PONV and The Role of Therapeutic Decision Support

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Content

- Contributing Factors
- Risk Assessment and Stratification
- Review Antiemetic Armamentarium
- Examine the Role of Multi-modal Therapy
- Cost Effectiveness of Antiemetics
- Review of Hot Topics

Incidence of PONV

- Overall range - 20% to 30%[1]
- Outpatient range - 20% to 80%, depending on the patient population[2]
- Study Variability

1. Watcha and White. ***Anesthesiology*** **1992;77(1):162-184.**
2. Natof et al. In: Wetchler, ad. ***Anesthesia for Ambulatory Surgery*** **2nd ed. 1991:chap 8.**

Contributors to PONV

- Patient characteristics
- Surgical factors
- Choice of anesthetic agent
- Anesthesia techniques
- Postoperative factors

No control over

Some control over

Adapted from Philip BK. Etiologies of postoperative nausea and vomiting. *P & T* 1997;22 (suppl7S): 18S-25S.

Patient Factors Affecting Incidence of PONV

- History of PONV or motion sickness
- Age (younger)
- Gender (female)
- Obesity
- Anxiety
- Concomitant Disease i.e., Gastroparesis
- Non-smokers

Watcha and White. *Anesthesiology* 1992;77(1):162-184. Sinclair et al. Anesthesiol. 1999;91:109-118

Surgical Factors

- Duration of surgery
  - > 1 Hour
- Surgical site and procedure
  - ENT: Middle Ear Vestibular Afferents 38-48%
  - Adenotonsillectomy 36-76%
  - Ophthalmic Strabismus 10% Early, 60% Delayed
  - Gynecologic D&C > C
  - Laparoscopy 40 - 77%
  - Breast Surgery
  - Shoulder Surgery
  - Abdominal Wall 15% vs. Intra-abdominal 70%
  - Plastic and Reconstructive
  - Dental

Lerman. Br J Anaesth 1992;69(suppl 1):24S-32S. Plazzo and Strunin, Can Anaesth Soc J 1984;31:178-187. Watcha and White. *Anesthesiology* 1992;77(1):162-184. Andrews. *Br J Anaseth* 1992;69 (suppl 1):2S-19. S Stein. *Plast Reconstruct Surg* 1982;70(4):505-511. Hill, Kovac, Gan, Sinclair et al. *Anesthesiology* 1999;19109-118.

Anesthetic Factors Affecting Incidence of PONV

- Premedications
- Anesthetic agents
- Duration and depth of anesthesia
- Anesthesia technique

Watcha and White. *Anesthesiology* 1992;77(1):162-184.
Bonica et al. *Anesthesiology* 1958;19:532-540.

Choice of Anesthetic Agents

- Opioids
  - m opioid receptors – area postrema
  - Delay gastric emptying, sensitize CNVIII, stimulate release of vasopressin and serotonin
- Hypnotics (Etomidate >Ketamine>Thiopental > Propofol)
- Nitrous Oxide (Lonie vs. Hovorka)
- Potent Inhaled Agents (Isoflurane > Enflurane > Sevo $\geq$ Des)
- Neuromuscular Blockade Reversal
  - Acetylocholinesterase inhibitors (neostigmine) GI and Central
  - Anticholinergic agents: Glycopyrrolate (p) > Atropine (p & c)

Watcha and White. *Anesthesiology* 1992;77(1):162-184. Philip BK. *P&T* 1997 (suppl 7S):18S-25S. Hannallah RS, et al. *Anesth Analg* 1996;83-917-920. Fragen RJ, et al. *AAAnesthesiology* 1979:50:242-244. Thompson GE, et al. *Anesth Analg* 1973;52:881-897. Borgeat, et al. *Anesth Analg* 1992;74:539-541. King, et al. *BR J Anaesth* 1988;61:403-406. Salmenpera M, et al. *Acta Anaethesiol Scand* 1992;36:445-448.

Postoperative Factors Affecting Incidence of PONV

- Pain
  - Pelvic, visceral
- Dizziness
- Early ambulation (vestibular)
- Post Pain Management
  - Opioid administration
- Premature oral intake
  - PACU discharge criteria

Watcha and White. *Anesthesiology* 1992;77(1):162-184.

Medical Consequences of PONV

- Patient discomfort (mild to severe)
- Wound dehiscence
- Aspiration of vomit
- Electrolyte imbalance and dehydration
- Interruption in or delay of oral drug therapy, fluid intake, or eating

Watcha and White. *Anesthesiology* 1992;77(1):162-184. Andrews. *Br J Anaesth* 1992;69(suppl 1):2S-19S.

Simplified Risk Scoring

- Four predictors
  - Female gender
  - History of motion sickness/PONV
  - Non-smoking
  - Use of postoperative opioids
- Incidence of PONV

0 - 10%	3 - 61%
1 - 21%	4 - 79%
2 - 39%	

Apfel C et al. *Anesthesiology.* 1999:91:693-700.

