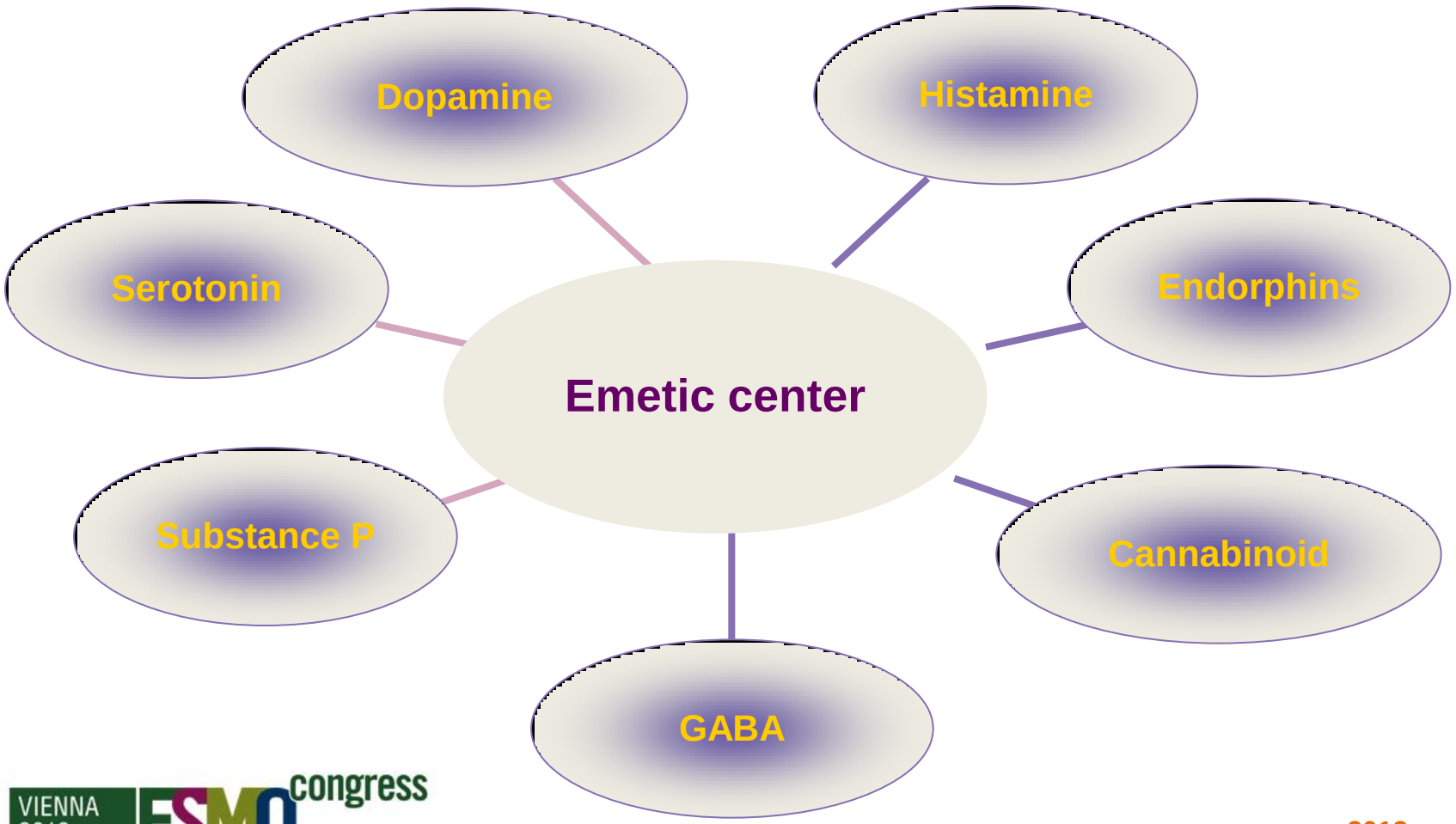
Antiemetics: A Window to Translational Medicine

