Opioid-Sparing Anesthesia: What Can We Learn from the Opioid Crisis?

Garry Brydges DNP, MBA, CRNA, ACNP-BC, FAAN
2019 WVANA Spring Meeting

Objectives

The learner will be able to:
• Describe the role of Opioid-Sparing Techniques in Anesthesia.
• Describe the outcomes achieved with opioid-sparing compared to traditional techniques.
• Differentiate the value of quality versus quantity of anesthesia through Opioid-Sparing Strategies

Opioids: Public Health Issue
Opioids: Public Health Issue

Opioid-related deaths, especially from synthetic opioids like Fentanyl, are on the rise in the U.S. By 2017, opioid deaths involving synthetic opioids (mainly Fentanyl and Heroin) outnumbered deaths involving natural and semi-synthetic opioids (mainly Opiates and Methadone).

3,000 X more potent than Morphine

What is Fentanyl? The Facts About the Opioid That Caused Prince’s Death

America’s Heroin Epidemic is Being Overtaken by Another Deadly Drug Addiction: Fentanyl
Philosophically

Dr. Charles Darwin

Is this ... "Social" Natural Selection?
Ethics versus Economics

DID THE FDA PLAY A ROLE IN THE OPIOID EPIDEMIC?

"Value" Based Healthcare Delivery
(Not Volume Based)
Quality (MACRA) NOT Quantity (FFS)

Value = \frac{Outcome}{Cost}

Efficacy  Safety

Quality  Resource tallies

$55$

$20$

$\text{Prescribing of opioids}$

1990s  2010s

\text{Big Pharma}

\text{Profits}
Why is this Important? ... Economists = MACRA

Medicare Access and CHIP Reauthorization Act

<table>
<thead>
<tr>
<th>Year</th>
<th>MIPS 2017</th>
<th>MIPS 2018</th>
<th>MIPS 2019</th>
<th>MIPS 2020</th>
<th>MIPS 2021</th>
<th>MIPS 2022</th>
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</tr>
</tbody>
</table>

+5% bonus (excluded from MIPS)

Opioids: Public Health Issue

- How did we get here?
  - Imbalance Serotonin - Octopamine


- Addiction: disrupting the positive feedback loop
  - Initial dose: exhilarating, but only with drug level threshold
    - Stopping:
      - Drug level drops
      - Toxins rise
    - Anxiety Centers: HYPER-RESPOND
    - Human Behavior: Fixing problem is easy

Opioids: Why Avoid?

1. Tolerance
2. Dependence
3. Addiction

What Can You Do?

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
The Evidence

Opioid-induced hyperalgesia: Cellular and molecular mechanisms

Laurel-Anne Recherche, Glaron-Marie Le Coz, Claire Genevieve-Ruff and Frederic Simonin
Neuroscience, 2015-12-05, Volume 336, Pages 160-162, Copyright © 2015 BMJ

The Evidence

Opioid-induced hyperalgesia: Cellular and molecular mechanisms

The Mechanism of Hyperalgesia and Anxiety Induced by Remifentanil: Phosphorylation of GluR1 Receptors in the Anterior Cingulate Cortex by Jie Zeng, Sai Li, Chao Zhang. See more...

Journal of Molecular Neuroscience, 05/2015

The Evidence

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Increased Hyperalgesia and Proinflammatory Cytokines in the Spinal Cord and Dorsal Root Ganglion After Surgery and/or Fentanyl...

by Chang, Lu; Ye, Fang; Luo, Qianhua. See more...
The Evidence

Opioid-induced hyperalgesia: Cellular and molecular mechanisms

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Increased Hyperalgesia and Proinflammatory Cytokines in the Spinal Cord and Dorsal Root Ganglion After Surgery and/or Fentanyl... by Cheng Lu, Ye Fan, Luo, Quahu. See more...

