



### Opioid Sparing Techniques: Are We Ripping Off Patients?



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## Objectives

The learner will be able to describe:

- Non-opioid modalities in pain management.
- The challenges of opioid modalities in pain management.
- Future directions in pain management.

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## Opioids: Public Health Issue



**THE BLOG** 06/06/2016 02:35 pm ET | Updated Jun 06, 2016

### What Is Fentanyl? The Facts About the Opioid That Caused Prince's Death

By Health.com

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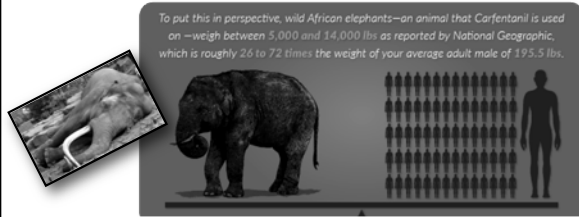
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# Opioids: Public Health Issue



3 Marylanders die from carfentanil overdoses

WBALTV | Updated: 4:47 PM EDT Apr 24, 2017

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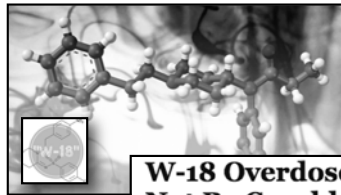
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# Opioids: Public Health Issue



This new street drug is 10,000 times more potent than morphine, and now it's showing up in Canada and the U.S.

## W-18 Overdoses In Alberta May Not Be Curable With Naloxone Kits

The Huffington Post Alberta | By Sarah Rieger | Posted: 05/24/2016 5:53 pm EDT | Updated: 05/24/2016 5:59 pm EDT

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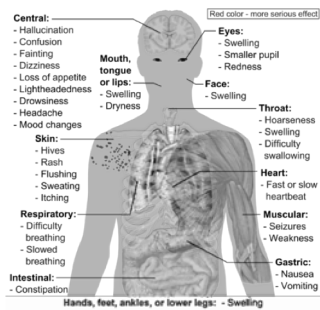
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# Opioids: Why Avoid?



1. Tolerance
2. Dependence
3. Addiction

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## Opioids: Why Avoid?

Acute in vitro morphine-induced increases in proinflammatory cytokine and chemokine release

	Control (pg/ml)		Morphine 10 µM (pg/ml)		Morphine 100 µM (pg/ml)	
	Mean	SEM	Mean	SEM	Mean	SEM
IL-1β	11.3	1.1	15.4	2.0	19.0*	2.5
IL-6	163.1	19.4	345.9	60.1	381.3*	55.7
IL-10	0.9	0.3	1.7	0.3	1.9	0.5
Fractalkine	44.6	1.0	74.0*	7.0	73.6*	7.5
GRO/KC	317.2	93.5	1232.5	520.9	2477.2*	500.4
MIP-1α	4.5	0.4	18.3*	3.3	23.8*	3.6
MCP-1	258.8	18.3	400.3	43.6	441.4*	57.3
RANTES	7.7	1.0	7.5	0.6	11.3	1.2
TNF-α	8.1	1.3	16.6	2.8	26.3*	2.0

Proinflammatory cytokine and chemokine release from lumbar dorsal spinal cord sections incubated for 180 min in vitro with morphine (10 and 100 µM) compared to media alone (\**P* < 0.05).

Hutchinson, M. R., Coats, B. D., Lewis, S. S., Zhang, Y., Sprunger, D. B., Rezvani, N., ... Watkins, L. R. (2008). Proinflammatory cytokines oppose opioid-induced acute and chronic analgesia. *Brain Behavior and Immunity*, 22(3), 1178-1189. doi:10.1016/j.bbi.2008.05.004

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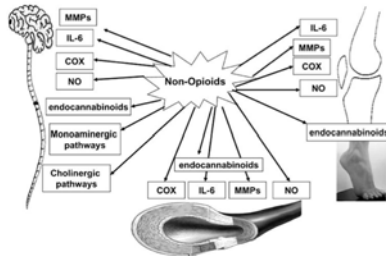
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## Opioid-Sparing: Underlying Premise



Hamza, M., & Dionne, R. A. (2009). Mechanisms of Non-Opioid Analgesics Beyond Cyclooxygenase Enzyme Inhibition. *Current Molecular Pharmacology*, 2(1), 1-14.

