Non-Opioid Medications

Increasing Our Options for Treating Chronic Non-Malignant Pain:

Bruce Vrooman, MD, MS
Section Chief, Pain Medicine
Associate Professor of Anesthesiology
Dartmouth-Hitchcock Medical Center
Geisel School of Medicine at Dartmouth
September 29th,2023

Opioid Response Network

Project ECHO

Dartmouth-Hitchcock

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"What's new with what's old?"

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Disclosures

Commercial Support/Sponsorship:
There is no commercial support for this training.

Conflict of Interest:
In accordance with continuing education guidelines, speakers and planning committee members are asked to disclose relationships with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

Faculty: Dr. Vrooman has no relevant financial relationship(s) with ineligible companies to disclose.

Planning Committee Members: Have no relevant financial relationship(s) with ineligible companies to disclose. .

Mitigation Steps Implemented:
There were no reported financial relationships to be mitigated.

Objectives

- Present categories of medications for consideration
- Include updates regarding recent research on select medications
- Discuss novel uses for one particular older medication

Acetaminophen

- Oral
  - Postoperative
  - Chronic Pain
- IV
  - Paracetamol

NSAIDs
(Non-Steroidal Anti-inflammatory Drugs)

- Ketorolac
- Ibuprofen
- Nabumetone
- Naproxyn sodium
- Diclofenac

- Aspirin

Considerations Regarding NSAIDs with Interventional Pain Management Procedures

- American Society of Regional Anesthesia
- Guidelines in 2018 regarding interventional procedures
- Low, Intermediate, and High Risk Procedures
- Varying days in holding medications
- Consider risks, benefits, and alternatives
- Fortunately for most NSAIDs, elective
- Controversy regarding whether to hold aspirin

Anticonvulsants (Antineuropathics) (Membrane Stabilizing Medications)

- Gabapentin
  - GABA + cyclohexyl group
  - Does not bind to GABA A or B receptors
  - Auxiliary subunit of voltage-sensitive Ca2+ channels

Taylor CP. Rev Neurol. 1997

- Pregabalin
  - Voltage gated Ca2+ channel antagonist
  - Binds to alpha-2-delta subunit

Verma V. Curr Neuropharmacol. 2014 Jan;12(1):44-56.

Anticonvulsants (Antineuropathics) (Membrane Stabilizing Medications)

- Topiramate
  - Blocks voltage-dependent sodium and calcium channels
  - Inhibits excitatory glutamate pathway
  - Enhances inhibitory effect of GABA
  - Used when treatment refractory to other medications

Nazarbaghi S. Electron Physician. 2017 Oct; 9(10:5617-5622)

- Carbemazepine
  - First anticonvulsant studied
  - Decreases conductance in Na+ channels
    - Trigeminal neuralgia
    - **Painful diabetic neuropathy**
    - PHN (Post-Herpetic Neuralgia)

Tremont-Lukats. Drugs. 2000 Nov;60(5):1029-52.

Muscle Relaxants

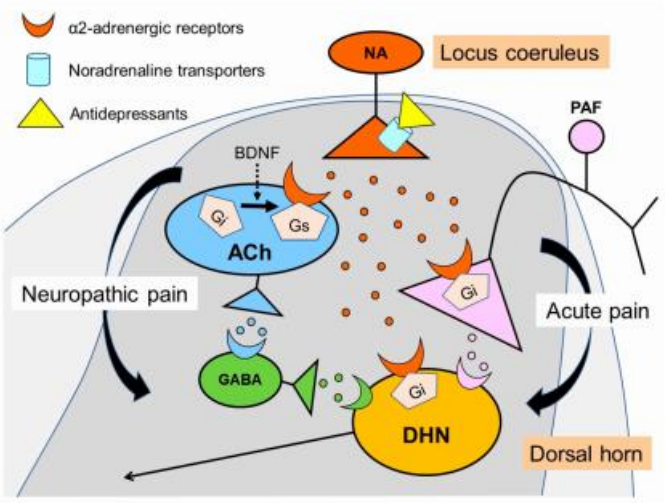
- Cyclobenzaprine
  - 5-HT2 receptor antagonist
- Tizanidine
  - Central alpha-2 adrenergic receptor agonist
- Carisoprodol
  - MOA (mechanism of action) unclear
  - Metabolite: mebrobamate active at $GABA_A$ receptor

