The Coming Wave of Novel Analgesics:

Antibody Therapies, Sodium Channel Modulators, Abuse Deterrent Opioids, Neuromodulation Platforms

John Markman MD
Director Neuromedicine Pain Management Center I Translational Pain Research
Associate Professor, Department of Neurosurgery
University of Rochester School of Medicine

Prepared for:
Advances in Pain Management X1
9 April 2016

Rochester Neurosurgery Partners | University of Rochester Medical Center — Medicine of the Highest Order

Disclosures

Research:

Depomed, Pfizer, New York State

Consultant:

Allergan, Chromocell, Biogen, Egalet, Collegium, Immune Pharma, Nektar, Teva, Endo, Grunenthal, Pfizer, Depomed, Chem

Overview

The Growing Unmet Need for Novel Analgesics

Antibody Therapies Anti NGF MAB (#4) for OA, CLBP,
Visceral Pain Anti CGRP MAB (#4) for Migraine

Nav 1.7 Sodium Channel Modulators

High Dose Capsaicin (TRPV1) Abuse

Deterrent Opioids

Neuromodulation Platforms (High Frequency, Burst, DRG)

Unmet Need for Analgesics is Growing

- Diminished Acceptance of Risk:
  - Opioids
  - NSAIDS
- Reconsideration of Efficacy
  - Neuropathic Drugs
  - Surgery
  - Spinal Interventions

Only one class of therapies is consistently reported as having strengthening evidence

Non-Pharmacological Interventions

Research

Original Investigation

Effect of Mindfulness-Based Stress Reduction vs Cognitive Behavioral Therapy or Usual Care on Back Pain and Functional Limitations in Adults With Chronic Low Back Pain

A Randomized Clinical Trial

Daniel C. Cherkin, PhD; Karen J. Sherman, PhD; Benjamin H. Balderson, PhD; Andrea J. Cook, PhD; Melissa L. Anderson, MS; Rene J. Hawkes, BS; Kelly E. Hansen, BS; Judith A. Turner, PhD

Cherkin *JAMA* 2016

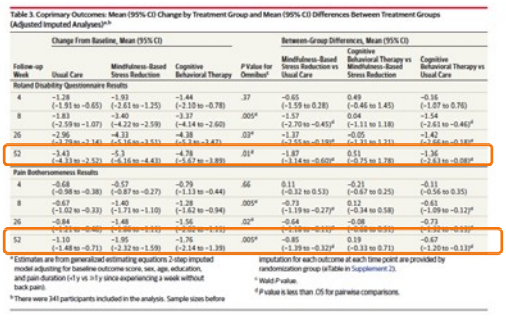


Table 3. Coprimary Outcomes: Mean (95% CI) Change by Treatment Group and Mean (95% CI) Differences Between Treatment Groups (Adjusted Imputed Analyses)[a,b]