Steven Grunberg, MD

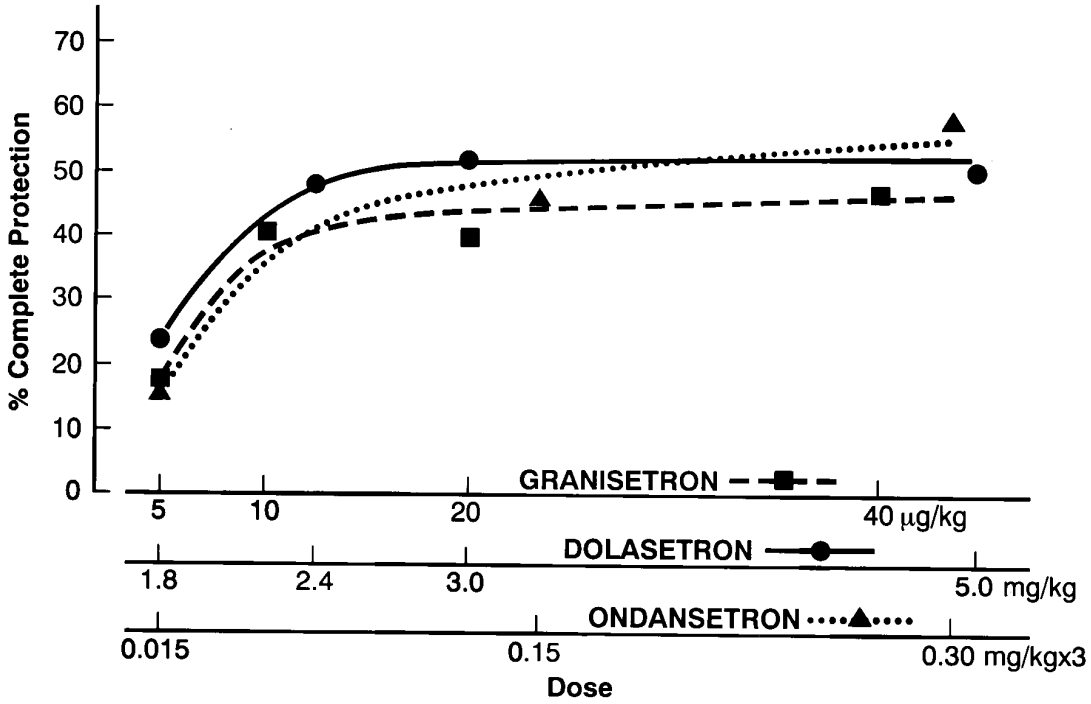
Disclosures

- Employment – None
- Consultant – Helsinn, Merck, TesaroBio, Amgen, Astra Zeneca, AP Pharma
- Stock - Merck
- Honoraria – Merck, Eisai

