Intravenous (IV) Tramadol for Use in Medically Supervised Health Care Setting

Avenue Therapeutics, Inc.

February 15, 2022

Joint Meeting of the Anesthetic and Analgesic Drug Products and the Drug Safety and Risk Management Advisory Committees

Introduction

Lucy Lu, MD

President and CEO

Avenue Therapeutics, Inc.

Rationale for IV Tramadol Registration

Provide an effective Schedule IV analgesic with the potential to displace intravenous Schedule II opioids in patients with post-operative acute pain

Advisory Committee Input Requested on Appeal

- Avenue submitted NDA for IV tramadol in 2019
- Received two complete response letters with same core clinical deficiency
- Appealed to Office of New Drugs
  - Deciding official asked for advisory committee input

IV Tramadol Application Overview

- IV tramadol NDA met regulatory requirements for approval
  - Safe and effective for intended population
  - Clinically adequate onset
  - IV tramadol offers Schedule IV option for multimodal analgesia
  - Adequately managed with NSAID rescue
- 26-year oral use in U.S. and 30-year IV use in Europe and other territories
- At therapeutic doses, IV tramadol has lower abuse potential than intravenous Schedule II opioids currently available

FDA Core Concerns Precluding Approval

Complete Response Letter, June 6, 2021

- "While the primary endpoint was met for both studies, meaningful pain relief was delayed…"
- "…combining tramadol IV with another opioid increases the risk of opioid "stacking" and of additive adverse reactions, including over-sedation and respiratory depression."
- "...combination therapy of an opioid with a non-opioid is not consistent with the intended use of intravenous opioids."

Avenue Position on Core Clinical Concern

- Data supports positive benefit-risk profile of IV tramadol and answers FDA's central concerns of opioid stacking and related harm
  - Totality of data indicates adequate onset of action
  - Clinical trials demonstrated no increased risk of opioid stacking
  - Clinical experience from Europe does not support a safety signal regarding overdose/harm from opioid stacking

While Labeling Not Previously Discussed, Amenable to Standard Opioid Indication

IV tramadol is indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Limitations of Use

Because of the risks of addiction, abuse, and misuse, with opioids, even at recommended doses [see **WARNINGS**], reserve IV tramadol for use in patients for whom alternative treatment options (e.g., non-opioid analgesics):

- have not been tolerated, or are not expected to be tolerated
- have not provided adequate analgesia, or are not expected to provide adequate analgesia

Agenda

MoA and IV Tramadol Experience in EU	**Prof. Richard Langford, MD** Lead Consultant, Pain Service The London Clinic
PK, Clinical Efficacy and Safety **Discussion of FDA Concerns**	**Lucy Lu, MD** President and CEO Avenue Therapeutics, Inc.
Epidemiology of Abuse of Tramadol	**Janetta Iwanicki, MD** Chief Scientific Officer Rocky Mountain Poison and Drug Safety
Clinical Perspective From a U.S. Investigator	**Harold Minkowitz, MD** Adjunct Associate Professor, Anesthesiology and Perioperative Medicine MD Anderson Cancer Center

Additional Experts

Abuse Liability

Jody Green, PhD
Chief Scientific Officer
Inflexxion

Analgesic Trial Design

Neil Singla, MD
Founder and Chief Scientific Officer
Lotus Clinical Research

Statistics

Mark Harnett, MS
Program Biostatistician
Avenue Therapeutics, Inc.

Mechanism of Action and IV Tramadol Experience in Europe

Prof. Richard Langford, MD

Lead Consultant, Pain Service

The London Clinic

IV Tramadol Has Two Mechanisms of Action[1], Both Important for Efficacy

Monoamine Reuptake Inhibitor (parent tramadol)	Synergistic Potentiation	Mu-opioid Agonist (primarily via key metabolite M1)

- Parent isomers are themselves analgesic and reach CNS rapidly with IV dosing
  - Monoamine reuptake inhibition block afferent pain impulses[2]
- Dual mechanisms confirmed in human volunteers
- Further opioid-based activity follows as result of metabolism in liver to M1 metabolite

1. Demonstrated in animal and human blocking studies; 2. Raffa et al. 1996

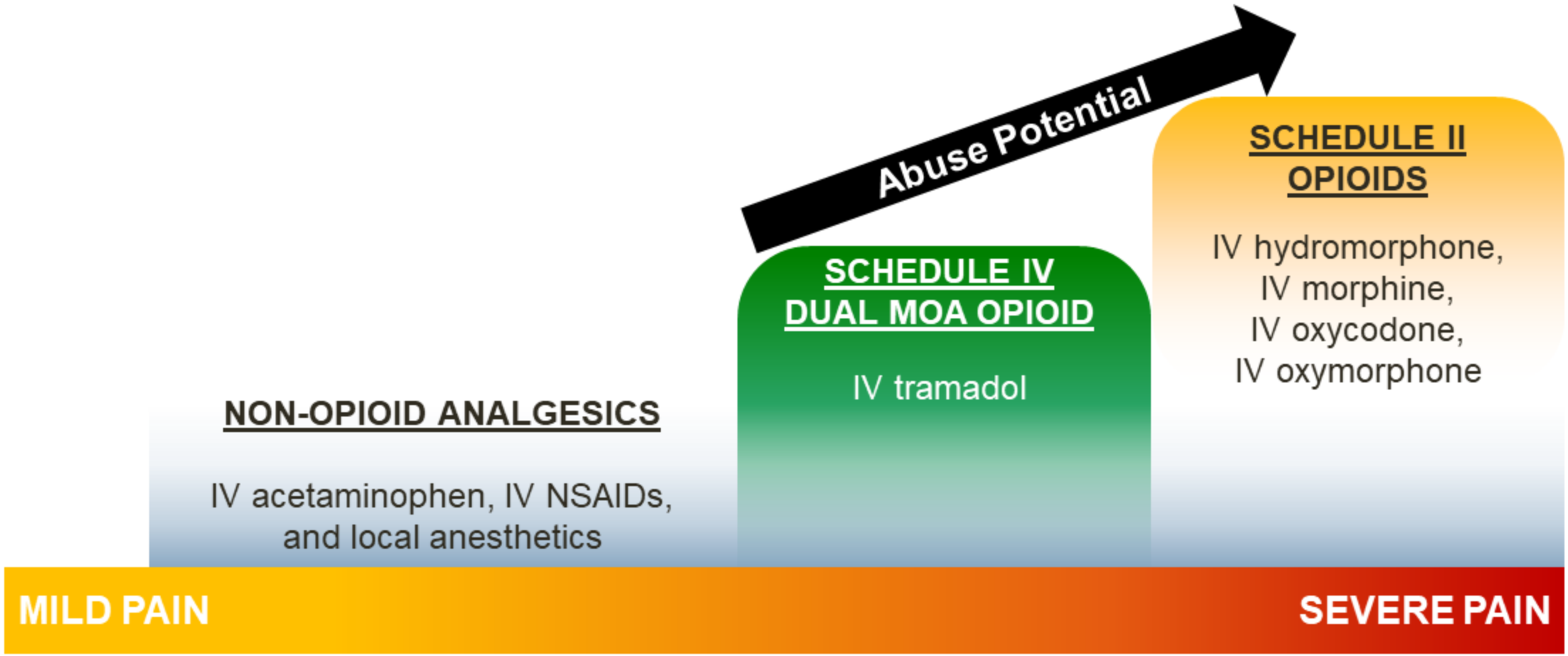
IV Tramadol Has Been Safely Used in Europe for 30 Years

- ~370 million doses administered in Europe from 2010 to 2019[1]
- Used in wide range of post-operative settings[2]
  - Intermediate surgeries (Hernia, Laparoscopy, Arthroscopy)
  - Major surgeries with nerve block / multimodal analgesia
- Effectively manages pain while reducing need for conventional opioid analgesia

1. IQVIA. Countries included: France, Germany, Italy, Spain, UK, Austria, Belgium, Bulgaria, Croatia, Czech Republic, Estonia, Finland, Greece, Hungary, Ireland, Latvia, Lithuania, Luxembourg, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, and Sweden.

2. NICE guideline NG180. August 2020. National Institute for Health and Care Excellence.

IV Tramadol Offers Freedom from Schedule II Opioids that Have Stronger Abuse Potential



IV Tramadol Has Acceptable Onset of Action

- Onset usually within 30 minutes
- Clinical experience consistent with clinical endpoints informing onset in IV tramadol pivotal studies

Adverse Outcomes Due to Opioid Stacking Not Reported as Safety Signal

- Risk due to stacking is low in in-patient setting
- Opioid rescue commonly practiced
  - Trained staff and routine monitoring mitigates risks
  - IV tramadol-related AEs well understood and consistent with other opioids[1]
- 50 mg is modest dose with opioid activity < 4 mg IV morphine

1. Schug SA et al. Acute Pain Management: Scientific Evidence (5th edition) ANZCA & FPM, Melbourne.SE Working Group of the Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine (2020)

Summary

- PK and dual mechanisms confer
  - Adequate onset and duration of effect
  - Reduced opioid-related risks, including abuse potential
- Hospital staff competent in post-operative pain management can safely incorporate tramadol into practice protocols

Peer-reviewed evidence and > 30 years of clinical experience support IV tramadol as effective component in real-world multimodal peri-operative pain management

