# Precision Medicine at the Bedside

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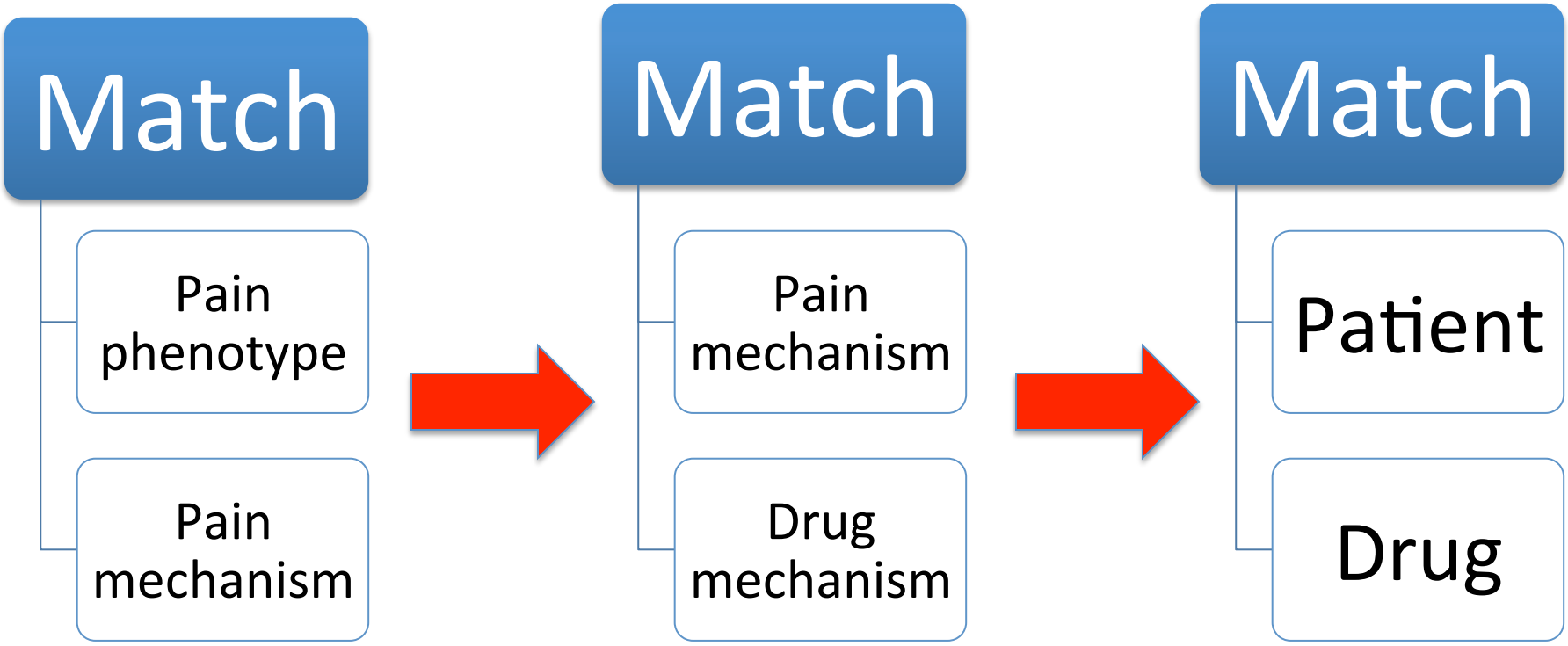
# The series of assumptions



# Clinical Symptoms – Diabetic and non-diabetic painful neuropathy

| | DPN | Non-DPN |
|---|---|---|
| • Numbness | 18 (51) | 22 (48) |
| • Paraesthesia | 32 (91) | 38 (83) |
| • Deep aching pain | 31 (89) | 40 (87) |
| • Pain paroxysms | 27 (77)* | 21 (46)* |
| • Pain on light touch | 11 (31) | 14 (30) |
| • Pain on pressure | 25 (71) | 31 (67) |

81 patient referred for clinical trials

Similar symptoms across etiologies

Paresthesias and deep aching pain most frequent

Paroxysms discriminates between DPN and non-DPN

Otto et al. Pain 101, 2003, Pages 187–192

# Clinical Signs – Diabetic and non-diabetic painful neuropathy

| | DPN | Non-DPN |
|---|---|---|
| • Hypaesthesia | 24 (69) | 29 (63) |
| • Dynamic mechanical allodynia | 17 (49) | 21 (46) |
| • Hypalgesia | 12 (34) | 15 (33) |
| • Hyperalgesia | 8 (23) | 11 (24 |
| • Thermal hypaesthesia | 14 (40) | 16 (35) |

Prominent hypaesthesia and dynamic mechanical allodynia suggest central mechanisms

[QST battery: Cotton wool, pinprick, Somedic thermotest]

Otto et al. Pain 101, 2003, Pages 187–192

# Neuropathic Pain Symptom Inventory

- Self-administered questionnaire with 10 different descriptors
  - Superficial and deep spontaneous ongoing pain (burning, squeezing pressure)
  - Brief pain attacks and paroxysmal pain (electric shocks, stabbing)
  - Evoked pain – provoked by brushing, pressure and contact with cold
  - Abnormal sensations in painful area (dysesthesia, paresthesia)
  - Temporal items (not included in these analyses)

Bouhassira D.et al. Development and validation of the Neuropathic Pain Symptom Inventory. Pain 2004;108:248–57.

