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Nociceptive processing: An option for targeting treatment?

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TOPICS

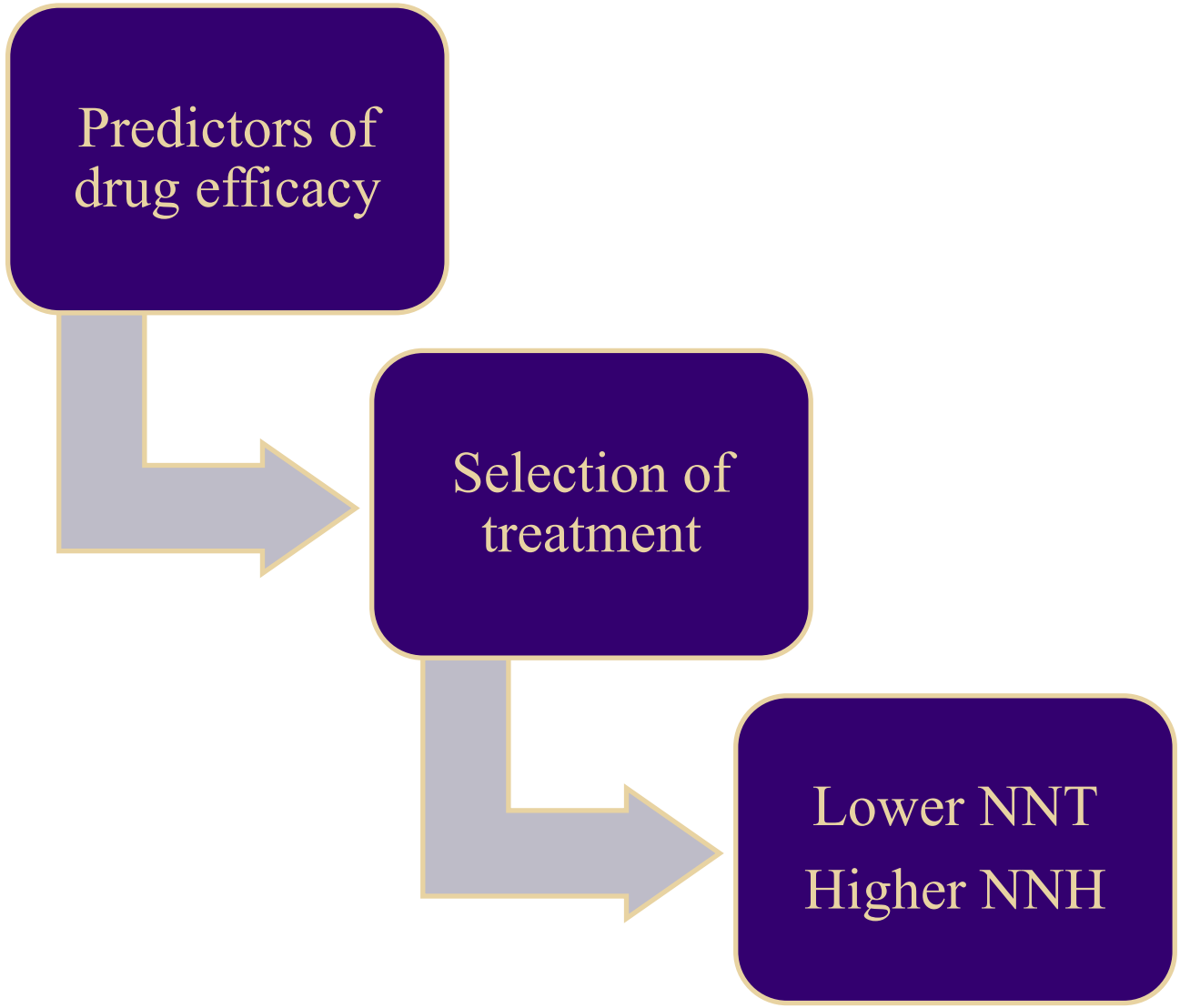
- Conceptual framework
- Phenotyping for nociceptive processes
- Current evidence on mechanism-based treatments
- Prospects

Limited to pharmacological treatments

Reasons for individualized pain treatment

- Response to pain medications:
  - Is typically low
  - Varies enormously
  - Is unpredictable

