Buprenorphine:

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

Mayuko Sakae, MD
Department of Supportive Care Medicine
City of Hope National Medical Center
Los Angeles, California

1

Disclosure

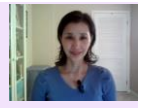
I have no relevant conflicts of interests to disclose.

2

Objectives

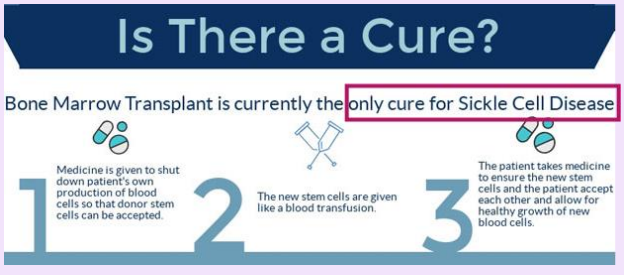
- Address the challenges of full-agonist opioid pain management in supportive care for intense medical treatments associated with pain
- Introduce the benefits of buprenorphine in the inpatient setting for acute pain management
- Support the continued education related to buprenorphine's unique clinical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

3



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

https://curesicklenow.org/index.php/what-is-bone-marrow-transplant, Https://www.onlymyhealth.com/what-are-paediatric-blood-disorders-and-how-bone-marrow-transplant-can-cure-the-condition-1603779371, https://www.slideshare.net/slideshow/bone-marrow-transplant-233262747/233262747#3, https://www.slideshare.net/slideshow/bone-marrow-transplant-233262747/233262747#3, https://abcnews.go.com/Health/2nd-hiv-patient-remission-stem-cell-transplant-doctors/story?id=61474356

4

Bone Marrow Transplant & PAIN

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

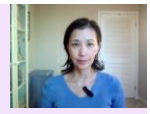
⬇

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

5. Vaquenza K. et al. Pain Management for Children during Bone Marrow and Stem Cell Transplantation: *Pain Manag Nurs.*. 2015 Jun;16(3):156-62
6. Wei X. et all. Tacrolimus-Induced Pain Syndrome After Bone Marrow Transplantation: A Case Report and Literature Review: *Transplant Proc.* 2018 Dec;50(10):4090-4095

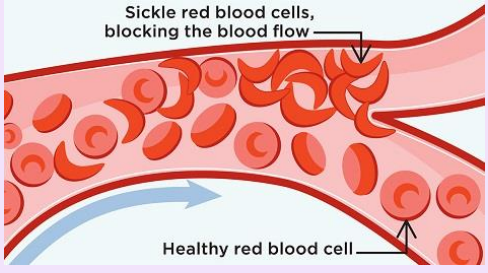
5



Sickle Cell Disease (SCD) & PAIN

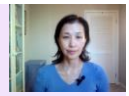
- Congenital hematologic disease with **LIFE-LONG PAIN**
- Vaso-Occlusive Episode **PAIN starts at 5-6 months of age**
- **Frequent pain → Chronic pain → HYPERALGESIA:**

Central & Peripheral Hypersensitization of PAIN



7. Irwin M. et al. Buprenorphine for Chronic Pain in a Pediatric Patient With Sickle-Cell Disease: *Journal of Pain and Symptom Manage*. 2021 Nov;62(5):1086-1091
8. Jang T. et al. Vaso-occlusive crisis in sickle cell disease: a vicious cycle of secondary events: *Journal of Transational Medicine*. 2021; 19: 397
9. Alban L. et al. Central sensitization: a generator of pain hypersensitivity by central neural plasticity: *Journal of Pain*. 2009 Sep;10(9):895-926
10. CDC. May 15, 2024, https://www.cdc.gov/sickle-cell/data/index.html

6



Sickle Cell Disease & PAIN

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

+

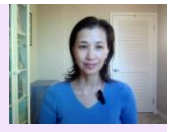
Bone Marrow Transplant (BMT)

↓

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

10. Karafin MS. et al. Chronic pain persists in adults with sickle cell disease despite regular red cell transfusions: *Transfus Apher Sci.* 2019 Aug;58(4):434-438
11. Eisenberg E. et al. Opioid-induced hyperalgesia (OIH): a real clinical problem or just an experimental phenomenon?: *J Pain Symptom Manage*. 2015 Mar;49(3):632-6
12. Jensen TS. Allodynia and hyperalgesia in neuropathic pain: clinical manifestations and mechanisms: Lancet Neurol. 2014 Sep;13(9):924-35. doi: 10.1016/S1474-4422(14)70102-4

7



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

13. Irwin M. et al. Buprenorphine for Chronic Pain in a Pediatric Patient With Sickle-Cell Disease: *Journal of Pain Symptom and Management*.2021 Nov;62(5):1086-1091
14. Prince E.et al. "Buprenorphine, It Works so Differently": Adults with Sickle Cell Disease Describe Transitioning to Buprenorphine for Treatment of Chronic Pain: *Journal of Pain.* 2024 Mar;25(3):632-641
15. Jang T. et al. Vaso-occlusive crisis in sickle cell disease: a vicious cycle of secondary events: *Journal of Translational Medicine.* 2021; 19: 397
16. David MS. et al. Converting adults with sickle cell disease from full agonist opioids to buprenorphine: A reliable method with safety and early evidence of reduced acute care utilization: *Am J Hematol.* 2022 ov;97(11):14351442

8

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.