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## Opioid-Sparing: Underlying Premise

### Endogenous Chemicals Causing Pain

- 5-HT = 5-hydroxytryptamine
- 5-HT1AR = 5-hydroxytryptamine 1A receptors
- 5-HT2AR = 5-hydroxytryptamine 2A receptors
- CB2R = cannabinoid CB2 receptors
- CCK-8 = cholecystokinin octapeptide
- COX-2 = cyclooxygenase-2
- CRF = corticotrophin-releasing factor
- GABA = γ-aminobutyric acid
- GDNF = glial cell line-derived neurotrophic factor
- GFRα-1 = GDNF family receptor α-1
- IAM-1 = intracellular adhesion molecule-1

- IL-6 = interleukin-6
- IL-1β = interleukin-1β
- NK-1 = neurokinin-1
- N/OFQ = nociceptin/orphanin FQ
- p38 MAPK = p38 mitogen-activated protein kinase
- PGE2 = prostaglandinE2
- p-GluN1 = phosphorylated GluN1
- TNF-α = tumor necrosis factor-α
- TRPV1 = transient receptor potential cation channel subfamily V member 1
- VIP = vasoactive intestinal polypeptides



Hamza, M., & Dionne, R. A. (2009). Mechanisms of Non-Opioid Analgesics Beyond Cyclooxygenase Enzyme Inhibition. *Current Molecular Pharmacology*, 2(1), 1-14.

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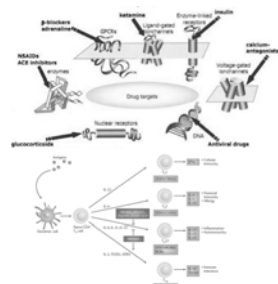
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## Opioid-Sparing: Theory



- **Pharmacological Agents**

- Receptor Model Theory
  - Ionic Channels
  - Opioid/mu
  - GABA
  - NMDA
  - Adrenergic
  - Muscarinic

- **Modulation & Feedback**

- Agonist/Antagonists
- Transporter Proteins
- Synergism Theory

Kovacs & Smith (2014). OPIOIDS & POC: another perspective on drug targets. *Nature Reviews Drug Discovery* 13: 197-216

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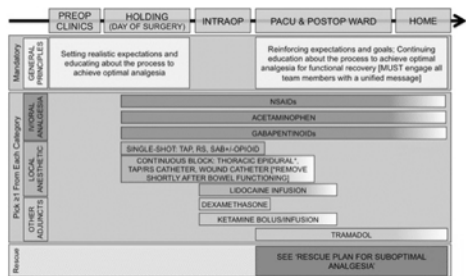
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## Opioid-Sparing: Innovation



Scott et al., (2017) American Society for Enhanced Recovery (ASER) and Perioperative Quality Initiative (POQI) Joint Consensus Statement on Optimal Analgesia within an Enhanced Recovery Pathway for Colorectal Surgery: Part 2—From PACU to the Transition Home. Retrieved from: <https://perioperativemedicinejournal.biomedcentral.com/articles/10.1186/s13741-017-0063-6>

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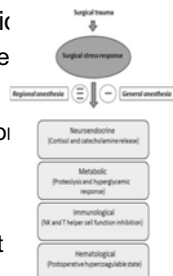
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## Goal: Opioid-Sparing

- Reduce Stress & Inflammation
  - Cortisol & Catecholamine release
- Optimize Immune Function
  - Natural Killer & T-Cell Function
- **Spare Opioids maximally**
- Reduce Symptom Burden
  - Rapid Rescue where prudent




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## ERAS: Controversy

- Procedure specific elements are applied to ALL Surgical Procedures
- Need more research in specific areas;
  - Carbohydrate Loading
  - Mechanical Bowel Preparation (removal)
  - Pre-habilitation: Is it procedure specific?
  - Goal-Directed Fluid Therapy: Questionable?
  - Pain Management: Regional versus Epidural?