Neurotransmitters Involved in Emesis

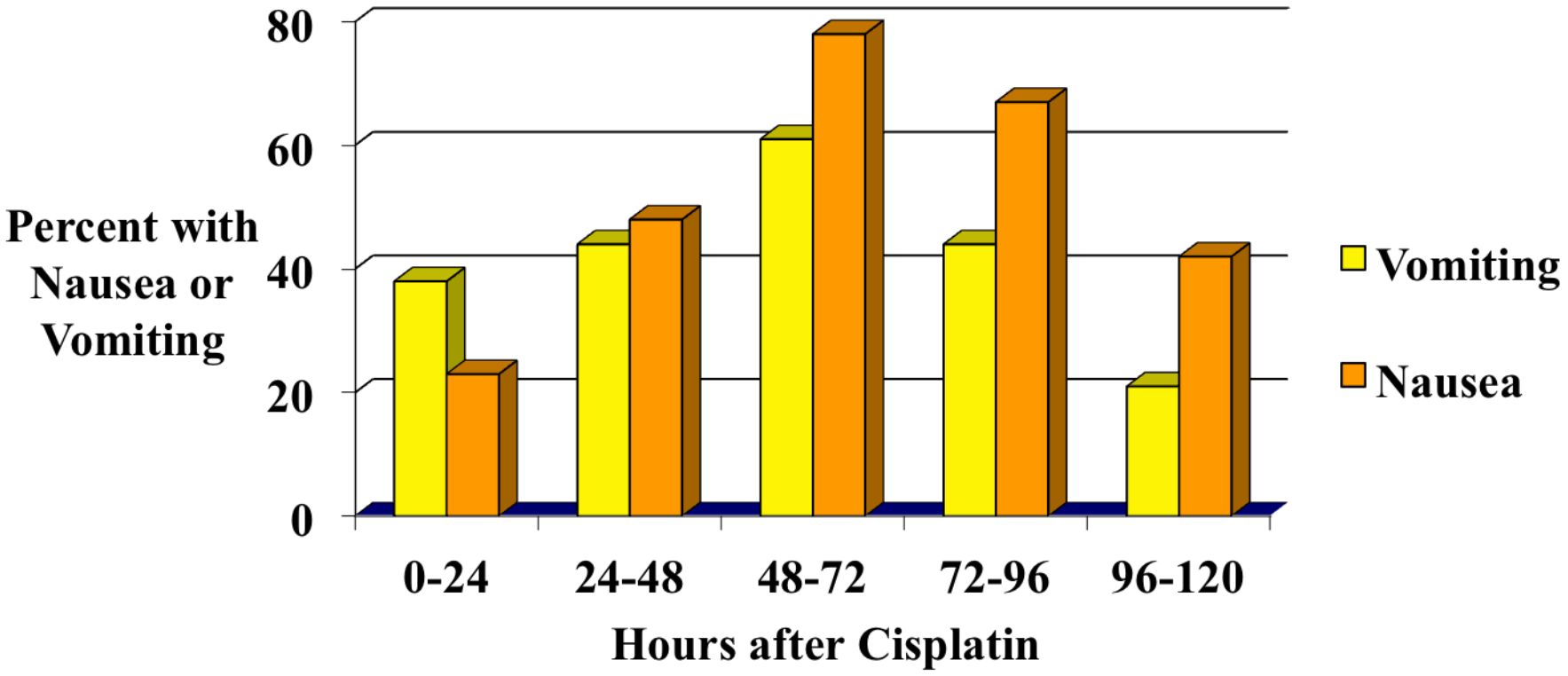


Serotonin Antagonist Dose-Response Curve



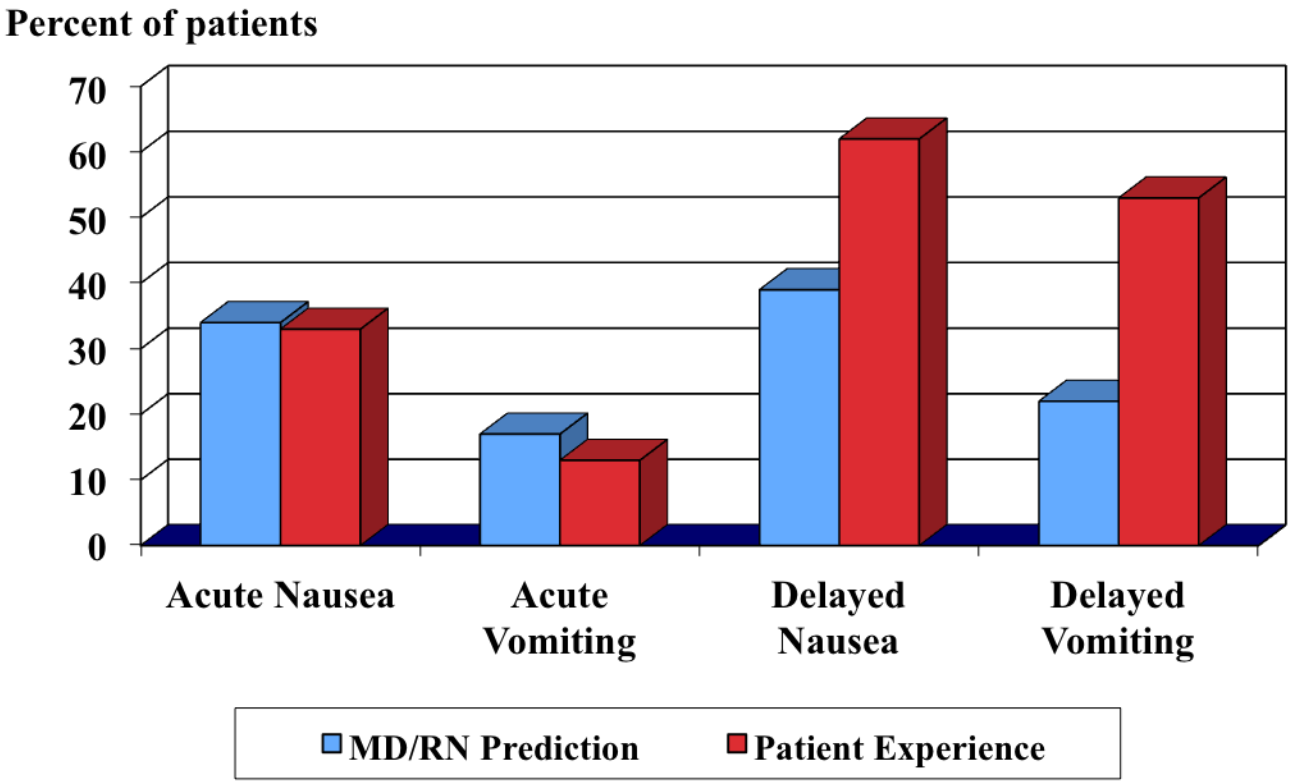
Grunberg, in Tonato, ESMO Monographs, 1996

