Ketamine & Other Non-Pharmacological Interventions in the Perioperative Period

Steven P. Cohen, MD

Pain & Addiction Common Threads Course | April 13, 2023

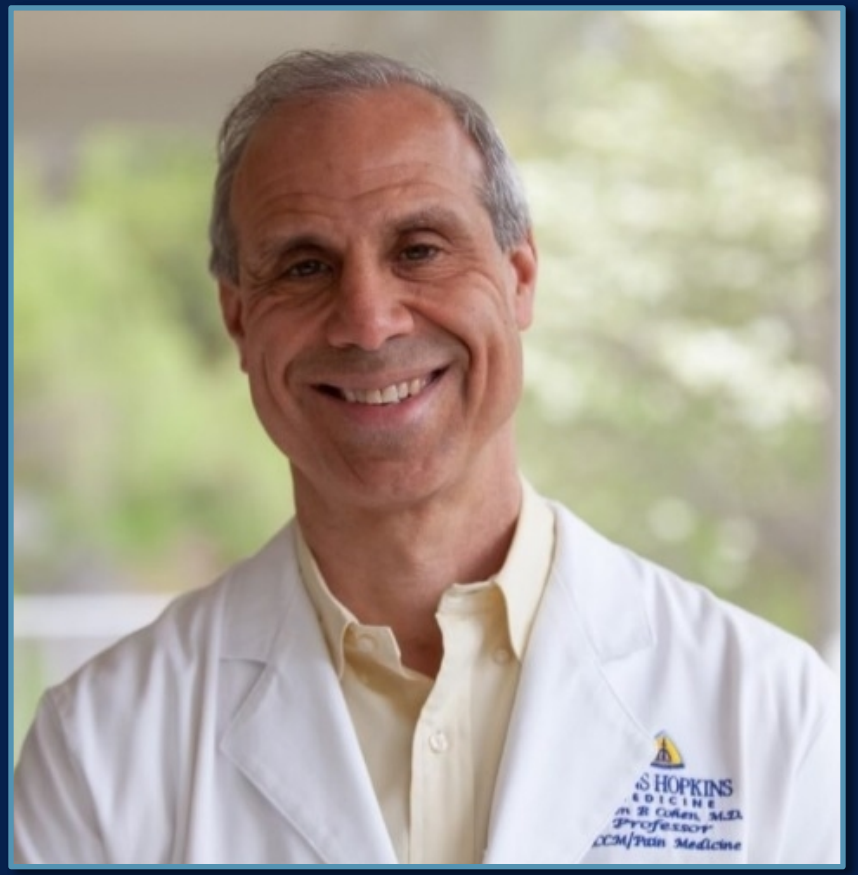
Disclosure Information (Required)

Ketamine & Other Non-Pharmacological Interventions in the Perioperative Period

April 13, 2023

Steven Cohen, MD

- **Consultant for Avanos, Scilex, Persica, Releviate, Clearing & SPR (none relevant to lecture)**
- **This presentation does discuss off-label usage**

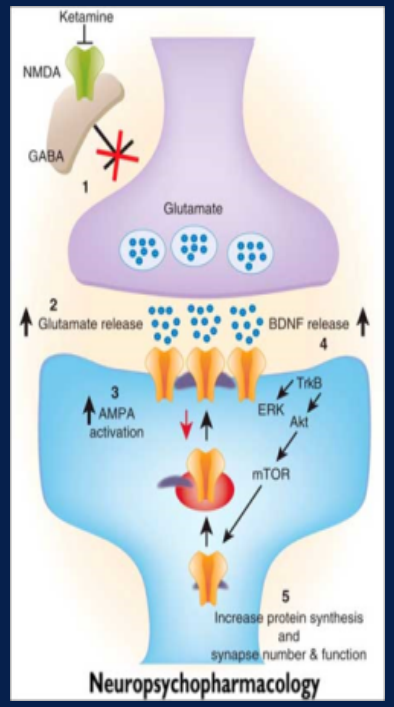


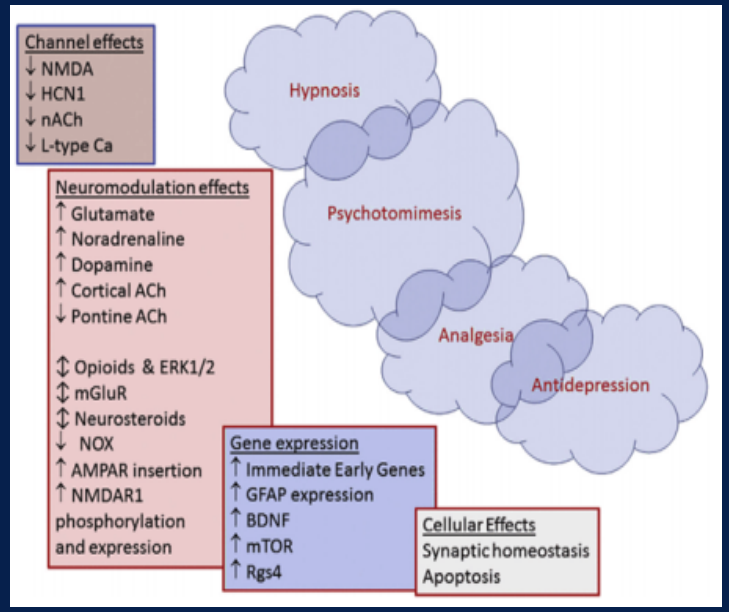
Learning Objectives

- Understand the evidence supporting the preemptive use of ketamine in the perioperative setting and its ability to reduce opioid consumption
- Be familiar with the evidence supporting PNS & RFA for postsurgical pain
- Be cognizant of the limitations in clinical trials evaluating regional anesthesia for prevention of postamputation pain
- Understand the rationale and outcomes for preoperative psych interventions in high-risk patients

Mechanisms of Action for Ketamine

- NMDA receptor antagonism
- Antagonism of nicotinic and muscarinic cholinergic receptors
- Blockade of Na+ and K+ channels
- Activation of D2 dopamine receptors
- Activation of L-type voltage-gated Ca++ channels
- Facilitation of GABA signaling
- Enhancement of descending modulatory pathways





Ketamine and Psychiatric Morbidity

- Co-prevalence rate of depression 30%-60%
- Ketamine makes people ‘feel good’
- Low-dose ketamine alleviates depression
  - IV ketamine, higher doses > Esketamine
  - Psychomimetic effects correlated with antidepressant effects in 37.5% of studies
- Evidence growing for PTSD & other psychiatric illnesses
- Growing rate of abuse
  - 2.3 million people in U.S. over 12 years old reported using ketamine
  - 3% of high school students
  - Increasingly implicated in MVCs
    - One study in Hong Kong found ketamine in 45% of subjects involved in non-fatal MVCs

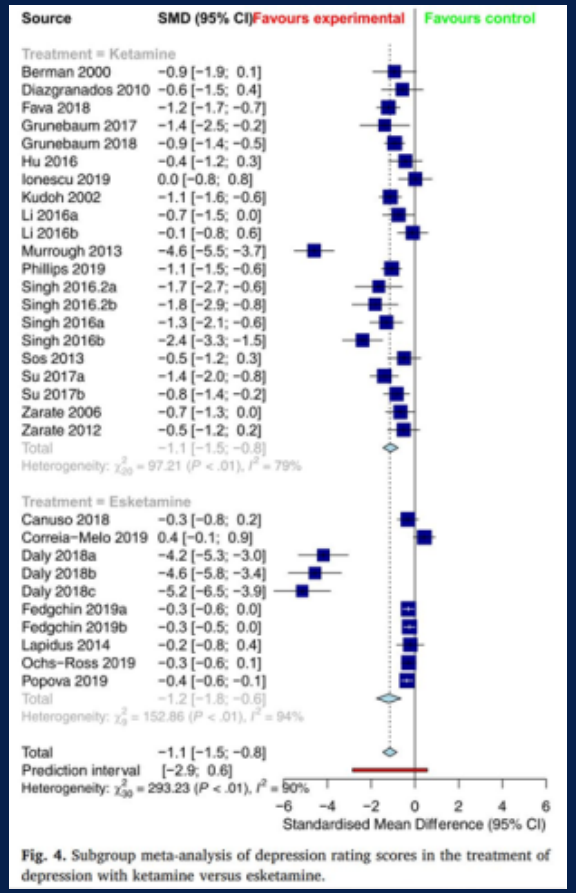
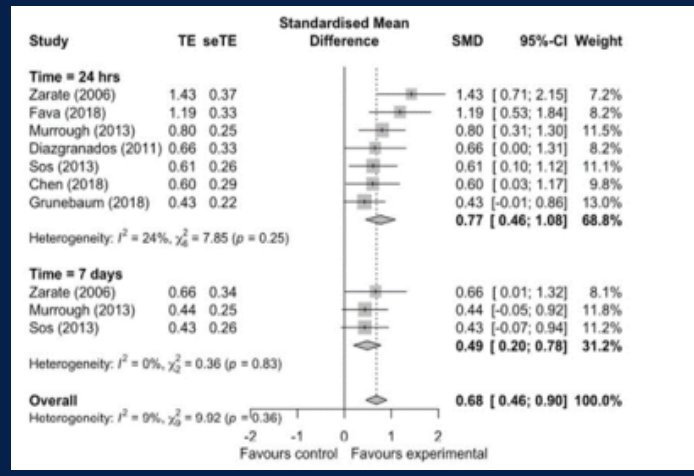
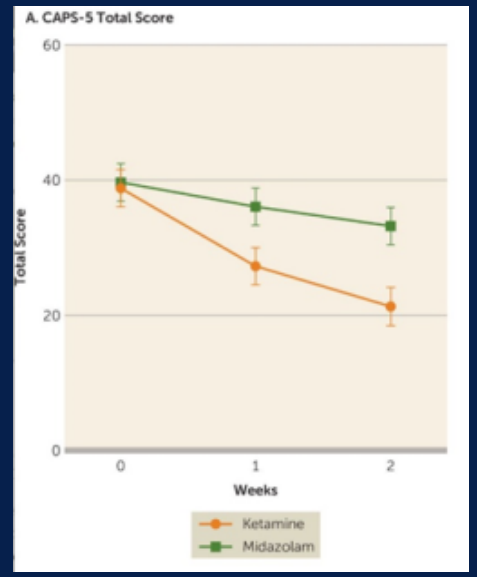


Fig. 4. Subgroup meta-analysis of depression rating scores in the treatment of depression with ketamine versus esketamine.

