

New Treatment Modalities in PONV

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PONV: The What, How, and Why.....

The WHAT....	PREVALANCE.....	CONSEQUENCES.....
PONV is the most common adverse side effect of Anesthesia Defined as Nausea, Retching, or Vomiting withing 24 hours of surgery	30% of ALL patients suffer from PONV in the post-op period 80% of all High-Risk patient suffer from PONV	Extended PACU time Increased Pain Complications (Aspiration, bleeding, hospital admission) Patient Satisfaction

RISK FACTORS FOR PONV

APFEL RISK SCORE PREDICTORS:

- Females
- Non-smokers
- A history of PONV or motion sickness
- Patients who are treated with opioids

APFEL SCORE:

Risk Level Per # of Traits

- 0-1 Low Risk
- 2 Medium Risk
- 3+ High Risk

APFEL SCORE:

Number of Risk Factors

4	80%	3+ agents
3	60%	
2	40%	2+ agents
1	20%	
0	10%	1+ agents

Incidence of PONV in Patients Undergoing General Anesthesia

References: 1. Gan TJ, Belmont RL, Berger S, et al. Anesth Analg. 2003;100(2):463-468.

Research Says.....

Study Looking at Outpatient Surgery Center showed losses of \$284,000 secondary to PONV

2nd Study estimated a cost of \$15,000 per PONV event that required admission.

Looking at ROI, the cost of prophalaxis far outweighs the cost of a PONV event.

What Does the Data show....

Relative Importance of Patient Postoperative Recovery Concerns (%) (N=220)

■ PONV
■ Pain
■ Alertness
■ Additional cost

PONV

- The most common reason for poor patient satisfaction during the perioperative period?
- A greater concern for some patients than pain, alertness, or additional cost^{1,3}

PONV: What does it Really Cost Us

- Research shows that PONV is the highest rank cause of patient dissatisfaction in the post-op period.
- PONV increases LOS in the PACU and increases number of unplanned admissions to the hospital.
- Patient Complications
 - Aspiration
 - Pain
 - Bleeding
 - Dehydration
 - Electrolyte Imbalances

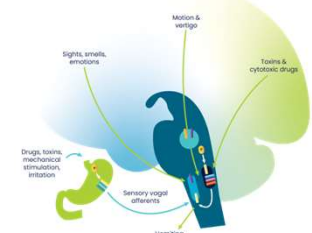


The Pathophysiology

- Chemo-Trigger Zone (CTZ) is the control center for PONV receptors
- Multiple Triggers for PONV
 - History
 - Type of Surgery
 - Type of Anesthesia
 - Need for post-op opioids
- Multi-modal approach to PONV prophylaxis is Essential
- Despite all treatments, 30% of patients will still have PONV

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The Brainstem: The Center for PONV



- NK₁ Receptor
- Muscarinic Receptor
- 5HT₃ Receptor
- 5HT₁ Receptor
- D₁ Receptor
- H₁ Receptor

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Treatment Modalities

Cholinergic/Muscarinic Receptor Antagonist

- Scopolamine
- Atropine

Histamine Receptor Antagonist

- Pepcid
- Benadryl

5HT₃ Receptor Antagonist

- Ondansetron
- Granisetron
- Dolasetron
- Ramosetron

NK-1 Receptor Antagonist

- Aprepitant

Dopaminergic Receptor Agonist

- Droperidol
- Haloperidol
- Metoclopramide
- Halidol

Corticosteroids

- Decadron
- Solu-Medrol

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High Risk Procedures related to PONV

Strabismus and other Eye Related Surgery

Tympanoplasty or other inner ear Surgery

Breast Surgery

- Mastectomy
- Lumpectomy
- Augmentation

Laparoscopic Surgery (including Robotic)

- Cholecystectomy
- Appendectomy
- Gastric Bypass or Gastric Sleeve
- Bowel Resection
- Etc.

Obstetric and Gynecology Surgery

- Hysterectomy
- Ovarian
- Etc.

