Buprenorphine:

Opioid Agonist-Antagonist Benefits for Opioid Resistant Pain Uncontrolled By Full-Agonist Opioids during Hematopoietic Stem Cell Transplant for Sickle Cell Disease

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Disclosure

I have no relevant conflicts of interests to disclose.

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Objectives

- Address the challenges of full-agonist opioid pain management in supportive care for intense medical treatments associated with pain
- Introduce the benefits of buprenorphine in the inpatient setting for acute pain management
- Support the continued education related to buprenorphine's unique clinical and pharmacological advantages

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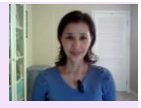
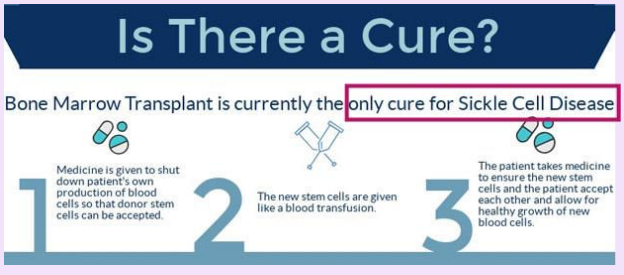


Background

Bone marrow transplant (BMT) offers **potential cure** for cancer and a spectrum of **otherwise incurable diseases**



INDICATIONS OF BMT

- Aplastic Anemia- a disorder in which the marrow stops making new blood cells
- Leukemia, Lymphoma
- Damaged bone marrow due to Chemotherapy
- Congenital Neutropenia- is an inherited disorder that causes recurring infections
- Sickle Cell Anemia- an inherited blood disorder that causes misshapen red blood cells

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Bone Marrow Transplant & PAIN

BMT multi-systemic complications from:
chemotherapeutic agents, transplant rejection prophylaxis, radiation, immunosuppressants, antimetabolites

⬇

Multi-Loci & Multi-Systemic PAIN

Arthralgia / Myalgia / Back Pain / Extremity Pain / Arthritis
Headache / Neurotoxicity / Neuropathy
Mucositis / Stomatitis / Odynophagia / Dyspepsia
Abdominal Pain / GVHD / Veno-Occlusive Disease
Radiation Pain / Inflammation / Infection Pain
Chest Pain / Pleural effusion / Alveolar hemorrhage

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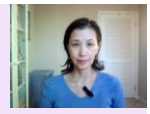
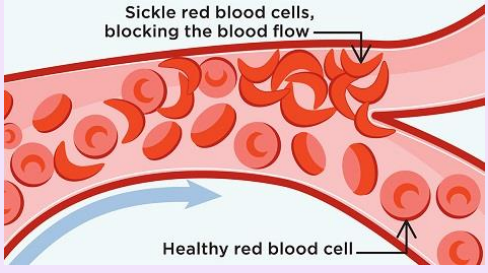


Sickle Cell Disease (SCD) & PAIN

- Congenital hematologic disease with **LIFE-LONG PAIN**
- Vaso-Occlusive Episode **PAIN starts at 5-6 months of age**
- **Frequent pain → Chronic pain → HYPERALGESIA:**

Central & Peripheral Hypersensitization of PAIN



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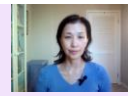

Sickle Cell Disease & PAIN

- Repetitive hypersensitization for years → **Severe hyperalgesia**
- Chronic frequent opioid use → **High opioid tolerance**

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Bone Marrow Transplant (BMT)

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Excruciating PAIN
Rapid opioid dose escalation
Uncontrolled by HIGH dose Opioid
Numerous opioid adverse effects

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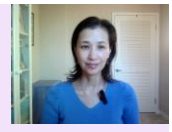

Pilot Prospective Clinical Trial BMT Pain of SCD Patients

- Pilot prospective clinical trial was initiated after observing serial cases of SCD patients' BMT-related pain uncontrollable by HIGH doses of full-agonist opioids
- Small, growing body of literature has shown superior effect of buprenorphine over full-agonist opioids for chronic SCD pain in the **<u>outpatient</u> setting**
- Pilot trial for SCD patients' acute severe pain to assess for the **<u>inpatient</u>-use efficacy** of buprenorphine during BMT, significant pain escalation factor

