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A presentation for HealthTrust members
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Perioperative Pregabalin & Ketamine as Multimodal Pain Management Strategies

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Disclosures

- The presenter has no financial relationships with any commercial interests pertinent to this presentation.
- This presentation reviews off-label indications for pregabalin and ketamine.

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Pharmacist & Nursing Learning Objectives

1. Review the evidence and guideline recommendations for the use of pregabalin and ketamine for perioperative pain management
2. Describe pregabalin and ketamine dosing and administration regimens
3. Discuss the major findings of a retrospective study utilizing pregabalin and ketamine as a multimodal pain management strategy within the bariatric surgery program at Parham Doctors' Hospital

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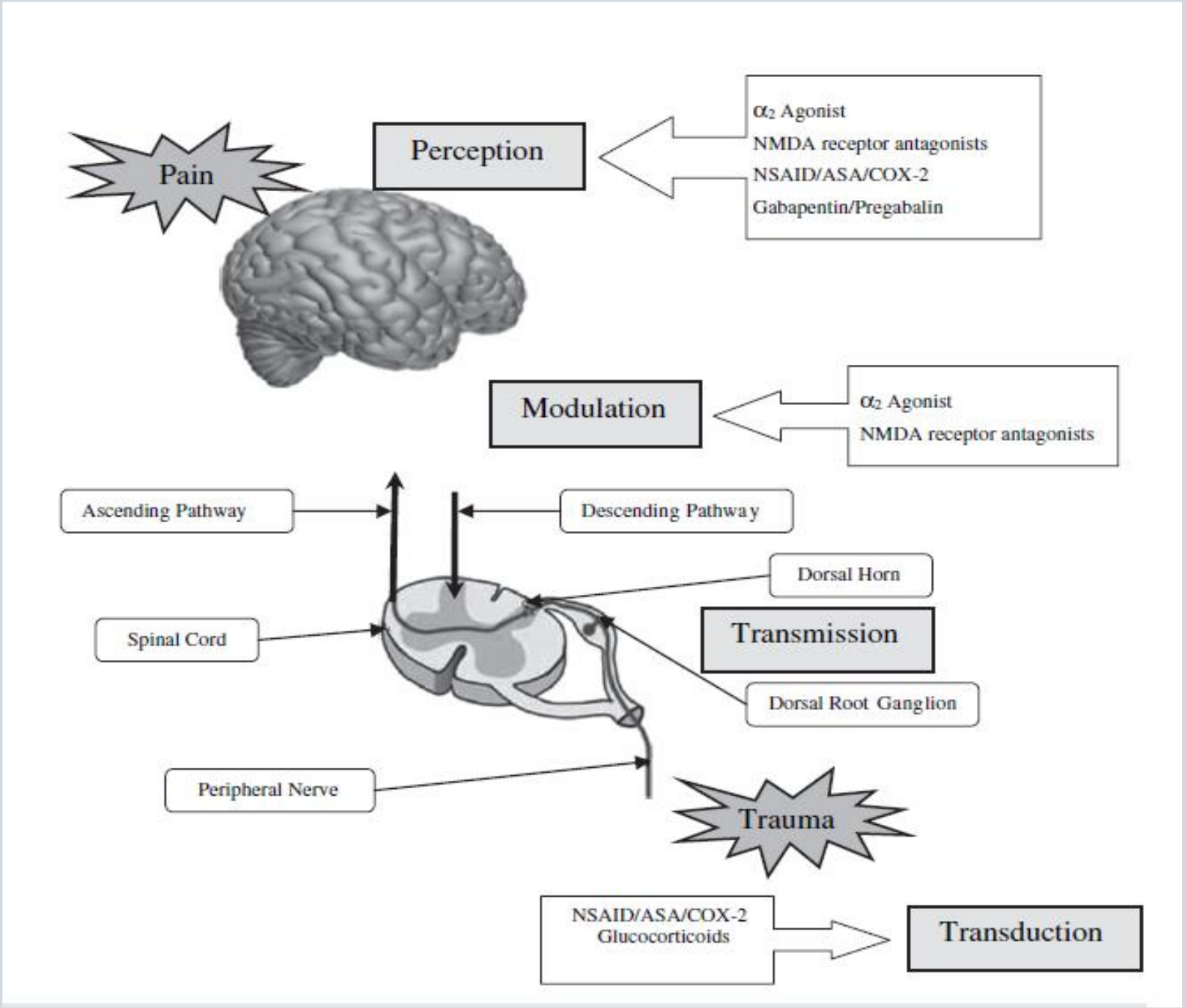
Pharmacy Technician Learning Objectives

1. Describe common dosage forms, dosages and adverse effects for pregabalin and ketamine
2. Describe the role of non-opioid adjuvant medications for pain management
3. List common complications of opioid use in obesity

Definitions

ADE – adverse drug effect	NMDA – n-methyl-d-aspartate
AAA – abdominal aortic aneurysm	NSAIDS – nonsteroidal anti-inflammatory drugs
BMI – body mass index	OHS – obesity-hypoventilation syndrome
CNS – central nervous system	OSA – obstructive sleep apnea
CrCl – creatinine clearance	PACU – post anesthesia care unit
GERD – gastroesophageal reflux	PCA/PCEA – patient controlled (epidural) analgesia
GFR – glomerular filtration rate	PK – pharmacokinetic
IBW – ideal body weight	POD – postoperative day
LOS – length of stay	PONV – postoperative nausea vomiting
MED – morphine equivalent dose	RYGB – roux-en-Y gastric bypass
MO – morbid obesity	TBW – total body weight
NAFLD – nonalcoholic fatty liver disease	T ½ – half life
NASH – nonalcoholic steatohepatitis	V_d – volume of distribution

Pathophysiology of Pain

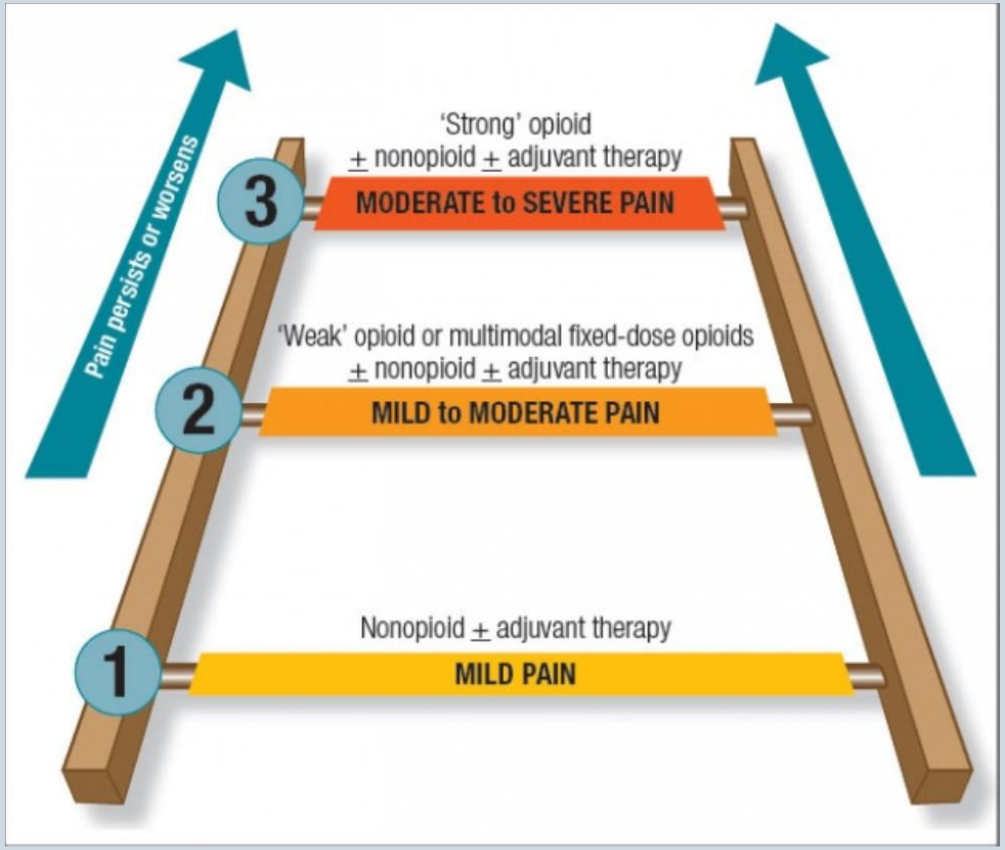


Source: Williams BS, Buvanendran A. Nonopioid Adjuvants in Multimodal Therapy for Acute Perioperative Pain. Advances in Anesthesia 27 (2009) 111-142

