ISAP 34th Annual Meeting

2025 Syllabus

Friday, October 10, 2025

The Westin Riverwalk

420 West Market Street, San Antonio, Texas, USA

EXCULSIVE EVENTS

LIFETIME ACHIEVMENT AWARD

Thomas Schnider, MD

Head of Department Institut für Anästhesiologie at Kantonsspital St. Gallen, Switzerland

(retired August 2023)

MOHAMED NAGUIB LECTURE

Guy Weinberg, MD

Professor, Department of Anesthesiology
University of Illinois - College of Medicine
Chicago, Illinois

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SAN ANTONIO, TX

34th Annual Meeting Schedule

0945–1730 Central Time Zone, USA

0945 – 1000 **Welcome and announcements**
Jerry Ingrande, MD, President

1000 – 1200 **Target Controlled Infusion Technology: An Update**
Talmage Egan, MD, Moderator

1000 – 1020 **TCI as a Gain Switch: Conceptual and Historical Overview**
Talmage D. Egan, MD, University of Utah, Salt Lake City, UT

1020 – 1040 **Lessons Learned from Decades of TCI Practice**
C.F. Minto, MD, Anesthesiologist, Royal North Shore Hospital, Sydney, New South Wales, Australia

1040 – 1100 **Do the New "Uber" Models Make a Difference**
Michel Struys, MD, PhD, FRCA (Hon), University of Groningen, University Medical Center Groningen, Netherlands

1100 – 1120 **From Target to Feedback: TCI in the Age of Closed-Loop Intelligent Autonomy**
Kai Kuck, PhD, Professor Dept. of Anesthesiology and Director of Bioengineering, University of Utah, Salt Lake City, UT, USA

1120 – 1200 **Q&A**

1200 – 1230 **ISAP Board of Directors Business Meeting**

1230 – 1400 **Luncheon & Keynote Speaker & Lifetime Achievement Awardee**
Thomas Schnider, MD
Head of Department Institut für Anästhesiologie at Kantonsspital, St. Gallen, Switzerland (retired August 2023)

1400 – 1445 **Mohamed Naguib Lecture**
Guy Weinberg, MD,
Professor, Department of Anesthesiology, University of Illinois - College of Medicine, Chicago, Illinois

1445 – 1700 **Abstract Presentations**

1700 – 1900 **Board Meeting**

LUNCHEON & KEYNOTE SPEAKER & LIFETIME ACHIEVEMENT AWARDEE

Thomas Schnider, MD
Head of Department Institut für Anästhesiologie at Kantonsspital, St. Gallen, Switzerland (retired August 2023)

Thomas Schnider is the former Head of Anesthesiology at Kantonsspital, St. Gallen, Switzerland. He received his MD degree from the University of Bern in Switzerland in 1984. Dr. Schnider worked as a Research Fellow at the Department of Anesthesiology, Stanford University, Stanford, California in clinical pharmacology. His main research interests are in pharmacokinetic/pharmacodynamic modeling and feedback control in anesthesia. He is the author or co-author of over 70 original publications, review articles case reports and and book chapters.

MOHAMED NAGUIB LECTURE

Guy Weinberg, MD
Professor, Department of Anesthesiology, University of Illinois - College of Medicine, Chicago, Illinois

Dr. Weinberg is best known for the discovery that infusing lipid emulsion (ILE) can attenuate or reverse local anesthetic systemic toxicity, LAST. This approach is now considered a standard of care for treating LAST. Dr. Weinberg initially trained at UCSF, receiving board certification in Internal Medicine and Medical Genetics before doing a research fellowship at the NIH. He then switched gears and careers to do a residency in Anesthesiology at UVA Charlottesville where he learned regional anesthesia working under Harold Carron, Cosmo DiFazio, and John Rowlingson. After moving to Chicago, where he worked at Michael Reese Hospital and the University of Illinois, a single peculiar clinical event led to studies of novel molecular targets of local anesthetics and eventually to the discovery that ILE can reduce related toxicity. His lab at the Jesse Brown VA focused on this phenomenon and its underlying mechanisms for more than 20 years. Dr. Weinberg chaired the ASRA working group on LAST for more than a decade and helped form the first advisories for treating LAST. He now co-hosts an annual workshop in Telluride, CO where leading scientists from around the world meet to discuss data on a set of genes, YAP and WWTR1 (TAZ), that contribute to many types of cancer.

Mohamed Naguib Lecture

Generous support provided by Senzime Corporation

ISAP has established the Mohamed Naguib Lecture to honor his many accomplishments, which will be presented at every ISAP Annual Meeting. The Inaugural Lecture was given at the 2021 ISAP Annual Meeting. ISAP has established a fund to endow the Mohamed Naguib Lecture and donations may be made at isaponline.org.

In the world of clinical pharmacology, Dr. Naguib was a renaissance man. As a man of many talents, his influential work has provided direction in many spheres of investigation and discovery. He made significant contributions to the scientific foundation and clinical applications of neuromuscular monitoring. He formed and led a coalition of thought leaders to prepare and disseminate expert consensus guidelines on neuromuscular monitoring. He had substantial interest in the mechanisms of and treatment for neuropathic pain. He led a laboratory that created molecules to treat neuropathic pain. At the time of his passing, he was a principal investigator on a NIH funded multi-center observational study focused on the discovery and validation of a biomarker signature for chemotherapy induced peripheral neuropathic pain. He was the co-founder of a company that is developing a novel therapy for neuropathic pain and Alzheimer's disease based on his research on the mechanisms of neuroinflammation. For each of these activities, he created a wake of opportunities for many that continue to have a vibrant and productive future. He was a prolific writer. He was the principal author or co-author of 130 peer-reviewed journal articles, 25 book chapters (including the premier Miller's Textbook of Anesthesia) and 150 abstracts.

Support the Mohamed Naguib Lecture

Donations can be made online (click here)

ISAP is a 501(c)(3) nonprofit organization which makes donations tax-deductible.

By way of professional service, for years, he served on the editorial board of numerous anesthesia journals and was influential not only in his reviews but in preparing thought provoking editorials and commentary. He also served for many years in various leadership positions, including President of ISAP.

Our Mission

The International Society for Anaesthetic Pharmacology (ISAP) is a nonprofit organization with an international membership, which is dedicated to teaching and research about clinical pharmacology in anesthesia, with particular reference to anesthetic drugs.

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INNOVATOR & MOHAMED NAGUIB LECTURE

Senzime

Senzime is a Swedish medical device company that develops, manufactures, and markets CE- and FDA-cleared patient monitoring systems. Senzime's employees worldwide are committed to the vision of a world without anesthesia- and respiratory-related complications.

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ISAP Abstract Awards 2025

1 First Place

Modulation of functional connectivity by propofol, dexmedetomidine, and fentanyl: A randomized controlled 7 T functional MRI study in healthy young adults

Presenting Author: Keith M. Vogt, MD, PhD, Department of Anesthesiology, University of Pittsburgh School of Medicine; Pittsburgh, PA, USA

2 Second Place

Brain modulation by sevoflurane and nitrous oxide during memory encoding and periodic painful stimulation: A 3 T functional MRI study in healthy young adults

Presenting Author: Derrick Liu, BS, MS, The Ohio State University College of Medicine; Columbus, OH, USA

3 Third Place (two awards)

Propofol Enhancement of Slow Wave Sleep as a Putative Mechanism for Treating Depression in Older Adults: A Pilot Study

Presenting Author: Ben Julian Palanca, MD, PhD, MSCI, Department of Anesthesiology, Washington University School of Medicine in St. Louis, St. Louis, MO, USA and Department of Psychiatry, Washington University School of Medicine in St. Louis, St. Louis, MO, USA

Pharmacological Effects of a New Halogenated Methyl-Ethyl Ether in Rats

Presenting Author: Joseph F. Antognini, MD, MBA, Expanesthetics, Inc. Davis, CA, Former Professor, UC Davis; Davis, CA

#1_Preoperative Implications of GLP-1 Receptor Agonists on Anesthesia Outcomes: A Systematic Review and Meta-Analysis

Haashim Rahman, Abbas Merchant, Aaryan Patel, Constantino G. Lambroussis

Affiliations

[1]Lake Erie College of Osteopathic Medicine, Erie, PA, USA

Abstract

Background: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are widely used for treating type 2 diabetes and obesity because they induce benefits like glycemic control and weight reduction. However, their further influence on perioperative anesthesia outcomes, such as gastric emptying, aspiration risk, hemodynamic stability, and glycemic variability, is a serious concern. This systematic review and meta-analysis evaluate the insights regarding the preoperative consequences of GLP-1 RA on anesthesia outcomes, leading to a better guide for perioperative management strategies.