Bahji et al. 2021: IV Ketamine vs. s-Ketamine for Depression



Marcantoni et al. 2020: 0.5 mg/kg IVfor Depression Ketamine vs. Placebo for Depression

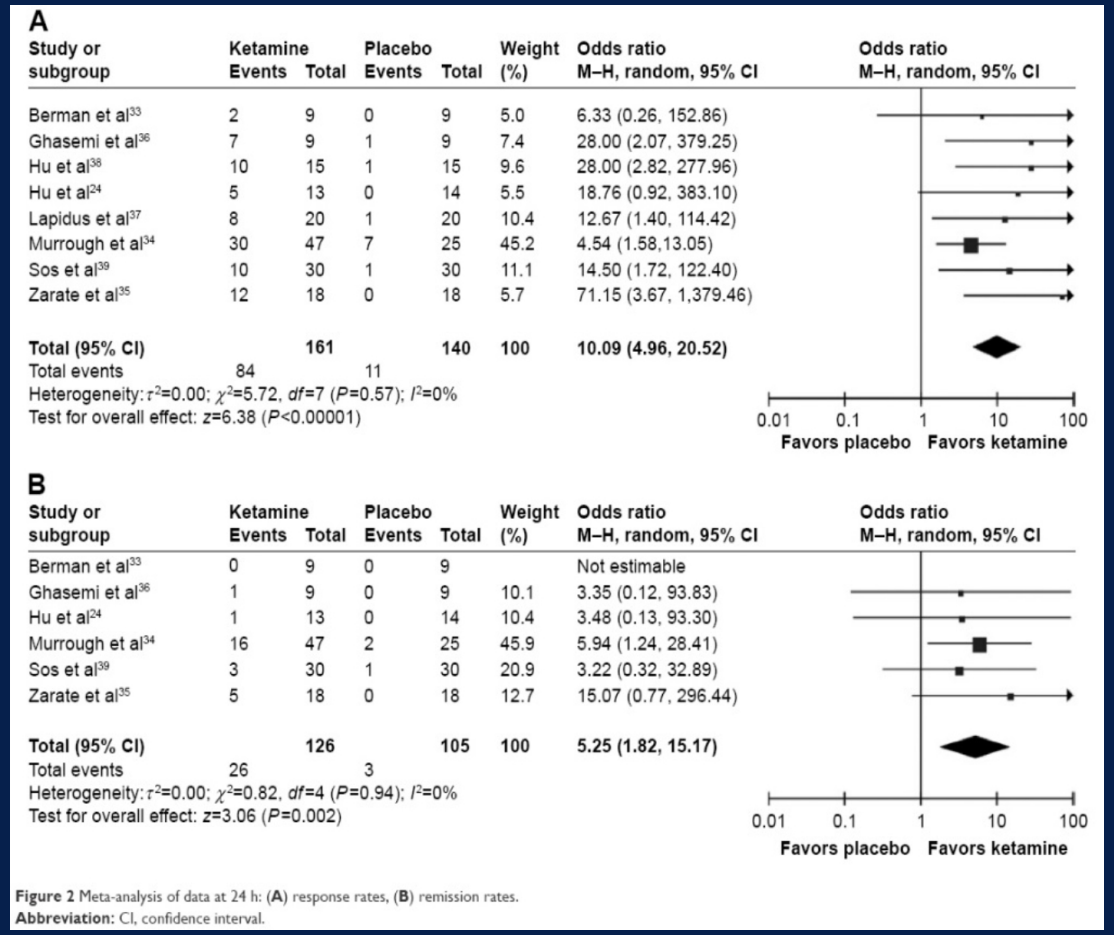


Feder et al. 2021: Repeat Ketamine vs. Versed for PTSD

2013 National Survey on Drug Use and Health in U.S.; Mathai et al. 2021; Wong et al. Hong Kong Med JBahjiet al. 2021: IV Ketamine vs.s-Ketamine for DepressionFeder et al. 2021: Repeat Ketamine vs. Versed for PTSD

Depression & Pain Treatment

- Ketamine similar to other drugs effective for depression & pain
  - TCAs, SNRI, SSRI, MAOI, ECT, tDCS/rTMS
- May involve AMPA receptor up-regulation, activation of BDNF & mammalian target of rapamycin (mTOR) signaling pathways
  - All potential pain targets
  - > 4200 PubMed citations for depression, >4400 for pain (< 800 for chronic pain), > 1000 for anxiety, > 300 for depression



A

Study or subgroup	Ketamine Events	Ketamine Total	Placebo Events	Placebo Total	Weight (%)	Odds ratio M–H, random, 95% CI
Berman et al[33]	2	9	0	9	5.0	6.33 (0.26, 152.86)
Ghasemi et al[36]	7	9	1	9	7.4	28.00 (2.07, 379.25)
Hu et al[38]	10	15	1	15	9.6	28.00 (2.82, 277.96)
Hu et al[24]	5	13	0	14	5.5	18.76 (0.92, 383.10)
Lapidus et al[37]	8	20	1	20	10.4	12.67 (1.40, 114.42)
Murrough et al[34]	30	47	7	25	45.2	4.54 (1.58,13.05)
Sos et al[39]	10	30	1	30	11.1	14.50 (1.72, 122.40)
Zarate et al[35]	12	18	0	18	5.7	71.15 (3.67, 1,379.46)
Total (95% CI)		**161**		**140**	**100**	**10.09 (4.96, 20.52)**
Total events	84		11			

Heterogeneity: τ^2=0.00; χ^2=5.72, df=7 (P=0.57); I^2=0%
Test for overall effect: z=6.38 (P<0.00001)

Odds ratio M–H, random, 95% CI
0.01 0.1 1 10 100
Favors placebo Favors ketamine

B

Study or subgroup	Ketamine Events	Ketamine Total	Placebo Events	Placebo Total	Weight (%)	Odds ratio M–H, random, 95% CI
Berman et al[33]	0	9	0	9		Not estimable
Ghasemi et al[36]	1	9	0	9	10.1	3.35 (0.12, 93.83)
Hu et al[24]	1	13	0	14	10.4	3.48 (0.13, 93.30)
Murrough et al[34]	16	47	2	25	45.9	5.94 (1.24, 28.41)
Sos et al[39]	3	30	1	30	20.9	3.22 (0.32, 32.89)
Zarate et al[35]	5	18	0	18	12.7	15.07 (0.77, 296.44)
Total (95% CI)		**126**		**105**	**100**	**5.25 (1.82, 15.17)**
Total events	26		3			

Heterogeneity: τ^2=0.00; χ^2=0.82, df=4 (P=0.94); I^2=0%
Test for overall effect: z=3.06 (P=0.002)

Odds ratio M–H, random, 95% CI
0.01 0.1 1 10 100
Favors placebo Favors ketamine

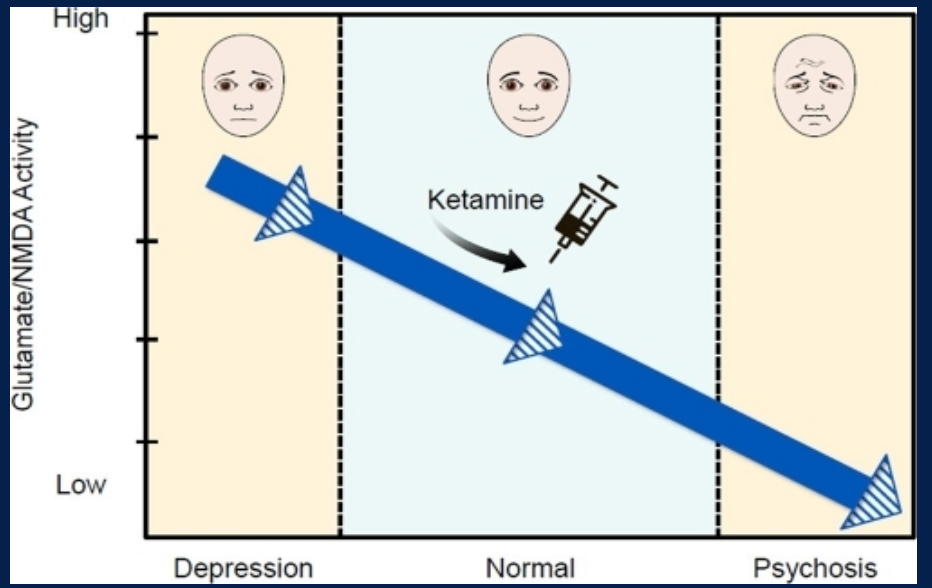
Figure 2 Meta-analysis of data at 24 h: (**A**) response rates, (**B**) remission rates.
Abbreviation: CI, confidence interval.

Han et al. Neuropsychiatr Dis Treat 2016

Pain Dimensions: More Effective for Affective Component?

- Described in 1968 by Melzack & Casey
- Sensory-Discriminative- Based on nociceptive input, includes magnitude & location
  - Can be measured by QST
- Affective-Motivational- Evolutionary arousal & negative emotions (unpleasantness), from limbic & reticular structures
- Cognitive-Evaluative- Provides contextual info based on past experiences and likely outcomes (attitudes and beliefs), processed via higher CNS structures

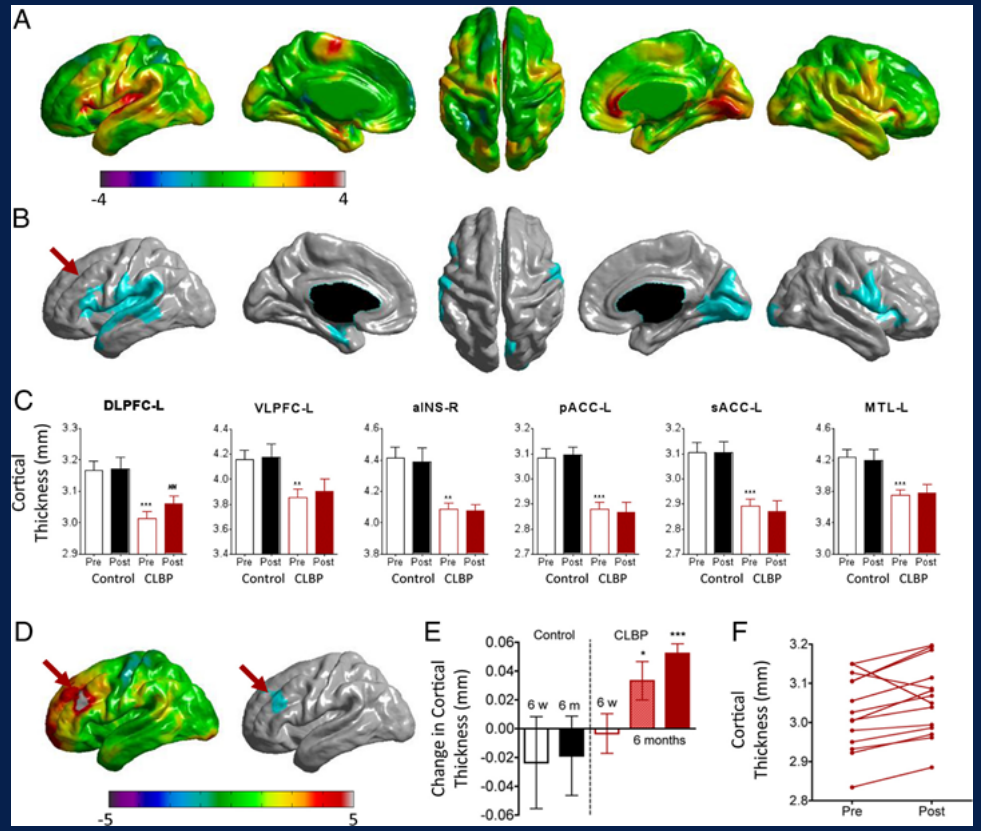
- Most studies have reported negative effects of ketamine on QST after 48h
- Schwartzman et al. RCT in 19 pts with CRPS: 31% reduction in S-D component vs. 46% in A-M component



Eichenberger et al. A & A 2008, Schwartzman et al. Pain 2009; Noppers et al. EJP 2011

Can Central Sensitization Actually Be Reversed?