Multimodal Pain Management

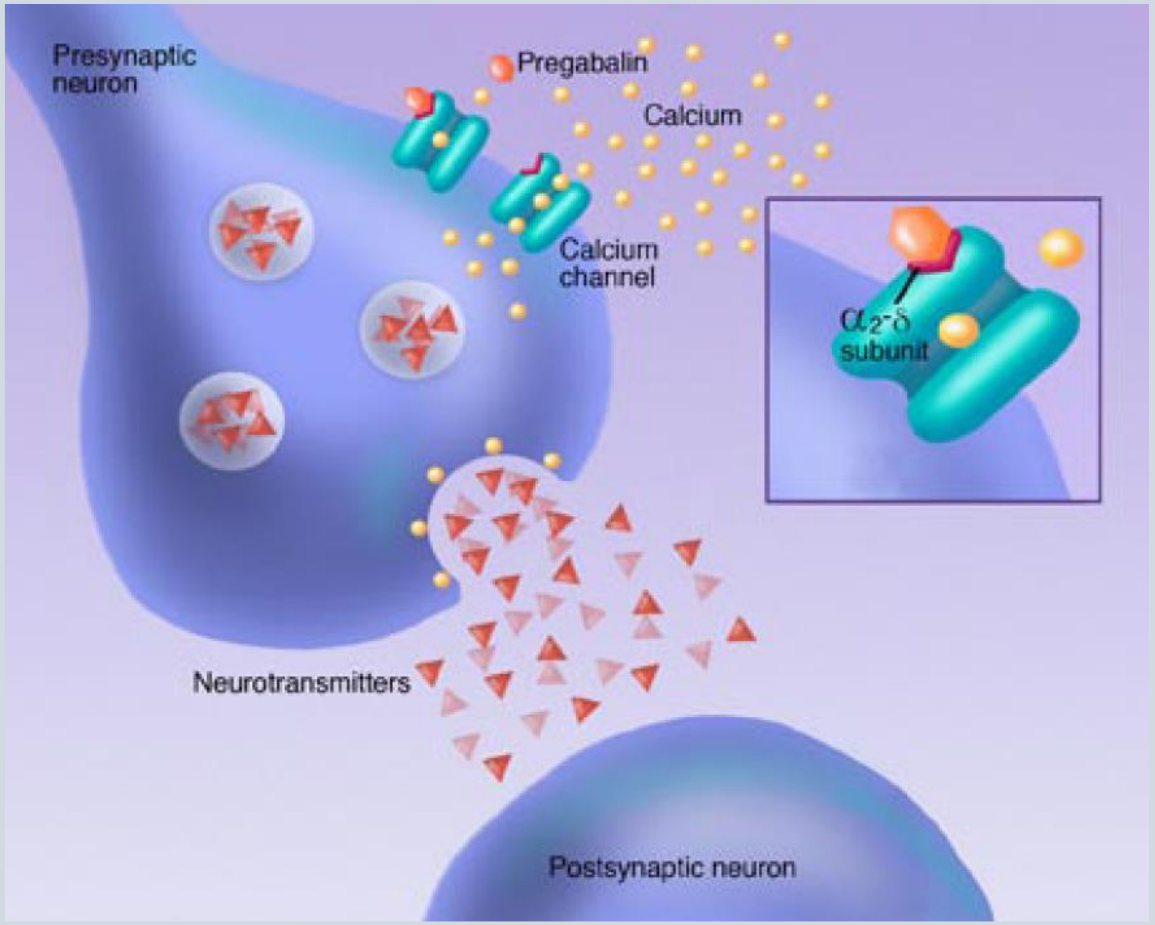
- Two or more analgesics acting by different mechanisms to provide perioperative analgesia.
  - Non-opioid analgesics
  - Systemic adjuvants
  - Regional anesthesia and analgesia

- Multimodal analgesia is recommended for the treatment of postoperative pain (strong recommendation, high-quality evidence)
  - Scheduled non-opioid analgesics
  - Superior pain relief
  - Opioid-sparing



Sources: Pain Ladder. Digital Image. Web. 21 Mar 2018. <www.practicalpainmanagement.com>
Chou, et al. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. The Journal of Pain 2016; 17(2): 131-157

Pregabalin Mechanism of Action



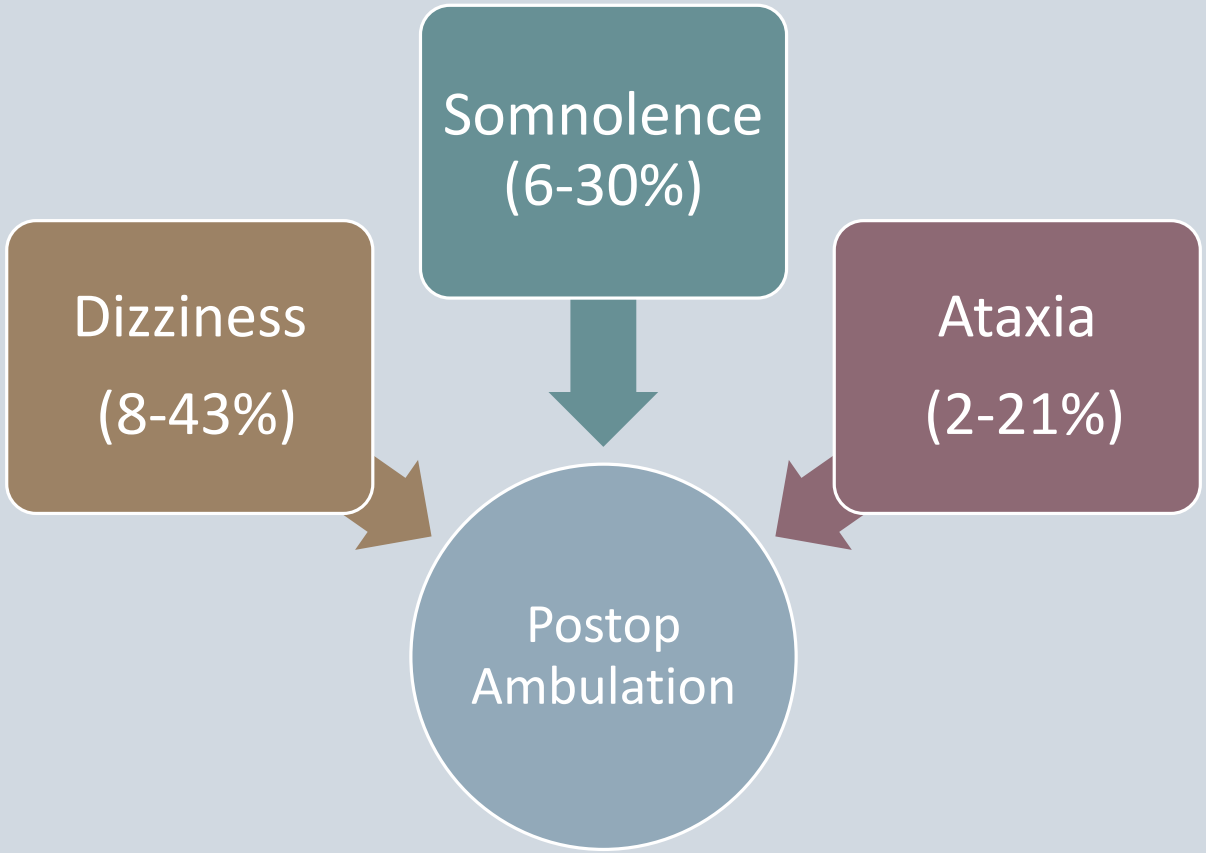
Source: Blommel ML, Blommel AL. Pregabalin: An antiepileptic agent useful for neuropathic pain. Am J Health-Syst Pharm . 2007; 64: 1475-82

Pregabalin Pharmacokinetics

- **A** Rapidly absorbed, bioavailability ≥ 90%, peak ~ 1.5 h
- **D** No plasma protein binding, wide distribution to spinal cord & brain
- **M** Negligible
- **E** ≥ 90% renal, unchanged drug, T ½ ~ 6 h

Source: Lyrica ® (Pregabalin) [Package Insert]. Pfizer Pharmaceuticals LLC. Vega Baja, PR: 2011

Pregabalin Adverse Effects



Sources: Am J Health-Syst Pharm . 2007; 64: 1475-82
Lyrica®(Pregabalin) [Package Insert]. Pfizer Pharmaceuticals LLC. Vega Baja, PR: 2011