	Change From Baseline, Mean (95% CI)				Between-Group Differences, Mean (95% CI)		
Follow-up Week	Usual Care	Mindfulness-Based Stress Reduction	Cognitive Behavioral Therapy	*P* Value for Omnibus[c]	Mindfulness-Based Stress Reduction vs Usual Care	Cognitive Behavioral Therapy vs Mindfulness-Based Stress Reduction	Cognitive Behavioral Therapy vs Usual Care
Roland Disability Questionnaire Results							
4	−1.28 (−1.91 to −0.65)	−1.93 (−2.61 to −1.25)	−1.44 (−2.10 to −0.78)	.37	−0.65 (−1.59 to 0.28)	0.49 (−0.46 to 1.45)	−0.16 (−1.07 to 0.76)
8	−1.83 (−2.59 to −1.07)	−3.40 (−4.22 to −2.59)	−3.37 (−4.14 to −2.60)	.005[d]	−1.57 (−2.70 to −0.45)[d]	0.04 (−1.11 to 1.18)	−1.54 (−2.61 to −0.46)[d]
26	−2.96 (−3.78 to −2.14)	−4.33 (−5.16 to −3.51)	−4.38 (−5.23 to −3.47)	.03[d]	−1.37 (−2.54 to −0.19)[d]	−0.05 (−1.31 to 1.21)	−1.42 (−2.64 to −0.18)[d]
52	−3.43 (−4.33 to −2.52)	−5.3 (−6.16 to −4.43)	−4.78 (−5.67 to −3.89)	.01[d]	−1.87 (−3.14 to −0.60)[d]	0.51 (−0.75 to 1.78)	−1.36 (−2.63 to −0.08)[d]
Pain Bothersomeness Results							
4	−0.68 (−0.98 to −0.38)	−0.57 (−0.87 to −0.27)	−0.79 (−1.13 to −0.44)	.66	0.11 (−0.32 to 0.53)	−0.21 (−0.67 to 0.25)	−0.11 (−0.56 to 0.35)
8	−0.67 (−1.02 to −0.33)	−1.40 (−1.71 to −1.10)	−1.28 (−1.62 to −0.94)	.005[d]	−0.73 (−1.19 to −0.27)[d]	0.12 (−0.34 to 0.58)	−0.61 (−1.09 to −0.12)[d]
26	−0.84 (−1.20 to −0.48)	−1.48 (−1.80 to −1.15)	−1.56 (−1.92 to −1.21)	.02[d]	−0.64 (−1.16 to −0.13)[d]	−0.08 (−0.60 to 0.51)	−0.73 (−1.25 to −0.21)[d]
52	−1.10 (−1.48 to −0.71)	−1.95 (−2.32 to −1.59)	−1.76 (−2.14 to −1.39)	.005[d]	−0.85 (−1.39 to −0.32)[d]	0.19 (−0.33 to 0.71)	−0.67 (−1.20 to −0.13)[d]

[a] Estimates are from generalized estimating equations 2-step imputed model adjusting for baseline outcome score, sex, age, education, and pain duration (<1 y vs ≥1 y since experiencing a week without back pain).

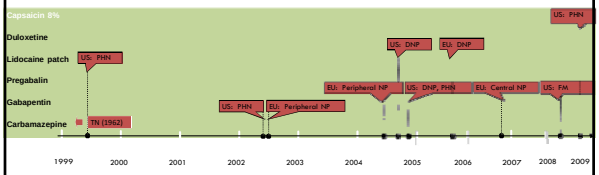
[b] There were 341 participants included in the analysis. Sample sizes before imputation for each outcome at each time point are provided by randomization group (eTable in Supplement 2).

[c] Wald *P* value.

[d] *P* value is less than .05 for pairwise comparisons.

Cherkin *JAMA* 2016

A lull in the development of non-opioid analgesics for chronic neuropathic pain?



Novel Therapies / Initial Target Indications

- Anti NGF- OA knee, CLBP, IC
- Anti CGRP Ab- migraine
- Nav 1.7 – Trigeminal Neuralgia (and possibly SFN/Radicular Pain)
- ADF Opioids - chronic (and now acute) pain
- High Dose Capsaicin- PHN (and peripheral neuropathic pain)

Considerations

- If antibodies are large molecules that do not cross the blood brain barrier how can these formulations be efficacious for chronic pain syndromes so profoundly modulated in the CNS?
- If the nociceptive pathways are polysynaptic and widely distributed throughout the neuraxis, why would a highly specific drug be more likely to have analgesic benefit than an agent interacting with multiple cell types, channels, and neurotransmitter systems?
- Will an abuse deterrent formulation that limits a relatively rarely used route of abuse and misuse have a substantial impact on the public health epidemic of opioid abuse?

Considerations *co.*

- Do novel routes of delivery of NSAIDs have equivalent analgesic benefit and reduced GI/cardiac toxicity relative to the oral route?
- How does the analgesic benefit of novel modes of spinal cord stimulation (high frequency, burst paradigm) and targets (dorsal root ganglion) compare to conventional spinal cord stimulation?

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Lessons from congenital insensitivity to pain HSAN IV and V

- HSAN conditions may highlight the key role NGF plays in the development and survival of primary nociceptors
- NGF function changes after development from survival in the infant to sensitization in the adult
- Question: does "developmental" HSAN predict effects of intermittent NGF/TrkA blockade in the adult?

