Pharmacologic Therapy for Neuropathic Pain: Current and Emerging Therapies

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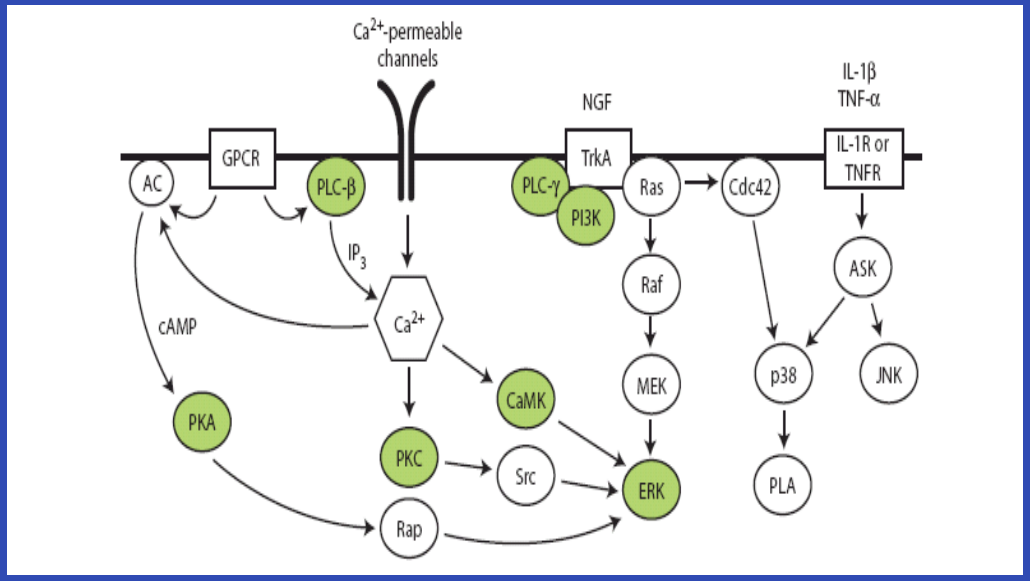
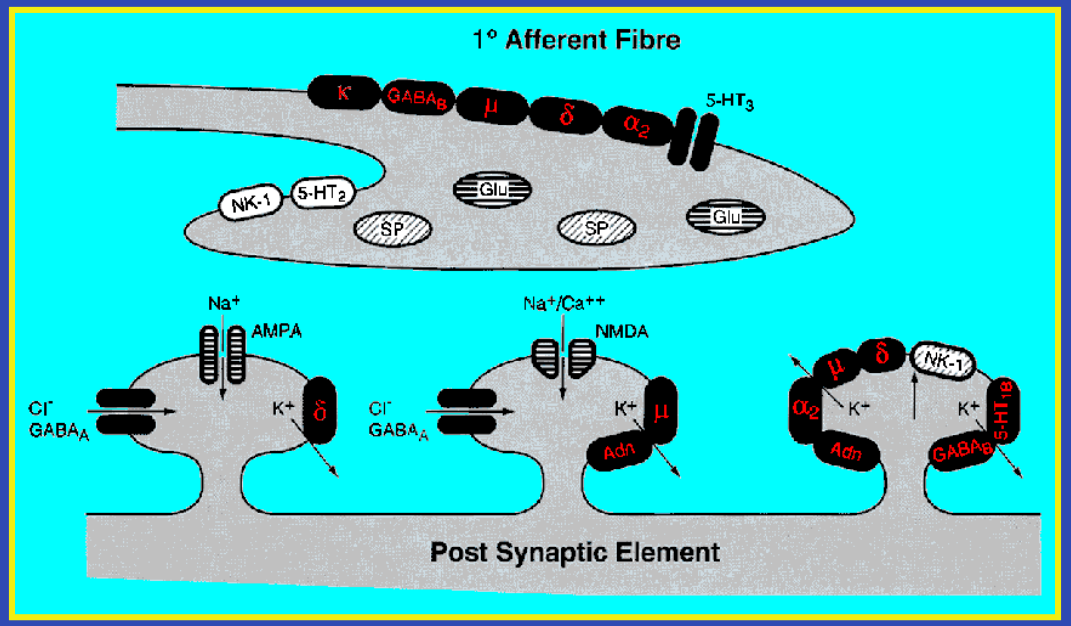
Peripheral Targets

- Sodium channels
  - $NaV_{1.8}$
- Calcium channels
- TRPV1 receptors
- Neuropeptide receptors
- Peripheral $\alpha 2$ adrenoceptors
- Neurotrophic factors
  - TrkA
- Adenosine receptors
  - P2X3



Central Targets

- Sodium and Calcium Channels
- Opiate receptors
- Serotonin/norepi pathways
- NMDA receptor/modulation of glutamate release
- α2 adrenoceptors



FDA-Approved Treatments for Neuropathic Pain

- Capsaicin Patch 8%
  - Postherpetic neuralgia
- Carbamazepine
  - Trigeminal neuralgia
- Duloxetine
  - Peripheral diabetic neuropathy
  - Fibromyalgia
- Gabapentin (1 short acting and 2 extended release)
  - Postherpetic neuralgia
- Lidocaine Patch 5%
  - Postherpetic neuralgia
- Milnacipran
  - Fibromyalgia
- Nucynta ER
  - Peripheral diabetic neuropathy
- Pregabalin
  - Peripheral diabetic neuropathy
  - Postherpetic neuralgia
  - Fibromyalgia
  - Spinal Cord Injury

Human Models for Neuropathic Pain

- Diabetic neuropathy (DN) and postherpetic neuralgia (PHN) are the most prevalent neuropathic pain disorders
- Majority of randomized controlled trials data are in PHN/DN
- PHN has been the most commonly used model for treating neuropathic pain in clinical trials

Targeting Sodium Channels

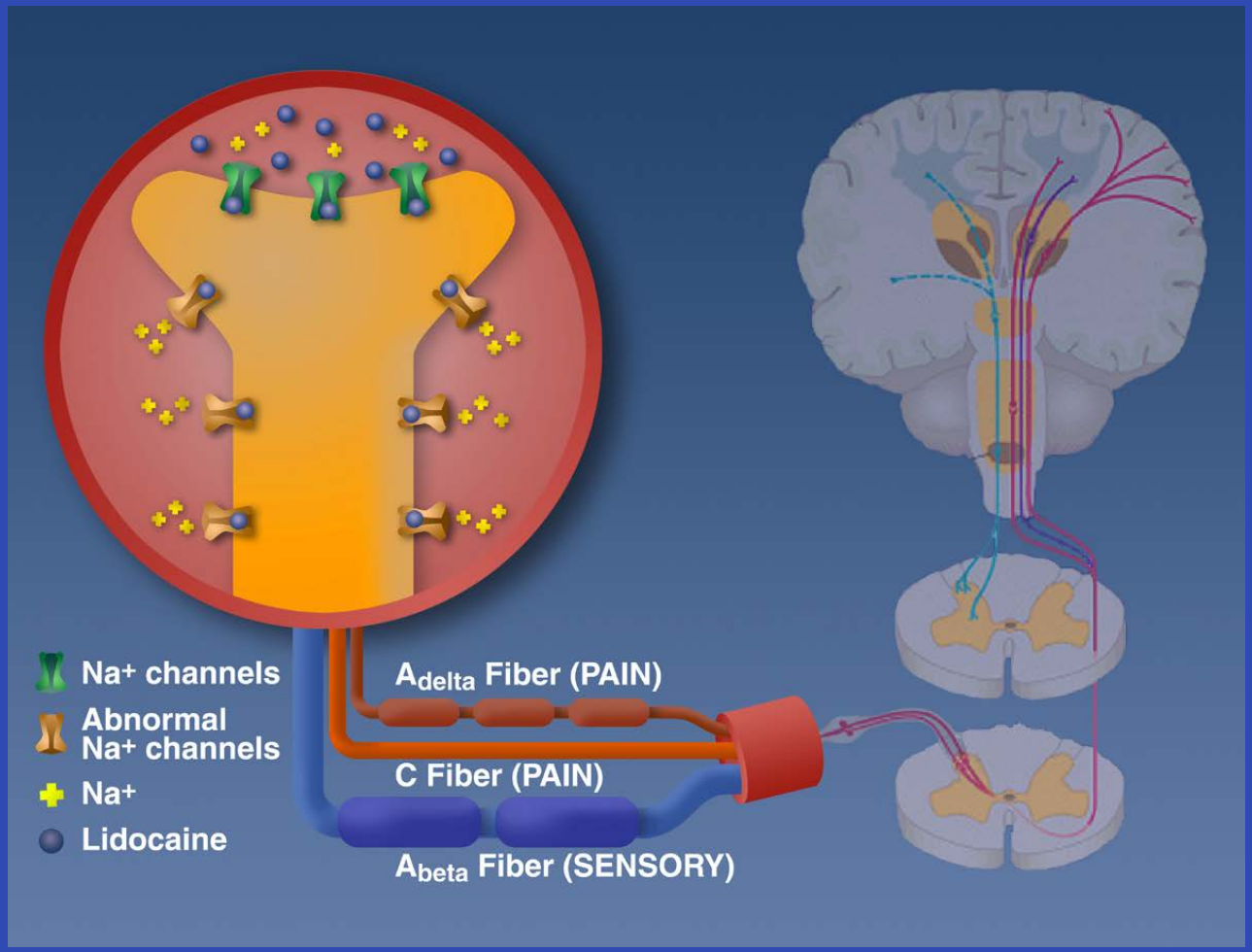
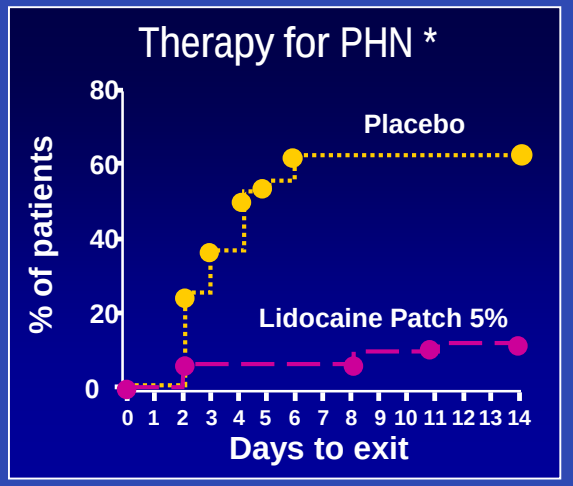