Remifentanil-induced postoperative hyperalgesia: current perspectives on mechanisms and therapeutic strategies

Local and Regional Anesthesia. 2015 Oct 11;18(10).
### Opioid-Sparing: Underlying Premise

**Endogenous Chemicals Causing Pain**

- 5-HT = 5-hydroxytryptamine
- 5-HT1AR = 5-hydroxytryptamine 1A receptors
- 5-HT2AR = 5-hydroxytryptamine 2A receptors
- CB1R = cannabinoid CB1 receptors
- CGR = cholecystokinin octapeptide
- COX-2 = cyclooxygenase-2
- CB1F = cannabinoid releasing factor
- GABA = γ-aminobutyric acid
- GDNF = glial cell derived neurotrophic factor
- GFRA-1 = GFRA family receptor α-1
- HAV-1 = intracellular adhesion molecule-1

- IL-4 = interleukin-4
- IL-15 = interleukin-15
- NK1 = neurokinin 1
- NOSF = nociceptin/orphanin FQ
- p38 MAPK = p38 mitogen-activated protein kinase
- PGE2 = prostaglandin E2
- p-GluN1 = phosphorylated GluN1
- TNF-α = tumor necrosis factor-α

**Inflammation: Tumorigenesis**

- **Immunoeediting**: tumor cell eradication by immune system

1. **Elimination**: non-self >>> destroy
2. **Equilibrium**: tumor – antitumor balance
3. **Escape**: immune suppression >>> imbalance
Inflammation: Tumorigenesis

• Surgery Causes:
  – Tissue Damage
  – Severe Pain
  – Immunosuppression (Profound)
  – Postoperative cancer recurrence

Opioids

• Contribute to:
  – Promoting Inflammation
  – Impaired Immune Function
  – Contribute to Cancer Metastasis

Inflammation: Tumorigenesis

• Inflammatory Mechanism causes:
  1. Nuclear transcription factor (NF-ab) release
  2. IL-6, IL-1β, TNF-α
  3. Angiogenic factors (VEGF)
  4. COX-2
  5. Src gene activation (tumor promotion)

* May play a role in tumor progression and metastasis
Inflammation: Tumorigenesis

- Inflammatory Mechanism causes:
  - Pro-oncogene c (Src) gene activation:
    - Tumor promoting gene activation
    - Promotes metastasis via
      - Upregulation intracellular adhesion molecule (ICAM-1) promoting neoplastic extravasation =>> Metastasis
    - IL-6 modulate non-cancer stem cells to cancer stem cells in breast cancer contributing to metastasis


Inflammation: Tumorigenesis

- Natural Killer (NK) Cells
  - Tumoricidal effects on neoplastic cell prevents tumor progression
  - Prevents metastasis

Opioids Blunt NK Activity
Dose Dependent


Why Avoid Opioids?

Role of Opioids

- Promotes:
  - Angiogenic stimulus for tumor vascularization
  - Increase in VEGF, Src Gene Activation
  - Increased NOS, NO, COX-2
  - Increased metastasis (solid tumors)

- MOR expression in lung cancer contributes to metastasis

- **silencing** the expression of the μ-opioid receptor (MOR) in lung cancer cells **inhibits lung metastasis** by about 75%.


Opioid-Sparing: Framework

Opioid-Sparing: Innovation
**Opioid-Sparing: Theory**

- **Regional Anesthesia**
  - Controversy M & M

- **Pre-emptive Analgesia**
  - Prevent “pain” sensitization
  - Controversy
    - Regional Anesthesia
    - Agents?
    - Research: Poor!


**Opioid-Sparing: Innovation**


**Opioid-Sparing: Theory**

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

- **Modulation & Feedback**
  - Agonist/Antagonists
  - Transporter Proteins
  - Synergism Theory
Opioid-Sparing: Innovation

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

Liposomal Bupivacaine: Background

Medication Dosing

- Liposomal Bupivacaine 266mg/20ml (13.3mg/ml)
- Dilute: up to 280ml sterile saline (300 ml Total)
  - With Free Bupivacaine: < 50% Liposomal Dose
  - Typical total volume 40ml to 60ml

"Bupivacaine HCl may be administered immediately before EXPAREL or admixed in the same syringe, as long as the ratio of the milligram dose of free bupivacaine HCl to EXPAREL does not exceed 1:2"
**Bupivacaine Comparison**

