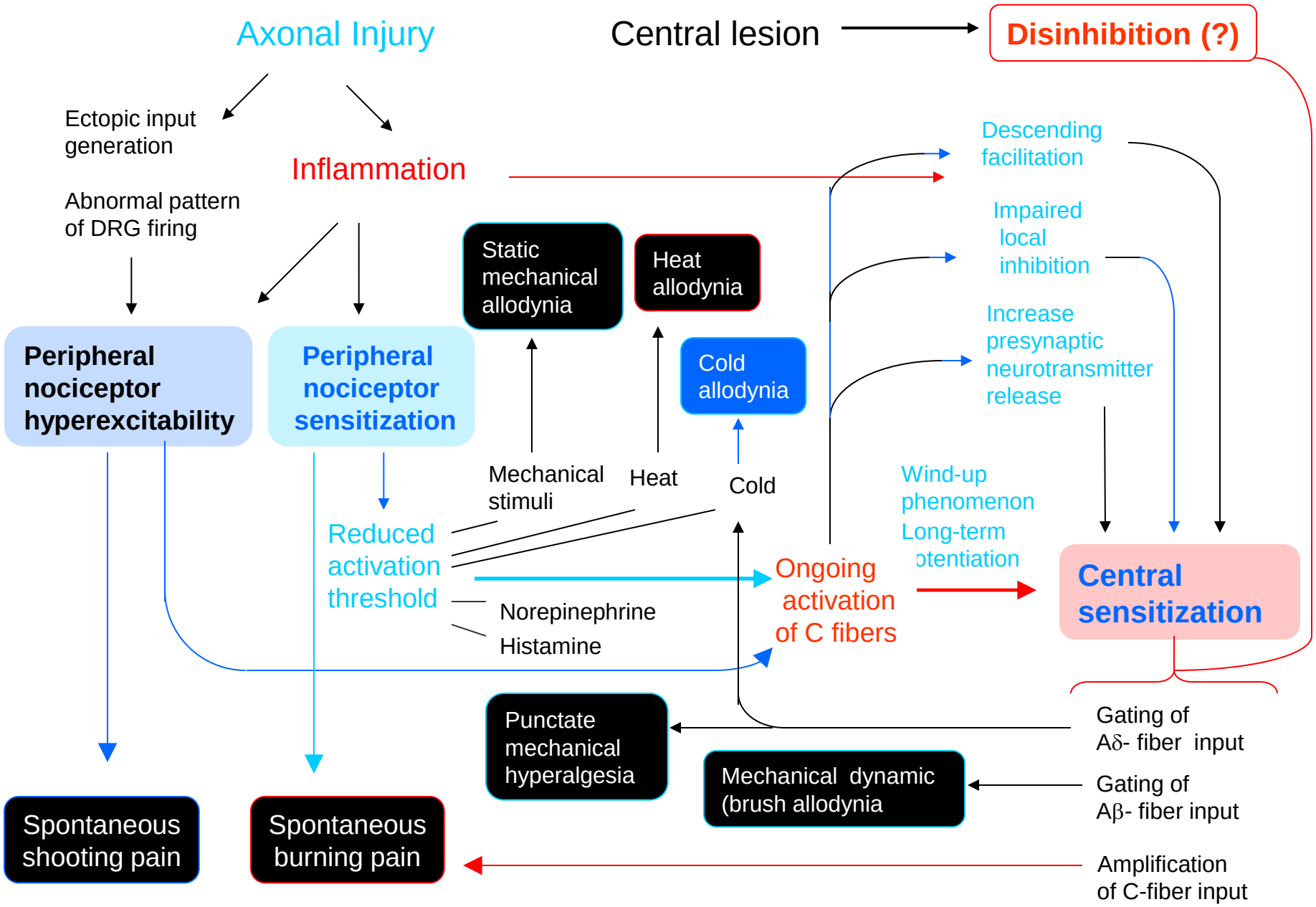
Mechanisms of Neuropathic Pain Symptoms



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Site of lesion/dysfunction

- Roots
- plexus
- nerve trunk
- distal nerve fibers

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Common painful neuropathies: Polyradiculopathies

- **Guillain-Barre'**
- **CIDP**
- **Diabetes**
- **Infections (CMV, HIV, West Nile)**
- **Secondary to meningeal processes (sarcoid, lymphoma etc.)**

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Plexopathies

- Idiopathic
- Diabetic
- Postradiation (occ.)
- Neoplastic
- Local pathology

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Mononeuropathies

- **Vasculitides**
- **Entrapment**
- **Postinfection/inflammation (PHN)**
- **Neuralgias**

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Polyneuropathies

- **Medications**
  - **Anti-infectious**
    - Chloroquine
    - Dapsone
    - Isoniazid
    - Metronidazole
    - Nitrofurantoin
    - Dideoxycytidine, etc.
  - **Chemotherapy**
    - Cisplatinum
    - Taxanes
    - Suramin
    - Thalidomide/Bortezomib
    - Vincristine
  - **Antirheumatic**
    - Chloroquine
    - Colchicine
  - **Cardiovascular**
    - Amiodarone
    - Hydralazine
    - Perhexiline
    - Propafenone
  - **Psychiatric**
    - Disulfiram
  - **Others**
    - B6
    - Phenytoin
    - Monoclonal Ab, anti-TNFα

- **HIV related neuropathies**
- **Diabetes:**
  - Distal sensory or sensorimotor neuropathy most common
  - Diabetic autonomic neuropathy (generalized SFN)
  - Distal small fiber neuropathy
  - LS radiculoplexus neuropathy/thoracic radiculopathy and cervical radiculoplexus neuropathy
  - Mononeuropathy multiplex
  - Multiple entrapment neuropathies
- **Neoplastic/paraneoplastic**
  - secondary to treatment toxicity
  - secondary to metabolic/immunologic derangement
- **Small fiber neuropathy:**
  - amyloid, Sjogren, acute autonomic neuropathy, idiopathic
- **Inherited:**
  - Fabry's, HSAN, porphyria, amyloid

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Small Fiber disorders

- Small, but important: DSFN and AN
- Can be associated to large fiber neuropathies
- Involvement may be underrecognized in other “non-neurological” conditions…
- …and in other pain syndromes (i.e., CRPS)
- How can/should we test them?