Methods: A systematic literature search was performed across PubMed, Web of Science, Cochrane Library, ClinicalTrials.gov, OpenGrey, and Embase. From the 524 records screened, only six eligible studies met the inclusion criteria and were analyzed. These studies investigated gastric food retention, aspiration risk, perioperative blood pressure changes, glycemic stability, nausea and vomiting, and vasopressor requirements. Statistical analysis was conducted using Open Meta-Analyst and Review Manager 5. The Cochrane Risk of Bias (RoB 1) tool was used for randomized controlled trials (RCTs), while the Newcastle-Ottawa Scale (NOS) assessed observational study quality.

Results: The use of GLP-1 receptor agonists (GLP-1 RAs) significantly increases the risk of gastric food retention (OR: 1.39 [1.25-1.56]; $p<0.00001$; $I^2=95\%$), with a 25.69-fold higher risk during elective EGD (OR: 25.69 [7.34-89.99]). Endoscopy discontinuation due to retained gastric contents was 37% more likely (OR: 1.37 [1.23-1.53]; $p<0.00001$). No significant increase in pulmonary aspiration risk was observed. GLP-1 RA use was associated with a reduction in mean arterial blood pressure (-2.76 mmHg [95% CI: -3.22, -2.30]; $p<0.00001$; $I^2=89\%$), leading to increased intraoperative vasopressor requirements (OR: 1.48 [1.09-1.99]; $p=0.01$). Perioperative glycemic control improved (mean glucose reduction: -14.93 mg/dL [95% CI: -15.81, -14.05]; $p<0.00001$). Postoperative nausea and vomiting were more frequent (OR: 1.37 [0.95-

1.97]; p=0.09), anesthesia duration extended by 9.86 min (95% CI: 9.12-10.59), and recovery prolonged by 10.01 min (95% CI: 9.42-10.61), with increased ICU admissions (OR: 1.53 [1.01-2.32]; p=0.04). Sensitivity analysis confirmed result robustness.

Conclusions: GLP-1 RAs delay gastric emptying, resulting in extended fasting protocols or gastric ultrasound evaluations concerning the aspiration risk. Their vasodilatory effects may result in hypotension during the perioperative phase, often warranting the use of vasopressors and modification of anesthesia techniques. While they stabilize sugar levels, they may also contribute to postoperative nausea and vomiting (PONV), thereby necessitating modifications in antiemetic guidelines. These observations support the need for personalized perioperative management strategies for users of GLP-1 RAs.

Keywords: GLP-1 receptor agonists, anesthesia outcomes, gastric emptying, perioperative glycemic control, vasopressor use, aspiration risk.

#2 _The Effectiveness and Safety of Intravenous Lidocaine in Thyroidectomy: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Presenting Author: Ibrahim Gamal[1]
Co-Authors: Abdelrahman Shata[2] Manar Ahmed AbdElfattah[3]Nada khalid asar[4]Sumaya Emad Mohammed[5]
Faculty of Medicine, Al-Azhar University Faculty of Medicine[1]; Horus University-Egypt, New Damietta, Egypt[2]; Faculty of Medicine, Ain Shams University, Cairo, Egypt[3]; Faculty of medicine, Mansoura University, Mansoura , egypt[4]; Anbar University College Of Medicine, Anbar Cancer Center[5]

Background/Introduction:
Thyroidectomy is commonly performed for both benign and malignant conditions, with varying postoperative pain levels among patients. While opioids are typically used for pain management, their side effects have driven interest in alternative analgesics. Intravenous lidocaine, known for its analgesic and anti-inflammatory properties, has been studied for its role in enhancing postoperative recovery. This meta-analysis aimed to evaluate the effect of IV lidocaine on postoperative quality of recovery (QoR-40), pain scores, anesthesia time, and incidence of postoperative nausea and vomiting (PONV) in patients undergoing thyroidectomy.

Methods:
A systematic literature search was conducted in PubMed, Scopus, Web of Science, and Cochrane databases up to May 2025. Sixteen randomized controlled trials (RCTs) met inclusion criteria, comprising adult patients undergoing thyroidectomy who received either systemic lidocaine or placebo. Data on QoR-40 scores (preoperative, POD1, POD2), postoperative pain scores (at 1h, 4h, 12h, 24h, and 48h), anesthesia time, and PONV were extracted and analyzed using Review Manager. Risk of bias was assessed using the Cochrane RoB 2 tool.

Results:
Lidocaine significantly improved QoR-40 scores on POD1 (MD: 7.96 [6.04, 9.89]) and POD2 (MD: 6.52 [5.22, 7.83]; $p < 0.00001$), with no baseline difference preoperatively. Pain scores were significantly reduced in the lidocaine group across all postoperative time points, particularly at 1h (Std.MD: -0.77, $p < 0.00001$) and 4h (Std.MD: -1.73, $p < 0.0001$). However, lidocaine had no significant effect on anesthesia time (MD: -3.12, $p = 0.21$). The incidence of PONV was significantly lower with lidocaine (OR: 0.34 [0.17, 0.65], $p = 0.001$).

Conclusions:
This meta-analysis confirms that intravenous lidocaine significantly improves postoperative recovery and reduces pain and PONV in thyroidectomy patients, without affecting anesthesia time. These findings support the inclusion of IV lidocaine as part of a multimodal analgesic strategy to enhance patient comfort and outcomes after thyroid surgery.

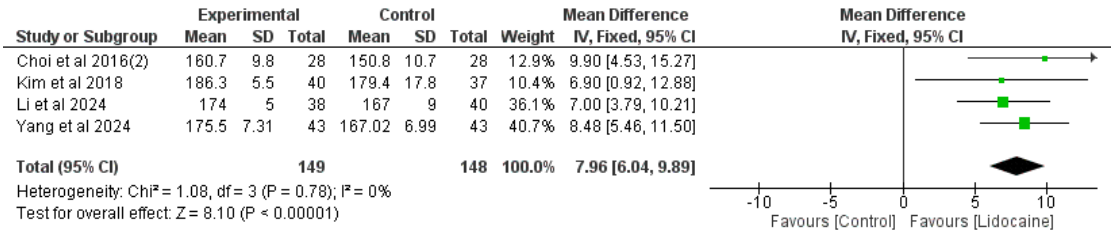

Figure 1. Forest plot showing the effect of intravenous lidocaine on postoperative Quality of Recovery (QoR-40) scores on postoperative day 1 (POD1) compared to control.

1 #3_Modulation of functional connectivity by propofol, dexmedetomidine, and fentanyl: A randomized controlled 7 T functional MRI study in healthy young adults

Presenting Author: Keith M. Vogt
Co-authors: Marcus A. Simmons, Courtney N. Kozdron, James W. Ibinson, Helmet T. Karim.
Department of Anesthesiology, University of Pittsburgh School of Medicine; Pittsburgh, PA, USA

Introduction: Anesthetic and analgesic drugs have distinct clinical profiles and are well-accepted to affect the brain and cognition, even at subanesthetic doses. This analysis sought to characterize the systems-level changes in resting brain connectivity for three different anesthetic agents using high-field functional MRI (fMRI). Functional connectivity can be calculated on any neural timeseries data, with temporal correlations well accepted to reflect brain areas that are interacting. Changes in resting-state connectivity can be calculated between experimental conditions, including under different anesthetics.

Methods: This was an IRB-approved, pre-registered clinical trial (NCT04062123) of healthy adults age 40 and under. There were two separate scan sessions, both with crystalloid infusion. In one session, a constant effect-site concentration (ESC) was targeted using stanpumpR (https://stanpumpr.io/). Participants were blinded and randomized to propofol (n= 22; ESC=1.0 mcg/ml), dexmedetomidine (n=25; ESC=0.15 ng/ml), or fentanyl (n=25, ESC=0.9 ng/ml). Blood oxygen-weighted images (1 s temporal resolution, 2 mm isotropic spatial resolution) were obtained at 7 T using a custom head coil. Data is from an 8-min resting scan obtained at the end of a session, after subjects experienced a painful stimulation paradigm (previously reported). Connectivity analysis was performed using atlas-defined regions of interest (ROIs) including, bilaterally, the anterior cingulate, posterior cingulate, insula, primary somatosensory cortex (S1), thalamus, hippocampus, and amygdala. A linear mixed effects model was run with subject as a random effect and drug as a fixed effect. Fixed effects were corrected using an FDR-adjusted $p < 0.05$.

Results: There were significant changes in resting-state connectivity between the selected ROIs, compared to the no drug scan, described in the Figures and Table, below. No drug-associated connectivity differences were seen for the thalamus, posterior cingulate, or amygdala. Propofol was associated with decreased connectivity between the right hippocampus and several subdivisions of the anterior cingulate. Both dexmedetomidine and fentanyl were associated with decreased connectivity between the left posterior insula and right S1. Somewhat unexpectedly, **IN**creases in connectivity for the right hippocampus were seen with dexmedetomidine (to the left insula) and fentanyl (to the anterior cingulate).