Pregabalin Evidence in Lap Cholecystectomy

Agarwal A, et al. 2008

- **Study Design:** Prospective, double-blind, randomized, placebo-controlled trial in patients undergoing laparoscopic cholecystectomy
- **Objectives:** Determine effect of pregabalin on pain scores, fentanyl consumption and ADE at 0, 4, 8, 12 & 24 h postop
- **Intervention**: Pregabalin 150 mg (N=27) vs. placebo (N=29) 1 h preop + postop fentanyl PCA
- **Results:** Reduction in postop pain scores ($p<0.05$) & fentanyl consumption ($p<0.05$), no difference in ADE
- **Limitations:** No multimodal analgesia described**,** non-U.S. (India), small sample size

Chang SH, et al. 2009

- **Study Design:** Prospective, double-blind, randomized, placebo-controlled trial in patients undergoing laparoscopic cholecystectomy
- **Objectives:** Determine effect of pregabalin on pain scores, ketorolac consumption & oversedation at 2, 4, 12, 24 & 48 h postop
- **Intervention**: Pregabalin 300 mg (N=39) vs. placebo (N=38) 1 h preop and 12 h postop + rescue ketorolac 30 mg IV upon request
- **Results:** No difference in pain scores or ketorolac consumption, pregabalin group with greater oversedation at 2 h ($p<0.03$)
- **Limitations:** No multimodal analgesia described, non-U.S. (South Korea), small sample size

Sarakatsianou C, et al. 2012

- **Study Design:** Prospective, double-blind, randomized, placebo-controlled trial in patients undergoing laparoscopic cholecystectomy
- **Objectives:** Determine effect of pregabalin on pain scores, morphine consumption & ADE at 0, 1, 8, 16 & 24 h postop
- **Intervention**: Pregabalin 300 mg (N=20) vs. placebo (N=20) night before surgery and 1 h preop + postop paracetamol 1 gm IV q8h, morphine PCA
- **Results:** Decreased pain scores ($p<0.001$) & morphine consumption ($p<0.01$-$p<0.05$) at all time points, increased dizziness ($p<0.0001$), no difference in PONV or sedation
- **Limitations:** Non-U.S. (Greece), small sample size

Sources: Chang SH, et al. An Evaluation of Perioperative Pregabalin for Prevention and Attenuation of Postoperative Shoulder Pain After Laparoscopic Cholecystectomy. Anesth Analg 2009;109:1284-6
Agarwal A, et al. Evaluation of a single preoperative dose of pregabalin for attenuation of postoperative pain after laparoscopic cholecystectomy. Br J Anaesth 2008; 101:700-4
Sarakatsianou C, et al. Effect of pre-emptive pregabalin on pain intensity and postoperative morphine consumption after laparoscopic cholecystectomy. Surg Endosc 2013; 27: 2504-11

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Pregabalin Evidence in Hysterectomy

Asgari Z, et al. 2017

- **Study Design:** Prospective, double-blind, randomized, placebo-controlled trial in patients undergoing laparoscopic hysterectomy
- **Objectives:** Determine effect of pregabalin on pain scores, meperidine use & sedation at 0, 2, 4, 6, 12 & 24 h postop
- **Intervention**: Pregabalin 75 mg, 150 mg, 300 mg (N=20 each) vs. placebo (N=22) night before, 30 min preop & 6 h postop + diclofenac 100 mg IV and/or meperidine 50 mg IM upon request
- **Results:** Reduced pain scores at all time points ($p<0.001$), less meperidine use ($p<0.001$), increased sedation ($p<0.001$)-300 mg driver for all
- **Limitations:** No multimodal analgesia described, non-U.S. (Iran), small sample size, post-hoc between groups

Rajappa GC, et al. 2016

- **Study Design:** Prospective, double-blind, randomized, placebo-controlled trial in patients undergoing vaginal hysterectomy
- **Objectives:** Determine effect of pregabalin on pain scores, rescue analgesics & sedation at 30 min., 1, 2, 6, 12, 24 h postop
- **Intervention**: Pregabalin 75 mg, 150 mg vs. placebo (N=45 each) 1 h preop + postop paracetamol 1 gm IV q8h, rescue diclofenac IV 75 mg & tramadol 50 mg IV
- **Results:** Reduction in pain scores at all time points ($p<0.001$) & rescue analgesics ($p<0.001$), increased sedation ($p<0.001$)-150 mg driver for all
- **Limitations:** Non-U.S. (India), small sample size, post-hoc between groups

Yucel A, et al. 2011

- **Study Design:** Prospective, double-blind, randomized, placebo-controlled trial in patients undergoing abdominal hysterectomy
- **Objectives:** Determine effect of pregabalin on pain scores, morphine consumption & sedation at 0, 2, 4, 6, 24 h postop
- **Intervention**: Pregabalin 150 mg, 300 mg vs. placebo (N=30 each) 4 h preop and 12 h postop + postop morphine PCA
- **Results:** Reduced 0-12 h pain scores ($p<0.001$), 24 h morphine use ($p<0.001$), increased 0-6 h sedation ($p<0.001$-$p<0.01$)–300 mg driver for all
- **Limitations:** No multimodal analgesia described, non-U.S. (Turkey), small sample size, post-hoc between groups

Sources: Asgari Z, et al. Dose ranging effects o fpregabalin on pain in patients undergoing laparoscopic hysterectomy. Journal of Clinical Anesthesia 2017; 38: 13-17
Rajappa GC, et al. Efficacy of Pregabalin as Premedication for Post-Operative Analgesia in Vaginal Hysterectomy. Anesth Pain Med 2016; 6(3): e34591
Yucel A, et al. Effects of 2 Different Doses of Pregabalin on Morphine Consumption and Pain after Abdominal Hysterectomy. Current Therapeutic Research 2011; 72(4):

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Pregabalin Evidence in Bariatric Surgery

Cabrera MC, et al. 2010

- **Study Design:** Prospective, double-blind, randomized, placebo-controlled trial in laparoscopic sleeve gastrectomy
- **Objectives:** Determine effect of pregabalin on pain scores, morphine consumption, PONV & ADE 24 h postop
- **Intervention**: Pregabalin 150 mg (N=39) vs. placebo (N=41) 2 h preop + postop ketoprofen 300 mg/24 h infusion + morphine 2 mg IV rescue
- **Results:** Reduction in total morphine use ($p<0.0001$), reduction in pain scores ($p<0.05$) and PONV ($p<0.05$), no ADE noted in either group
- **Limitations:** Multimodal pain management not described, non-U.S. (Chile), small sample size

Alimian M, et al. 2012

- **Study Design:** Non-randomized trial in laparoscopic gastric bypass
- **Objectives:** Determine effect of pregabalin on pain scores and PONV 24 h postop
- **Intervention**: Pregabalin 300 mg 1 h preop (N=30) vs. historic control (N=30) + postop morphine PCA
- **Results:** Reduction in pain scores ($p<0.001$) and PONV ($p<0.001$)
- **Limitations:** Multimodal analgesia, morphine use & sedation not described, non-randomized, small sample size, non-U.S. (Iran)

Sources: Cabrera MC, et al. Analgesic Effects of a Single Preoperative Dose of Pregabalin after Laparoscopic Sleeve Gastrectomy. Obes Surg (2010) 20:1678-1681
Alimian M, et al. Effect of Oral Pregabalin Premedication on Post-Operative Pain in Laparoscopic Gastric Bypass Surgery. Anesth Pain (2012); 2(1): 12-16