# Bedside QST

- Sensory thresholds measured using graded Von Frey hairs
- Static allodynia
- Dynamic allodynia,
- Punctate hyperalgesia
- Temporal summation to tactile stimuli
- Cold allodynia
- Cold hyperalgesia

# General instructions

- All testing should be performed in a quiet environment with the patient lying comfortably.
- Testing should be performed over the area of maximal pain.
- The supplied instruments must be used for all tests
- The tests must be performed in the same order
- **Each test procedure must be explained to the patient prior to testing using the wording provided**
- For all test except the sensory threshold, the patient will be asked to rate the pain produced by the applied stimulus on a 11-point numerical rating scale (scale provided in tool box).
- Wait 30 seconds between tests to avoid temporal summation

# Sensory Threshold Testing

- Instruct subjects to close or cover their eyes during testing.
- Apply the filament to the skin at a 90° angle with sufficient force to bend or bow the filament.
- Hold the filament in place for 1.5 sec and then remove. Do not move the filament while in contact with the skin.
- When a stimulus is felt, subjects should respond by saying "yes“
  - For the 4.31 (2 g) monofilament and below, i.e., 3.61 (0.4 g) and 2.83 (0.07 g) the filament can be applied up to three times.
  - For the 4.56 (4 g) monofilament and above, i.e., 5.07 (10 g) and 6.56 (300 g) one stimulus is sufficient.
- The complete test is performed three times, each time beginning with the 4.31 (2 g) monofilament (see figure below).
- Note the lowest (softest) filament detected for each trial

# Sensory Threshold

Start here

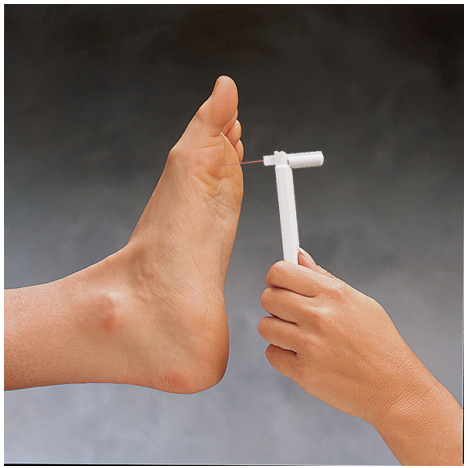
2.83 3.61 **4.31** 4.56 5.07 6.65

**If perceived, go down**

Up to 3 trials per filament

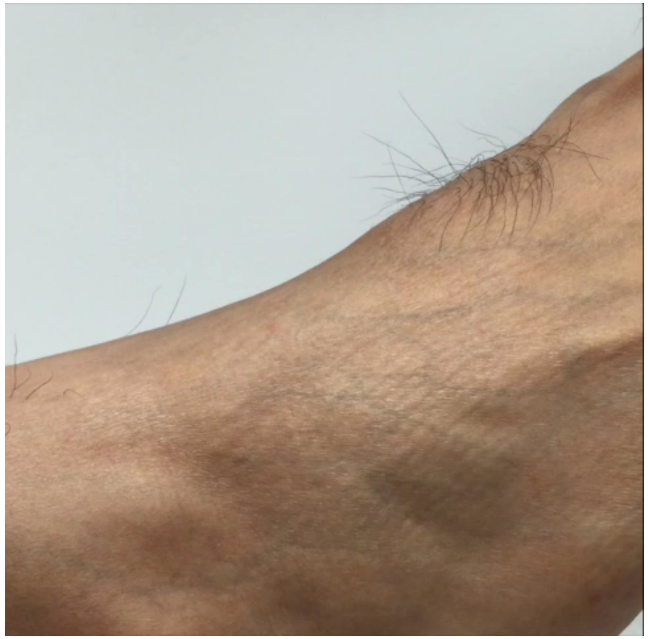
If **not** perceived, go up

Only one trial per filament



# Static Mechanical Allodynia

- Evoked by gentle constant mechanical pressure
- Produced by application of the plastic base of a Von Frey hair in the area of maximum pain for 10 seconds
- Pressure should be sufficient to indent the skin



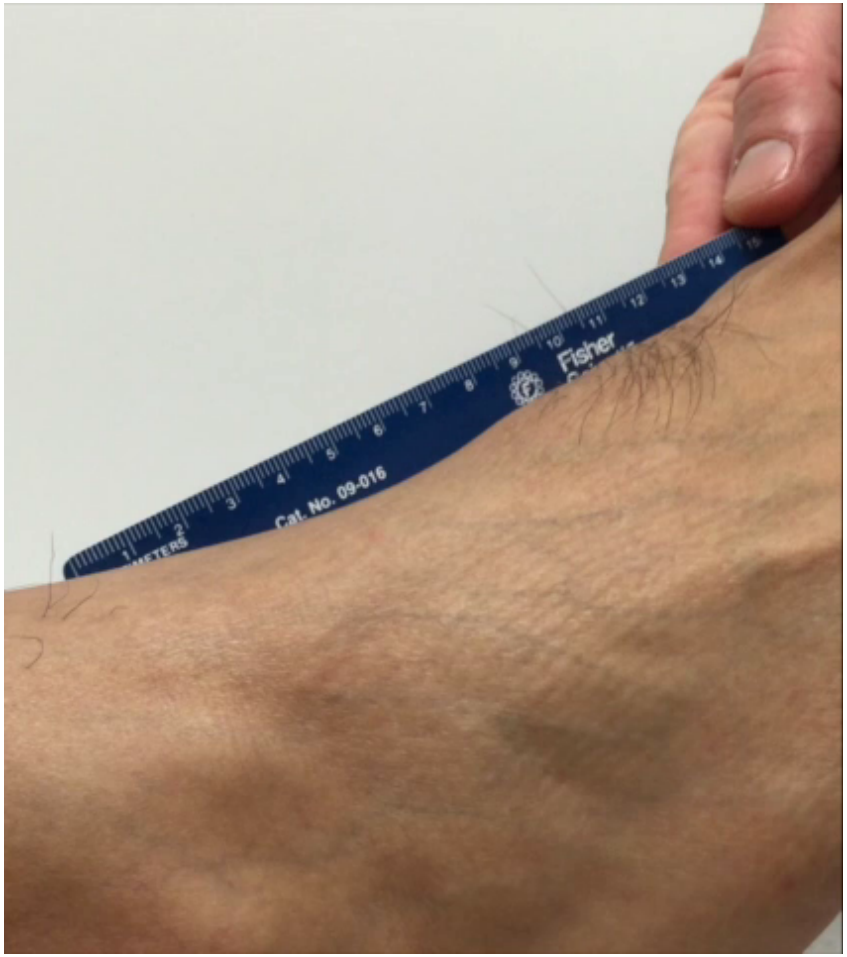
# Static mechanical allodynia

**Tester – Read this explanation to subject before testing static mechanical allodynia**

- I will now touch the site of maximal pain with the tip of a plastic probe
- The amount of pressure will be just enough to indent the skin
- The test will last for 10 seconds
- After that, I will ask you to rate the pain produced by pressure with the plastic probe using a scale where zero means no pain and 10 means worst possible pain.
- Remember, I will ask you to rate the pain produced by the plastic probe

