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The Outer Limits: Analgesics of the Future

Disclosure

- Director, Pain Management and Palliative Care
  - Englewood Hospital and Medical Center
- Former Clinical Instructor
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- Board Certified
  - Pain Management, Anesthesiology, Addiction Medicine, Hospice and Palliative Medicine
Learning Objectives

- Describe the challenges of the chronic pain landscape
- List future opioid and non-opioid analgesics
- Describe opioid-like molecules
- Describe analgesic properties of cannabinoids

Chronic Pain Landscape and Challenges

- Partial efficacy of analgesic therapies
- Bothersome and dangerous AE profile
- Lack of potential cure
- Treatment focuses on condition management, not prevention or coping
- Similar to approach taken with other chronic conditions (e.g. diabetes)
- Overriding goal is to help patients learn how to live with pain & improve quality of life
Pain is a Disease

Prevalence in Millions

- Cancer: 3
- Heart: 53
- Diabetes: 73
- Pain: 453

Ref: Medical Association websites

LIMITED analgesic options

APAP
NSAIDS
Tram/Tapentadol
Opioids

Gabapentinoids
SNRI/SSRI
Topicals
Local Anesthetics
Treating only one problem... IS A PROBLEM!

- Treating pain but not deconditioning fails
- Treating pain but not depression fails; sometimes treating depression but not pain fails
- Treating pain not addiction fails; sometimes treating addiction but not pain fails
- Growing appreciation for link between comorbidities, psychosocial factors and treatment failures

The Opioid Pendulum

Opiophobia

Balance of Addiction Medicine and Pain Management Principles

Opiophilia

Pain Docs or Drug Dealers?

The media doesn’t seem to think there is a difference!

Should we eliminate opioids from the practice of Pain Management?

When all you have is a hammer.....
Jumping Out of the Frying Pan and into the Fire

OPIOIDS

1. Nausea/vomiting
2. Constipation
3. Pruritus
4. Ileus, Urinary retention
5. Sedation
6. Respiratory depression
7. Endocrine effects
8. Tolerance development
9. Misuse/abuse/addiction/diversion
10. Hyperalgesia
11. Drug:Drug interactions

The Long-term Analgesic Effectiveness of Opioid Therapy in Chronic Non-Cancer Pain Patients:

- Review of 70 studies of various designs on chronic opioid therapy
- Studies demonstrated reductions on pain that were maintained to the end of the study which were at least 6 months and in some cases up to 3 years in duration- supporting the effectiveness of LOT for those patient who are able to tolerate opioids and remain treated over long-term
- Secondary endpoints of physical and mental functionality in 11 studies showed improved functionality which appeared to correlate with the relief of pain with LOT

IT'S NOT ALL BAD!
## The OUTER LIMITS: Analgesics of the Future

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### Non-Opioids

- α2-adrenergic agonists (e.g. clonidine and dexmedetomidine)
- NMDA receptor antagonists (e.g. ketamine, dextromethorphan, magnesium)
- Gabapentanoid compounds
- Novel NSAIDs
- NGF antagonists
- TrkA inhibitors
- Glial cell modulators
- Cannabinoids

### Abuse Deterrent Formulations

- Physicochemical
  - PEO
- Agonist/antagonist
  - Naloxone, Naltrexone
- Prodrug
  - Benzhydrocodone
- Delivery systems
  - Depots, implants
- Combination agents
- Aversive therapies
- New chemical entities
  - NKTR-181 slow entry opioid
**Combination Agonist/antagonist**


- Oral, fixed-dose combination of SR oxycodone and SR naloxone
  - UK label therapeutic indication:
    - “Severe pain, which can be adequately managed only with opioid analgesics. The opioid antagonist naloxone is added to counteract opioid-induced constipation by blocking the action of oxycodone at opioid receptors locally in the gut.”
  - First launched in Germany in 4Q 2006
  - Now approved in US, multiple countries
  - Available in 4 combination ratios:
    - 5/2.5, 10/5, 20/10, and 40/20

Compared to oxycodone alone, oxy/naloxone phase 3 studies demonstrated significant improvement in BFI, significant increase in # of complete SBMs, and decrease in laxative use, without compromising analgesia of oxycodone.