<table>
<thead>
<tr>
<th>Liposomal</th>
<th>Free</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset: 5 minutes</td>
<td>Onset: 5-10 minutes</td>
</tr>
<tr>
<td>Peak Onset: 30-120 minutes</td>
<td>Peak Onset: 30-45 minutes</td>
</tr>
<tr>
<td>Half-Life: 24-34 Hours</td>
<td>Half-Life: 3.5 Hours</td>
</tr>
<tr>
<td>Duration: 24 Hours (Local) &amp; 66 Hours (Systemic)</td>
<td>Duration: 6-8 Hours</td>
</tr>
</tbody>
</table>

**Surgical Wound Infiltration**

![Image of surgical wound infiltration](http://example.com/image1.png)

**Lidocaine Infusion**

Infusion: 2mg/minute

![Image of lidocaine infusion](http://example.com/image2.png)
Lidocaine Infusion

Infusion: 2mg/minute

Key points
- 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.

IV Lidocaine

- Rimback et al: decrease POI & Visceral Pain
- Potent Anti-Inflammatory
  - Enhanced NK Cell activity
  - Decrease IL-β, IL-6, IL-8, ICAM-1, Src
  - Inhibits prostanoids, thromboxane, leukotrienes, and downregulates VGSC

- Inhibits human adenocarcinoma cell migration & proliferation
  - Due to Src Kinase inhibition

- Increase DNA methylation
  - Causes: Tumor activity suppression
  - Decrease breast cancer cells (estrogen pos & neg)

Infusion: 2mg/minute


Opioid-Sparing: Innovation

- Gabapentinoids


Opioid-Sparing: Innovation

- NSAIDS
- COX-2 Inhibitors


NSAIDs and COX-2 Inhibitors

- Reduce COX-2 and prostaglandins
- Breast Cancer & Colon Cancer
  - Reduced metastatic cancer: breast surgery
    - 20% Relative/10% Absolute reduction
  - Aspirin reduced metastatic colon cancer
  - COX-2 reduction
    - Decreased lung adenocarcinoma

Opioid-Sparing: Innovation

- Acetaminophen

Rutkowski, K., Nasser, 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

Acetanilide Derivative (Acetaminophen)

1000mg IV Q6 Hours

- Pharmacodynamic Profile
- IV is Superior: Why?
  - IV 70% Availability

Res ipsa loquitur

Opioid-Sparing: Innovation

- Alpha-2 Agonists
- NMDA Antagonist
- GABA-type A
- Local Anesthetics
- Steroids
- Beta-Blockade
Opioid-Sparing: Innovation

• Alpha-2 Agonists

Alpha-2 Agonist (Clonidine, Dexmedetomidine)

• anti-hypertensive effect
• sedative, anxiolytic, analgesic
  – Modulation Pain Pathway
• side effects:
  1. Bradycardia
  2. Hypotension
  3. Sedation

Infusion: 0.3 mcg/Kg/Hr
Alpha-2 Agonist
(Clonidine, Dexmedetomidine)

• Analgesic, sedative
  – Not studied to date for immune modulation

Infusion: 0.3 mcg/Kg/Hr

Opioid-Sparing: Innovation

• NMDA Antagonist

Infusion: 10 mg/Hr

NMDA Receptor Antagonist
(Ketamine)

Infusion: 10 mg/Hr
NMDA Receptor Antagonist (Ketamine)

Infusion: 10 mg/Hr

“survived the strong winds of time”

Wide variety of clinical applications & newly found effects;
1. Neuroprotective
2. Anti-inflammatory
3. Anti-tumor Effects

“usefulness of low dose ketamine regimens have helped to widen the clinical application profile of ketamine.”