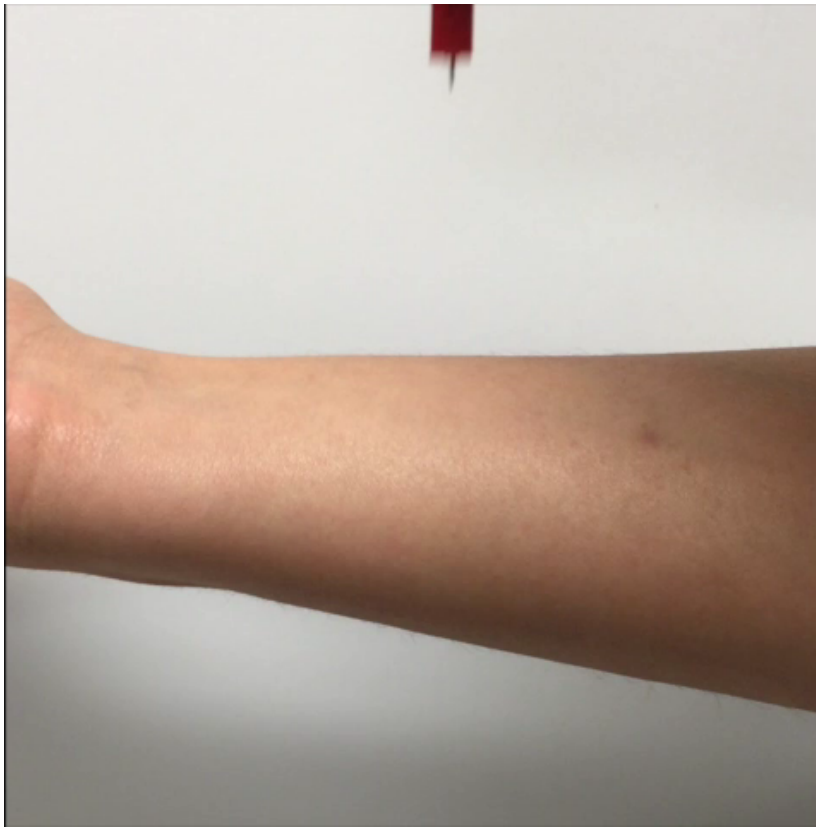
# Dynamic Mechanical Allodynia

- Evoked by gently stroking the area of maximum pain with the foam brush
- Stroke, in the shape of a cross through the area of maximum pain
- Stroke 4 times (twice from each direction) at a speed of 3-5 cm/s
- Stroke length ~ 5-10 cm over 1-2 sec
- A 5 sec. interval between strokes



# Punctuate Hyperalgesia

- Evoked by pinprick over the reference area first (the upper arm ), then over the area of maximum pain with supplied safety pin
- Interval of at least 30 second between tests
- The stimulus is applied twice for about half a second with a 5 second interval between stimuli for each site
- Ask the subject to rate the pain evoked by the safety pin for both reference and pain areas and note the respective pain intensities on the CRF
- Safety pin to be discarded after each test



# Temporal summation to tactile stimuli

- Evoked by repeatedly tapping the area of maximum pain with a stiff von Frey hair just below threshold for pain in normal skin (~200g)
- Tap at a rate of 2Hz for 60 seconds or less if the pain is intolerable.
- Contact time with the skin of ~ 300 ms.
- Note time to intolerability and pain score at end of test

# Cold allodynia

- Evoked by application of the standardized cool round metal rod
- Probe must be cooled in **ice water (15°C ± 2°C)** and then dried
  - ***Do not leave metal rod in water overnight. It could oxidize.***
- It will take ~15 minutes in ice water to cool the rod
- Confirm the temperature of the rod with the supplied thermometer
- Apply the long end of the rod to the area of maximum pain for 10 seconds. The rod should rest lightly on the limb without additonal pressure.
- Ask the subject to rate his/her pain evoked by contact of the metal rod to the skin and note the pain intensity on the CRF