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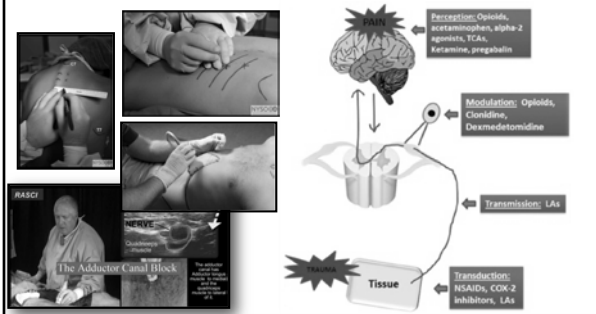
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## Opioid-Sparing: Innovation




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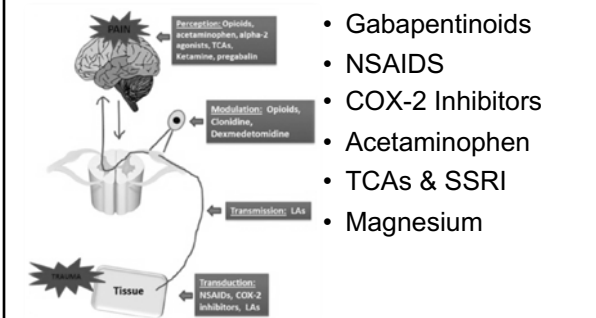
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## Opioid-Sparing: Innovation



- Gabapentinoids
- NSAIDS
- COX-2 Inhibitors
- Acetaminophen
- TCAs & SSRI
- Magnesium

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## Opioid-Sparing: Innovation

- Gabapentinoids

Blommel & Blommel. (2007). Pregabalin: An antiepileptic agent useful for neuropathic pain. Am J Health Syst Pharm. 64(14): 1475-1482

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## Gabapentinoid (Neurontin, Gabapentin)

Gabapentin 300mg PO q8h

**Precautions**

- Sedation Risk
- Post-Operative Confusion

**Consider withholding in patient**

- i. Over 75 years
- ii. Mental status changes
- iii. Poor functional status
- iv. Malnourished (BMI < 18.5)
- v. Avoid if Creatinine Clearance < 30 ml/min.

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## Opioid-Sparing: Innovation

- NSAIDS
- COX-2 Inhibitors

DeMena. (2017). NSAIDs, Coxibs, and Cardio-Renal Physiology: A Mechanism-Based Evaluation: COX-2 Inhibitors and Vascular Physiology. Retrieved from www.coxibs.com

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## NSAID (Ibuprofen, Diclofenac, Ketorolac)

Ketorolac 15-30mg IV q6h  
Maximum 120mg per day

**Brewer, A. R., McCarberg, B., & Argoff, C. E. (2010). Update on the use of topical NSAIDs for the treatment of soft tissue and musculoskeletal pain: A review of recent data and current treatment options. *The Physician and Sportsmedicine*, 38(2), 62.**

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## NSAID (Ibuprofen, Diclofenac, Ketorolac)

- Reduce opioid consumption by 30%
- Caution:
  - Renal or Hepatic Impairment

**WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS**

**Cardiovascular Thrombotic Events**

- Nonsteroidal and inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use.
- COX-2 is contraindicated in the setting of coronary artery bypass graft (CABG) surgery.

**Gastrointestinal Bleeding, Ulceration, and Perforation**

- NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestine, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of gastric ulcer disease appear to be at greater risk for serious GI events.