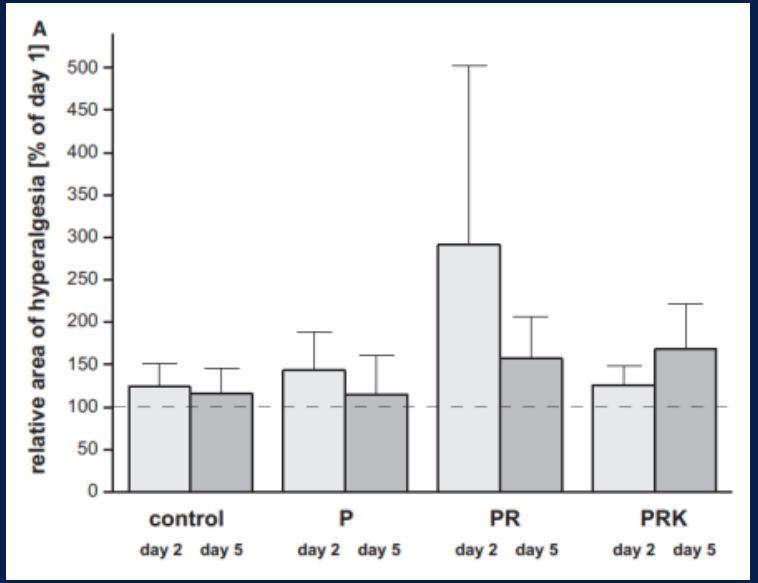
- Chronic pain-induced changes occur on a chemical, functional and anatomical level
- Seminowicz et al. J Neurosci 2011
  - C-LBP associated with decreases in gray matter & cognitive changes
  - 18 pts with c-LBP > 1 yr and 16 controls underwent structural and f-MRIs, and cognitive and functional assessments
  - Relative to controls, patients before treatment had significantly thinner cortex in left dorsolateral prefrontal cortex (DLPC), bilateral anterior insula/frontal operculum, left mid/posterior insula, left S1, left medial temporal lobe, and right anterior cingulate cortex (ACC), and greater cognitive deficits and physical disability
  - 6 mo post-treatment with surgery or facet blocks, the 14 pts who rec'd f/u had increased left DLPC, which was assoc. with improved pain and function.
  - Increased thickness in 1º motor cortex & right anterior insula assoc. with reduced disability and pain, respectively

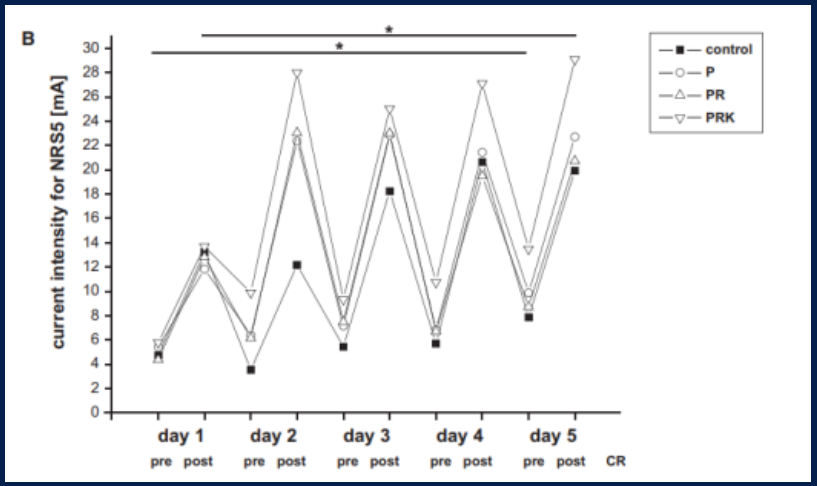


Rows A & B: Yellow and Red (A) and Blue (B) areas represent decreases in gray matter in cLBP pts. D represents areas of increased thickness in treatment responders. E shows increased cortical thickness at 6 wks (minimal) and at 6 mos in all cLPB patients (thatched red bar) and responders (solid red bar) following spine surgery (n=8) or facet blocks (n=6)

Can Ketamine Reverse Central Sensitization

- Conditioned Pain Modulation is a surrogate marker for descending pain inhibition and abnormal pain processing/ central sensitization.
- Niesters et al. Br J Anaesth 2013: Crossover study in 10 pts with neuropathy comparing ketamine (.57 mg/kg/h x 1 h) to MS04 to placebo
  - Ketamine caused larger decreases in pain than morphine & placebo, but no significant differences in CPM augmentation was noted between groups (ketamine 10.9%; MS04 7.0%; and placebo 12%)
- Nickel et al. Pain Pract 2016: 48 volunteers underwent conditioning noxious electrical stimulation x 5 days and day 22 with general anesthesia x 2 h after baseline QST: control, propofol, prop/remifentanil, prop/remi/ketamine in double-blind study
  - Prop/remi showed trend toward greater 2^{o} hyperalgesia @ 2 d than other groups (NS with Bonferroni correction). Differences in groups for other variables were non-significant showing pro- and anti-nociceptive effects



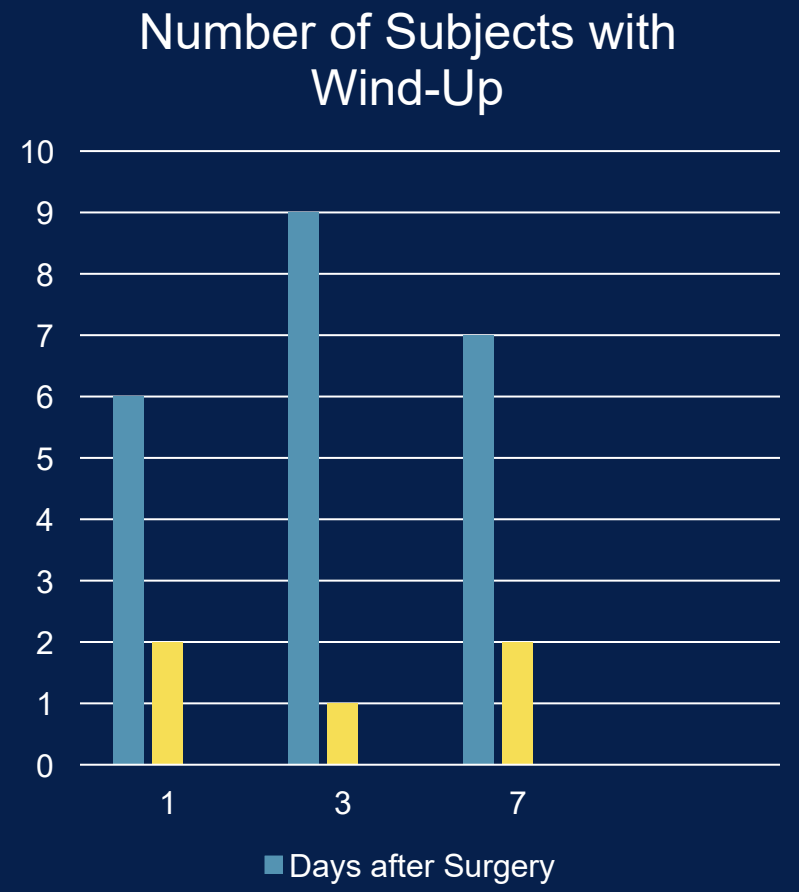


RCTs Evaluating Ketamine on Quantitative Sensory Testing

- Kvarnstrom et al. 2003: Crossover study in 12 pts with post-traumatic NeuP
  - Ketamine dose 0.4 mg/kg over 40 min
  - VAS reduction of 55%, 34% and 22% for ket, lidocaine and placebo over 2.5 hrs
  - No significant difference in QST between responders and non-responders, or dose-response
  - High incidence of AE's with ketamine limits its usefulness
- Kvarnstrom et al. 2004: Crossover DB study in 10 pts with SCI
  - Same dose regimen & methodology as first study
  - 50% of ket vs. 10% of lido vs. 0% of placebo pts responded over 2.5 hrs, but no treatment was associated with QST changes
- Baad-Hansen 2007: Compared ket, fentanyl and NS in 10 pts with intraoral pain and 10 healthy controls
  - No effect of either drug on spontaneous intraoral pain
  - For QST, fentanyl > ketamine on some measures
- Eichenberger et al. 2008: Crossover study 20 pts with PLP who rec'd calcitonin, ketamine and placebo
  - Ketamine > calcitonin & placebo up to 48h (no benefit for calcitonin-ketamine combo)
  - Ketamine/calcitonin > calcitonin & placebo for electrical pain threshold & tolerance but not for pressure or heat
- Kiefer et al. 2008: No effect on pain scores or QST in 4 pts with refractory CRPS in pilot study
- Nickel et al. 4-arm RCT comparing no treatment, propofol, propofol/remi and propofol/remi/ketamine after noxious stimulus in 48 volunteers
  - No effect of regimen on pain modulation or hyperalgesia