# Pregabalin for painful HIV neuropathy

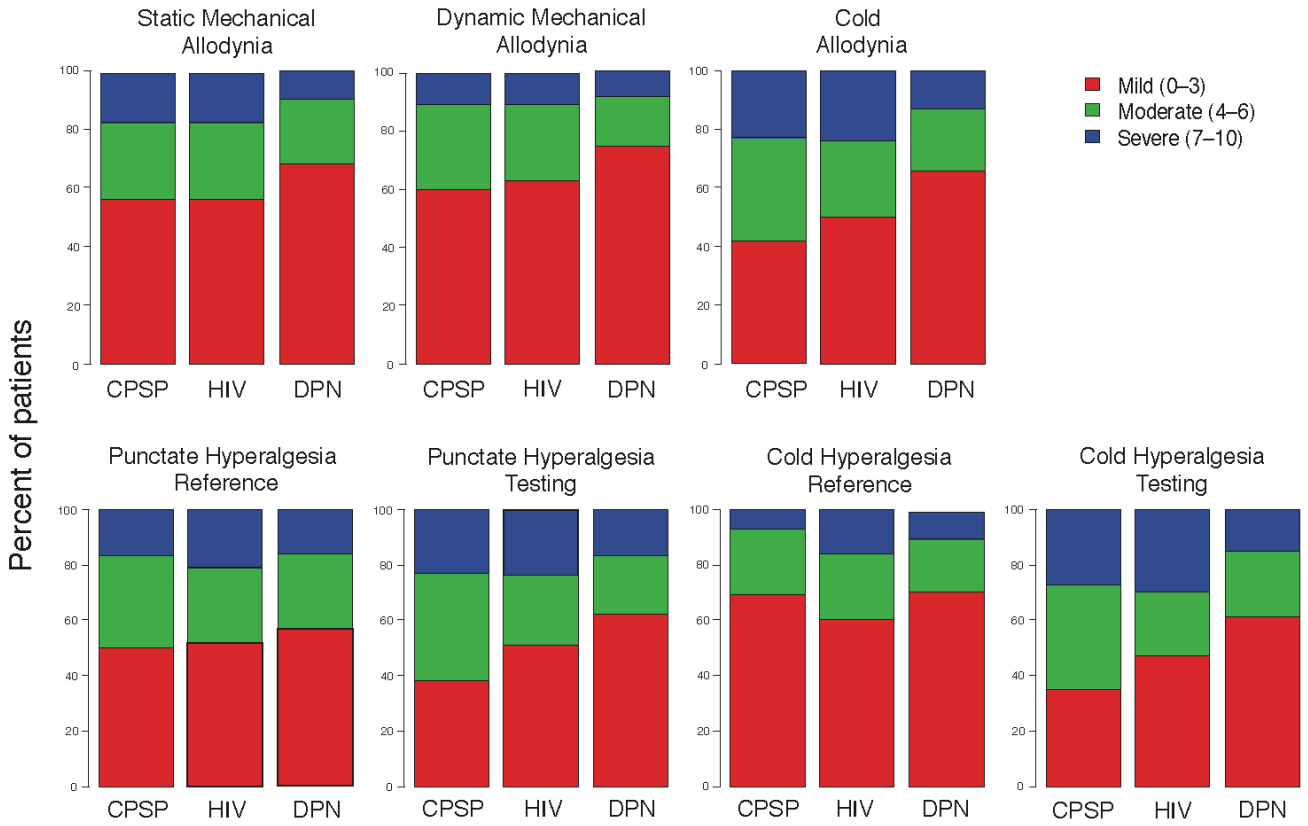
A randomized, double-blind, placebo-controlled trial

The difference in the change from baseline to endpoint for any assessment of the evoked pain measures between the pregabalin and placebo groups was not significant. However, ARF analysis indicated that treatment effects differ greatly in subjects with the greatest sensitivity to pinprick at baseline (baseline punctate hyperalgesia score ≥8, n = 39). For these subjects, the change from baseline in mean NPRS scores at endpoint LOCF showed a 2.14-point greater improvement for pregabalin compared to placebo ($p = 0.0111$). For subjects with a low-to-moderate sensitivity to pinprick at baseline (a score ≤7 on assessment of punctate hyperalgesia), change from baseline difference was 0.06 points ($p$ =

# The Trials

- Primary Analysis Studies
  - Central post-stroke pain (219 patients)
  - HIV neuropathy pain (302 patients)
  - Painful diabetic peripheral neuropathy (450 patients)
  - Post-traumatic neuropathic pain (254 patients)*