Prophylactic Antiemetic Intervention Assessment Scale (T.J. Gan)

3 Points Each

- History of PONV
- History of motion sickness
- Gynecological laparoscopy
- Breast reconstruction

2 Points Each

- Facelift surgery
- Strabismus or middle ear surgery
- Neurosurgery
- Obesity

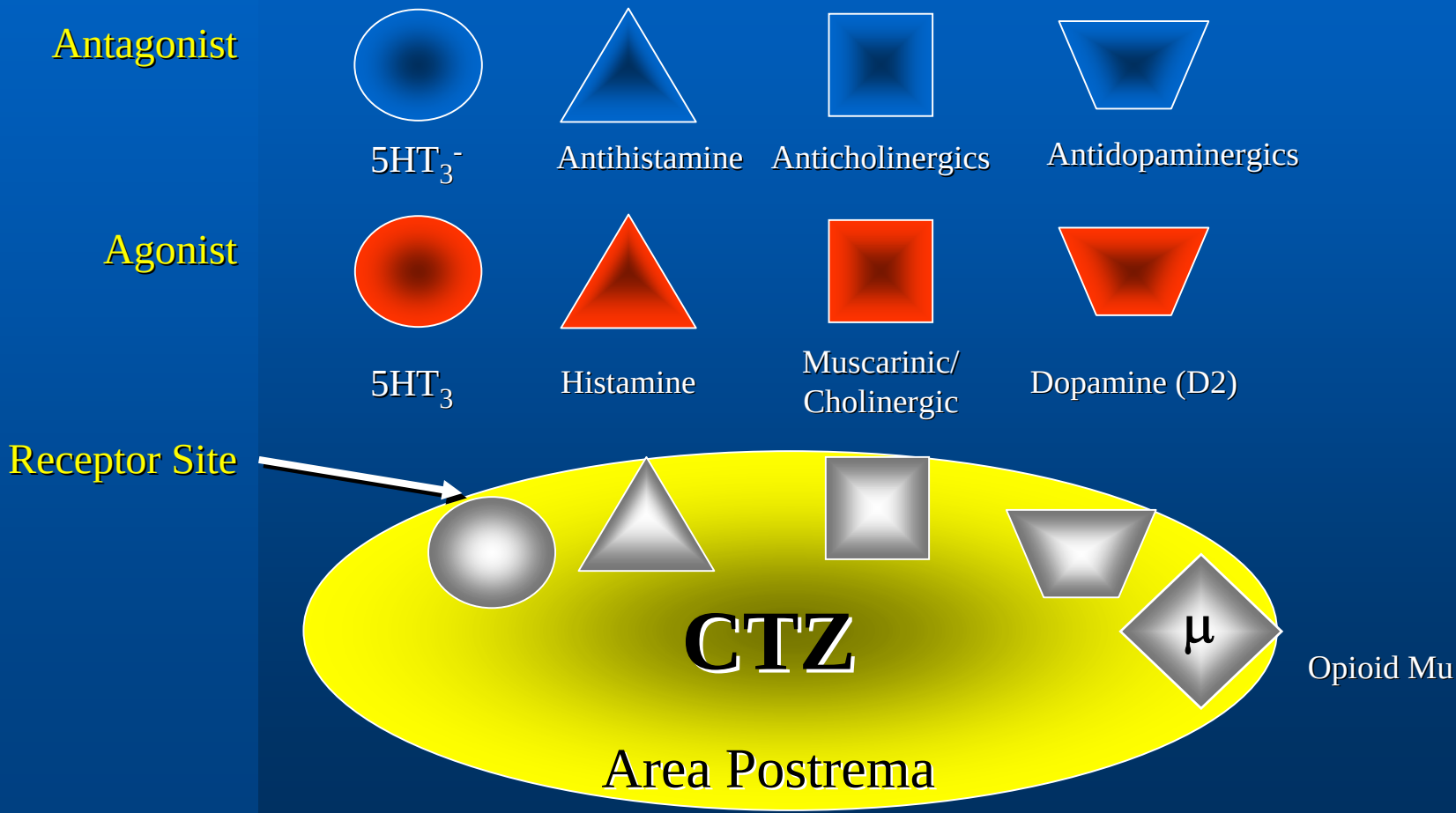
3 or More Points

Prophylactic Antiemetic is Indicated

1 Point Each

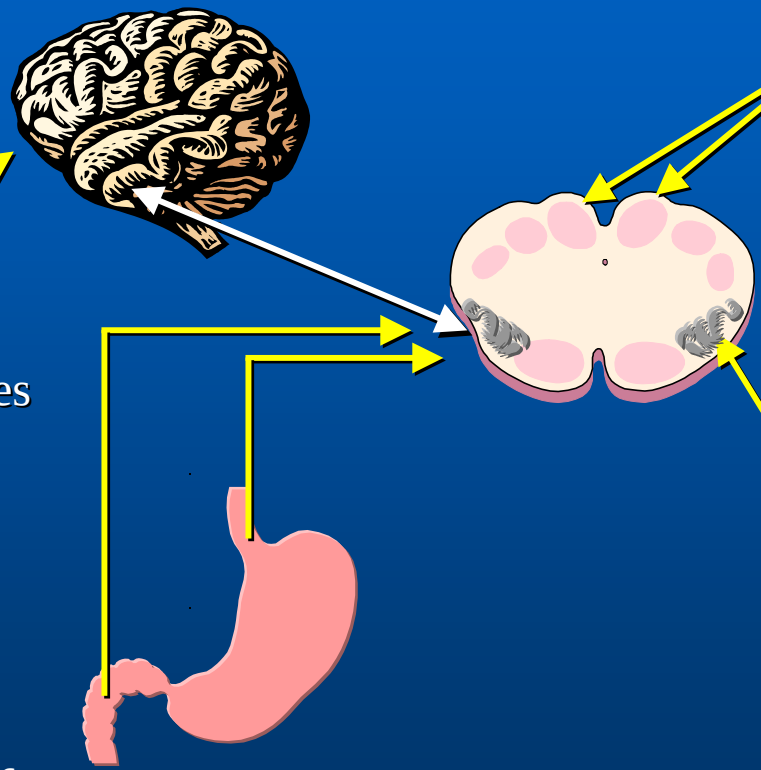
- Preadolescent
- Female
- Anxiety
- Laparoscopic cholecystectomy
- Intraoperative or postoperative opioid
- Duration of anesthesia > 60 min

Receptor-Based Pharmacology and Physiology



Adopted Watcha and White. *Anesthesiology* 1992;77(1):162-184.

Proposed Sites of Action: Antiemetic Drug Classes



- **Cortical**
  Cannabinoids
  Benzodiazepines

- **Chemoreceptor Trigger Zone**
  Phenothiazines
  Butyrophenones
  Metoclopramide
  Serotonin Antagonists

- **Vomiting Center**
  Antihistamines
  Anticholinergics

- **Visceral Afferents**
  Metoclopramide (high dose)
  Serotonin Antagonists

Tortorice and O'Connell. *Pharmacotherapy* 1990;10:129-145.

Receptor Site Affinity of Antiemetic Agents

Pharmacologic group/drug	Dopamine (D_2)	Muscarinic Cholinergic	Histaminic	Serotonin (5-HT_3)
Phenothiazines				
Fluphenazine	++++	+	++	-
Chlorpromazine	++++	++	++++	+