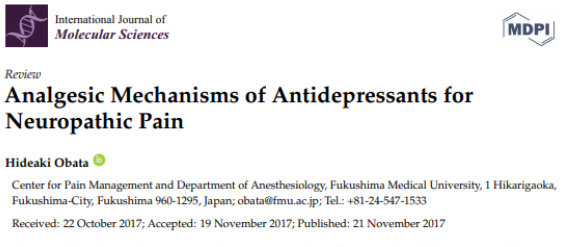
Anti-Depressants

✧ TCAs

(tricyclic antidepressants)

- Amitriptyline
- Nortriptyline




International Journal of *Molecular Sciences*

MDPI

Review

Analgesic Mechanisms of Antidepressants for Neuropathic Pain

Hideaki Obata

Center for Pain Management and Department of Anesthesiology, Fukushima Medical University, 1 Hikarigaoka, Fukushima-City, Fukushima 960-1295, Japan; obata@fmu.ac.jp; Tel.: +81-24-547-1533

Received: 22 October 2017; Accepted: 19 November 2017; Published: 21 November 2017

✧ SNRIs

(serotonin & norepinephrine reuptake inhibitors)

- Duloxetine
- Milnacipran

SNRIs increase NEp by blocking transporters at terminal of descending noradrenergic fiber from the locus ceruleus.

In neuropathic pain states (as compared with acute pain), alpha2-adrenergic receptors in cholinergic interneurons change from inhibitory to excitatory. Released acetylcholine binds to muscarinic receptors which produce analgesia through GABA release.

Obata H. et al. Int J Molec Sci 2017

Topicals

- Patches
  - Lidocaine
  - Capsaicin
- Creams
  - Diclofenac OTC (over the counter)
  - Compounded
    - Gabapentin
    - Clonidine
    - Etc.

Pain Medicine

Pain Medicine 2015; 16: 1610–1621
Wiley Periodicals, Inc.

ACUTE & PERIOPERATIVE PAIN SECTION

Original Research Articles

Lidocaine 5% Patch for Treatment of Acute Pain After Robotic Cardiac Surgery and Prevention of Persistent Incisional Pain: A Randomized, Placebo-Controlled, Double-Blind Trial

Vrooman et al.

ized, placebo-controlled, double-

are academic medical center.

Table 2 The effect of lidocaine 5% patch versus placebo on PDI

PDI	Lidocaine 5% patch ($N = 39$)	Placebo ($N = 39$)	Mean difference of lidocaine vs. placebo (95% CI)*	*P* value *
Modified intent-to-treat analysis				
Treatment × time				0.58
Main effect model			−2.5 (−7.11, 2.06)	0.28
Baseline	3.3 ± 6.8	3.0 ± 7.7		
POD 7	26 ± 17	30 ± 19		
POD 30	12 ± 14	13 ± 16		
POD 90	3.2 ± 7.8	5.0 ± 13.3		
POD 180	1.7 ± 6.4	4.8 ± 15.5		
All available data analysis				
Treatment × time				0.59
Main effect model			0.48 (−1.87, 2.84)	0.68
POD 7	27 ± 17†	30 ± 18‡		
POD 30	12 ± 14‡	11 ± 14§		
POD 90	2.4 ± 5.6‡	2.1 ± 6.5¶		
POD 180	0.5 ± 2.1§	1.9 ± 10.6¶		

Data are presented as mean ±SD; POD = Postoperative day.

* Repeated measures analysis of variance adjusting for baseline PDI; the higher the PDI, the greater the person's disability due to pain.

†,‡,§, and ¶ present for 1, 2, 3, and 4 missing data points, respectively.

Topicals

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  - Capsaicin
- Creams
  - Diclofenac OTC
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    - Etc.

Crit Care Nurse. 2019 Oct;39(5):51-57. doi: 10.4037/ccn2019849.