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Method

- Buprenorphine was started as scheduled and as-needed analgesics IV, supplemented by full-agonist opioids for SCD patients enrolled in clinical trials with BMT upon consultation for uncontrolled pain
- Patients' 24-hr opioid requirement by morphine equivalent daily doses (MEDD) assessed at 3 time points. (Table 1)
  1) **Before pain level escalation**
  2) **Consultation day for uncontrolled pain**
  3) **Discharge day**
- MEDDs were **retrospectively compared** to those of SCD patients treated with full-agonist opioids only during their BMT admission.

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Results

Morphine Equivalent Daily Dose

Pre-consult vs. Discharge day

Table 1. MEDD) for BMT Pain Management in SCD Patients

24-hour MEDD:	Case	Pre-Consult MEDD	Consultation Day MEDD:	Discharge MEDD: % Increase
Full-Agonist Opioid Regimen • Morphine • Oxycodone • Methadone • Hydromorphone • Fentanyl • Oxymorpone	1	240 mg	840 mg	3192 mg (1230%)
	2	74 mg	170 mg	1220 mg (1548%)
	3	10 mg	352 mg	1640 mg (16300%)
BUPE-Based Opioid Regimen	4	30 mg	40 mg	125 mg (317%)
	5	7.5 mg	22.5 mg	24 mg (220%)

Table 2. Patient Demographics and Disease Genotype

Case	Age	Gender	Ethnic Background	SCD Genotype
1	18	M	Nigerian	HgbSS
2	22	M	Nigerian	HgbSS
3	39	F	Congolese	HgbSS
4	19	M	African American	HgbSS
5	7	M	African American	HgbSS

Full-agonist opioid cases:

MEDD increase by 1230 - 16300%

Buprenorphine - supported cases:

MEDD increase by 220 - 317%

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Results

MEDD: 24hr Opioid Requirement	Case	Pre-Consultation MEDD: Immediately Prior to Pain Escalation	Consultation Day MEDD: Pain Uncontrolled	Discharge Day Post-BMT MEDD: Pain Controlled (% Increase in MEDD)
Full-Agonist Opioid Analgesic Regimen	1	240 mg	840 mg	3192 mg (1230%)
	2	74 mg	170 mg	1220 mg (1548%)
	3	10 mg	352 mg	1640 mg (16300%)
Buprenorphine Based Opioid Regimen	4	30 mg	40 mg	125 mg (317%)
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Table 1. Morphine Equivalent Daily Dose (MEDD) for BMT Pain Management in SCD Patients Receiving Full-Agonist Opioids vs. Buprenorphine-Based Management

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Conclusions

Pilot clinical trial data suggests the buprenorphine benefits of:

1. **Potent analgesic effect despite the baseline hyperalgesia of SCD patients**
2. **Limiting opioid tolerance development through the multiple exposure to the painful adverse effects of BMT-related therapies**

Buprenorphine may provide the similar benefits to non-SCD patients with complex pain background and experiencing severe, difficult-to-control pain during BMT or other painful therapies due to hyperalgesia and opioid tolerance.

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Buprenorphine Benefits for SCD

- Buprenorphine clearance NOT increased in SCD
  Chronic hemolytic anemia ➔ increased cardiac output
  - ➢Hepatic blood flow increased → accelerated glucuronidation
  - ➢Renal blood flow increased → accelerated elimination
- Quality of life with buprenorphine for treatment of chronic pain: The first qualitative, descriptive study for chronic pain of SCD, 2023*
  - ❖Improves **functionality** in multiple domains of life
  - ❖Enables improvements in **social relationships**
  - ❖Significantly decreases **acute care utilization**