Conclusions: Even using very conservative thresholding, propofol, dexmedetomidine, and fentanyl distinctly modulate resting brain connectivity, with significant changes commonly affecting the right hippocampus. Given the well-known hippocampal role in explicit memory formation, this suggests that all three drugs have the potential to affect long-term memory. Additionally, both fentanyl and dexmedetomidine decreased connectivity between the posterior insula and S1, two brain areas characteristically involved in the sensory-discriminative dimension of the pain experience. These results further demonstrate that distinct anesthetic agents modulate connectivity of memory and pain-processing brain circuits, even in the absence of experimental tasks or specific cognitive effort engaging these areas.

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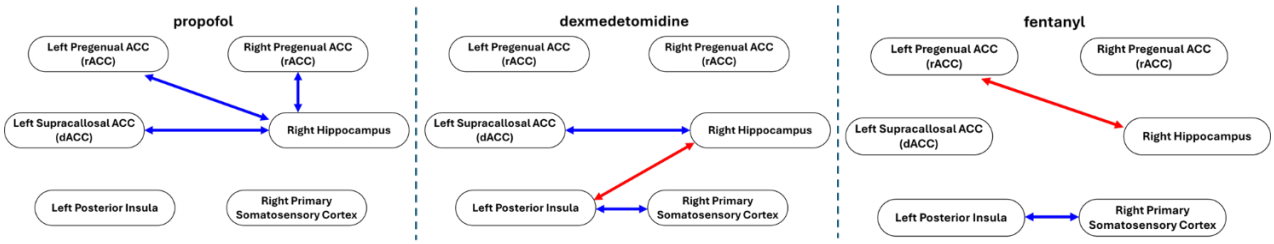

Figure 1. Connectivity changes shown by ROI. Blue lines indicate decreases and red indicate increases in functional connectivity, after overall false detection rate correction.

Table 1: Significant connectivity changes between drug and placebo sessions Legend: ROI= region of interest, CC= correlation coefficient, SE= standard error, t-stat= t-statistic, FDR-p= p-value corrected for false detection rate, L= Left, R= Right, ACC_sup= supracallosal division of the anterior cingulate cortex, AAC_pre= pregenual division of the anterior cingulate cortex

ROI 1	ROI 2	Drug	CC change	SE	t-stat	FDR-p
ACC_sup_L	Hippocampus_R	propofol	-0.1025	0.0394	-2.60	0.010600
ACC_sup_L	Hippocampus_R	dexmedetomidine	-0.0999	0.0393	-2.54	0.012386
ACC_sup_L	Hippocampus_R	fentanyl	0.0847	0.0395	2.14	0.034026
ACC_pre_L	Hippocampus_R	propofol	-0.1845	0.0434	-4.25	0.000039
ACC_pre_L	Hippocampus_R	dexmedetomidine	-0.0798	0.0434	-1.84	0.068464
ACC_pre_L	Hippocampus_R	fentanyl	0.0530	0.0434	1.22	0.224445
ACC_pre_R	Hippocampus_R	propofol	-0.1665	0.0423	-3.94	0.000128
ACC_pre_R	Hippocampus_R	dexmedetomidine	-0.0339	0.0423	-0.80	0.424073
ACC_pre_R	Hippocampus_R	fentanyl	0.0559	0.0423	1.32	0.187998
Hippocampus_R	Insula_L_posterior	propofol	0.0323	0.0380	0.85	0.397179
Hippocampus_R	Insula_L_posterior	dexmedetomidine	0.1585	0.0377	4.21	0.000057
Hippocampus_R	Insula_L_posterior	fentanyl	-0.0161	0.0382	-0.42	0.673917
Insula_L_posterior	Postcentral_R	propofol	-0.0136	0.0497	-0.27	0.784493
Insula_L_posterior	Postcentral_R	dexmedetomidine	-0.1034	0.0494	-2.09	0.038664
Insula_L_posterior	Postcentral_R	fentanyl	-0.2102	0.0498	-4.22	0.000049

Note: Corrected p < 0.05 are highlighted in green. Significant drug-related changes in connectivity are highlighted: decreases in blue and increases in red.

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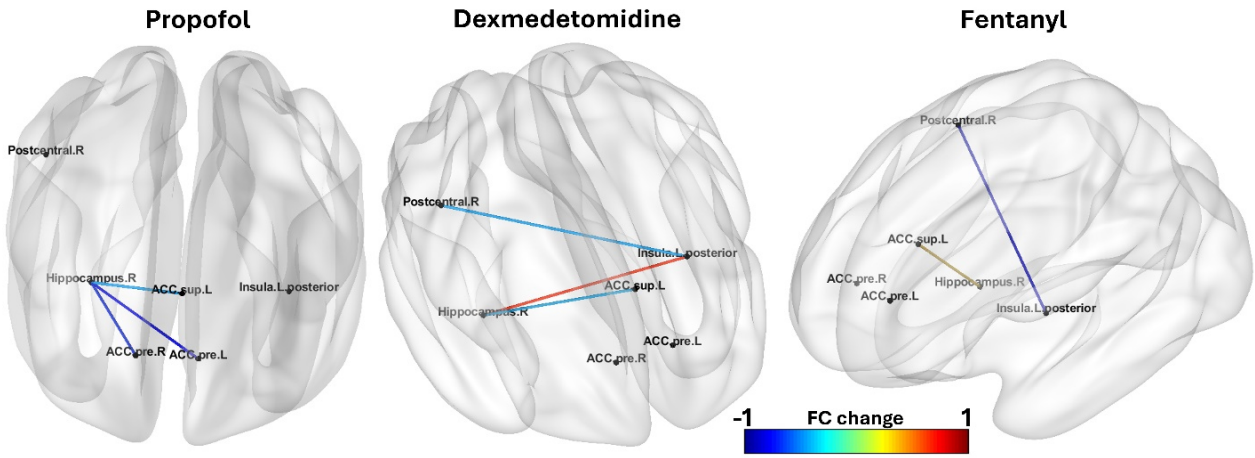


Figure 2. Connectivity changes by drug shown on brain underlays, to illustrate anatomical relationships between involved regions. Dots are located at central coordinates within the ROI they represent. ROI labels are as in Table 1 legend. Color bar represents change in functional connectivity (FC), based on numerical difference in correlation coefficients between no-drug and drug scans, with cool colors showing decreases under drug, and warm colors showing increases.

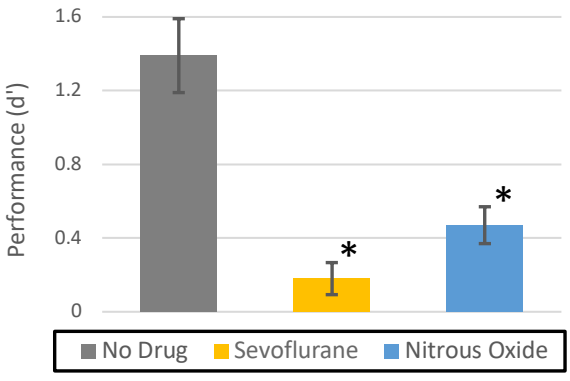
2 #4_Brain modulation by sevoflurane and nitrous oxide during memory encoding and periodic painful stimulation: A 3 T functional MRI study in healthy young adults

Presenting Author: Derrick Liu[1,2]
Co-authors: Taylor Duffy[1], Marcus A. Simmons[1], Courtney N. Kozdron[1], James W. Ibinson[1], Keith M. Vogt[1]
[1]Department of Anesthesiology, University of Pittsburgh School of Medicine; Pittsburgh, PA, USA
[2]The Ohio State University College of Medicine; Columbus, OH, USA

Introduction: Sevoflurane and nitrous oxide (N_2O) are mechanistically distinct inhalational anesthetic agents with different clinical profiles for memory impairment and analgesia. While both agents are known to affect cognitive function and pain perception, their effects on human brain systems for memory encoding and pain processing during concurrent aversive stimulation remain poorly characterized. In this study, we employ a novel experimental paradigm of periodic painful stimulation during an auditory memory encoding task to imitate the clinical conditions under which anesthetic agents are commonly used. This paradigm was used to study the effects of sevoflurane and N_2O using 3 T functional MRI (fMRI).

Methods: This data is from two IRB-approved, pre-registered clinical trials (NCT06702631, NCT06044740) which recruited healthy adults between ages 18 and 59. A nerve stimulator connected to the left index finger was set to the subject's personal 7/10 intensity rating. Subjects listened to a series of 35 words and were instructed to create a mental picture involving the word, adding more detail as the word repeated over 6s. Twelve of the 35 words were accompanied by a 2 s painful shock. After the no-drug baseline, this experimental paradigm was then performed under 0.5 % sevoflurane (n = 29) or 70 % N_2O (n = 15) using different words. Blood oxygen-weighted images (0.8 s temporal resolution, 2.1 mm isotropic spatial resolution) were obtained at 3 T. Testing 1 day afterwards included 70 novel words, and word recognition was assessed using the normalized signal detection metric, d-prime (d'), for which 0 indicates chance performance. FMRI analysis was performed with FSL 6 (https://fsl.fmrib.ox.ac.uk/), and group results were thresholded for Z > 2.0 and cluster significance adjusted to an overall p < 0.05.