The NGF Story

- Survival factor for sensory and sympathetic neurons in early development
- More recently, recognized to play a role in the genesis of pain and hyperalgesia
- Increased NGF in injured/inflamed tissues
- Activates trk A (tyrosine kinase) on nociceptive neurons—triggers/potentiates pain signaling through "multiple" mechanisms

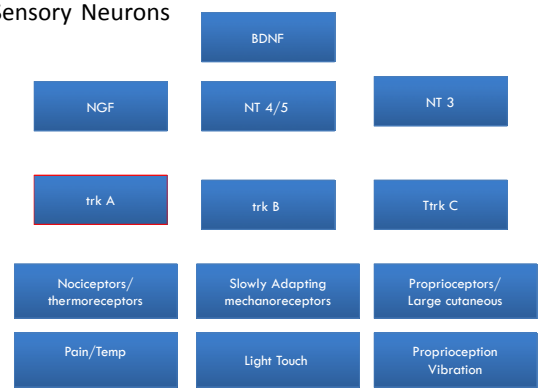
Evidence Linking NGF and Pain

- NGF levels are upregulated in injury, inflammation, and chronic pain states
  - OA, prostatitis, cystitis
- Administration of NGF provokes pain and hyperalgesia
  - Sq NGF produces allodynia for ~3 wks in healthy volunteers/ generalized muscle pain
- Congenital Insensitivity to Pain w anhidrosis
  - AR disorder from null mutation of gene encoding for trk A

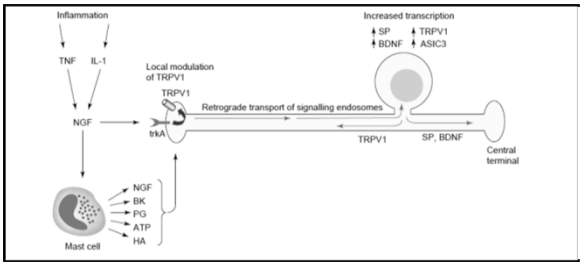
Therapeutic Strategies

- NGF Capture
- Block NGF binding to trkA
- Inhibit trk A signaling

Neurotrophin Family and Their Receptors on Sensory Neurons

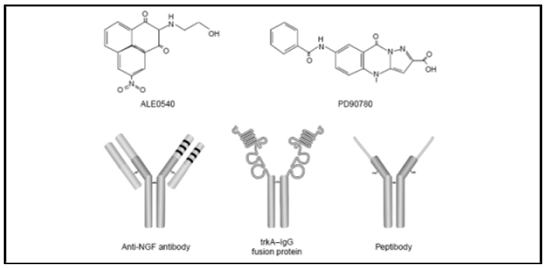


The Pathway



Nerve Growth Factor NGF Intervention Strategies:

NGF sequestration or receptor interference



Hefti *Trends Pharmacol Sci* 2006

Tanezumab

- Knee OA
- Lane et al (100, 200µg/kg
- 32 wk DBPCRT
- N=690 (4 required a total of 5 TKR)
- Week 16 significant reduction in WOMAC/NRS
- OA hip and knee studies developed osteonecrosis
- Superior to NSAID and CR oxycodone
- Greater effect in OA than CLBP and IC

Anti-NGF toxicity signal?

- There is a signal linking the use of NGF drugs with joint deterioration—possibly when these drugs are used in combination with NSAIDS and in higher doses
- Treatments for OA are desperately needed. Rheums are anti opioid

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Anti-CGRP/CGRP-receptor antibodies

- ALD403 (Alder Biopharmaceuticals)
- AMG334 (Amgen)(receptor antibody)
- Eli Lilly & Company)
- TEV48125 (Teva Pharmaceutical Industries)

Anti-CGRP Antibody

- Humanized monoclonal antibody that binds CGRP (K_D = 31 pM)
- Prevents CGRP-mediated biological effects *in vitro* and *in vivo*
- Has >10,000-fold selectivity for CGRP *versus* related peptides (adrenomedullin, amylin, calcitonin, intermedin)