Topical Lidocaine Patch for Postthoracotomy and Poststernotomy Pain in Cardiothoracic Intensive Care Unit Adult Patients

Michael Liu [1], Mabel Wai [2], James Nunez [2]

Table 1 Studies evaluating topical lidocaine patch for perioperative pain management

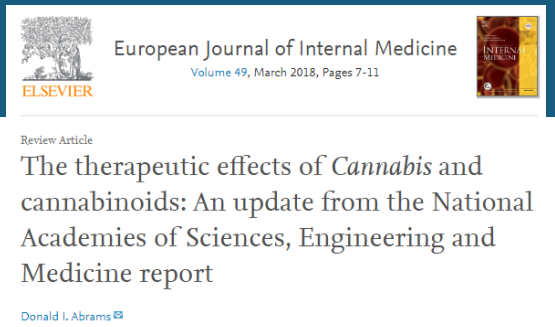
Source	Trial design	Population	Interventions	Outcomes and results
Saber,[12] 2009	Randomized, single-center, open-label study	Inpatient, general surgery; laparoscopic ventral hernia repair (n=30)	Lidocaine 5% patch vs no lidocaine 5% patch	Lidocaine 5% patches significantly reduced postoperative pain at discharge compared with no lidocaine 5% patch (VAS, 3.1 vs 4.8; *P*=.007). No difference in hospital LOS existed (1.2 vs 2.5 days; *P*=.14).
Khanna,[13] 2012	Prospective, single-center, cohort study	Orthopedic surgery, total knee arthroplasty (n=31)	One or more lidocaine 5% patches vs no lidocaine 5% patches. All patients were also provided with nonopioid and opioid analgesics and patient-controlled analgesia.	Lidocaine 5% patches resulted in a statistically significant difference in VAS on day 3 (5.1 vs 6.3; *P*=.05); pain improvement by end of hospital stay was similar. No difference in hospital LOS after surgery existed (12.3 vs 13.2 days; *P*=.14).
Vrooman,[3] 2015	Randomized, placebo-controlled, single-center, double-blind trial	Cardiothoracic surgery, acute pain after cardiac robotic surgery and prevention of persistent incisional pain (n=80)	Up to 3 lidocaine 5% patches per day vs placebo for up to 6 months or until analgesia was no longer required. Opioid and nonopioid analgesics were also provided.	No difference in mean VAS pain reduction scores from baseline between lidocaine 5% patch and placebo groups existed (-0.39 vs -0.13; *P*=.27).

Abbreviations: LOS, length of stay; VAS, visual analogue scale.

Conclusion

This retrospective study demonstrates that the addition of transdermal lidocaine 5% patches to standard care did not reduce acute postthoracotomy and poststernotomy pain in CTICU patients after cardiothoracic surgery. CCN

Cannabis



- National Academy of Sciences Report

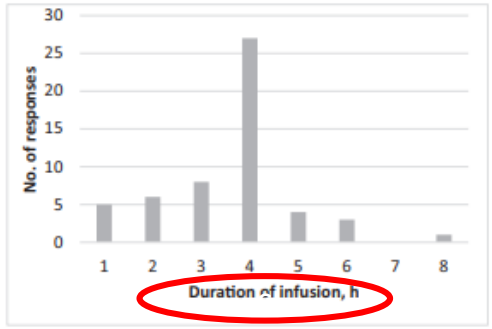
- 11 Prioritized Health Endpoints:
  - Therapeutic Effects
  - Cancer Incidence
  - Cardiometabolic Risk
  - Respiratory Disease
  - Immune Function
  - Injury and Death
  - Perinatal and postnatal outcomes
  - Psychosocial Outcomes
  - Mental Health
  - Problem cannabis use
  - Use of other substances

- Difficult to Study, Though Presented the Following:
- Conclusive or Substantial Evidence of Benefit:
  - Treatment of Pain in Adults
  - CTX-Induced N/V
  - MS-Associated Spasticity
- Moderate Evidence:
  - Secondary Sleep Disturbances
- Limited, Insufficient or Absent Evidence:
  - Appetite
  - Tourette Syndrome
  - Anxiety
  - PTSD
  - CA
  - IBS
  - Epilepsy
  - Neurodegenerative Disorders

Ketamine

- Troches
- Nasal Spray
- Infusions

Intravenous Ketamine Infusion for Complex Regional Pain Syndrome: Survey, Consensus, and a Reference Protocol
Pain Medicine
Xu, Jijun et al. Vol. 20 Issue 2, pp. 323–334, 2019.