# Clinical QST
# Analyses of 3 clinical trials

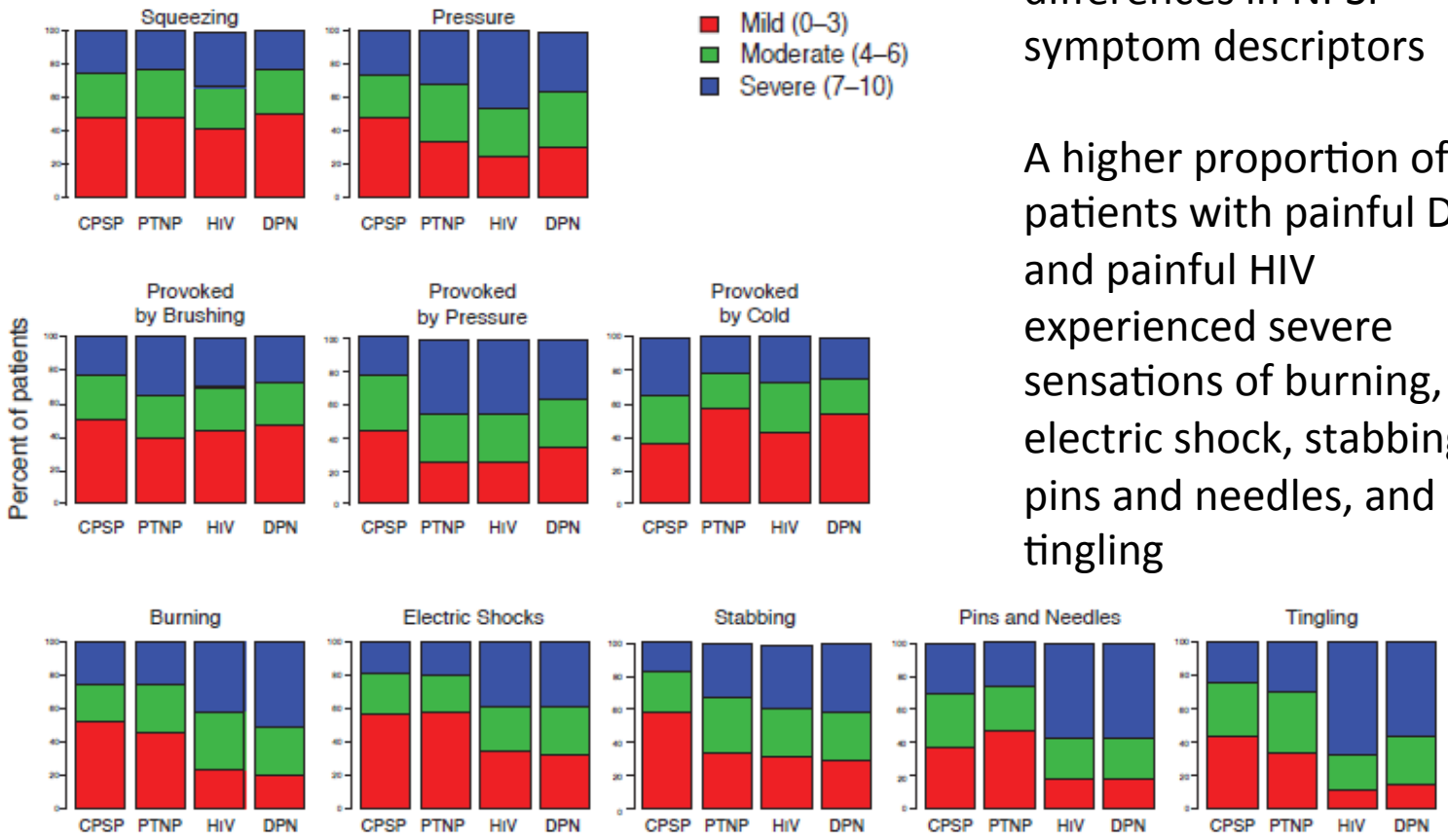



More similarities than differences in QST results

A lower proportion of patients with DPN reported higher scores with assessments of static mechanical allodynia, cold allodynia, punctate hyperalgesia testing, and cold hyperalgesia testing compared with CPSP or painful HIV neuropathy

Freeman R et al. Pain 2014;155:367–76.

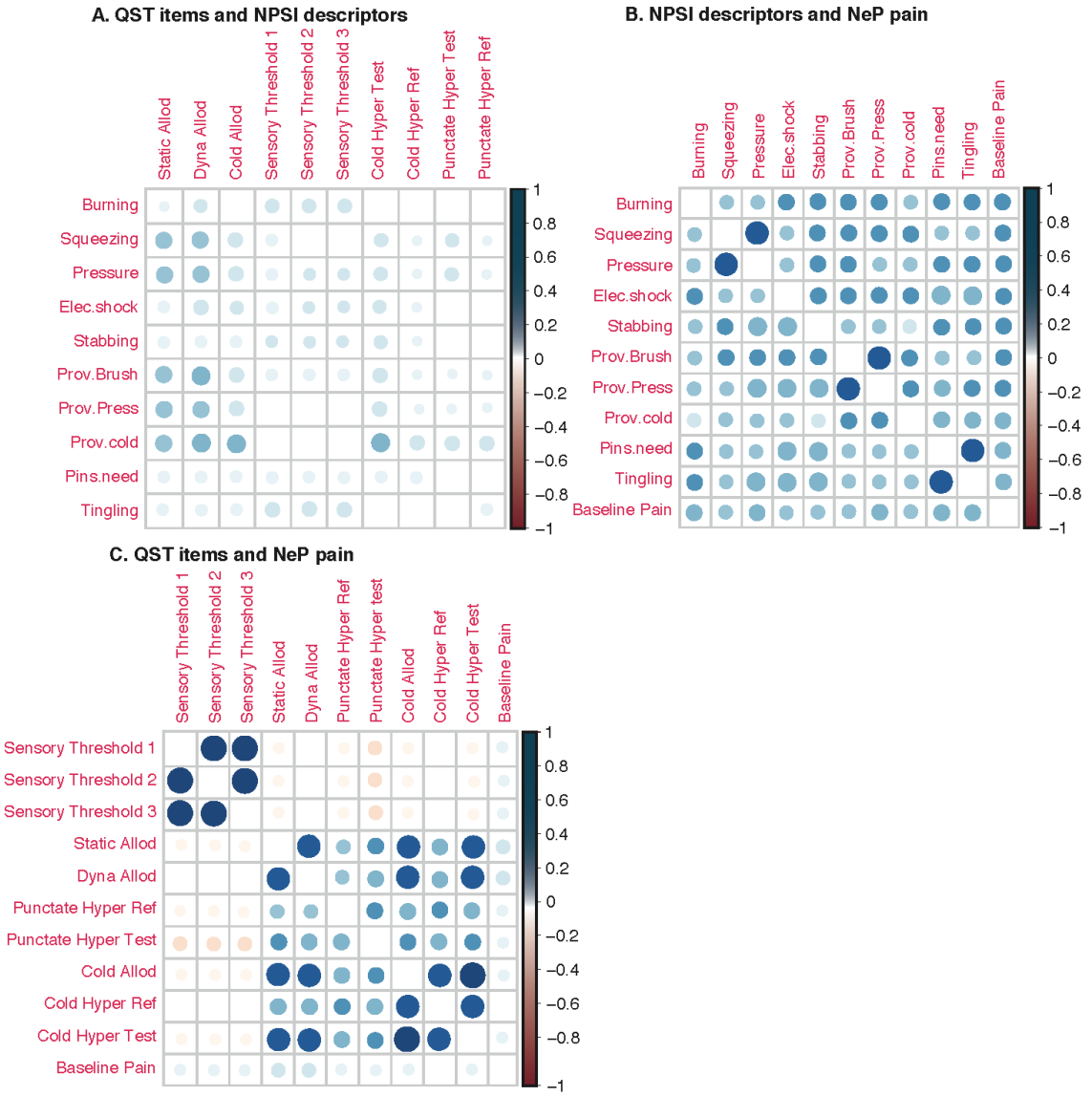
# NPSI
# Analyses of 4 clinical trials




More similarities than differences in NPSI symptom descriptors

A higher proportion of patients with painful DPN and painful HIV experienced severe sensations of burning, electric shock, stabbing, pins and needles, and tingling

Freeman R et al. Pain 2014;155:367–76.