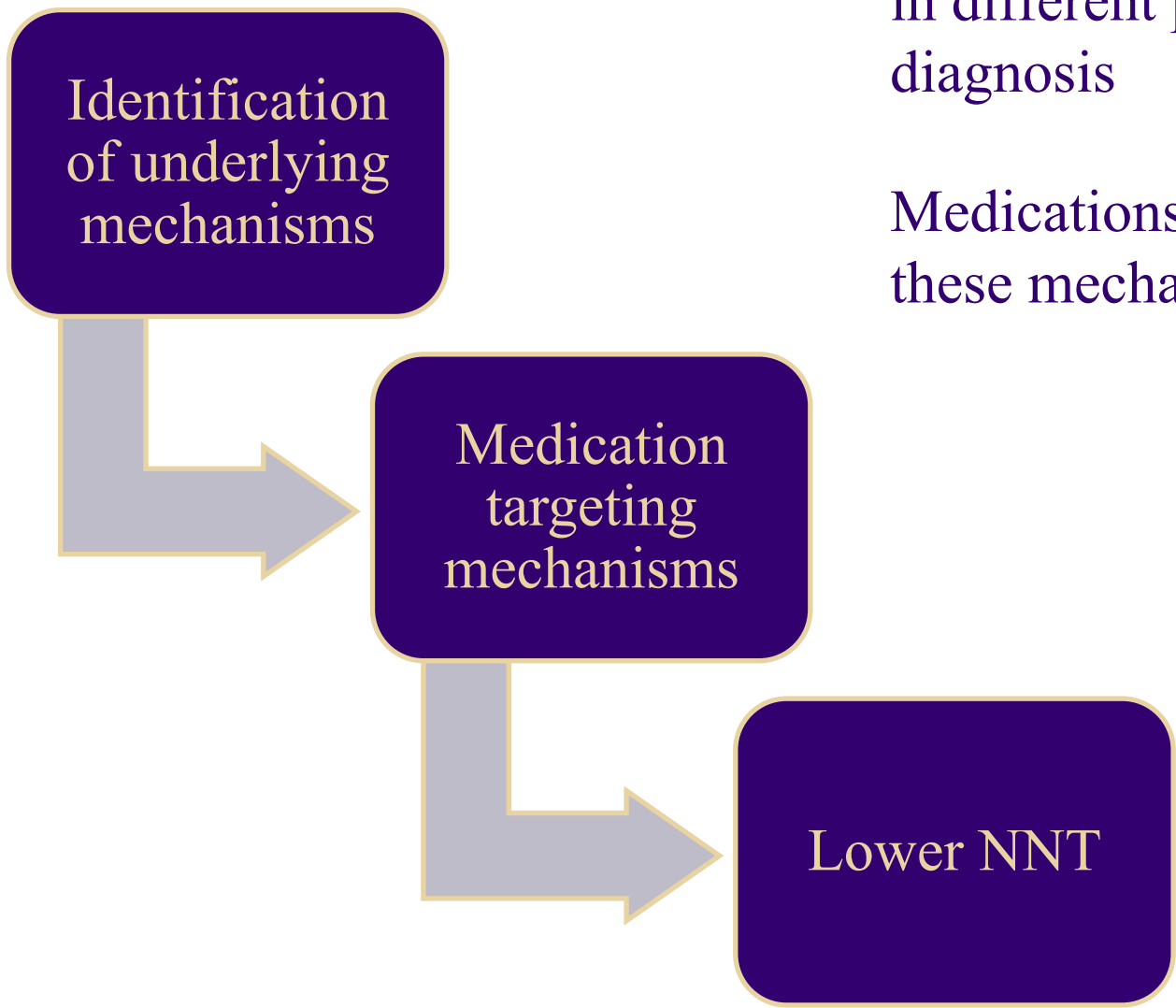
- Trial-and-error is associated with:
  - Prolonged times to identify the right medication
  - Exposure to side effects and complications with uncertain benefits


Predictors of drug efficacy
Selection of treatment
Lower NNT
Higher NNH

Mechanism-based approach - Rationale

- Medication management is currently targeted to diagnostic categories (LBP, PHN, etc.)

- Within the same diagnostic categories, different mechanisms are involved, e.g. for neuropathic pain:
  - Ectopic nerve activity (enhanced expression of voltage-gated Na^+ channels, TRPV1, etc.)
  - Central sensitization (enhanced neuron excitability, dis-inhibition, neuro-inflammation, etc.)
  - Etc.



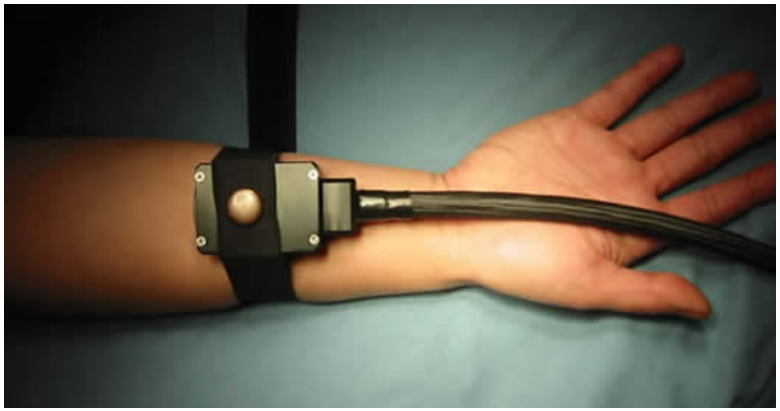
Different mechanisms are involved in different patients with the same diagnosis

Medications work only in part of these mechanisms

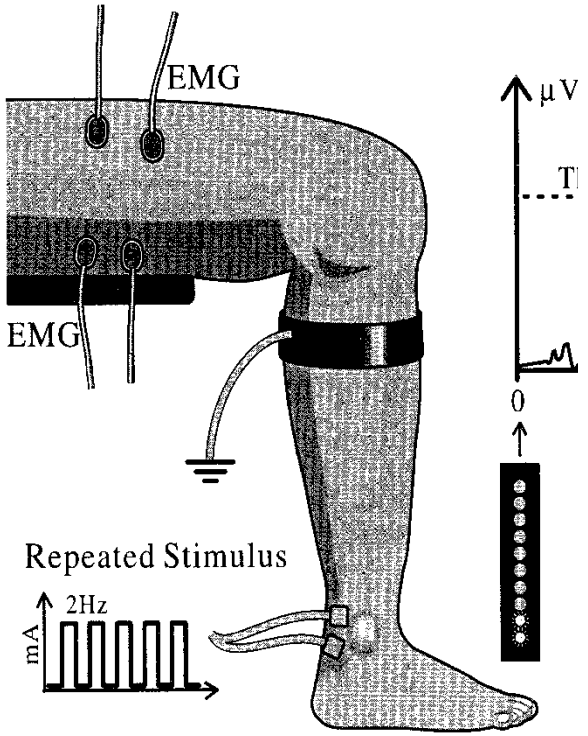
Challenges

Methods to study directly nociceptive processes in humans are

- **> Limited in scope**
- **> Not for clinical practice**



We have to use surrogate measures / biomarkers



Courtesy L. Arendt-Nielsen

What is a biomarker?