Main in- and exclusion criteria

- Men and women age 18-65 years
- Migraine with and/or without aura
- 4-14 migraine headache days per month
- <15 headache days per month
- No preventive treatment or medication-overuse headache

Subject demographics

Reason	Verum (n = 107)	Placebo (n = 110)
Age	40.9 ± 11.4 years	41.9 ± 11.7 years
Women	82%	87%
Caucasian	71%	67%
Aura	43%	40%

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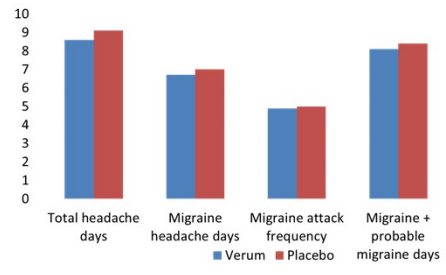
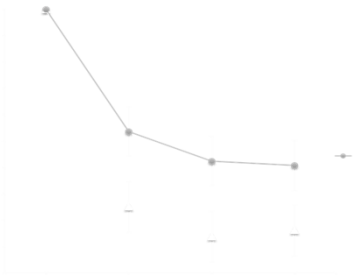
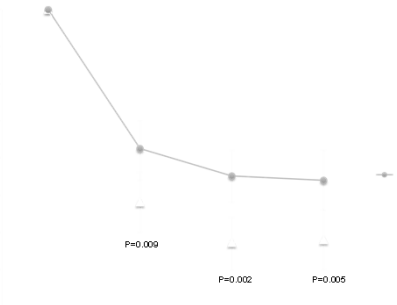
Baseline headache data (28 days)



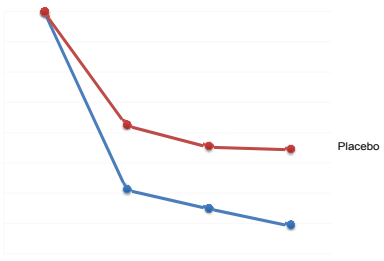
Mean change (%) from baseline in migraine headache days per month



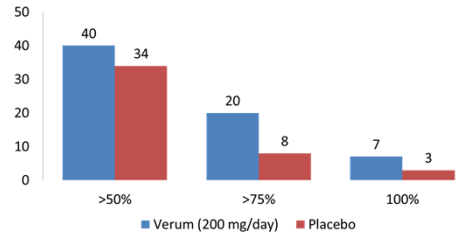
Mean change (%) from baseline in migraine attacks per month



Responder analysis: >50% reduction in migraine headache days from baseline

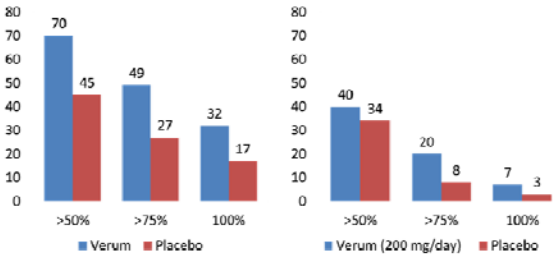


Responder analysis topiramate



Silberstein *et al*., *Clinical Therapeutics* 2006; 28:1002-1011

(left) *vs* topiramate (right)



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Neuromodulation Platforms (High Frequency, Burst, DRG)

$Na_V1.7$ (SCN9A) is a Validated Target for Pain Treatment

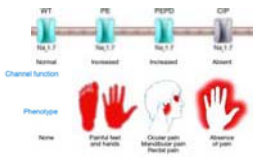
Human mutations in SCN9A have been linked to a number of inherited pain disorders:

Primary Inherited Erythromelalgia, PE
- Burning pain, redness and heat in the extremities
- Mutations affecting $Na_V1.7$ activation

Paroxysmal extreme pain disorder, PEPD
- Burning pain in rectal, ocular and mandibular areas
- Mutations affecting $Na_V1.7$ fast inactivation

Idiopathic Small Fiber Neuropathy, I-SFN
- Pain attacks starting in extremities
- Mutations affecting $Na_V1.7$ slow inactivation