Image provided by the National Institute of Pain Control

Lidocaine Patch 5% Works Through Sodium Channels

- Lidocaine 5% in pliable patch
- Up to 3 patches applied once daily directly over painful site
  - –12 h on, 12 h off (FDA-approved label)
  - –recently published data indicate 4 patches (18–24 h) safe
- Efficacy demonstrated in 3 randomized controlled trials on postherpetic neuralgia
- Drug interactions and systemic side effects unlikely
  - –most common side effect: application-site sensitivity
- Clinically insignificant serum lidocaine levels
- Mechanical barrier decreases allodynia



*Galer et al. *Pain.* 1999;80:533–538.

Lidocaine: 2007 Cochrane Review

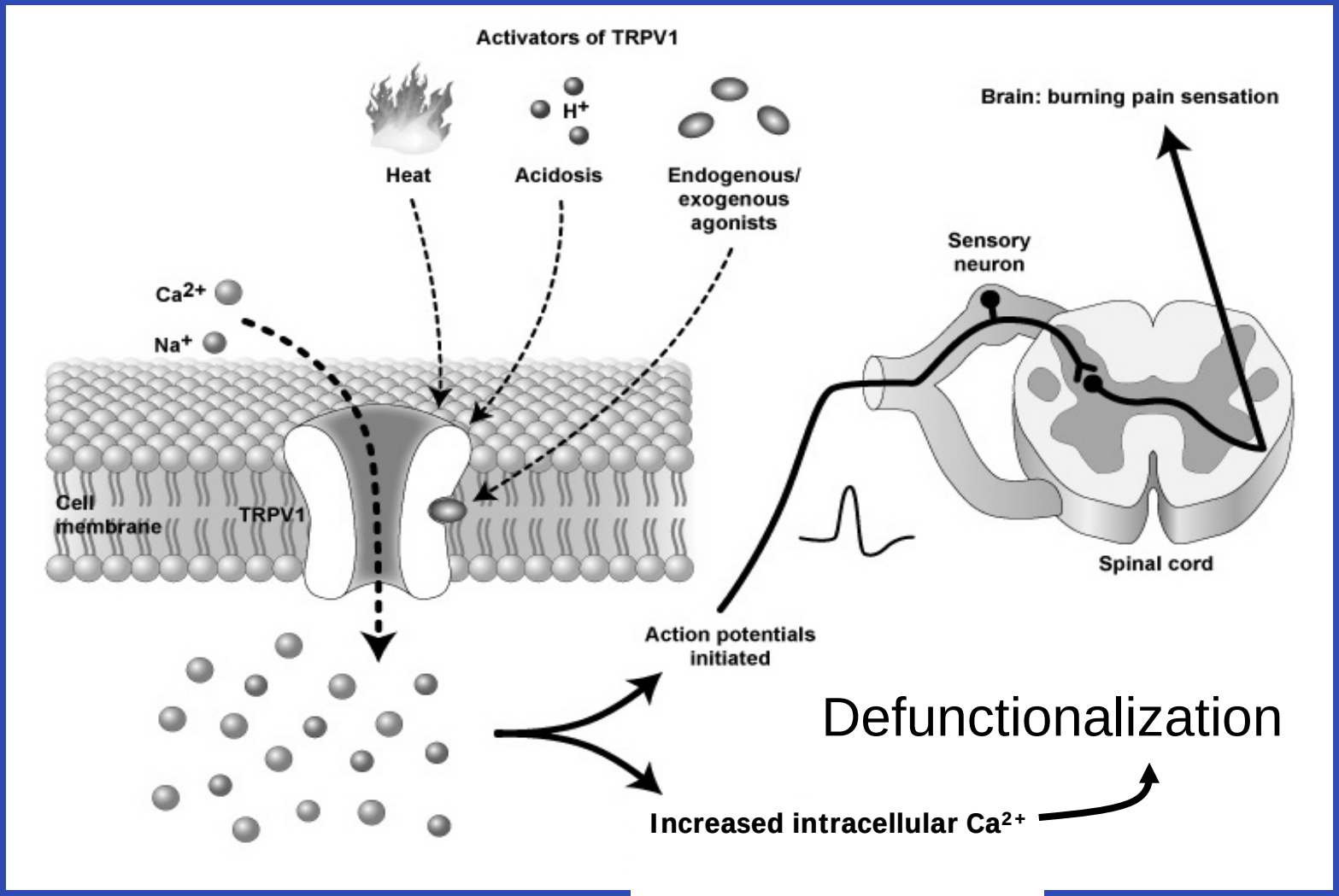
- Three randomized or quasi-randomized trials assessing topical applications of lidocaine were identified
  - 182 lidocaine-treated patients
  - 132 control patients
- In a meta-analysis of 2 of the studies with similar outcome measures, topical lidocaine conferred significantly greater pain relief than placebo (*P*=0.003)
- Incidence of adverse skin reactions was similar between lidocaine and placebo

Khaliq et al. The Cochrane Database of Systematic Reviews 2007 Issue 2, DOI10.1002/14651858.CD004846.pub2.

Selective sodium channel blockers

- Nav 1.7, Nav 1.8, Nav 1.3
- Non-specific sodium channel blockers (lidocaine, mexilitine, lamotrigine) have not been very successful clinically due to side effects
- Selective blockers better tolerated (not located in heart tissue or CNS)
- Central versus peripheral effects unclear
- Nav 1.8 blocker to currently in Phase II trials in small fiber peripheral neuropathy
- Intrathecal agent in development

Targeting TRPV1 Receptors: Capsaicin



Rice and Hill. Annu Rev Med 2006;57:535-551.