Evidence for Ketamine Reversing Central Sensitization

- Neuroinflammation implicated in chronic pain, neurodegeneration (e.g. MS, PD, stroke) and cognitive impairment
  - Activates NMDA receptors & can be prevented by NMDA-R antagonism (e.g. inhibits microglial activation and pro-inflammatory cytokines)
- Prominent in nociplastic conditions
- Stubhaug et al. 2008: 20 living kidney donors randomized to 0.5 mg/kg ketamine bolus pre-incision followed by 48 h infusion or saline control
  - Ketamine group had decreased area of punctate hyperalgesia and temporal summation (wind-up) compared to control



Stubhaug et al. Acta Anaesthesiol Scand 1997

Surgery and New Opioid Use & Abuse

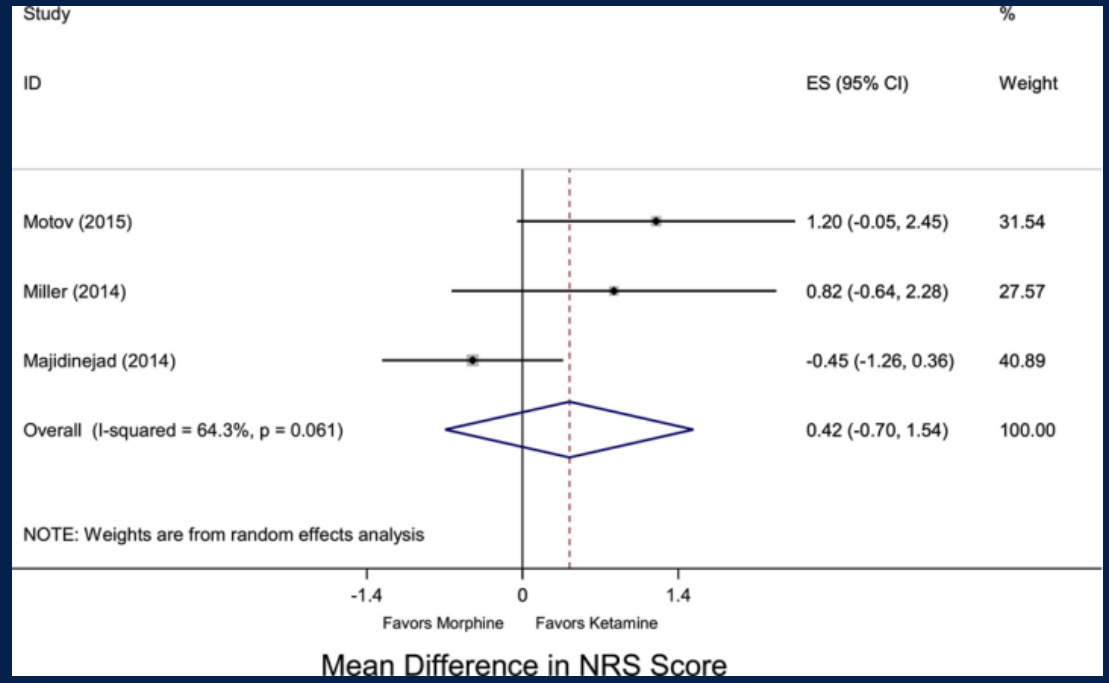
- Opioids are “gold standard” for treating acute pain
  - Approximately 6% of people given opioids after surgery will continue long-term
  - Baseline RF (chronic pain condition, h/o substance abuse, baseline psychopathology) > type of surgery
  - Rate of PPSP is high (about 12% for moderate pain, < 5% for severe, > 50% for certain operations)
- Poorly treated acute pain increases risk for PPSP
- Poorly treated substance abuse contraindication for chronic pain rx, not acute

- Namiranium et al. J Subst Abuse Treat 2020
  - Compared relapse rates in 87 veterans in opioid agonist program > 1 yr. undergoing surgery vs. 249 control vets not receiving surgery
  - Within 1 yr, 58% of surgical pts had misuse vs. 31% of control groupe (OR 1.91, 95% CI 1.05–3.48, p=0.034)
  - Overdose rate 2.3% vs. 0.5%
  - Increased rates of (+) opioids and BZD on 1st urine tox screen

Brummett et al. JAMA Surg 2017; Karlow et al. Ann Emerg Med 2018

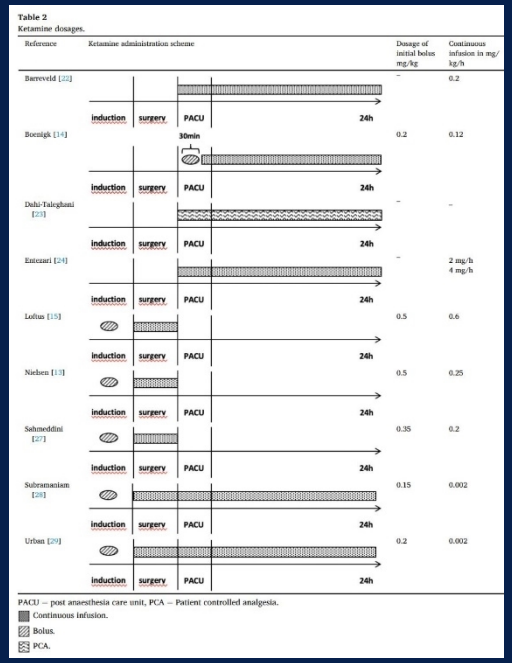
Ketamine vs. Opioids for Acute Pain

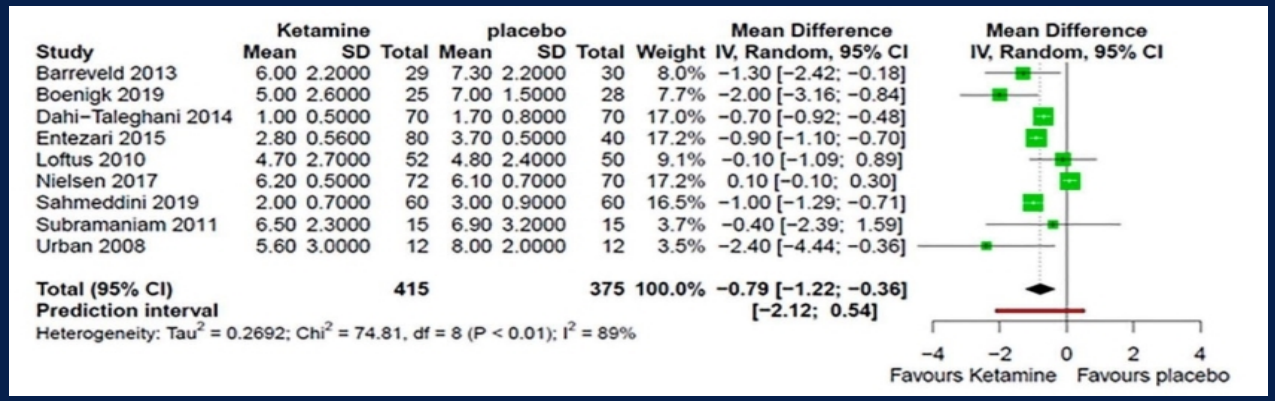
- Karlow et al. Ann Emerg Med 2018: Meta-analysis comparing low-dose (≤ 0.5 mg/kg) IV ketamine to opioids for acute pain in ED
  - 1º outcome- Reported pain closest to 10" after administration
  - 3 studies, 251 patients
- Mean difference in pain scores 0.42 (95% CI = –0.70 to 1.54)
- Ketamine had more AEs (18 vs. 8) and requests for repeat dosing (4 vs. 0)
  - None serious
- Concluded ketamine non-inferior to opioids



Placebo-Controlled Trials for Postoperative Pain in Opioid-Tolerant Patients

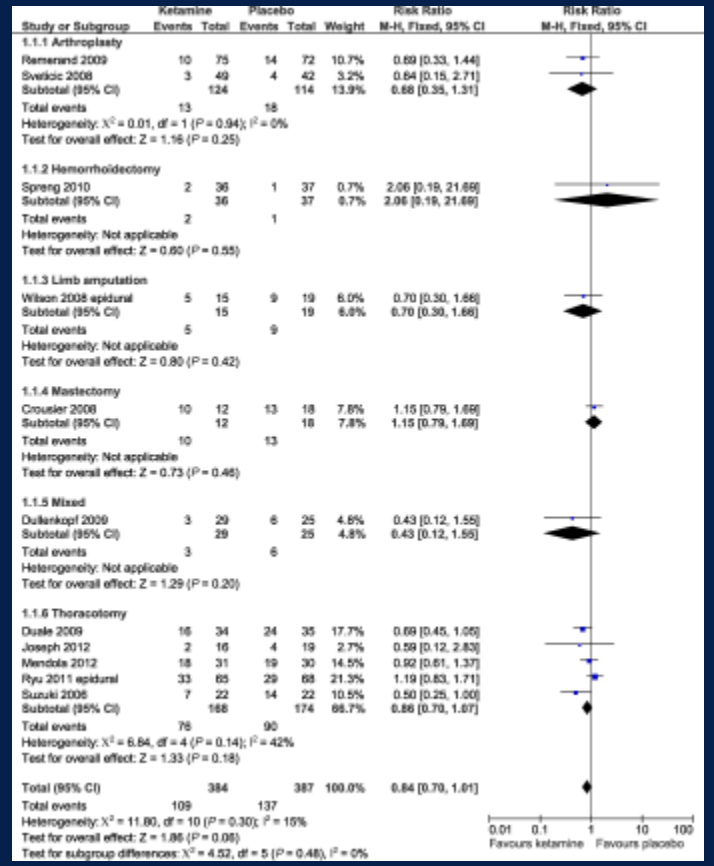
- Meyer-Frießem et al. J Clin Anesth 2022: Meta-analysis comparing ketamine to placebo for postoperative pain in patients on opioids (N=9 studies, 802 patients)
- Infusions started pre-induction (N=3), in OR after induction (N=2), or in PACU (N=4) and continued for 24 hr (6 of 9)
  - Small reduction in pain with movement (MD – 0.79 points; 95% CI: – 1.22 to – 0.36) & pain at rest (N=3; MD – 0.6 points; 95% CI:- 2.01 to 0.8)
  - Patients treated with ketamine had mean reduction in OME consumption of 97.3 mg (95% CI: – 164.8 to – 29.7) after 24 h and 186.4 mg (95% CI: – 347.6 to – 25.2) after 48 h
  - 8 of 9 studies had high risk of bias