Freeman R et al. Pain 2014;155:367–76.

# Pain phenotype as response predictor

# The Trials

- Primary Analysis Studies
  - Central post-stroke pain
  - HIV neuropathy pain
  - Painful diabetic peripheral neuropathy
  - Post-traumatic neuropathy*
- Confirmatory Analysis Study
  - Chronic central neuropathic pain after spinal cord injury

# NPSI

- Moderate-to-severe pain provoked by cold, moderate pain provoked by pressure, and mild pain provoked by brushing were associated with a significantly better response to pregabalin than to placebo in both primary and confirmatory analysis
- Primary Analysis
  - Difference between the effects of pregabalin and placebo = 0.77; P = 0.013
- Confirmatory Analysis
  - Difference between the effects of pregabalin and placebo = 1.40; P = 0.016

# Bedside QST

- Severe punctate hyperalgesia, moderate-to-severe cold hyperalgesia, and moderate-to-severe temporal summation to tactile stimuli were associated with a better response to pregabalin in both primary and confirmatory analysis
- Presence or absence of deafferentation was not a predictor
- Primary analysis
  - Difference between the effects of pregabalin and placebo of 1.34 ± 0.53 (P = 0.013)
- Confirmatory analysis
  - Difference 1.88 ± 0.86 (P = 0.044) between the effects of pregabalin and placebo

# Selected other studies

PAIN® 153 (2012) 1815–1823

PAIN®

www.elsevier.com/locate/pain

# Randomized control trial of topical clonidine for treatment of painful diabetic neuropathy

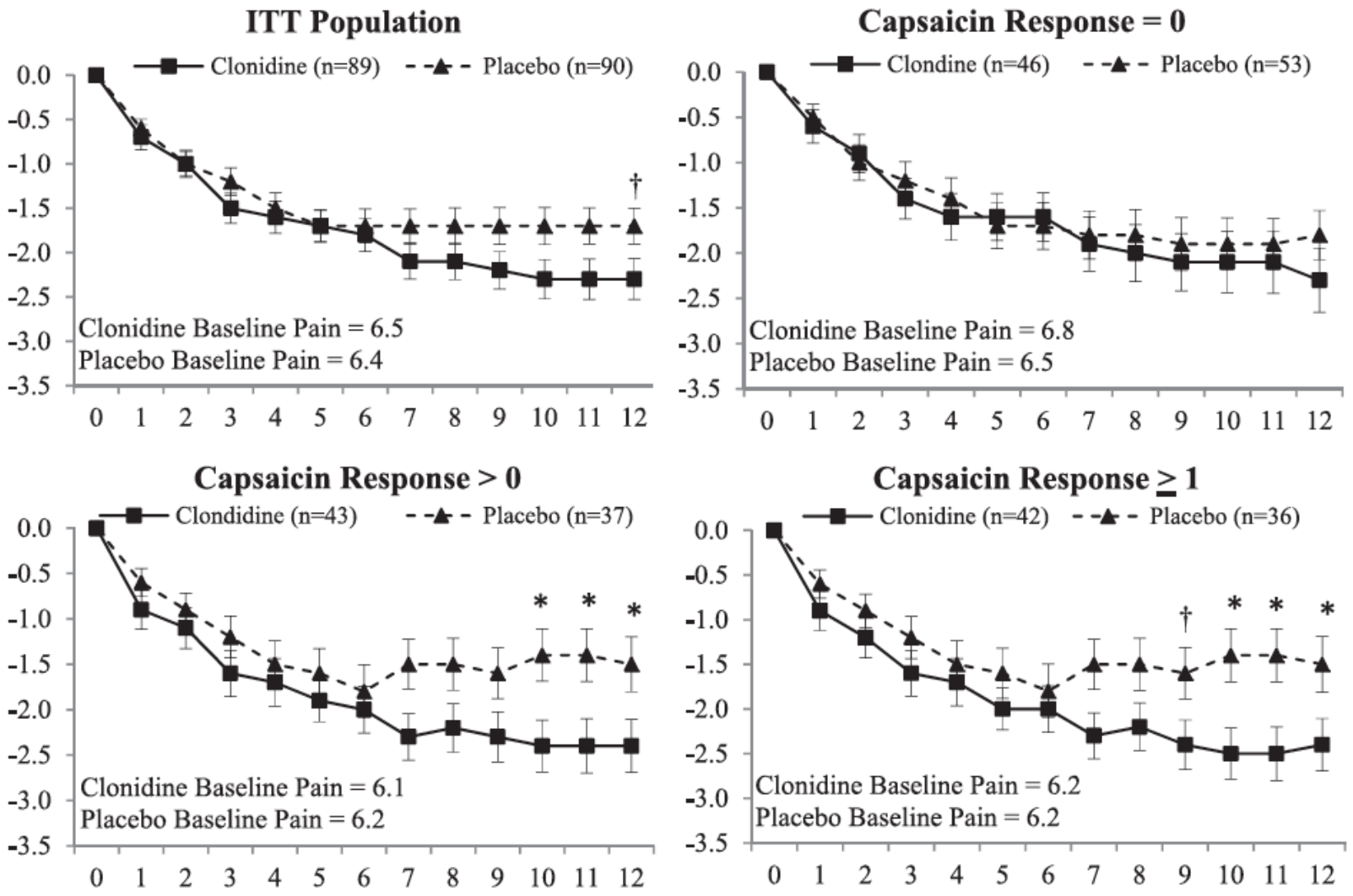
Claudia M. Campbell [a,*], Mark S. Kipnes [b], Bruce C. Stouch [c], Kerrie L. Brady [d], Margaret Kelly [d], William K. Schmidt [d], Karin L. Petersen [e,f], Michael C. Rowbotham [e,f], James N. Campbell [d]