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SMALL FIBER NEUROPATHIES

- Core features:
  - loss of small fiber function (pain, temp)
  - autonomic failure (generalized or focal)
  - itch
  - distal burning/dysesthesias/erythromelalgia
  - distal vasomotor changes, pallor/rubor, sudomotor (hyper/anhidrosis)
- Causes:
  - diabetes
  - amyloid
  - AAN
  - HSAN, Fabry's
  - idiopathic

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Erythromelalgia: Introduction

- **Erythromelalgia is a rare clinical syndrome (Mitchell, 1878) characterized by redness (erythros) affecting the extremities (melos) with burning pain (algia)**
- **Patients (females more commonly than males) usually complain of symmetrical red, hot, and painful feet; often the process extends up the legs.**

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Clinical features

- The temperature of the affected extremity undergoes an excessive increase with physical activity, so that patients become often exercise intolerant, or an increase in ambient temperature. Occasionally, the extremity redness, heat, and pain become persistent.
- Primary and secondary forms of the disorder have been reported, with secondary forms especially associated with myeloproliferative disease
- A variety of medications have been tried in erythromelalgia, with acetylsalicylic acid and NSAIDs being the most effective particularly in secondary forms.

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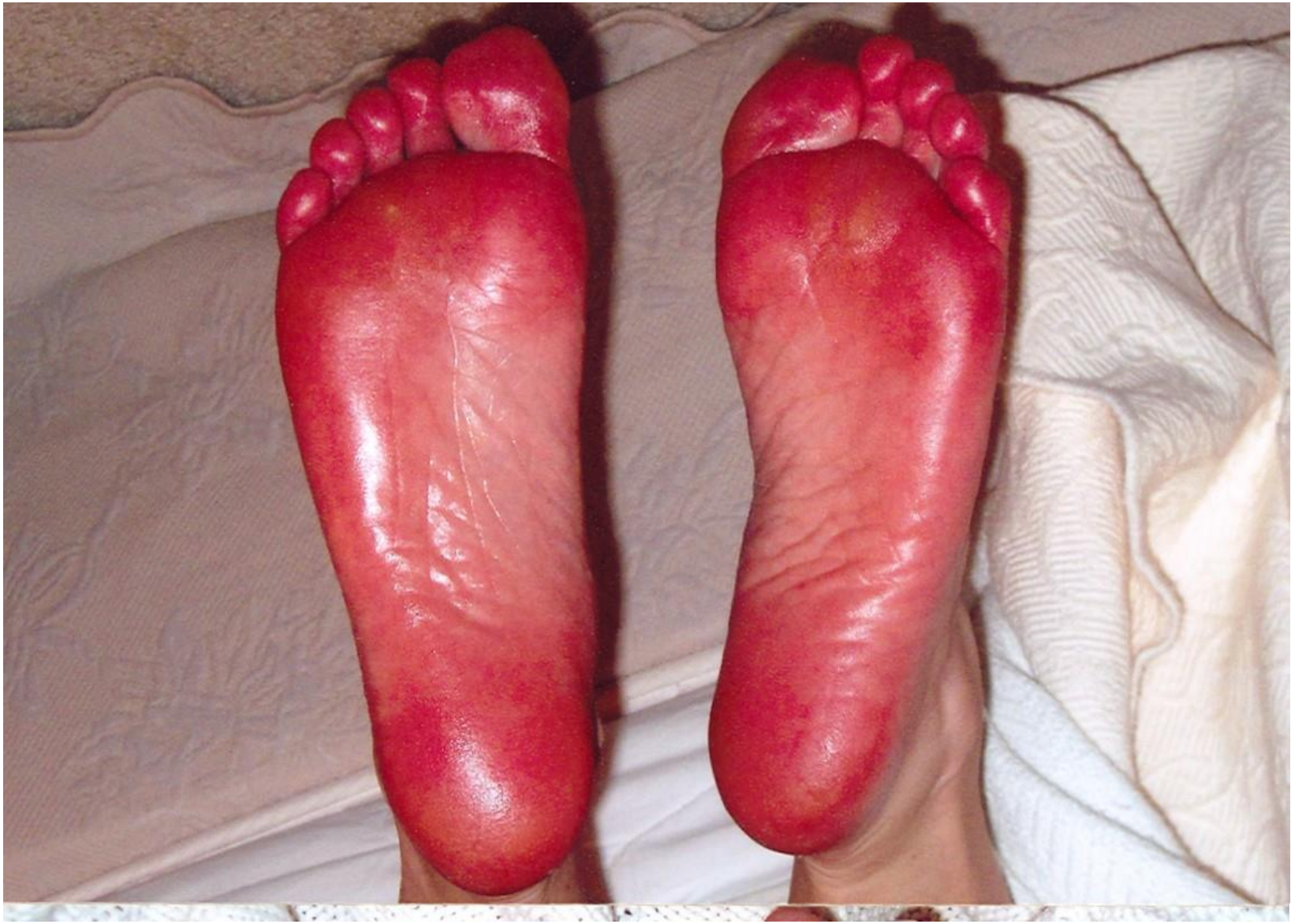

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Discussion

- shunting may be occurring
- neuropathy may contribute to shunting: SFN underlies the majority of cases of erythromelalgia, with lesser involvement of large nerve fibers
- cellular metabolism may be increased, leading to increased temperature, hypoxemia, and increased waste products of cellular metabolism
- Genetic abnormalities in gene coding for sodium channel $Na_v1.7$ found in familial form
- Could $Na_v1.8$ and $Na_v1.9$ be involved too?

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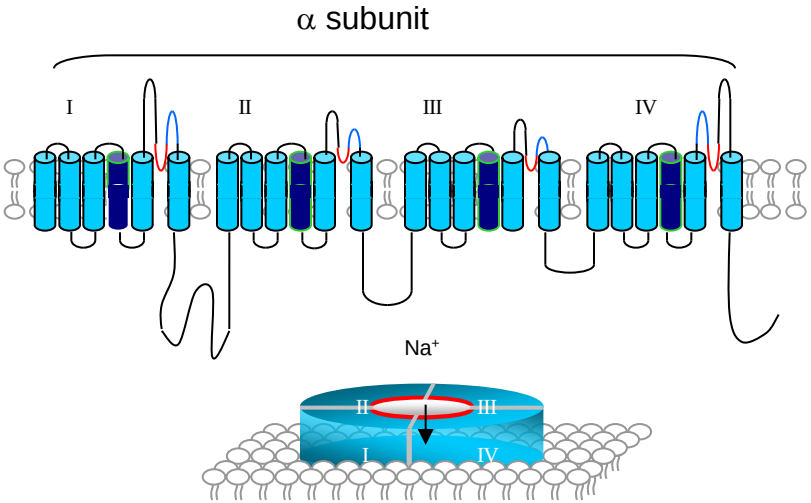
Voltage-gated Na^+ channels and their role in pain