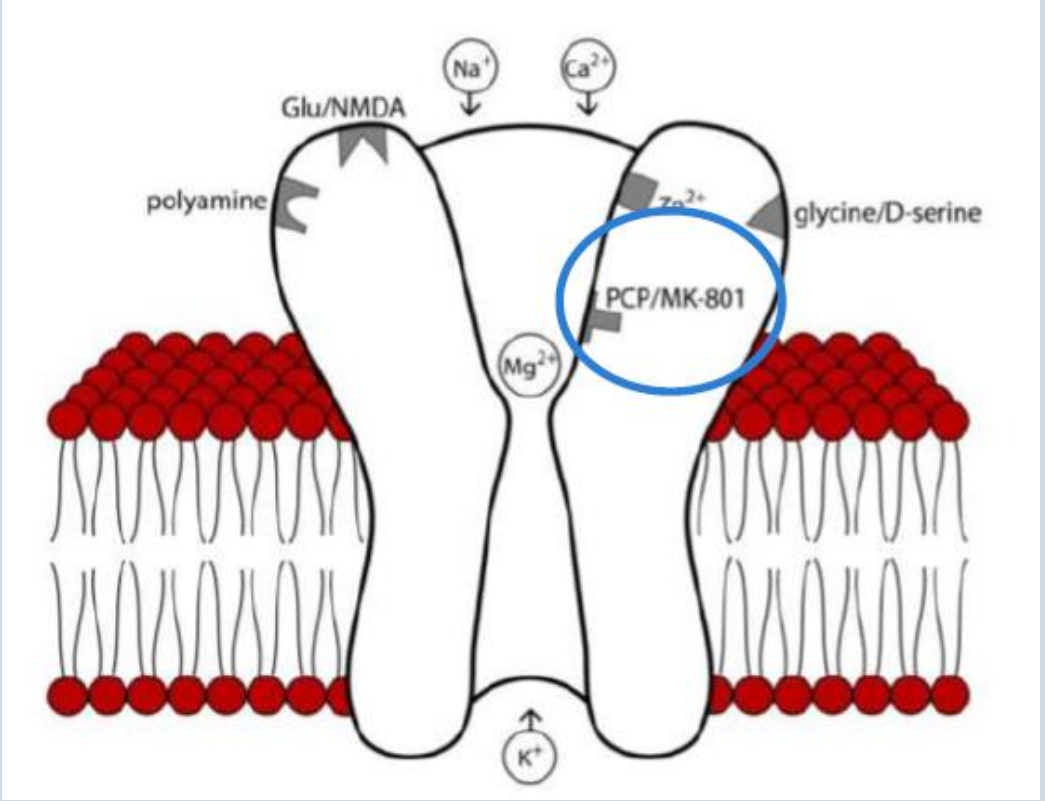
Pregabalin in the Guidelines

- Recommends that clinicians consider use of pregabalin as a component of multimodal analgesia (strong recommendation, moderate-quality evidence)
  - Associated with reduced opioid requirements and lower postoperative pain scores after major or minor surgical procedures
  - Typical doses: pregabalin 150-300 mg PO, 1-2 h preoperatively, although some trials also found regimens that included postoperative dosing to be effective (150-300 mg after 12 h)
    - Insufficient evidence to determine optimal dose; although higher doses might be more effective, they might also be associated with more sedation

Source: Chou, et al. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. The Journal of Pain 2016; 17(2): 131-157

Ketamine Mechanism of Action

Primarily a NMDA receptor antagonist	
Other Mechanisms	❑ Opioid receptors ❑ Monoaminergic, muscarinic, nicotinic receptors ❑ Voltage sensitive electrolyte channels



Sources: Tomek S. Pharmaceuticals. 2013; 6(2): 251-268
NMDA Receptor. Digital image. Pharmaceuticals. 20 Nov 2012. Web. 21 Mar 2018. <mdpi.com>

Ketamine Pharmacokinetics

- **A** Rapidly absorbed, onset ~ 30 sec
- **D** High lipid solubility and low plasma protein binding
- **M** Hepatic metabolism via N-dealkylation to active metabolite norketamine
- **E** Primarily renal, T ½ 2-3 h

Sources: Ketalar © (Ketamine) [package insert] Rochester, MI: JHP Pharmaceuticals, LLC; Revised March 2012.
World Health Organization/Expert Committee on Drug Dependence. Update Review Report. Agenda item 6.1. 2015: 1-46
Clements JA, Nimmo WS, Grant IS. Bioavailability, Pharmacokinetics, and Analgesic Activity of Ketamine in Humans. Journal of Pharmaceutical Sciences 1982; 71(5): 539-541

Anesthesia vs. Analgesia

ANESTHESIA	ANALGESIA
➢ Anesthesia is obtained with dose of ▪ 2 mg/kg IV ➢ ADE ▪ Emergence reactions – dose related ○ Vivid hallucinations ▪ CV system stimulation ○ Tachycardia ○ Hypertension ○ Increased cardiac output ▪ Bronchodilation ▪ Nausea/vomiting	➢ "Low dose" ketamine considered < 1 mg/kg ➢ Analgesia is obtained with doses of ▪ 0.2-0.75 mg/kg IV ➢ ADE ▪ Generally well tolerated at sub-anesthetic doses ▪ Nausea/vomiting ▪ Emergence reactions ○ Sub-anesthetic doses 0.1-1 mg/kg IV

Sources: Ketalar © (Ketamine) [package insert] Rochester, MI: JHP Pharmaceuticals, LLC; Revised March 2012.
World Health Organization/Expert Committee on Drug Dependence. Update Review Report. Agenda item 6.1. 2015: 1-46

Ketamine Evidence in Abdominal Surgery

Guillou N, et al. 2003

- **Study Design:** Prospective, randomized, double-blinded, placebo-controlled trial in patients undergoing major abdominal surgery
- **Objectives:** Determine the effect of ketamine on pain scores, morphine consumption & ADE 48 h postop
- **Intervention**: Ketamine 0.5 mg/kg IV bolus with 2 mcg/kg/min x 24 h then 1 mcg/kg/min x 24 h (N=41) vs. saline placebo (N=52) + postop morphine PCA
- **Results:** Surgery type mainly hepatectomy (54% & 44%). No difference in pain scores, sedation or ADE. Morphine consumption lower at all time points up to 48 h postop ($p<0.05$).
- **Limitations:** Multimodal analgesia not described, small sample size, non-U.S. (France)

Zakine J, et al. 2008

- **Study Design:** Prospective, randomized, double-blinded, placebo-controlled trial in patients undergoing major abdominal surgery
- **Objectives:** Determine the effect of ketamine on pain scores, morphine consumption & ADE 48 h postop
- **Intervention**: Ketamine 0.5 mg/kg IV bolus & 2 mcg/kg/min x 48 h (N=23) vs. bolus + intraoperative infusion only (N=27) vs. saline placebo (N=27) + postop morphine PCA
- **Results:** Surgery types included nephrectomy, prostatectomy & AAA evenly distributed between groups (~30% each). Less morphine consumption in the 48 h group vs. other groups ($p=0.008$) & no difference between intraop vs. placebo. Pain scores lower in both treatment groups compared to placebo ($p=0.001$). No difference in sedation. No psychiatric ADE. Less PONV at 48 h vs. placebo ($p=0.005$).
- **Limitations:** No postop multimodal analgesia provided, small sample size, non-U.S. (France), post hoc between groups

Sources: Guillou N, et al. The Effects of Small-Dose Ketamine on Morphine Consumption in Surgical Intensive Care Unit Patients After Major Abdominal Surgery. Anesth Analg 2003; 97: 843-7
Zakine J, et al. Postoperative Ketamine Administration Decreases Morphine Consumption in Major Abdominal Surgery: A Prospective, Randomized, Double-Blind, Controlled Study. Anesth Analg 2008; 106: 1856-61

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Ketamine Evidence in Laparoscopic Surgery

Singh H, et al. 2003

- **Study Design:** Prospective, randomized, double-blind, placebo-controlled trial in patients undergoing laparoscopic cholecystectomy
- **Objectives:** Determine effect of ketamine on postop pain scores, opioid consumption & ADE
- **Intervention**: Ketamine 1 mg/kg, 0.75 mg/kg and 0.5 mg/kg IV (N=20 each) vs. saline placebo (N=20) + post op IV fentanyl rescue
- **Results:** Reduction in pain scores at 0, 0.5, 3-6 & 12 h all groups vs. placebo. Total opioid doses lower in treatment groups vs. placebo. No differences in pain scores/opioid doses between treatment groups. No differences in PONV. Hallucinations 10% with 1 mg/kg, 0% in other groups.
- **Limitations:** No reported p values, no multimodal analgesia described, small sample size, non-U.S. (India), post hoc between groups

Saxena D, et al. 2017

- **Study Design:** Prospective, observational study in patients undergoing laparoscopic gynecological surgery
- **Objectives:** Evaluate the effect of ketamine on rescue analgesia requirements & ADE within 8 h postop
- **Intervention**: Ketamine 0.5 mg/kg IV, repeated q0.5h with 0.25mg/kg until end of surgery (N=70) + postop fentanyl IV rescue
- **Results:** No rescue analgesia required up to 8 h in 93% (<30 min), 70% (31-60 min), 57% (61-90 min), 67% (91-120 min), 62% (121-150 min), 60% (151-180 min). PONV occurred in 2.85% of patients, psychotomimetic reactions and sedation occurred in 4.28% of patients.
- **Limitations:** No control group, no multimodal analgesia described, did not evaluate pain scores, small sample size, non-U.S. (India)

Gadre VN, et al. 2017

- **Study Design:** Prospective, randomized, double-blind, placebo-controlled trial in patients undergoing laparoscopic surgery
- **Objectives:** Compare efficacy of three small doses of ketamine for improving 24 h postop pain scores, opioid use & ADE
- **Intervention**: Ketamine 1 mg/kg (N=30), 0.75 mg/kg (N=30), 0.5 mg/kg (N=30) vs. saline IV control (N=30) + postop fentanyl IV rescue
- **Results:** Reduction in pain scores in all groups at 24 h at rest vs placebo ($p<0.001$). Lower total fentanyl IV rescue doses in all groups vs. placebo ($p<0.0001$). No reported hallucinations or PONV in any group.
- **Limitations:** Type of surgery or postop multimodal analgesia not described, post hoc between group analyses, small sample size, non-U.S. (India)