Congenital Insensitivity to Pain, CIP
- Severe defect in pain perception but otherwise normal phenotype
- Mutations result in truncated non-functional $Na_V1.7$ channels

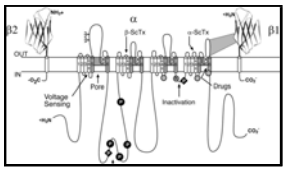


Alterations in $Na_V1.7$ properties can profoundly impact pain sensitivity
Selective inhibition of $Na_V1.7$ presents a promising approach for treatment of pain

From Dreinth JP, Waxman SG., J Clin Invest. 2007 Dec;117(12):3603-9

$Na_V1.7$ is a member of the sodium channel family

Na_V	Expression	Effect of mutations
1.1	CNS, PNS	Epilepsy
1.2	CNS, embryonic PNS	Epilepsy
1.3	CNS, embryonic PNS	Epilepsy?
1.4	Skeletal muscle	Periodic paralysis
1.5	Cardiac muscle	Cardiac
1.6	CNS, PNS	Cerebellar ataxia
1.7	PNS, SNS	Pain
1.8	PNS	Pain
1.9	PNS	Pain



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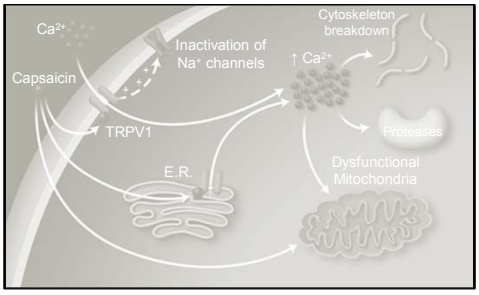
The Vanilloid Receptor TRPV1

- Ion channel highly expressed in nociceptive primary afferent sensory neurons (cell body and termini)
- Activated by specific stimuli (noxious heat >42)
  - Capsaiscin, H^+, anandamide
- Activation of TRPV1 results in release of neurotransmitters in pns and cns
- TRPV1 null mice can sense heat but do not develop thermal hypergalgesia
- Thermal hyperalgesia is associated with inflammatory pain

TRPVI Agonist MOA

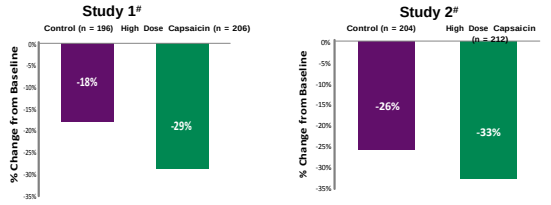


Two Phase 3 Double-Blind Controlled Studies

- 402 and 416 subjects: 8% capsaicin vs low-dose control (capsaicin 0.04% w/w)
  - Single, 60-minute application
  - PHN pain for ≥ 6 months
- 12-week controlled evaluation period
- Half of patients enrolled on stable concomitant pain medications*
- Baseline Numeric Pain Rating Scale (NPRS)# score 3-9, inclusive
  - Average baseline pain was 6
- Endpoints
  - Mean % change from baseline for average pain for past 24 hours using NPRS at week 8
  - Proportion of patients with ≥ 30% response through week 12

* Concomitant pain medications included anticonvulsants, non-SSRI antidepressants, or opioids.
# The Numeric Pain Rating Scale is a 11-point scale from 0 (no pain) to 10 (worst possible pain).

Primary Efficacy Endpoint: Percent Change in Pain from Baseline to Wk 8*



* "Average Pain for Past 24 Hours" score, as recorded by patients in a standardized daily pain diary.
# Differences between Control groups statistically significant in Studies 1 and 2.