PK, Efficacy, and Safety Data

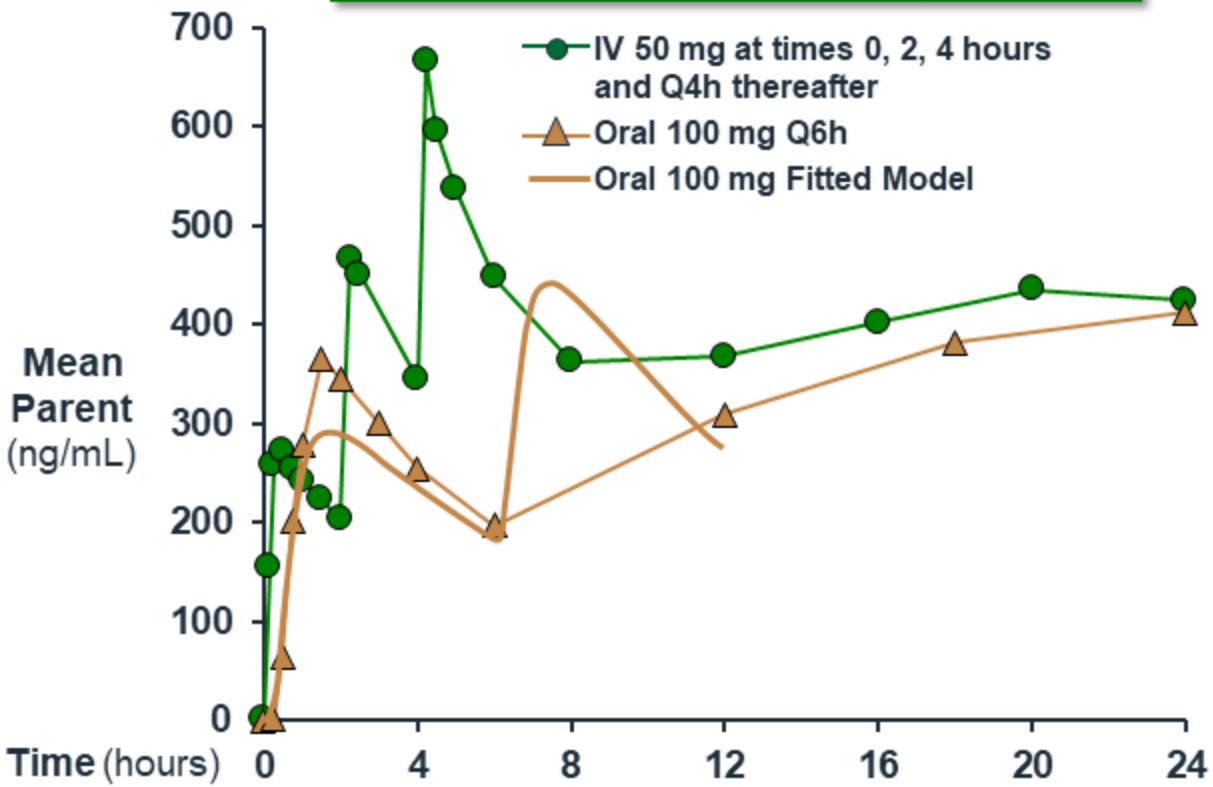
Lucy Lu, MD

President and CEO

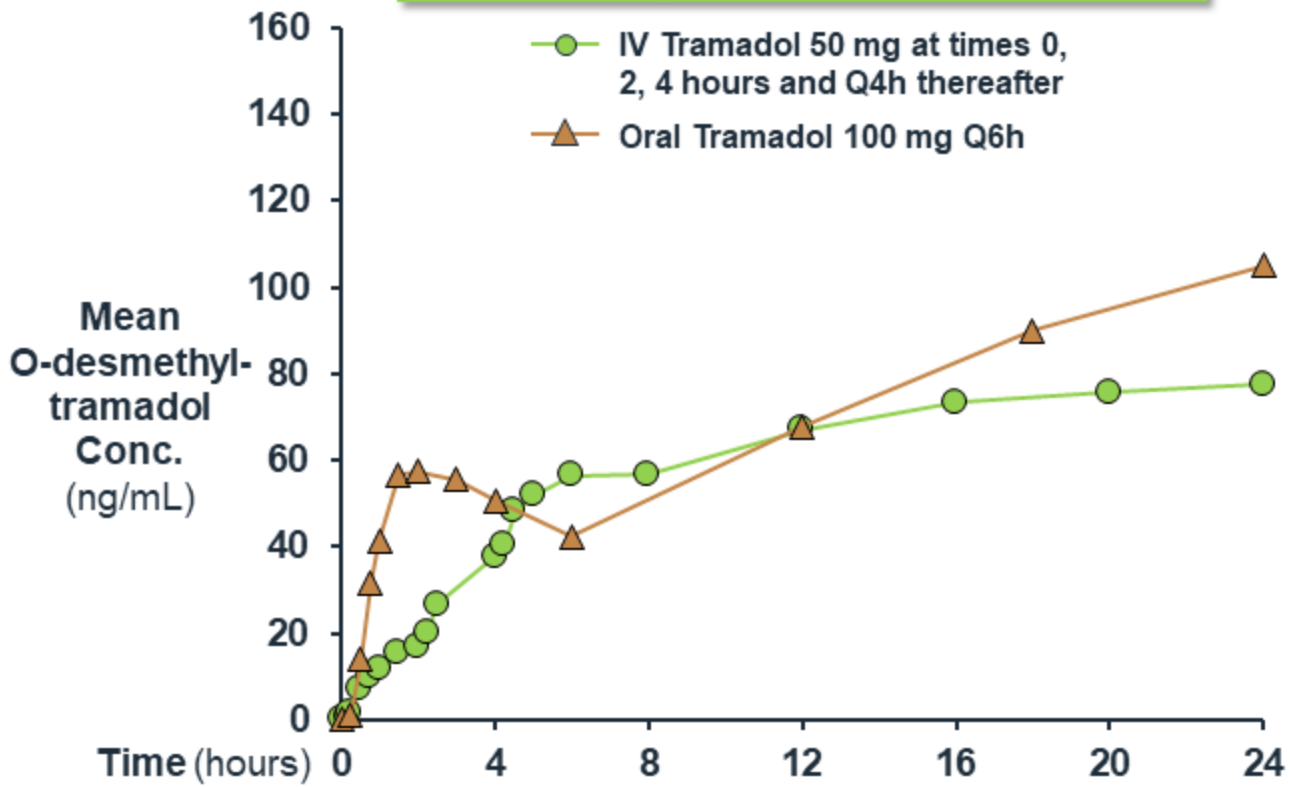
Avenue Therapeutics, Inc.

Study 101: IV Tramadol PK Begins with Early Availability of Parent Compound

Tramadol Parent Compound



Key Metabolite M1



"The relative contribution of both tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound" – ULTRAM Label

IV Tramadol PK is Predictable[1]

- Parent compound (IV vs oral): similar C_{max} and AUC
- M1 (IV vs oral): C_{max} ~30% lower and AUC ~20% lower
  - IV tramadol provides less mu agonist activity than oral

1. IV dosing 50 mg (15 min infusion T0, T2, T4, & every 4 hrs) compared to oral dosing 100 mg (every 6 hrs), Study AVE-901-101 (PK study)

Phase 3 Efficacy Trials Characterized IV Tramadol's Independent Effect

102

Bunionectomy Study (N=409)

Multicenter, double-blind, placebo-controlled randomized study of **IV tramadol 25 mg and 50 mg with oral Ibuprofen rescue**

50 mg

103

Abdominoplasty Study (N=380)

Multicenter, double-blind, placebo-controlled, active-controlled randomized study of **IV tramadol 50 mg and IV morphine 4 mg with oral Ibuprofen rescue**

Isolate the efficacy, safety, and other characteristics of IV tramadol's independent effect

Patients could discontinue at any time to receive other opioids

Phase 3 Safety Study Assessed IV Tramadol in Setting Similar to Anticipated Real-World Use

104

Open-label Safety Study (N=251)

IV tramadol in the setting of multimodal analgesia without another opioid in various elective surgery models

IV tramadol 50 mg added to baseline multimodal analgesia

Reflects real-world clinical use of IV tramadol

Patients could discontinue at any time to receive other opioids

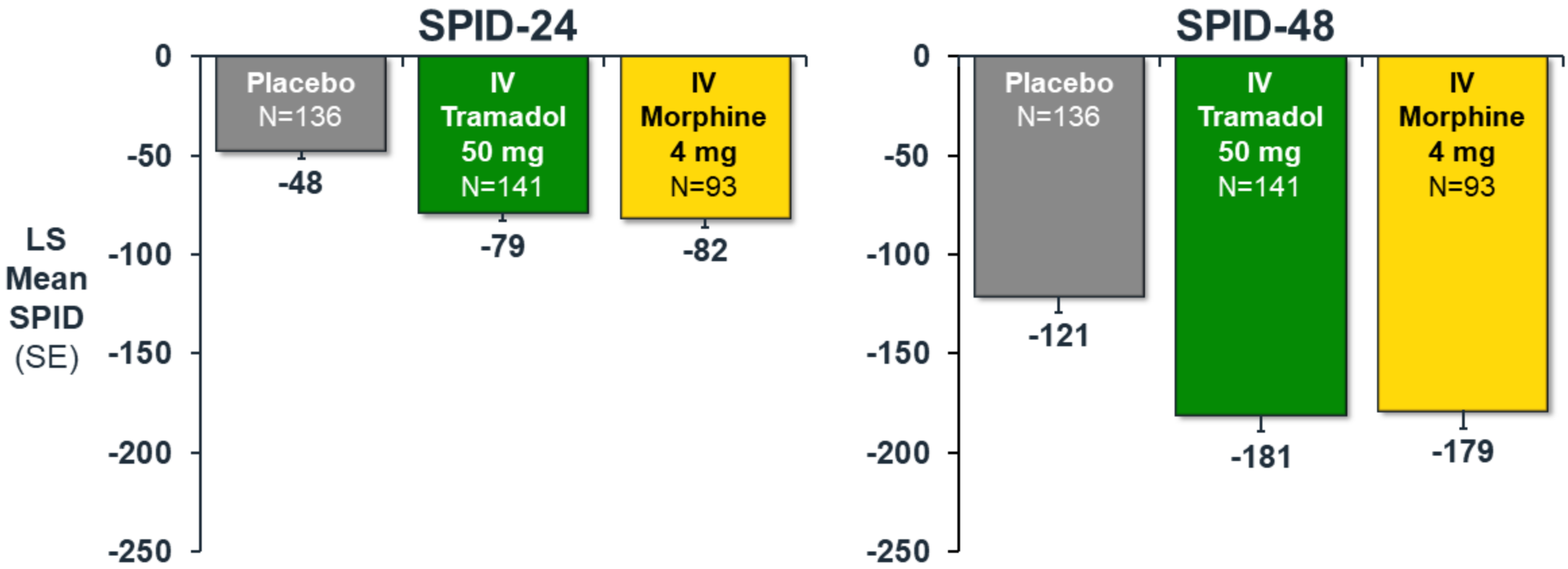
- Demonstrated safe and effective use of IV tramadol and established that the benefits outweigh the risks

Primary Endpoints Met in Phase 3 Efficacy Studies

	Study 102 (bunionectomy) N=409		**Study 103** (abdominoplasty) N=380	
	Endpoint	**p-value** IV Tramadol 50 mg vs Placebo	**Endpoint**	**p-value** IV Tramadol 50 mg vs Placebo
Primary Endpoints[1]	**SPID-48**	**0.005**	**SPID-24**	**< 0.001**

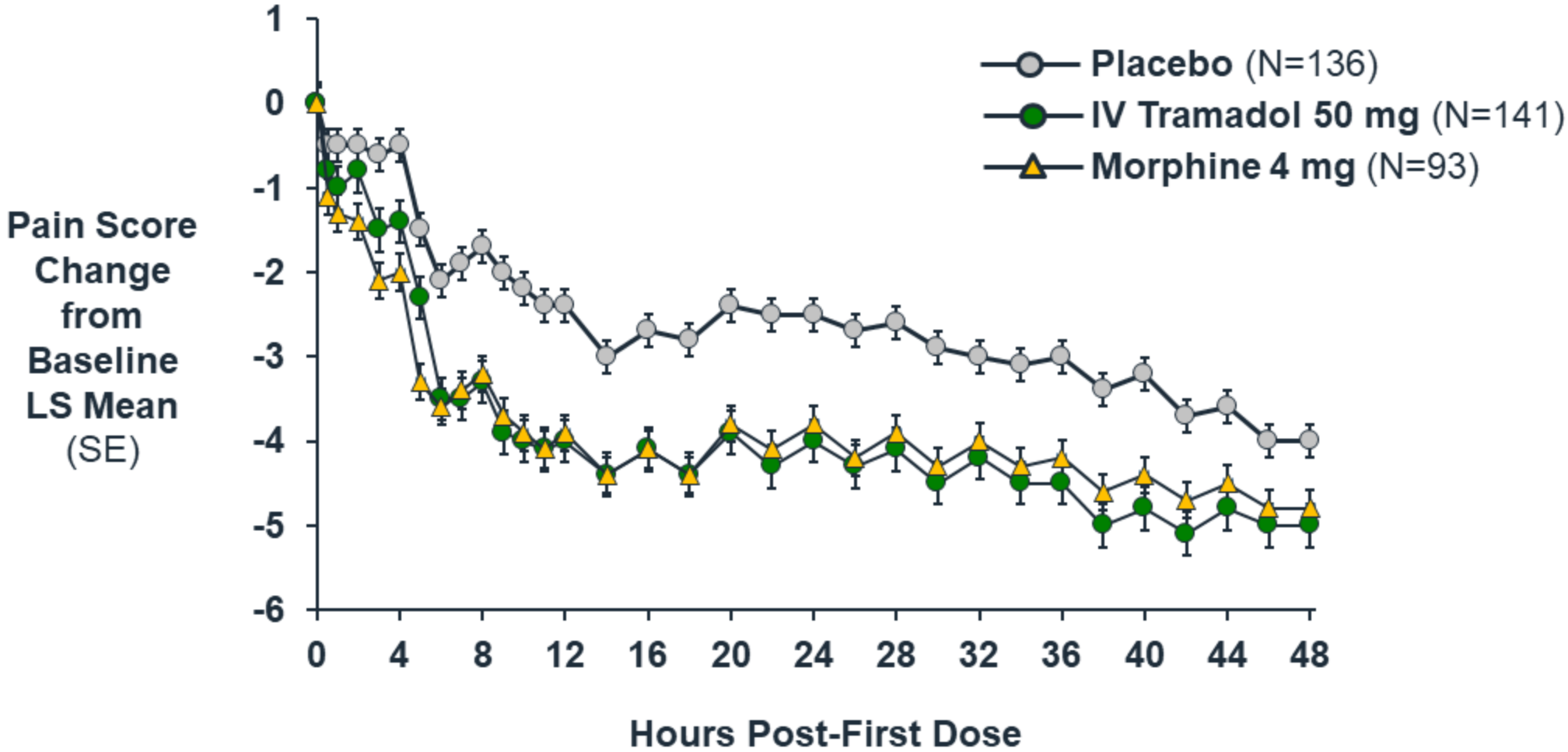
1. SPID-48 = Sum of Pain Intensity Differences (SPID) over 0 to 48 hours
   SPID-24 = SPID over 0 to 24 hours