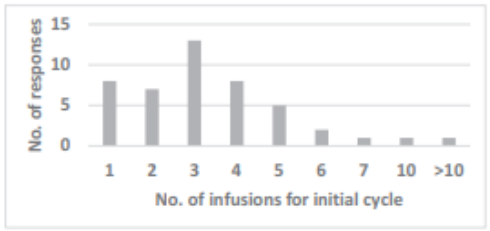


Figure 2 Number of outpatient infusions for initial cycle (adult).

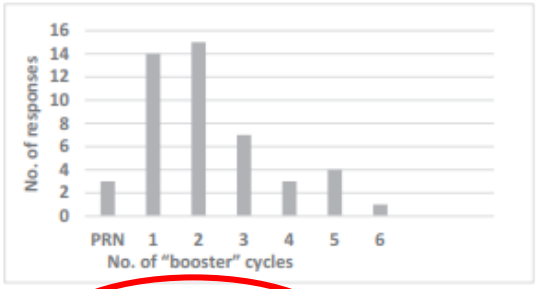


Figure 3 Sessions for outpatient intravenous ketamine "booster" infusion cycles (adult).

Ketamine

- Troches
- Nasal Spray
- Infusions

Intravenous Ketamine Infusion for Complex Regional Pain Syndrome: Survey, Consensus, and a Reference Protocol
Pain Medicine
Xu, Jijun et al. Vol. 20 Issue 2, pp. 323–334, 2019.

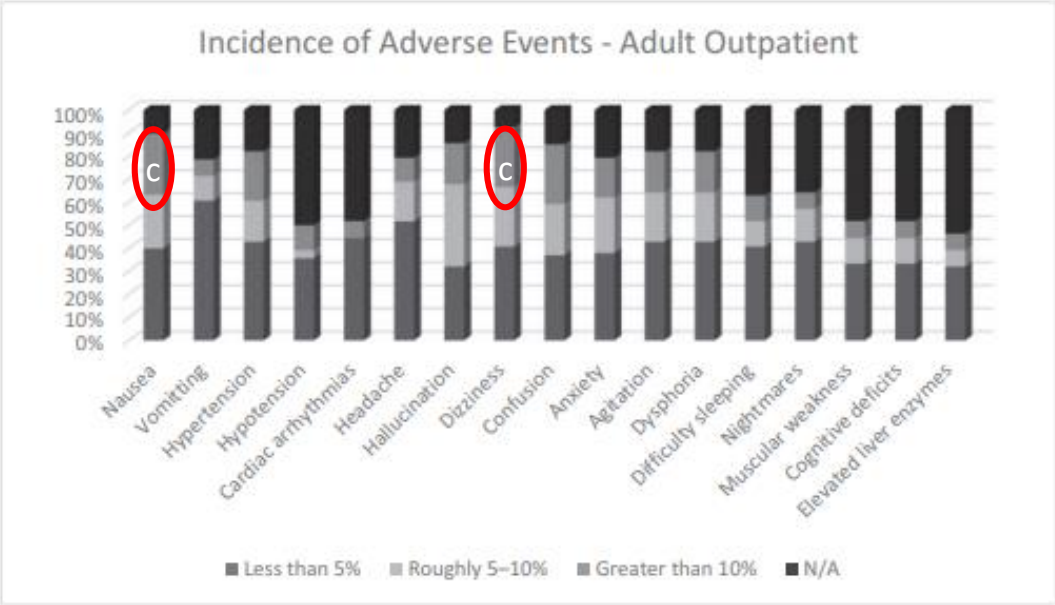


Figure 4 Reported adverse effects of intravenous ketamine infusion in complex regional pain syndrome patients.