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Multi-Modal Approach to PONV

- Research shows that in high risk patients a multimodal approach is essential to prevention
- Administration of >3 agents decreases the incidence of PONV to 25%
- The Anesthetic matters
 - Regional Anesthesia
 - TIVA Anesthesia
 - Propofol
 - Precedex
 - No Inhalation Agents or N2O
- DO NOT Rescue with a drug that has already been used for prophylaxis,

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Current PONV Prophylaxis

Drug group	Drugs	Dose	Timing	Adverse effect
Serotonin (5-HT ₃) receptor antagonists	Ondansetron	4-8 mg intravenously (IV) every 4-8 hours	End of surgery	Headaches, constipation, flushing, fatigue, malaise, raised liver enzymes
	Granisetron	1-2 mg IV		
	Ramosetron	0.3 mg IV		
Corticosteroids	Pakrosseton	0.075-0.25 mg IV	After induction of anesthesia	Elevated blood glucose level, diabetes mellitus, hypertension/hypertension
Butyrophenone	Droperidol	0.625-1.25 mg IV	After induction of anesthesia	Psychomotoric effects, extrapyramidal side effects, Parkinson's disease, malaise, light-headedness, prolong of QT interval
	Decamethasone	4-10 mg IV		
Neuroleptic antagonists (NK ₁ receptor)	Aprepitant	40 mg orally	2-3 hours prior to induction	Headaches, constipation, fatigue
	Apoprime	32 mg IV	After induction of anesthesia	
Anticholinergics	Transdermal patch	0.3-0.6 every 24 hours	Evening prior to surgery or in preoperative period	Dizziness, dry mouth, visual disturbances, tachycardia, confusion, urinary retention
	Scopolamine	10-20 mg IV	15-30 minutes prior to end of surgery	Sedation, hypotension (fast injection), headache, extrapyramidal symptoms
Dopamine antagonists	Metoclopramide	5-10 mg IV	Attribution of anesthesia	
Histamine antagonists	Benadryl	12.5-25 mg IV	Attribution of anesthesia	

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NK-1 Receptor Antagonist

- **Aponvie** (aprepitant)
- Only NK-1 Receptor Antagonist Agent
- Crosses the BBB blocking Substance-P at the P₃ receptor
- IV push 32mg
- Onset is 5 min.
- Efficacy is up to 72 hours
- Peak plasma concentration is 2,029ng/ml



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NK-1 Receptor Antagonist (cont.)

- **Emend** (Aprepitant)
- Only NK-1 Receptor Antagonist Agent
- PO dose (40mg)
- Onset is 2-3 hours
- Efficacy up to 72hours
- Peak plasma concentration is 542ng/ml
- Most Common Side Effect is Constipation (9%)



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Research Study: Aprepitant Outperformed Multimodal PONV Therapies

- Study Assessed Efficacy in patients receiving Epidural Morphine
- One group of patients received ondansetron and dexamethasone, combined with either metoclopramide, diphenhydramine, or prochlorperazine
- The other group received **only** oral aprepitant preoperatively
- **Aprepitant used as a single agent significantly reduced the incidence of PONV compared to a multimodal antiemetic regimen**
 - **75%** of patients who received Aprepitant experienced **No PONV**
 - **ONLY 25%** of patients who received the multimodal therapy experienced **No PONV**.

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The Gold Standard in PONV

5-HT₃ Antagonist Agents

- Zofran
- Granisetron

Can be used either for prophylaxis or rescue

- Understand that if used for prophylaxis then only 20% efficacy for rescue

Use with caution in patients with QT elongation

- EKG Monitoring required

More Effective against Vomiting vs. Nausea



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Research: What does it say for 5HT-3

893 patients; Comparing Ramosetron and Ondansetron

Ramosetron noted as the most effective 5HT-3 antagonist

Ondansetron the most utilized 5HT-3 agent

Data showed no statistical difference in PONV rate at 24 hours

Data did show that 0-2 hours that Ramosetron has a higher efficacy than ondansetron

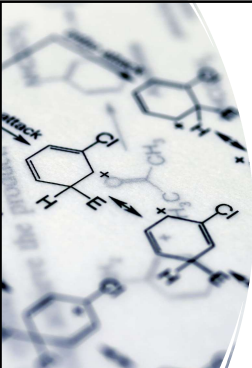
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Dopamine Receptor Antagonist

- Long Standing antiemetic Reinvented
 - Halodol
 - Droperidol
- Act on D₁, D₂, and D₃ Receptors
- Dose .625mg-.125mg IV
- Has some alpha antagonist effects causing decrease in SBP
- Sedation and Anxiolytic Effects
- Can be used for prophylaxis or for rescue