Prochlarperazine	++++			
Butyrophenones				
Droperidol	++++	-	+	+
Haloperidol	++++	-	+	-
Domperidone	++++			
Antihistamines				
Diphenhydramine	+	++	++++	-
Promethazine	++	++	++++	-
Anticholinergic				
Scopolamine	+	++++	+	-
Benzamides				
Metoclopramide	+++	-	+	++
5-HT_3 Receptor Antagonists				
Ondanensetron	-	-	-	++++
Granisetron	-	-	-	++++
Tricyclinic Antidepressants				
Amitriptyline	+++	+++	++++	-
Nartriptyline	+++	++	+++	-

Number of positive signs (+) indicates degree of activity; negative sign (-) indicates no activity.

Watcha and White. *Anesthesiology* 1992;77(1):162-184.

Agents Overview

Drug	Class	Route	Onset	Doses in 24h	Dur-ation	Side Effects
Ondansetron	5-HT_3-receptor antagonist	IV IM PO/ODT	10 min 41 min 15 min	1	24 h	HA, light-headedness abdominal pain constipation
Dolasetron	5-HT_3-receptor antagonist	IV PO	30-35 min 1 h	1	24 h	HA, hypotension, dizziness
Promethazine	Phenothiazine	IV IM/PO/PR	5 min 20 min	4-6	4-6 h	Dry mouth, blurred vision
Prochlorperazine	Phenothiazine	IV/IM PO/PR	-	2-4	-	EPS, drowsiness, dizziness
Reglan	Substituted benzamide	IV IM PO	1-3 min 10-15 min 30-60 min	4	1-2 h	EPS, drowsiness, lassitude
TD Scop	Anticholinergic	Patch	3-4 h	1/3	24 h	Dry mouth, drowsiness

Prescribing information for Zofran, Anzemet, Phenergan, Compazine, Reglan, and Transderm Scop.