Study 103: IV Tramadol Demonstrated Similar Overall Analgesic Efficacy to IV Morphine

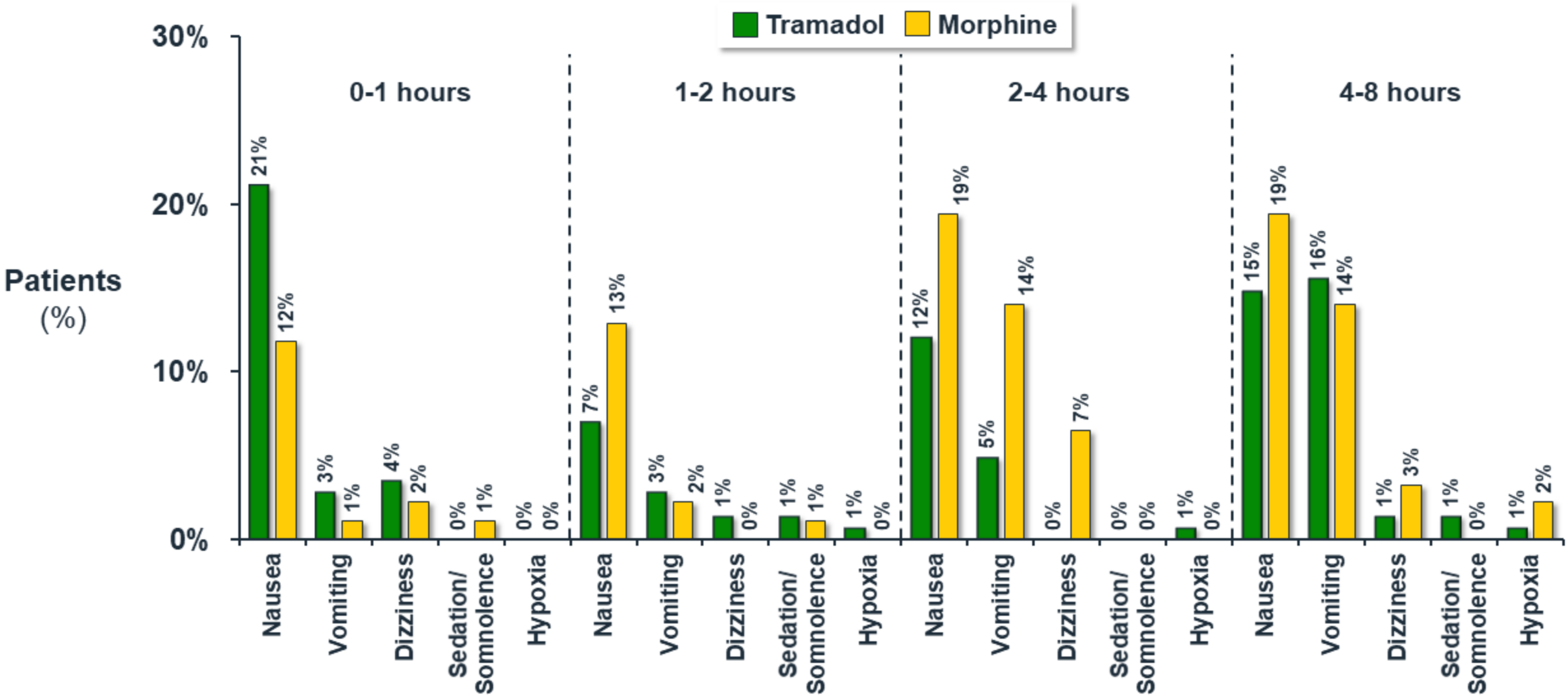


IV tramadol 50 mg administered as 15-minute infusion at T0, T2, T4 and then every 4 hours
IV morphine 4 mg administered as IV push at same timepoints

Study 103: PID Confirms Similar Overall Efficacy for IV Tramadol and IV Morphine



Study 103: IV Tramadol AE Profile Consistent with Dual Mechanism of Action



Study 103: AE or SAE Leading to Discontinuation

	Placebo (N=136)	IV Tramadol 50 mg (N=141)	IV Morphine 4 mg (N=93)
Discontinuations due to AE or SAE	**2 (2%)**	**12 (9%)**	**6 (7%)**
SAE-Post procedural hematoma	-	2 (1.4%)	-
GI related AEs (nausea, vomiting)	1 (< 1%)	5 (3.3%)	2 (2.2%)
Hypoxia related AEs	-	4 (2.8%)	3 (3.2%)
Other AEs	1 (< 1%)	1 (< 1%)	1 (1.1%)

Review of FDA Concern Regarding Onset of Analgesia

Stopwatch Metric

- 2 stopwatches are started at start of dosing
- Patients are instructed to stop
  - 1st stopwatch when pain relief is perceptible
  - 2nd stopwatch when pain relief is considered meaningful

Onset of analgesia = median time to meaningful pain relief

Stopwatch Metric: Multiple Approaches to Data Collection and Analysis

- Different methods have been used and accepted by the FDA
- Results vary based on different methodologies

Product	Data Collection	Data Analysis Censoring
IV Tramadol	After taking rescue, could not stop 2nd stopwatch	Patients who needed rescue censored as not achieving meaningful pain relief (uniformly at 6 hrs; end time for endpoint)
ANJESO[1] (IV Meloxicam)	After taking rescue, could still stop 2nd stopwatch	Patients who never reached meaningful pain relief censored at time of rescue

1. Based on our interpretation of the publicly available information found in ANJESO Review.

Stopwatch Results Dependent on Methods for Collection and Analysis

Median Time to (minutes)	Study 102 (Bunionectomy) Placebo (N=136)	Study 102 (Bunionectomy) IV Tramadol 50 mg (N=139)	Study 103 (Abdominoplasty) Placebo (N=136)	Study 103 (Abdominoplasty) IV Tramadol 50 mg (N=141)	Study 103 (Abdominoplasty) IV Morphine 4 mg (N=93)
Original Analysis					
Confirmed perceptible pain relief	NA[1]	167	69	27	5
Meaningful pain relief	**NA**	**321**	**145**	**106**	**42**
Alternative Analysis[2]					
Confirmed perceptible pain relief	NA	55	66	25	5
Meaningful pain relief	**NA**	**135**	**90**	**81**	**42**

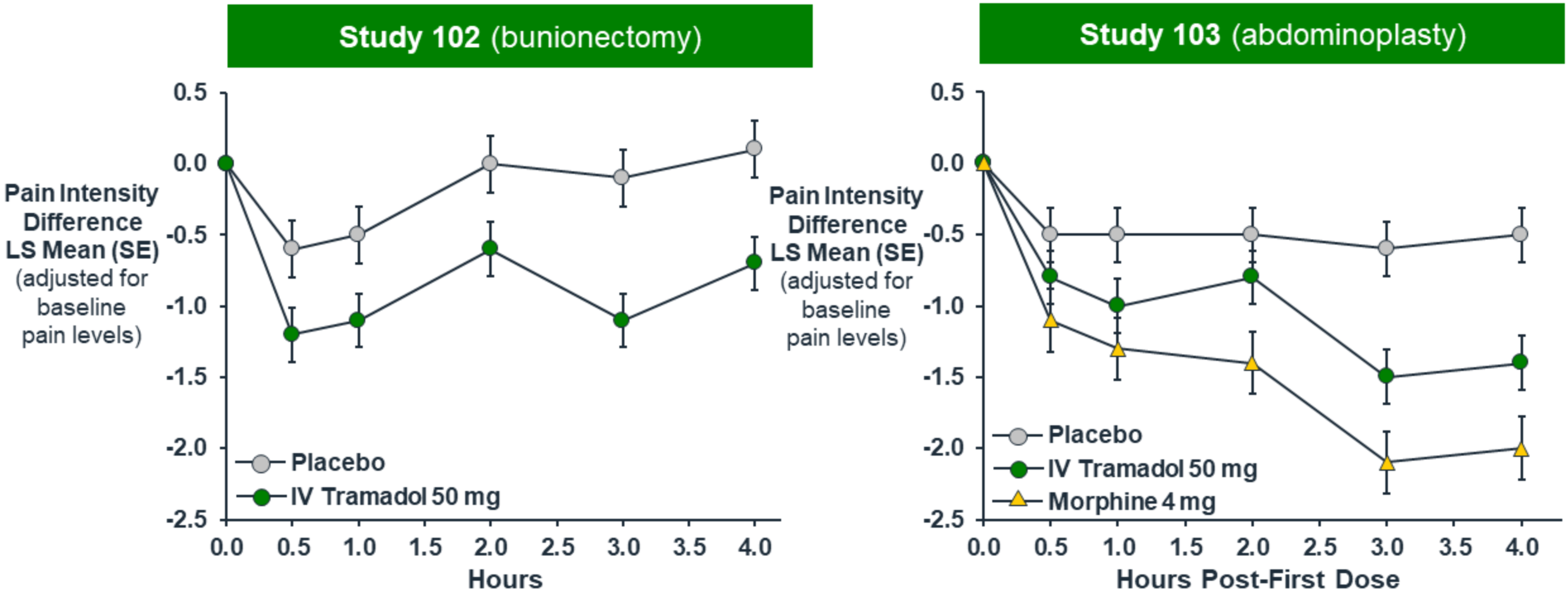
[1]NA = not achieved

[2]Alternative Analysis Using Methods in IV Meloxicam NDA - Not Submitted to FDA

Stopwatch Results Inconsistent with Other Endpoints Defining Onset of Clinical Benefit

- Clinical endpoints measuring meaningful pain relief at early timepoints
  - Patient reported pain intensity difference (PID)
  - Time to first rescue
  - Patient satisfaction during the first 24 hours (PGA-24)

IV Tramadol: Pain Intensity Differences Demonstrate Pain Relief at Early Timepoints



Time to First Rescue Confirms Adequate Onset of Action

	Study 102 (Bunionectomy)		Study 103 (Abdominoplasty)		
Median Time to	Placebo (N=136)	IV Tramadol 50 mg (N=139)	Placebo (N=136)	IV Tramadol 50 mg (N=141)	IV Morphine 4 mg (N=93)
First rescue	2.5 hours	5.1 hours	1.7 hours	22.9 hours	Median not reached

These results confirm adequate onset, consistent with PID and PGA results

Totality of Data: IV Tramadol Provides Meaningful Pain Relief at Early Timepoints

- Parent compound tramadol exerts analgesia via the monoaminergic effect and at mu receptor providing early analgesia
  - PID separated from placebo at 30 minutes
  - Time to rescue significantly longer than placebo
  - Patient perception of pain relief better than placebo on PGA-24
- Very few patients discontinued in the absence of another opioid

Study 104 demonstrates that IV tramadol be used safely and effectively in real-world clinical practice with no concern about onset of action