Meta-Analyses of Ability of Ketamine to Reduce Persistent Postsurgical Pain

- Systematic review of epidural and IV ketamine: Failed to demonstrate significant reduction in risk of PPSP with ketamine (17 studies, 771 pts)
  - 28% incidence in ketamine vs. 35% in placebo group; 16% risk reduction (p=0.06) @ 3 months
  - Epidural ketamine may be associated with neurotoxicity
- IV Only: RR 0.75, NNT 12 @ 3 mo; RR 0.70, NNT 14 @ 6 mo.
- Systematic review (10 studies, 784 pts) found a small preemptive effect @ 1 mo but not afterwards (3 of 10 studies positive)
- Tena et al. CJP 2014: RCT (n=104) found neither preemptive epidural nor IV ketamine reduced PPSP after thoracotomy
- Kang et al. Pain Physician 2020, RCT (n=184): Ketamine reduced PPSP after mastectomy (87% vs. 69%), but not avg pain scores
- Anwar et al. Anesthesiology 2019, RCT (n=150): Pregabalin with (0%) or without ketamine (6%) reduced PPSP after cardiac surgery compared to placebo (34%) at 3 months
- Khashan et al. Arch Orthop Trauma Surg 2016, RCT (n=45): Intra-articular MS04 = IA MS04 + ketamine > IA placebo for PPSP up to 2 weeks after rotator cuff repair



Forest plot showing incidence of PPSP @ 3 months in RCT comparing ketamine to placebo

McNicol et al. Acta Anaesthesiol Scand 2014; Klatt et al. Scand J Pain 2015

Considerations for PNS for Postoperative Pain

- Greater efficacy for neuropathic pain than inflammatory pain
  - High placebo response rate
  - Most PPSP non-neuropathic
- Temporary, percutaneous implants ideally suited for "dynamic" postsurgical pain
- High rate (> 50%) of lead migration with permanent/ retained fragment with temporary devices, expensive
- Indirect, but no direct evidence for preemptive analgesic effects
  - Studies would require hundreds of patients per group
- Effect size in RCTs relatively small
- Tolerance to effect after 1-2 years

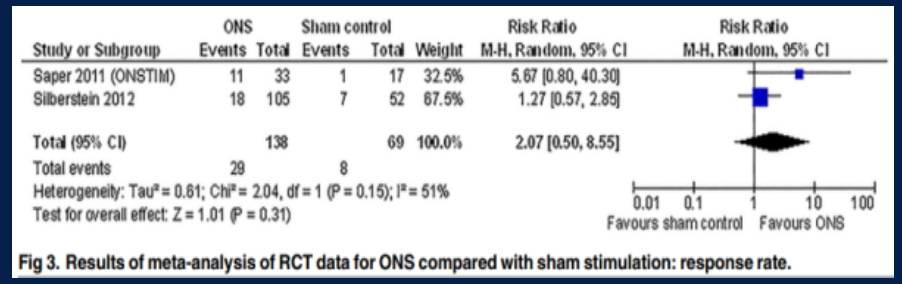


Fig 3. Results of meta-analysis of RCT data for ONS compared with sham stimulation: response rate.

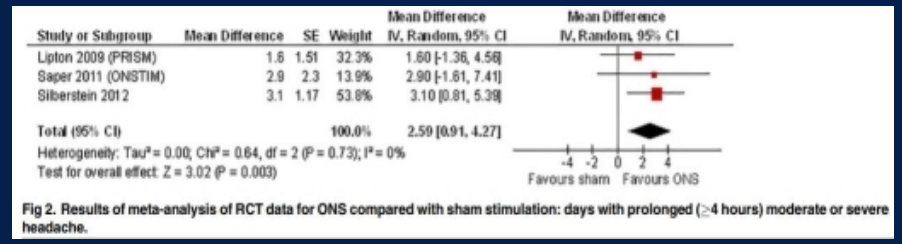
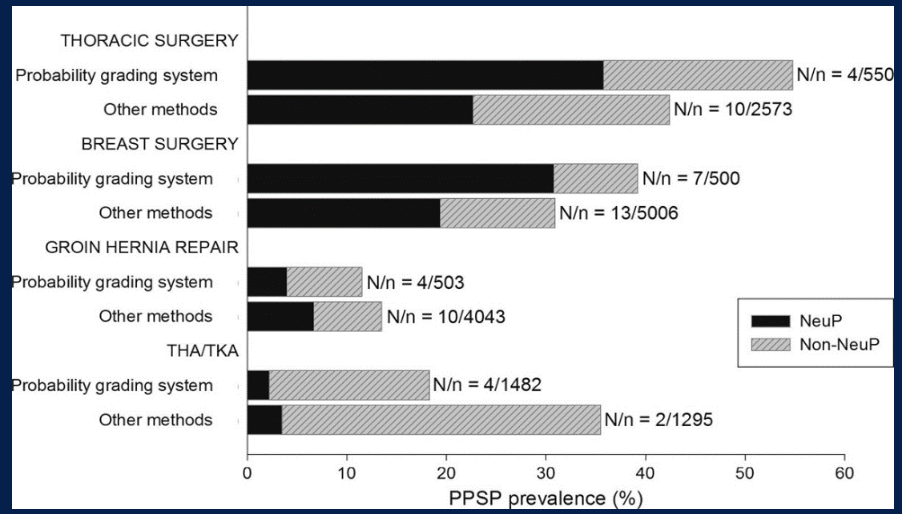


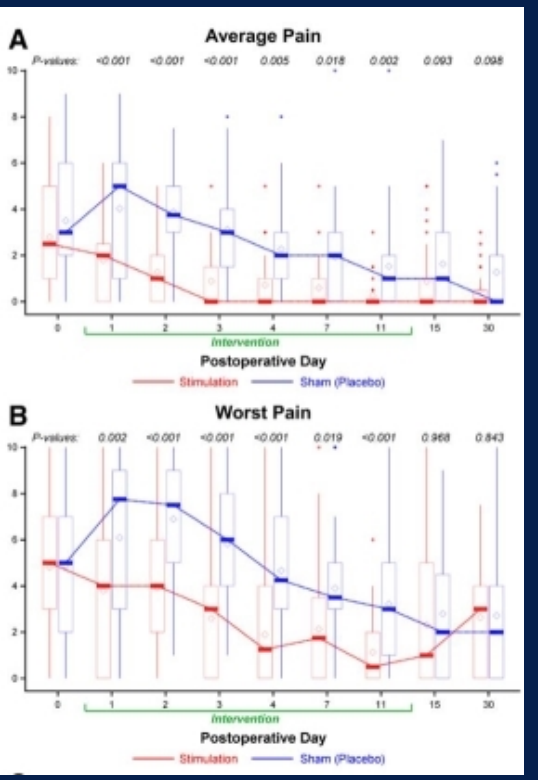
Fig 2. Results of meta-analysis of RCT data for ONS compared with sham stimulation: days with prolonged (≥4 hours) moderate or severe headache.

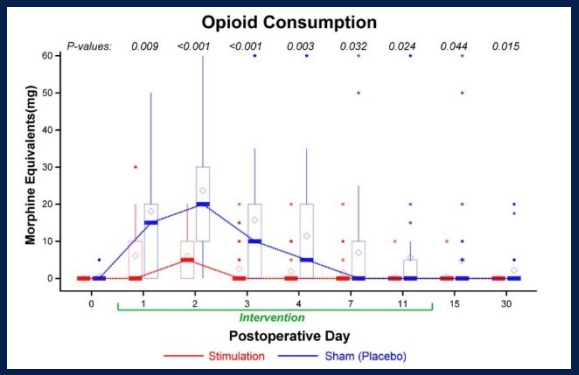


PNS vs. sham for migraines: Chen Y-F et al. PLoS One 2015; Proportion of pts with neuropathic & non-neuropathic pain after surgery: Haroutiunian et al. Pain 2013

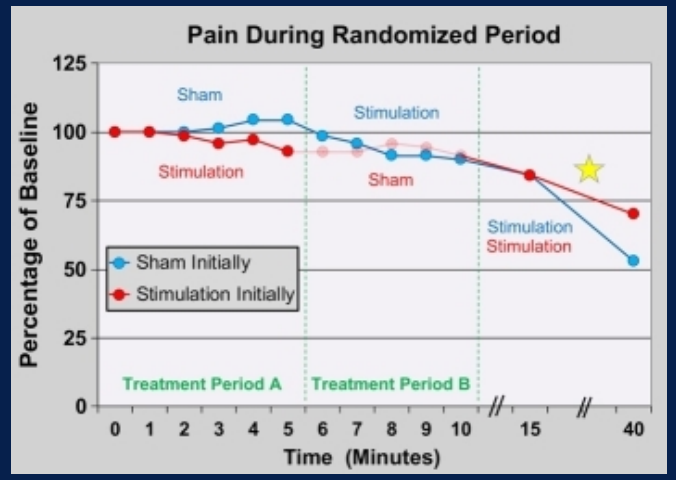
Randomized Controlled Trials Evaluating PNS

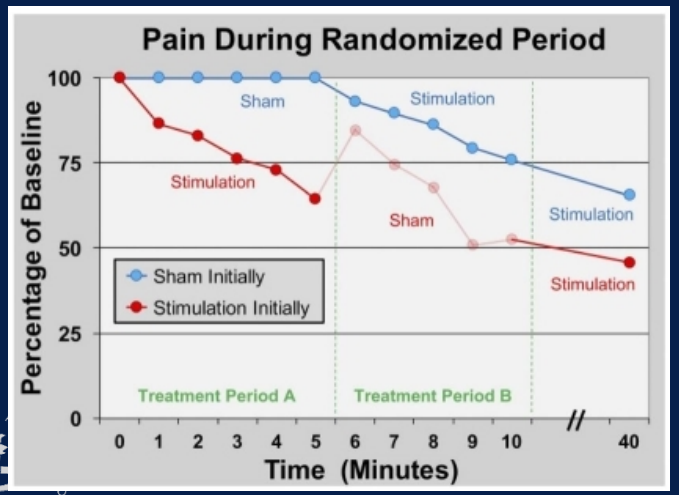
- Ilfeld et al. Anesthesiology 2021
  - 66 pts scheduled for ambulatory orthopedic surgery (ACL, rotator cuff, bunionectomy, TKA)
  - Electrode tested at 100 Hz, increasing current until sensation achieved
  - Randomized to PNS or sham PNS *postoperatively.* All rec'd single-shot nerve block + GA; patients & investigators blinded
  - PNS group rec'd stimulation at lowest perceived threshold for 2 weeks
  - Mean pain intensity 1st week 1.1 ± 1.1 vs. 3.1 ± 1.7, median OME consumption 5 mg (0-30) vs. 48 (25-90) mg
  - No differences in outcomes from 1-4 months except 0 in PNS group vs. 6 in sham group were on opioids





Short-Term Randomized & Observational Studies Evaluating PNS for Postoperative Pain