- Randomized, double-blind, placebo-controlled, parallel-group, multicenter trial.
- Subjects randomized to receive 0.1% topical clonidine gel (n = 89) or placebo gel (n = 90) applied 3 times a day feet for 12 weeks.
- Treated subjects treated showed a trend toward decreased foot pain compared to the placebo-treated group; P = 0.07)

# Psychophysical assessment

- Nociceptor function was measured by determining the painfulness of 0.1% topical capsaicin applied to a 1 cm diameter area in the pretibial region for 30 minutes during screening.
- Subjects who felt any level of pain to capsaicin, clonidine was superior to placebo ($P < 0.05$).
- Subjects with a capsaicin pain rating >2 (0–10, NPRS), the mean decrease in foot pain was 2.6 for active compared to 1.4 for placebo ($P = 0.01$)
- Other tests of sensory functions (mechanical, vibration, thermal) did not correlate with the responses to clonidine

Campbell et al. Pain 153 (2012) 1815–18232

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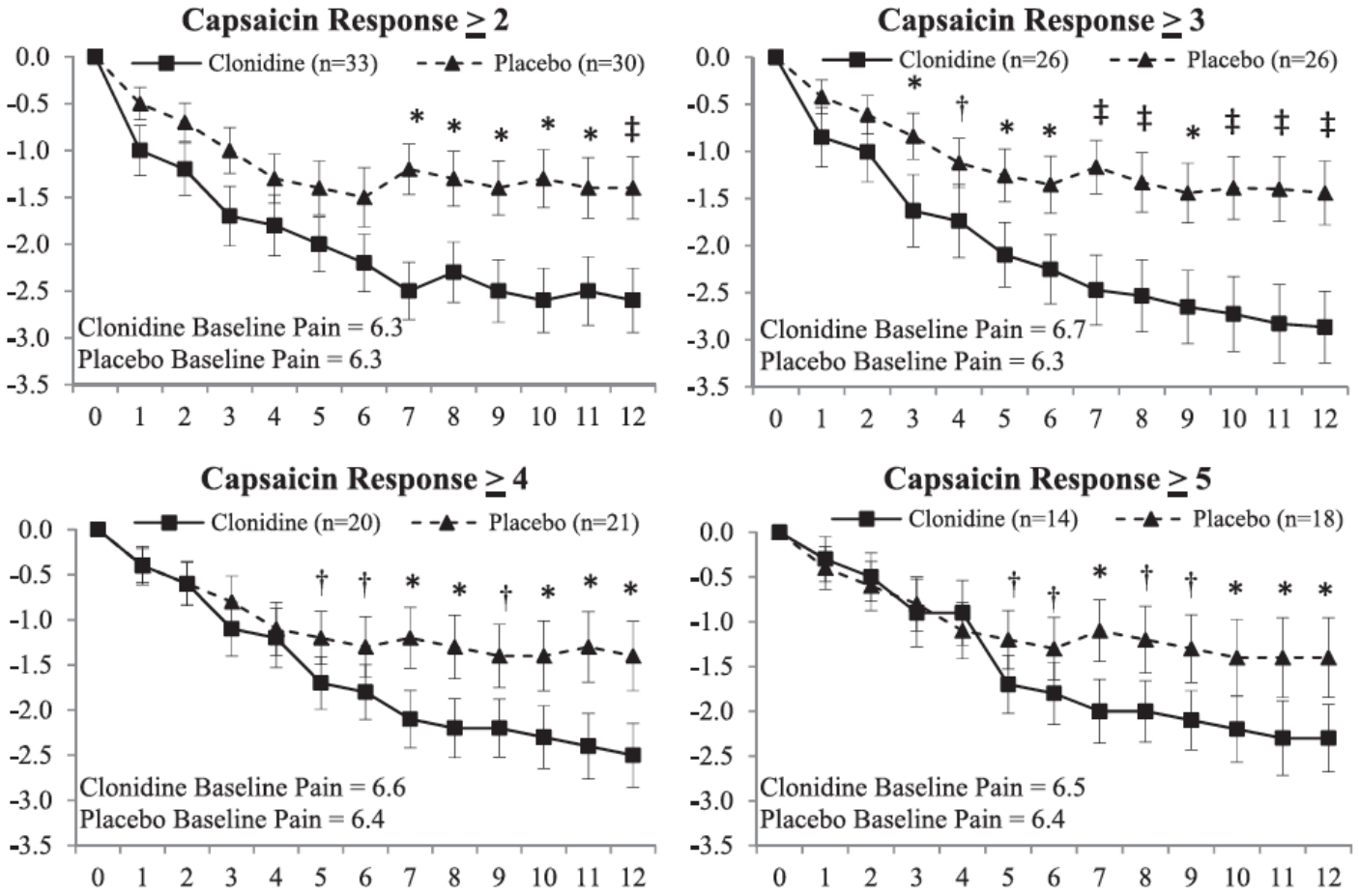