Effect of TPRV1 Agonist Over 24 weeks in Normal Healthy Volunteers

All subjects were dosed with 8% capsaicin at two sites and two sites were identified as control sites

Neurological function assessments at Baseline, Week 1, Week 12 and Week 24
- Tactile threshold (von Frey)
- Sharp pain (pinprick)
- Quantitative sensory testing (QST) for heat pain and cooling detection thresholds

Biopsies obtained at treatment and control sites 1, 12 and 24 weeks after dosing
- Epidermal nerve fiber density
- Sections were stained for protein gene product 9.5 for nerve (green or yellow), type IV collagen for basement membrane (red), and Ulex for epidermal cells (blue)

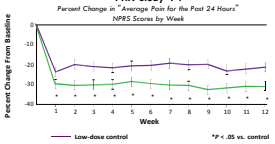
C115: Effect on Sensory Function

- Exposure to (NGX-4010) resulted in:
  - a 15% reduction from baseline in the detection of sharp pain
  - an 8% increase in tactile threshold, which normalized by week 12
- No differences were reported in cool sensation or heat pain perception between treated and untreated sites at any time point

Percent Change in Pain in 12 Week Trials

PHN Study 1[2]:

Percent Change in "Average Pain for the Past 24 Hours" NPRS Scores by Week

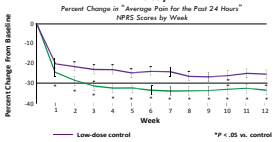


Results from a 12-week double-blind, randomized, dose-controlled, multicentered study of 402 PHN patients persisting for at least 6 months.

Individual patient results may vary. Mean (+/- SEM) changes for each group by study week.

PHN Study 2[2]:

Percent Change in "Average Pain for the Past 24 Hours" NPRS Scores by Week



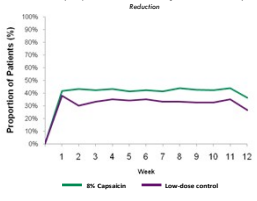
Results from a 12-week double-blind, randomized, dose-controlled, multicentered study of 416 PHN patients persisting for at least 6 months.

Individual patient results may vary. Mean (+/- SEM) changes for each group by study week.

Weekly Proportion of Patients Receiving ≥30% Pain Relief

PHN Study 1[1]:

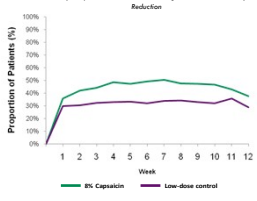
Weekly Proportion of Patients Achieving ≥ 30% Pain Intensity Reduction



The same patients may not have responded at each time point.

PHN Study 2[1]:

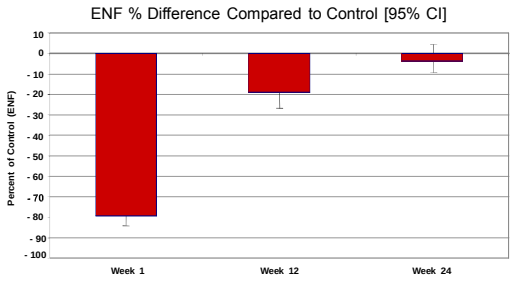
Weekly Proportion of Patients Achieving ≥ 30% Pain Intensity Reduction



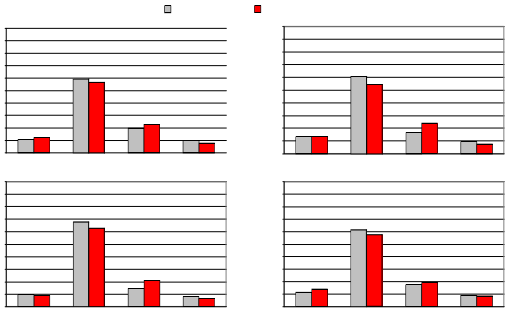
The same patients may not have responded at each time point.

1. Prescribing Information, Section 14.1 CLINICAL STUDIES, Postherpetic Neuralgia, Figures 3 (left, above) and 5 (right).