Natural History of Delayed Nausea and Vomiting



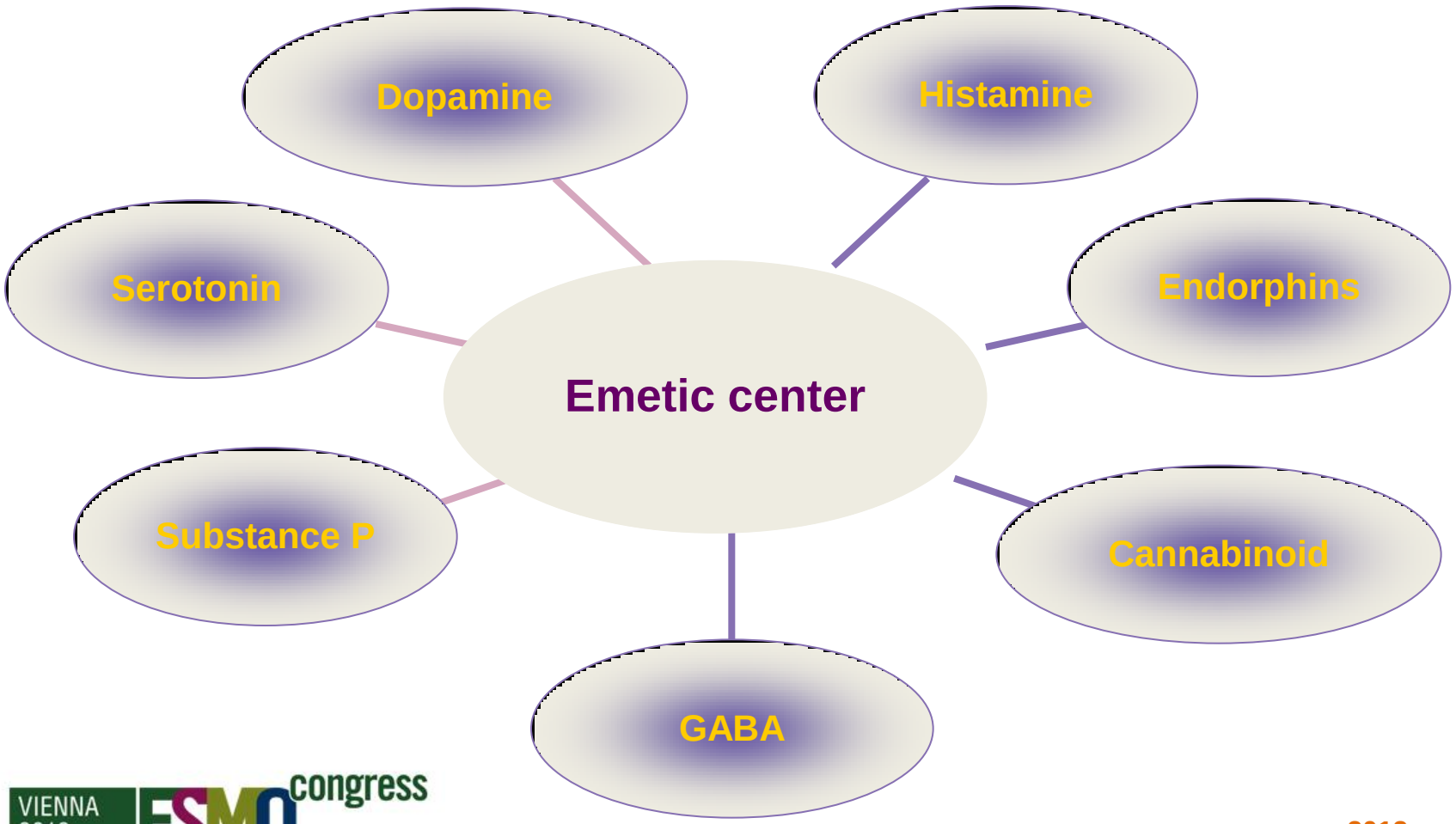
Kris, J Clin Oncol 3:1379, 1985

Perception vs Reality
Highly Emetogenic Chemotherapy

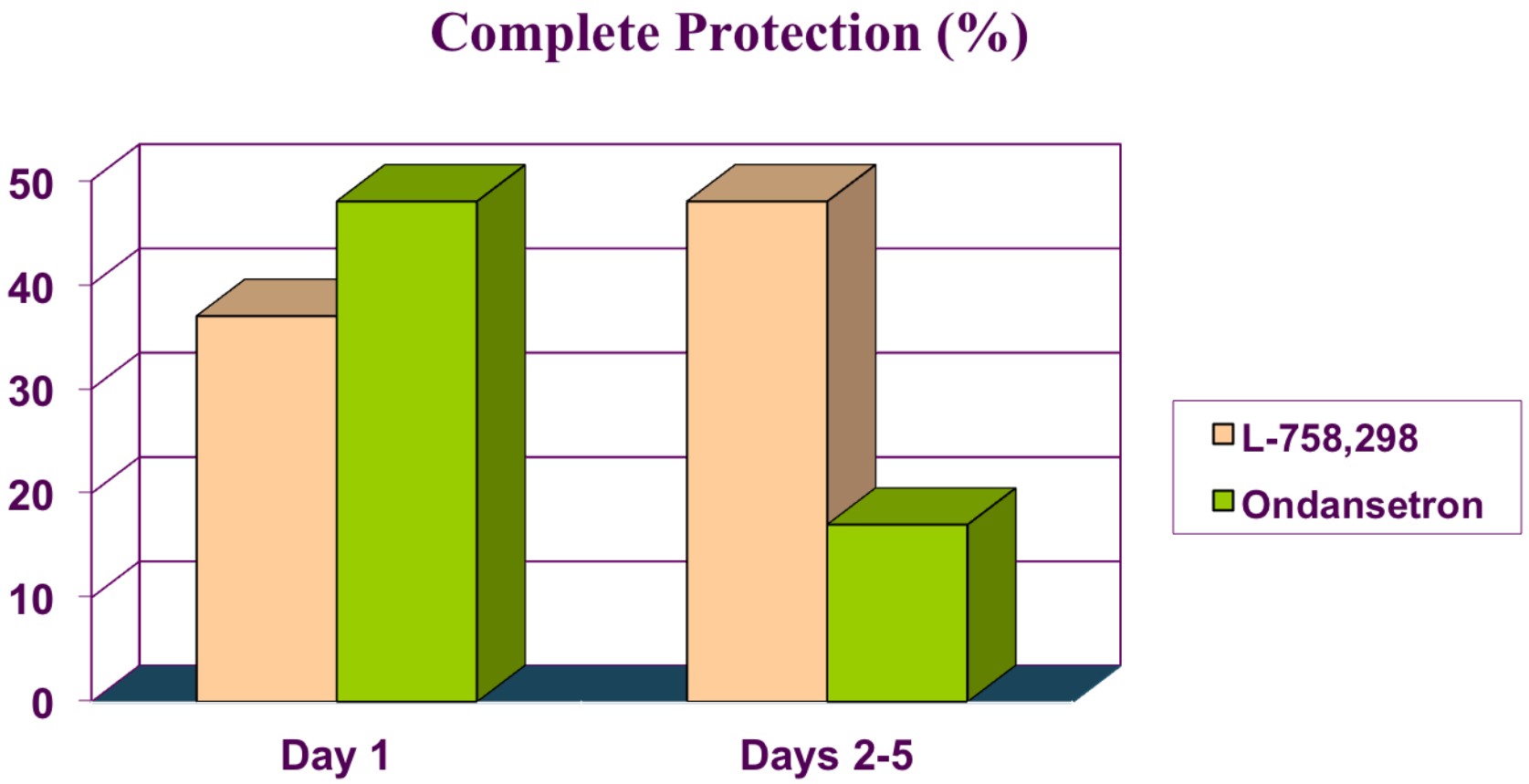


Grunberg, Cancer 100:2261, 2004

Neurotransmitters Involved in Emesis



L-758,298 vs Ondansetron for Cisplatin-Induced Emesis