Results: Memory performance both under sevoflurane and N_2O was reduced compared to baseline (Fig. 1). FMRI signatures at baseline included robust increased bilateral activation in the anterior cingulate cortex (ACC) and lateral prefrontal and parietal cortices, including the precuneus (Fig. 2, top). The addition of the painful stimulus produced increased bilateral activation in the amygdala and insula (Fig. 3, top). Sevoflurane was associated with bilaterally decreased activation of the superior and middle temporal lobes and increased activation in the ACC, inferior temporal lobe, and the prefrontal cortex. In response to the painful stimulus, sevoflurane was associated with decreased activation in the right secondary somatosensory cortex and bilateral insula, and increased activation in the left parietal and primary somatosensory cortex (S1). N_2O was associated with bilaterally decreased activation of the superior and middle temporal lobes. In response to the painful stimulus, N_2O was associated with bilateral decreases in the insula, anterior and posterior cingulate, posterior prefrontal cortex, S1, parietal lobes, and cerebellum.



using the normalized signal detection metric d' (d-prime). Asterisks denote statistically significant differences from the no-drug condition (p < 0.001).

Discussion:
Sedative doses of sevoflurane and N_2O both impaired memory performance and showed reduced auditory cortex activation. Both sevoflurane and N_2O showed decreased pain-related activation in the posterior insula, a key region in pain processing. N_2O was also associated with more widespread decreases in activation throughout the pain neuromatrix, including ACC and S1, which are consistent with their analgesic

effects. Future work, including additional subject recruitment and analyses investigating successful memory encoding, will help elucidate the systems-level neural correlates for these agents.

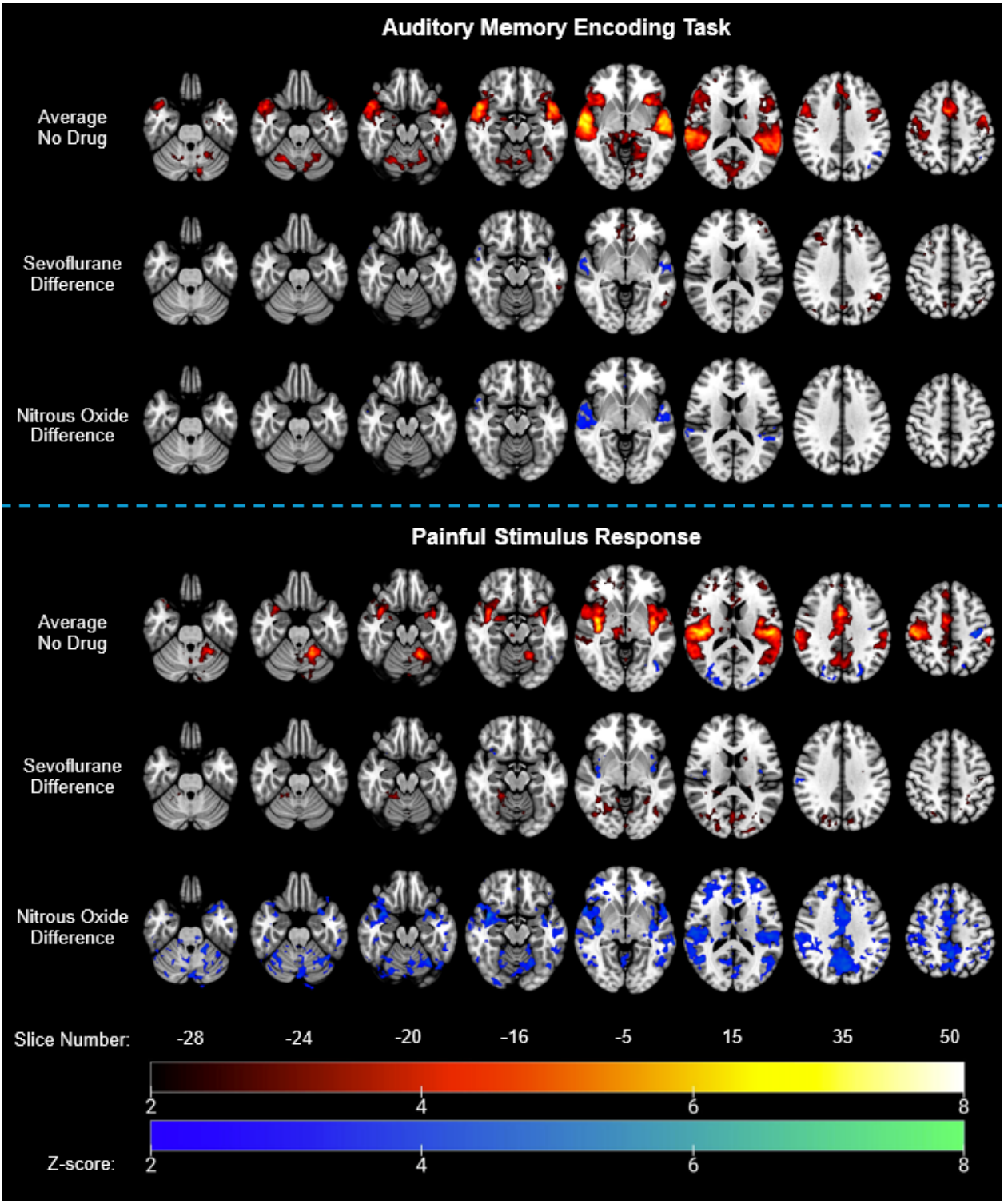


Fig. 2. All-subject average fMRI task activation for words encoded (top) and during periods experiencing painful electric nerve stimulation (bottom) for selected axial slices (left brain on right side of figure), with MNI-152 slices shown. The color bar indicates Z-score, according to the scale shown. The top row in each sub-panel shows the brain with significant positive (warm colors) or negative (cool colors) correlation to the task under the no-drug condition. The subsequent

#5_A Phase 1b Double Blind Multiple Ascending Dose Study of the Safety and Pharmacokinetics of NTRX-07

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Background: NTRX-07 is an orally administered, brain-permeable, selective cannabinoid receptor type 2 (CBR2) agonist under development for treating neuroinflammatory-related diseases, including neuropathic pain (NP) and Alzheimer's Disease (AD). Preclinical studies of NTRX-07 have demonstrated decreased inflammatory changes in the brain, decreases in pain response in NP models, and improved clearance of A-beta proteins, improved long-term potentiation, and improved learning and memory in rodent AD models.[1] A previous Phase 1a study of NTRX-07 demonstrated no significant adverse effects with single doses up to 2 mg/kg in healthy volunteers.[2] The objectives of the present study were to study the safety and pharmacokinetics (PK) of repeat dosing in older volunteers and a cohort of subjects with AD. Exploratory endpoints included a food effect cohort and plasma biomarkers of inflammation.
Methods: The IRB approved study procedures, and informed consent was obtained. Three cohorts of volunteers 45-80 years of age with well-controlled comorbidities and one cohort of AD patients diagnosed with cognitive impairment consistent with prodromal AD per International Working Group criteria or mild AD per National Institute on Aging - Alzheimer's Association criteria (n=6 active, 2 placebo per cohort) were enrolled. Participants were admitted to the site for the dosing duration and returned 7-12 days after the last dose for a safety visit. Participants received NTRX-07 (10, 30, or 90 mg) or a placebo in a double-blinded randomization orally once daily for seven days. Subjects were assessed for changes in vital signs, including maneuvers to induce lightheadedness, electrocardiograms, electroencephalograms (EEG), and laboratory studies. The second cohort returned and received a single repeat dose after a standard high-fat meal. The AD cohort also underwent cognitive testing and had blood samples for biomarkers drawn. Subjects had PK sampling done after the first and final dose of the study drug.
Results: There were no dose-limiting or serious adverse events during the trial. One subject withdrew from the trial due to social reasons. Five participants had orthostatic changes in blood pressure, three of whom were asymptomatic, and none required treatment. No participants had changes in the timed get-up and go, Nystagmus test, or Romberg test. No participants had abnormalities on the EEG. No clinically meaningful changes in ECG or safety labs were observed. PK at the high dose was similar between Non-AD and AD participants with an average of AUC0-24h (h•ng/mL) of 1291 and 1556, and Cmax (ng/ml) of 439 and 477, respectively. A decrease in levels on Day 7 suggested a change in clearance. The high-fat meal decreased Cmax, but AUC was comparable. No significant changes in cognitive scores were observed, though there was an interesting trend toward improvement in the AD participants. No significant changes in biomarkers were observed.
Conclusions: NTRX-07 was safely administered for 7 days at doses up to 90 mg/day. The primary side effect observed was mild transient orthostatic changes in blood pressure, usually with early doses. Plasma levels were within the target ranges based on the allometric scaling of preclinical data.
Disclosures: Drs. Foss, Kiraly, and Giordano are employees of NeuroTherapia, Inc. and hold stock options in the company. This study was supported in part by the Alzheimer's Drug Discovery Foundation. This data was reported previously in part at the Clinical Trials on Alzheimer's Disease (CTAD) conference, October 24–27, 2023, in Boston, Massachusetts.
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#6_Pharmacodynamic Interaction between Remimazolam and Remifentanil for Loss of Consciousness*

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Co-Authors: Kazue Araya[2], Hiromi Wakayama[1, 2], Yusuke Arai[1, 2], Ayako Tojo[2]

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Background/Introduction: An anesthetic/sedative and an opioid generally exhibit a synergistic pharmacodynamic interaction. This study examined the pharmacodynamic interaction between remimazolam and remifentanil for loss of consciousness.