Study 104: IV Tramadol in Setting Similar to Anticipated Real-world Use

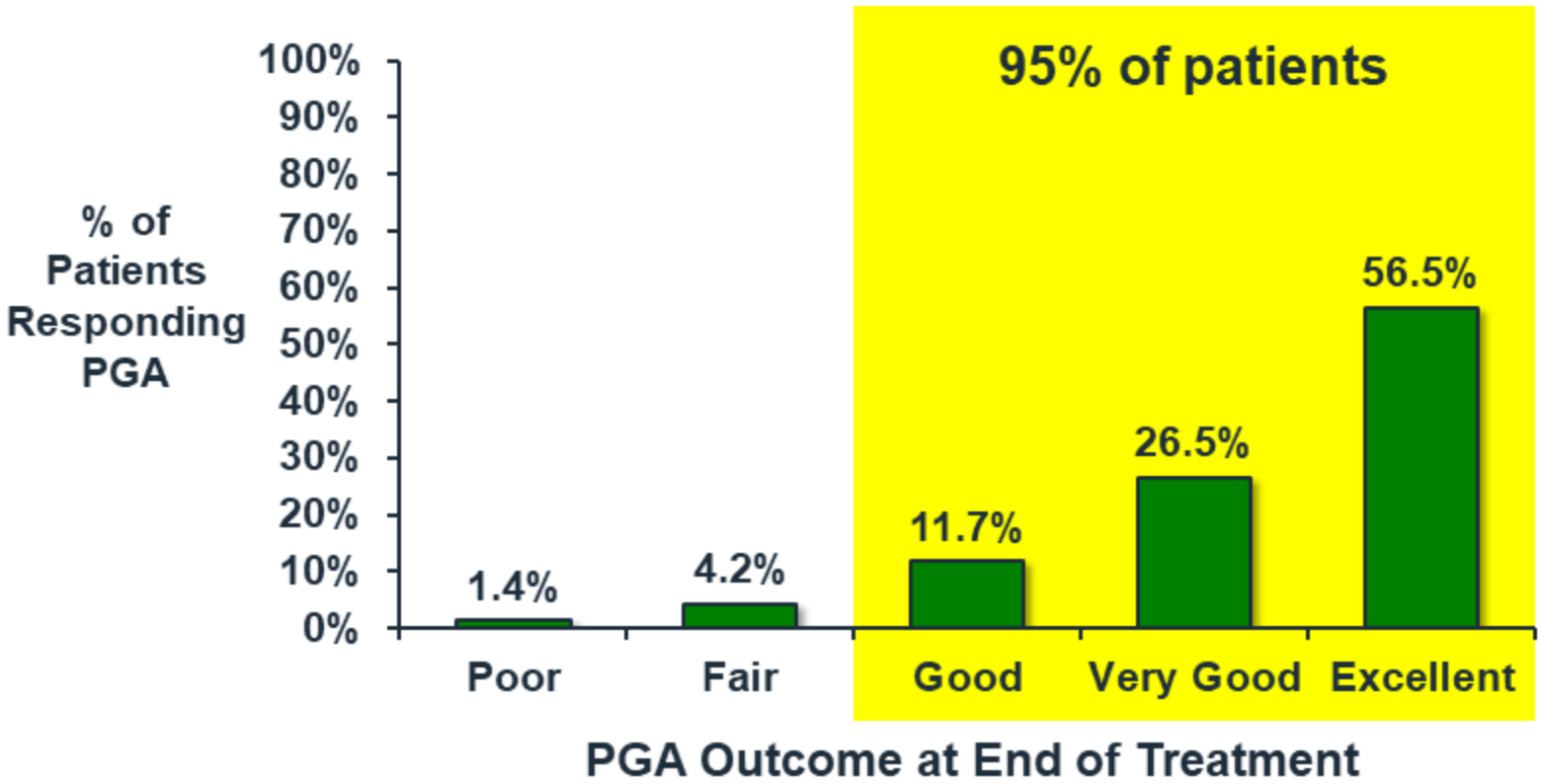
- Study 104 demonstrates how IV tramadol can be used safely and effectively in multimodal analgesia for post-operative pain
- Supports a favorable benefit-risk balance and clinical utility of IV tramadol by offering patients successful post-operative analgesia without intravenous Schedule II opioids

Study 104: Open-Label Safety Study Reflecting Real-World Use of IV Tramadol

- Patients undergoing painful surgeries (e.g. total joint replacement) were managed with IV tramadol and optional non-opioid analgesics
  - Typically treated with Schedule II opioids
  - Non-opioids permitted as needed
- Patients could request another opioid and exit study at any time

No patient discontinued the study to request another opioid

Study 104: High Patient Satisfaction with IV Tramadol on Patient Global Assessment (PGA)



- Patients experienced sustained and adequate pain relief, as shown by not needing rescue with a Schedule II opioid
- Demonstrated utility of IV tramadol in helping patients avoid intravenous Schedule II opioids
- Consistent with decades of European experience and how parenteral tramadol is used outside the U.S.

N=249

Review of FDA Concern Regarding the Need for Opioid Rescue (Stacking)

No Safety Signal for Increased Need for Opioid Rescue (Stacking) in Phase 3 or Harm from Stacking from Extensive Clinical Use

FDA Concern	Data / Evidence
Risk of Opioid Rescue (Stacking)	▪ Efficacy studies showed adequate analgesia with IV tramadol and NSAID rescue, with 2% D/C due to lack of efficacy ▪ Open label safety study: 0% discontinued to get Schedule II opioid after painful surgeries, with high levels of satisfaction
Risk of Harm from Stacking	▪ No unexpected findings in Vigibase report over 10-year span with ~370 million doses of IV tramadol administered in Europe (2010-2019) ▪ No safety signal described in literature after 30 years of use

Study 103: Rescue Use

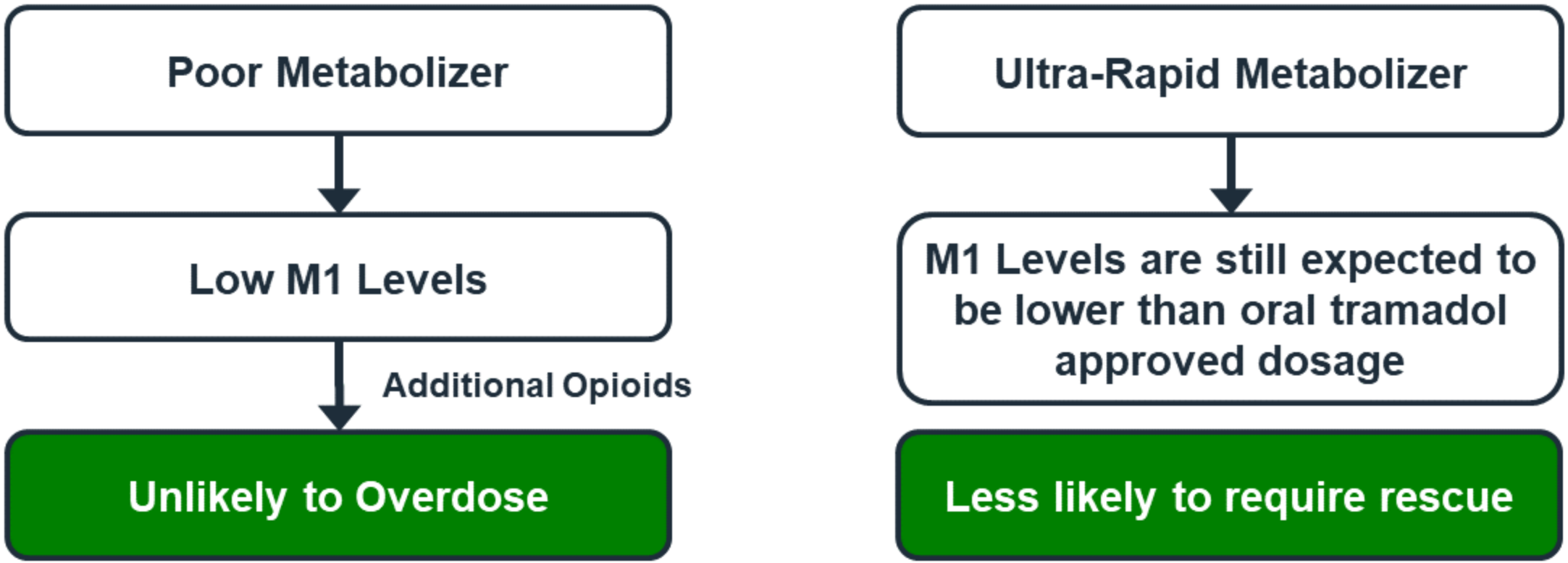
Table 8 from FDA Briefing Document

Planned Treatment	Within 30 minutes	Within 1 hour	Within 2 hours
Morphine IV 4 mg	5 (5.4%)	16 (17.2%)	26 (28.0%)
Placebo	15 (11.0%)	36 (26.5%)	69 (50.7%)
Tramadol IV 50 mg	10 (7.1%)	25 (17.7%)	60 (42.6%)

- Many required little rescue - mean 48-hour total ibuprofen dose was low:
  - 409 mg in IV tramadol arm, 271 mg in IV morphine arm
- IV tramadol patients avoided post operative exposure to Schedule II opioids

CYP2D6 Phenotypes Do Not Pose An Undue Risk with IV Tramadol

- Neither the poor metabolizer nor ultra-rapid metabolizer phenotypes are likely to place patients at risk for harm from IV tramadol



CYP2D6 Conclusions

- IV tramadol is widely used in territories with different ethnicities enriched with different 2D6 phenotypes (Europe, Asia, Africa, Middle-east, South America, Australia and New Zealand)
- Postmarketing safety data and available literature have not identified a safety signal for IV tramadol due to 2D6 phenotype variability
- Oral tramadol continues to be used safely in most adults without prior determination of 2D6 phenotype

IV Tramadol Will Be Used Only in Medically Supervised Setting

- Opioid rescue commonly practiced in peri-operative setting
- Use of multiple opioids is common and recognized as safe in medically supervised setting
  - Protocols in place
  - Mandatory monitoring following IV opioid therapy at hospitals and ambulatory surgical centers[1]
  - Healthcare professionals, not patients, administer IV opioids

1. https://www.jointcommission.org/-/media/tjc/documents/standards/r3-reports/r3_14_pain_assess_mgmt_ahc_6_20_18_final.pdf

Risks Associated with Use of > 1 Opioid (Stacking) Addressed with Class Labeling

- There is a range of patient responses to any particular opioid analgesic based on many factors, both intrinsic and extrinsic.[1] This variability in response to one opioid may result in the need for rescue with a different opioid analgesic.
- All opioid labels warn prescribers about the concomitant use of opioids and other CNS depressants (…other opioids)[2,3] with suggestions to reduce the dose of one or both drugs.

1. Muralidharan A and Smith M 2011
2. OLINVYK label
3. ULTRAM label

IV Tramadol Has Less Abuse Potential than Intravenous Schedule II Opioids

Oral Tramadol: 26-Year History in U.S.

- Tramadol is Schedule IV drug and has lower abuse potential than other commonly used Schedule II opioids[1]

Schedule II: high potential for abuse, with use potentially leading to severe psychological or physical dependence

Schedule IV: low potential for abuse and low risk of dependence

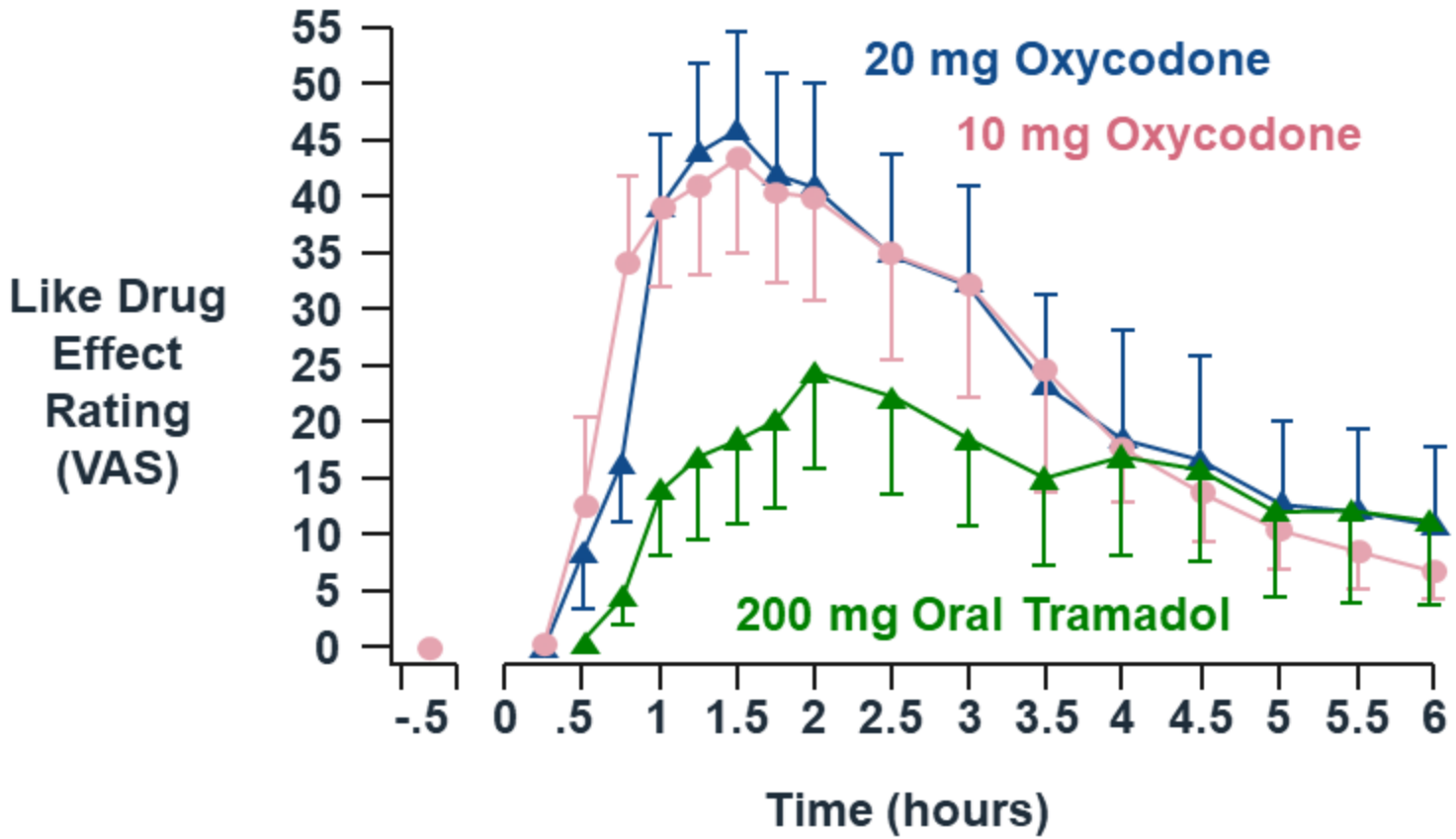
1. https://www.dea.gov/drug-information/drug-scheduling