$Na_v1.7$ → Sets threshold for nociceptor activation

- → Gain-of function *SCNA9* mutations
  - Familial erythermalgia
  - Extreme paroxysmal pain disorder
- → Loss-of function *SCNA9* mutations
  - Channelopathy-associated insensitivity to pain

$Na_v1.8$ → Action potential In nociceptor

$Na_v1.9$ → Prolonged firing of nociceptor

Sensitized by products of inflammation → Inflammatory pain

$Na_v1.3$ → Downregulated In adult DRG → Up-regulated following axonal injury → Neuropathic pain

Examination

- Focus on sensory exam: careful assessment of all modalities
- Allodynia (dynamic, static, thermal)
- Hyperalgesia - hyperpathia
- Central vs. peripheral component:
  - cold and dynamic allodynia, summation-hyperpathia are “central”
- Look for signs of autonomic dysfunction

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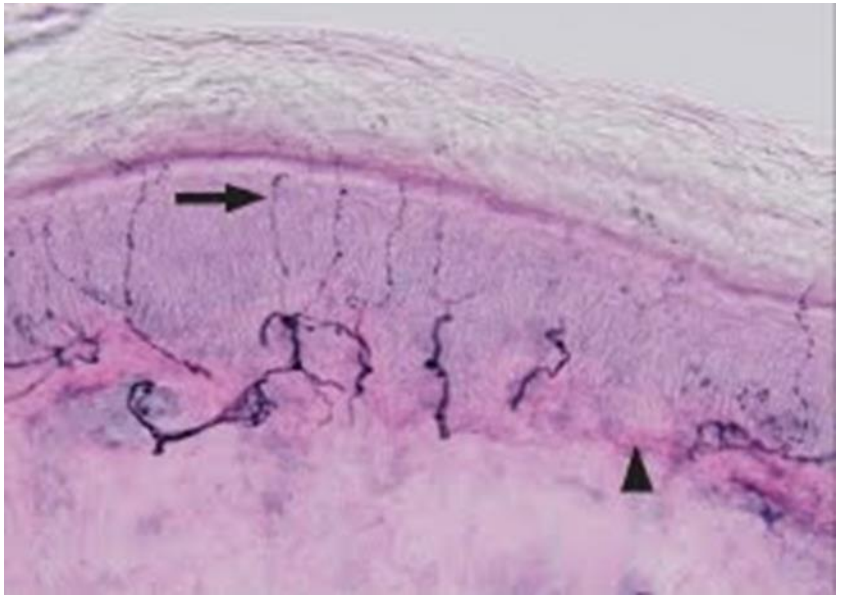
Investigations: to identify specific pathology…not pain

- **Blood tests, urine, CSF…**
- **Fat aspirate for amyloid**
- **Lip biopsy; Rose-Bengal stain for Sjogren**
- **Nerve biopsy: vasculitis, amyloid, sarcoid**
- **Skin biopsy**



Practice Parameter: Evaluation of distal symmetric polyneuropathy: Role of laboratory and genetic testing (an evidence-based review)

Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation

Neurology® 2009;72:185-192

- **Fasting blood glucose**
- **B12 +/- methylmalonic acid**
- **SPEP/SIFE**

  - **Consider:**
    - **CBC**
    - **Comprehensive metabolic panel**
    - **Thyroid function tests**
    - **ESR**

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Other tests to consider…

Neuropathy pattern	Common causes	Proposed laboratory studies
Distal symmetric length-dependent neuropathy	Diabetes mellitus	Fasting blood glucose[a]
	B12 deficiency	B12 and methylmalonic acid[a]
	MGUS-associated neuropathy	Serum protein electrophoresis and immunofixation[a]
	Impaired fasting glucose	Oral glucose tolerance test[a]
	Charcot-Marie-Tooth	*PMP22* duplication,[a] Cx32,[a] *PMP22* deletion, MPZ, MFN2[a]
	Uremia	Creatinine, creatinine clearance
	Alcohol	CBC, liver function tests
	Hypothyroidism	TSH
	Thiamine deficiency	Whole blood thiamine
Demyelinating poly(radiculo)neuropathies	CMT1	*PMP22* duplication, Cx32, MPZ, *PMP22* deletion
	AIDP	CSF
	CIDP/MADSAM/DADS	Serum protein electrophoresis and immunofixation, CSF
	MMN	GM1 antibodies
	HNPP	*PMP22* deletion
Somatic neuropathies with prominent autonomic involvement	Diabetes mellitus	Fasting blood sugar
	AIDP	CSF
	Primary systemic amyloidosis	Serum protein electrophoresis and immunofixation
	Sjögren syndrome	ESR, ANA, SS-A, SS-B
	Vincristine toxicity	None
	Familial amyloidosis	TTR amyloid mass spectrometry
Multifocal neuropathies	Systemic and nonsystemic vasculitis	CBC w/diff, CMP, ESR, ANA, CRP, CCP, PR3, MPO, hepatitis B and C serologies, cryoglobulins, HIV, urinalysis
	Entrapment neuropathies	None
	MADSAM	CSF
	HNPP	*PMP22* deletion testing

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Other tests to consider…

Axonal polyradiculo(neuro)pathy	Lyme	Lyme serology and CSF
	Sarcoid	Serum ACE, CSF
	AMAN, AMSAN	CSF
	West Nile	Serum West Nile serology
	Lymphomatous/carcinomatous meningitis	CSF with cytology
Sensory neur(on)opathy	Diabetes mellitus	Fasting blood glucose
	B12 deficiency	B12 and methylmalonic acid
	Sjögren syndrome	ESR, ANA, SS-A, SS-B
	HIV	HIV serology
	DADS	Serum protein electrophoresis and immunofixation
	Paraneoplastic	Paraneoplastic antibodies
	Leprosy	None
Small fiber neuropathy	Diabetes mellitus	Fasting blood glucose
	Impaired glucose tolerance	Oral glucose tolerance test
	Alcohol	CBC, liver function tests
	Sjögren syndrome	ESR, ANA, SS-A, SS-B
	Sarcoidosis	Serum ACE
	Primary systemic amyloidosis	Serum protein electrophoresis and immunofixation
	Familial amyloidosis	TTR amyloid mass spectrometry
	Fabry disease	α-Galactosidase
	HSAN	None

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Diagnostic Tests: Caveats/Limitations