Methods: After receiving approval from the institutional review board, written informed consent was obtained from forty adult patients. The crisscross design was used to develop a robust pharmacodynamic interaction model. In the first 20 patients, remifentanil was infused using an effect-site-targeted target-controlled infusion at 1.4-5.6 or 2-8 ng/mL for patients aged ≥65 or <65 years (n=10 in each age group), respectively. Three minutes later, a continuous infusion of remimazolam besylate was initiated at 1.0 or 1.5 mg/kg/h for patients aged ≥65 or <65 years, respectively, followed by an increment of 0.5 mg/kg/h every 5 minutes. In the second 20 patients, remimazolam was infused using a target-controlled infusion at 0.3-1.25 or 0.4-1.8 μg/mL for patients aged ≥65 or <65 years (n=10 in each age group), respectively. Three minutes later, a continuous infusion of remimazolam besylate was initiated at 0.10 or 0.15 μg/kg/min for patients aged ≥65 or <65 years, respectively, followed by an increment of 0.05 μg/kg/min every 5 minutes. Loss of consciousness was assessed as the Modified Observer's Assessment of Alertness Sedation scale <2. To determine the basic pharmacodynamic model structure, we developed both a basic logistic regression pharmacodynamic model for remimazolam and the reduced Greco pharmacodynamic interaction model between remimazolam and remifentanil using NONMEM 7 (ICON Clinical Research LLC, North Wales, PA). The model equations were as follows: logistic model; $P = RemimCe^{\gamma} / (RemimCe_{50}^{\gamma} + RemimCe^{\gamma})$, and reduced Greco model $P = \{RemimCe/RemimCe_{50} \times (1+(RemifCe/RemifCe_{50})\}^{\gamma} / [1+\{RemimCe/RemimCe_{50} \times (1+(RemifCe/RemifCe_{50})\}^{\gamma}]$, where P: probability of unconsciousness, RemimCe: remimazolam effect-site concentration (Ce), $RemimCe_{50}$: remimazolam Ce for 50% maximal effect, RemifCe: remifentanil Ce, $RemifCe_{50}$: remifentanil Ce for 50% maximal effect, and γ: steepness of the Ce *vs* response relationship. When the latter model

decreased NONMEM objective function value (OFV) by 6.63 ($P<0.01$, chi-square test with 1 degree of freedom) compared with the former model, we selected the latter as the basic model structure. Then, age and sex were examined as potential covariates of the remimazolam Ce and remifentanil Ce. A log-normal distribution was applied as interindividual variability of Ce. The Ces of remimazolam and remifentanil were calculated using the Masui and Minto pharmacokinetic models, respectively. When a covariate decreased the OFV by 6.63, the covariate was considered significant.

Results: The patient characteristics (mean±SD [range]) were as follows: 65±14 [34-89] years old, 20 males and 20 females, 59±10 [40-85] kg total body weight, and 162±9 [144-184] cm height. The reduced Greco model was better than the logistic model ($P<0.001$). The final reduced Greco model included $RemimCe_{50}$ of 0.22 μg/mL, $RemifCe_{50}$ of 17.2 ng/mL with 31% and 33% interindividual variability, respectively, and γ of 153. The model included age (27.5 decrease in OFV, $P<0.001$) as a covariate for $RemimCe_{50}$.

Conclusions: We found a pharmacodynamic interaction between remimazolam and remifentanil for loss of consciousness similar to other anesthetics. Additionally, age influenced the remimazolam effect for loss of consciousness.

*This abstract has been accepted for an oral presentation at the ASA Annual Meeting 2025.

#7_Perioperative intravenous methadone and QTc interval: An observational study.

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Background:
A single dose of intravenous (IV) methadone (0.2-0.3 mg/kg) in patients undergoing surgery under general anesthesia provides excellent intraoperative antinociception and superior postoperative analgesia with significant opioid sparing up to 72 hours postoperatively. Chronic oral methadone can cause prolonged corrected QT interval (QTc), and carries a black box warning, but QTc effects usually occurs at higher doses for prolonged duration (months). QTc effects of low-dose perioperative IV methadone may be a potential safety concern to practitioners. QTc effects of low-dose perioperative IV methadone are unknown.

Purpose:
The research goal is to identify the effects of intraoperative intravenous methadone on the cardiac QTc interval, and to compare QTc intervals in patients receiving and not receiving methadone for induction of anesthesia.

Methods:
We conducted an observational study of QTc intervals in patients receiving intraoperative opioid (methadone, fentanyl or other, and dose, chosen at the discretion of the anesthesia care team). QTc interval (corrected using Fridericia's formula) was evaluated at baseline and 1, 5, 10, 15, 30, 45, and 60 min after dosing.

Outcome measurements:

Primary outcome: QTcF (Fridericia's formula) > 500 msec.

Secondary outcomes: QTcF increase > 60 msec from baseline**,** QTcF >450 msec in males or QTcF >470 msec in females.

Results:
QTcF data were analyzed from 282 patients receiving methadone and 144 patients receiving other opioids (non-methadone) during induction of anesthesia. Demographic data and outcome measurements are described in the table below. Methadone dose (mean±SD) was 19±6 mg and fentanyl dose in non-methadone group was 277±165 µg. Baseline QTcF was 412±16 msec in methadone group and 418±22 msec non-methadone group.

Primary outcome: New onset QTcF >500 msec were observed in 7 patients (2.5%) with methadone, compared to 15 patients (10.4%) in the non-methadone group.
Secondary outcomes:
Any QTcF >60 msec were observed in 12 patients (4.3%) after methadone vs 22 patients (15.3%) in the non-methadone group. Peak 1-60 min QTcF with methadone was 442±29 msec vs 460±28 msec in non-methadone group. Peak 1-60 min QTcF change from baseline with

methadone was 30±15 msec vs 42±19 msec in the non-methadone group. Any QTcF >450 msec (male) or >470 msec (female) were observed in 59 patients (21%) with methadone vs 65 patients (45%) in non-methadone group. No adverse cardiac events were observed in any patient.

Conclusions: IV methadone (0.2-0.3 mg/kg at induction) was found to cause no clinically meaningful changes in QTc, particularly at peak plasma concentrations. QTc changes were not greater after methadone compared with no methadone. No adverse cardiac events were noted. Current results provide clinical assurance regarding methadone and QTc. Routine preoperative QTc assessment and postoperative ECG telemetry monitoring do not appear warranted.

Table:

	Methadone (N=282)*	**Non-methadone (N=144)****
Demographics		
Age, mean (SD)	55 ± 16	58 ± 16
Sex, M:F (n, %)	148:134 (52%:48%)	61:83 (43%:57%
Weight (Kg), mean±SD	86±20	85 ± 24
Baseline QTcF (msec), mean±SD	412±16	418±22
QT interval (Fridericia correction)		
new onset QTcF>500 msec, n (%)	7 (2.5%)	15 (10.4%)
Peak 1-60 min QTcF (msec), mean±SD	442±29	460±28
Peak 1-60 min QTcF change from baseline (msec), mean±SD	30±15	42±19
Any QTcF>60 msec, n (%)	12 (4.3%)	22 (15.3%)
Any QTcF >450 msec (male) or >470 msec (female), n (%)	59 (21%)	65 (45%)

Induction opioid administered at time zero. ECG (II, V5) obtained 1, 5, 10, 15, 30, 45, 60 min after opioid

* Induction dose methadone 19±6 mg

**Induction dose fentanyl 277±165 µg

#8_Postoperative naloxone administration after perioperative methadone: A retrospective analysis

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Background:
Intravenous (IV) methadone is commonly used perioperatively due to excellent intraoperative antinociception and superior postoperative analgesia with significant opioid sparing up to 72 hr postoperatively. Some practitioners may have concerns of potential postoperative respiratory depression due to the long methadone half-life of 1-2 days. The goal was to evaluate postoperative naloxone administration as a surrogate for respiratory depression after intraoperative methadone.