Localized Effect on Nociceptors

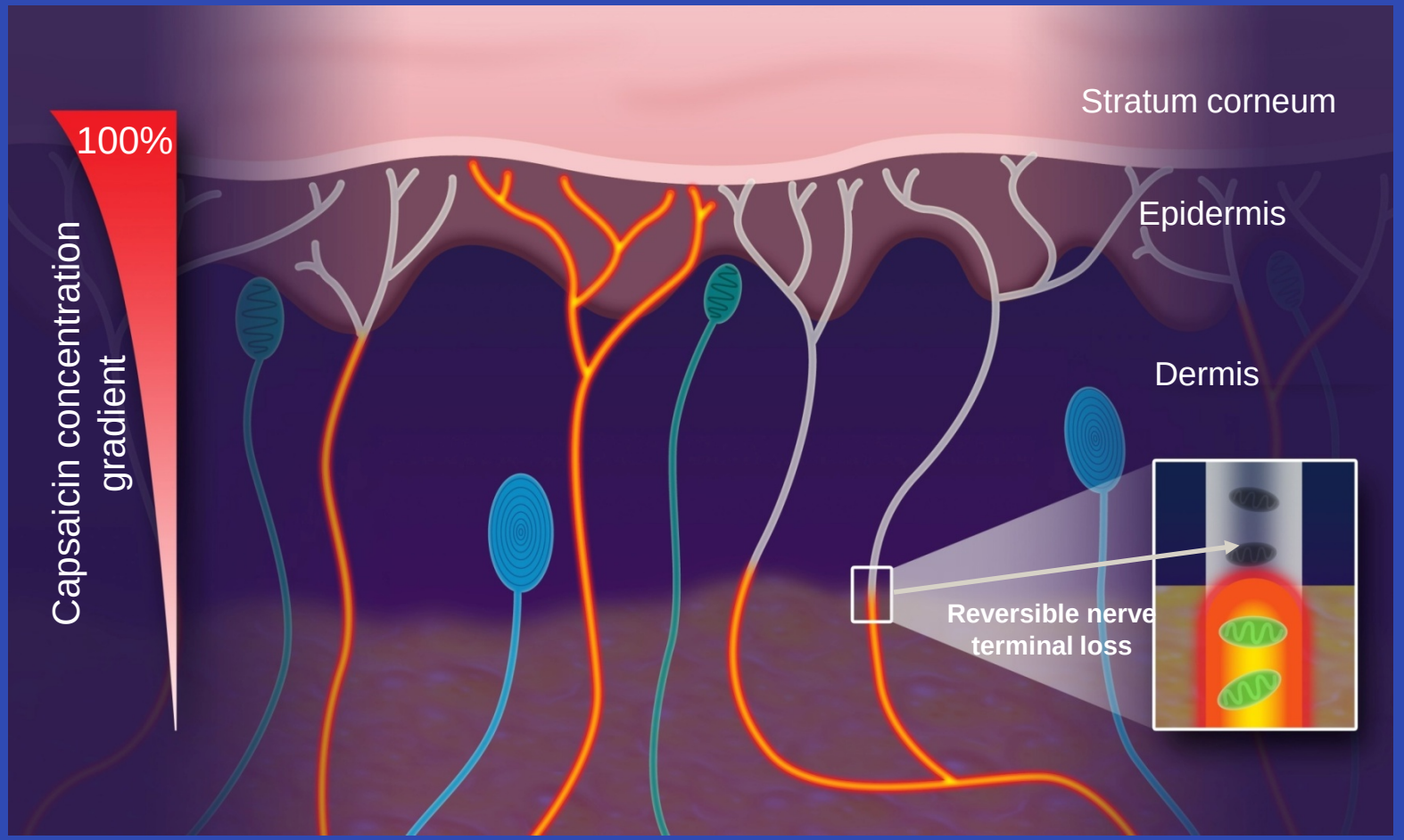
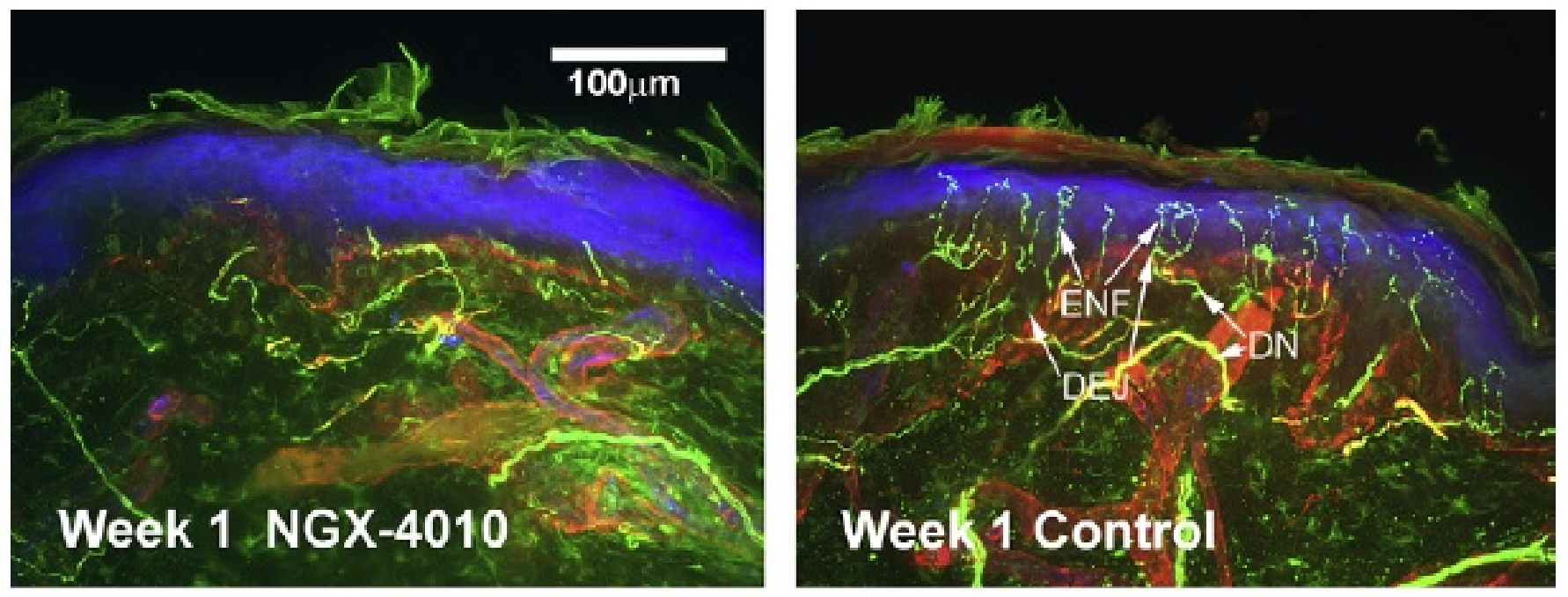


Image provided by NeurogesX, Inc.

Capsaicin-Induced Nociceptor (ENF) Reduction



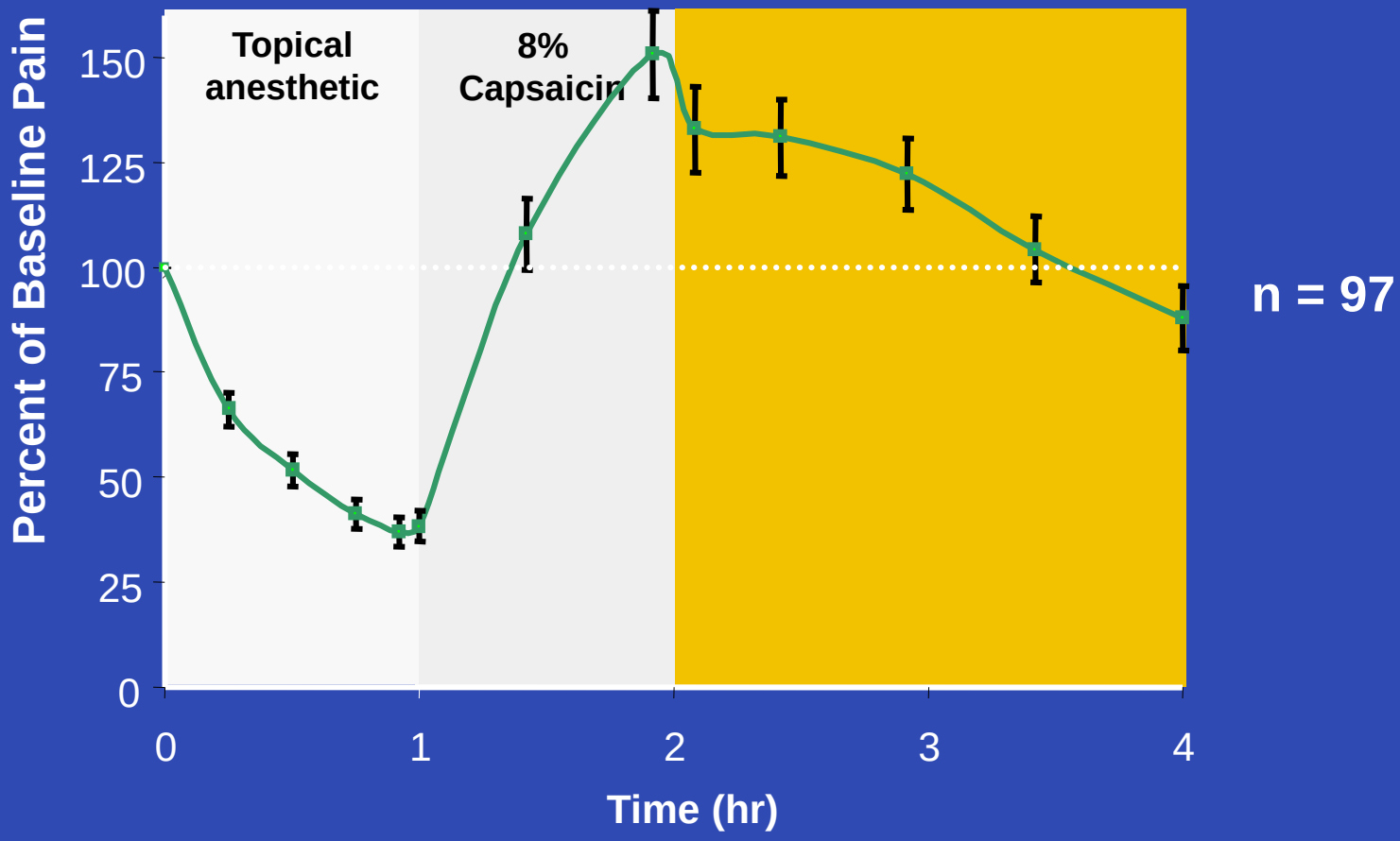
Kennedy, et al. *J Pain*, 2010 April 16

8% Capsaicin Patch

Identify	Anesthetize	Apply	Remove	Cleanse
The treatment area is identified and marked and washed with soap and water. The patch is cut to match the area	Application of topical anesthetic, which remains in place until skin is anesthetized; then remove and wash	Previously cut patch is applied; patch remains in place for 1 hour	Patch is removed gently by rolling inward	Treatment area is cleansed with proprietary Cleansing Gel which is left on for at least 1 minute