- **A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions**

Robb et at, JAMA 2016

- **Biomarkers are not clinical endpoints**

Any useful biomarker must eventually show a link to a relevant clinical endpoint

Quantitative sensory tests

- Application of a stimulus
- Response (subjective, electrophysiological, etc.)

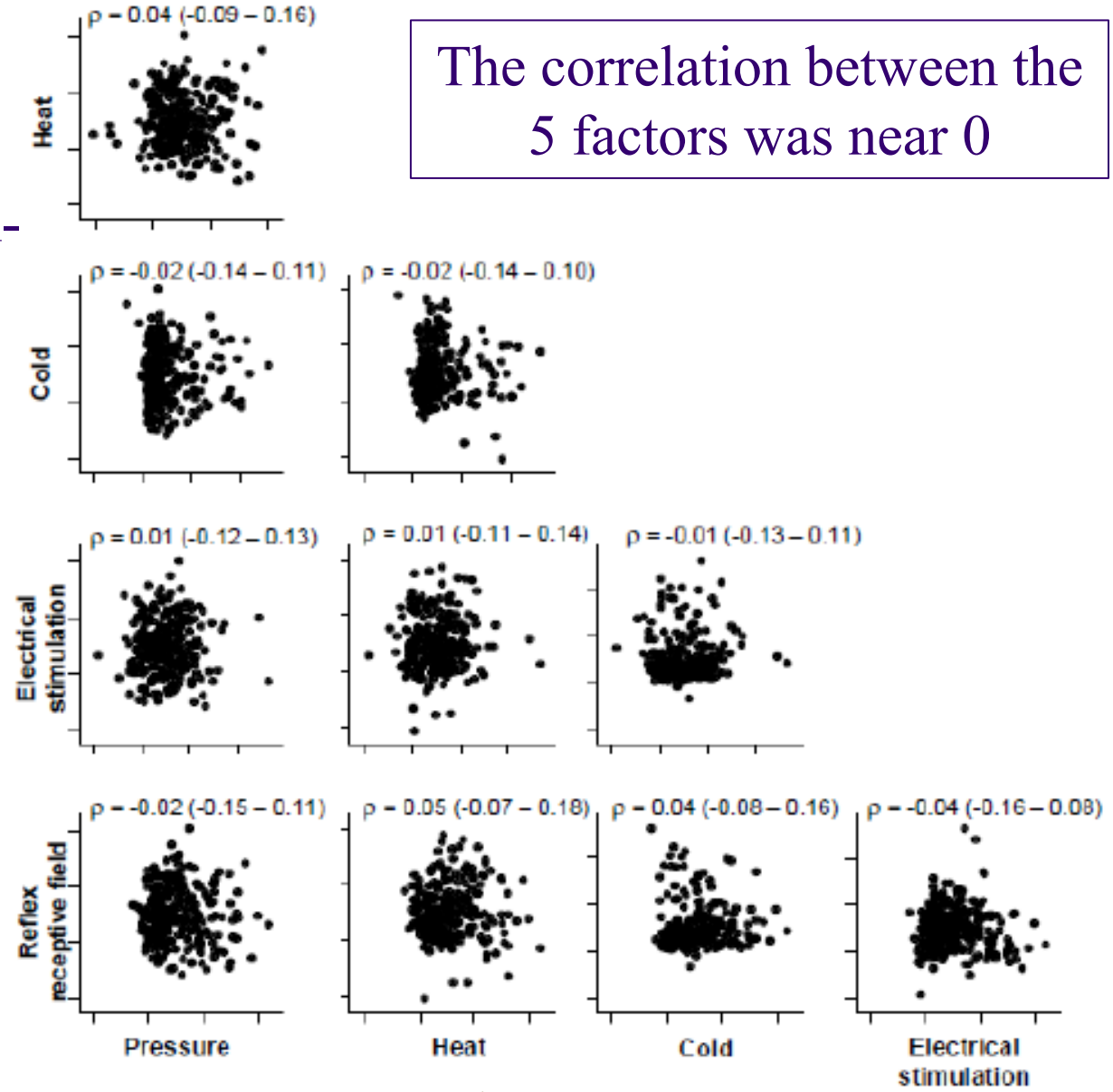
- Can be used bed-side
- Are reliable

- Have been used extensively in research
- Have some clinical use, particularly in neuropathic pain

- Their validity for nociceptive processes is unclear due to lack of reference standards

Are QST all the same?

- Factor analysis in 272 pain-free subjects
- 5 factors cumulatively explained 94% of the variance: pressure, heat, cold, electrical stimulation and reflex receptive fields



The correlation between the 5 factors was near 0

Responses to different modalities represent different dimensions of pain perception

Neziri et al, Pain 2011

Mechanisms that can be assessed in humans

- **Sensitization**
  - QST at non-injured areas → Widespread sensitization
  - QST at injured areas → Nociceptor sensitization / Central sensitization
- **Spinal cord nociceptive hypersensitivity (NWR)**
- **Temporal summation (pain threshold, NWR)**
- **Receptive fields (reflex receptive fields)**
- **Gain/loss of nerve fiber function**
- **Endogenous modulation (CPM)**
- **…**

Phenotyping patients with neuropathic pain

- 902 Patients with different types of neuropathic pain
- Validation on another set of 233 patients
- Etiologies: polyneuropathy, peripheral nerve injury, post-herpetic neuralgia and radiculopathy