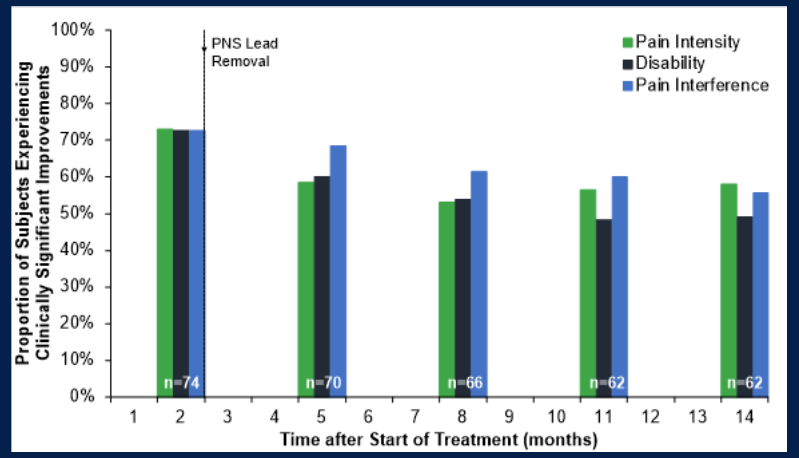


Author, Year	Design	Patients/ Surgery	Nerves	Duration	Results
Ilfeld, 2017	Prosp	5 pts < 60 d from TKA	Fem +/- Sciatic	< 1 d	93% decr in rest pain, 27-30% during ROM
Ilfeld, 2017	Prosp	5 pts mean 42 d after TKA (6-97d)	Fem +/- Sciatic	< 1 d	63% decr in rest pain, 14% & 50% during passive & active flexion
Ilfeld, 2019	Prosp	7 pts s/p TKA	Fem + Sciatic	Turned on < 24h after surgery x 8d -6 wk f/u	6 of 7 had pain scores < 4 in 1st wk. 4 of 7 discontinued opioids within 1 wk
Ilfeld, 2019*	Rand, DB crossover, open-label f/u	10 pts, ACL repair	Fem	5" on/off, 5" washout; 2-4 wks open-label	Stim resulted in 7% decr vs. 4% incr w/ sham stim. With adductor canal block, 80% had pain scores < 1.5 thru POD-3
Ilfeld, 2018*	Rand, DB crossover, open-label f/u	7 pts, hallux valgus osteotomy	Sciatic	5" on/off, 5" washout; 2-4 wks open-label	Stim resulted in 35% decr vs. 0% incr w/ sham stim. During 30" open-label stim, pain scores decr 52%
Ilfeld, 2019	Rand,DB crossover, open-label f/u	14 pts, rotator cuff repair	Brachial plexus (BP)	5" on/off, 5" washout; 2-4 wks open-label	No difference between active & sham stim. 64% required a n. block & 64% opioids in PACU.
Ilfeld, 2021	Rand, DB	66 pts, outpt orthopedic surg	BP, em or sciatic	2 wks	Stim decr pain (mean 3.1 vs. 1.1) and opioid consumption (mean 48 MME vs. 5) over 1st 7 d. No diff @ 1 m except no (vs. 6) PNS pts on opioids
Brooke-Trainer, 2022	Rand, open-label study comparing SMT to SMT/PNS	16 pts s/p amputation after 5-7 d continuous n block	Fem + Sciatic	8 wks	Decr avg. PLP 76% v 29% @ 5-8 wk, 76% v 58% @12 wk. Decr avg. RLP 86% v 52% @ 5-8 wk, 100% v 75% @ 12 wk. Opioid reduction: PNS > control.

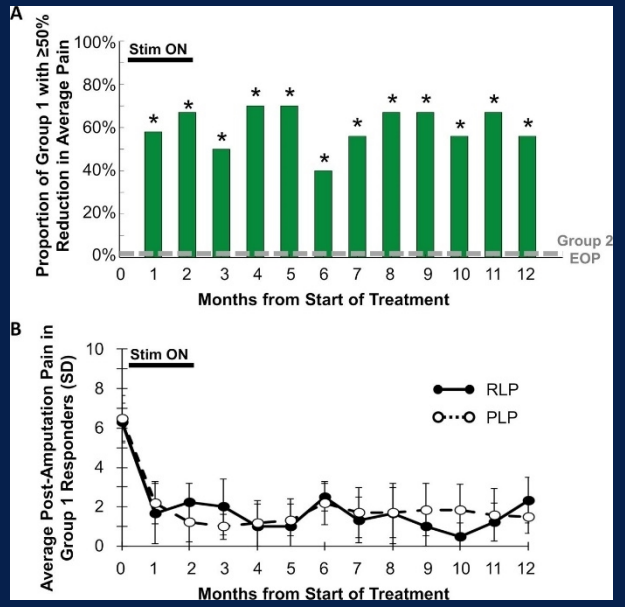
Short Course of PNS May Provide Long-Term Relief

Mechanisms

- Reversing central & peripheral sensitization (breaking cycle of pain)
- Improved sleep (raises pain thresholds & tolerance)
- Long-term physiological effects
- Improved activity, reversal of deconditioning
- Improved mood
- Placebo effect



Cohen et al. presented at MHSRS 2022, for LBP



Gilmore et al. RAPM 2019: Postamputation Pain

Summary of PNS for Postoperative Pain

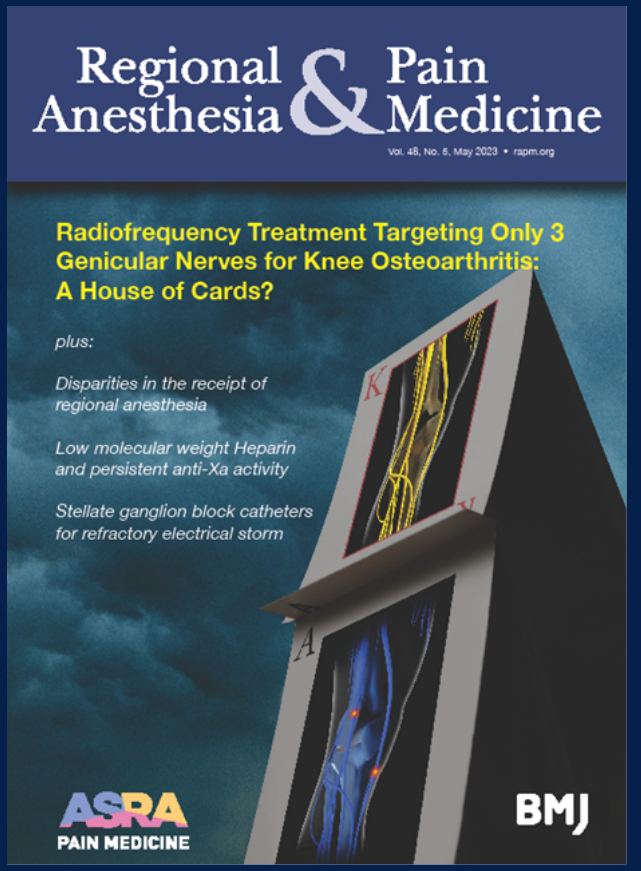
- SPRINT received FDA approval for implantation to treat postoperative (and post-traumatic) pain
  - Scant evidence or basis for permanent implants
- Strongest evidence as ‘rescue’ therapy for refractory pain
  - May be beneficial in high-risk patients (high-risk surgery, individuals with poorly controlled baseline pain or multiple pain co-morbidities/ nociplastic pain, on high-dose opioids, etc.)
  - Studies need to be performed regarding preemptive use in patients with preoperative pain (orthopedic procedures, limb amputation)
- Short-term therapy may provide long-term relief, but variability in study results
- Because of costs & risks, a ‘personalized’ medicine approach may be ideal

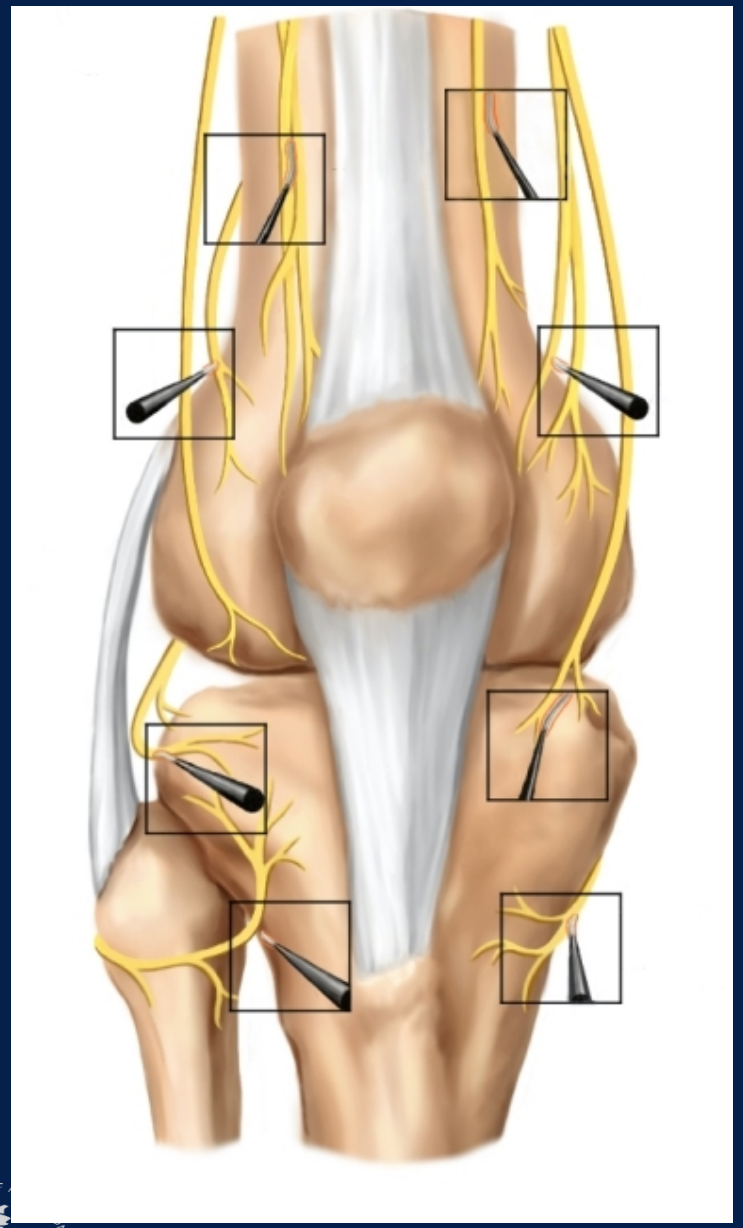
RCT Evaluating RFA before TKR Surgery

- > 600,000 TKRs performed each year in U.S.
- 20%-45% will have persistent pain, with 15% describing pain as severe
- Walega et al. RAPM 2019
  - 70 pts allocated to RFA vs. sham RFA 2-6 weeks before elective TKA
  - Targeted 3 nerves with large-gauge electrodes and long heating times
    - No prognostic blocks
  - RFA as part of a multimodal pain management regimen had no effect on opioid use (mean MME over 48 h 144 in control group vs. 192 in RFA group), analgesia or function 48 h post-surgery
  - There was also no long-term benefit on outcome measures through 6-months
- Mishra et al. RAPM 2021
  - 60 pts allocated to RFA vs. sham RFA 2-4 weeks before elective TKA
  - Targeted 3 nerves, and only RFA group rec'd LA
    - No prognostic blocks
  - RFA group younger, higher BMI and more male
  - No differences in any outcome measure through 6-week follow-up
    - Opioid use not reported, exluded pts with psych history or on > 100 MME

