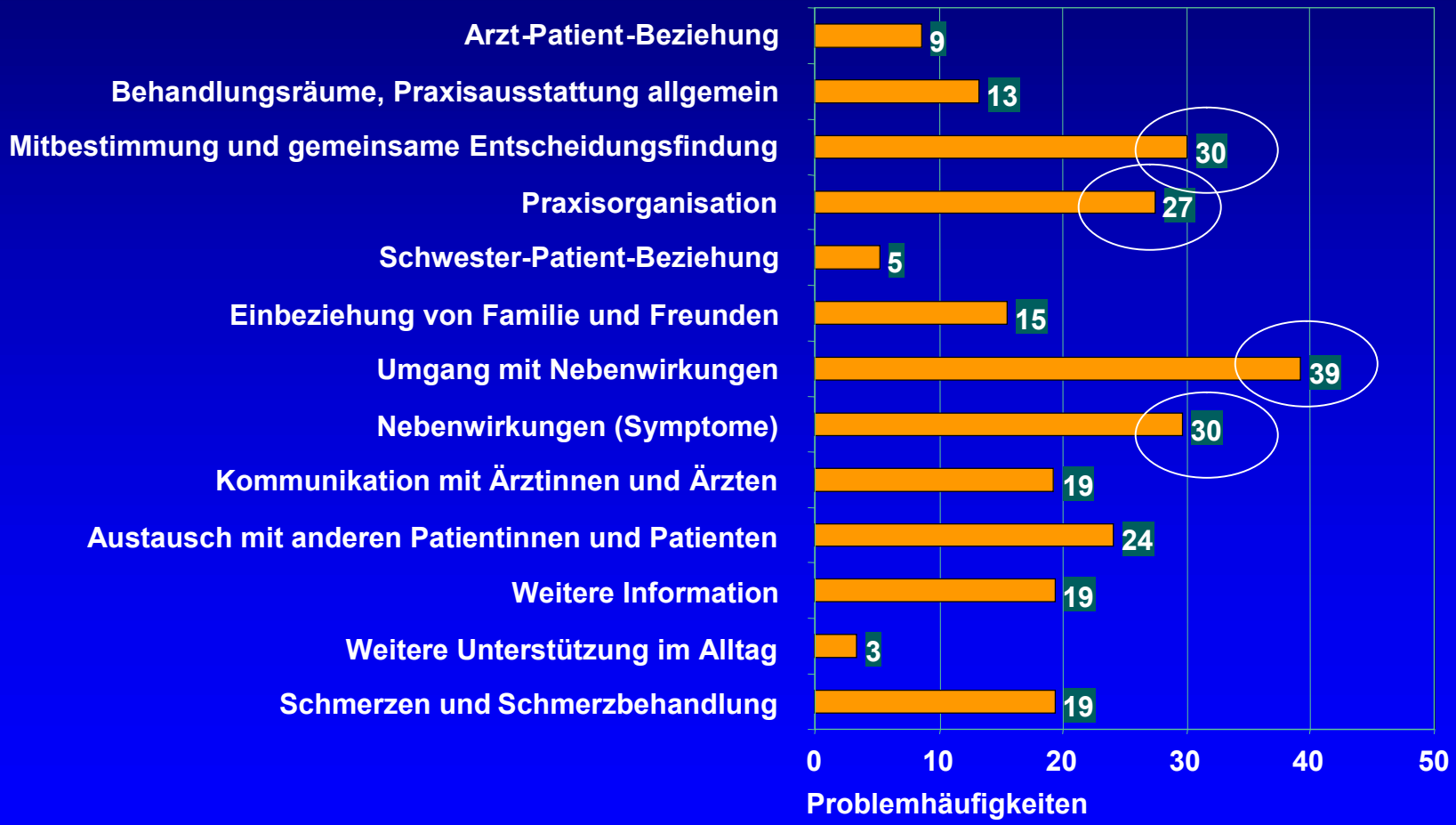
# State of the Art
# in der Antiemese 2009
# - Ausblick 2010 -