- 13 different mechanical and thermal QST
- Z scores calculated based on previous studies on healthy subjects as reference values
  - Z scores >0 = gain in function
  - Z scores <0 = loss in function

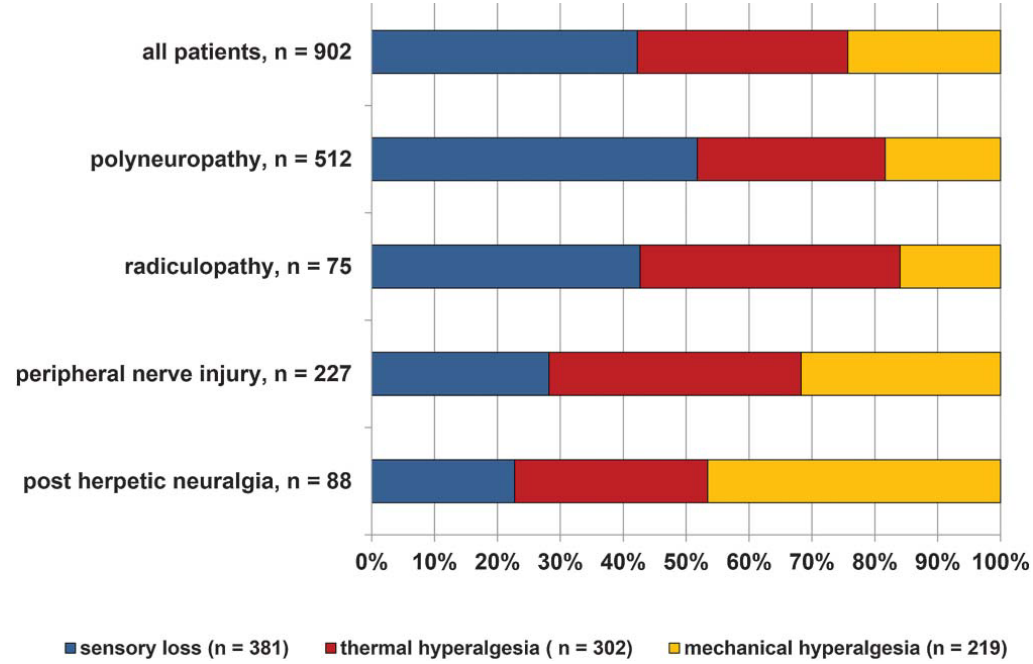
Baron et at, Pain 2017

Clusters:

1. Sensory loss (loss of fiber function; ectopic activity)
2. Thermal hyperalgesia (mostly peripheral sensitization; spontaneous activity in surviving nociceptors)
3. Mechanical hyperalgesia (mostly central sensitization; possibly ectopic activity in nociceptors)

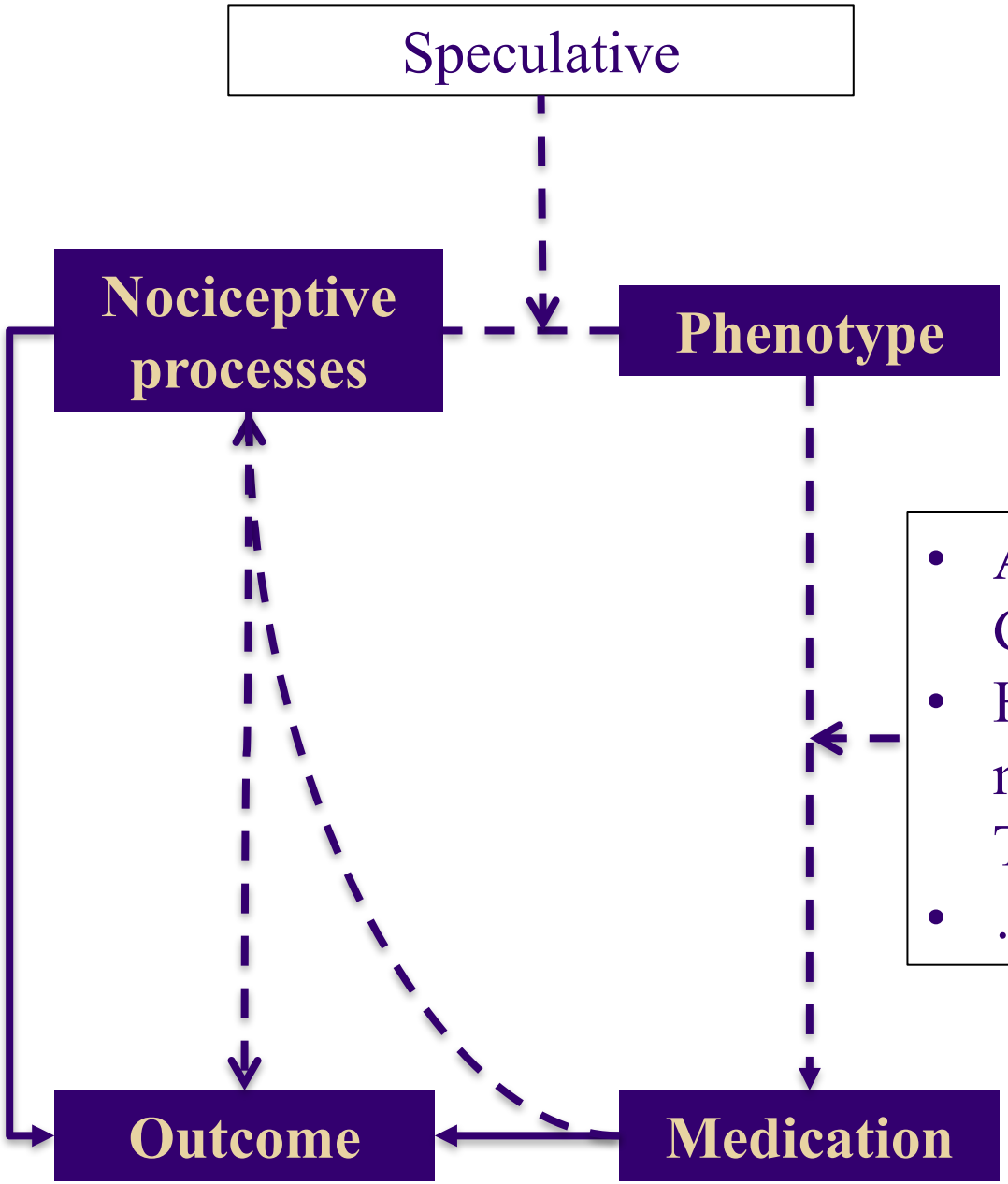
- All 3 clusters distributed across all 4 etiologies
- Some quantitative differences