Development of Transdermal Scopolamine

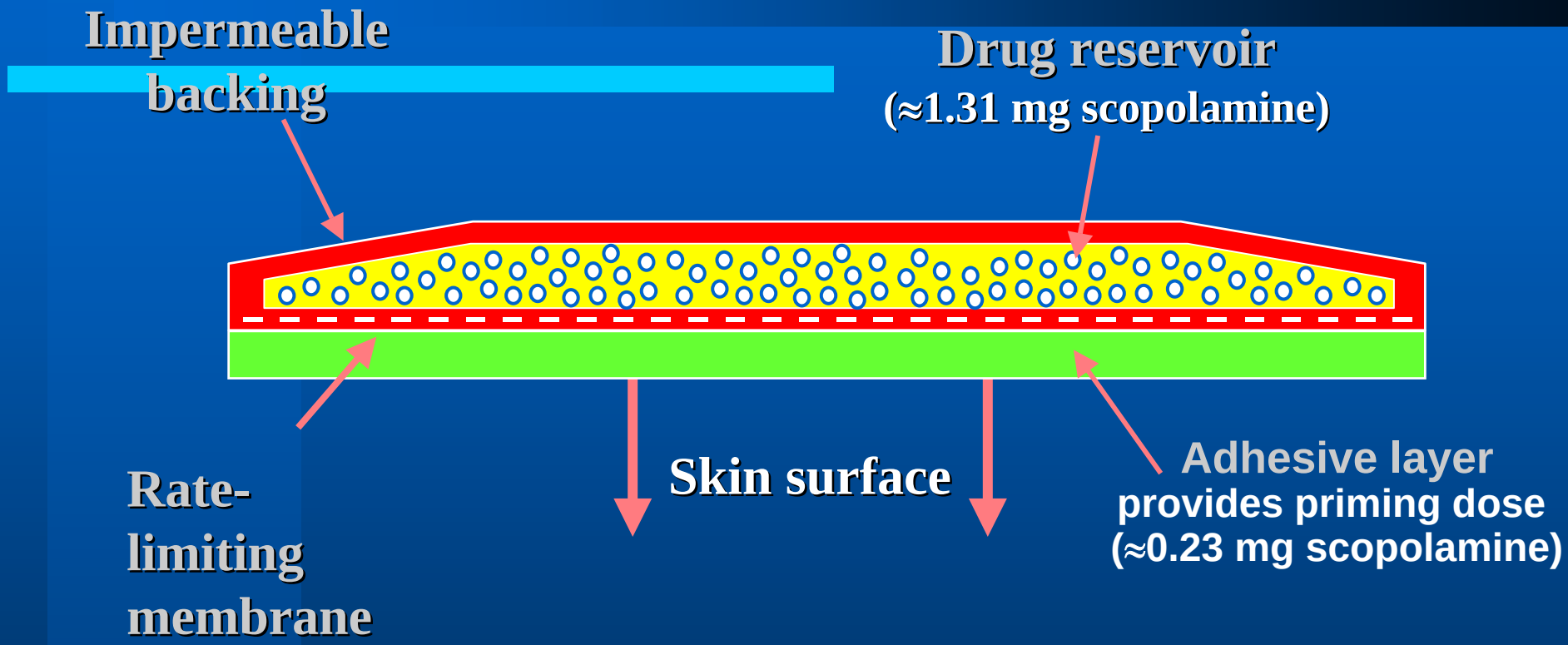
- 1979: Received FDA approval for prevention of nausea and vomiting associated with motion sickness
- 1994: Product voluntarily withdrawn by company
- Crystal formation, which posed a risk of subpotency
  - NOT an issue with efficacy/safety
- 1997: Transderm Scop was reintroduced with a new manufacturing process

Indications

- Prevention of nausea and vomiting associated with:
  - Motion sickness
  - Recovery from anesthesia and surgery

Transdermal scopolamine prescribing information.

Transdermal Scopolamine for PONV



Schematic representation of the transdermal delivery skin patch

Transdermal scopolamine prescribing information.

Pharmacokinetics of Transdermal Scopolamine

- Detected in plasma within 4 hr, peak within 24 hr
- Crosses placenta and blood-brain barrier
- Extensively metabolized
- Half-life 9.5 hr after patch removal
  - Potential drug interactions
  - Decreased absorption of oral drugs
  - Additive CNS effects with sedatives, tranquilizers, alcohol
  - Additive anticholinergic effects with antihistamines, TCAs, muscle relaxants

Prescribing information. Transderm Scop.