Sources: Singh H, et al. Preemptive analgesia with Ketamine for Laparoscopic cholecystectomy. Journal of Anaesthesiology Clinical Pharmacology 2013; 29 (4): 478-484
Saxena D, et al. Efficacy of Low-dose Ketamine as Sole Analgesic Agent in Maintaining Analgesia and Intraoperative Hemodynamics During Laparoscopic Gynecological Surgeries. Anesth Essays Res 2017; 11:385-9
Gadre VN, Dhokte NS. Postoperative analgesia in laparoscopic surgeries with small dose of preemptive ketamine: A comparative study of three small doses. Indian Anaesth Forum 2017; 18: 3-8

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Ketamine Evidence in Bariatric Surgery

Feld JM, et al. 2003

- **Study Design:** Randomized, double-blind trial in patients undergoing gastric bypass by open laparotomy
- **Objectives:** Determine the effect of a non-opioid analgesic regimen including ketorolac, clonidine, lidocaine**, ketamine,** magnesium & methylprednisolone compared to fentanyl analgesia on 16 h postop morphine use and pain scores
- **Intervention**: Ketamine 0.17 mg/kg/h (max 1 mg/kg) IV during case (N=15) vs. fentanyl 50 mcg bolus (Max 6 mcg/kg IBW) (N=15)
- **Results:** Reduction in total PACU morphine use ($p<0.05$) and PACU sedation ($p<0.01$). No difference in 16 h total morphine use ($p=0.71$) or pain scores ($p=0.97$)
- **Limitations:** Gastric bypass by open laparotomy no longer commonly performed, non-U.S. (Canada), small sample size, concomitant clonidine & lidocaine, sedation only evaluated in PACU, no postop multimodal analgesia described

Sollazzi L et al. 2009

- **Study Design:** Randomized, open-label trial in patients undergoing biliopancreatic diversion
- **Objectives:** Determine the effect of preop ketamine-clonidine on pain scores use at 30 min., 1, 6 & 12 h and total IV tramadol use
- **Intervention**: Ketamine 0.5 mg/kg-clonidine 3 mcg/kg (IBW) IV over 20 min (N=23) vs. control group (N=27) prior to induction of anesthesia + postop ketorolac 90 mg + tramadol 200 mg 2 mL/h continuous infusion + rescue tramadol IV 100 mg
- **Results:** Reduction in total tramadol use ($p<0.05$) and pain scores during first 6 h post-op ($p<0.05$)
- **Limitations:** Open biliopancreatic diversion no longer commonly performed, non-U.S. (Italy), open label, small sample size, concomitant clonidine

Sources: Feld JM, et al. Non-opioid analgesia improves pain relief and decreases sedation after gastric bypass surgery. Can J Anesth 2003; 50(4): 336-41
Sollazzi L, et al. Preinductive use of clonidine and ketamine improves recovery and reduces postoperative pain after bariatric surgery. Surgery for Obesity and Related diseases 2009; 5: 67-71

Ketamine in the Guidelines

- Recommends that clinicians consider use of IV ketamine as a component of multimodal analgesia in adults (weak recommendation, moderate-quality evidence)
  - Associated with reduced opioid requirements and lower postoperative pain scores after major or minor surgical procedures
  - Ketamine has been administered preoperatively, intraoperatively, and/or postoperatively, at widely varying doses (ranging from boluses of 0.15-2 mg/kg before incision and at closure, with or without infusions ranging from 0.12 mg/kg/h to 2 mg/kg/h)
    - Insufficient evidence to determine optimal method for dosing ketamine, but suggests using a preoperative bolus of 0.5 mg/kg followed by an infusion at 10 mcg/kg/min intraoperatively, with or without a postoperative infusion at lower dosage

Source: Chou, et al. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. The Journal of Pain 2016; 17(2): 131-157

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Efficacy of Preoperative Pregabalin & Ketamine as a Bariatric Surgery Pain Management Strategy

Bariatric Surgery Indications

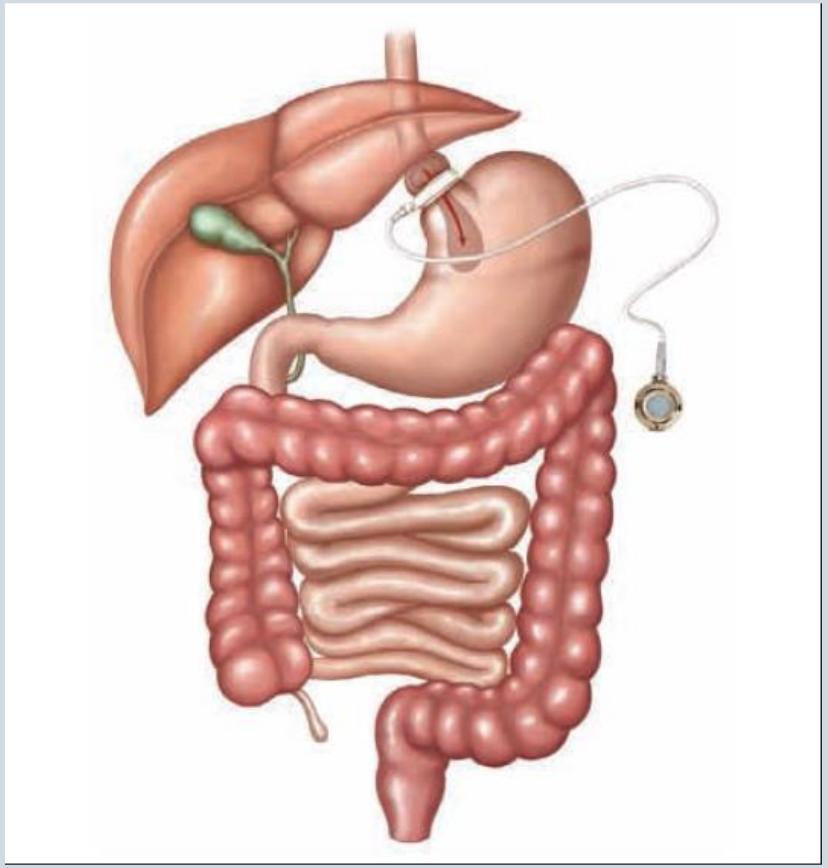
- BMI ≥ 40 kg/m^2 without coexisting medical problems
- BMI ≥ 35 kg/m^2 and one or more severe obesity-related co-morbidities
  - Type 2 diabetes
  - Hypertension
  - Hyperlipidemia
  - OSA
  - OHS
  - Pickwickian syndrome (combination of OSA & OHS)
  - NAFLD or NASH
  - GERD
  - Pseudotumor cerebri
  - Asthma
  - Venous stasis disease
  - Severe urinary incontinence
  - Debilitating arthritis

Source: Mechanick JI, et al. Clinical Practice Guidelines for Perioperative Nutritional, Metabolic, and Nonsurgical Support of the Bariatric Surgery Patient. Surgery for Obesity and Related Diseases 9 (2013) 159-191