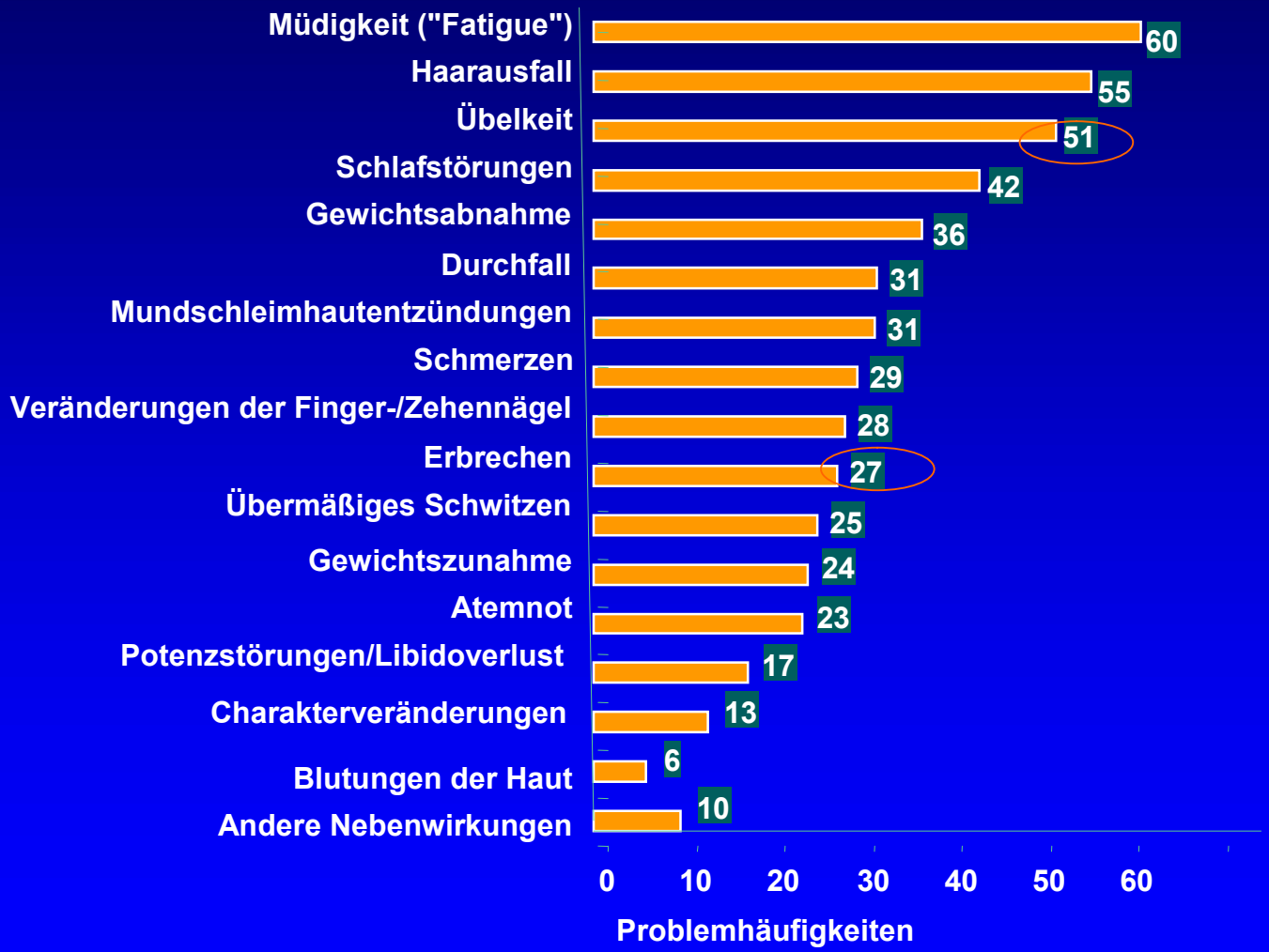
# Stärken und Schwächen in der onkologischen Versorgung