Cocquyt, Eur J Cancer 37:835, 2001

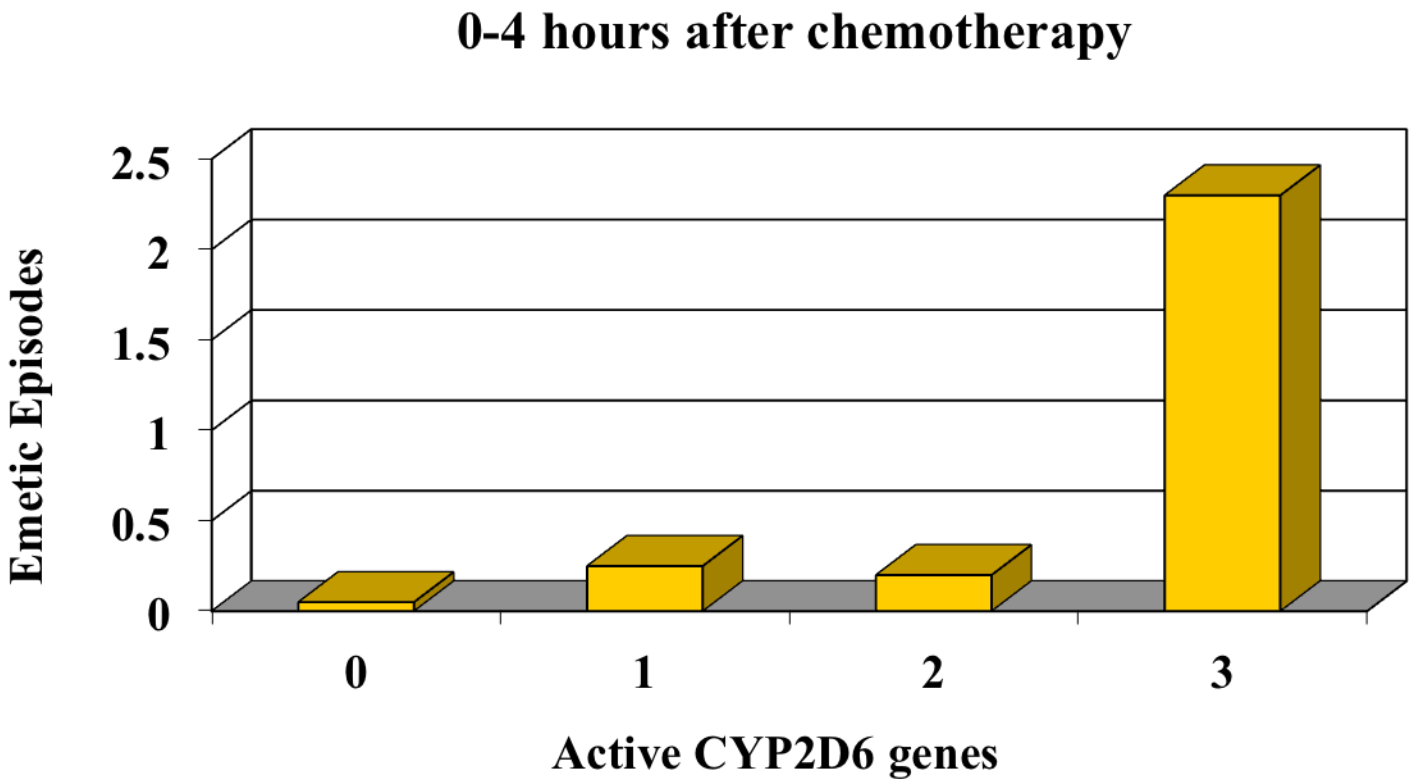
Antiemetic Guidelines III

Emetogenic Classification	Acute Emesis Antiemetics	Delayed Emesis Antiemetics
High	5HT3+DXM+NK1	DXM
High-Moderate	5HT3+DXM+NK1	None
Moderate	PALO+DXM	DXM
Low	5HT3/DXM/DRA	None
Minimal	None	None