Bariatric Surgical Procedures

INTRAGASTRIC BALLOON

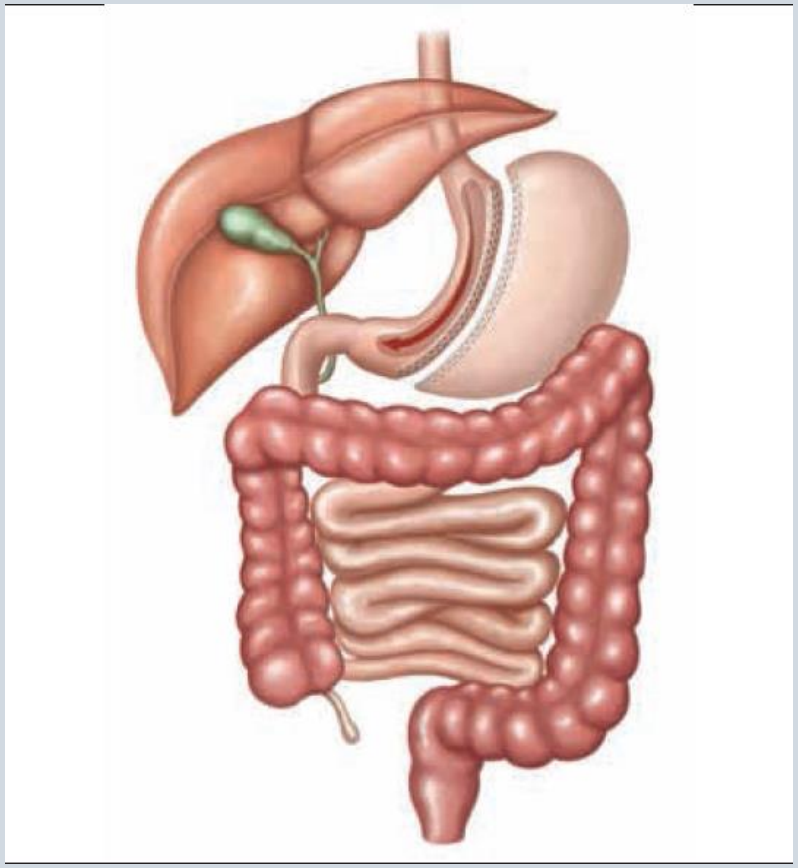
LAPAROSCOPIC ADJUSTABLE GASTRIC BAND



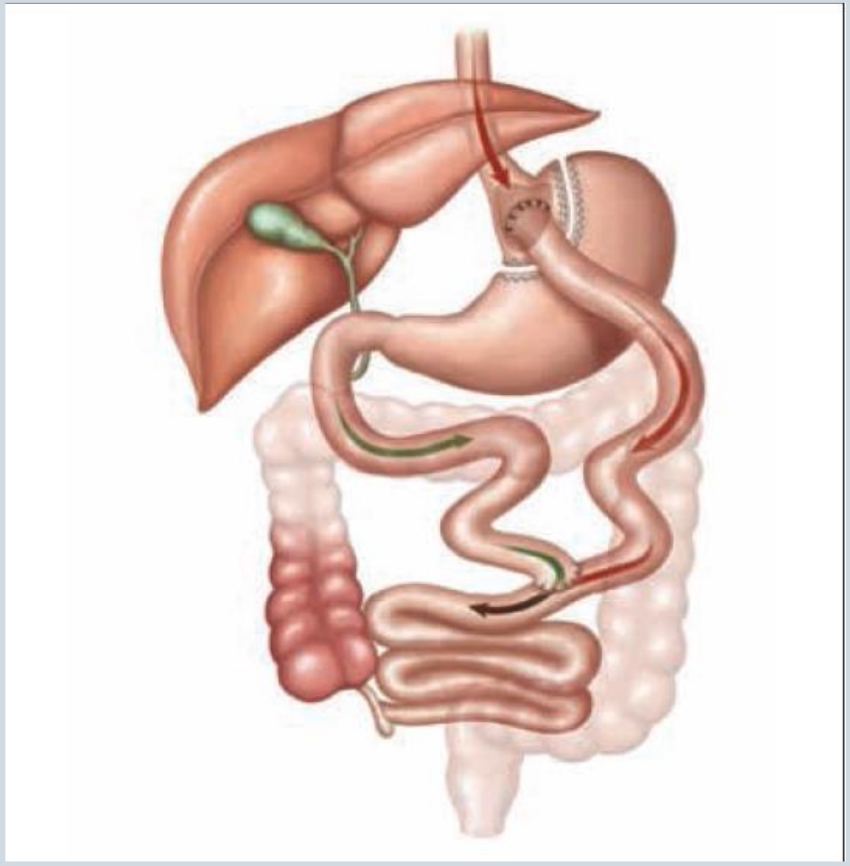
Sources: Intragastric Balloon. Digital image. Web. 4 Apr 2018. <www.freedomfromobesity.com>
Am J Health-Syst Pharm. 2014; 71: 1253-64

Bariatric Surgical Procedures

LAPAROSCOPIC SLEEVE GASTRECTOMY



LAPAROSCOPIC RYGB



Source: Am J Health-Syst Pharm. 2014; 71: 1253-64

Limitations of Opioids in Obesity

Predisposed to Opioid induced Airway Obstruction

- Approximately 70% of morbidly obese patients are afflicted with OSA
- Increased overall oxygen consumption
- Reduced functional residual capacity
- Anatomic changes including large necks, excess adipose tissue obstructing the airways

Hormonal Dysregulation

- Excess endogenous opioids
- Decreased opioid receptors in the brain
  - Postulated to regulate eating habits may also support need for reduction in opioid dose

Physiologic Changes

- Increased adipose tissue
- Higher cardiac output
- Increased blood volume
- Decreased total body water
- Increased GFR
- Altered protein binding

Sources: Alvarez A, Singh PM, Sinha AC. Postoperative Analgesia in Morbid Obesity. Obes Surg (2014) 24: 652-659
Aman MM, Mahmoud A, Sinha AC (2017). Postoperative Analgesia in Morbid Obesity. Nutritional Modulators of Pain in the Aging Population. Watson R, Zibadi S. Academic Press, 2007. 171-180.

Pharmacokinetic Considerations in Obesity

Morphine

- Hydrophilic
- Conjugated by UGT2B7 which is increased in obesity
- Dose increases likely necessary but risk of over sedation is high
- Use with caution

Hydromorphone

- Intermediate hydrophilic/lipophilic
- No data in obesity
- Use with caution

Fentanyl

- Lipophilic
- Large V_d
- CYP3A4 metabolism
- Increased cardiac output decreases concentrations
- Higher bolus (TBW), lower maintenance (IBW)
- Use with caution

Pregabalin

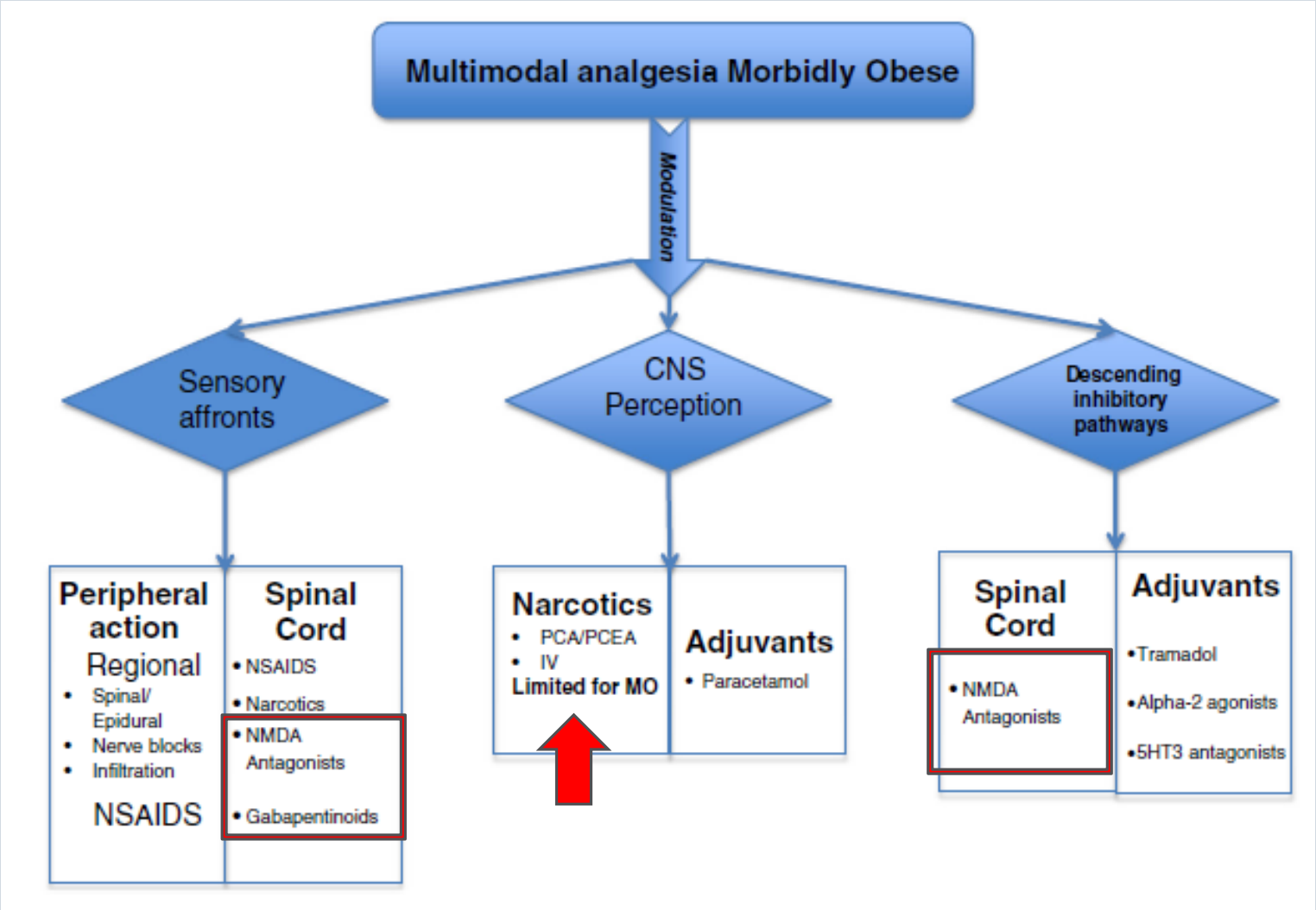
- Hydrophilic
- No data in obesity

Ketamine

- Lipophilic
- No data in obesity

"Investigation of appropriate dosing strategies for opioids in obese patients should continue. Even when PK modeling is available, predicting the differences in analgesic requirements between lean and obese patients is difficult. The risk of adverse effects with the use of these agents in obese patients is high."