Pharmacokinetics of Transdermal Scopolamine

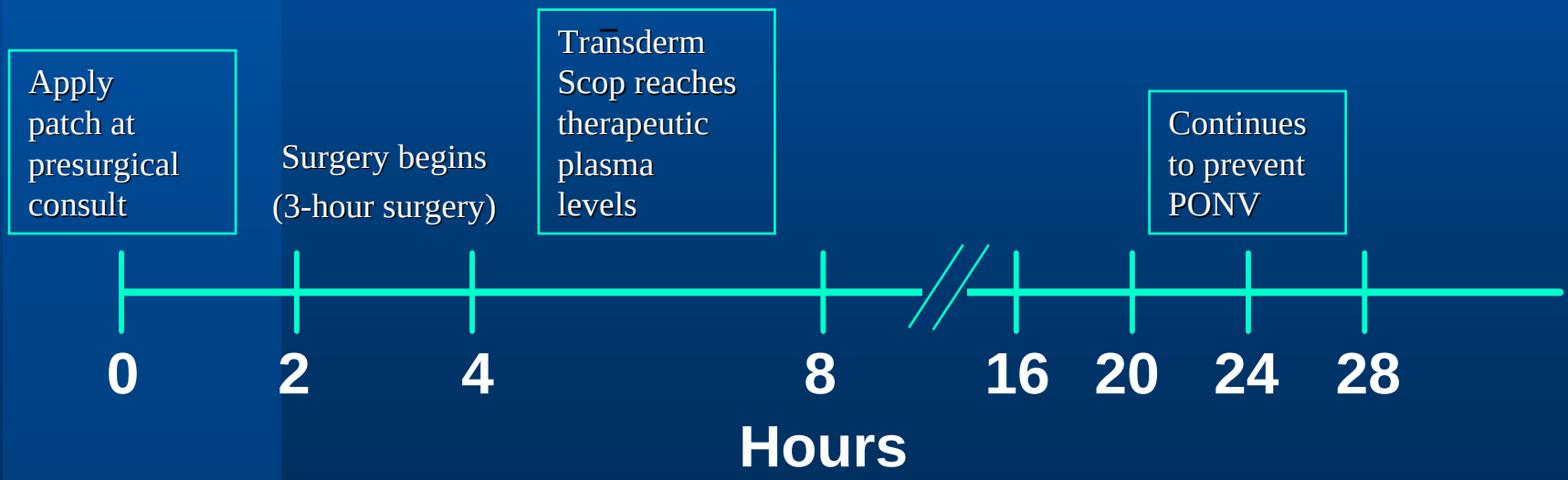
Absorption	**Reaches therapeutic levels at 4 hrs**
Distribution	**Crosses placenta and blood-brain barrier**
Metabolism	**Extensively metabolized**
Excretion	**Half-life 9.5 h after patch removal**
Drug interactions	**Potential drug interactions** – **Additive CNS effects with sedatives, tranquilizers, alcohol** - **Additive anticholinergic effects with antihistamines, TCAs, muscle relaxants** - **Decreased absorption of oral drugs**

Transdermal scopolamine prescribing information.

Prophylaxis Protocol Using Transderm Scop®

- One Transderm Scop patch prevents PONV for up to 24 hours post surgery

PONV Prevention With Transderm Scop



Transdermal Scopolamine in PONV

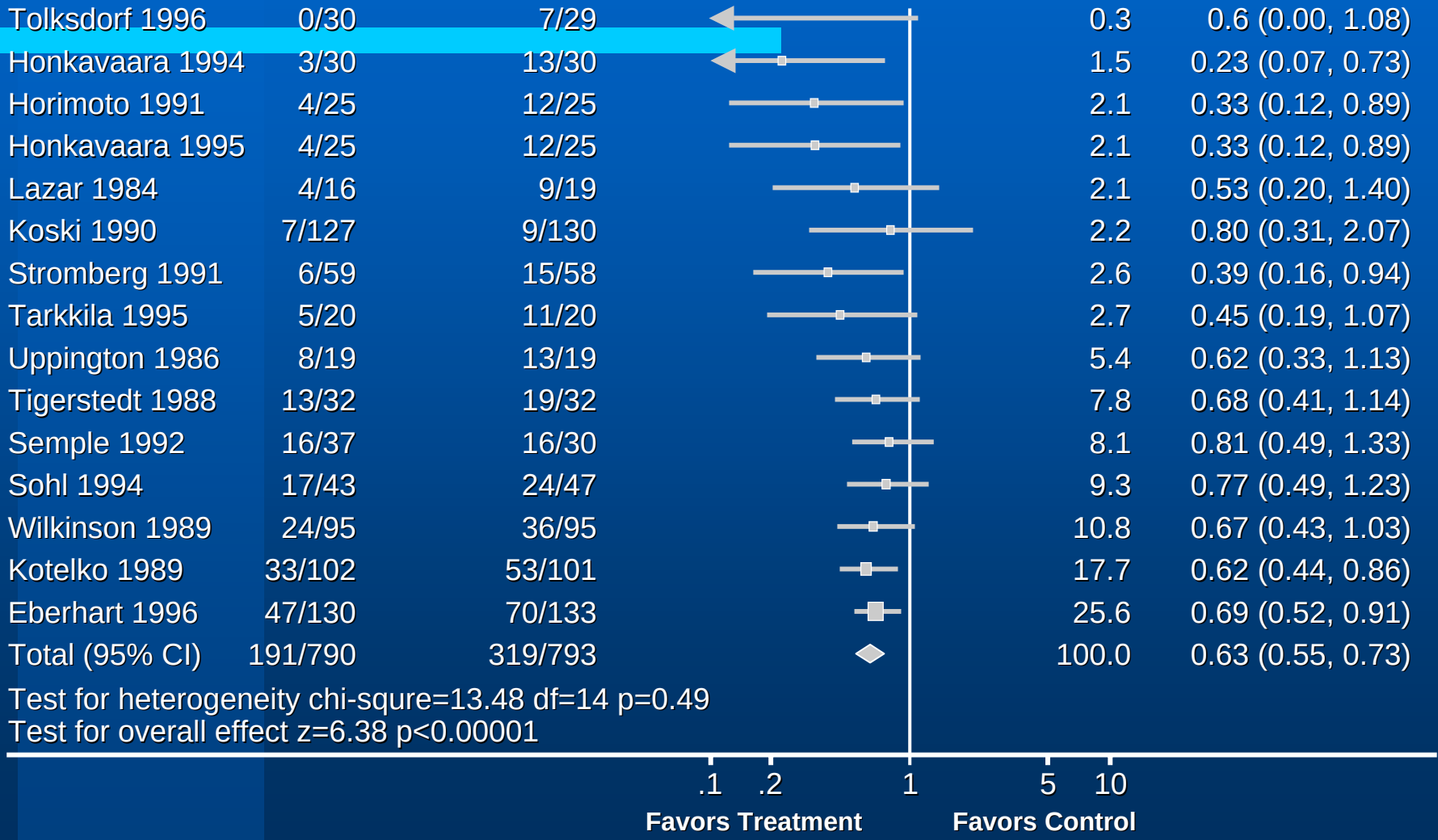
Type of Surgery	Control	N	Outcome
Cesarean section	Placebo	203	↓ PONV during hours 2 to 10 and antiemetic drug requirements
Outpatient laparoscopy	Placebo	138	↓ PONV, antiemetic drug requirements, and time to discharge
Major gynecologic	Placebo	42	↓ PONV in first 24 h postop
Major gynecologic	Placebo	32	↓ Nausea in first 24 h postop and ↓ antiemtic drug requirements
Intra-abdominal gynecologic	None (open label)	34	↓ Frequency and severity of PONV
Plastic or orthopedic	Placebo	190	↓ PONV in first 24 h postop and antiemetic drug requirements
Otoplasty	Atropine	50	↓ PONV
Ear (outpatient)	Placebo	39	↓ Nausea and vertigo after discharge
Middle ear (inpatient)	Placebo	60	↓ PONV