DEA Scheduling Analysis of Tramadol[1]

- "… the available information regarding reinforcing effects and drug dependence shows that the abuse potential of tramadol is less than that of morphine (C-II), oxycodone (C-II) or buprenorphine (C-III)…"
- Supratherapeutic doses of oral tramadol (350 mg - 700 mg) were required to achieve comparable drug-liking effect to middle therapeutic range of oxycodone (20 mg)[2]

1. https://www.regulations.gov/document/DEA-2013-0010-0004
2. Page 47 FDA Briefing Document, NDA# 213231, Tramadol Hydrochloride 50 mg/mL injection

Less Drug Liking for Oral Tramadol 200 mg Supratherapeutic Dose Compared to Oxycodone

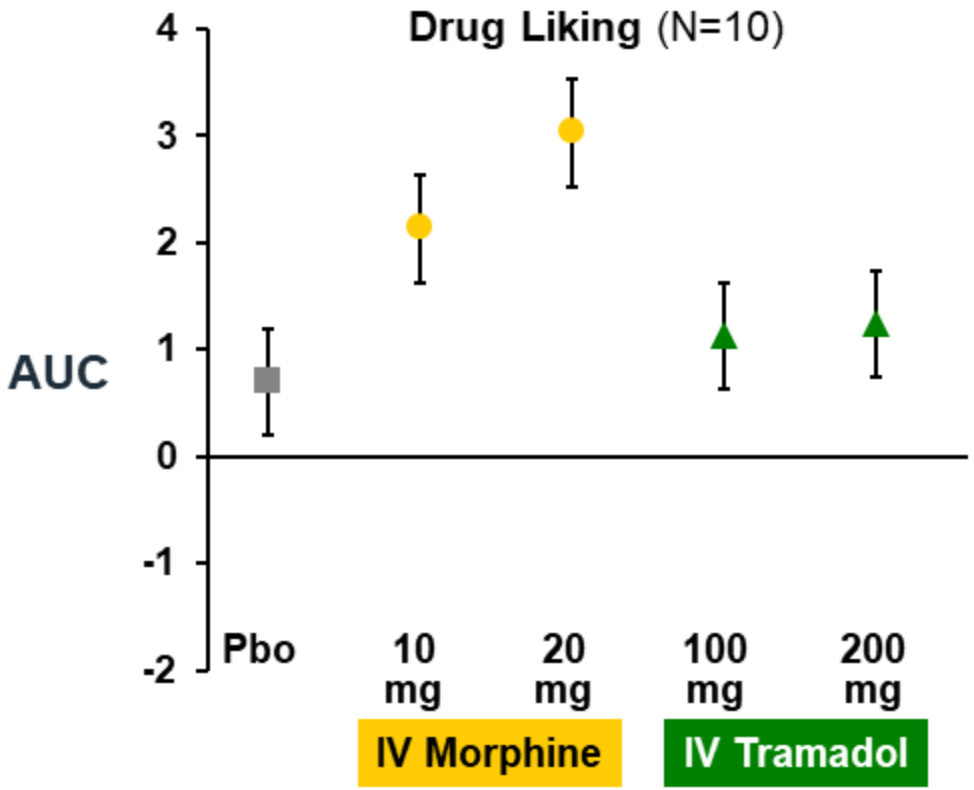


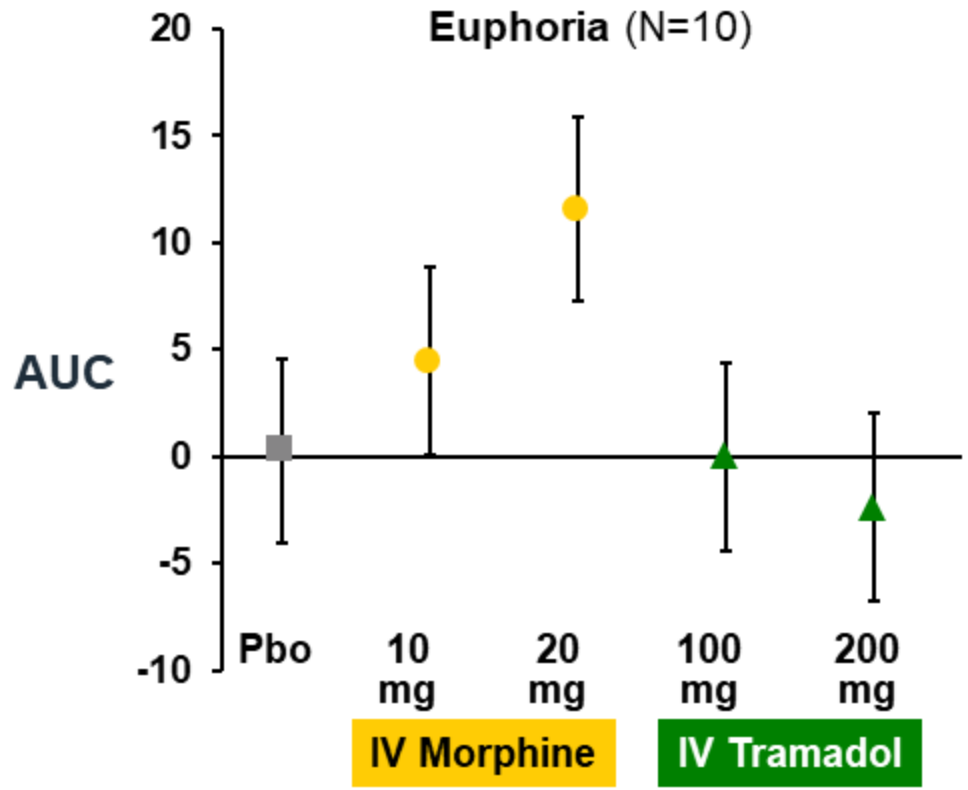
- Lower tramadol peak drug liking score
- Longer time to tramadol peak drug liking
- IV tramadol has delayed M1 formation

Babalonis et al., 2013

Less Abuse Potential with IV Tramadol Than IV Morphine[1]

- Drug liking and euphoria scores not increased with supratherapeutic dose
- Less opiate-like effects with IV than oral tramadol





1. Recreated from Epstein DH 2006

IV Tramadol Has Less Abuse Potential than Oral Tramadol

- "…(IV) tramadol is less likely to be identified as an opioid because M1 production is minimalised" – WHO Expert Committee on Drug Dependence[1]
- Laboratory evidence supports that abuse potential of tramadol likely decreases when administered IV[2]
  - Low ratings of positive effects
  - Not reliably identified as an opioid

1. https://www.who.int/medicines/access/controlled-substances/Tramadol.pdf
2. Dunn KE, Bergeria CL, Huhn AS and Strain EC (2019) A Systematic Review of Laboratory Evidence for the Abuse Potential of Tramadol in Humans. Front. Psychiatry 10:704.

"Likely No Potential for a 'Rush' of Rewarding Effect from Tramadol IV"[1]

- Drugs that produce greater magnitude and faster onset of positive effects identified as having greater abuse risk[2,3]
- Likely no "rush" of rewarding effect from IV tramadol[1]
  - IV tramadol administered via 15-minute fixed regimen infusion with less and slower increase in M1 than oral

1. Page 48 of FDA Briefing Document, NDA# 213231, Tramadol Hydrochloride 50 mg/mL injection
2. Comer SD, Ashworth JB, Sullivan MA, Vosburg SK, Saccone PA, Foltin RW. Relationship between rate of infusion and reinforcing strength of oxycodone in humans. J Opioid Manag (2009) 5(4):203–12.
3. Farre M, Camí J. Pharmacokinetic considerations in abuse liability evaluation. Br J Addict (1991) 86(12):1601–6.

Trade-off Between Onset of Action and Rewarding Effect/Abuse Potential

- Available opioids with fast onset and potential high rewarding effect (i.e. IV fentanyl)
- IV tramadol provides good overall pain relief with clinically adequate onset slower than intravenous Schedule II opioids
  - Trade-off for less rewarding effect and lower abuse potential
- Decades of EU experience with IV tramadol do not support concern of increased AE risk from opioid stacking
- Hundreds of millions of doses used in EU reduced exposure to intravenous Schedule II opioids

Clinicians can properly determine when to use this Schedule IV option

Review of FDA Concern Regarding Use of Non-Opioid Analgesics with IV Opioids

"Combination Therapy of an Opioid with a Non-opioid" are Indicated in Recent Approvals

- FDA stated "...combination therapy of an opioid with a non-opioid is not consistent with the intended use of intravenous opioids."
- Recent approvals of intravenous Olinvyk (Schedule II opioid), Caldolor, Ofirmev all allow the combination
- FDA statement inconsistent with
  - Successful management of patients' pain in clinical trials
  - Expert opinion[1] that "(i)t is important to exploit the benefits of multimodal, non-opioid approaches in acute pain management in conjunction with possible opioid therapy."

1. Pain Management Best Practices Inter-Agency Task Force Report: Updates, Gaps, Inconsistencies, and Recommendations. (HHS, May 2019).

Benefits of IV Tramadol

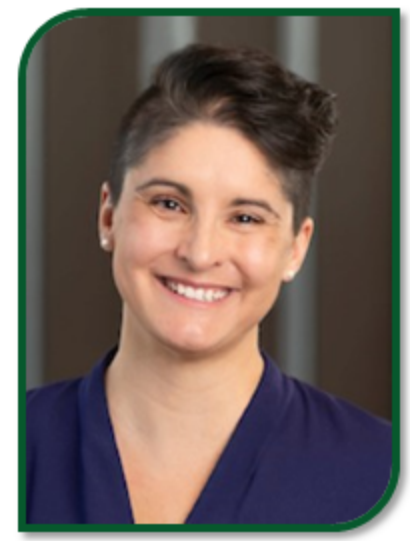
- Clinicians moving towards multimodal analgesia and products with lower abuse potential
- IV tramadol would offer U.S. clinicians and patients a safe and effective alternative to intravenous Schedule II opioids
  - Less rewarding effect and lower abuse potential
- Decades of European experience support its safety and utility
- Benefit outweighs FDA's perceived safety concern