Risk Factors

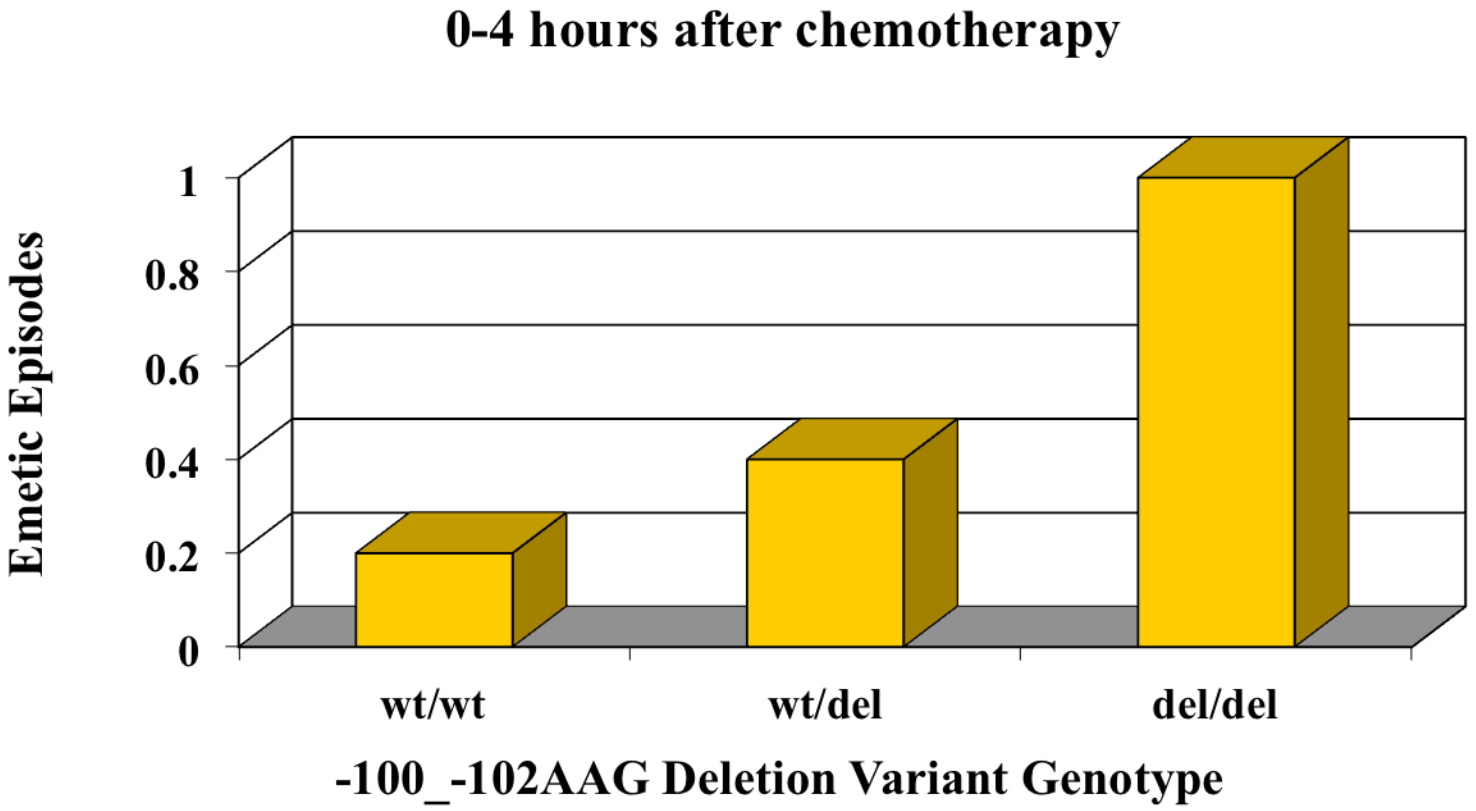
- Age
- Gender
- Alcohol History
- Previous Emesis Experience/Expectations
- Genetics (Pharmacogenetics)
- Genetics (Race)