What next?



Baron et at, Pain 2017

Open issues

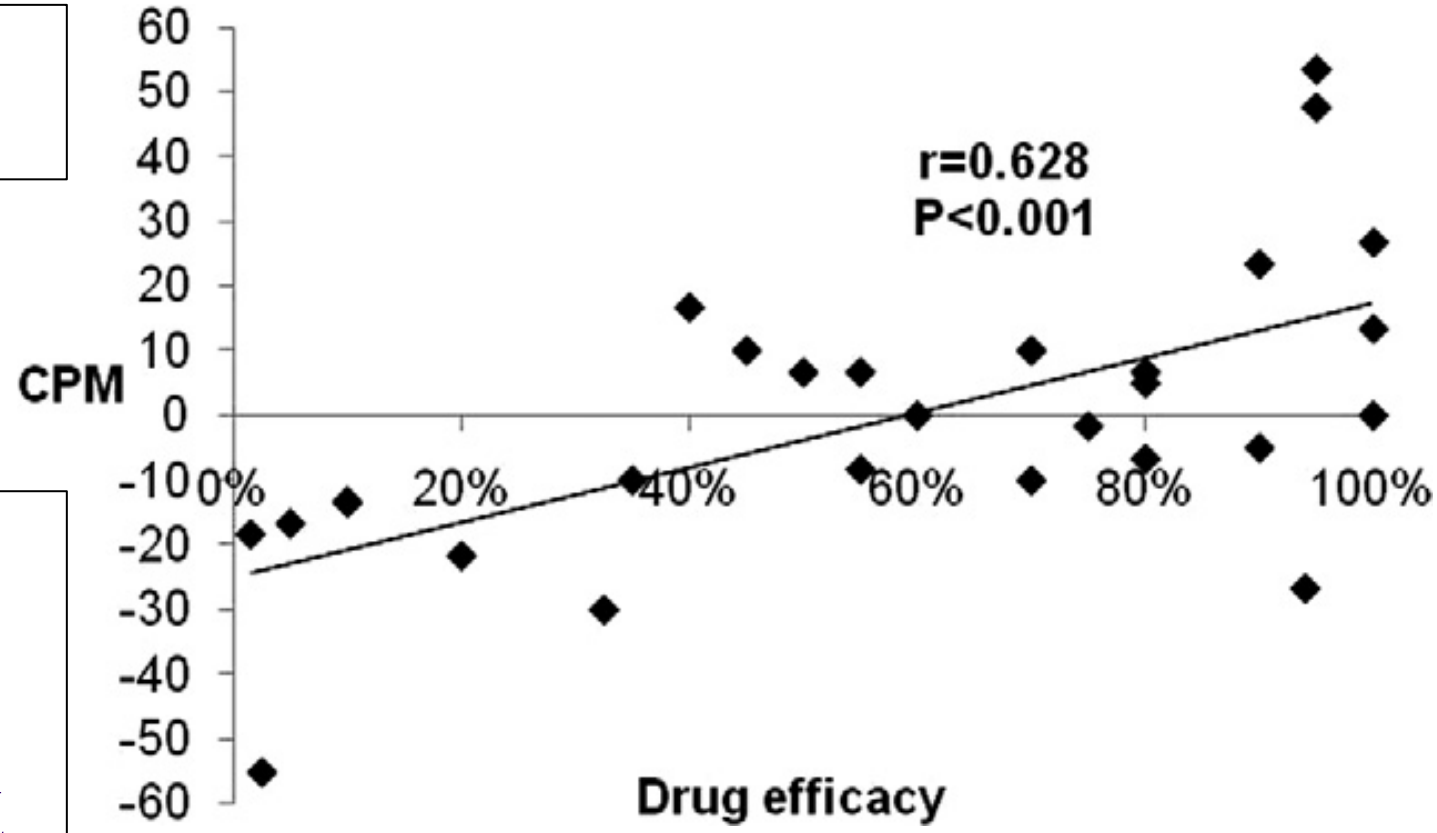


- Altered CPM → Antidepressants? GABA-agonists?
- Heat hyperalgesia / irritable nociceptor → Na-channel blockers? Topical capsaicin?
- …?