Bailey PL, et al. *Anesthesiology*. 1990;72:977–980.
Kotelko DM, et al. *Anesthesiology*. 1989;71:675–678.
Uppington J, et al. *Anaesthesia*. 1986;41:16–20.
Honkavaara P, et al. *Laryngoscope*. 1999;109:108–112.
Honkavaara P, et al. *Br J Anaesth*. 1994;73:763–766.
Wilkinson AR, et al. *Anaesth Intens Care*. 1989;17:285–289.
Loper KA, et al. *Anesth Analg*. 1989;68:144–146.
Reinhart DJ, et al. *Anesth Analg*. 1994;79:281–284.
Harris SN, et al. *Obstet Gynecol*. 1991;78:673–677.

TDS Quantitative Review of Efficacy

Comparison: 02 Overall interval (0-24 hr)

Outcome: 01 Postoperative vomiting



Kranke et al. Anesth Analg. 2002;95:133-143.

Nonpharmacologic Strategies

- Supplemental oxygen
- Perioperative rehydration
- Acupuncture, electroacupuncture, TENS, acupoint stimulation, acupressure
- Ginger
- Isopropyl alcohol
- Behavioral interventions: relief of anxiety, relaxation, guided imagery, therapeutic touch

Greif R, et al. *Anesthesiology.* 1999;91:1246-1252. Lee A, Done ML. *Anesth Analg.* 1999;88:1362-1369. Ernst E, Pittler MH. *Br J Anaesth.* 2000;84(3):367-371. Wang SM, et al. *J Clin Anesth.* 1999;11(3):231-234. Thompson HJ. *J Adv Nurs.* 1999;29:1130-1136.

Prophylactic Combinational Antiemetic Therapy

- "Gold Standard" for very high risk patients

  Increased Efficacy

  Improved Patient Satisfaction

  Cost Effective

Common Prophylactic Multi-Modal Antiemetic Therapies

- Ondanestron & Droperidol
- Ondanestron & Droperidol
- Ondanestron & Transderm Scop
- Ondanestron & Dexamethasone
- Droperidol & Reglan
- Droperidol & Dexamethasone

FDA Strengthens Warnings for Droperidol

12/05/01

The FDA has strengthened the warnings and precautions sections in the labeling for droperidol, a tranquilizer used most often as a premedication for anesthesia, as treatment for nausea after anesthesia, and for sedation of agitated patients. Droperidol has been associated with fatal cardiac arrhythmias.

Specific changes to the droperidol labeling include a "black box" warning, the most serious warning for an FDA-approved drug. The new warning is intended to increase the physician's focus on the potential for cardiac arrhythmias during drug administration, and to consider use of alternative medications for patients at high risk for cardiac arrhythmias.

Droperidol currently carries a warning about cases of sudden death at high doses (greater than 25 mg) in patients at risk for cardiac arrhythmias. Recent research has shown QT prolongation (delayed recharging of the heart between beats) within minutes after injection of a dose of droperidol at the upper end of the labeled dose range. Prolonged QT is dangerous because it can cause a potentially fatal heart arrhythmia known as torsades de pointes (TdP).

