Emerging Pharmacotherapies for Pain and Headache Disorders

Nathaniel M. Schuster, MD
Pain and Headache Neurologist
UC San Diego Center for Pain Medicine
nmschuster@ucsd.edu

Disclosures

- Consulting: Averitas, Eli Lilly, Lohocla, Lundbeck, Rapport, Salvia, Schedule 1 Therapeutics, Syneos, and Vertex.

- Research (funding to institution): Migraine Research Foundation, ShiraTronics, NINDS U24 NS115714, NINDS 3OT2NS122680-01S3, NCCIH 5R00AT009466-04, NIH CTSA Grant UL1TR000100

Overview

- Sodium channel inhibitor
- TRP receptor antagonist
- Lyn tyrosine kinase inhibition
- Pituitary adenylate cyclase-activating polypeptide mAb
- Cannabinoids
- Psychadelics
- More

Sodium channel (Nav) inhibitor

- Recent attention with FDA approval of suzetrigine (JOURNAVX)
- Nav receptors are highly expressed in nociceptive neurons
- Human loss-of-function mutations in SCN9A gene (encoding Nav1.7) causes congenital insensitivity to pain
- Studies targeting Nav1.7 were unsuccessful
- Nav1.8 primarily found in peripheral sensory neurons, especially C-fibers
- Nav1.8 receptors upregulated in diabetic neuropathy

VX-548 (suzetrigine, JOURNAVX) Nav1.8 inhibitor

- VX-548 for acute post-operative pain after bunionectomy and abdominoplasty showed pain benefit similar to hydrocodone/acetaminophen and superior to placebo

- VX-548 in phase 2 dose-ranging study for painful diabetic peripheral neuropathy showed pain benefit similar to pregabalin and well-tolerated and announced plans to advance to phase 3 trials

- VX-548 in phase 2 study for lumbosacral neuropathy was similar to placebo but Vertex reported variability in placebo responses across study sites and announced plans to advance to phase 3 trials

Transient Receptor Potential (TRP) Receptor Antagonists

- 2021 Nobel Prize – Dr. David Julius for work on TRPV1 and capsaicin
- TRP channels on peripheral sensory neurons involved in pain sensation
- Activation of TRP channels -> release of inflammatory mediators including CGRP

BHV-2100 TRPM3 antagonist

- TRPM3 has broader expression in peripheral neurons than TRPV1 and TRPA1 and unlikely to affect body temperature homeostasis
- Present on large subset of somatosensory neurons including nociceptors
- Upregulated in nerve injury models in animals
- Gain-of-function mutation in TRPM3 in humans is associated with altered pain sensation in humans
- Has completed phase 1 study, well-tolerated
- Currently in phase 2 study for acute migraine and planned phase 2 study for painful diabetic peripheral neuropathy

Lyn tyrosine kinase inhibition

- Lyn tyrosine kinase is a member of the Src family kinases
- Key role in modulating immune responses and inflammatory signaling
- Preclinical studies show Lyn tyrosine kinase inhibition can reduce neuroinflammation and nerve damage in diabetic models

NRD135S.E1 Lyn tyrosine kinase inhibitor

- Phase 2a dose-ranging study showed clinically relevant placebo-corrected treatment effect pain reductions and well-tolerated
- Currently in phase 2b study for painful diabetic peripheral neuropathy

Tiecke et al. NRD.E1, an innovative non-opioid therapy for painful diabetic peripheral neuropathy-A randomized proof of concept study. Eur J Pain. 2022 Sep;26(8):1665-1678. doi: 10.1002/ejp.1989. Epub 2022 Jun 21. PMID: 35671086; PMCID: PMC9540529.

Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP)

- Neuropeptide found in trigeminal, sphenopalatine, and otic ganglia and trigeminocervical complex
- Binds to VIP and PAC1 and PAC27 and PAC38 receptors
- Elevated venous PACAP plasma levels seen in migraine and cluster attacks
- Infusion of PACAP-38 triggers pain behavior in animals and delayed migraine-like attacks in people with migraine

Edvinsson L, et al. PACAP and its role in primary headaches. Journal of Headache and Pain. 2018;19:1-7.

IV Lu AG09222 PACAP-38 ligand monoclonal antibody (mAb)

- AMG 301, a mAb targeting the PAC1 receptor was ineffective in a phase 2 study
- In a proof of concept phase 2a study (Ashina et al, NEJM 2024) IV Lu AG09222 was superior to placebo for migraine prevention
- A phase 2b dose-ranging study of Lu AG09222 versus placebo is ongoing

Ashina M, et al. A Monoclonal Antibody to PACAP for Migraine Prevention. N Engl J Med 2024;391:800-809