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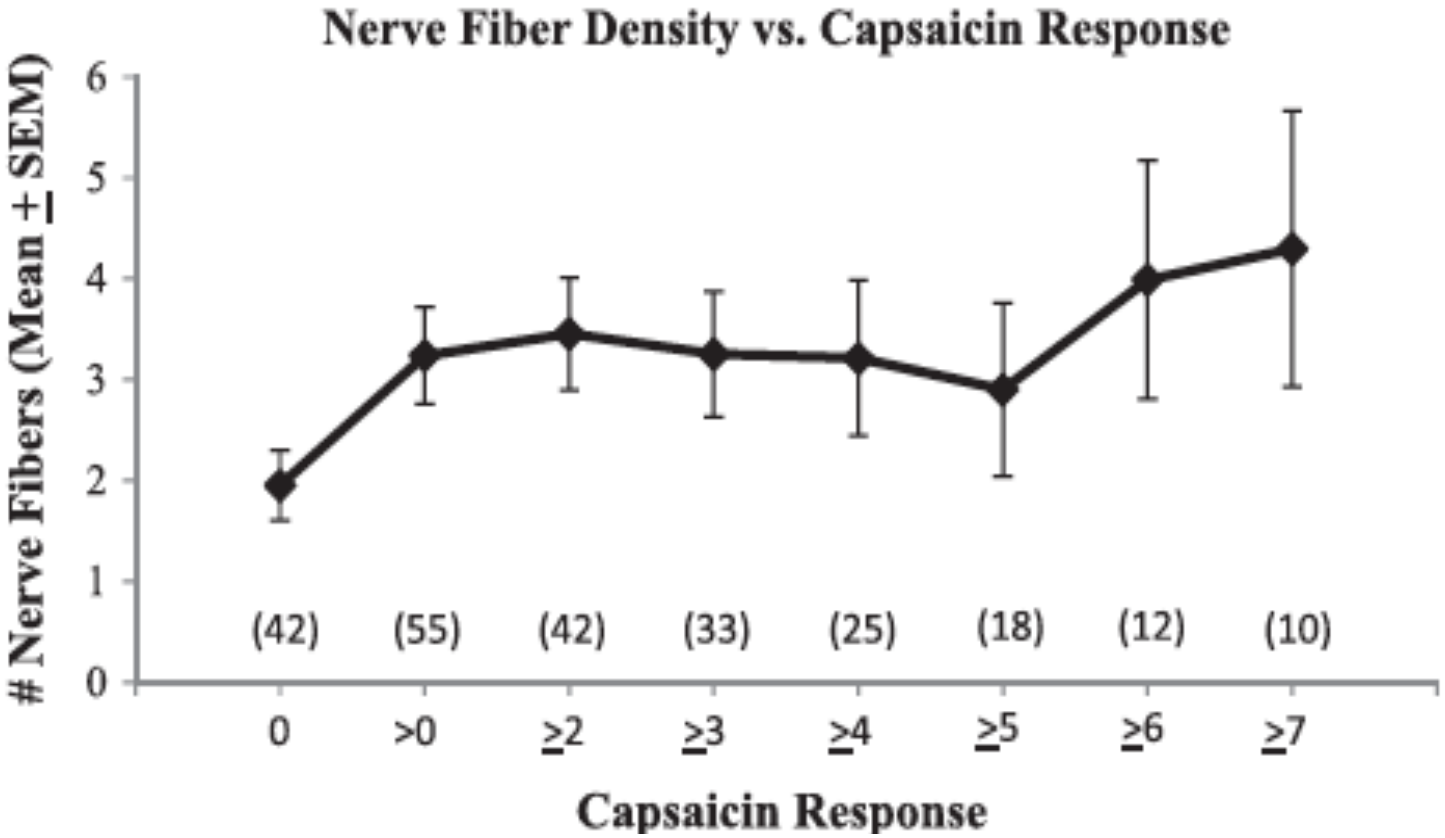



C-fiber density in epidermis lower in 42 capsaicin non-responders

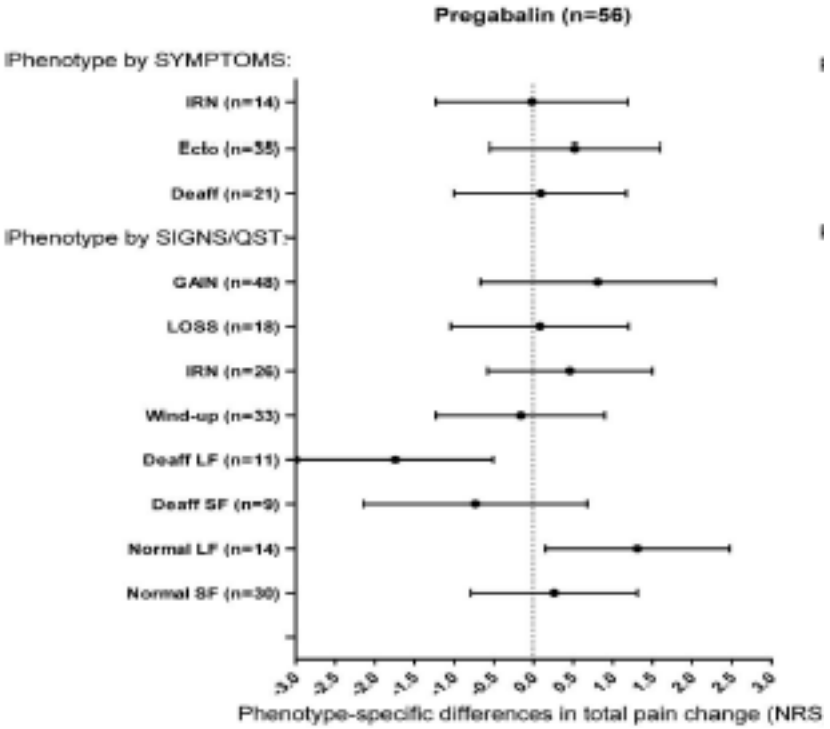
Campbell et al. Pain 153 (2012) 1815–18232

Research Paper
PAIN

# Pain phenotype as a predictor for drug response ir painful polyneuropathy—a retrospective analysis o data from controlled clinical trials

Jakob V. Holbech[a,*], Flemming W. Bach[b], Nanna B. Finnerup[c], Troels S. Jensen[c,d], Søren H. Sindrup[a]

Thus, this post hoc analysis of 8 drugs with mainly nonselective actions on neuropathic pain mechanisms found limited usefulness of sensory phenotyping in pain as the basis for individualized treatment.



# Roadmap

- Dynamic approach to specialty center based QST and other phenotyping assessments – streamline, constantly refine, expand the multi-national aspects
- Similar approach to community based QST batteries and phenotyping assessments
- Obligatory phenotyping for all Phase 2 and Phase 3 studies
- Opportunity for academia-industry interaction
- Mechanism for pooling of data across trials to allow assessment of drugs with different mechanisms of action