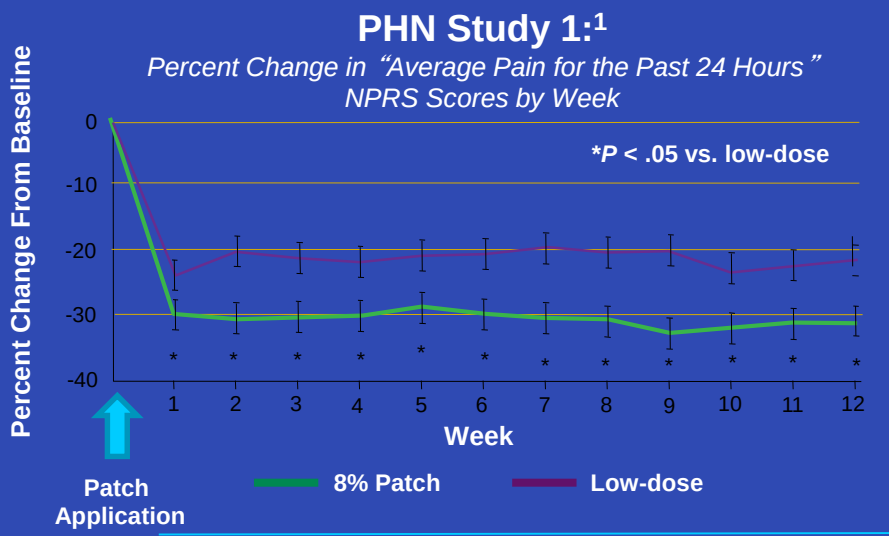
- The recommended dose of 8% Capsaicin patch is a single, 60-minute application of up to 4 patches applied to the painful skin area
- Treatment with 8% Capsaicin patch may be repeated every 3 months or as warranted by the return of pain (but not more frequently than every 3 months)

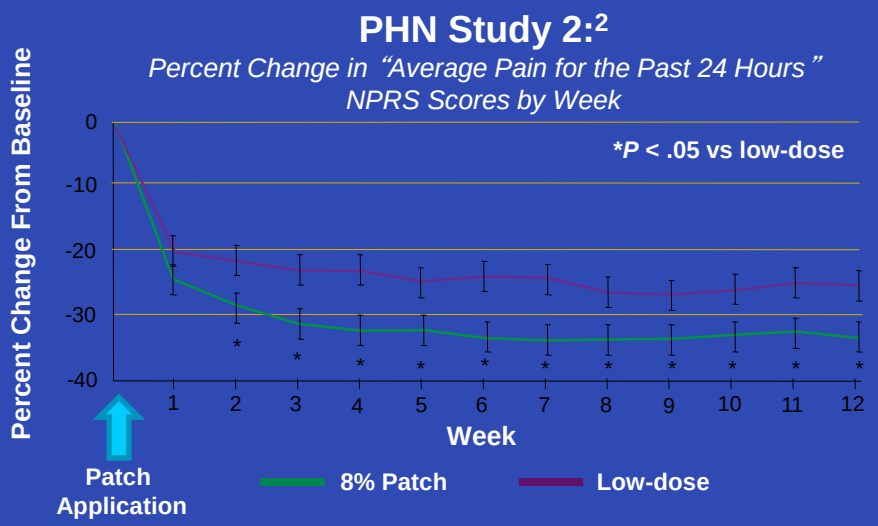
PHN: Treatment-Associated Pain



Data on file, Neurgesx, Inc., 2010

Percent Change in Pain in 12-Week Trials





Percent Patients Achieving ≥30% Reduction on NPRS Scores from Baseline (Average Pain Past 24 Hours) to Weeks 2-12

Study 1[1]		Study 2[2]	
8% Patch	Control	8% Patch	Control
44%	33%	47%	35%
p=0.0487		p=0.0212	

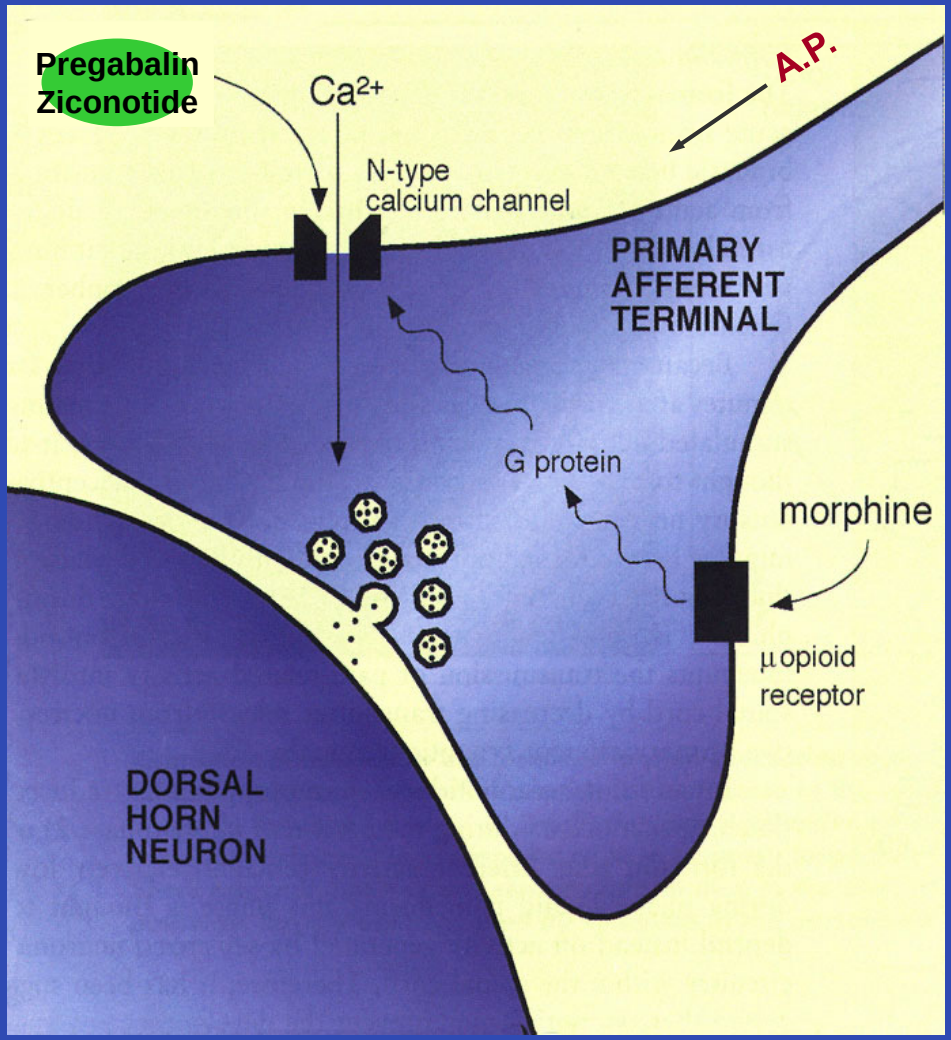
1. Backonja, *Lancet Neurol*, 2008;7:1106-1112
2. Data on file

Resiniferatoxin

- Intrathecal administration for cancer pain
- Activates the vanilloid receptors in dorsal horn leading to C-fiber death
- Cancer Canine studies impressive
- Currently in phase I Cancer Pain Study

Targeting Calcium Channels

- Activation of channels increases intracellular calcium.
  - Mediates neurotransmitter release
  - Triggers cascades that alter membrane excitability and initiate protein transcription
- Of multiple types of calcium channels, the high-voltage-activated N-type and the low-voltage-activated T-type voltage-sensitive channels show most promise with respect to antihyperalgesic and antiallodynic effects.
- Auxiliary subunits of calcium channels may play an important role:
  - Agents that bind to $\alpha 2\delta$ auxiliary subunit reduce membrane excitability without blocking channel function.



Yaksh. J Pain 2006;7 (1 suppl 1):S13-S30.

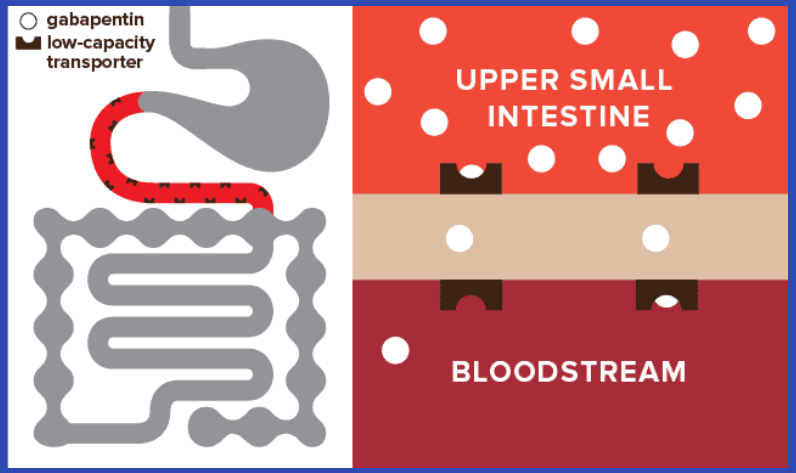
Gabapentin in Neuropathic Pain Disorders

- FDA approved for postherpetic neuralgia
- Anticonvulsant
- Limited intestinal absorption due to saturation of the transport mechanism in the upper intestines
- Usually well tolerated; serious adverse effects rare
  - dizziness and sedation can occur
- No significant drug interactions
- Peak time: 2 to 3 h; elimination half-life: 5 to 7 h
- Usual dosage range for neuropathic pain up to 3,600 mg/d (tid–qid)*

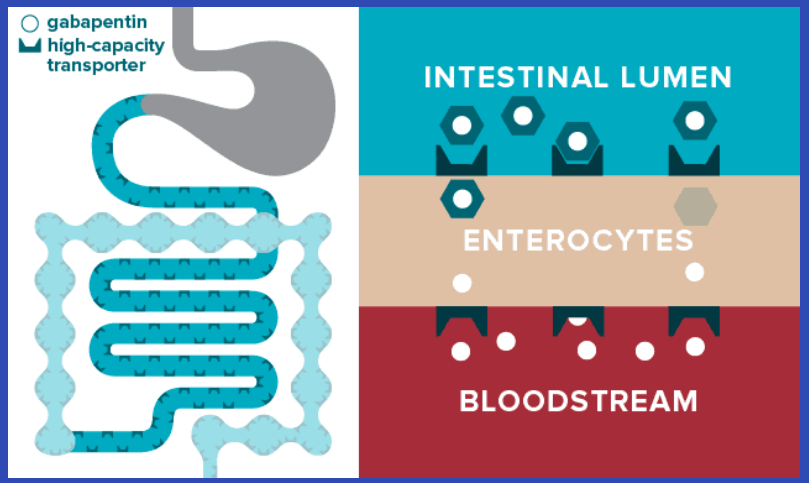
*Not approved by FDA for this use.