Effect of P-450 CYP 2D6 Genotype on Emetic Response



Kaiser, J Clin Oncol 20:2805,2002

Effect of -100_-102AAG Deletion Variant of the 5-HT_{3B} Gene on Emetic Response



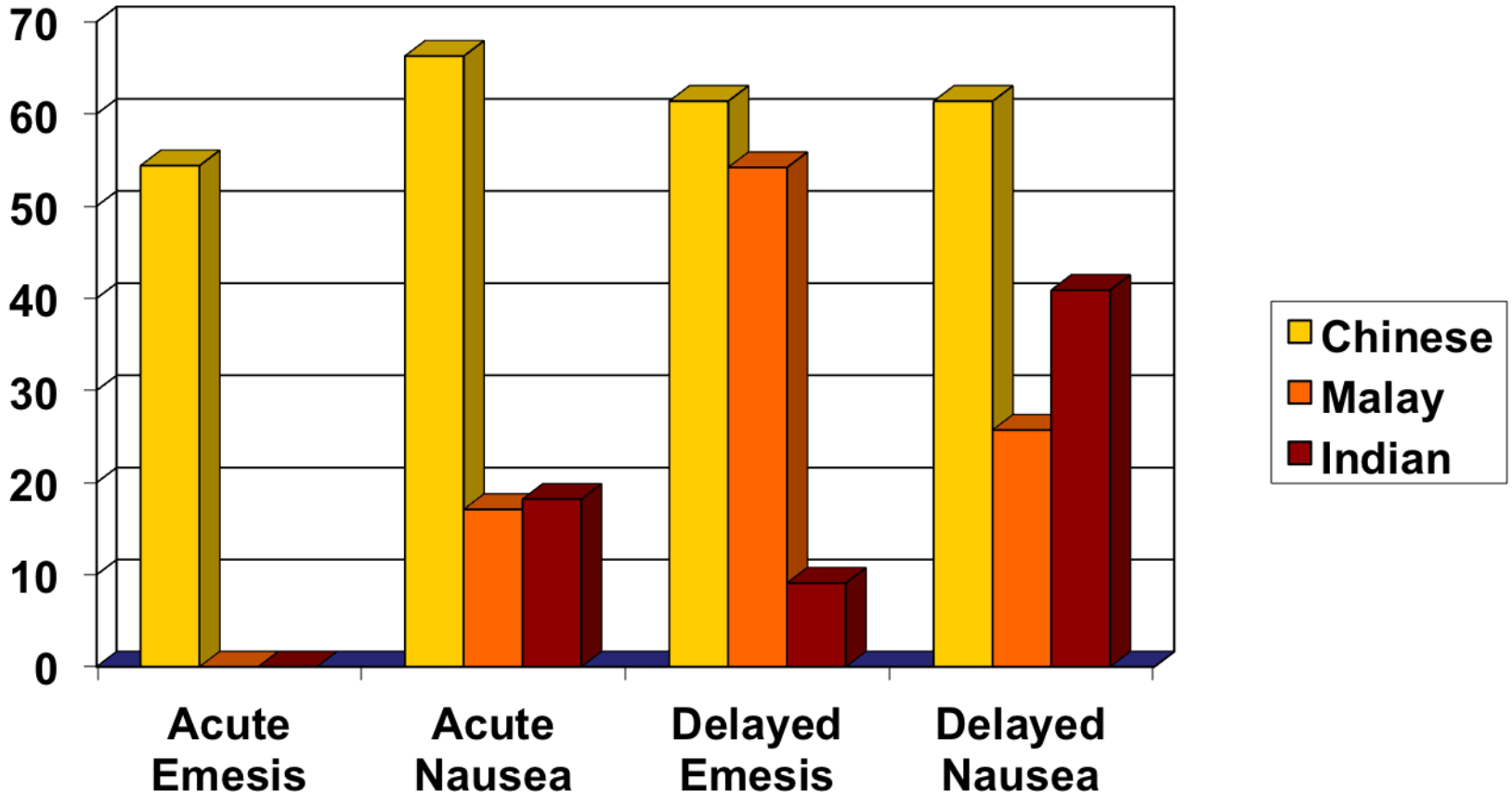
Tremblay, J Clin Oncol 21:2147,2003

Polymorphisms and Emesis Population Effects

- 158 breast cancer patients in one hospital in Malaysia
- Prospective observational study
- Received common chemotherapy (cyclophosphamide and anthracycline) and common acute antiemesis (granisetron-containing combination)
- Analyzed by ethnic groups (Chinese, Malay, Indian) that differ in CYP3A4 polymorphisms
- Granisetron was less effective in Chinese patients

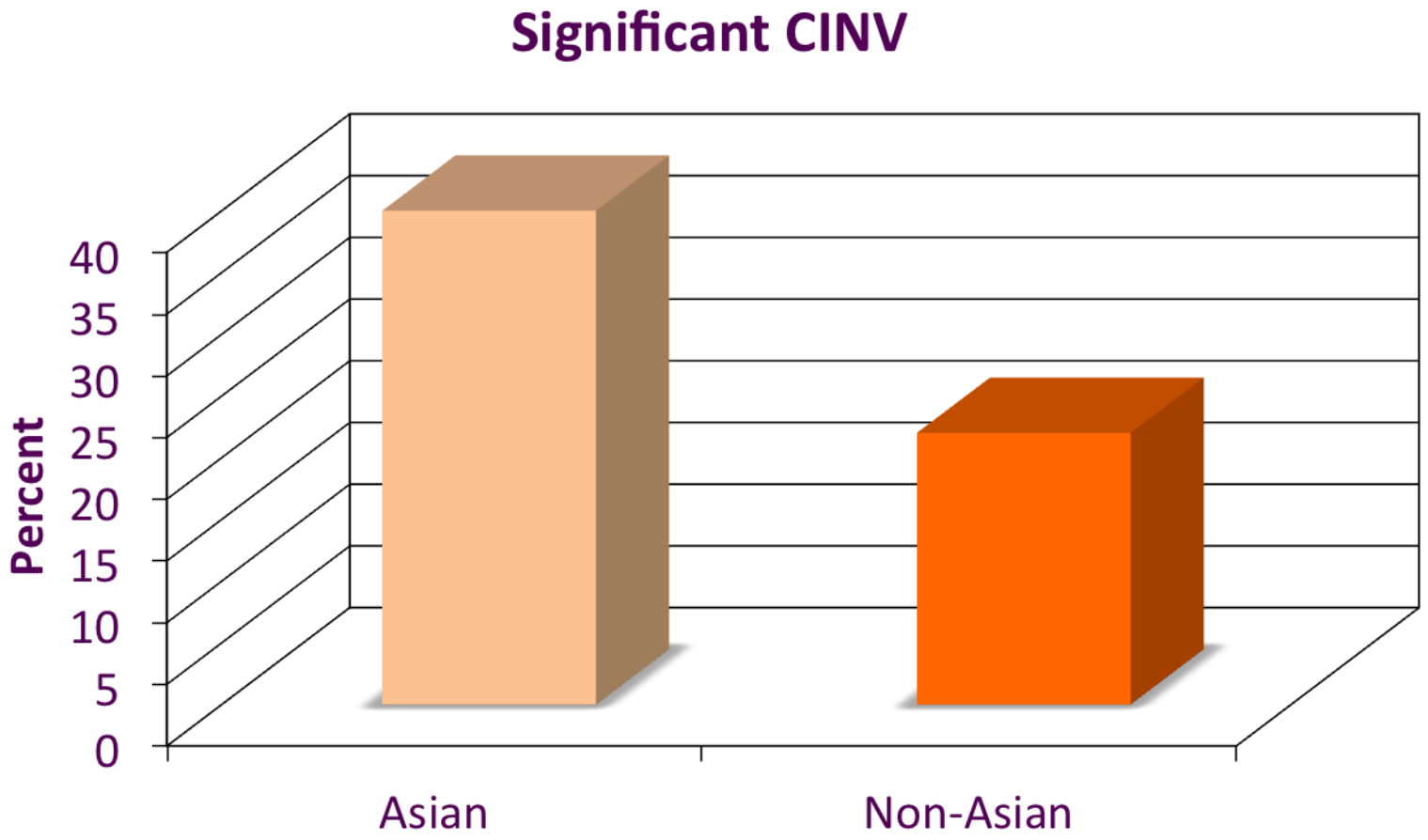
Hassan, Asian Pac J Cancer Prev 12:185, 2011