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## Opioid-Sparing: Innovation

- Acetaminophen

Paracetamol (Acetaminophen)

- Penetrates the blood-brain barrier
- Blocks Cyclooxygenase (COX) in brain
- Blocks the formation and release of prostaglandins (PGE) in the central nervous system
- Inhibit the action of endogenous pyrogens on the heat-regulating centers in the brain
- Antipyretic effect

Rutkowski K, Nesser S M, & Ewan P W (2012). Paracetamol hypersensitivity: Clinical features, mechanism and role of specific IgE. *International Archives of Allergy and Immunology*. 159(1), 60-64. doi:10.1159/000335213

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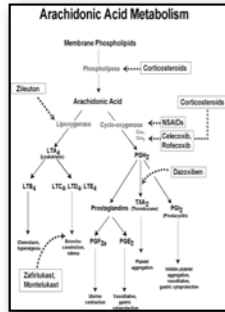
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**Acetanilide Derivative**  
(Acetaminophen) 1000mg IV Q4Hours

- MOA: Unclear
- Inhibit PG's Centrally
  - Unlike NSAIDs
    - Not a Peripheral COX-I Inhibitor




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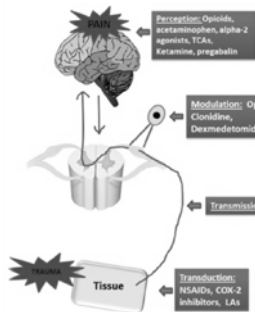
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**Opioid-Sparing: Innovation**



- Lidocaine
- Alpha-2 Agonists
- NMDA Antagonist
- GABA-type A
- Local Anesthetics
- Steroids
- Beta-Blockade

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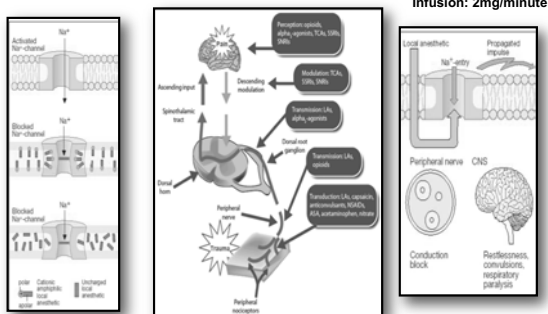
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**Lidocaine Infusion**




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## Lidocaine Infusion

### Key points

Infusion: 2mg/minute

- a **potent anti-inflammatory**, anti-hyperalgesic, and **gastrointestinal pro-peristaltic** drug.
- Level 1 evidence from gastrointestinal surgery demonstrates **decreased pain scores, opioid analgesic consumption, and side-effects**.
- Useful acute pain adjunct to achieve enhanced recovery after surgery outcomes.
- Patients may show particular benefit when they have **acute hyperalgesia**, when opioids are not effective in treating acute pain, or both.
- lidocaine infusions may be safely continued for several days after operation.

Intensive Medicine for acute pain: an evidence-based clinical update  
© 2014, 2015, 2016, 2017, 2018, 2019, 2020, 2021, 2022  
Intensive Medicine for Acute Pain, 2nd Edition, © 2014, 2015, 2016, 2017, 2018, 2019, 2020, 2021, 2022  
Intensive Medicine for Acute Pain, 2nd Edition, © 2014, 2015, 2016, 2017, 2018, 2019, 2020, 2021, 2022

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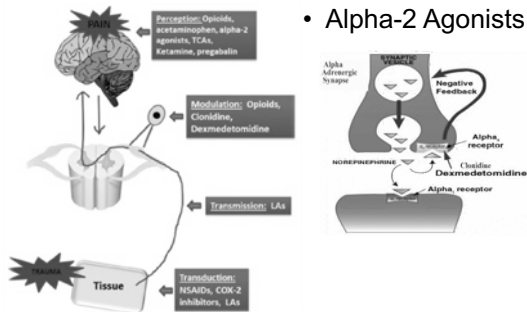
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## Opioid-Sparing: Innovation