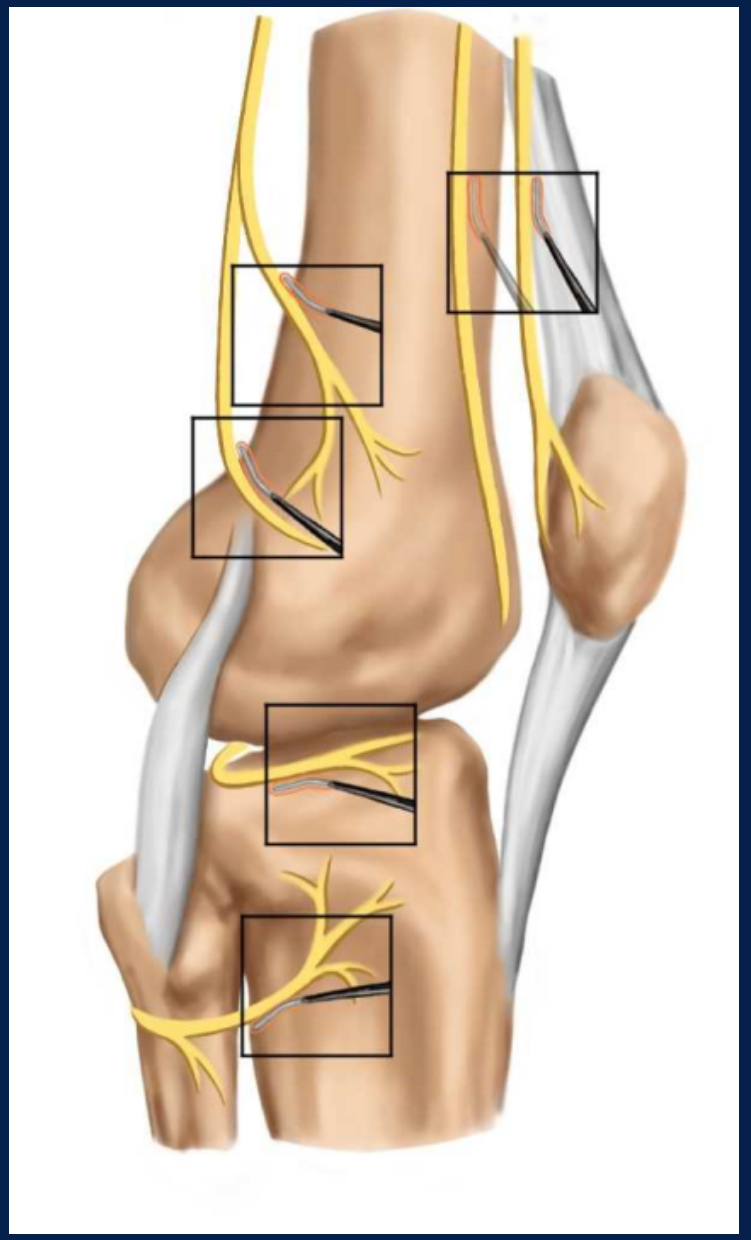
Are More Nerves Better?

- Chen et al. RAPM 2021
  - 265 pts who underwent GN RFA
  - Factors associated with RFA outcome: obesity, larger electrodes, ≥ 80% pain relief with GNB, not being on opioids, no psychiatric morbidity, > 3 nerves, lower baseline pain score, non-TKR surgery
- Fonkoue et al. Pain Med 2021
  - 55 pts randomized to GNB with 2 mL LA and steroid at Choi sites (SMGN, SLGN, IMGN) or revised sites (n=5) to include deeper n targets + RFN and IPBSN
  - Revised targets > classic targets @ 1-hr and 1-day post-block
  - > 40% of pts had prolonged relief at 3 months
- Kose et al. Pain Med 2021
  - DB study in which 80 pts were randomized to US-guided RFA at 5 sites (including RFN and IPBSN) vs. 3 sites after (+) GNB
  - 5 sites > 3 sites
  - At 6 mo, 70% vs. 47.5% of pts in 5 & 3 nerve group had ≥ 50% pain relief

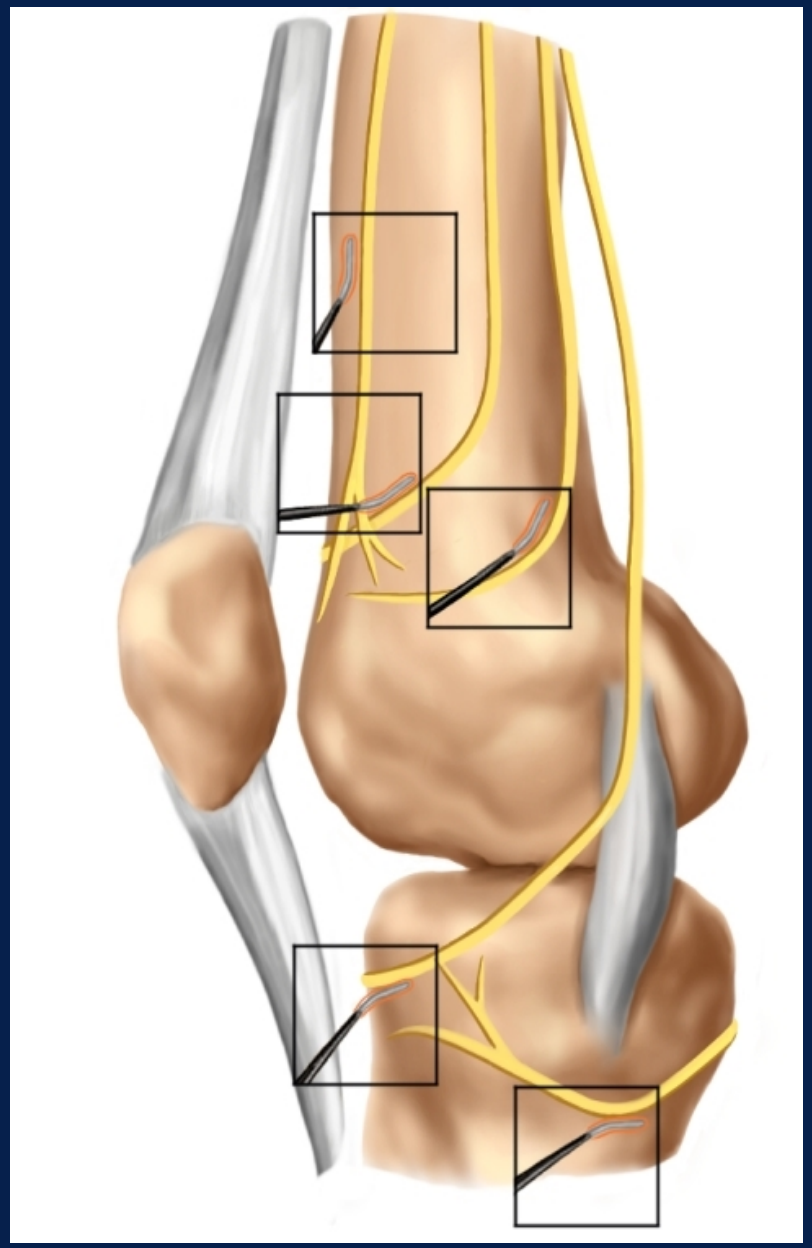




Anterior View



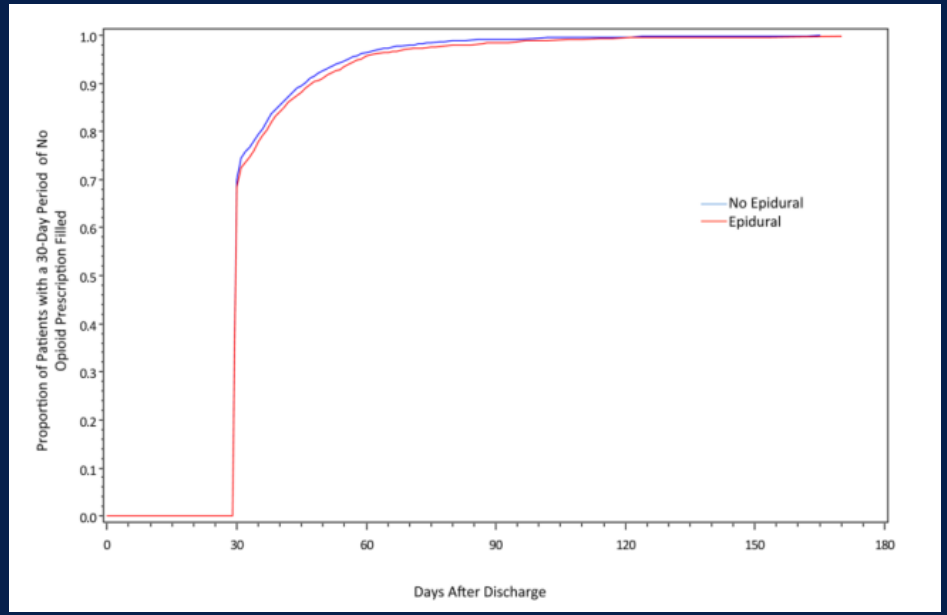
Lateral View



Medial View

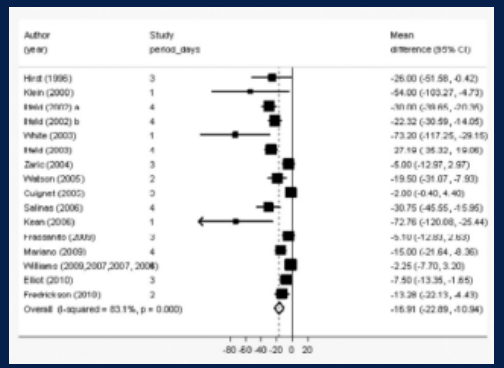
Can Epidurals Decrease Postoperative Opioid Prescriptions?