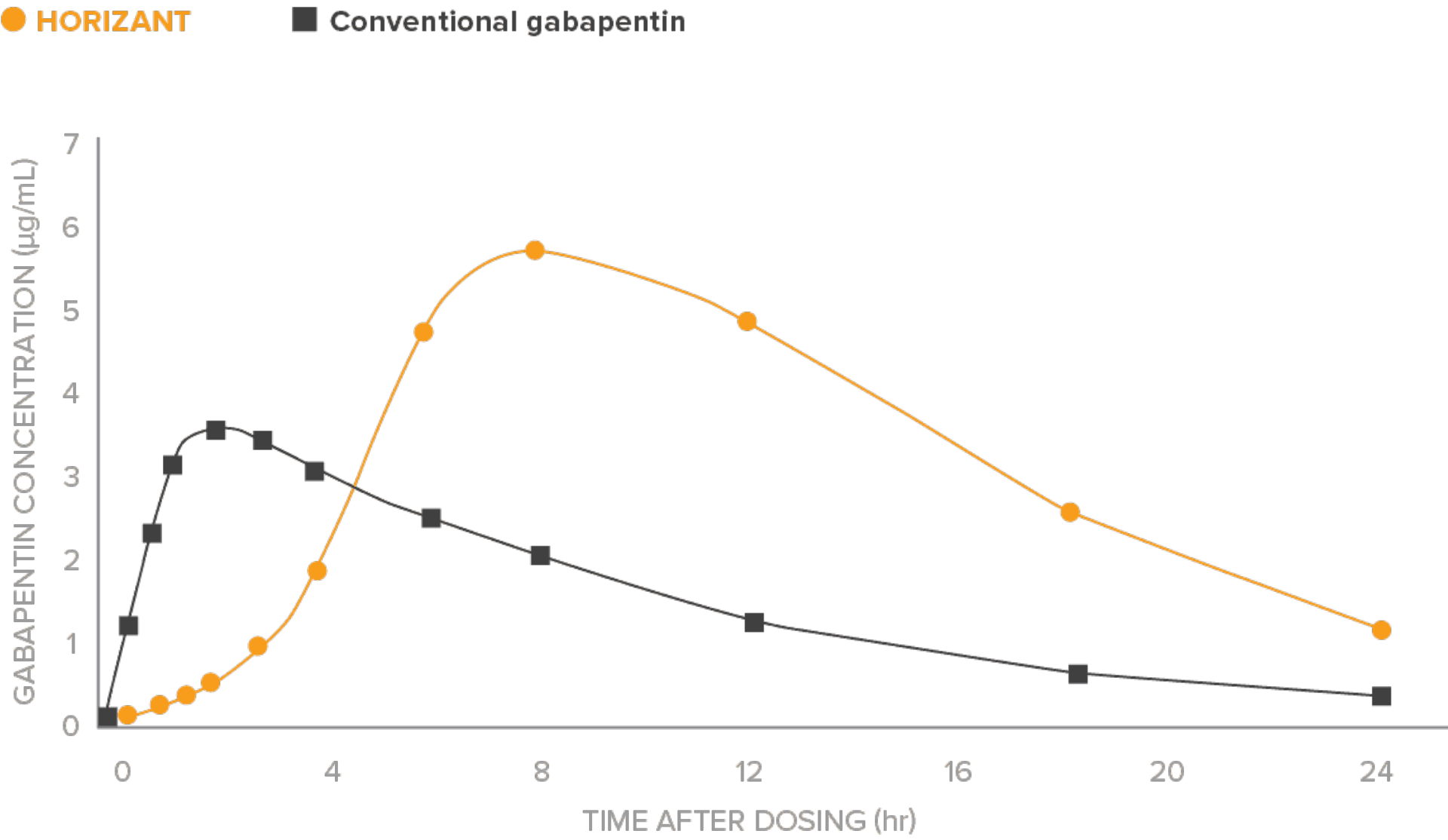
Increasing Gabapentin Absorption

Conventional gabapentin absorbed by a low capacity transporter in the upper intestinesthat becomes saturated as the dose increases



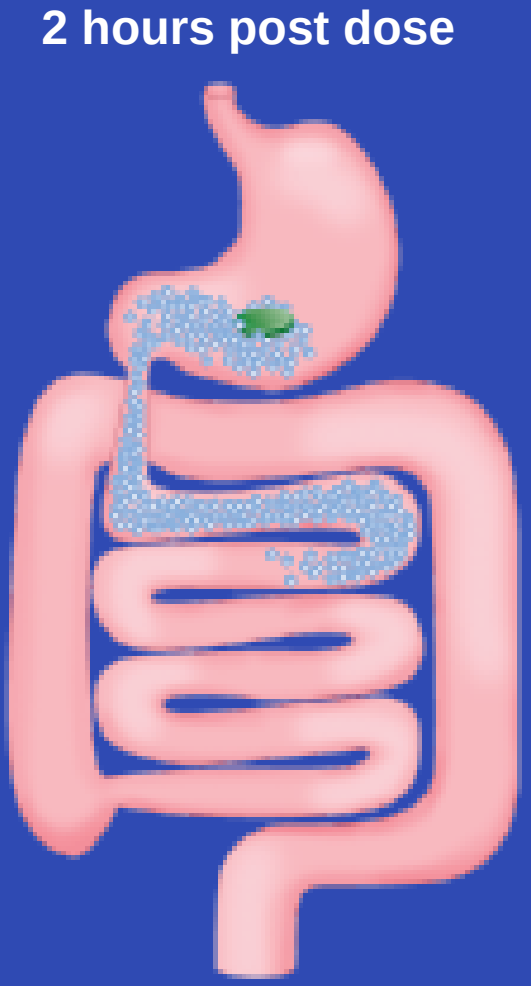
An attachment to the gabapentin molecule enables transport through enterocytes throughout the small intestines.




HORIZANT
Conventional gabapentin
GABAPENTIN CONCENTRATION (µg/mL)
0
1
2
3
4
5
6
7
0
4
8
12
16
20
24
TIME AFTER DOSING (hr)

Gastric Retentive Gabapentin

- Single bedtime dose
- Bolus dose in first few hours followed by slow release over 24 hours
- Better tolerated than gabapentin



Phase II/III Clinical Trial with Intrathecal Gabapentin

- Double-blind, placebo-controlled RCT of three doses of gabapentin versus placebo
- Open label extension: patients on drug as monotherapy for over 2 years
- Last patient implanted November 2009; data lock December 2009
- No effect of any dose as compared to placebo

Gabapentin Acts Within the Locus Coeruleus to Alleviate Neuropathic Pain

- Spinal nerve (L5-6) ligated rats received GPN and other drugs in the LC or by systemic routes
- Mechanism of action: GPN acts directly in the brainstem via a glutamate-dependent mechanism to stimulate descending inhibition
  - The descending inhibition produces anti-hypersensitivity after peripheral nerve injury

    - Hayashida, Obata, Nakajima, Eisenach, Anesthesiology, 2008: 109: 1077-84

Pregabalin Overview

- FDA approved for postherpetic neuralgia, painful diabetic peripheral neuropathy, spinal cord injury
- Phase II trials failed for peripheral nerve injury pain
- Modulates voltage-gated Ca^{+} channels through the $\alpha 2\delta$ subunit
- Robust efficacy confirmed in 6 positive trials
  - Reduction in pain within one week
  - High responder rates
- Favorable safety and tolerability profile
  - Most common adverse events: somnolence and dizzyness
- Linear pharmacokinetics, high bioavailability
  - Predictable consistent absorption