Microglial Attenuating Medications – A History Regarding Naltrexone

- Naltrexone synthesized in 1963
- 1971 President Nixon created Special Action Office for Drug Abuse Prevention
- Dr. Alan I. Green, recently passed, played advisory role
- 1980 Low Dose Naltrexone (LDN)discovered at Penn State
- 1983 Dr. Patricia McLaughlin published paper in Science in 1983
- 1985 Clinical use by Dr. Bernard Bihari for MS
- 1995: FDA approved 50mg dose for alcohol abuse
- Subsequent Development:
  - Low Dose Naltrexone
  - Very Low Dose Naltrexone
  - Ultra Low Dose Naltrexone

LDN (Low-Dose Naltrexone)

- Revisit Fibromyalgia
- Consider Other Indications
- Prospective Study at D-H

Fibromyalgia Pilot - 2009

Pain Medicine

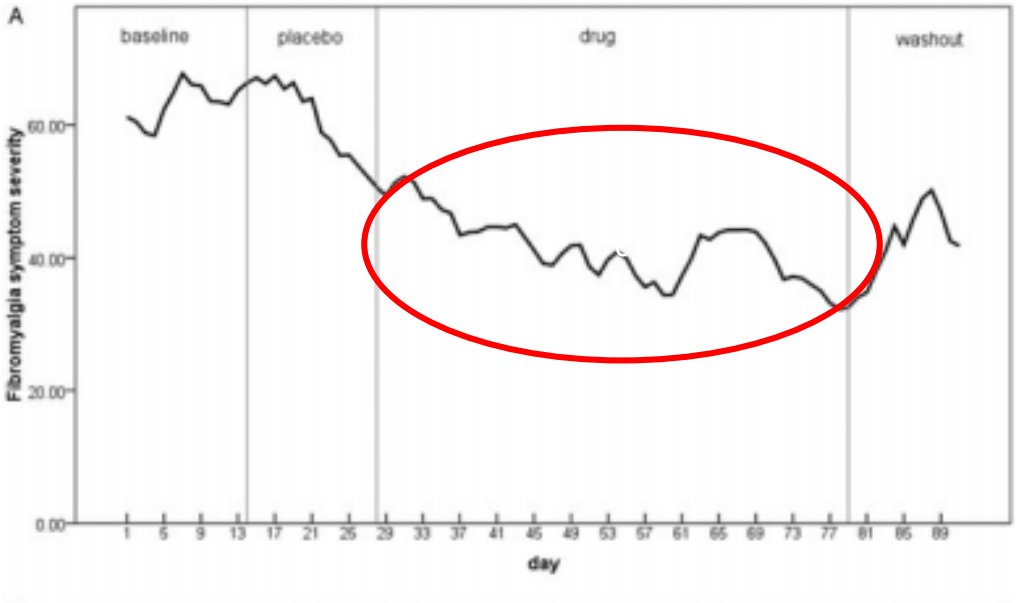
PAIN MEDICINE
Volume 10 • Number 4 • 2009

PRELIMINARY RESEARCH

Fibromyalgia Symptoms Are Reduced by Low-Dose Naltrexone: A Pilot Study

Jarred Younger, PhD, and Sean Mackey, MD, PhD

School of Medicine, Department of Anesthesia, Division of Pain Management, Stanford University, Palo Alto, California, USA



Subsequent Study

ARTHRITIS & RHEUMATISM
Vol. 65, No. 2, February 2013, pp 529–538
DOI 10.1002/art.37734

Low-Dose Naltrexone for the Treatment of Fibromyalgia

Findings of a Small, Randomized, Double-Blind, Placebo-Controlled, Counterbalanced, Crossover Trial Assessing Daily Pain Levels

Jarred Younger, Noorulain Noor, Rebecca McCue, and Sean Mackey

NALTREXONE FOR THE TREATMENT OF FIBROMYALGIA

Figure 1. Outline of the study protocol.