### • Alpha-2 Agonists

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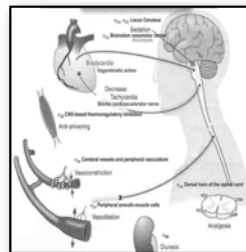
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## Alpha-2 Agonist (Clonidine, Dexmedetomidine)



Infusion: 0.3 mcg/Kg/Hr

- anti-hypertensive effect
- sedative, anxiolytic,
- analgesic
- side effects:
  - bradycardia
  - hypotension
  - sedation




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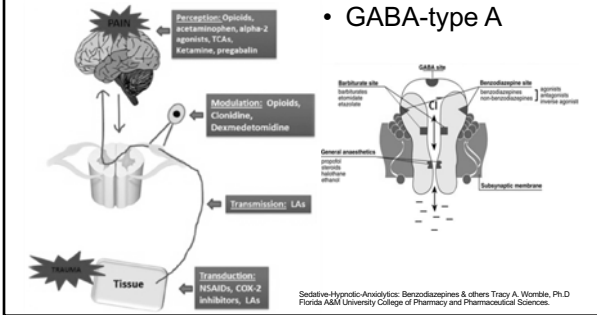
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## Opioid-Sparing: Innovation



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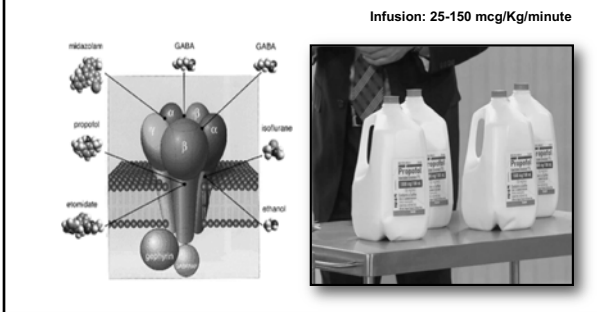
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## Sedative Hypnotic (Propofol)



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## Opioid-Sparing: Does it Work?



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## Opioid-Sparing: PCA

- Retrospective analysis N=297
- laparoscopic surgery for colorectal cancer
- Compared: **conventional opioid-based PCA post-operatively** to a **non-PCA group (intravenous anti-inflammatory drugs) PRN.**
- **No difference** in pain scores or use of rescue analgesia on POD 1-5.
- Another study, reported improved functional recovery with an ERP for CRS patients
- **IV PCA opioids went from 94% in historical controls (N = 179) to <5% after ERP implementation (N = 365)**
- **Overall opioid use was reduced by ~80%**
- no change in pain scores

Choi YY, Park JS, Park SY, Kim HJ, Yeo J, Kim JC, Park S, Choi GS. Can intravenous patient-controlled analgesia be omitted in patients undergoing laparoscopic surgery for colorectal cancer? Ann Surg Treat Res. 2015;88:86-91.

McEvoy MD SM, Gordon D, Grant S, Thacker JKM, Wu WL, et al.: American Society for Enhanced Recovery (ASER) and Perioperative Quality Initiative (POQI) Joint Consensus Statement on Optimal Analgesia within an Enhanced Recovery Pathway for Colorectal Surgery: Part 1 – From Preop to PACU. Perioper Med (Lond) 2016; xx: 00

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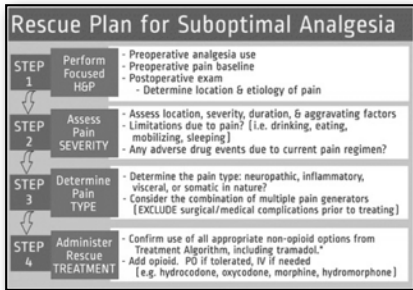
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## Opioid-Sparing: Rescue