Methods:
We conducted a retrospective review of postoperative naloxone administration in adults ≥18 yr receiving perioperative opioids from January 2022 to February 2025. Any patients receiving the opioids methadone, fentanyl, hydromorphone, morphine, sufentanil or remifentanil any time between anesthesia start and stop; or receiving naloxone 0-48 hours after anesthesia stop were included. Excluded were cases with another surgery within 24 hours before or after the index case.

Results:
208,198 adult non-cardiac surgical patients were included in our analysis. There was no significant difference between naloxone administration in patients who received methadone (11/1154, 0.95%) and those who did not receive methadone (1384/207044, 0.67%); P=0.237. Methadone use was uncommon (1154; 0.55% of cases). Methadone dose was 20 mg (median), range 1-100 mg. Methadone and non-methadone groups were similar in size, age, weight, and sex. Methadone administration was more common in neurosurgery, ENT, urology and pediatric surgery. Methadone dose was not different between patients who did or did not receive naloxone (P=0.227). Naloxone administration occurred more commonly after thoracic and general surgery. The large majority of naloxone administration was by infusion (78%), and most naloxone (99%) was administered to patients who had not received methadone. Naloxone infusions were most common in thoracic, general surgery, and gynecology cases. Most adults (90%) went to post anesthesia care unit (PACU) postoperatively. The majority (89%) of naloxone administration occurred outside of the PACU, and only 11% occurred in the PACU. Only 1 patient who received perioperative methadone also received naloxone in the PACU. In patients receiving naloxone post-PACU, the average time to administration was 18 hour after anesthesia stop (12 hr in those who received methadone and 18 hr in those who had not received methadone). In neurosurgery. naloxone use was 1.26% in patients receiving methadone and 0.22% in patients not receiving methadone. Methadone use in craniotomy and spine was not a risk factor for naloxone administration. In patients receiving methadone, naloxone administration was not more frequent in patients receiving PACU methadone. In patients receiving methadone, naloxone administration was not associated with administration of PACU analgesics. No intraoperative pharmacologic risk factor, alone or in combination with methadone, for the administration of

postoperative naloxone, was identified. Anesthesia duration was substantially longer in patients receiving methadone. PACU LOS adjusted for duration of surgery was not longer in patients receiving methadone.

Conclusions:

Analysis of data from 208,198 patients does not suggest a statistically significant or clinically meaningful association between perioperative methadone administration and postoperative naloxone administration. Methadone, compared with other opioids, or no opioids, does not appear as a risk factor for respiratory depression, as assessed by naloxone administration.

Table 1. Adult patient cohort demographics

	Methadone	SD	No Methadone	SD	Total	SD
No of patients	1154		207044		208197	
Age (yr)	54	16	58	17	58	17
Weight (kg)	85	22	84	31	84	22
Male	545		86091		86636	
Female	609		120941		121550	
Anesthesia Duration (median)	4.8		1.9			
PACU LOS hr (median)	2.4		1.3		1.3	
PACU LOS hr (relative) median	0.57		0.83		0.83	

SD: Standard deviation

Table 2. Naloxone administration, location, type and methadone administration in adults

Total Patients 208198		Any Methadone			Naloxone %	
		Yes	No	Total	Methadone Y	Methadone N
Any naloxone	Yes	11	1384	1395	0.95%	0.67%
	No	1143	205660	206803		
	Total	1154	207044	208198		
a. Naloxone given in PACU	Yes	1	179	180		
	No	4	214	218		
	Total	11	1384	1395		
a.1.PACU naloxone by injection	Yes	1	73	74		
a.2 PACU naloxone by infusion	Yes	0	106	106		
b. Naloxone given post-PACU	Yes	4	214	218		
b.1 Post-PACU naloxone injection	Yes	2	54	56		
3.b.2. Post-PACU naloxone infusion	Yes	2	160	162		

Table 3. Methadone and naloxone administration in neurosurgery patients, and craniotomy and spine surgery

		Methadone Yes			Methadone No		
		Naloxone Yes		Naloxone No	Naloxone Yes		Naloxone No
	N	Injection	Infusion		Injection	Infusion	
Neurosurgery	12684	3	2	392	26	1	12260
Craniotomy	4060	1	1	91	5	0	3962
No craniotomy	8624	2	1	301	21	1	8298
Spine Surgery	180	0	0	16	5	0	163

Non invasive assessment of the inflammatory states using the TSI index

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INTRODUCTION:

Inflammation monitoring can support the early identification of systemic inflammatory response syndrome (SIRS) and sepsis [1,2]. As one of the main causes of death in intensive care units, sepsis demands prompt diagnosis and treatment. Many commonly used biomarkers are either invasive or unsuitable for continuous, real-time assessment [3]. Heart rate variability (HRV) provides insight into autonomic function and inflammatory status [4,5]. Anesthesia can affect HRV [6]. The TSI index compensates for the effects of anesthesia in HRV using the Brain Activity Index, which quantifies the level of consciousness. The non-invasive Trending of Sepsis and Inflammation (TSI) index combines HRV with EEG-based consciousness monitoring to evaluate inflammatory activity and estimate sepsis risk [7].

OBJECTIVE:

To validate the TSI index in abdominal surgery and HIPEC procedures.

METHODS:

A database was used for this post-hoc study. Approvals from the local ethics committees at Quirónsalud and UMCG were obtained for the original data. The study included cohorts of abdominal surgery patients at Quirónsalud Barcelona (n=41) and HIPEC patients at UMCG (n=62). The TSI was derived using RMSSD, heart rate, LF/HF ratio, and the EEG-based Brain Activity (BA) index, measured with the CoreSys One system (1 ECG and 2 EEG channels, sampled at 1024 Hz). Data recordings were segmented into phases: for Quirónsalud patients, basal and intraoperative phases; for UMCG patients, basal and HIPEC phases.

RESULTS:

TSI demonstrated significant differences (all $p<0.05$) across all pairwise comparisons between clinical states (surgical/HIPEC phases). Figure 1 showcases the distribution of the TSI across the different clinical states.

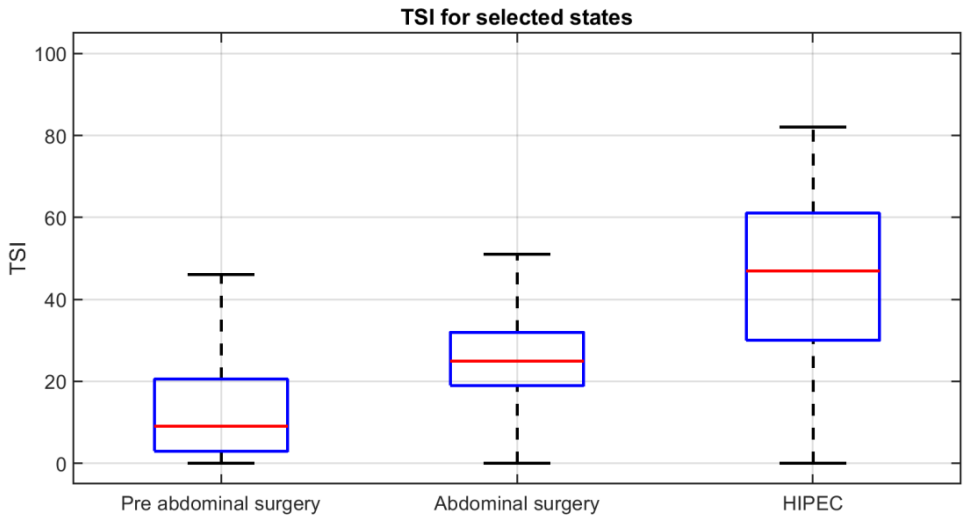

Figure 1 TSI values across clinical states. Surgical patients (Quirónsalud Barcelona, n=41) shown at pre-surgery and intraoperative (abdominal surgery) phases. HIPEC patients (UMCG Groningen, n=62) showcasing the HIPEC phase. TSI is derived from CoreSys One monitor (ECG and EEG).

CONCLUSIONS:

TSI reliably differentiates inflammatory states across various clinical settings and reflects severity levels, demonstrating its potential for non-invasive monitoring.

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3

#10_Propofol Enhancement of Slow Wave Sleep as a Putative Mechanism for Treating Depression in Older Adults: A Pilot Study

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Background/Introduction: Propofol is a commonly used anesthetic that serves as a positive allosteric modulator of GABAA receptors. Rodent models have demonstrated the ability of propofol to address homeostatic needs for non-rapid eye movement sleep. In small clinical trials, propofol has shown some promise as a novel antidepressant and enhancer of slow wave sleep (SWS) in patients with insomnia. While sleep disturbances have been recognized as a core pathophysiology of depression, it remains unknown whether promoting SWS may be important for enhancing response to oral antidepressants. We utilized propofol as a therapeutic probe in a mechanistic trial to address whether 1) propofol may augment an oral antidepressant regimen in geriatric patients with treatment-resistant depression, and 2) whether antidepressant effects are mediated through SWS enhancement.