- **Presence of an abnormality does not mean a person has pain: lack of abnormality does not mean the patient can't have pain**
- **The site of abnormal physiology may not be in the area of pain**
- **<u>There is NO test to assess pain</u>**

Neurophysiologic studies

- EMG/NCS: they assess large fibers only. Maybe be nl in pure SFN
- Contact heat evoked potentials (CHEPS): we may be able to test entire pain pathways soon
- CASE: neuropsychophysiologic test. Very useful to assess sensory thresholds to various modalities corresponding to different fiber type
  - A-β: vibration
  - A-δ: cold
  - C: pain and heat

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Autonomic studies

- Deep breathing
- Tilt
- Valsalva maneuver
- QSART/QSWEAT
- Thermoregulatory sweat test

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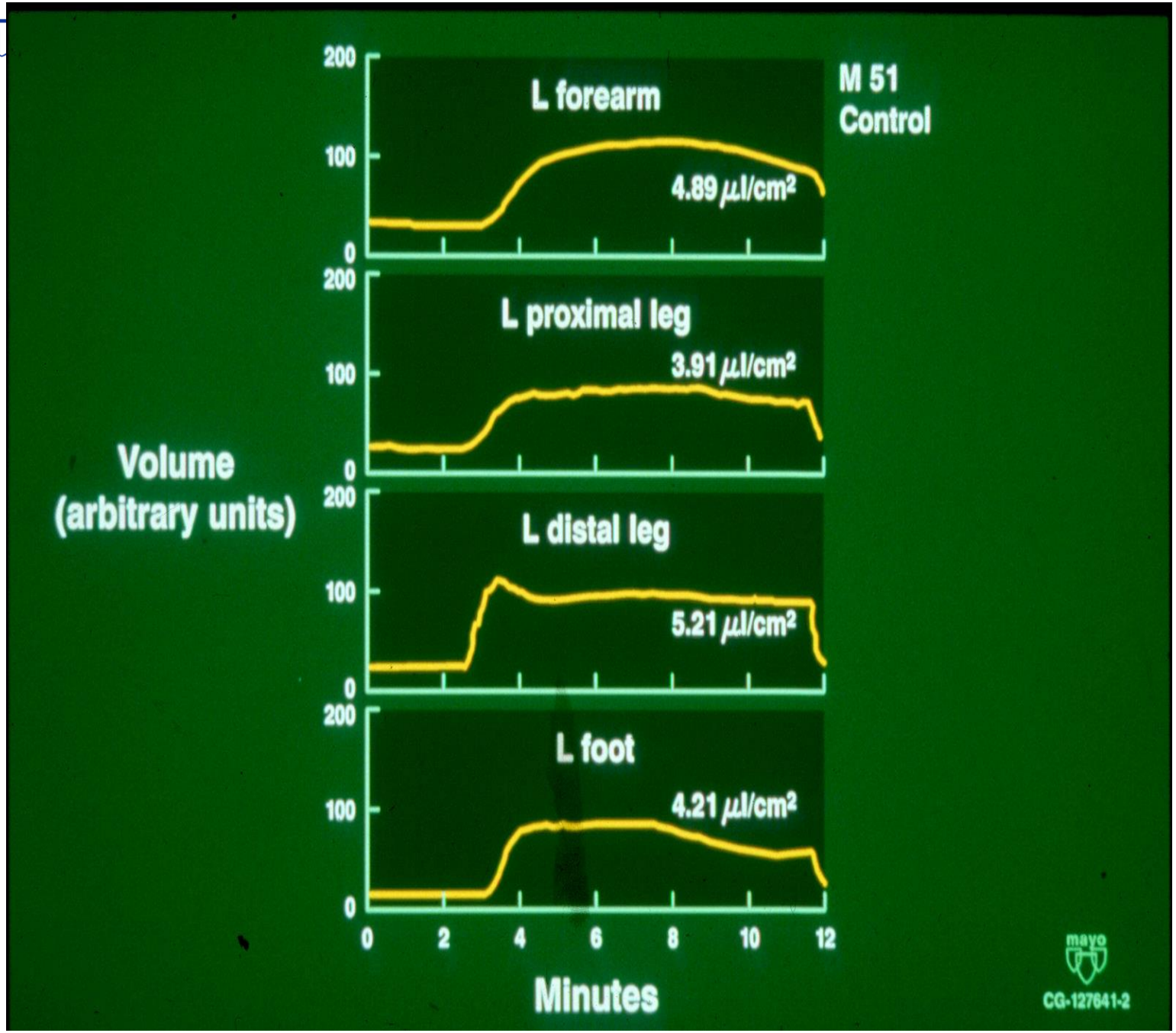
Review of 150 consecutive cases of SFN

- **91% had abnormal TST; 75% had abnormal QSART for a composite 97% of the patients who presented with symptoms of DSFN demonstrated sweating abnormalities in either of the sudomotor tests**
- **Most common pattern was a distal, length-dependent one (seen in 75% of TST and 61% of QSART)**
- **54% had primarily mild involvement in other autonomic functions, as shown on the ARS**
- **1/3 of the patients had abnormal NCV/EMG**