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## Outcomes: Patient

Postoperative outcome	ERAS group (n = 68)	Conventional group (n = 98)	P
LOS days, median (range)	7.3 (6-19)	12 (7-61)	0.000
Readmission <sup>a</sup> (n)	0 (0)	6 (6.1)	0.098*
Reoperation <sup>a</sup> (n)	2 (2.9)	5 (5.1)	0.771
Dindo-Clavien classification <sup>a</sup> (n)			0.000 <sup>b</sup>
0	34 (50)	9 (9.2)	
I	16 (23.5)	39 (39.8)	
II	16 (23.5)	29 (29.6)	
III	2 (2.9)	20 (20.4)	
IV	0 (0)	1 (1.0)	
Total hospital costs <sup>a</sup> , median (range)	79790.40 (62753.88-131073.64)	102982.81 (83068.07-246688.32)	0.000

LOS: length of stay.  
<sup>a</sup> - Correction for continuity test.  
<sup>b</sup> - Fisher exact test.

Dai, J., Jiang, Y., & Fu, D. (2017). Reducing postoperative complications and improving clinical outcome: Enhanced recovery after surgery in pancreaticoduodenectomy – A retrospective cohort study. *International Journal of Surgery*, 39, 176-181. doi:10.1016/j.ijsu.2017.01.089

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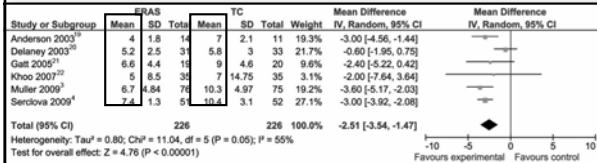
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### Length of Hospital Stay (days)

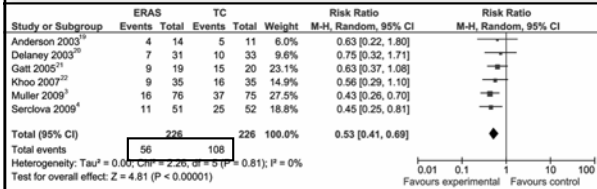


Experimental group= Enhanced Recovery After Surgery (ERAS)  
 Control = Traditional Care (TC)

**LOS Reduction: 2.54 to 3.54 Days**

Li, L., Shao, Y. F., & Zhou, Y. B. (2012). The enhanced recovery after surgery (ERAS) pathway for patients undergoing colorectal surgery: an update of meta-analysis of randomized controlled trials. *Int J Colorectal Dis*, 27(12), 1549-1554. doi: 10.1007/s00384-012-1577-5

### Complications

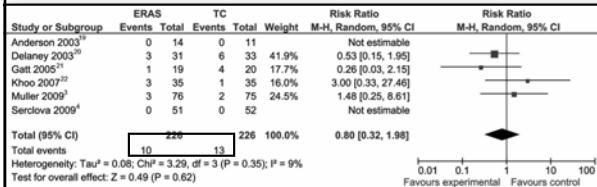


Experimental group= Enhanced Recovery After Surgery (ERAS)  
 Control = Traditional Care (TC)

**Total Complication Events: 48% reduction overall**

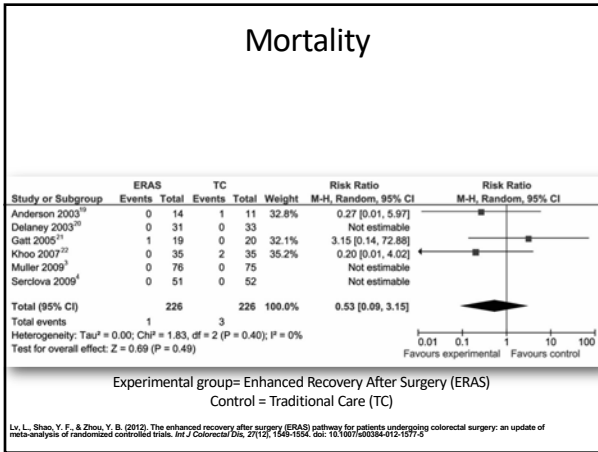
Li, L., Shao, Y. F., & Zhou, Y. B. (2012). The enhanced recovery after surgery (ERAS) pathway for patients undergoing colorectal surgery: an update of meta-analysis of randomized controlled trials. *Int J Colorectal Dis*, 27(12), 1549-1554. doi: 10.1007/s00384-012-1577-5