Methods: Sixteen depressed participants, age 60 years and older who failed at least 2 oral antidepressant trials, were enrolled in an open-label trial. Participants were instructed to maintain a consistent oral antidepressant regimen throughout the study period. Two 2-hour propofol infusions were administered 2-6 days apart, with real-time monitoring to target maximal induction of slow waves on 64-channel high-density electroencephalographic (EEG). The Eleveld pharmacokinetic (PK) model was utilized for target-controlled infusions to allow stepwise titration of propofol based on the EEG, enable stable modeled brain effect-site concentrations, and post-hoc evaluation of drug exposure durations. Wireless wearable headbands were utilized to acquire at-home EEG during overnight sleep before and up to two weeks after infusions. Recordings were scored manually by AASM-registered technologists. Depression was assessed using the Montgomery-Asberg Depression Rating Scale (MADRS). Assessments were performed within one week before the infusions and approximately 1-, 3-, and 10-weeks afterwards. Changes from baseline were calculated. Exposure durations were calculated for different ranges of modeled brain PK effect-site concentrations. Linear regressions and slope tests were utilized to evaluate associations. Nonparametric Mann-Whitney U-tests were utilized to evaluate difference in medians. The investigation was registered on ClinicalTrials.gov (NCT04680910).

Results: There were no serious adverse events and only one withdrawal. Results were based on the fifteen participants who completed both infusions. Post-infusion MADRS scores were reduced compared to baseline at 1-week (median change -4, 95%CI [-7,1], p=0.014), 3-weeks (median change -5, 95%CI [-13,1], p=0.026), and at 10-weeks (median change -3, 95%CI [-11,1], p=0.010). Weight-adjusted average propofol dose negatively correlated with MADRS changes at 1-week (r^2=0.32, p=0.029), 3-weeks (r^2=0.52, p=0.003), and 10-weeks (r^2=0.41, p=0.010) after the second infusion (**Figure 1**). Average change in duration of SWS on infusion nights correlated with post-infusion reductions in MADRS scores at 1-week (r^2=0.27, p=0.047) and 3-weeks (r^2=0.28, p=0.040). Duration of exposure at moderate modeled propofol effect-site concentrations (2.5-4.5 mcg/ml) correlated with SWS enhancement on nights following infusions (r^2= 0.28, p=0.04) and MADRS changes at 3-weeks (r^2=0.42, p=0.009).

Conclusions: These open-label trial findings suggest that serial propofol infusions may augment oral antidepressant therapy in geriatric patients in a dose-dependent manner. Enhancement of post-infusion SWS is a potential mechanism for subsequent antidepressant response. These safety, feasibility, and response data support an ongoing experimental double-blind randomized controlled trial (ClinicalTrials.gov NCT06867549).

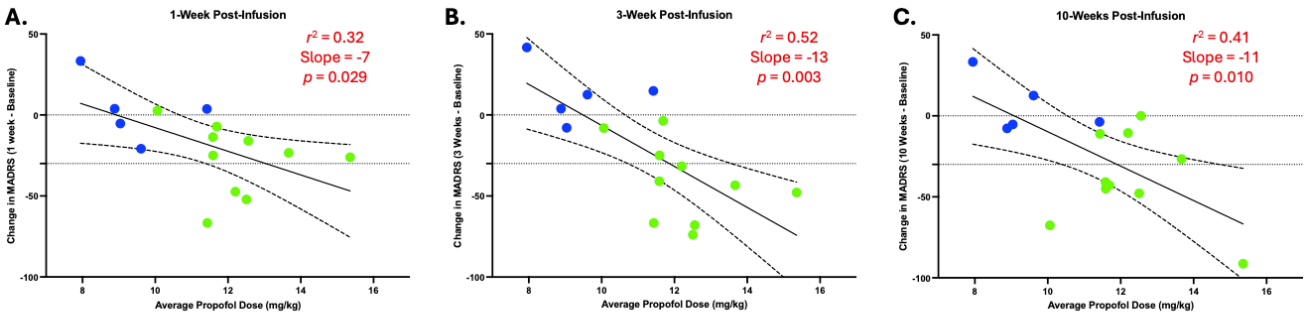

Figure 1. Average weight-based propofol dose as a predictor of relative change in MADRS at 1-, 3-, and 10-weeks after the second infusion. A. Percentage change in baseline MADRS at 1-week correlates inversely with average propofol dose administered during the two infusions. **B.** A stronger association is noted at 3-weeks post-infusion. **C.** Average propofol dose predicts percentage change at 10-weeks. Blue symbols indicate 5 non-responders, with 30% of baseline threshold indicated on the graphs. Green symbols denote 10 responders, defined as individuals who had at least 30% change in baseline MADRS during the 10-week follow-up period.

3 #11_Pharmacological Effects of a New Halogenated Methyl-Ethyl Ether in Rats

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Background/Introduction: We studied a halogenated methyl-ethyl ether (BTTE: 1-bromo-1,1,2-trifluoro-2-(trifluoromethoxy)ethane, CAS: 2356-55-0) to evaluate its potential as an inhaled general anesthetic. We measured partition coefficients, stability in CO_2 absorbents, and effects on NMDA and $GABA_A$ receptor currents. In rats, we measured potency to produce immobility in response to noxious stimulation, and bromide and fluoride levels to determine extent of metabolism. For comparison, we also studied groups of rats anesthetized with sevoflurane or halothane.

Methods: Saline:gas, oil:gas and blood:gas partition coefficients were determined using headspace techniques (n=4 for each). Stability was evaluated during two-hour exposure at room temperature of BTTE in Amsorb and SodaSorb. Effects of BTTE on NMDA and $GABA_A$ receptor currents were determined using standard techniques in oocytes. Sprague-Dawley rats (N=4) were anesthetized in acrylic cylinders using vaporizers that delivered BTTE. Blood pressure was determined by the tail cuff method. Anesthetic requirements were determined by adjusting the inspired BTTE concentration (measured using gas chromatography), and applying a tail-clamp to elicit gross, purposeful movement. The BTTE concentration was adjusted in an up-and-down method to find the concentrations that permitted, and prevented, movement in response to the clamp; the

minimum alveolar concentration (MAC) was the average of these bracketing concentrations. After 120 minutes of anesthetic exposure, a laparotomy was performed and each rat exsanguinated; bromide and fluoride levels were determined. Two other groups of rats were anesthetized with sevoflurane (N=4) or halothane (N=4) for comparative purposes.

Results: The partition coefficients were: S:G = 0.051 ± 0.008; O:G = 31 ± 2; B:G = 0.129 ± 0.013. BTTE was stable in Amsorb, while there was 17.5 ± 0.9% loss in Sodasorb (similar to sevoflurane). At saturated BTTE concentrations, $GABA_A$ currents were enhanced 195 ± 24% (n=5) while NMDA currents (n=6) were unaffected. Anesthetic requirements (MAC) for BTTE were 13.1 ± 0.0%; sevoflurane and halothane requirements were 2.3 ± 0.3% and 1.3 ± 0.1%, respectively. MAP was 91 ± 11 mmHg with BTTE, while it was 76 ± 9 mmHg with sevoflurane and 75 ± 12 mmHg with halothane ($p<0.05$ one-tailed t-test: BTTE vs. sevoflurane and BTTE vs. halothane). After BTTE anesthesia, fluoride concentrations were <LOQ, and bromide ranged from 0.3 ppm to <LOQ. After sevoflurane, fluoride was 0.3 ± 0.0 ppm; after halothane, bromide was 11 ± 5 ppm and fluoride 0.3 ± 0.1 ppm.

Conclusions: BTTE appeared to be well tolerated in rats. Receptor data suggest that BTTE acts at $GABA_A$ receptors, but not NMDA receptors. Blood pressure was greater during BTTE anesthesia as compared to those measured during sevoflurane and halothane anesthesia. The fluoride and bromide concentrations were less than those found with sevoflurane and halothane anesthesia, suggesting minimal metabolism. The low B:G partition coefficient suggests that BTTE would have fast kinetics. BTTE shows potential as a new inhalational anesthetic.

#12_Morphine and hydromorphone pharmacodynamics in human volunteers: Population-based modeling with focus on response variability and utility

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BACKGROUND: Morphine and hydromorphone have been standard opioids for pain treatment for many years. We previously showed that the onset, magnitude, and duration of effects and side effects for both opioids are considerably different for various clinical endpoints, and exhibit considerable interindividual variability.[1] The present investigation is a secondary analysis of our study in healthy volunteers.[1] The purpose is to model morphine and hydromorphone pharmacodynamics (concentration-effect relationships), with a focus on interindividual pharmacodynamic variability.