In the last year, there have been reports of TdP within or below the currently labeled dose range. There have also been reports of sudden death or other serious cardiac adverse events.

The FDA will continue to monitor the postmarketing safety data for droperidol to determine if further action is needed.

The manufacturer, Akorn Pharmaceuticals, is sending a "Dear Healthcare Professional" letter to physicians, pharmacists, and other healthcare professionals in the U.S. The letter explains the black box warnings and highlights the potential for QT prolongation or torsades when this drug is administered.

For more information, patients and healthcare providers can call Akorn Pharmaceuticals at 1-888-519-8384.

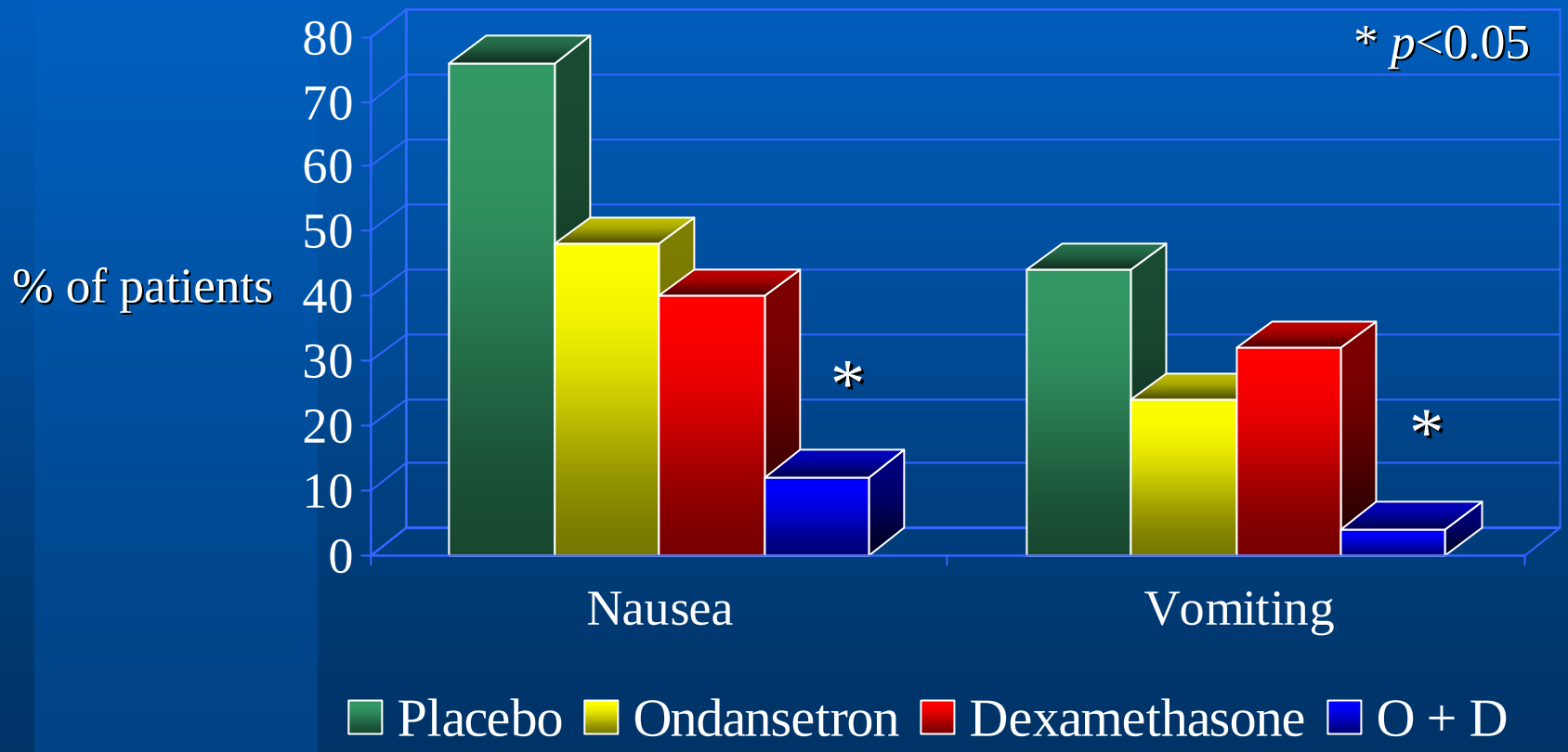
FDA Press Release

Dexamethasone

- Inhibition of prostaglandin synthesis is the proposed antiemetic mechanism action
- Increase in the release of endorphins results in mood elevation, a sense of “well-being”, and appetite stimulation.
- Many caveats to be aware of, should obtain consensus with surgeon
- Used heavily in CIE.

Baxendale BR. Anaesthesia 1993;48:961-4. Skjelbred P. *Eur J Clin Pharm* 1982;21:391-6. Henzi I. *Anesth Analg* 2000;90:186-94. Harris AL. *Lancet* 1982;1:714-6. Huber p. *Anesth Analg* 2001;92:85-8.