Polymorphisms and Emesis Population Effects



Hassan, Asian Pac J Cancer Prev 12:185, 2011

Ethnicity and Emesis



Bourdeanu, J Support Oncol 10:149, 2012

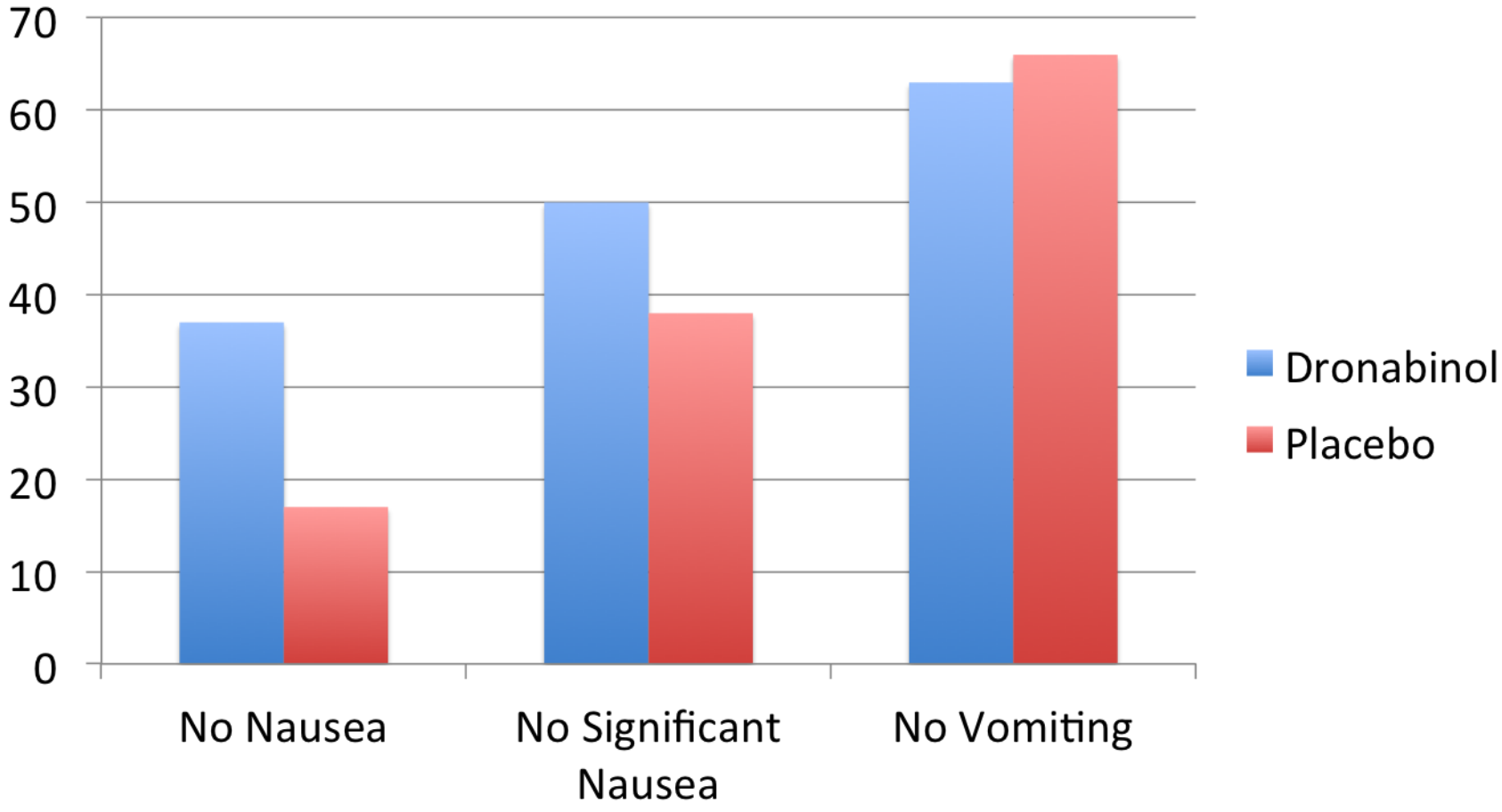
NAUSEA

- Nausea is correlated with Vomiting but is not the same as Vomiting
- Nausea is subjective; Vomiting is objective. Therefore the accurate measurement of Nausea is more of an obstacle
- It is more difficult to interpret an animal model of Nausea than an animal model of Vomiting

Treatment Plan

- Active arm
  - Palonosetron 0.25 mg IV Day 1
  - Dexamethasone 10 mg IV Day 1
  - Dronabinol 5 mg PO TID x 5 days
- Placebo arm
  - Palonosetron 0.25 mg IV Day 1
  - Dexamethasone 10 mg IV Day 1
  - Matched placebo PO TID x 5 days

Efficacy Outcomes - Nausea



Grunberg, J Clin Oncol 30:2012 (Abst 9061)

Conclusions

- Supportive care and translational medicine have a mutually beneficial relationship.
- Neurotransmitter receptor theory led to advances in antiemetic care
- Pharmacogenomics led to refinement of our understanding of antiemetic care
- Evaluation of ethnicity and emesis may lead to further understanding of pharmacogenomics
- Evaluation of nausea may lead to further understanding of neurotransmitter receptor pathways