METHODS: In a balanced crossover, 51 subjects received a single 2 h intravenous infusion of 0.05 mg/kg morphine or 0.2 mg/kg hydromorphone. Measurements lasted for 12 h and included analgesic response to thermal stimulus (maximally tolerated or limit temperature, and verbal analog pain scores at specific temperatures), pupil diameter, respiratory rate, and end-expired CO_2 concentration. Predicate pharmacokinetic analyses used three-compartment models for both opioids.[2] For each clinical endpoint, morphine and hydromorphone pharmacodynamic data were analyzed together in a single model, with drug as a covariate, to allow assessment of interindividual and drug differences. In addition, a physiological model was implemented to characterize respiratory rate and CO_2 concentration in combination. Pharmacodynamic parameters were centered at their average, which improves estimation stability, while a factor (φ) determined the difference from the average. Models were fitted to the data in NONMEM using a sequence of estimation steps. Utility functions were then constructed as a function of the opioid effect-site concentrations.

RESULTS: Analysis focused on potency parameters, blood-effect-site equilibration half-lives ($t½k_{e0}$) and their inter-individual variabilities. For limit temperature, the combined potency ($C_{1D,Limit}$ = 14.9 ng/mL) had a φ = 0.32, which is significantly different from 1. This yields two separate potency values for morphine (46.9 ng/mL) *versus* hydromorphone (4.4 ng/mL). The combined estimate for $t½k_{e0}$ (0.73 min) has a value of φ (1.02) not significantly different from 1, yielding 0.71 h for morphine and 0.75 h for hydromorphone which are not different. Similarly, the φ value of the other parameters, for other outcomes, baseline value, γ and σ, were not significantly different from 1, indicative that morphine and hydromorphone do not differ significantly in these parameter estimates. The $t½k_{e0}$ for morphine was generally slower than for hydromorphone. Pupil diameter was a more sensitive

measure of opioid effect compared with respiratory effects and analgesia. Interindividual variabilities (% coefficient of variation) in parameter estimates for potency (generally referred to as C_{50}) and $t_{½k_{e0}}$ for the effect outcomes were large, and varied between different effect measures, but none of the interindividual variabilities were significantly different between the opioids (Table).

CONCLUSIONS: There was considerable interindividual variability in pharmacodynamic effect parameters for both morphine and hydromorphone, but no major variability differences between the opioids. Pharmacodynamic potencies for the various endpoints were different between hydromorphone and morphine, but of the same order of magnitude within each opioid. The utility function was more favorable for hydromorphone than for morphine. These results may influence opioid selection.

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Table. Estimated parameter variabilities (% coefficient of variation) of the potency parameters and blood-effect-site equilibration half-lives ($t_{½k_{e0}}$) for various clinical effects

	Coefficient of variation	
Parameter	**Potency**	**$t_{½k_{e0}}$**
limit temperature	57%	64%
T_{50} of VAS scores	180%	190%
end-expired CO_2	35%	75%
respiratory rate	85%	90%
physiological model	47%	72%
pupil size	25%	52%

Data are from the combined analyses of morphine and hydromorphone. %CV = $\sqrt{\exp(\omega^2 + \nu^2) - 1} \cdot 100$, with ω^2 = variance for interindividual variability and ν^2 = variance for inter-occasion variability.

Conflict of interest: KM – none, EO – none, In the last 36 months, AD received consultancy and/or speaker fees from Enalare Therapeutics Inc. (USA) and Trevena Inc. (USA); EDK – serves on an Independent Data Monitoring Committee for Vertex Pharmaceuticals.

#13_Validation of the NAS index in TIVA

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Introduction: The autonomic nervous system (ANS) modulates cardiovascular responses to nociception during anesthesia and analgesia. Heart rate variability (HRV) analysis provides a non-invasive way to track these dynamics. The CoreSafe One (CoreSafe, Barcelona, Spain) is a chest-worn device that acquires electrocardiogram (ECG) signals for real-time HRV feature extraction. This study expands on previous work by increasing the dataset and retraining an Adaptive Neuro-Fuzzy Inference System (ANFIS) to develop the Neuro-Autonomic State (NAS) index, an ECG-based indicator of nociception likelihood for continuous intraoperative monitoring.

Methods: After approval from the local ethics committee, data was collected from 29 surgical patients undergoing general anesthesia with propofol and remifentanil; the ECG signals were recorded from a single chest placement throughout surgery. Raw ECG data were preprocessed to remove noise and artifacts, detect R-peaks, and compute HRV metrics. Four normalized HRV features (heart rate (HR), root mean square of successive differences (RMSSD), percentage of successive intervals differing by more than 50 ms (PNN50), and the low-frequency to high-frequency power ratio (LF/HF)) were extracted in two-minute windows, updated every 6 seconds. An ANFIS model was trained using three Gaussian membership functions per input, a linear output function, and 500 training epochs. The target output was an index of analgesia based on EEG signals. In contrast, the ANFIS model was trained exclusively on ECG-derived HRV features from the CoreSafe One and given a scale from 1 to 100.

Results: The ANFIS model demonstrated a moderate correlation with the target index from the EEG-based reference device ($R^2 = 0.5047$; smoothed $R^2 = 0.6205$), with an average absolute error of 37.28 and RMSE of 39.10. As shown in Figure 1, NAS values were lowest during deep analgesia, intermediate during adequate analgesia, and highest when patients were awake. This separation between conditions supports the potential of NAS to discriminate autonomic states associated with different levels of nociception.

Conclusion: The proposed ANFIS-based NAS index shows potential for estimating nociception using only ECG-derived HRV features, providing a non-invasive and portable alternative to EEG-based monitoring. Although performance is moderate, the improved correlation after smoothing suggests that temporal averaging can enhance reliability.

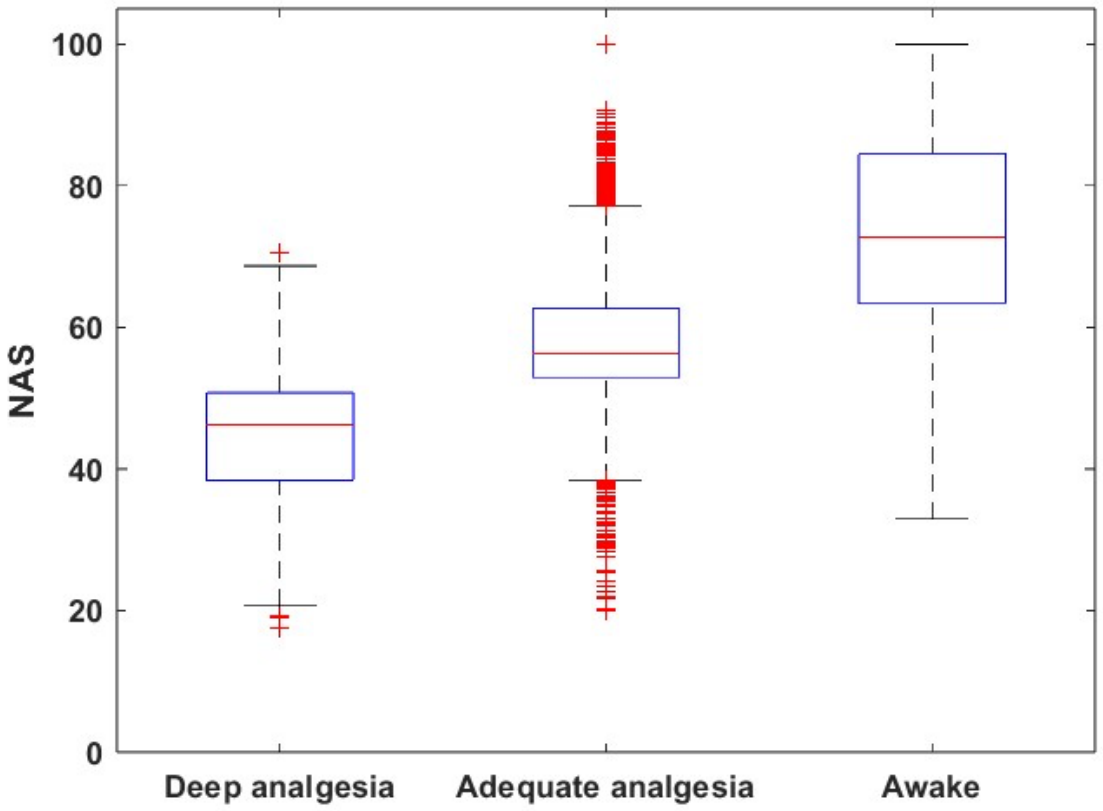

Figure 1. Distribution of NAS values across different surgical states (Deep analgesia, Adequate analgesia, Awake).

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