M 51
Control
L forearm
4.89 µl/cm²
L proximal leg
3.91 µl/cm²
L distal leg
5.21 µl/cm²
L foot
4.21 µl/cm²
200
100
0
Volume
(arbitrary units)
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2
4
6
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Minutes
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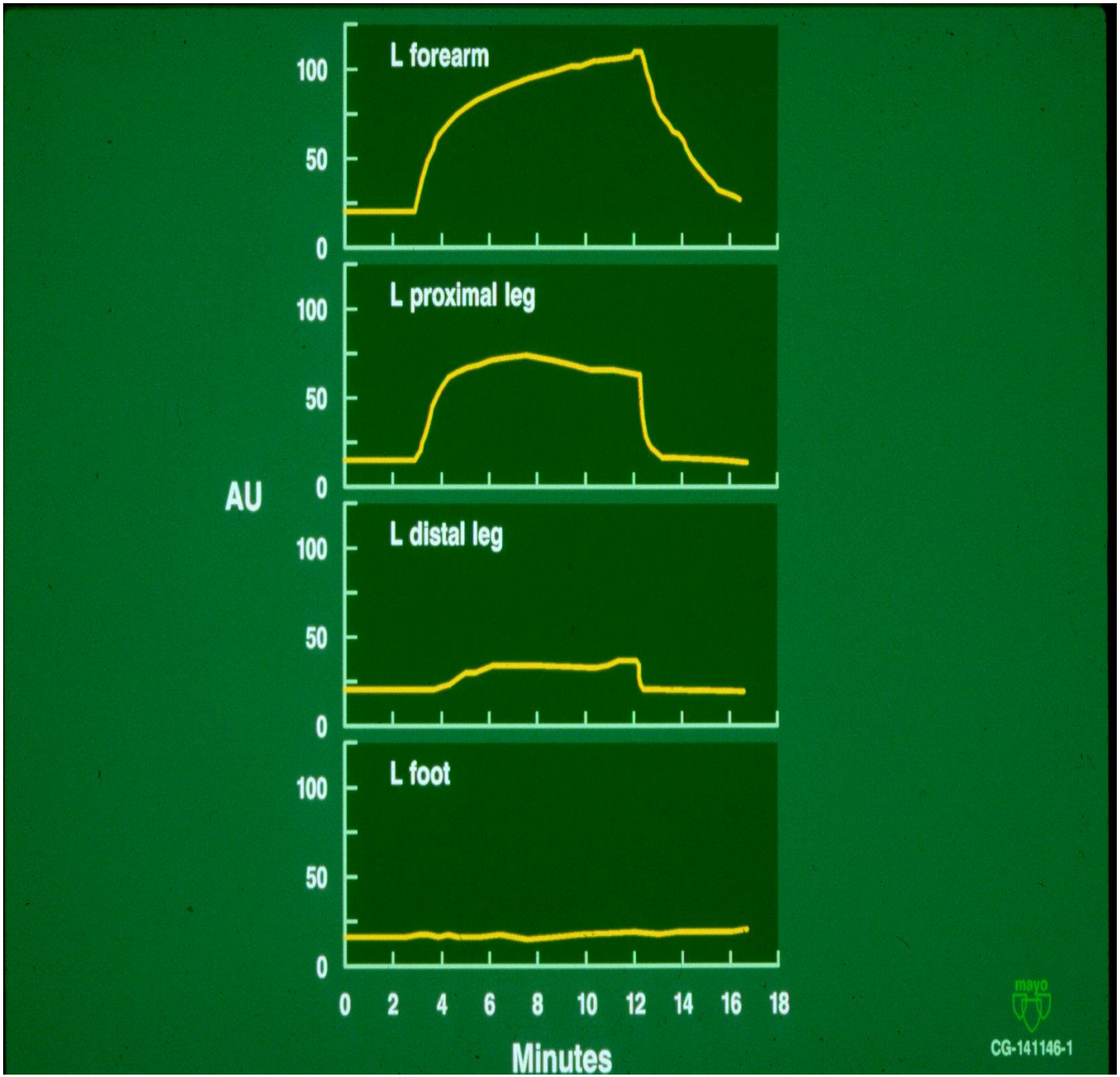
L forearm
L proximal leg
L distal leg
L foot
100
50
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0 2 4 6 8 10 12 14 16 18
Minutes
mayo
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THERMOREGULATORY SWEAT TEST (TST)

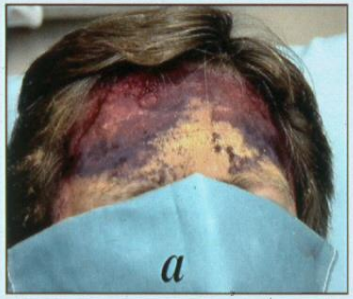
Afferent: blood, skin temperature

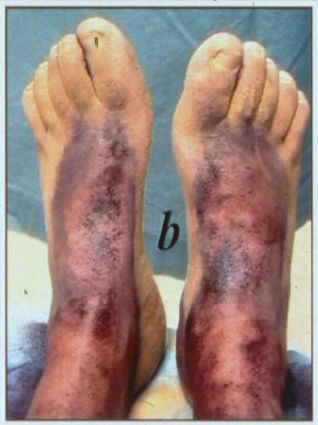
Efferent: pre and post ganglionic sympathetic sudomotor

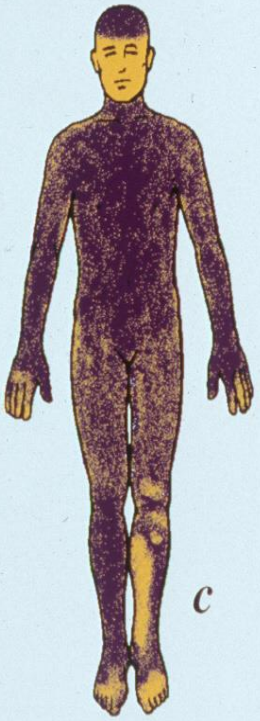
a cluster headache

b small fiber neuropathy

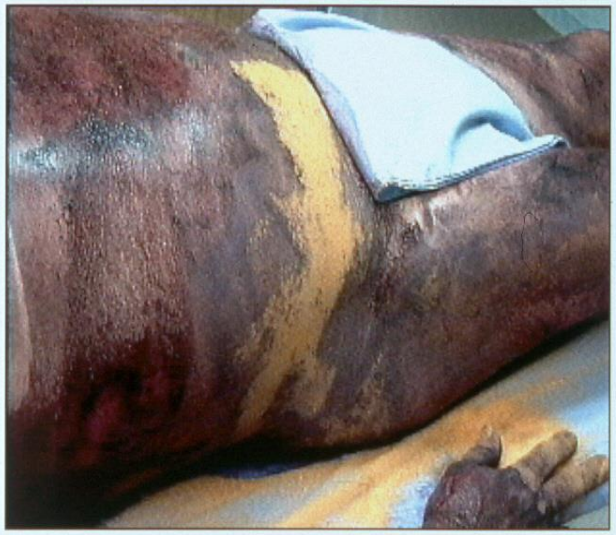
c color computerized drawing used in reports

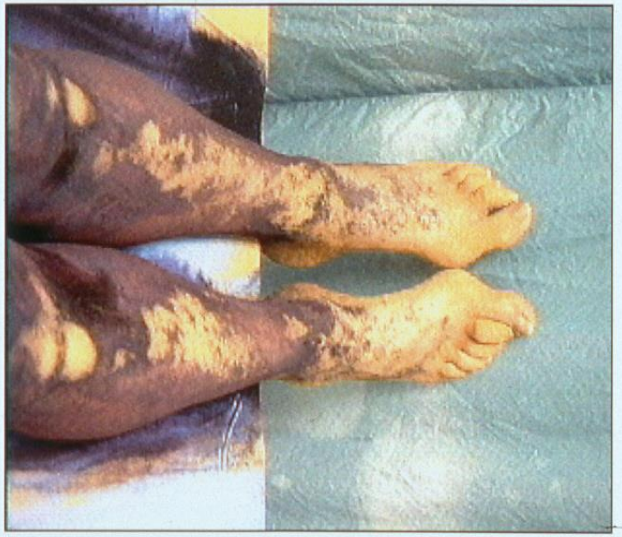






DIABETIC NEUROPATHY





- Left: A dermatomal band of anhidrosis c/w truncal neuropathy. Right: Distal sweat loss c/w SFN.