NMDA Receptor Antagonist (Ketamine)

Infusion: 10 mg/Hr

• Activates the innate immune function
• Significantly reduced lung metastasis when administered prior to surgery
• Decrease: IL-6, TNF-α
• Optimizes NK cells (benefit)
  – Doses as low as 0.15 mg/kg

Opioid-Sparing: Innovation

• GABA-type A

**Sedative Hypnotic**

(Propofol)

Infusion: 25-150 mcg/Kg/minute

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**Traditional Methodology: Direct Cost**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cost per Unit</th>
<th>Units</th>
<th>Total Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>$2.40</td>
<td>1</td>
<td>$2.40</td>
</tr>
<tr>
<td>Famotidine</td>
<td>$2.53</td>
<td>1</td>
<td>$2.53</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>$8.00</td>
<td>3</td>
<td>$24.00</td>
</tr>
<tr>
<td>Propofol</td>
<td>$2.30</td>
<td>1</td>
<td>$2.30</td>
</tr>
<tr>
<td>Cis-Atracurium</td>
<td>$24.40</td>
<td>3</td>
<td>$73.20</td>
</tr>
<tr>
<td>Glycopyrrolate</td>
<td>$46.75</td>
<td>1</td>
<td>$46.75</td>
</tr>
<tr>
<td>Neostigmine</td>
<td>$52.85</td>
<td>1</td>
<td>$52.85</td>
</tr>
<tr>
<td>Desflurane</td>
<td>$6.99</td>
<td>6</td>
<td>$41.94</td>
</tr>
<tr>
<td>Crystalloid</td>
<td>$1.95</td>
<td>3</td>
<td>$5.85</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>$0.70</td>
<td>2</td>
<td>$1.40</td>
</tr>
<tr>
<td>Bupivicaine</td>
<td>$36.64</td>
<td>1</td>
<td>$36.64</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>$8.08</td>
<td>1</td>
<td>$8.08</td>
</tr>
<tr>
<td><strong>Total Cost</strong></td>
<td></td>
<td></td>
<td><strong>$297.94</strong></td>
</tr>
</tbody>
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**ERAS Methodology: Direct Cost**

(The Alternative)

<table>
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<tr>
<th>Drug</th>
<th>Cost per Unit</th>
<th>Units</th>
<th>Total Cost</th>
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<tbody>
<tr>
<td>Gabapentin</td>
<td>$12.00</td>
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<td>$12.00</td>
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<tr>
<td>Celebrex</td>
<td>$4.15</td>
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<td>$4.15</td>
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<tr>
<td>Tramadol</td>
<td>$7.15</td>
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<td>$7.15</td>
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<tr>
<td>Acetaminophen</td>
<td>$39.40</td>
<td>3</td>
<td>$118.20</td>
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<td>Alvimopan</td>
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<td>$700.00</td>
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<tr>
<td>Domperidone</td>
<td>$31.92</td>
<td>1</td>
<td>$31.92</td>
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<tr>
<td>Propofol</td>
<td>$2.30</td>
<td>9</td>
<td>$20.70</td>
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<tr>
<td>Ketamine</td>
<td>$21.24</td>
<td>3</td>
<td>$63.72</td>
</tr>
<tr>
<td>Lidocaine 0.4%</td>
<td>$2.53</td>
<td>1</td>
<td>$2.53</td>
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<tr>
<td>Albumin 5%</td>
<td>$81.72</td>
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<td>$245.16</td>
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<tr>
<td>Glycopyrrolate</td>
<td>$46.75</td>
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<td>Neostigmine</td>
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<td>$52.85</td>
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<td>Crystalloid</td>
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<tr>
<td>Ondansetron</td>
<td>$0.70</td>
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<td>Bupivicaine</td>
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<td>Liposomal Bupivicaine</td>
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<td>Hydromorphone</td>
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<tr>
<td><strong>Total Cost</strong></td>
<td></td>
<td></td>
<td><strong>$1,428.30</strong></td>
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</table>
Variable Cost of Adverse Drugs Events (ADE)

- PONV
- Ileus
- Respiratory Depression
- Immobility/DVT
- Urinary Retention
- Mental Status Change
- Increased LOS
- 30 Day Readmission

Post-Operative Nausea & Vomiting (PONV)