Epidemiology of Abuse of Tramadol

Janetta Iwanicki, MD

Chief Scientific Officer

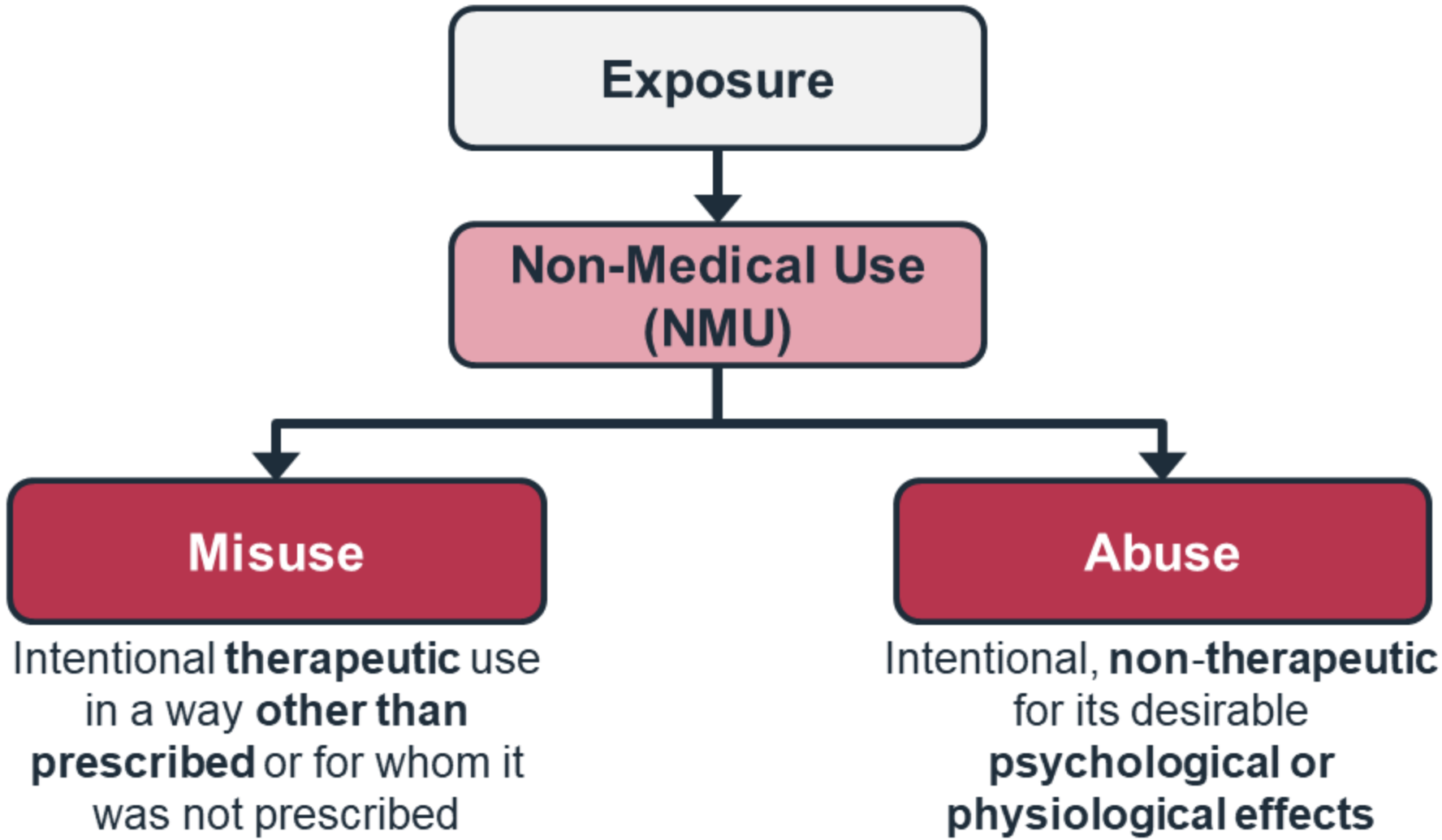
Rocky Mountain Poison and Drug Safety



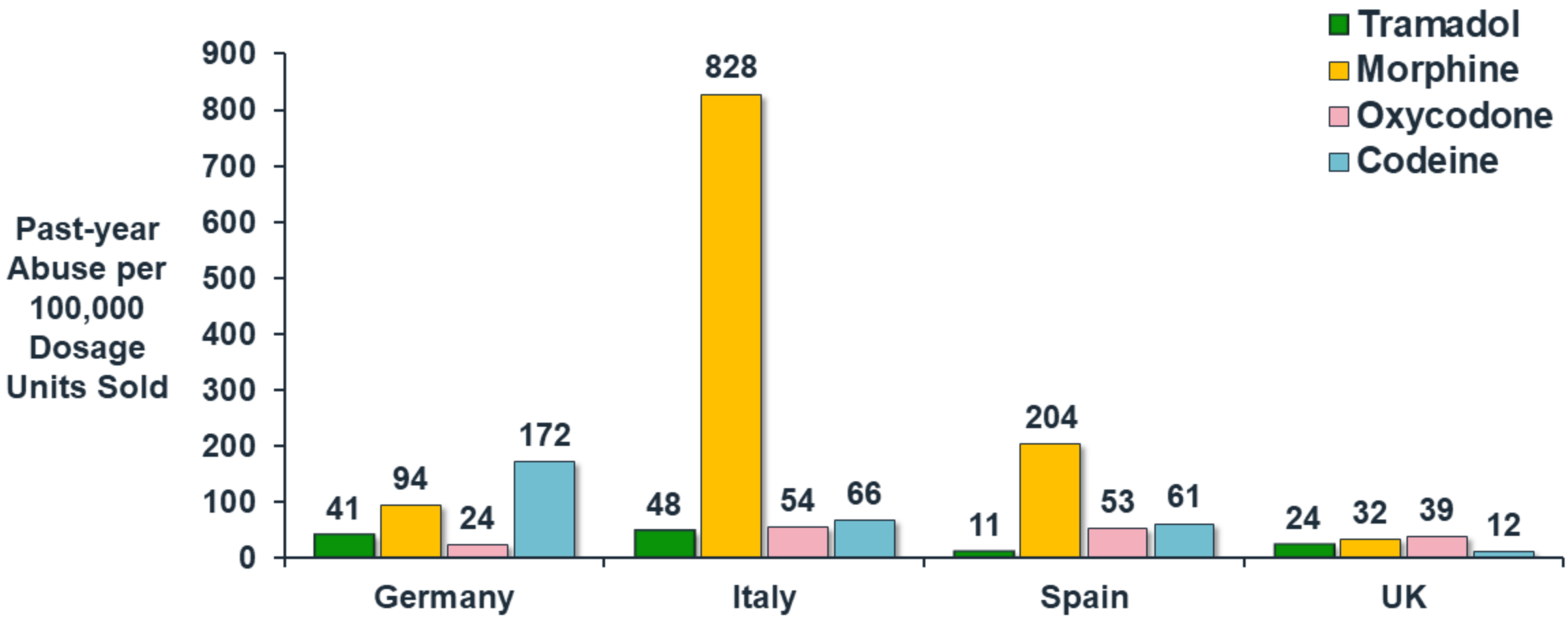
Overview of Approach

- Mosaic strategy for epidemiologic research
  - Evaluates drug misuse and abuse from several different angles using several data sources
- Tramadol misuse, abuse, diversion, and non-medical use
  - United States
  - Europe
- IV vs oral tramadol abuse

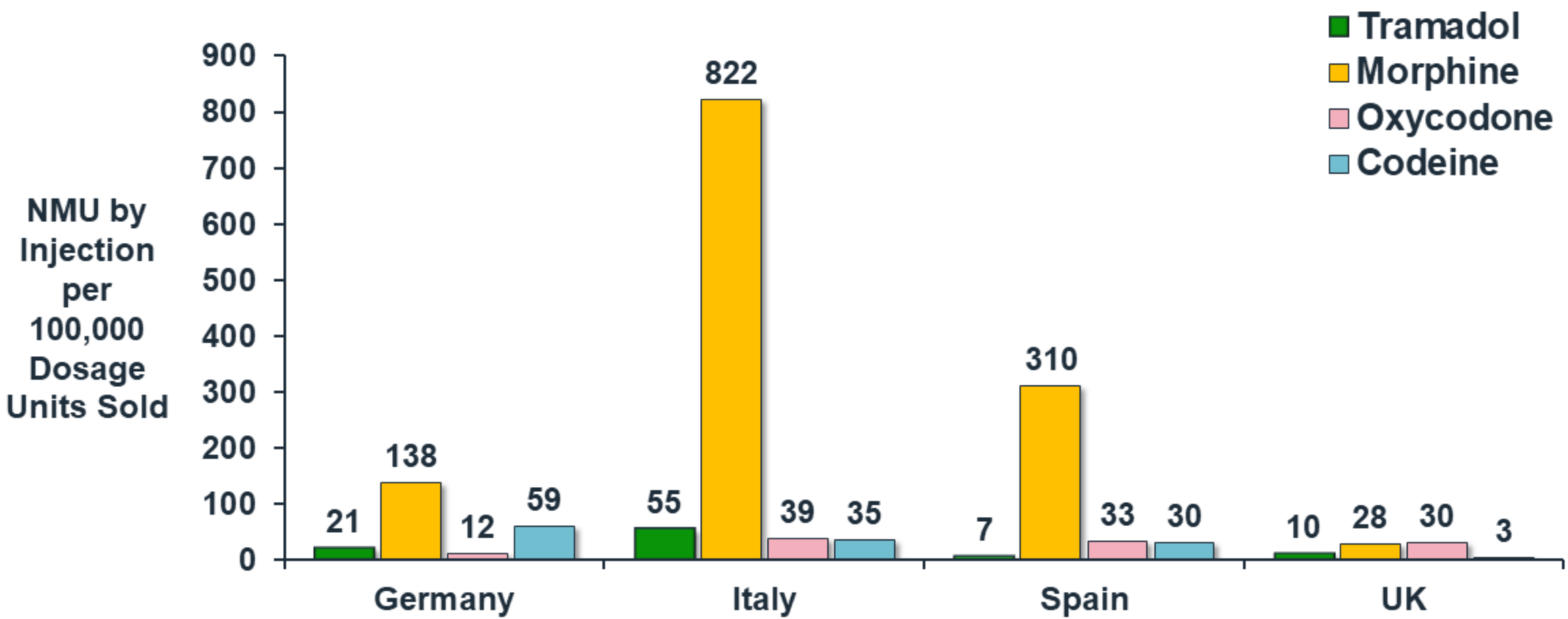
Prescription Drug Non-Medical Use Paradigm



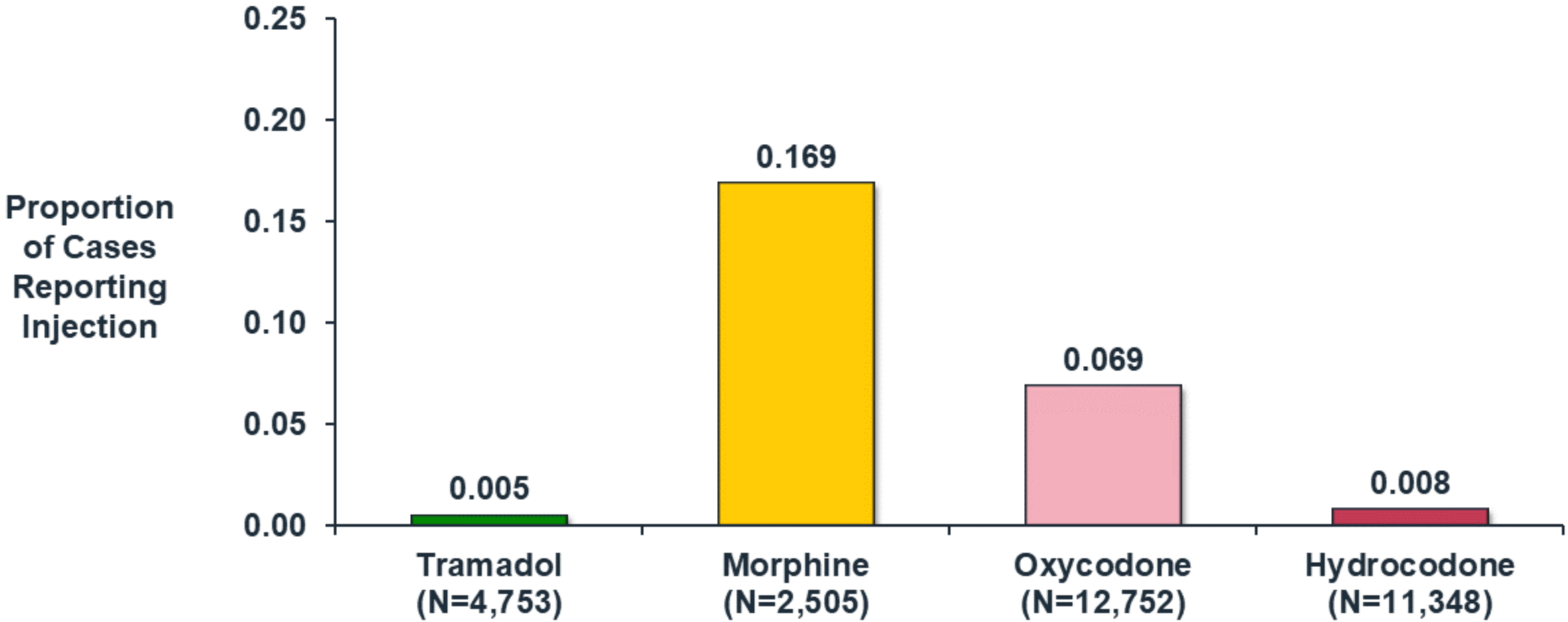
RADARS Europe: Abuse of Tramadol is Low Compared to Other Opioids (NMURx)