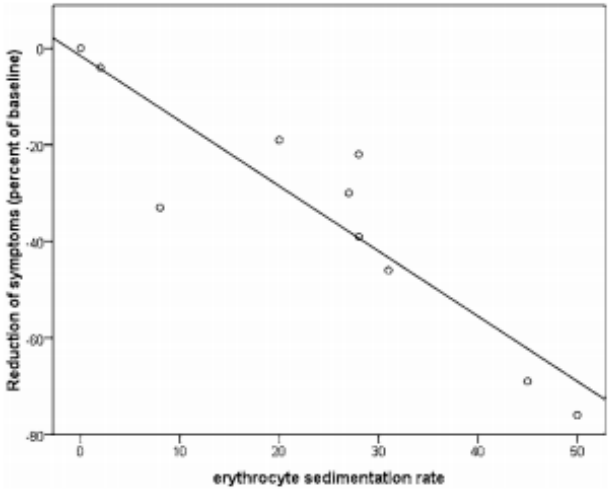


Figure 3 Relationship between drug response (reduction of fibromyalgia symptoms in the drug condition) and baseline erythrocyte sedimentation rate.

LDN

- Naltrexone
- Low Dose Naltrexone
- Very Low Dose Naltrexone

Low-Dose Naltrexone (LDN)—Review of Therapeutic Utilization

Medical Sciences

Toljan, Karlo; Vrooman, Bruce

Vol. 6 Issue 4, p. 82, 2018.

Table 1. Mechanisms of action and clinical use in regard to different doses of naltrexone used.

Dose Range	Dose Specific Mechanism of Action	Clinical Use
Standard (50–100 mg)	Opioid receptor antagonism	Alcohol and opiate abuse
Low-dose (1–5 mg)	Toll-like receptor 4 antagonism, opioid growth factor antagonism	Fibromyalgia, multiple sclerosis, Crohn's disease, cancer, Hailey-Hailey disease, complex-regional pain syndrome
Very low-dose (0.001–1 mg)	Possibly same as low-dose	Add-on to methadone detoxification taper
Ultra low-dose (<0.001 mg)	Binding to high affinity filamin-A (FLNA) site and reducingμ-opioid receptor associated Gs-coupling	Potentiating opioid analgesia

Table 4. A summary of clinical experience on ultra low-dose naloxone/naltrexone per peer-reviewed literature.

Syndrome/Model	Type of Study (Number of Subjects)	Notable Outcomes	Reference
Cholestasis pruritus	Case report (1)	• Reduction of pruritus and improved mental status despite concurrent opioid therapy	Zylicz et al. [40]
Osteoarthritis	Phase II randomized controlled trial (362)	• Adding 2 μg of naltrexone to concurrent opioid therapy provides greater analgesia • High dropout rate due to opioid side effects	Chindalore et al. [88]
Low back pain	Phase III randomized controlled trial (719)	• Adding 2 μg of naltrexone to opioid therapy provides a more favorable response and reduces side effects • High dropout rate precluded further application	Webster et al. [86]
Axillary brachial plexus blockade	Randomized controlled trial (112)	• Onset of time for motor and sensory blockade were longer with additional 100 ng of naloxone • Added naloxone prolongs motor blockade and analgesia	Movafegh et al. [92]
Buprenorphine antinociception in healthy subjects	Double-blind crossover trial (10)	• Applying buprenorphine with naloxone in 166:1 ratio boosts tolerance to cold pressor test	Hay et al. [93]
Postoperative pain control following colorectal surgery	Randomized controlled trial (72)	• Adding 0.25 μg/kg/h of naloxone during surgery and postoperative period lowered opioid consumption, shortened length of stay, and hastened bowel function recovery	Xiao et al. [91]
Postoperative pain control following lumbar discectomy	Randomized controlled trial (80)	• Adding 0.25 μg/kg/h of naloxone during first 24 h postoperative period reduced opioid consumption and side effects	Firouzian et al. [90]

LDN Prospective Study on PDN (Painful Diabetic Neuropathy)

- Titration Regimen:

LDN: 1.5mg/capsule.

Do not use calcium as a filler.

Start with one capsule each day for a week.

After one week may increase to 2 capsules a day.

After one week may increase to 3 capsules a day.

Summary

- Multiple non-opioid pain medications may be considered, each with their own risks, benefits, and alternatives.
- There has been recent interest and research in ketamine, among other medications
- Novel applications and dosing for naltrexone are being discovered.
- Please email me if you have patients for consideration of LDN for Painful Diabetic Neuropathy pilot study.

Thank you!

Bruce.M.Vrooman@Hitchcock.org