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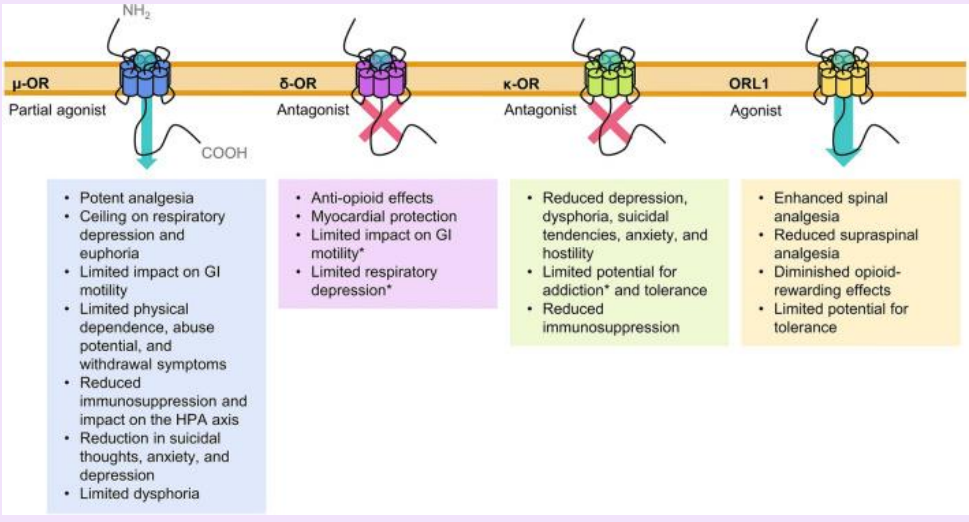
Buprenorphine Benefits: Opioid Agonist-Antagonist



Partial Mu opioid receptor AGONIST & Opioid Receptor Like 1 opioid receptor AGONIST
~~Delta~~ and ~~Kappa~~ opioid receptor Antagonist

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Opioid Receptors

Opioid Receptors	Therapeutic Effects	Adverse Effects
Mu Opioid Receptors	Analgesia	• Respiratory depression • Constipation (GI dysmotility) • Rewarding effect → Abuse potential • HPA axis suppression • Hyperalgesia
Kappa Opioid Receptors	(Analgesia)	• Dysphoria / Stress-like effects • Depression / Anxiety → Craving • Immune suppression • Sedation
Delta Opioid Receptors	(Analgesia)	• Respiratory depression • Constipation • QT prolongation • Opioid tolerance

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Buprenorphine Benefits: Pharmacodynamics
Opioid Agonist-Antagonist

- **Partial μ-OR AGONISM** ***Beta-arrestin signaling reduced**
  Less euphoria, less hyperalgesia/tolerance, less receptor endocytosis, less respiratory depression, less constipation, limits HPA-axis effect
- **ORL-1 AGONISM → PREFERRED** SPINAL receptor action:
  less supraspinal receptor action = less reward effect,
  limits tolerance, limits respiratory depression
- **κ-OR ANTAGONISM (inverse agonism)**→Anxiolytic, less addictive potential, less constipation, less immunosuppression
- **δ-OR ANTAGONISM** → less gastrointestinal effect, less respiratory depression, less cardiac side effect