RADARS Europe: Non-Medical Use of Tramadol by Injection is Uncommon (NMURx)



RADARS U.S.: Tramadol Abuse by Injection Route is Rare (Poison Center Data)



Data from 3rd Quarter 2010 through 4th Quarter 2018

Summary: Tramadol Abuse is Low in US and EU, and Rare via Injection

- Lower drug liking and abuse liability compared to other opioids in laboratory evidence from human abuse liability studies[1]
- Pharmacokinetic and pharmacodynamic properties lead to less mu activation by IV route than oral tramadol and other opioids
- **Real-world evidence show low rates of tramadol abuse, including IV route, compared to other opioids**

1. Dunn et al. Front Psychiatry 201910:704.

Clinical Perspective from a U.S. Investigator

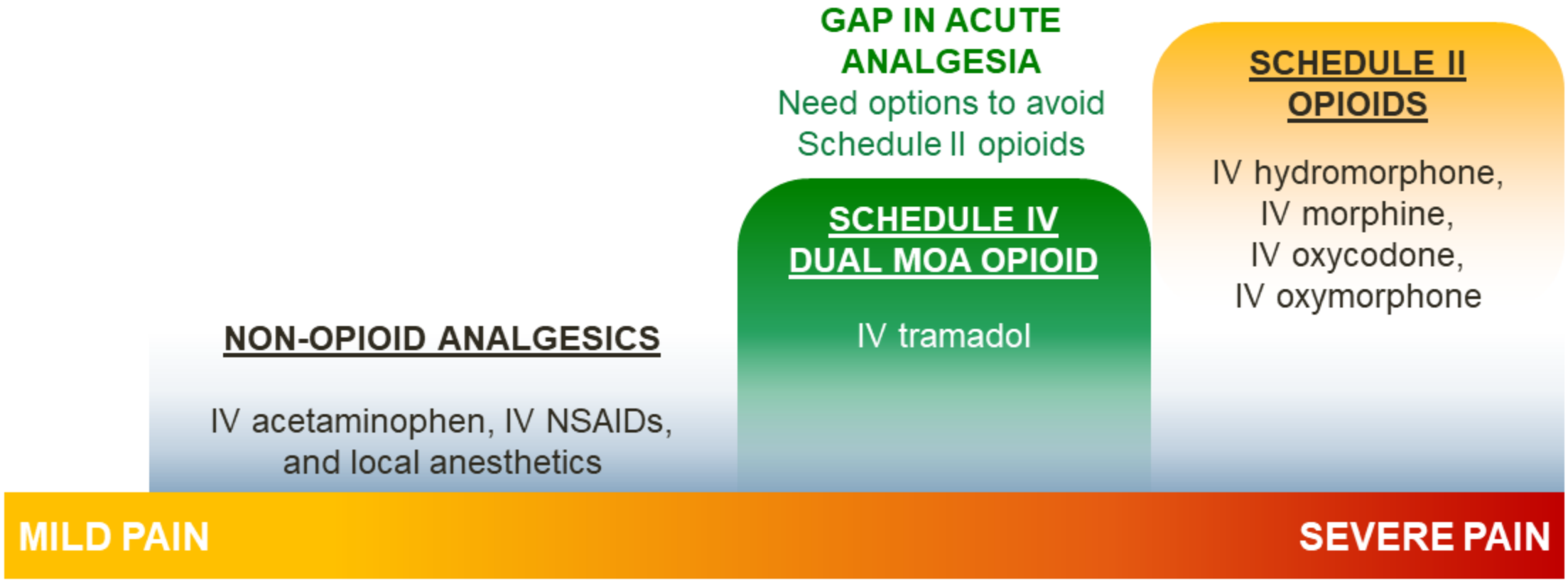
Dr. Harold Minkowitz, MD

Adjunct Associate Professor
Anesthesiology and Perioperative Medicine
MD Anderson Cancer Center

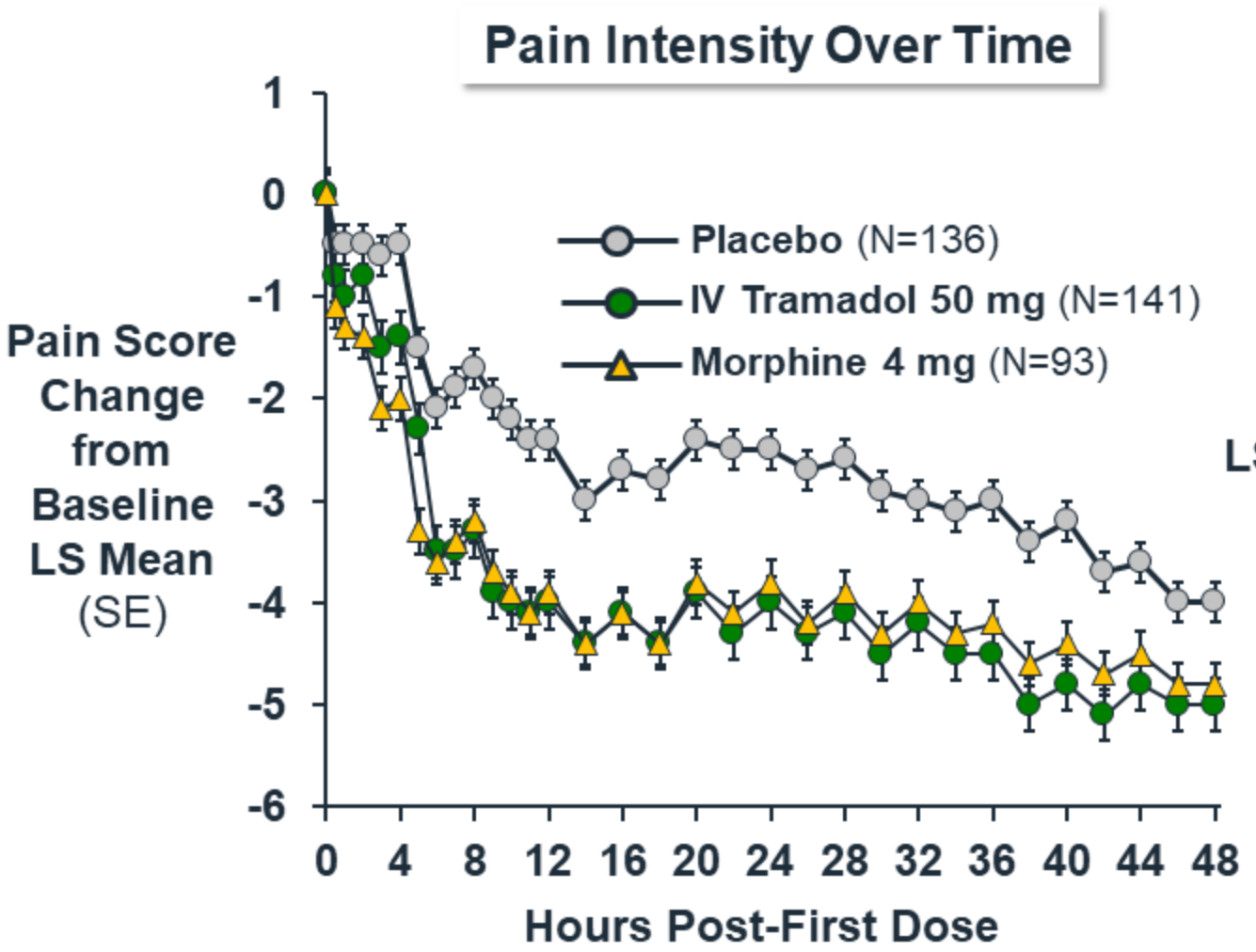
President
Analgesics, Perioperative and Hospital Based Research
HD Research LLC

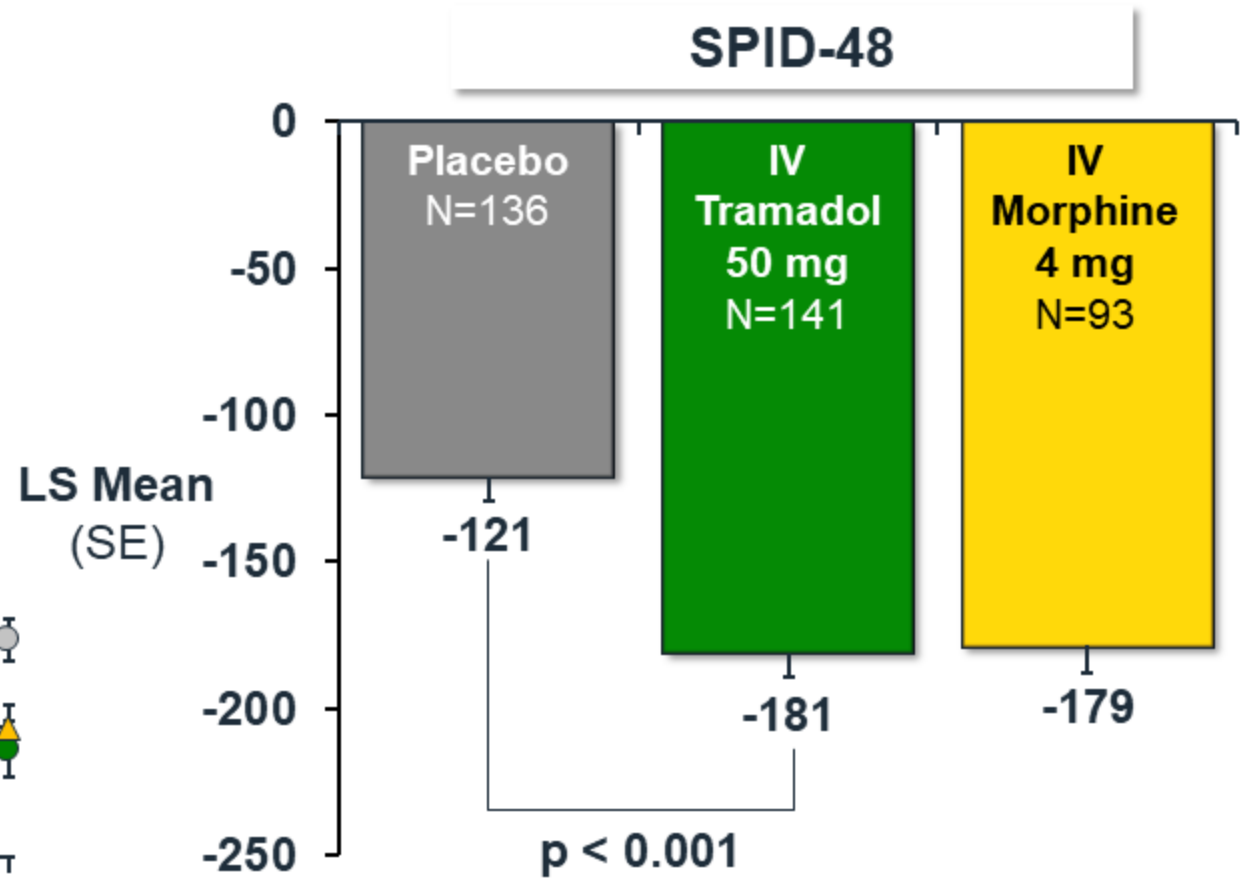
Only Current Choice After Non-Opioid Analgesia is Schedule II Opioid

- Clinicians outside U.S. have used IV tramadol with non-opioids for decades to avoid more abusable opioids



Study 103: IV Tramadol Provides Similar Overall Pain Relief as IV Morphine





Study 104: Patients Experienced Sustained Pain Relief Following Major Procedures

- > 100 patients treated at Memorial Hermann Memorial City Hospital, Houston, TX

Surgery Type	Patients Enrolled at Memorial Hermann City Hospital
Total knee replacement	32
Total hip replacement	57
Colon surgeries	15
Hysterectomy	2

Study 104: No Patients Required Conventional Opioids to Control Pain

- Painful major surgeries traditionally managed with IV opioids
- With IV tramadol not one patient required conventional opioids
  - Pain well controlled and patients happy with pain management
  - Patients able to undergo rehab easily
  - Well tolerated with no observed safety signals
  - 95% rated study treatment as good, very good, or excellent