Alteration of endogenous modulation → **Efficacy of duloxetine in diabetic polyneuropathy**

- Placebo-controlled

- 30 patients
- No data on sensitivity-specificity-LR
- Other QST not predictive



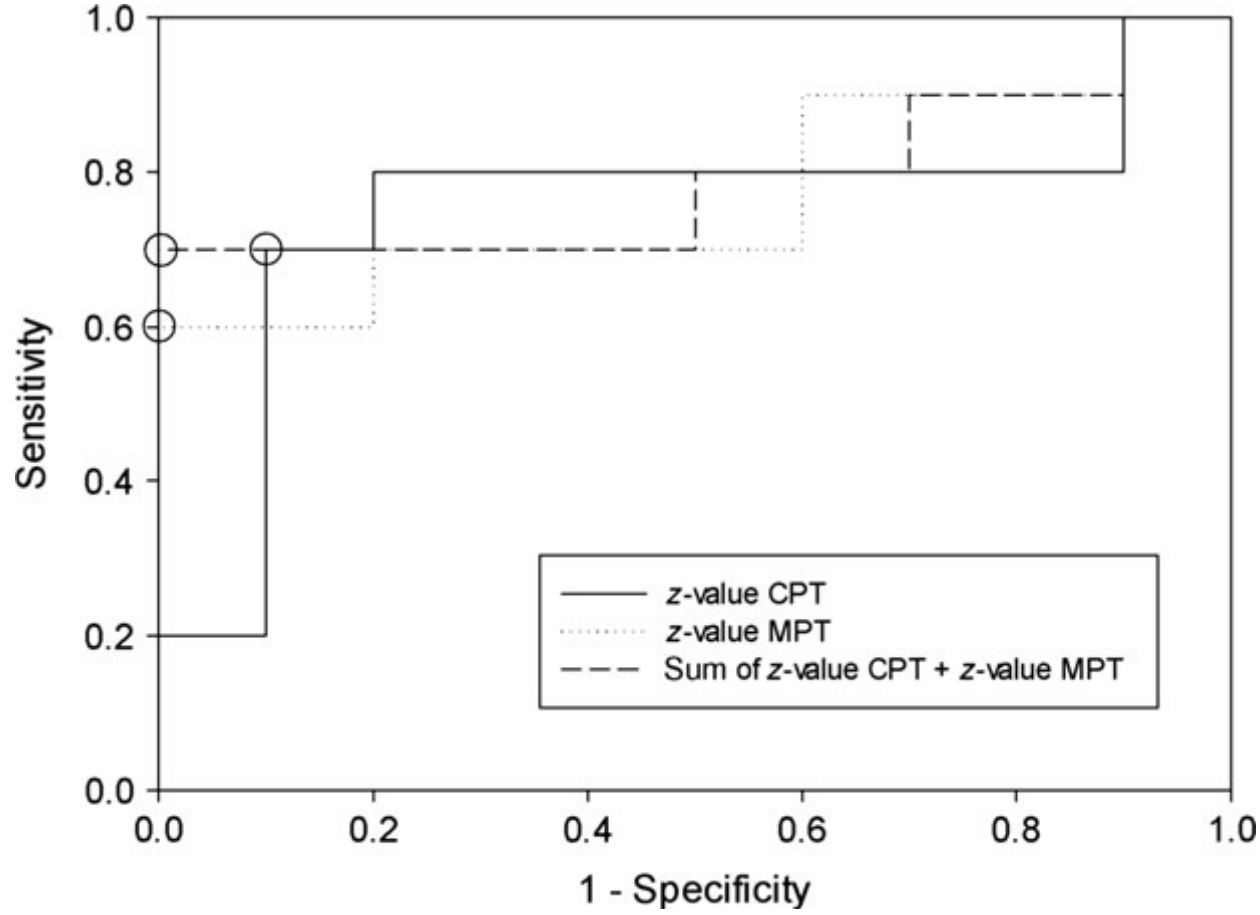
Yarnitsky et al, Pain 2012

QST
Multiple tests

↓

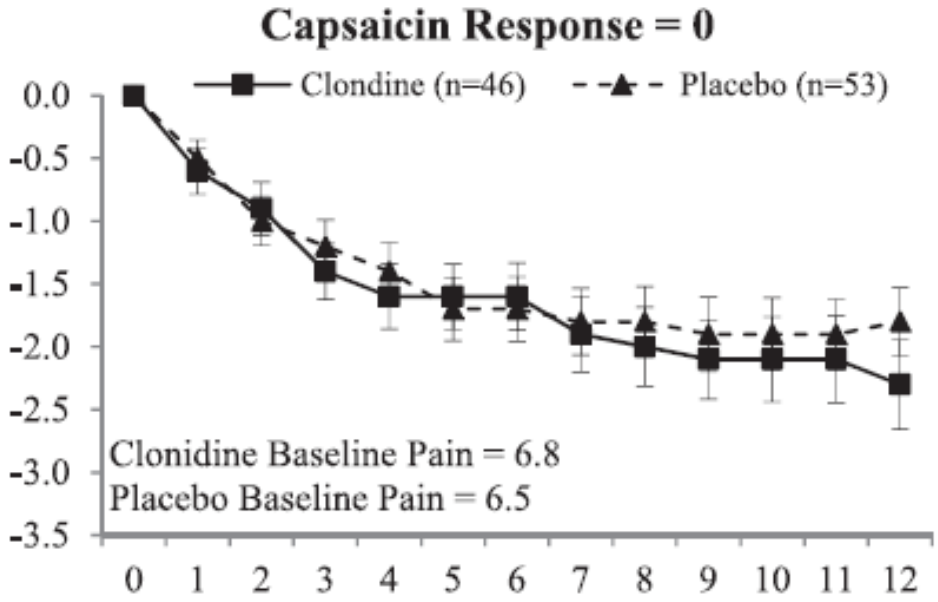
Efficacy of capsaicin patch 8% in peripheral NP