Mirogabalin

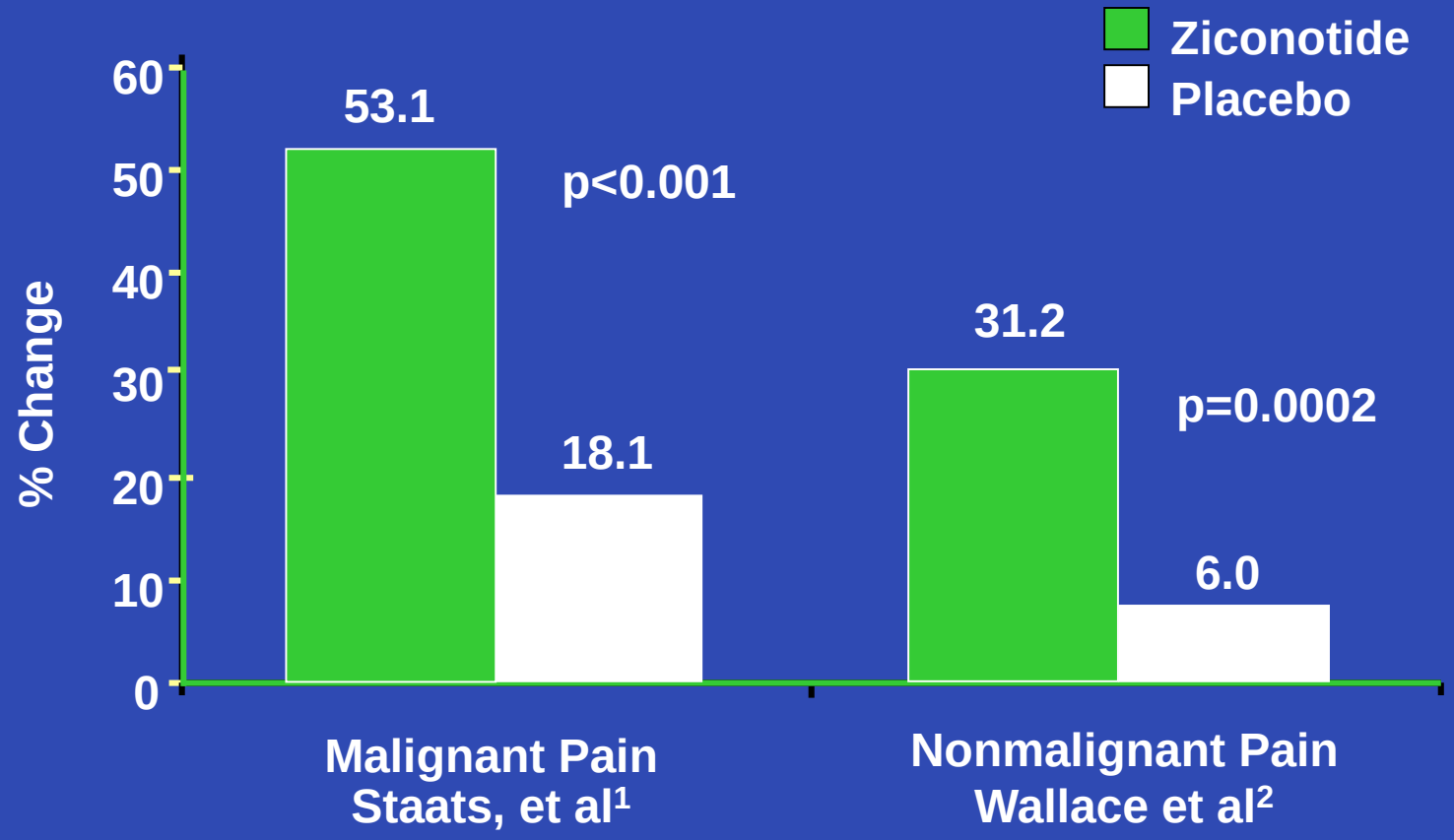
- N-type calcium channel modulator
- Specific to the α-2-delta type II subunit
- Less side effects that non-specific modulators (i.e. pregabalin)
- Less side effects may result in ability for higher doses and improved efficacy
- Recent study in DPN showed significant pain reductions at 15, 20, 30 mg doses vs placebo. Pregabalin 300 mg nonsignificant
  - Vinik et al. Diabetes Care, 2014

T-Type Calcium Channel Antagonists

- T-Type Ca calcium channels found on peripheral and central endings of primary afferent neurons
- Type 3.2 antagonism void of sedation and may be better tolerated
- Preclinical studies positive in capsaicin pain, arthritis and neuropathic pain
- Phase I healthy volunteer pain model negative as compared to pregabalin
- Mechanism may be through modulation at the thalamus (affective component)