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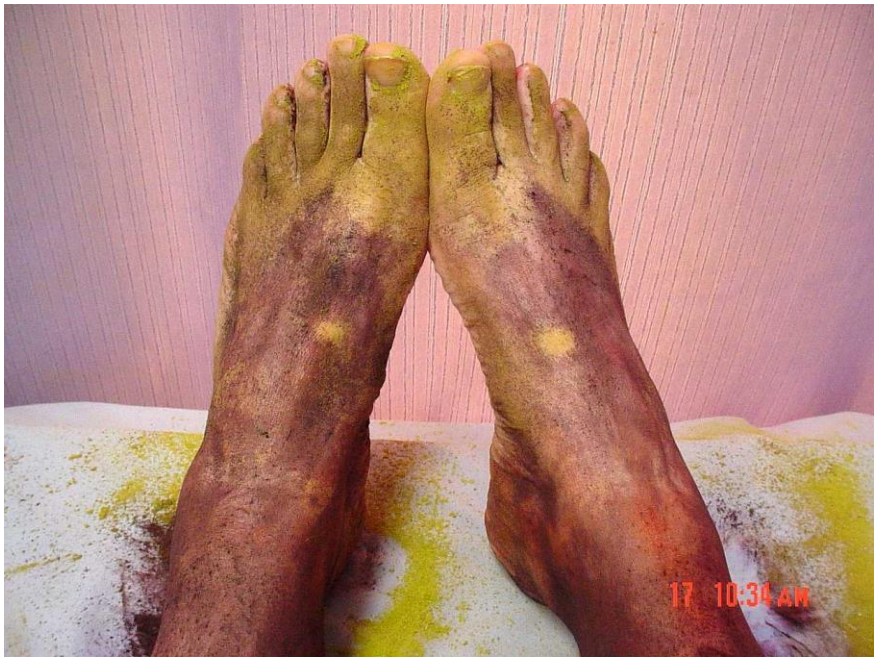
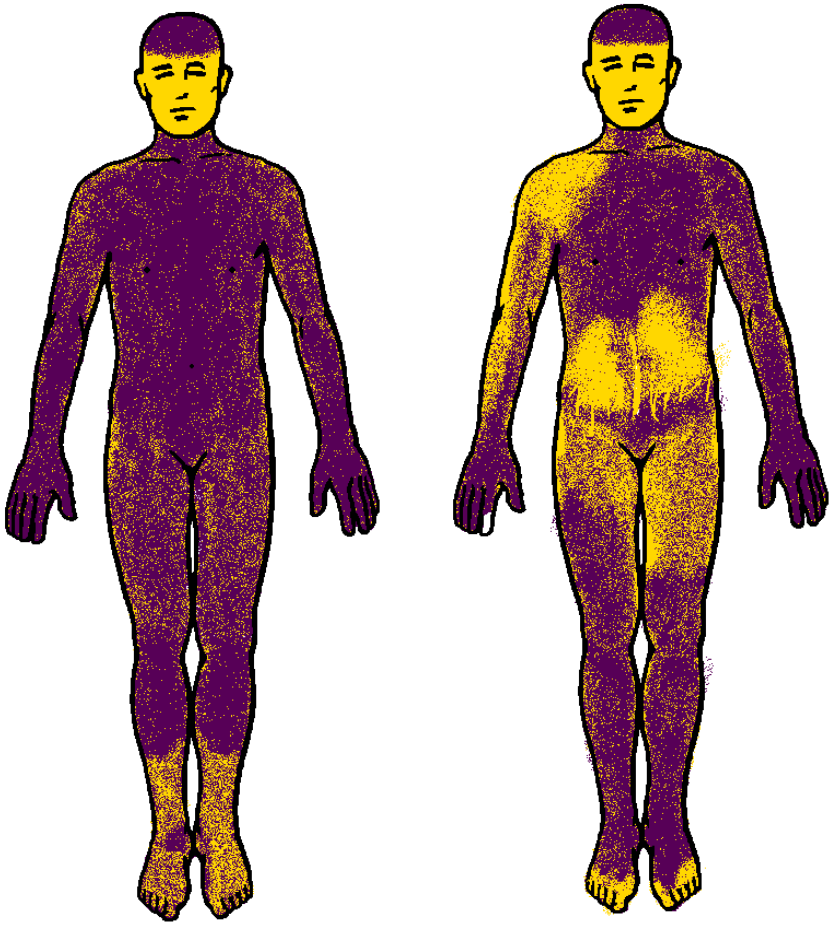
TST - Distal Patterns