Sources: Shank BR, Zimmerman DE. Demystifying Drug Dosing in Obese Patients. Bethesda, MD: American Society of Health Systems Pharmacists, 2016. Print.
Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. MMWR Recomm Rep 2016;65 (No. RR-1):1–49.
World Health Organization/Expert Committee on Drug Dependence. Update Review Report. Agenda item 6.1. 2015: 1-46



Source: Alvarez A, Singh PM, Sinha AC. Postoperative Analgesia in Morbid Obesity. Obes Surg (2014) 24: 652-659

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Bariatric Center of Excellence

- Parham Doctors' Hospital (PDH) in Richmond, VA received accreditation by the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP) in February 2015
- Earned designation as a Blue Distinction® Center+ for Bariatric Surgery in 2017
- PDH performs > 350 bariatric surgeries annually
  - Intragastric balloon
  - Laparoscopic adjustable gastric banding
  - Laparoscopic sleeve gastrectomy
  - Laparoscopic RYGB
- PDH has a multidisciplinary Metabolic and Bariatric Surgery Collaborative Practice Group (MBSCPG) which meets monthly to discuss all aspects of current practice, including multimodal pain management strategies

Blue Distinction® Center+ Bariatric

MBSAQIP®
METABOLIC AND BARIATRIC SURGERY ACCREDITATION AND QUALITY IMPROVEMENT PROGRAM

Multimodal Pain Management Protocol

- Acetaminophen 1000 mg IV preoperative
- Ketorolac 15-30 mg IV preoperative
- Local bupivacaine 0.5% with epinephrine injection around laparoscopic sites
- Ketorolac 15-30 mg IV q6h x 6 doses postoperative
- Acetaminophen 1000 mg IV q6h x 3 doses postoperative
- Hydromorphone 0.5 mg IV q3h PRN pain scale 1-3
- Hydromorphone 1 mg IV q3h PRN pain scale 4-6
- Hydromorphone 2 mg IV q3h PRN pain scale 7-10
- Hydromorphone 2 mg PO q4h PRN pain scale 1-10 when tolerating PO

Change to the Multimodal Pain Management Protocol

- Lack of studies utilizing pregabalin and ketamine in bariatric surgical patients
  - Pain management guidelines do not specifically address bariatric surgical patients
- The MBSCPG discussed the addition of pregabalin and ketamine as non-opioid adjunctive therapies in an attempt to improve patient satisfaction by reducing opioid use and pain scores
- Beginning April 3, 2017, bariatric surgery patients at PDH began receiving
  - Pregabalin 150 mg PO 1 h preoperatively
  - Ketamine 40 mg IV at the induction of anesthesia

Study Overview

PURPOSE	OBJECTIVES
➢ Determine if the addition of pregabalin and ketamine improved postsurgical pain control in patients undergoing primary bariatric surgery	➢ Primary objective ▪ Reduction in opioid consumption ➢ Secondary objectives ▪ Reduction in pain scores ▪ Safety of pregabalin and ketamine

Methods

- Study Design
  - Retrospective, observational chart review
- Inclusion criteria
  - 50 patients who underwent primary bariatric surgery prior to April 3, 2017
  - 50 patients who underwent primary bariatric surgery on or after April 3, 2017
- Exclusion criteria
  - Chronic pain
  - Secondary revision surgeries
  - Prior pregabalin or gabapentin use
  - CrCl < 15 ml/min or hemodialysis

- Data collection
  - Surgery type
  - Age
  - Weight, BMI
  - LOS
  - Pregabalin and ketamine doses
  - Pain scores
  - Antiemetic usage
- Statistical Analysis
  - A two tailed, student t-test for unpaired continuous data using Excel©
  - $\alpha < 0.05$

Demographics		Pre-Intervention (N=50)	Post-Intervention (N=50)
Surgery Type N (%)	Band	0 (0%)	1 (2%)
	Sleeve	43 (86%)	34 (68%)
	RYGB	7 (14%)	15 (30%)
Age (yr)	Median (Range)	49 (23-69)	47 (22-62)
Weight (kg)		133 (83-244)	130 (83-211)
BMI (kg/m^2)		47 (31-82)	44 (31-62)
LOS (days)		1 (0-2)	1 (0-2)
Antiemetics (# doses)		2 (0-9)	1 (0-6)
Ketamine Dose N (%)	40 mg	N/A	28 (56%)
	50 mg		22 (44%)
Pregabalin Dose N (%)	150 mg	N/A	50 (100%)

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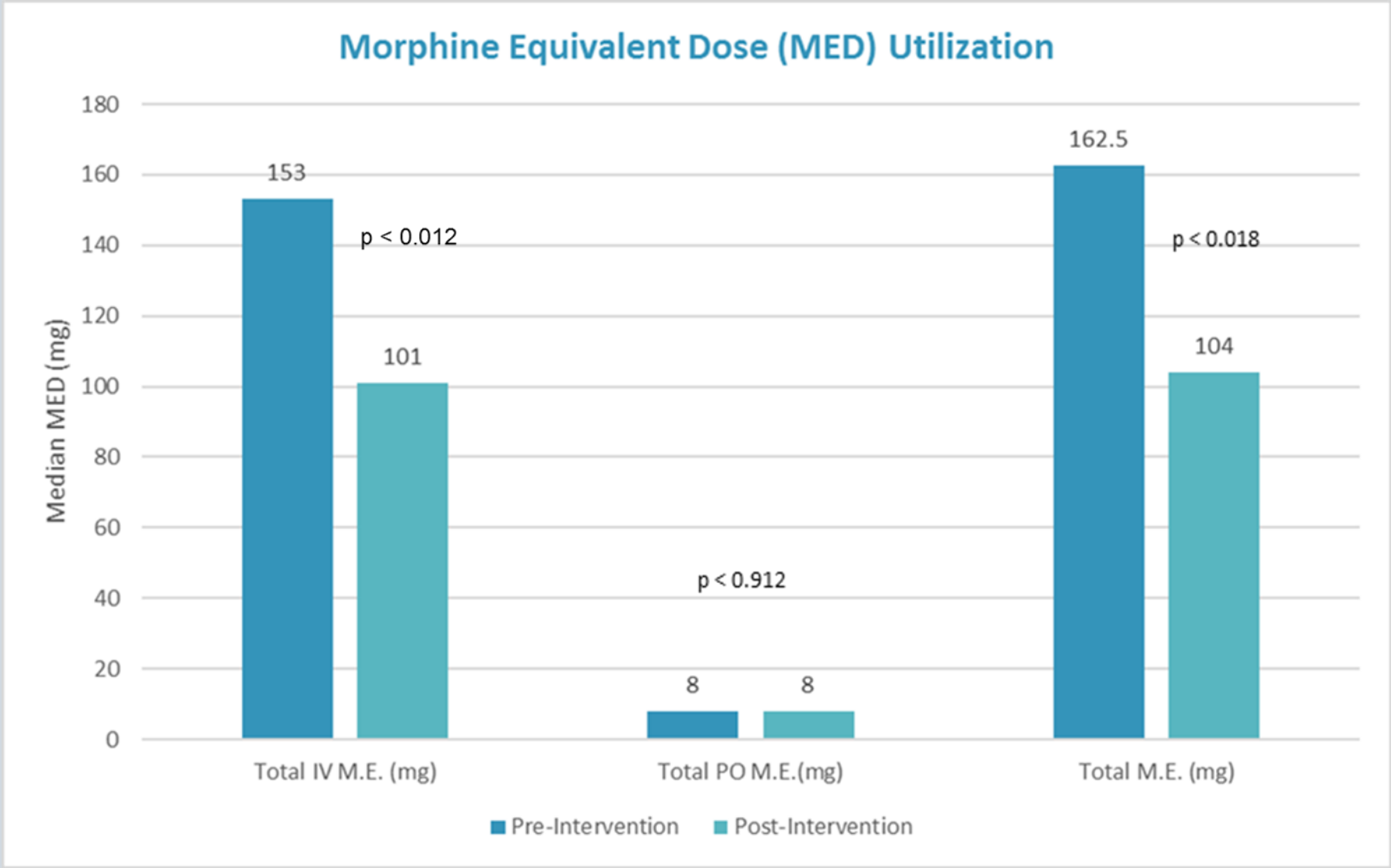