- 15%-33% occurrence surgical outpatients
- Adjusted incremental cost $75 (95% CI - $67-$86) per patient
  - $87.12 per patient today
- Average Delayed Discharge by 60 minutes (234 min. versus 171 min.)
- Lasting Effects: up to 72 hours
- Quality of Life: lower for PONV – The Intangible
  - Only 49% rate 1 for PONV versus 94% rated 1 for POD 1 to 3
  - Most Patients experiencing PONV at 72 hours
Post-operative Ileus (POI)

- **Occurrence:** 10-40% in patients undergoing Radical Cystectomy
  - Average Occurrence Rate: 15.6%
  - POI contributes to 50-70% of all complications
  - Increases LOS: mean of 4 days (Range: 3-10 days)
  - Doubles the cost of Hospital Stay
- **Cause:** Opioid binding to gastrointestinal mu-receptors
- **Additional Overall Cost due to POI:** $10,246.00 per event

- **Prevention:** Alvimopan which binds to gastrointestinal mu-receptors
- **Direct Cost:** $700 per hospital stay
- **Results:** 50% Rate Reduction in POI to 7.8%

Respiratory Depression: ORAE
Respiratory Depression:

- N = 319,898
- Incidence: 3.3% (12.2% Overall)
- Cost: $155.33 per patient
- LOS: 3.3 Days
- 30-Day Readmission: 6.4%

Post-Operative Urinary Retention (POUR)

- Occurrence: 2.1%, based on the Surgical Care Improvement Project
  - Sample Size: 415,409 surgical patients
  - Study: 43,030 developed POUR
  - POUR Contributed 9.2% of Urinary Tract Infections
  - Increases LOS: mean of 1.1 days
  - CAUTI Literature: $1357 per incidence
Variable Cost Benchmarks

Incidence: Variable Cost Per Episode

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Cost Per Episode</th>
<th>Probability</th>
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<tbody>
<tr>
<td>Respiratory Depression</td>
<td>$568.00</td>
<td>3.30%</td>
</tr>
<tr>
<td>PONV</td>
<td>$87.12</td>
<td>15.00%</td>
</tr>
<tr>
<td>Post-Operative Ileus</td>
<td>$10,247.00</td>
<td>15.60%</td>
</tr>
<tr>
<td>Urinary Retention</td>
<td>$1,357.00</td>
<td>2.00%</td>
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<tr>
<td>Mental Status Change</td>
<td>$2,500.00</td>
<td>15.00%</td>
</tr>
<tr>
<td>DVT</td>
<td>$4,159.00</td>
<td>2.20%</td>
</tr>
<tr>
<td>30-Day Readmission</td>
<td>$11,200.00</td>
<td>5.40%</td>
</tr>
<tr>
<td>Length of Stay</td>
<td>$2,064.00/Day</td>
<td>10.0 Days</td>
</tr>
</tbody>
</table>

Cost Benefit & Cost Effectiveness

A Factor of 5.6

<table>
<thead>
<tr>
<th>Traditional Strategy</th>
<th>Incidence</th>
<th>Opioid Sp</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.00%</td>
<td>Pruritus</td>
<td>0.00%</td>
</tr>
<tr>
<td>3.30%</td>
<td>Respiratory Depression</td>
<td>0.00%</td>
</tr>
<tr>
<td>15.00%</td>
<td>PONV</td>
<td>7.50%</td>
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<tr>
<td>15.60%</td>
<td>Post-Operative Ileus</td>
<td>7.80%</td>
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<tr>
<td>2.00%</td>
<td>Urinary Retention</td>
<td>0.00%</td>
</tr>
<tr>
<td>15.00%</td>
<td>Mental Status Change</td>
<td>3.00%</td>
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<tr>
<td>2.20%</td>
<td>DVT</td>
<td>1.00%</td>
</tr>
<tr>
<td>5.40%</td>
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<td>0.00%</td>
</tr>
<tr>
<td>10.0 Days</td>
<td>Length of Stay</td>
<td>7.00 Days</td>
</tr>
</tbody>
</table>

$1,379.38 Cost Per Episode (Probability) $247.69
Summary

- Public Health: Opioid Pandemic
- Opioid Crisis
- Non-Opioid Framework
- Non-Opioid Premise
- Non-Opioid Theory
- Non-Opioid Techniques
- Opioid Rescue