### Readmissions (days)



Experimental group= Enhanced Recovery After Surgery (ERAS)  
 Control = Traditional Care (TC)

Li, L., Shao, Y. F., & Zhou, Y. B. (2012). The enhanced recovery after surgery (ERAS) pathway for patients undergoing colorectal surgery: an update of meta-analysis of randomized controlled trials. *Int J Colorectal Dis*, 27(12), 1549-1554. doi: 10.1007/s00384-012-1577-5




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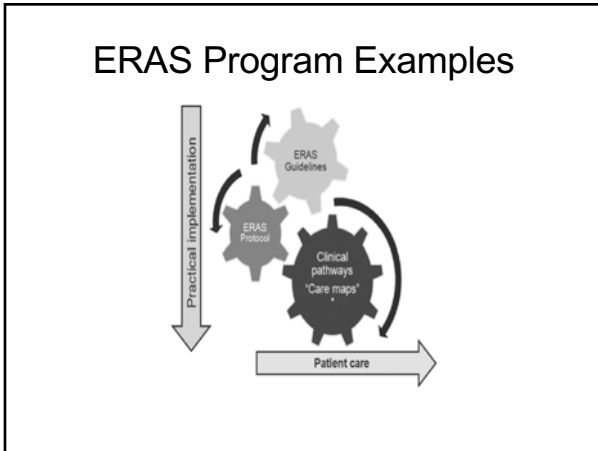
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**Andrew Hill**  
 Colorectal Surgeon  
 Middlemore Hospital, University of Auckland

Auckland Enhanced Recovery After Surgery Group

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Outcomes Measured	ERAS Group (n = 50)	Control Group (n = 50)	P Value
<b>Intravenous fluids</b>			
Intra-operative	2 (1 – 8)	3 (1 – 7.5)	<0.0001†
First 3 days	2 (1 – 10)	6.5 (1 – 12)	<0.0001†
<b>Epidural analgesia</b>			
No. of patients	44 (89%)	38 (76%)	0.223‡
Duration of use (days)	2 (0 – 3)	3 (0 – 4)	<0.0001†
<b>Recovery</b>			
Days to 1 <sup>st</sup> full meal	1 (1 – 3)	2 (1 – 15)	<0.0001†
Days to passage of flatus	2 (0 – 8)	3 (0 – 18)	<0.0001†
Days to independent mobilisation	1 (1 – 3)	3 (1 – 7)	<0.0001†
<b>Day stay</b>			
No. admitted > 1 day before surgery	12 (24%)	29 (58%)	<0.0001‡
Postoperative stay (days)	4 (3 – 34)	6.5 (3 – 18)	<0.0001†
Total hospital stay (days)	4 (3 – 34)	8 (4 – 29)	<0.0001†
<b>Readmissions</b>			
No. patients readmitted	6	7	0.766‡

Auckland Enhanced Recovery After Surgery Group (2012). ERAS Program Implementation

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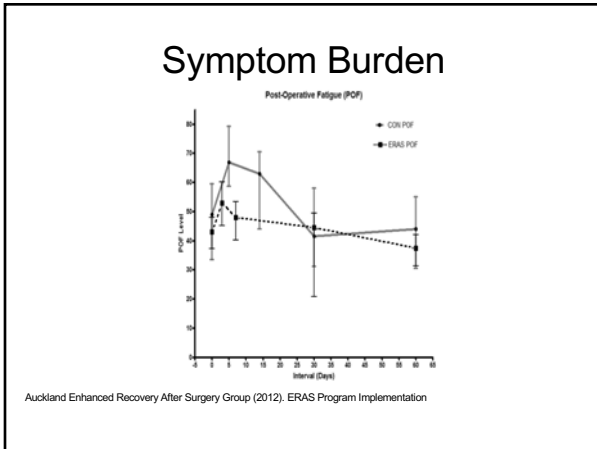
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### Differential cost analysis