Ondansetron & Dexamethasone



Lopez-Orlondo L, et al. *BJA* 1996;76:835-40.

Review of Recent Topics

- Timing Administration
- “Tron Wars”
- Repeat Dosing Versus Receptor Switch
- Opioid Induced Emesis and PONV
- Role of Complimentary and Alternative Medicine in PONV
- Incremental Costs
- Post Discharge PONV

Features of DUR and TDS

- Drug Utilization Review
  - Surrogate diagnosis is made based on the drug
  - Initiated by the pharmacist
  - Cost-saving focus
  - Tries to reduced drug use
  - Money saved due to reduced expenditure on drugs
  - Alerts are in reaction to therapy chosen
  - Occurs after patient visit to the physician

- Therapeutic Decision Support
  - The drug used is chosen on the basis of the physician's diagnosis
  - Initiated by the physician
  - Patient-based focus
  - Tries to increase appropriate drug use in order to solve underutilization
  - Money saved is dependent on reduction in total healthcare costs of the patient
  - Alerts influence in the choice of therapy
  - Occurs at time of patient visit to the physician

Blum, R. *Clinical Researcher* 2001;9:32-5.

TDS in Practice

Predictors

- Female
- Previous PONV
- Motion sickness
- Duration >60 min
- Non-smoker
- Laparoscopic GYN
- Breast Surgery
- Special Considerations

Agents

- Ondansetron
- Dolasetron
- Promethazine
- Prochlorperazine
- Metoclopramide
- TD Scop
- Droperidol
- Benadryl
- Dexamethasone

Adapted from Blum, R. Clinical Researcher 2001;9:32-5.

PONV Incidence & Management Tool

Post-op Opioids	
Anesthesia/Surgery greater than 60 min.	
Antiemetics used pre-/post-op	

	Pre	In	Post		Pre	In	Post
Ondansetron	☐	☐	☐	Dolasetron	☐	☐	☐
Metoclopramide	☐	☐	☐	Droperidol	☐	☐	☐
Diphenhydramine	☐	☐	☐	Hydroxyzine	☐	☐	☐
Promethazine	☐	☐	☐	Prochlorperazine	☐	☐	☐
Decadron	☐	☐	☐	Atropine	☐	☐	☐
Scopolamine	☐	☐	☐	Ephedrine	☐	☐	☐

PACU Status:	Nausea ☐	Emesis ☐
Intervention:		
Rx to Home:		

Reasons to Avoid PONV

- A survey found that people* are willing to accept a variety of trade-offs to avoid PONV:
  - Dysphoria
  - Increased cost
  - Decreased mental acuity
  - Increased postoperative pain

*Anesthesiologists, nurses, support staff at two teaching hospitals, and computer personnel who attended a national meeting.

Orkin. *Anesth Anig* 1992;74:S225 Abstract.

The Great Unknown: Post-discharge PONV

- Currently in the U.S., > 60% of surgical procedures performed on an ambulatory basis.
- Trend: Ever increasing number of ASC, office based anesthesia, and out patient surgeries.
- One study: PONV 48 h after discharge 16.8% compared with incidence in PACU (9.8%)
- Numbers may even be higher (30+%).

Adapted from US CDC report 1996. Carroll NV, et al. Anesth Analg.1995;80:903-909

Tramer's Meta-Analysis PONV / OIE Management

Drug	NNT(95% CI) Vomiting	NNT (95% CI) Nausea and Vomiting
Droperidol	3.1 (2.3-4.8)	2.8 (2.1-3.9)
Transdermal Scopolamine	10 (2.9 – infin)	5.4 (2.8- 56)
Ondansetron	5.1 (2.8 –23)	2.9 (21-4.7)
Tropisetron		4.7 (3.0-11)
Proprofol		-75 (-3.6 – infin)
Metoclopramide		7.8 (3.4 – infin)
Clonidine PO	2.3 (1.5 –6.0)	
Promethazine		2.5 (1.4 –14)

Suggested OINV Treatment Strategies

- Regimens
  - Zofran 4mg at start of IV PCA, then maintain with
    - Benadryl 12.5 mg t.i.d x 24 hrs; or
    - Reglan 10 mg b.i.d x 24 hrs
  - Promethazine 12.5 mg added to morphine 1 mg/mL,= total of 17.6 mg over 24 hrs ? sedation
  - Clonidine (5 µg/kg) 1.5 hours before surgery and at 12 and 24 hours after the initial dose, with IV morphine PCA for pain management
  - Ondansetron—4 mg IV single dose and 8 mg (0.13 mg/mL)
  - Droperidol —0.15 mg/ml MS: watch total daily dose 5mg- 60 mg
  - Perphenazine (1 mg - Trilafon) is especially useful for the prevention and treatment of PONV caused by opioids.
  - TDS as soon as possible.

Our Role

Multidisciplinary Team Approach

- “Perioperative Medicine”
- Pharmacist, MD, CRNA, RN…
- Outpatient SurgiCenters