- Ladha et al. Anesthesiology 2016
  - Propensity-matched database review evaluating opioid prescriptions in 6432 opioid-naïve patients undergoing open abdominal surgery
  - Primary outcome: Time-to-event for 30-day period without opioid refill after surgery
  - No relationship between epidural placement & time to cessation of opioids (propensity-matched HR 0.96 (95% CI 0.91, 1.01) or 90-day MME doses
  - Pts who rec'd epidural more likely to fill >2 opioid prescriptions within 90 d of surgery (30.4% vs 27.5%, p=0.0138).



Can Regional Anesthesia Prevent Persistent Postsurgical Pain?

- Weinstein et al. Cochrane Syst Database Rev 2018
  - 7 Studies (n=499) found epidural anesthesia reduced risk of PPSP after 3 mo. for thoracotomy (OR 0.52, 95% CI 0.32, 0.84)
  - 18 studies (n=1297) found RA reduced risk of PPSP after 3 mo. for breast ca. surgery (OR 0.43, 95% CI 0.28, 0.68) & for C-section (4 studies, n=551, OR 0.46, 95% CI 0.28, 0.78)
  - 3 studies (n=123) found inconclusive evidence for LA infiltration to reduce PPSP after ICBG (OR 0.20, 95% CI 0.04, 1.09)
  - 2 studies (n=97) found IV lidocaine reduced risk of PPSP after 3 mo. for breast ca. surgery (OR 0.20, 95% CI 0.04, 1.09)
- Bingham et al. RAPM 2012
  - In meta-analysis (7 studies, n=702), compared with single-shot PNB, continuous PNB associated with decreased pain on POD 0 Effect size 1.29; 95% CI 2.19, 0.40) and POD 2 (ES 2.03; 95% CI 2.78, 1.29), decreased opioid use (ES 15.70, 95% CI, 21.84 to 9.55), nausea/vomiting & increased satisfaction

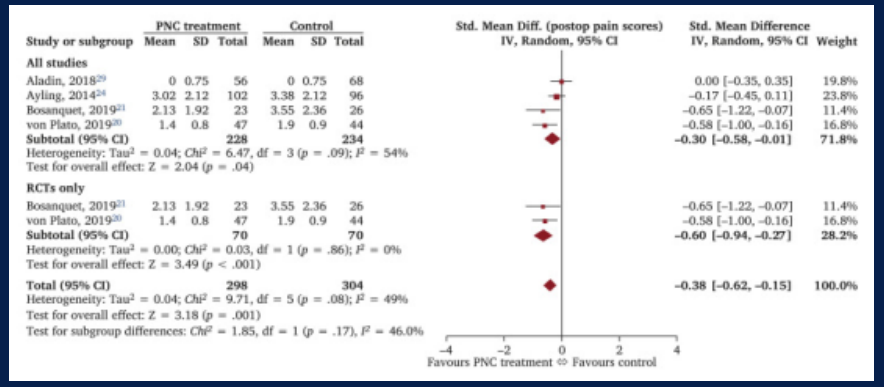


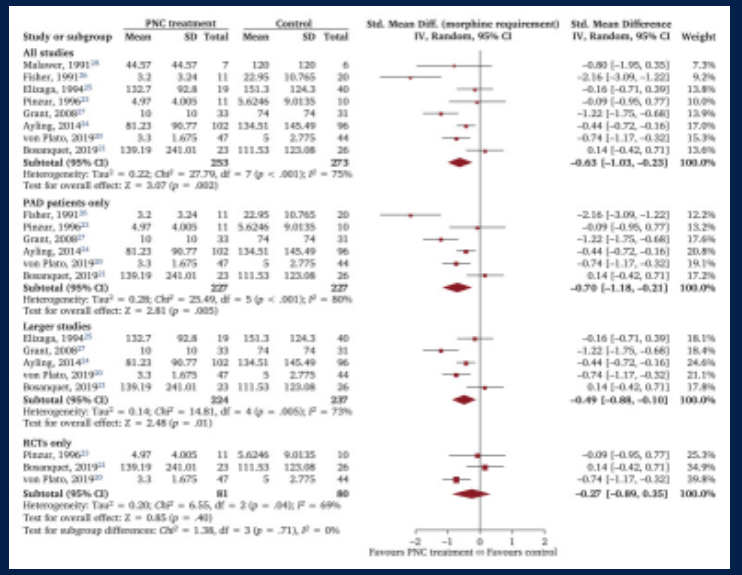
Prospective Studies Evaluating Epidural Effect on Preventing PLP

Author	# Pts	Rando m- ization	Blinding	Pre-op	Hrs. Pre-op	Intra- op	Post- op	Effect
Bach 1988	25	+	-	+	72	+	-	+
Jahangiri 1994	24	-	-	+	> 24	+	+	+
Schug 1995	23	-	-	+	24	+	+	+
Katsuly 1996	45	+	?	+		+	+	+
Nikolajsen 1997	60	+	+	+	18	+	+	_
Lambert 2001	30	+	-	+	24	+	+	No difference between epid & PN grps
Wilson 2008	53	+	+	-	0	+	+	No difference between epid grps
Karanikolas 2011	65	+	+	+	48	+	+	+
Yousef 2017	60	+	+	-	NA	-	+	Epid Bup-Calc-Fent > Epid Bup @ 6 m and 1 yr, but not earlier

Meta-Analysis of Peripheral Nerve Catheters on Postamputation Pain

- Laloo et al. Eur J Vasc Endovasc Surg 2021
  - 10 studies (4 RCT, 6 retrospective), 350 rec'd PNC, 381 SoC
  - PNC associated with reduction in postop pain (SMD −0.30, 95% CI −0.58 – −0.01, p = .04) and opioid requirements (SMD −0.63, 95% CI −1.03 – −0.23, p = .002) overall but not in RCTs only
  - No significant difference in chronic RLP or PLP

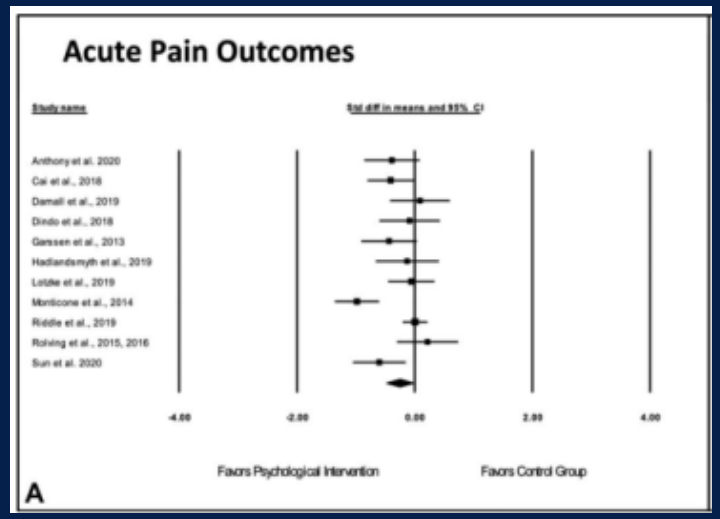


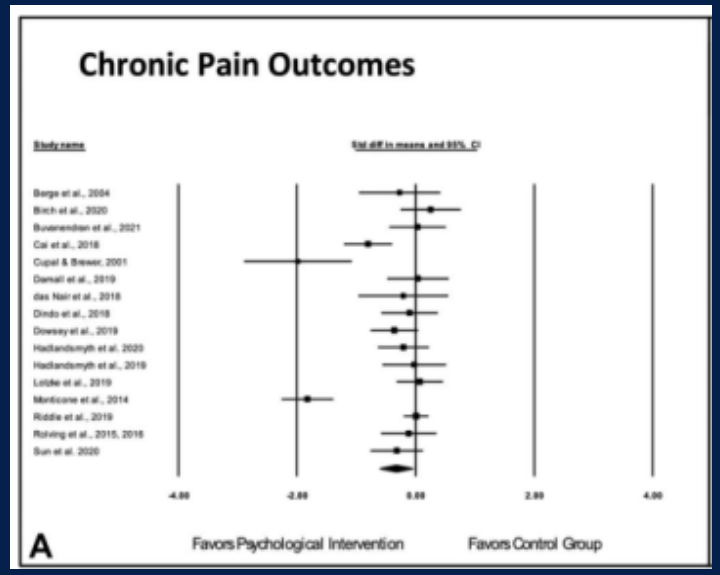


Forrest plots showing postoperative pain scores & opioid consumption for PNC vs. control

Can Preprocedural Psychological Interventions Improve Outcomes?

- Co-morbid psychiatric conditions (depression, anxiety & substance use disorder) more common in surgical pts
- Patients with psychiatric comorbidity more like to experience PPSP, chronic opioid use, and opioid use disorder
- Mixed for psych interventions to reduce postsurgical pain
  - Tong et al. 2020: Meta-analysis of 19 RCTs (n=1893) found pre-op psych interventions reduced postop anxiety (g = −0.26 (−0.49, −0.03), P=.02)) and improved mental QoL (g = 0.25 (0.02, 0.49), P=0.03) but not postop pain after orthopedic surgery (g = −0.15 (95% CI −0.42, 0.13), P=0.31)
  - Nalinda et al. 2022: Meta-analysis of 21 RCTs found pre-op psych interventions reduced (sub)acute (d= -0.26 95% CI -0.48 to -0.04) & chronic (d= -0.33 95% CI -0.61 to 0.06) pain after surgery
    - Stronger effect for interventions delivered after surgery & by psychologist





Tong et al. ANZ J Surg 2020; **Nalinda et al. Pain 2022**

Take Home Points

- Evidence for small preemptive effect for ketamine perioperatively, and for ketamine to reduce opioid consumption
  - Studies are inherently flawed
- Ketamine may have greater effect on affective-motivational component than sensory-discriminative component
  - Negative evidence based on preclinical studies evaluating QST
  - Unclear whether it can ‘reverse central sensitization’
- Ketamine is at least as effective as opioids for acute pain, but has a shorter duration and possibly more side effects

Take Home Points

- RCTs evaluating genicular nerve RFA before TKR negative
  - Neither used prognostic blocks & both used suboptimal technique
- Cadaveric studies and clinical trials suggest greater effectiveness when more nerves are targeted
- There is conflicting, positive evidence for the use of PNS to treat severe postsurgical pain
- Conflicting evidence for regional anesthesia to prevent postsurgical and PLP