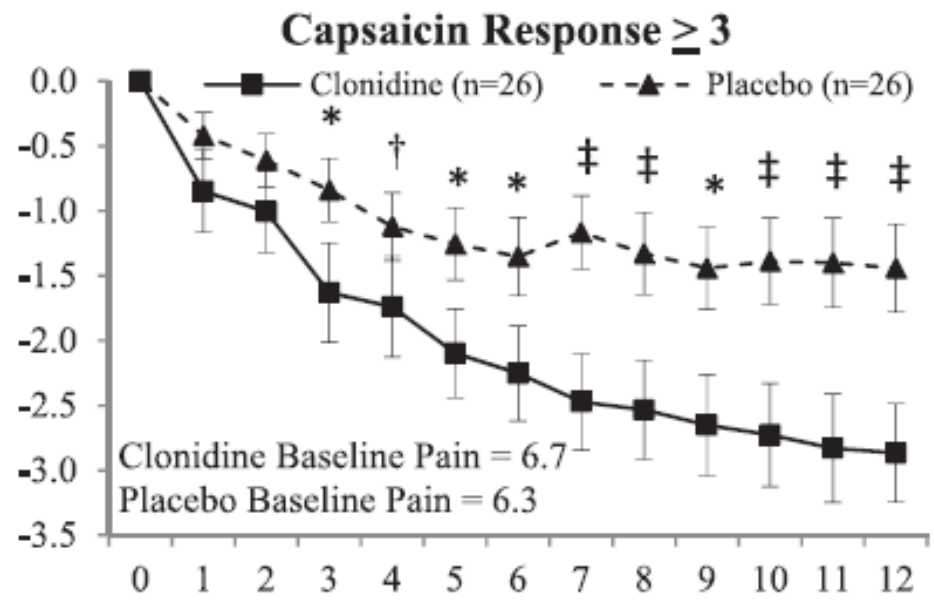
Mainka et al, EJP 2016



- Cold and pinprick hyperalgesia: prediction of responders with 100% specificity and 70% sensitivity
- Many analyses, 20 patients, no control group, not powered on sensitivity and specificity, likely large CI (no data)

Pain after 0.1% topical capsaicin (hyperactive nociceptor) → **Efficacy of topical clonidine in diabetic polyneuropathy**





- No data on sensitivity-specificity-LR
- Other QST not predictive

Campbell et al, Pain 2012

Mechanical and/or heat hyperalgesia (irritable nociceptor)

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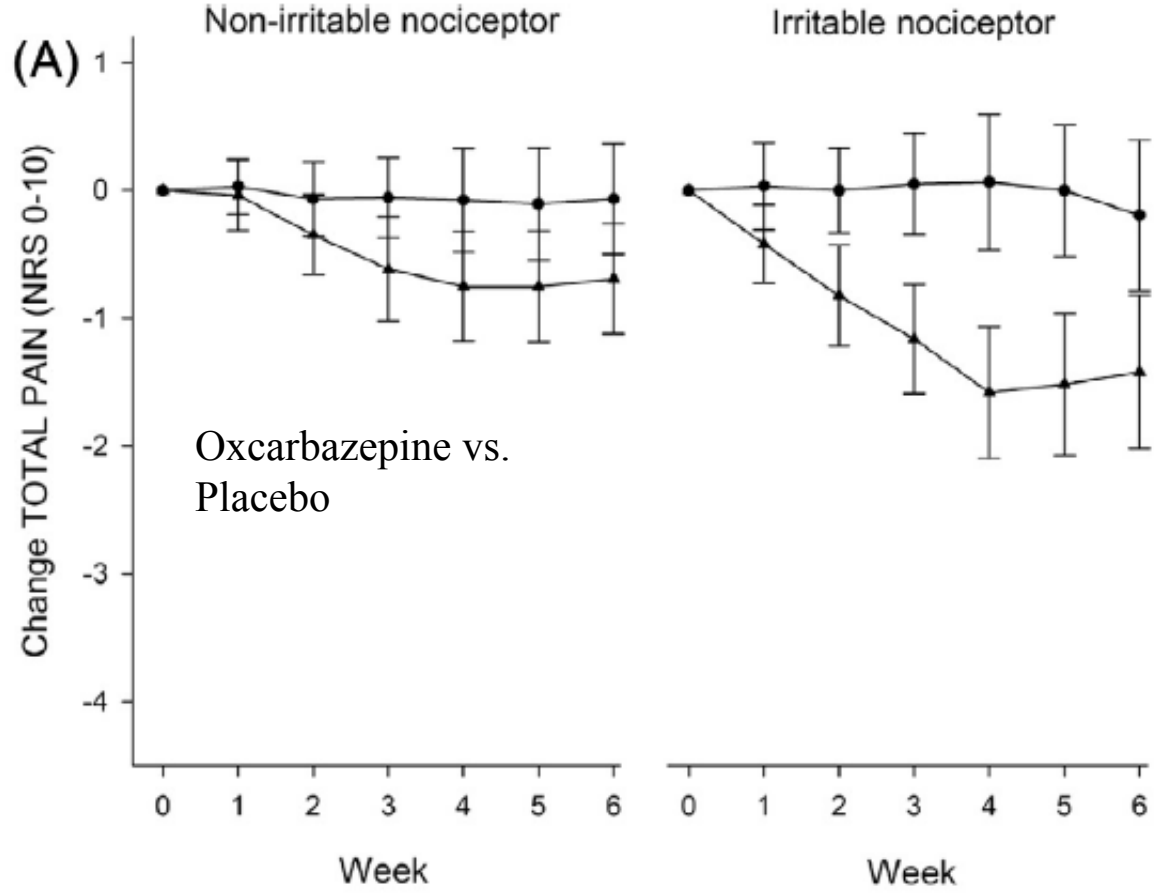
Efficacy of oral oxcarbazepine in neuropathic pain



NNT for 50% pain relief:

- 3.9 (95% CI 2.3-12) irritable nociceptor
- 13 (95% CI 5.3-1) non-irritable nociceptor

Demant et al Pain 2014

Phenotyping for neuropathic pain

- Retrospective, from 7 placebo-controlled clinical trials
- Similar design and outcome recordings
- 4 antidepressants and 4 anticonvulsants
- Imipramine and pregabalin: better effect in patients with gain of sensory function
- Pregabalin: better effect with preserved large fiber function
- No phenotype-specific effects for venlafaxine, escitalopram, oxcarbazepine, valproic acid, levetiracetam, or St. John's wort

- **Overall, doubtful usefulness of phenotyping**

Holbech et al, Pain 2014

Predicting medication effect in low back pain

- 50 patients with chronic low back pain
- Imipramine
- Oxycodone
- Clobazam
- Placebo-controlled, crossover
- 2h observation after administration
- Extensive QST protocol for potential predictors
- Pharmacogenetics

Siegenthaler et al, BMC Pharmacol Toxicol 2015
(Study protocol)

Results

Oxycodone and clobazam

> Superior to placebo for pain relief

> No QST predicted the analgesic effect

Imipramine

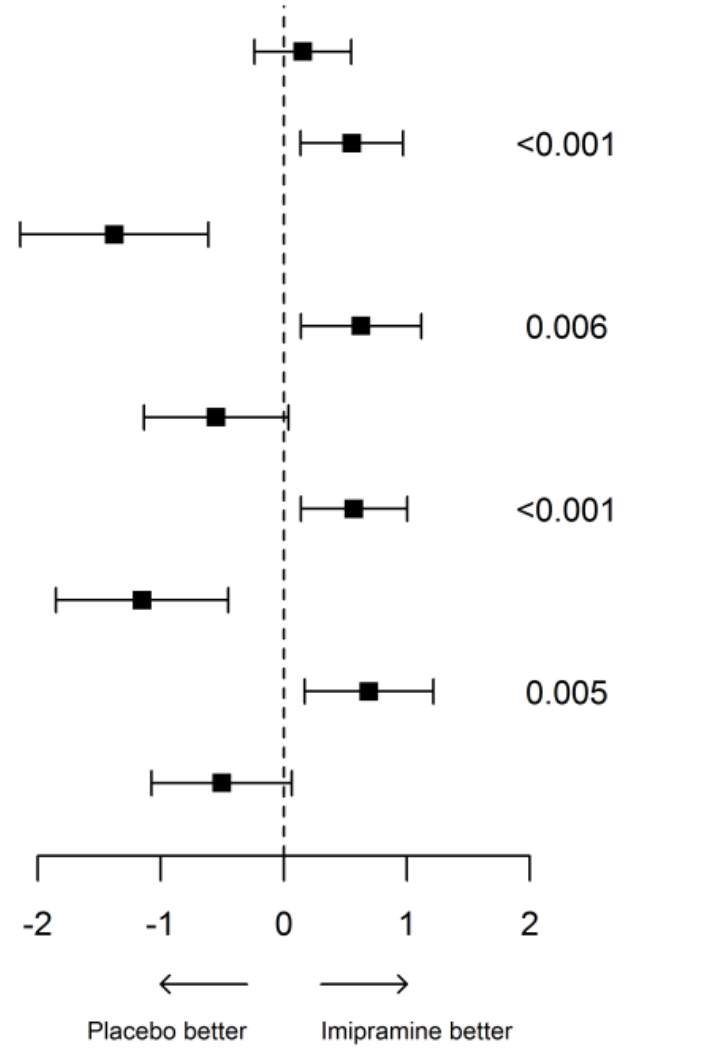
> Overall not better than placebo

> Better than placebo in patients with heat or cold hyperalgesia

Schliessbach et al, unpublished

Imipramine

		n	treatment effect	p value for interaction
Overall		98	0.15 (-0.24 to 0.55)	
Baseline HPTT (arm) at limit	no	70	0.55 (0.13 to 0.97)	<0.001
	yes	21	-1.38 (-2.14 to -0.61)	
Baseline HPTT (leg) at limit	no	58	0.63 (0.14 to 1.12)	0.006
	yes	39	-0.55 (-1.14 to 0.04)	
Baseline CPDT (arm) at limit	no	65	0.57 (0.14 to 1)	<0.001
	yes	26	-1.15 (-1.85 to -0.45)	
Baseline CPDT (leg) at limit	no	52	0.69 (0.17 to 1.22)	0.005
	yes	45	-0.51 (-1.08 to 0.06)	



Schliessbach et al, unpublished

TAKE-HOME MESSAGES (I)

- Pharmacological treatment targeted to nociceptive processes has the potential to improve pain management
- Phenotyping patients to identify nociceptive processes at individual level is challenging
- Recent research is encouraging – we see some signal
- The most consistent finding is a better response to medications in patients with thermal hyperalgesia

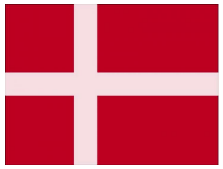
TAKE-HOME MESSAGES (II)

Limitations:

- **Inconsistent findings regarding predictive value of QST**
- **No QST found to be clearly predictive across studies**
- **Sensitivity, specificity and likelihood ratio either not analyzed or shown to be low**

- **Targeting nociceptive processes at individual level is still a research aim, not yet an achievement**
- **Search for more mechanistic biomarkers is a relevant aim of future research**

Acknowledgments



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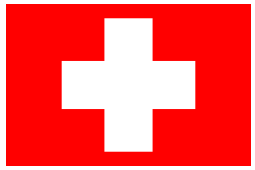

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