Efficacy Results

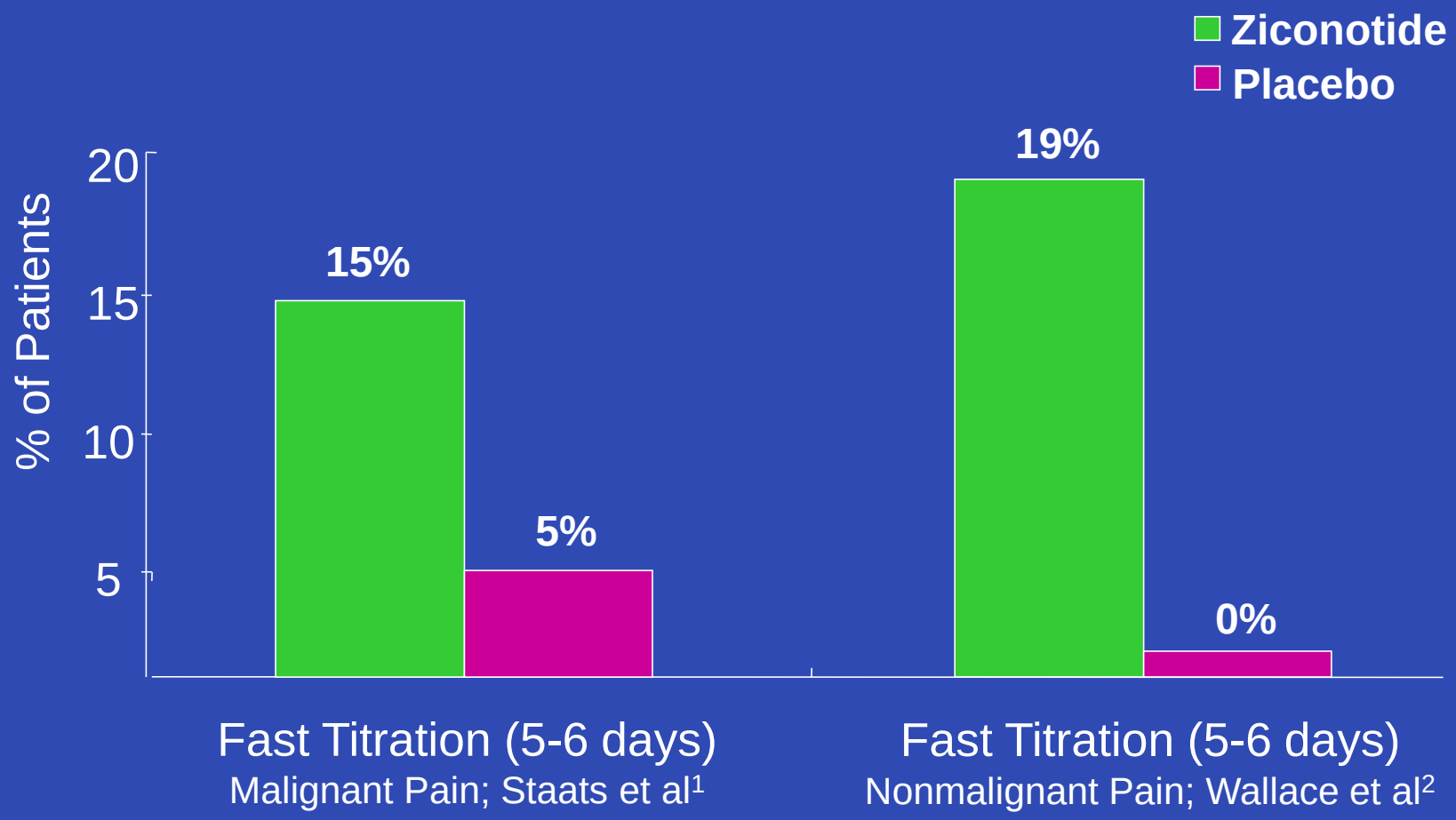
Intrathecal Ziconotide: Fast Titration



1. Staats P, et al. JAMA 2004;291(1):63-70. 2. Wallace M, et al. Neuromodulation 2006; 9(2):75-86.

Fast Titration Study

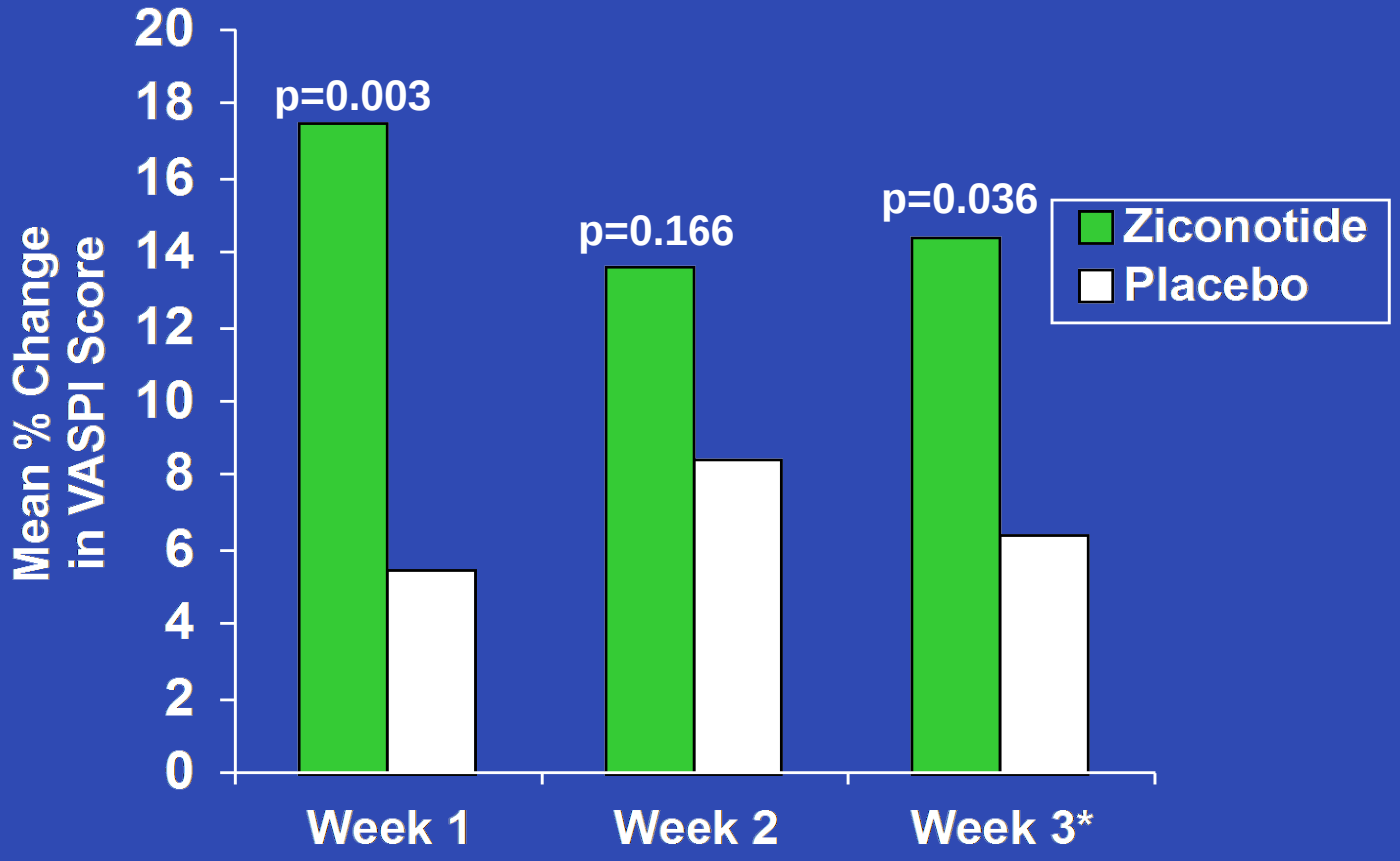
Discontinued for AEs



1. Staats P, et al. JAMA 2004;291(1):63-70. 2. Wallace M, et al. Neuromodulation 2006; 9(2):75-86.

Efficacy Results

Intrathecal Ziconotide: Slow Titration



VASPI improved from baseline to the end of Week 3 by a mean 14.7% in the ziconotide-treated group and 7.2% in the placebo group (p=0.036; two-sample t-test)
*Primary Efficacy Variable

Rauck et al. Journal of Pain and Symptom Management. 2006; 31(5): 393-406.

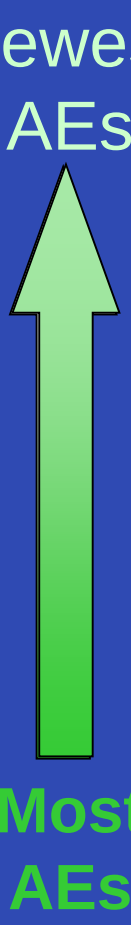
Antidepressants in Neuropathic Pain Disorders*

- Multiple mechanisms of action
- Randomized controlled trials and meta-analyses demonstrate benefit of tricyclic antidepressants (especially amitriptyline, nortriptyline, desipramine) for postherpetic neuralgia and diabetic neuropathy
- Selective serotonin reuptake inhibitors (SSRIs): inconsistent in diabetic neuropathy
- Onset of analgesia variable
  - analgesic effects independent of antidepressant activity
- Improvements in insomnia, anxiety, depression
- Desipramine and nortriptyline have fewer adverse effects

*Not approved by FDA for this use.

Tricyclic Antidepressants: Adverse Effects

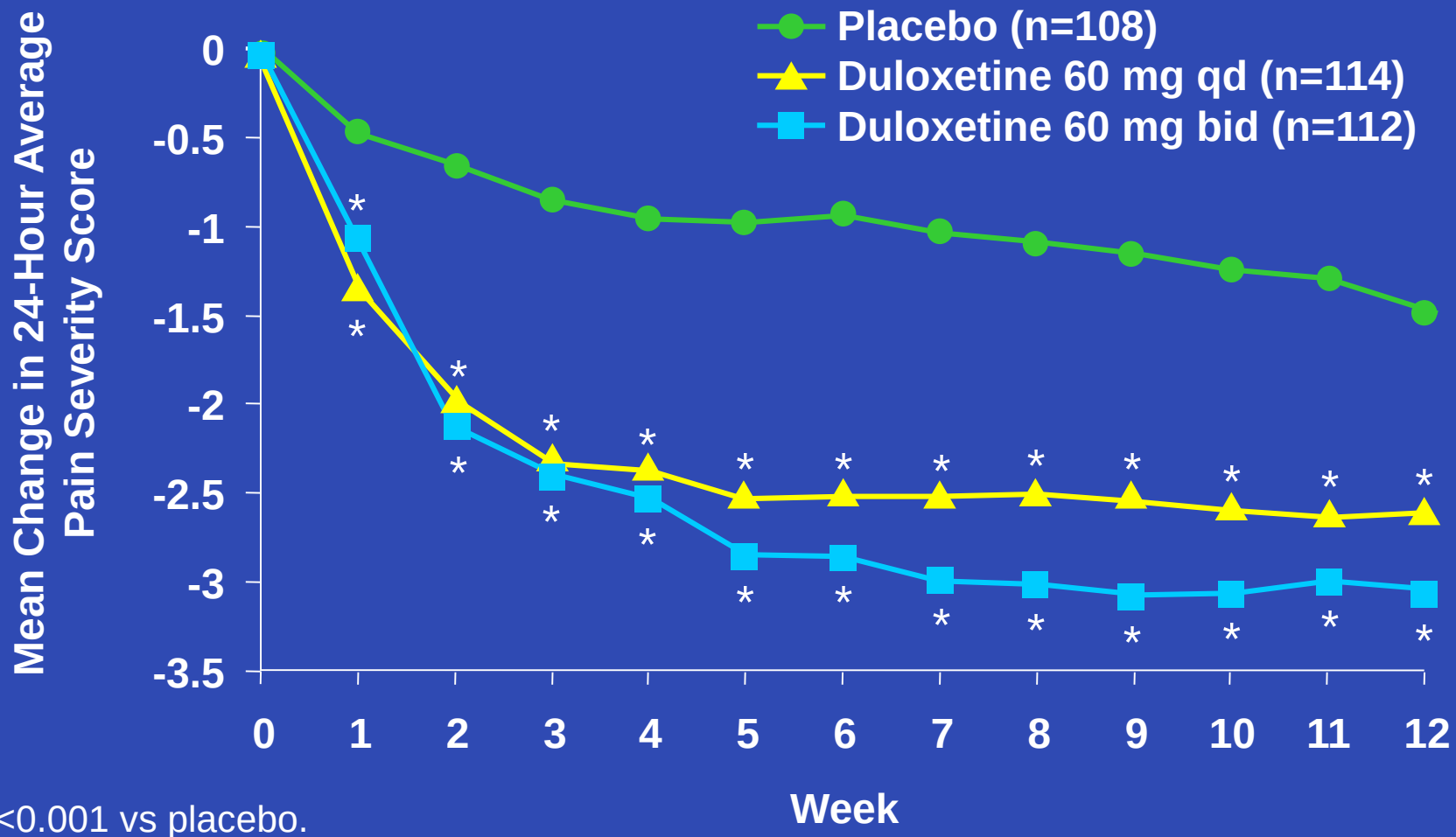
- Commonly reported AEs (generally anticholinergic):
  - blurred vision
  - cognitive changes
  - constipation
  - dry mouth
  - orthostatic hypotension
  - sedation
  - sexual dysfunction
  - tachycardia
  - urinary retention



- Desipramine
- Nortriptyline
- Imipramine
- Doxepin
- Amitriptyline

AEs = adverse effects.