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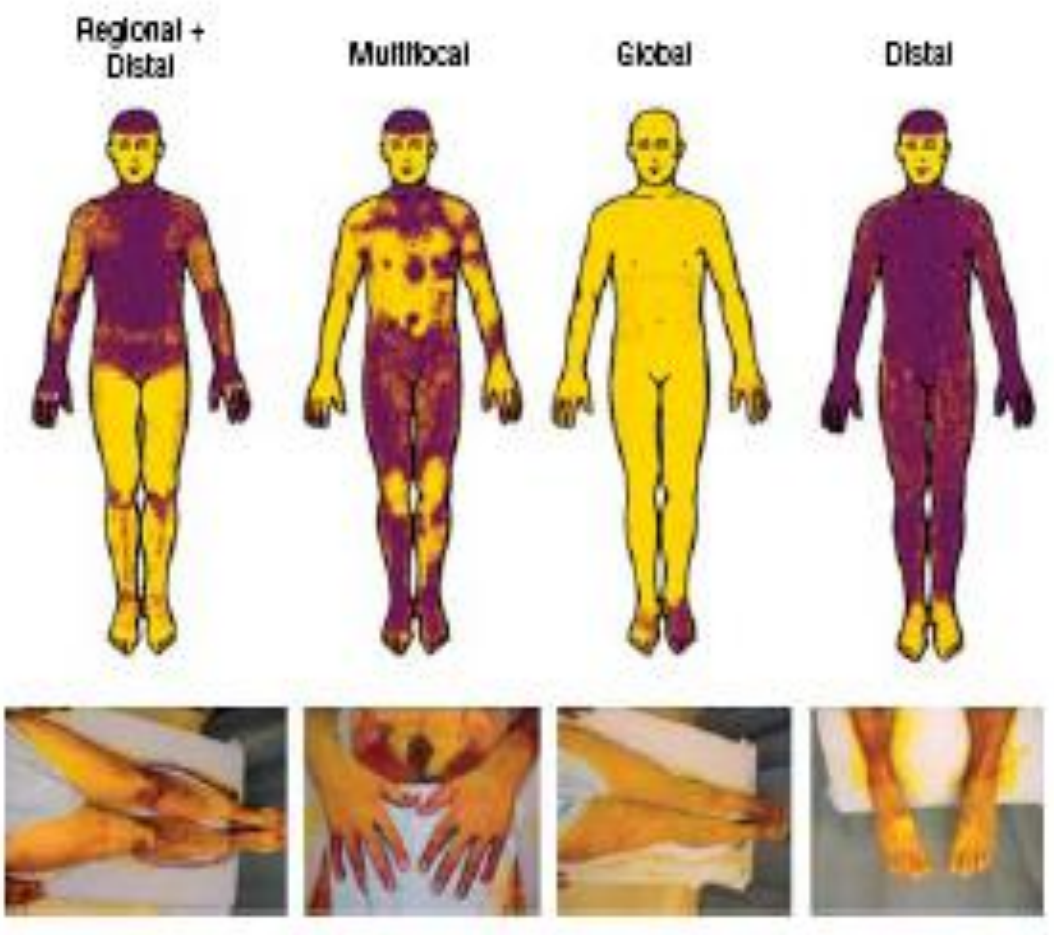
Pattern of sweating abnormality in EM

- **87.5% had abnormal TST (prosp.).**
- **25% of subjects had global anhidrosis, suggesting a more widespread dysfunction.**
- **In a few cases, the affected areas sweat normally (dissociation somatic/autonomic small fibers)**



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Reasons for Treatment Failure

- Incorrect diagnosis
- Use of wrong medication(s)
- Under dosing neuropathic medications
- Too rapid titration → side effects
- Psychological/rehabilitation needs not addressed
- Insufficient follow-up, use of VAS scores
- Pt needs to be educated/empowered

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Management

- **EDUCATION!**
- **Physical therapy and physical measures**
- **Psychology**
- **Neurology**
- **Anesthesia**

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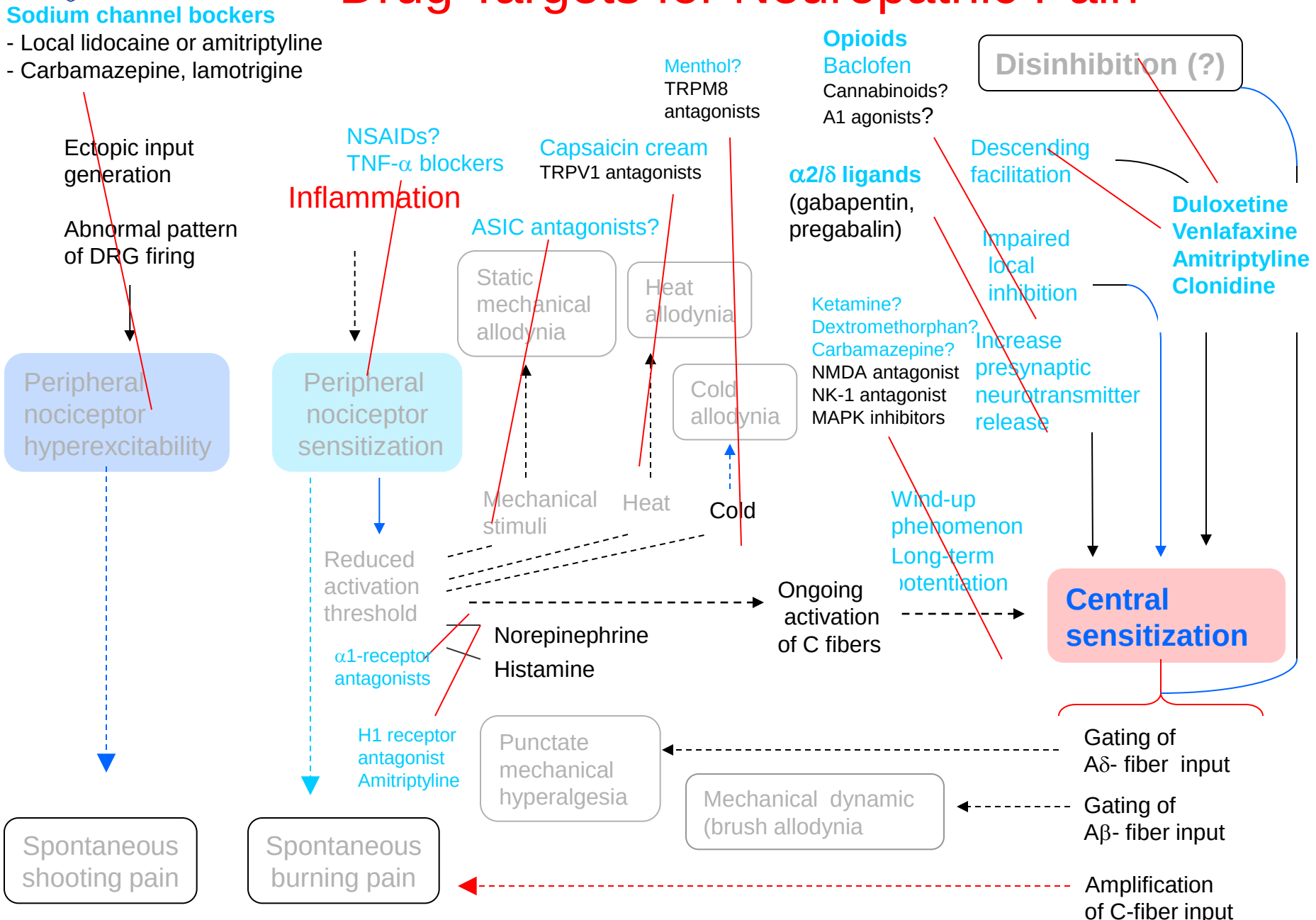
Drug Targets for Neuropathic Pain



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Non-pharmacologic treatment

- Soaking feet (or other affected body part) in cool water
- Massage, desensitization
- Acupuncture
- Relaxation, meditation, biofeedback