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Comparing the Dopamine Receptor Antagonist

- Highly protein bound except Barhemsys
- Can Selectively or unselectively act on D₁, D₂, and D₃ receptors
- 1.25mg is superior to .625mg IV
- .625mg with Zofran 4mg have the same efficacy as 1.25mg (62%-63%)
- Does have extrapyramidal side effects
- Black Box warning of QT elongation was at doses of 5mg.
- Promethazine is effective but side effects make it undesirable

Cholinergic/Muscarinic Antagonist



- Scopolamine
- For PONV the Transdermal Patch is the best route
- Onset in 1-2 hours
- Last for up to 3 days
- Make patients aware that they need to wash hands after removal
- Side Effects
 - Dry Mouth
 - Headache
 - Blurred Vision
 - Confusion in Geriatric patients

Cochrane Meta-Analysis

44 single agent treatments and 51 multi-agent combination treatments evaluated

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585 studies and 97,516 patients

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Most effective single dose treatments

Aprepitant

Ramosetron

Granisetron

Dexamethasone

Ondansetron

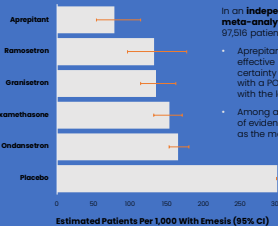
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Aprepitant is more effective than most combination treatments

NK-1 RECEPTOR ANTAGONIST :

The True culprit in PONV

Cochrane Meta-Analysis: Ranking of most effective single-agent prophylactic with high-confidence evidence through 24 hours



In an **Independent 2020 Cochrane meta-analysis** of 585 studies and 97,516 patients:

- Aprepitant was ranked as most effective single agent with high certainty of evidence among drugs with a PONV prophylactic indication, with the lowest rate of vomiting.
- Among agents with a high certainty of evidence, aprepitant was ranked as the most effective single agent

META-ANALYSIS (CONT.)

Drug	Vomiting & Nausea	SSR	Any AE	Headache	Constipation	Extrapyramidal symptoms	Isolation	Arrhythmia	QT prolongation	Wound infection	Visual disturbances
5HT₃ antagonists											
Ondansetron	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Granisetron	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ramosetron	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Palonosetron	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Benadryl	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
D₂ receptor antagonists											
Haloperidol	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Prochlorperazine	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Metoclopramide	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Benadryl	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5HT₃ receptor antagonists											
Ondansetron	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Granisetron	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ramosetron	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Palonosetron	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Anticholinergics											
Scopolamine	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Benadryl	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Other											
Acupressure	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

- Granisetron and Barhemsys had the lowest incidence of side effects
- Scopolamine and Benadryl had the highest incident of side effects.

What Can Pre-op Do to Prevent PONV

- Perform a Thorough Pre-up
- Notifying anesthesia if a patient has a history of PONV.
- Preop modalities
 - **Pepcid** (if active heartburn)
 - **Scopolamine Patch**
 - **Emend** (>1hr before transport to OR then PO, if < 1hr **Aponvie**)
 - If SAB or Epidural is the planned anesthetic , then **500ml fluid bolus**
- Communication with CRNA or Anesthesiologist



RESCUE: How do we Approach?

- **The Facts**
 - Rescuing with an agent that was used for prophylaxis fails 80% of the time
 - Use an agent that has not been used.
 - Be progressive and ask for newer agents
- **Best Agents**
 - Barhemsys: 10mg IV Only FDA approved agent for Rescue
 - Selective D₂-D₃ antagonist
 - Unlike other Dopaminergic Agents does not cause sedation or hypotension
 - Aponivie: 32mg IV "Off Label Use"
 - NK-1 Receptor Agonist
 - 5min onset with peak plasma concentration 4x that of the PO
 - Droperidol: .625mg-1.25mg
 - Causes Sedation, hypotension, and potential QT elongation

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A New Approach: PONV Rescue

- **Barhemsys (amilsulpride)**
 - Selective D₂-D₃ Receptor Antagonist
 - At PONV dose targets the limbic vs striatal structures
 - Elimination Half-life is 4-5 hours
 - Can Redose every 10 hours
 - 72% Efficacy in 0-2 hours post-op
 - Most-common side effect was Site-Injection Pain (6%)
 - Dose is 10mg IV over 1 minute
- **ONLY** FDA approved agent for PONV Rescue



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