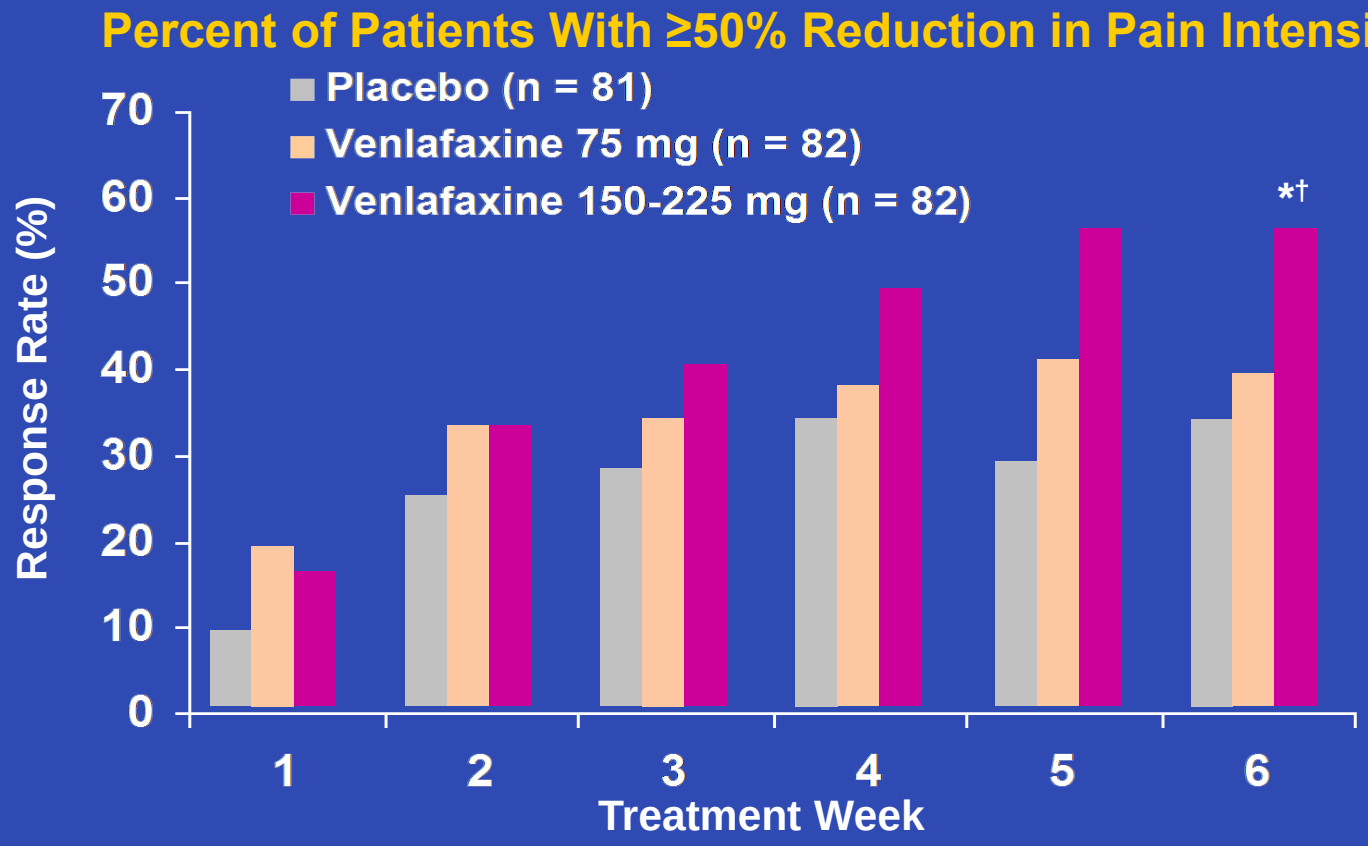
Duloxetine for Diabetic Neuropathic Pain



*P<0.001 vs placebo.

Wernicke J et al. *J Pain.* 2004;5(suppl 1):48.

Venlafaxine#: Efficacy in Diabetic Peripheral Neuropathy



 # not approved by the FDA for this use

*P < .01 venlafaxine extended release (ER) 150-225 mg vs placebo.

†P < .05 venlafaxine ER 150-225 mg vs venlafaxine ER 75 mg.

Adapted with permission from Rowbotham MC et al. *Pain.* 2004:110;697-706.

Nerve Growth Factor

- Neurotropin
- Upregulated in painful conditions
- Inhibition reverses pain in animal models
- Tanezumab and Fulranumab
  - Monoclonal Ab to NGF
  - Studies:
    - Tanezumab
      - Positive in OA, CLBP, Cancer
      - Negative in DPN, PHN, IC, Pancreatitis
      - Phase III trials in Cancer pain being conducted outside the US
    - Fulranumab
      - Negative in LBP and OA
  - Some abnormal peripheral sensations
  - Report of AVN (NSAID Dependent) leading to FDA hold that has now been lifted

Angiotensin II type 2 receptor antagonist (EMA-401)

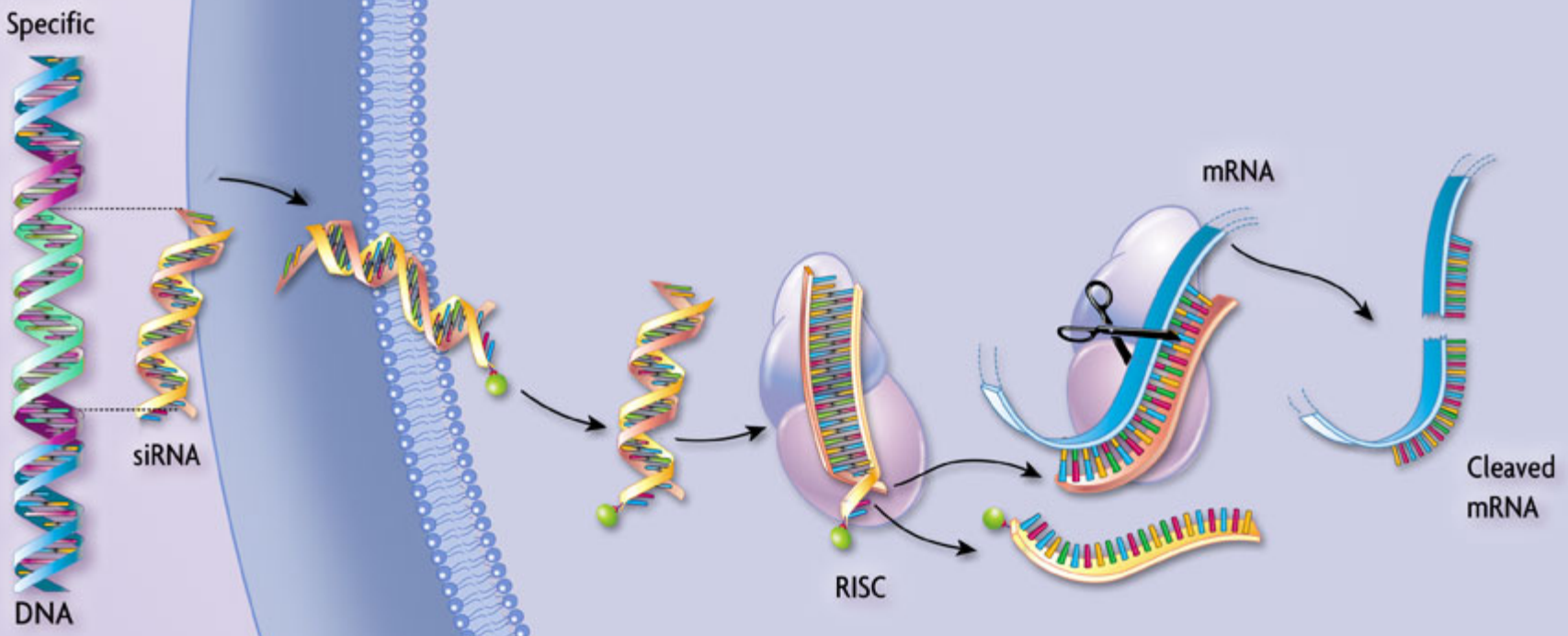
- AT2 receptors expressed on small fibers and DRG
- Angiotensin I $\xrightarrow{\text{ACE}}$ Angiotensin II
- Phase II study in PHN
  - N=183
  - Primary outcome positive: Pain Intensity
  - Secondary outcomes positive: Onset, 30 and 50% responder rate, McGill, PGI of change
  - Safe and well tolerated
- Phase III trial in PHN soon to start

Rice AS, Dworkin RH, McCarthy TD, et al. Lancet 2014; 383

Si RNA therapeutics

- Short interference RNA (S iRNA) designed to block gene expression mechanisms leading to disease manifestation
- Used to target a number of disease states
- Currently focusing on neuropathic pain

The RNAi Therapeutic Mechanism



A Short interfering RNA (siRNA) designed to correspond to gene target

B siRNA synthesized with drug-like properties: stability and conjugation for delivery

C Modified siRNAs penetrate the cell membrane and harness the RNAi mechanism for gene silencing

D Gene silencing achieves a therapeutic effect

Substance-P Saporin (SP-SAP)

- Intrathecal administration for cancer pain
- Selectively taken up by the C-fibers in the dorsal horn leading to C-fiber death
- Currently in phase I cancer study

Botulinum Toxin

- Has been used for spasticity, dystonia, and pain syndromes such as migraine
- Has not been systematically assessed in neuropathic pain although small studies and case reports suggest efficacy
- Is difficult to administer, particularly for large treatment areas
- Requires further study to define its place in the treatment of neuropathic pain

Wittekindt et al. Laryngoscope 2006;116:1168-1171.
Liu et al. Pain Med 2006;7:79-81.
Argoff. Clin J Pain 2002;18(6 suppl):S177-S181.

The End