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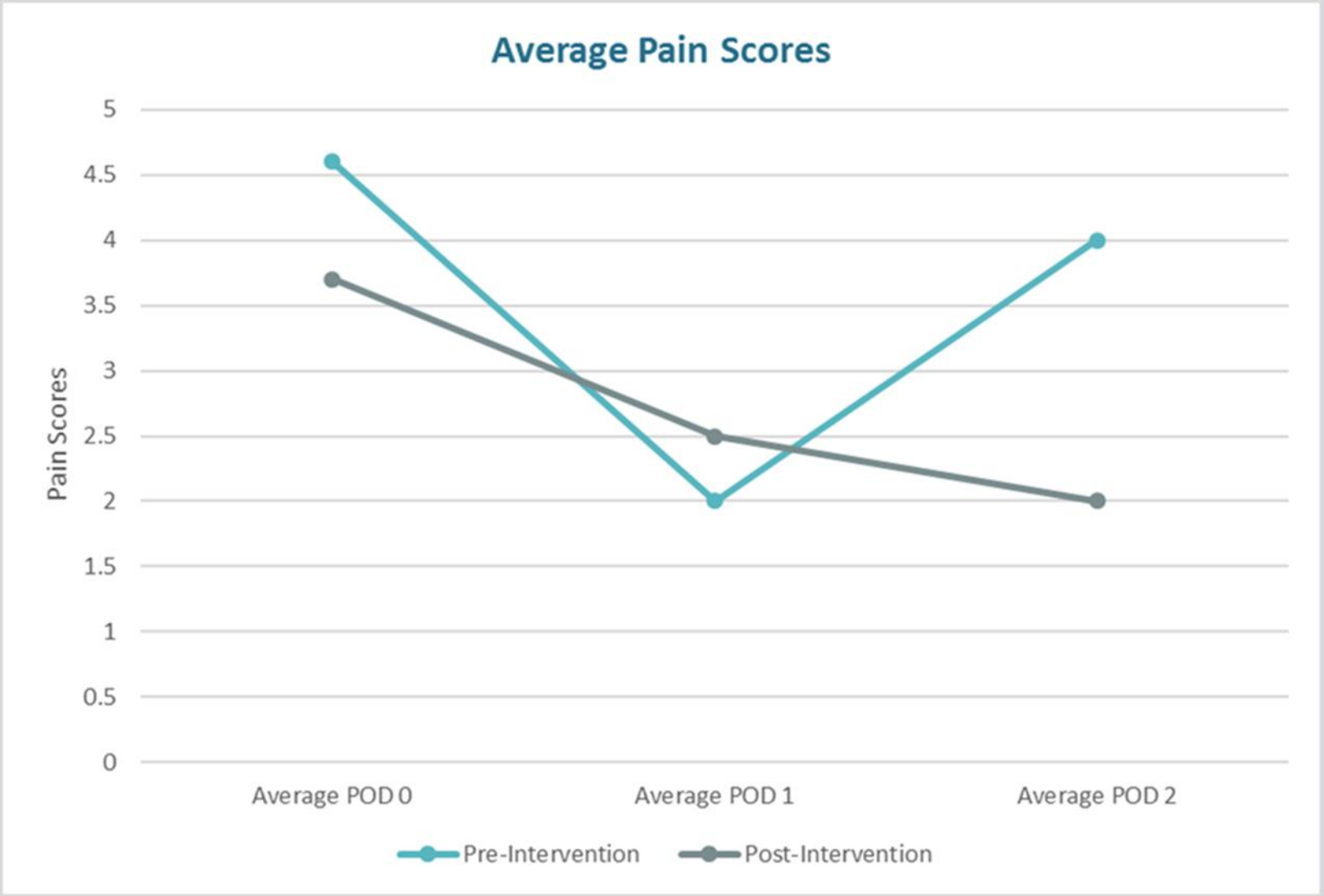

Limitations

- Retrospective, observational design
- Small sample size
- Varying mg/kg ketamine dose
- Initiated two interventions simultaneously

Conclusions

- Addition of preoperative pregabalin and ketamine in bariatric surgery
  - Reduced opioid use
  - Reduced pain scores
  - Well tolerated
- Findings consistent with general surgical population
- The bariatric surgery program at PDH continues to utilize pregabalin and ketamine as part of a multimodal pain management strategy

Summary

- Despite numerous limitations of available studies, pregabalin and ketamine have consistently demonstrated the ability to reduce postoperative opioid consumption and pain scores in a variety of surgeries
  - Pregabalin 150 mg PO 1 h prior to surgery most commonly balanced efficacy with risk of ADE
  - Ketamine doses < 1 mg/kg IV bolus at the induction of anesthesia likely safe and effective
- Obese patients are highly susceptible to ADE of opioids such as respiratory depression and investigation of non-opioid adjuvants are of particular importance in this patient population
- There is a lack of evidence for use of pregabalin and ketamine in bariatric surgery
  - Findings in a study by PDH are consistent with current literature in the general surgical population

Assessment Question 1

Which of the following adverse drug effects is not associated with pregabalin?

A. Dizziness
B. Sedation
C. Emergence reactions
D. Ataxia

Response Question 1

Which of the following adverse drug effects is not associated with pregabalin?

A. Dizziness
B. Sedation
C. **Emergence reactions**
D. Ataxia

Assessment Question 2

True or False:

Pregabalin and ketamine have demonstrated an ability to reduce pain scores but not opioid consumption in various types of surgeries.

Response Question 2

True or **False**:

Pregabalin and ketamine have demonstrated an ability to reduce pain scores but not opioid consumption in various types of surgeries.

Assessment Question 3

Which of the following preoperative pregabalin and ketamine dosing regimens most likely balances safety with efficacy?

A. Pregabalin 300 mg 1 h preop and Ketamine 1 mg/kg IV at the induction of anesthesia
B. Pregabalin 150 mg 1 h preop and Ketamine 0.5 mg/kg IV at the induction of anesthesia
C. Pregabalin 150 mg 1 h preop and Ketamine 2 mg/kg IV at the induction of anesthesia
D. Pregabalin 300 mg 1 h preop and Ketamine 0.5 mg/kg IV at the induction of anesthesia

Response Question 3

Which of the following preoperative pregabalin and ketamine dosing regimens most likely balances safety with efficacy?

A. Pregabalin 300 mg 1 h preop and Ketamine 1 mg/kg IV at the induction of anesthesia

B. **Pregabalin 150 mg 1 h preop and Ketamine 0.5 mg/kg IV at the induction of anesthesia**

C. Pregabalin 150 mg 1 h preop and Ketamine 2 mg/kg IV at the induction of anesthesia

D. Pregabalin 300 mg 1 h preop and Ketamine 0.5 mg/kg IV at the induction of anesthesia

Assessment Question 4

Use of opioids in obese patients are limited by which of the following?

A. Predisposition to airway obstruction due to anatomic changes and high incidence of obstructive sleep apnea

B. Hormonal dysregulation including excess endogenous opioids and decreased opioid receptors

C. Physiologic changes including higher cardiac output and GFR

D. All of the above

Response Question 4

Use of opioids in obese patients are limited by which of the following?

A. Predisposition to airway obstruction due to anatomic changes and high incidence of obstructive sleep apnea

B. Hormonal dysregulation including excess endogenous opioids and decreased opioid receptors

C. Physiologic changes including higher cardiac output and GFR

D. **All of the above**

Assessment Question for Pharmacy Techs

Which of the following statements are true?

A. The benefit of adding non-opioid adjuvant medications to a multimodal pain management protocol is the potential reduction of postoperative opioid consumption and superior pain relief

B. Pregabalin is only available as an oral dosage form, while ketamine is available in both oral and IV dosage forms

C. A common complication of opioid use, particularly in obese patients, is respiratory depression

D. A & C

Response Question for Pharmacy Techs

Which of the following statements are true?

A. The benefit of adding non-opioid adjuvant medications to a multimodal pain management protocol is the potential reduction of postoperative opioid consumption and superior pain relief

B. Pregabalin is only available as an oral dosage form, while ketamine is available in both oral and IV dosage forms

C. A common complication of opioid use, particularly in obese patients, is respiratory depression

D. **A & C**

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Questions?

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