9

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%

10

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%)
	5	7.5 mg	22.5 mg	24 mg (220 %)

Table 1. Morphine Equivalent Daily Dose (MEDD) for BMT Pain Management in SCD Patients Receiving Full-Agonist Opioids vs. Buprenorphine-Based Management

11

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.

12

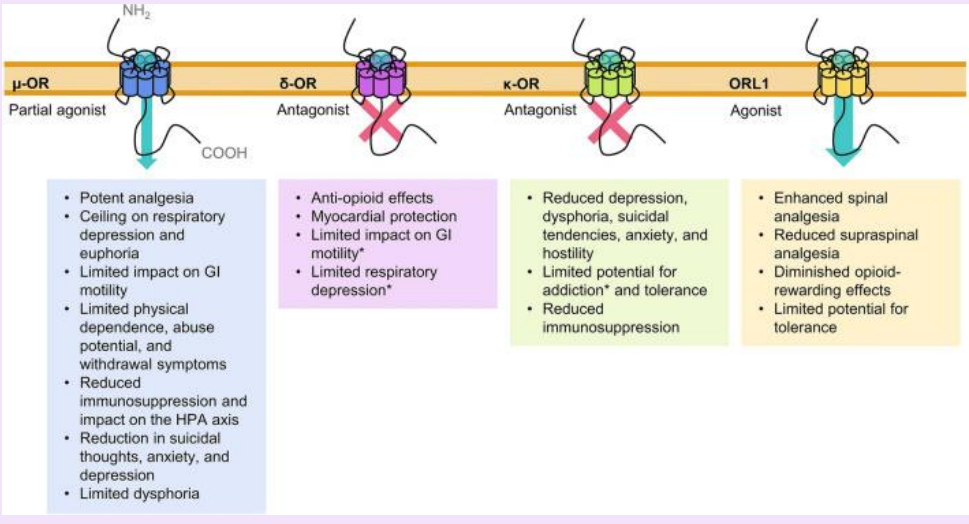
Buprenorphine Benefits for SCD

- 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**

17. Darbari DS, et al. Increased clearance of morphine in sickle cell disease: implications for pain management:*J Pain*. 2011 May;12(5):531-8
18. Prince E. et al. "Buprenorphine, It Works so Differently": Adults with Sickle Cell Disease Describe Transitioning to Buprenorphine for Treatment of Chronic Pain: *J Pain*. 2024 Mar;25(3):632-641
19. David MS. et al. Converting adults with sickle cell disease from full agonist opioids to buprenorphine: A reliable method with safety and early evidence of reduced acute care utilization: *Am J Hematol*. 2022 Nov;97(11):1435-1442

13

Buprenorphine Benefits: Opioid Agonist-Antagonist



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

20. Jeffrey G. et al. A Narrative Pharmacological Review of Buprenorphine: A Unique Opioid for the Treatment of Chronic Pain: *Pain Ther*. 2020 Jun; 9(1): 41–54.

14

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

21. Eshleman AD. et al. Affinity, potency, efficacy, selectivity, and molecular modeling of substituted fentanyls at opioid receptors: *Biochem Pharmacol.* 2020 Dec:182:114293.
22. Dhaliwal A. et al. Physiology, Opioid Receptor (Gi protein): In: StatPearls Publishing; 2024 Jan
23. Friedman A. et al. Opioids: Pharmacology, Physiology, and Clinical Implications in Pain Medicine: *Phys Med Rehabil Clin N Am.* 2020 May;31(2):289-303
24. Vanderah TW. Delta and kappa opioid receptors as suitable drug targets for pain: Clin J Pain. 2010 Jan:26 Suppl 10:S10-5