Rapid Onset Not Needed for Drugs Given in Fixed Dose Regimen

- Clinicians choose drug with best clinical effect per patient need
- For clinical situation requiring very rapid onset of pain relief when duration is less important, commonly use IV fentanyl
- IV tramadol has been well characterized as a monotherapy and can be easily incorporated into multimodal analgesia
- Will be added to baseline multimodal analgesia in anticipation of pain
- Clinicians experienced in pain management can formulate a regimen to provide patients with adequate analgesia

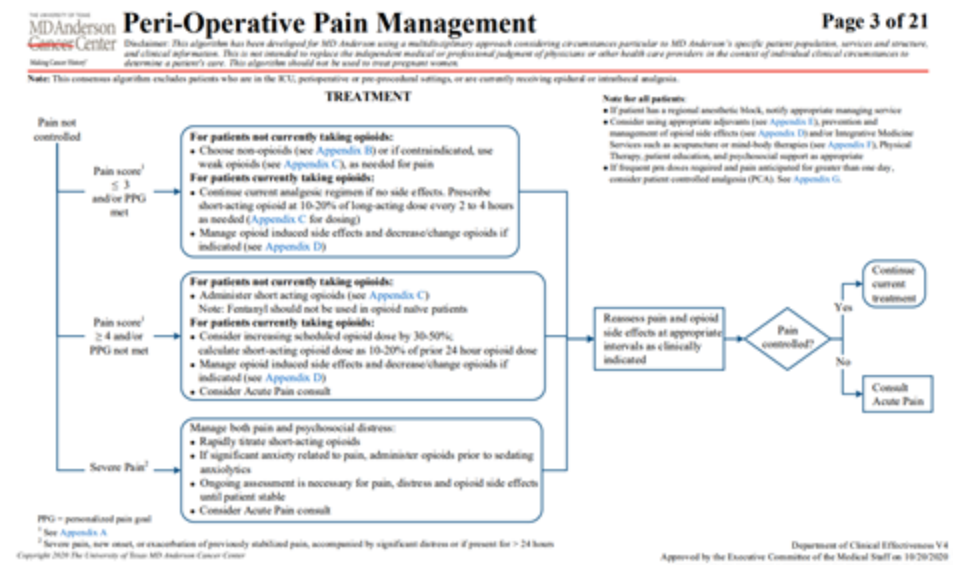
Current Typical Post-Operative Pain Management Regimen Process

- Prevention, assessment, and treatment of pain is persistent challenge for clinicians and health systems
- Hospitals have protocols and controls for pain management
- Continuous assessment of analgesic efficacy and patient safety
- Initially use multimodal non-opioid therapy
- Limit opioids unless needed
- All treatments tracked

Use of Multiple Opioids is Common and Standard of Care

- Most facilities use peri-operative pain management algorithms
- Allows safe dosing of various opioids at different doses
- Health care professionals are familiar with opioid rescue added to background opioid therapy

Example of Pain Management Algorithm from MD Anderson Cancer Center



MD Anderson Cancer Center

Peri-Operative Pain Management

Page 3 of 21

Disclaimer: This algorithm has been developed for MD Anderson using a multidisciplinary approach considering circumstances particular to MD Anderson's specific patient population, services and structure, and clinical information. This is not intended to replace the independent medical or professional judgment of physicians or other health care providers in the context of individual clinical circumstances to determine a patient's care. This algorithm should not be used to treat pregnant women.

Note: This consensus algorithm excludes patients who are in the ICU, perioperative or pre-procedural settings, or are currently receiving epidural or intrathecal analgesia.

TREATMENT

Pain not controlled

Pain score[1] ≤ 3 and/or PPG met

For patients not currently taking opioids:
- Choose non-opioids (see Appendix B) or if contraindicated, use weak opioids (see Appendix C), as needed for pain

For patients currently taking opioids:
- Continue current analgesic regimen if no side effects. Prescribe short-acting opioid at 10-20% of long-acting dose every 2 to 4 hours as needed (Appendix C for dosing)
- Manage opioid induced side effects and decrease/change opioids if indicated (see Appendix D)

Pain score[1] ≥ 4 and/or PPG not met

For patients not currently taking opioids:
- Administer short acting opioids (see Appendix C)

Note: Fentanyl should not be used in opioid naïve patients

For patients currently taking opioids:
- Consider increasing scheduled opioid dose by 30-50%; calculate short-acting opioid dose as 10-20% of prior 24 hour opioid dose
- Manage opioid induced side effects and decrease/change opioids if indicated (see Appendix D)
- Consider Acute Pain consult

Severe Pain[2]

Manage both pain and psychosocial distress:
- Rapidly titrate short-acting opioids
- If significant anxiety related to pain, administer opioids prior to sedating anxiolytics
- Ongoing assessment is necessary for pain, distress and opioid side effects until patient stable
- Consider Acute Pain consult

Reassess pain and opioid side effects at appropriate intervals as clinically indicated

Pain controlled?

Yes → Continue current treatment

No → Consult Acute Pain

Note for all patients:
- If patient has a regional anesthetic block, notify appropriate managing service
- Consider using appropriate adjuvants (see Appendix E), prevention and management of opioid side effects (see Appendix D) and/or Integrative Medicine Services such as acupuncture or mind-body therapies (see Appendix F), Physical Therapy, patient education, and psychosocial support as appropriate
- If frequent prn doses required and pain anticipated for greater than one day, consider patient controlled analgesia (PCA). See Appendix G.

PPG = personalized pain goal

[1] See Appendix A

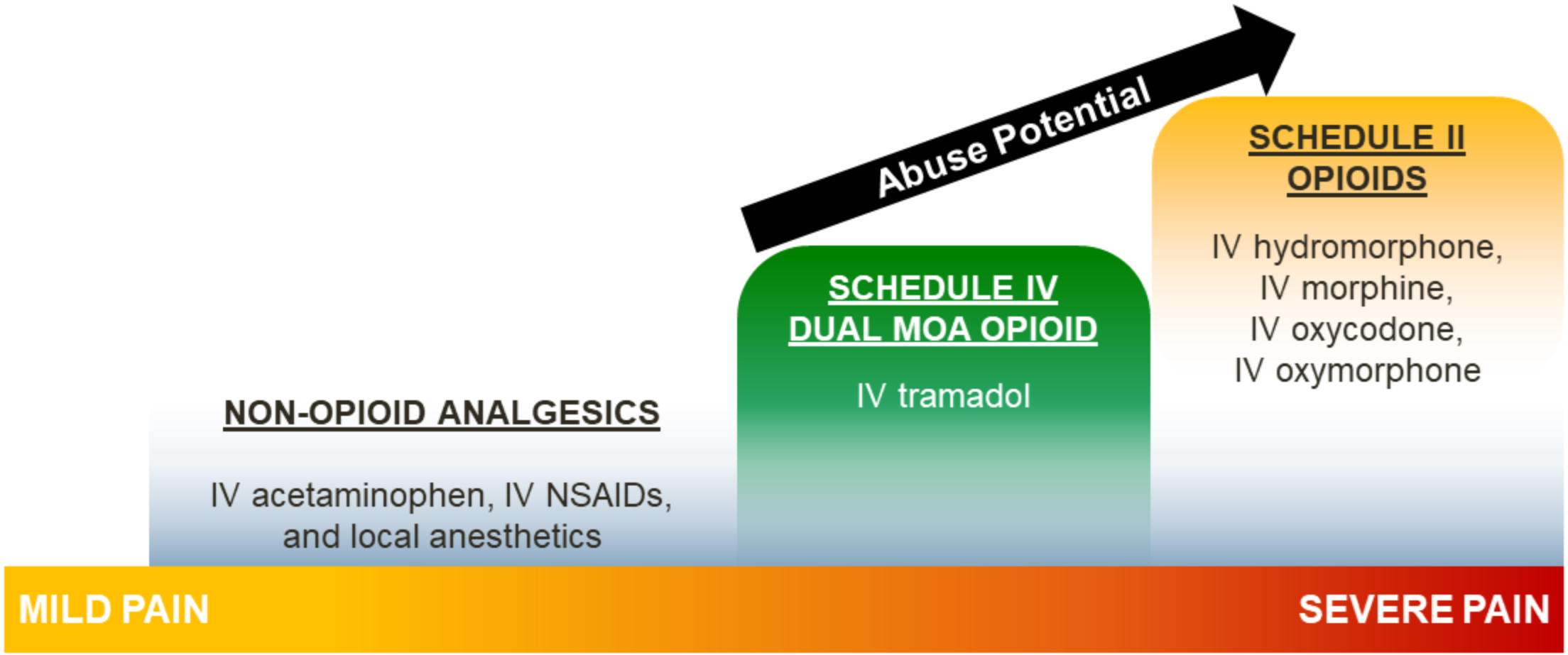
[2] Severe pain, new onset, or exacerbation of previously stabilized pain, accompanied by significant distress or if present for > 24 hours

Department of Clinical Effectiveness V4

Approved by the Executive Committee of the Medical Staff on 10/20/2020

https://www.mdanderson.org/documents/for-physicians/algorithms/clinical-management/clin-management-post-op-pain-web-algorithm.pdf

IV Tramadol is Effective Schedule IV Analgesic, Helping to Avoid Schedule II Opioids



Conclusion

Lucy Lu, MD

President and CEO

Avenue Therapeutics, Inc.

IV Tramadol Provides Alternative to Intravenous Schedule II Opioids

- Robust safety and efficacy demonstrated in two distinct surgical models
- High patient satisfaction in open-label safety study without another opioid
- 30-year history in Europe and 26-year history with oral tramadol (comparable or higher dose) in U.S.
- Intended for use in medically supervised setting by an HCP
- Will reduce need for use of Schedule II intravenous opioids

Intravenous (IV) Tramadol for Use in Medically Supervised Health Care Setting

Avenue Therapeutics, Inc.

February 15, 2022

Joint Meeting of the Anesthetic and Analgesic Drug Products and the Drug Safety and Risk Management Advisory Committees

Q&A SLIDES SHOWN

Study 103: Surgical and Anesthetic Protocol

- Anesthetic regimen of general anesthesia with midazolam, fentanyl and propofol.
- 0.5% Lidocaine without epinephrine injected into the muscle plication and skin incision
- During immediate postoperative period IV doses of fentanyl allowed
- Patients transferred to the PACU must meet pain criteria within 3 hours after the end of surgery to enter the study

Study 102: Surgical and Anesthetic Protocol

Anesthesia Protocol

- IV midazolam administered pre-operatively for anxiolysis.
- Regional anesthesia via popliteal nerve block and local acting Mayo block using short acting lidocaine without epinephrine
- Propofol given as initial bolus followed by continuous infusion for sedation
- Intraoperatively given 50ug fentanyl at propofol induction
- Pneumatic ankle tourniquet applied to achieve homeostasis

Study Disposition

	Study 102		Study 103		
Population	**Placebo** (N=136)	**IV Tramadol 50 mg** (N=139)	**Placebo** (N=136)	**IV Tramadol 50 mg** (N=141)	**IV Morphine 4 mg** (N=93)
Completed study	**120 (88%)**	**137 (99%)**	**127 (93%)**	**124 (88%)**	**85 (91%)**
Discontinuation due to					
Adverse event	-	**1 (< 1%)**	**2 (2%)**	**12 (9%)**	**6 (7%)**
Protocol violation	-	-	**1 (<1%)**	-	-
Consent withdrawal	**3 (2%)**	-	**1 (<1%)**	-	-
Lack of efficacy	**11 (8%)**	**1 (<1%)**	**6 (4%)**	**5 (4%)**	**2 (2%)**
Other	**2 (2%)**	-	-	-	-

Study 104: Discontinuation Due to AEs

	IV Tramadol 50 mg (N=251) n (%)
AEs leading to discontinuation	11 (4.4%)
GI related AEs	5 (2.0%)
Procedural complications	3 (1.2%)
Other AEs	4 (1.6%)

Availability of IV Tramadol Could Influence Post-Discharge Oral Tramadol Use

	Oral Tramadol % of Post-Discharge Opioid Rx	IV Tramadol Available?
US	3.5 – 4%[1,2]	No
Sweden	29.0%[1]	Yes

1. Ladha, 2019; 2. Thiels, 2019