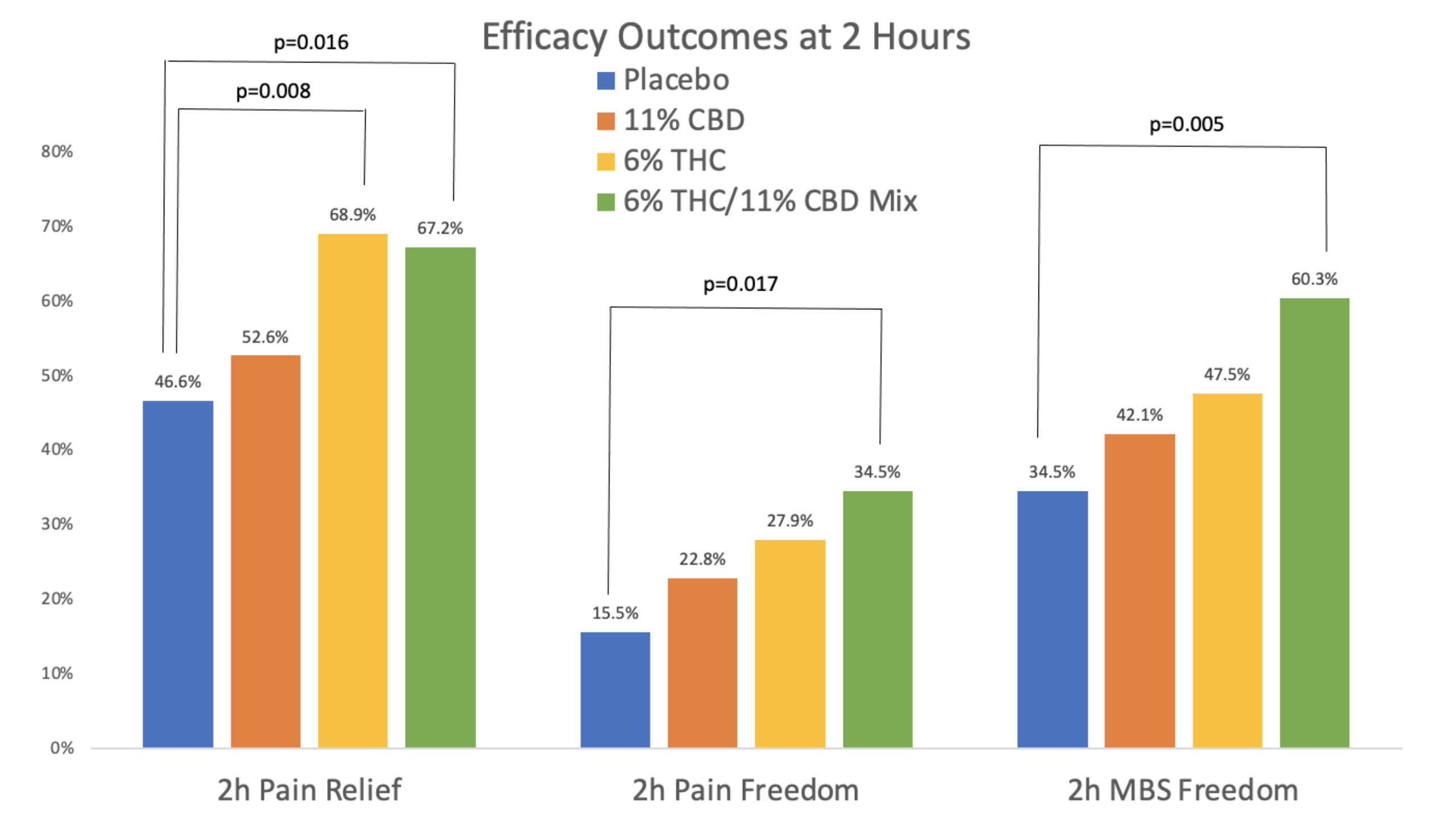
That’s not it

Noceptin/orphanin (NOP) Receptor Agonists

LY3016859- Epiregulin/TGFalpha mAb
LY3556050- Somatostatin receptor 4 antagonist
LY3526318- TRPA1 Antagonist
LY3857210- P2X7 Receptor Antagonist
LX-921- AAK1 Inhibitor
…and more

Cannabinoids

- NASEM 2017 report- conclusive or substantial evidence that cannabis is effective for treatment of chronic pain in adults
- None US FDA approved for pain or headache
  - Cannabidiol (EPIDIOLEX) for Lennox-Gastaut, Dravet, and Tuberous Sclerosis Complex
  - Dronabinol (MARINOL) for chemotherapy induced nausea and vomiting and AIDS-related anorexia
  - Nabilone (CESAMET) for chemotherapy induced nausea and vomiting
  - Nabiximols (SATIVEX) not approved in the US, approved for Multiple Sclerosis-related spasticity in 29 other countries
- In a national survey of 1724 US patients with chronic pain living in areas with medical cannabis laws in 36 states and the District of Columbia, 31.0%reported ever using cannabis to manage pain, 25.9% reported using cannabis within the past 12 months, and 23.2% reported using cannabis in the past 30 days.


Efficacy Outcomes at 2 Hours
Placebo
11% CBD
6% THC
6% THC/11% CBD Mix
p=0.016
p=0.008
p=0.017
p=0.005
80%
70%
60%
50%
40%
30%
20%
10%
0%
46.6%
52.6%
68.9%
67.2%
15.5%
22.8%
27.9%
34.5%
34.5%
42.1%
47.5%
60.3%
2h Pain Relief
2h Pain Freedom
2h MBS Freedom

Psychedelics

- Psychedelics including LSD and psilocybin were explored in psychiatric research in the 1950s and 60s.
- People with cluster headache started reporting benefit from psychedelics since the 1980s and 90s.
- Clusterbusters, a patient-led advocacy group, was founded in the 2000s and its members shared their experiences with psychedelics for cluster headache
- Investigators at Yale in 2006 interviewed patients about effects of LSD and psilocybin for cluster headache and in recent years have been conducting RCTs studying psilocybin for cluster headache and migraine.
- Other institutions including UCSF and UCSD are studying psychedelics for conditions including lower back pain and CRPS

Thanks!

nmschuster@ucsd.edu