(1<sup>st</sup> 50 patients)

(Savings on day stay and complications) = \$446,000

**minus**

(Full implementation + maintenance cost) = \$102,000

Profit/Loss

= \$446,000 – \$102,000

= \$344,000 Savings for 50 Patients

= **\$6880 per patient**

Auckland Enhanced Recovery After Surgery Group (2012). ERAS Program Implementation

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## Kelowna General Hospital

**British Columbia Enhanced Recovery After Surgery (ERAS) Collaborative  
Guidance on Mechanical Bowel Preparation**

[www.enhancedrecoverybc.ca](http://www.enhancedrecoverybc.ca)



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### The KGH ERAS Pilot Project: LOS

Number	Procedure	eLOS	aLOS
1	Transverse Colectomy	9 days	3 days
2	Resection Terminal Ileum	16 days	14 days
3	Anterior Resection (*)	9 days	4 days
4	Low Anterior Resection	9 days	5 days
5	Sigmoid Resection	9 days	4 days
6	Hemicolectomy	9 days	4 days



Kelowna General Hospital, British Columbia, Canada (2010), KGH ERAS Group

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### ERAS: After Colorectal Surgery Program Implementation

Kelowna General Hospital Colorectal Patient Length of Stay Starting 3/09/2010

ERAS March 4.1

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## ERAS: After Colorectal Surgery Program Implementation

Length of stay reduced from **12.8 to 4.0 days**.

Benefit/cost ratio: 2.18

**“anything great than 1, means benefits & costs are discounted at the opportunity cost of capital – project MUST be done”**

Return On Investment: **118%**

Estimated cost reduction of **48.4%**.

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## Outcomes: Financial

Event	Incidence	Cost per incident
Postoperative nausea and vomiting	15.0%	\$87.12
Postoperative ileus	15.6%	\$10,246.00
Postoperative urinary retention	2.1%	\$1,357.00
Postoperative respiratory depression	3.3%	\$568.00
Deep vein thrombosis	2.2%	\$4,159.00
Postoperative cognitive disorder	15.0%	\$2,500.00
Length of stay		\$2,084.00
30-day readmission	5.4%	\$11,200.00

Event	Traditional strategy	ERAS strategy
Respiratory depression	3.30%	0.00%
Postoperative nausea and vomiting	15.00%	7.80%
Postoperative ileus	15.60%	7.80%
Urinary retention	2.00%	0.00%
Mental status change	15.00%	3.00%
Deep vein thrombosis	2.20%	1.00%
30-day readmission	5.40%	0.00%
Length of stay	10.0 days	7.0 days
Cost per episode (probability)	\$1,379.38	\$247.68

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## Outcomes: Financial

Sensitivity Analysis: Assuming 100 Cases

Traditional Strategy	Incidence	ERAS Strategy
\$1,874.00	Respiratory Depression	***
\$1,306.80	PONV	\$653.40
\$249,132.00	Post-Operative Ileus	\$12,456.60
\$2,714.00	Urinary Retention	\$0.00
\$37,500.00	Mental Status Change	\$7,500.00
\$9,149.80	DVT	\$4,159.00
\$60,480.00	30-Day Readmission	\$0.00
\$619,200.00	Length of Stay	\$0.00
\$29,794.00	Direct Cost	\$142,830.00
\$1,011,150.60		\$167,599.00

A Factor of 6.0

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## Summary

- Public Health: Opioid Pandemic
- Opioid Crisis
- Non-Opioid Framework
- Non-Opioid Premise
- Non-Opioid Theory
- Non-Opioid Techniques
- Opioid Rescue
- Patient & Financial Outcomes

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