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Topical Agents

- Capsaicin
  - Five RCTs: not great, higher (x10 or more) concentration was messy, difficult to use and of questionable benefit
- Lidocaine cream 2.5%
  - Two RCTs for PHN: adjunctive therapy use
- Lidocaine patch 5%
  - RCT for PHN: good results, excellent tolerability
- Cannabinoid: topical CB1 agonists were disappointing
- Ketamine topical: anecdotal positive results
- Amitriptyline topical is effective as well (in combination)

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Comparison among selected antidepressants

	Neurotransmitters Transporters blockade potency			Receptors blockade potency			
	NE	5-HT	DA	H1	Ach-musc.	Alpha 1-adrenergic	5-HT 2 and 3
Amitriptyline	++	++++	+/-	+++++	++++	+++	**0**
Desipramine	++++	++	+/-	++	++	++	**0**
Venlafaxine	++	++++	+/-	+/-	+	**0**	**0**
Duloxetine	++++	+++++	+	+/-	+/-	+/-	**0**
Mirtazapine	+++	+++	**0**	++++	++	++	+++

Summary of AED Mode of Action

AED	↓ AP Firing	Block CA^{++}	Block GLU	GABA
CBZ	Na^{+} -ch. block	L	NMDA	--
VPA	Na^{+} -ch. block	T	NMDA	↑ [GABA]
GBP	?	High VGCC	↓ [Glu]	↑ [GABA]
LTG	Na^{+} -ch. block	N	↓ release	?
TPM	Na^{+} -ch. block	?	KA	↑ ↑ [GABA]
PB	Na^{+} -ch. block	VGCC	↓resp. EAA	↑ GABA-A
ZNS	Na^{+} -ch. block	T		
TGB				↑ ↑ [GABA]

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Second-generation Anticonvulsants

- **Lamotrigine**
- **Topiramate**
  - **NEW LARGER TRIAL: NOT EFFECTIVE**
  - **But may still work in some patients: do not abandon them completely**

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Tramadol

- **Weak opiate agonist (10% of morphine potency), but also 5-HT and NE uptake inhibitor**
- **Two trials showed efficacy in NP (NNT=3.5 with >50% pain reduction)**
- **Side effects, drug interactions may be a problem**
- **It is metabolized by CYP2D6 into M1 (active metabolite)**

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Opiates

- Multiple routes of administration: TTS, oral, IT
- Various agents: agonist/antagonist option, toxicity varies significantly, so does price
- Probably of similar efficacy, but some have more favorable profile
- Only long-acting to be used in chronic NP
- Fentanyl, hydromorphone, methadone have no active metabolites
- Methadone probably best choice as has NMDA antagonist activity. But long, variable half-life can be a problem.
- Levorphanol appears to be good choice also: potent, selective μ agonist, has simple pharmacokinetics

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NMDA receptor antagonists

- **Dextromethorphan and memantine:**
  - **1 small study showed benefit in PDN, not PHN**
- **Amantadine, Riluzole: not effective**
- **Ketamine: promising anecdotal reports, significant side effects. Can be very effective if properly used**
- **Methadone: weak, but useful additional mechanism of action also to reduce the development of tolerance**

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Other useful drugs

- **Mexiletine: good** Na+ ch. blocker**,** but too many GI side effects and CV risk
- **Clonidine:** alpha 2-agonist, IT best, but 1 study shows efficacy in PDN with transdermal clonidine
- **Baclofen:** GABA-B agonist, best as adjuvant
- **Lithium:** membrane stabilizer, alters neuronal sodium transport
- **Calcitonin:** for (CRPS). Serotoninergic and cathecholaminergic mechanisms, protein phosphorylation, prostaglandin inhibition, or stimulation of beta endorphins.
- **Steroids**: inflammation is often a significant factor
- **Alpha-lipoic acid:** in PDN

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Comparison amongst various agents: NNT and NNH

	NNT	NNH
Anti-depr.	3.1	16
Anti-conv.	4.2	10.6
Opiods	2.5	17.1

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Antidepressants

	NNT	NNH
TCA	3.1 (1.9-3.8)	14.7 (10-25)
SSRI	6.8 (3.4-441)	ns
SNRI*	5.5 (3.4-14)	ns
DNRI	1.6 (1.3-2.1)	ns

**duloxetine is better: 4.1 (2.9-7.2), 3.8 (2.6-7.3) for PDN*

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Anticonvulsants

	NNT	NNH
Carbamazepine	2 (1.6-2.5)	21.7 (13-79)
Lamotrigine	4.9 (3.5-8.1)	ns
Gabapentin/pregabalin	4.7 (4-5.6)	17.8 (12-30)
Topiramate	7.4 (4.3-28)	6.3 (5-8)

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Interventions

- epidurals, local blocks, sympathetic blocks
- intrathecal pumps
- Neuromodulation (TENS, scrambler, PNS, DCS, rTMS, MCS, DBS)
- destructive interventions (DREZ, sympathectomy, tractotomy, cordotomy, thalamotomy...)

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Repetitive Transcranial Magnetic Stimulation (rTMS)

- rTMS of the right dorsolateral prefrontal cortex (R-DLPFC) has been shown to be effective for the treatment of depression: rTMS now approved for depression treatment
- Pain pathways overlap with those controlling emotions and mood: many medications are indeed effective in treating both
- A few anecdotal reports indicate rTMS of motor cortex may be effective in the treatment of pain (fibromyalgia, neuropathic). More data needed, but it is non invasive…

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Surgical options

- **Motor Cortex Stimulation: probably best for facial and deafferentation pain. Response rate: 50%, maybe more in well selected cases**
- **Deep Brain Stimulation: targets VPL/VPM/VC thalamic nuclei (but not well tolerated), PAG or PVG. Although preliminary studies were encouraging, more recent data was negative. But stay tuned…**

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How to tackle chronic neuropathic pain?

- Relax
- Education of patient
- Remember you are first drug to pt
- Be realistic, be patient

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Practical tips

- **Start with education, education, education and non-pharmacologic approach**
- **Then choose simplest options, with the least side effects: there is no need to be fancy**
- **Pick your first line looking at side effect profile and quality of “main” pain (i.e., lancinating – AED, burning – TCA): chance of success is 30%**

(cont.)

- Add second drug with different mode of action: if effective, taper then off first one
- Occasionally, rotating drugs is helpful
- DO NOT induce addiction or pseudo addiction by using short acting opiates and combination analgesics