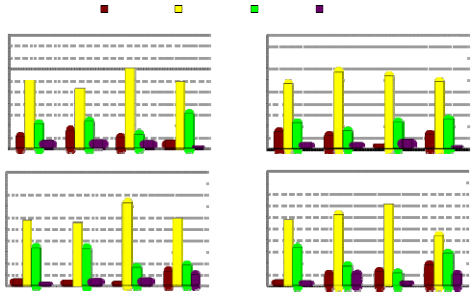
C115: ENFD Reduction at Weeks 1, 12 & 24



No Adverse Effect of High Dose Capsaicin 8% Treatment on Neurological Function (PHN)



No Adverse Effect of Long-term Repeated High Dose Capsaicin 8% Treatment on Neurological Function (PHN)



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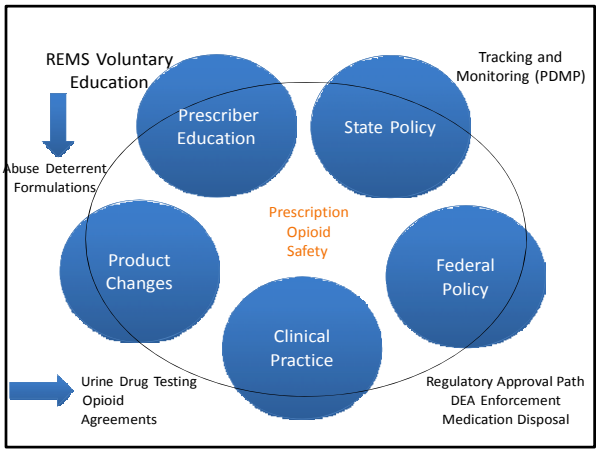
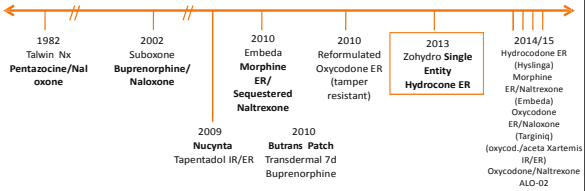


The Wave of *New or Reformulated* Opioids



Prediction:
Toxicity/safety profile of opioids will drive therapeutic decision making—more than efficacy–over the the next decade.

Different Types of Abuse-deterrent Opioid Formulations

- **Physical/Chemical Barriers**
  - Gelling agents
- **Agonist/antagonist combinations**
  - Reduce/defeat euphoria associated with abuse
- **Aversion**
  - Unpleasant effect (e.g. flushing) if manipulated or overused
- **Delivery System**
  - Sustained release depot injectable/subq implant
- **New molecular entities/prodrugs**
  - Prodrugs, differential receptor binding, CNS penetration
- **Combination**

Abuse-deterrent oxycodone formulations*

Characteristic	DETERx	OxyContin OP	Targiniq ER	Oxy/Naltrexone	Remoxy
Abuse-deterrent classification	Physical/Chemical	Physical	Agonist/ Antagonist	Agonist/ Antagonist	Physical
Sprinkle, NG/G Tube Administration	✔	✖	✖	✖	✖
Precautions regarding choking or gagging tablet	✔	✖	✖	✖	✖
No change in PK after crushing, breaking, chewing	✔	✖	✖	✖	✖
Crushing followed by oral administration not likely to be desirable to abusers	✔	✖	✔	✔	✖
Crushing followed by intranasal administration is not likely to be desirable to abusers	✔	✔	✔	✔	✔
Crushing followed by IV administration is not likely to be desirable to abusers	✔	✔	✔	✔	✔
No risk of serious withdrawal symptoms (from antagonist)	✔	✔	✖	✖	✔
No risk of serious AE's if injected	✔	✖	✖	✖	✖
Time to Market	2H 2015	On Market	Approved	Q4 '15 / Q1 '16	Resubmitted

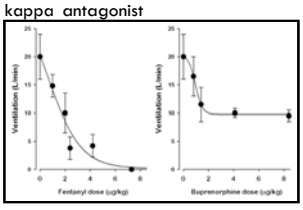
*Combination oxycodone/acetaminophen (Xartemis) not included

Buprenorphine

- Mu opioid receptor binding with extremely tight binding affinity
- Kappa opioid antagonism
- Decreased risk of respiratory depression (Ceiling effect)
- Mixed agonist/antagonist
- Transdermal preparation in a 7 day patch for pain (5,10,20mcg/hr)
- Sublingual formulation for opioid detoxification/maintenance in substance abuse (SPECIAL LICENSING REQUIRED)