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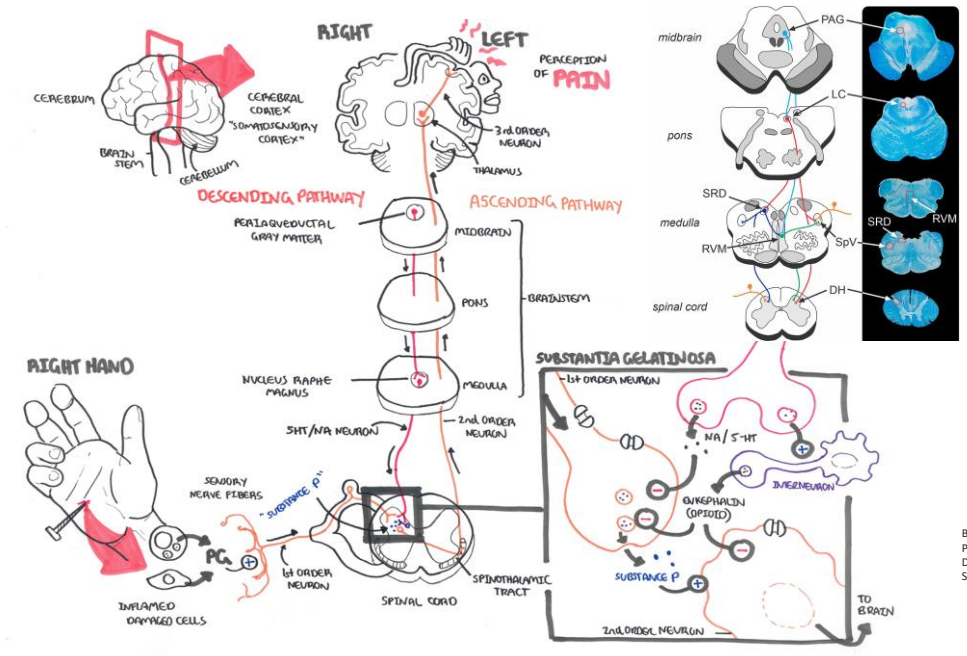

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Biology and Medicine Tutorials: PAIN Physiology - The Ascending Pathway, Descending Pain Pathway and the Substantia https://armandoh.org

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Other Buprenorphine Benefits

- Slower dissociation from the μ-OR resulting in prolonged analgesia and less potential for withdrawal27
- SAFE in renal insufficiency and hepatic impairment
- Less risk for in the elderly population: less cognitive impairment, sedation, risk of falls
- Long-term use is safer than full-agonist opioids: less HPA-axis, less tolerance, less dependence

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Buprenorphine Challenges & Disadvantages

- High dose full-agonist opioid conversion to buprenorphine can cause withdrawal in stop/start opioid rotation method – requires patience
- Slow peak-effect – related frustration
  - Transdermal form: needs 3-5 days to reach steady state
  - Sublingual form: onset of action 30-60 mins; peak effect 3-4H
- Buprenorphine dose >16 mg daily may block another opioid
- Buprenorphine overdose requires high-dose naloxone to reverse respiratory depressions

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Buprenorphine Challenges & Disadvantages

- Stigma and public misconception related to buprenorphine/naloxone
  - Buprenorphine does not show in standard urine toxicity screen
- FDA approval, relatively new:
  1)2002 - **Sublingual** form for opioid dependence
  2)2010 - **Trandermal** form for pain management
  3)2015 - **Buccal** film form for pain management
- Insurance denial for co-administration with other opioids
- Insurance pre-authorization requirement for home discharge prescription

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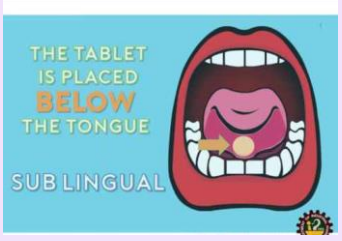
Reported "side effects"

Sublingual buprenorphine (Subutex)

- "Sour taste"
- "Chalky feel and taste"
- "Burning" pain under the tongue
- "Just feel weird" – not anxious but heebie jeebies
- Tolerance in 1 week - "it was working well but not any more"



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Surprising positive effects! (anecdotal)

- "**Only Subutex works** for my **headache**" s/p development of tolerance to Tylenol and max. Fioricet, hydromorphone methadone, – long history of chronic headache
- **Opioid taper difficulty resolved**, cancer in remission
  1. Step-wise Fentanyl transdermal (TD) weaning
  2. Withdrawal started with smallest dose Fentanyl TD 12mcg/h
  3. Return to Fentanyl 25mcg/h → Repetitive tapering failure to 12mc/h
  4. Rotation to the Buprenorphine TD 10mcg/h → 5mg/hr
  5. "**All the withdrawal symptoms stopped!" and no pain**
- "**Only pain medication** that **doesn't make me nauseous**"

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Thank you!!

Contact Info
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References

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