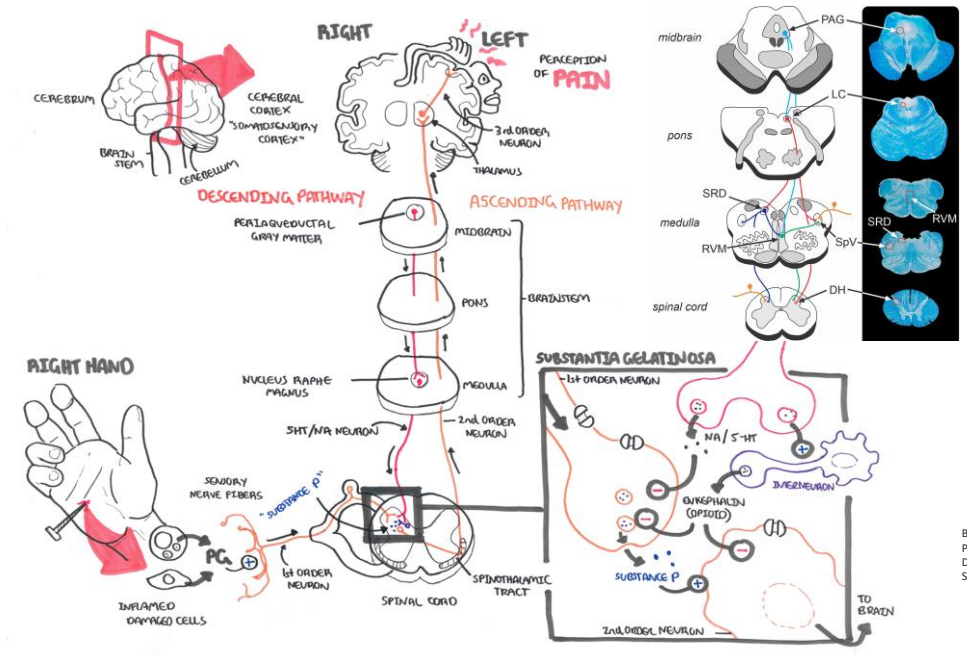
15

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

25. Davis M. et al. Treating Chronic Pain: An Overview of Clinical Studies Centered on the Buprenorphine Option. *Drugs*. 2018 Aug;78(12):1211-1228.
26. Tian X et al. β-arrestins and G protein-coupled receptor trafficking. *Handb Exp Pharmacol.* 2014:219:173-86.
27. Case AA. et al. Treating Chronic Pain with Buprenorphine-The Practical Guide: Curr *Treat Options Oncol.* 2021 Nov 18;22(12):116

16



Mills, EP. et al., *Brainstem Pain-Modulation Circuitry and Its Plasticity in Neuropathic Pain: Insights From Human Brain Imaging Investigations,* Front Pain Res. 2021 Jul 30:2:705345

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

17

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

27. Case AA. et al. Treating Chronic Pain with Buprenorphine-The Practical Guide: Curr Treat Options Oncol. 2021 Nov 18;22(12):116
30. Darbari DS. et al. Increased clearance of morphine in sickle cell disease: implications for pain management: *J Pain*. 2011 May;12(5):531-8
31. Pergolizzi J, et al. A consensus panel that recommends using buprenorphine as first-line opioid analgesic for the elderly. *Pain Pract*. 2008;8(4):287–313.
32. Davis MP. Twelve reasons for considering buprenorphine as a frontline analgesic in the management of pain. *J Support Oncol*. 2012;10(6):209–19

18

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

27. Case AA. et al. Treating Chronic Pain with Buprenorphine-The Practical Guide: Curr *Treat Options Oncol.* 2021 Nov 18;22(12):116

19

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

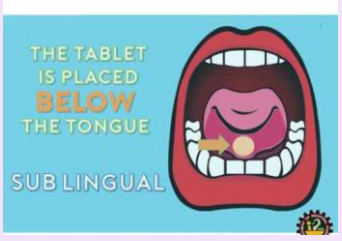
33. Case AA. et al. Treating Chronic Pain with Buprenorphine-The Practical Guide: Curr Treat Options Oncol. 2021 Nov 18;22(12):116
34. https://www.fda.gov/drugs/food-and-drug-administration-overdose-prevention-framework/timeline-selected-fda-activities-and-significant-events-addressing-substance-use-and-overdose
35. Phillips JK, Ford MA, Bonnie RJ, editors. Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use: National Academies Press (US); 2017 Jul 13.

20

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"



21

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**"

22

Thank you!!

Contact Info
Mayu Sakae, MD
msakae@coh.org

23

References

1) https://curesicklenow.org/index.php/what-is-bone-marrow-transplant,

2) https://www.onlymyhealth.com/what-are-paediatric-blood-disorders-and-how-bone-marrow-transplant-can-cure-the-condition-1603779371

3) https://abcnews.go.com/Health/2nd-hiv-patient-remission-stem-cell-transplant-doctors/story?id=61474356

4) https://www.slideshare.net/slideshow/bone-marrow-transplant-233262747/233262747#3

24