Buprenorphine
Risk of Respiratory Depression and Margin of Safety

- Partial mu-opioid agonist and kappa antagonist
- Respiratory effects
  - 7.1ug/kg fentanyl v. 8.6ug/kg BUP
  - Respiratory depression ceiling at 3.0ug/kg BUP
  - Dose-dependent depression of minute ventilation with apnea at ≥2.9ug/kg fentanyl



  - Ceiling effect shown after 0.2mg/70kg fentanyl and 0.4mg/70kg BUP
    - Conclusion – partial agonist for the respiratory depressive effects while maintaining analgesia
  - 35ug/h TD BUP showed no clinically relevant respiratory depression effect

Dahan A Br J Anaesth 2005;94:825-834
Dahan A Br J Anaesth 2006;96;627-632

Overview

The Growing Unmet Need for Novel Analgesics
Antibody Therapies Anti NGF MAB (#4) for OA, CLBP,
Visceral Pain Anti CGRP MAB (#4) for Migraine
Nav 1.7 Sodium Channel Modulators
High Dose Capsaicin (TRPV1) Abuse
Deterrent Opioids Alternate Route
NSAIDS
Neuromodulation Platforms (High Frequency, Burst, DRG)

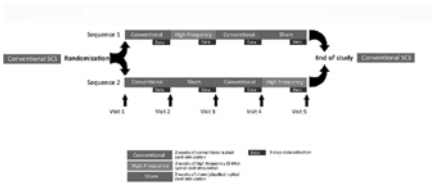
High Frequency (10kHz) SCS Therapy

HF10™
Senza System
- Pulse rate of 2-10,000hz
- 10 year battery life (CE mark)

- Paresthesia – independent: no continuous or movement-induced sensations
- Anatomic lead placement – no paresthesia mapping
- Commercially-available in Europe and Australia: >2,500 patients
- Investigational device in the US

HF10 Evidence

- US Pivotal
  - RCT comparing HF10 to traditional SCS
  - 10 centers (US)
  - 198 patients randomized
  - Comparative safety and efficacy at 1 year



Pivotal Trial : High Frequency SCS vs Conventional SCS (Boston Scientific)

- Comparative safety and efficacy
- Parallel design
- Sample size estimation based on non-inferiority

Inclusion

- Chronic intractable pain of the trunk and limbs refractory to conservative therapy for >3mo
- Average back pain of ≥ 5 (back and leg)
- Oswestry of 41-80/100
- Appropriate surgical candidates

Exclusion

- Active disruptive psychological disorder
- Mechanical spine instability
- Prior experience with SCS
- Injury claim in litigation or WC
- Medical Condition at another site

HFS Critical Issues

- Primary outcome: percent of patients with >50% pain relief AND no adverse events
- Adverse events—includes "uncomfortable paresthesias"
- Real efficacy data for conventional SCS would be improved if paresthesias were not considered an AE
- Study population is FBSS and not PHN, DPN etc

HF RCT: Uncomfortable Stimulation

	Active HF10	Control Traditional SCS
Month 3	0	33 (46.5%)
Month 12	0	28 (44.4%)

Novel Therapies / Initial Target Indications

- Anti NGF- OA knee, CLBP, IC
- Anti CGRP Ab- migraine
- Nav 1.7 – Trigeminal Neuralgia (and possibly SFN/Radicular Pain)
- ADF Opioids - chronic (and now acute) pain
- High Dose Capsaicin- PHN (and peripheral neuropathic pain)

The Coming Wave of Novel Analgesics:

Antibody Therapies, Sodium Channel Modulators, Abuse Deterrent Opioids, NSAIDs, Neuromodulation Platforms

John Markman MD
Director Neuromedicine Pain Management Center Translational Pain Research
Associate Professor, Department of Neurosurgery
University of Rochester School of Medicine

Prepared for:
Advances in Pain Management IX
9 April 2016

Rochester Neurosurgery Partners | University of Rochester Medical Center — Medicine of the Highest Order