**NKTR 181**

- A new chemical entity (NCE) fast-tracked by FDA
- Analgesic with less rewarding properties inherent to its novel molecular structure
  - strategic alteration of brain-entry kinetics
  - independent of any ADF technology
- Exhibits reduction in CNS-mediated side effects, like euphoria

*HAP study demonstrated significantly lower abuse potential than oxycodone*

*Previous HAP study rated 181 comparable to placebo*
Opioid-like Molecules

- Cebranopadol - a nociceptin/orphanin FQ peptide receptor and opioid receptor agonist
- Tramadol
  - Opioid + SSRI, C-IV
- Tapentadol
  - Opioid + SNRI, C-II
- Tapentadol is the first and only FDA-approved long-acting opioid designed to control both nociceptive pain and the neuropathic pain associated with diabetic peripheral neuropathy (DPN)
- Shown an improved safety profile
- including for respiratory depression

Cebranopadol Pharmacology: **μ-opioid + NOP agonist**

**μ-opioid Activation**
- Effective against nociceptive pain
- Visceral and neuropathic pain are relatively opioid resistant
- Respiratory depression
- Addiction risk

**NOP Activation**
- Effective against neuropathic, inflammatory, and visceral pain
- Broad therapeutic index with low risk of respiratory depression and addiction

- Potent and broad analgesic activity
- Reduced risk of respiratory depression and addiction risk vs. “traditional” opioids
Biased Ligands

- Studies have suggested that opioid-induced analgesia results from $\mu$ OR signaling through the G protein, while many side effects, including respiratory depression and constipation, may be conferred via $\beta$-arrestin pathway signaling downstream of $\mu$ OR activation.

- Agonists specific to the $\mu$ OR and biased towards the G signaling pathway are therefore sought both as therapeutic leads and as molecular probes to understand $\mu$ OR signaling.


Oliceridine and PZM21

Computerized models generate new scaffolds unrelated to known opioids.
Peripheral k-Opioid Agonists

CR845 has been formulated both as an IV and oral formulation.

To date, it has shown analgesic, anti-pruritic properties in 5 different Phase 2 studies for acute postoperative pain, chronic pain and pruritus.

Additionally, it has been studied in a human abuse liability (HAL) study which supports the view that it is unlikely to be recreationally abused or lead to physical dependence.
**NGF Inhibitors**

- Inflammation, angiogenesis, nerve growth and pain are all interconnected processes.
- Nerve growth factor (NGF) plays a key role in persistent inflammatory pain, is expressed within the inflamed synovium and osteochondral junction, and may contribute to arthritic pain.
- NGF sensitizes peripheral nerves and may also stimulate blood vessel and nerve growth into structures such as the articular cartilage, which are not normally innervated.
- Sensory nerves, in turn, might augment inflammation by releasing neuropeptides.
- Injection of NGF into rat knees induces pain behavior and synovitis.
- Inhibiting NGF signaling might therefore have particular benefit in patients with inflammatory pain, including those with rheumatoid arthritis (RA).


**Glial Cell Activation**

- Activation of glial cells and neuro–glial interactions are emerging as key mechanisms underlying chronic pain.

Glial mediators have been shown to powerfully modulate excitatory and inhibitory synaptic transmission - at pre, post, and extrasynaptic sites

Pain Pract. 2010 May-Jun;10(3):167-84
Accumulating evidence has implicated 3 types of glial cells in the development and maintenance of chronic pain:

- microglia and astrocytes of the central nervous system (CNS), and satellite glial cells of the dorsal root and trigeminal ganglia
Medical Marijuana

- Research published in *JAMA* suggests that recent moves to legalize the use of medical marijuana for pain management may help to reverse the tide of opioid drug overdoses.

  - The researchers found that cannabinoids show promise as therapeutics, but more research is needed to maximize their potential use in a clinical setting.

Cannabinoids

- Neurotransmission via the endocannabinoid pathway is increasingly appreciated to regulate pain perception and modulation

- CB1 receptor plays an important role; analgesics effects are lost when CB1 antagonist (rimonabant) is given

- Both enandamide and NADA activate a Ca channel known as the vanilloid receptor (TRPV-1) found on sensory nerves

- May promote analgesia through CB1 and CB2, but potentially increase pain via TRPV-1

- Progress is being made in the development of novel agonists and antagonists with receptor subtype selectivity which should help in providing a greater understanding of the physiological role of the endocannabinoid system and perhaps also in a broad number of pathologies.

Judge the Treatment, Not the Patient!

**DETERMINE ...**
- Do the benefits outweigh the risks to the patient and society?
- Is functioning affected?
  - Better or worse with Rx?
  - Physical, Mental, Social

**NOT ...**
- Is the Patient good or bad?
- Does the patient deserve meds?
- Should the patient be punished or rewarded?

### Conclusion
- Opioids remain a mainstay for the treatment of severe chronic pain
- We DO need a better mousetrap
  - AE profile intolerable
- Novel opioid and adjuvant analgesics in development that should change the landscape and improve safety and tolerability and patient satisfaction
  - Maybe even improve efficacy???
- Until that time, clinicians need to understand rationale use of opioids
  - Partial efficacy
  - Complemented by multimodal techniques
- Always have an exit strategy
Thank you

Jeff Gudin MD