Feyer et al.: Support Care Cancer (2008) 16:567-575

PASQOC® 2004

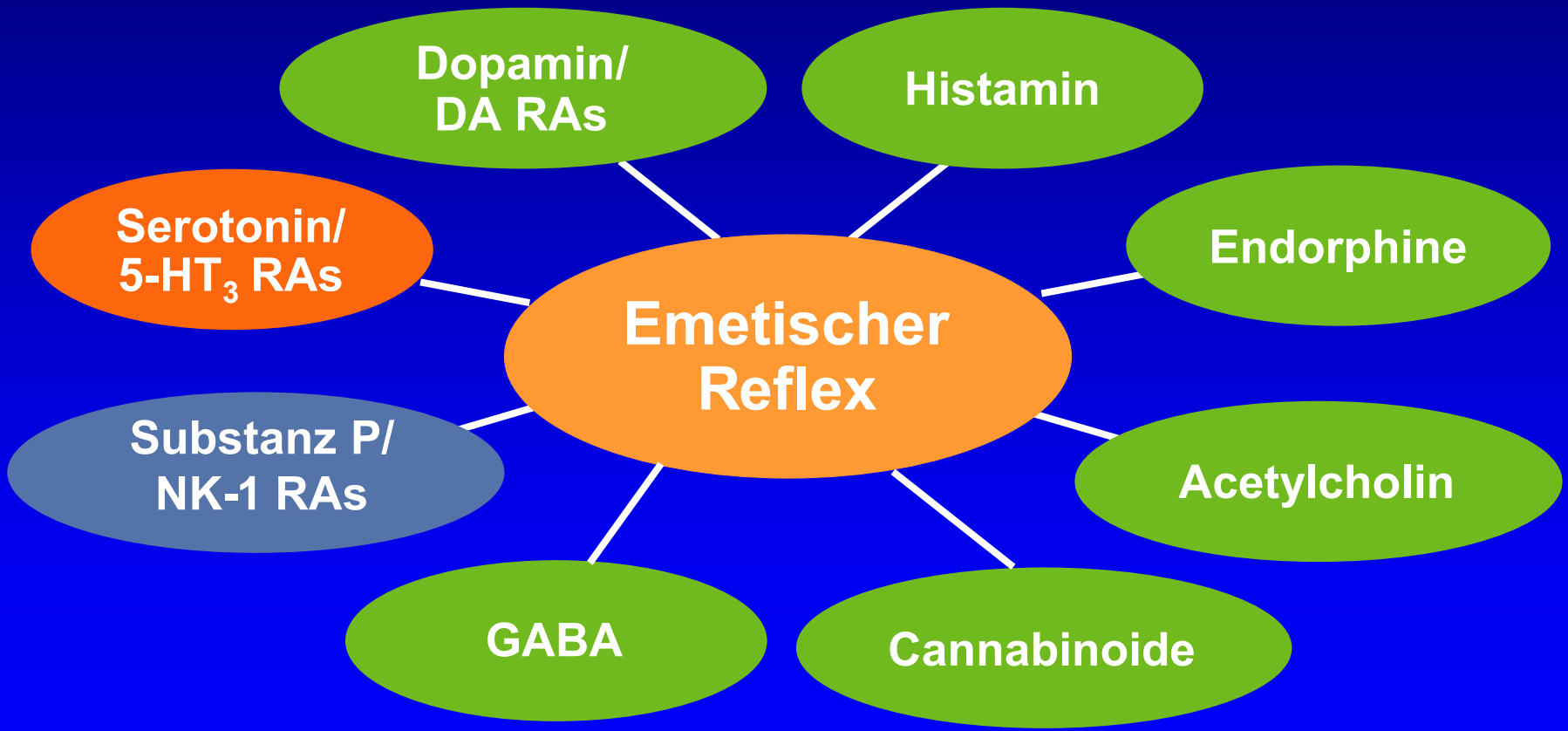
# Nebenwirkungen
## Problemhäufigkeiten aus Patientensicht




Feyer et al.: Support Care Cancer (2008) 16:567-575

PASQOC® 2004

# Neurotransmitter und Substanzen mit Einfluss auf die Emesis

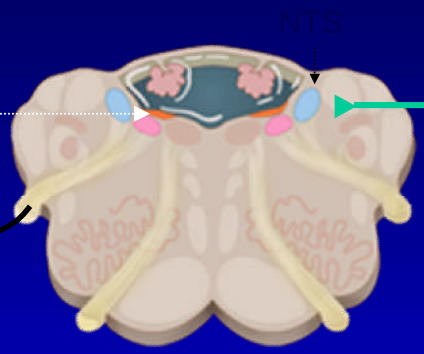



DA = Dopamin; GABA = Gamma-Aminobuttersäure; NK = Neurokinin; RAs = Rezeptorantagonisten

# The emetic reflex induced by chemotherapy

## Central pathway

Chemotherapeutic drugs and/or their metabolites enter the AP and activate chemoreceptors



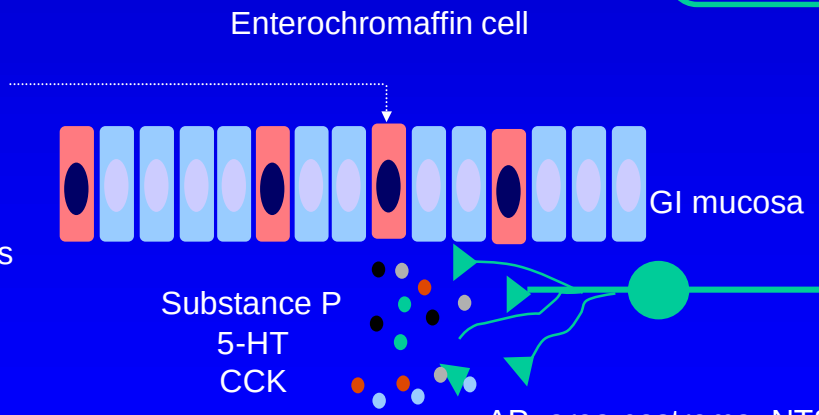

Sequence of events coordinated in the NTS, DMN and central pattern generator and relayed by the efferent vagus leads to emesis

Branches originate in GI mucosa and terminate in NTS

Afferent vagus

## Peripheral pathway

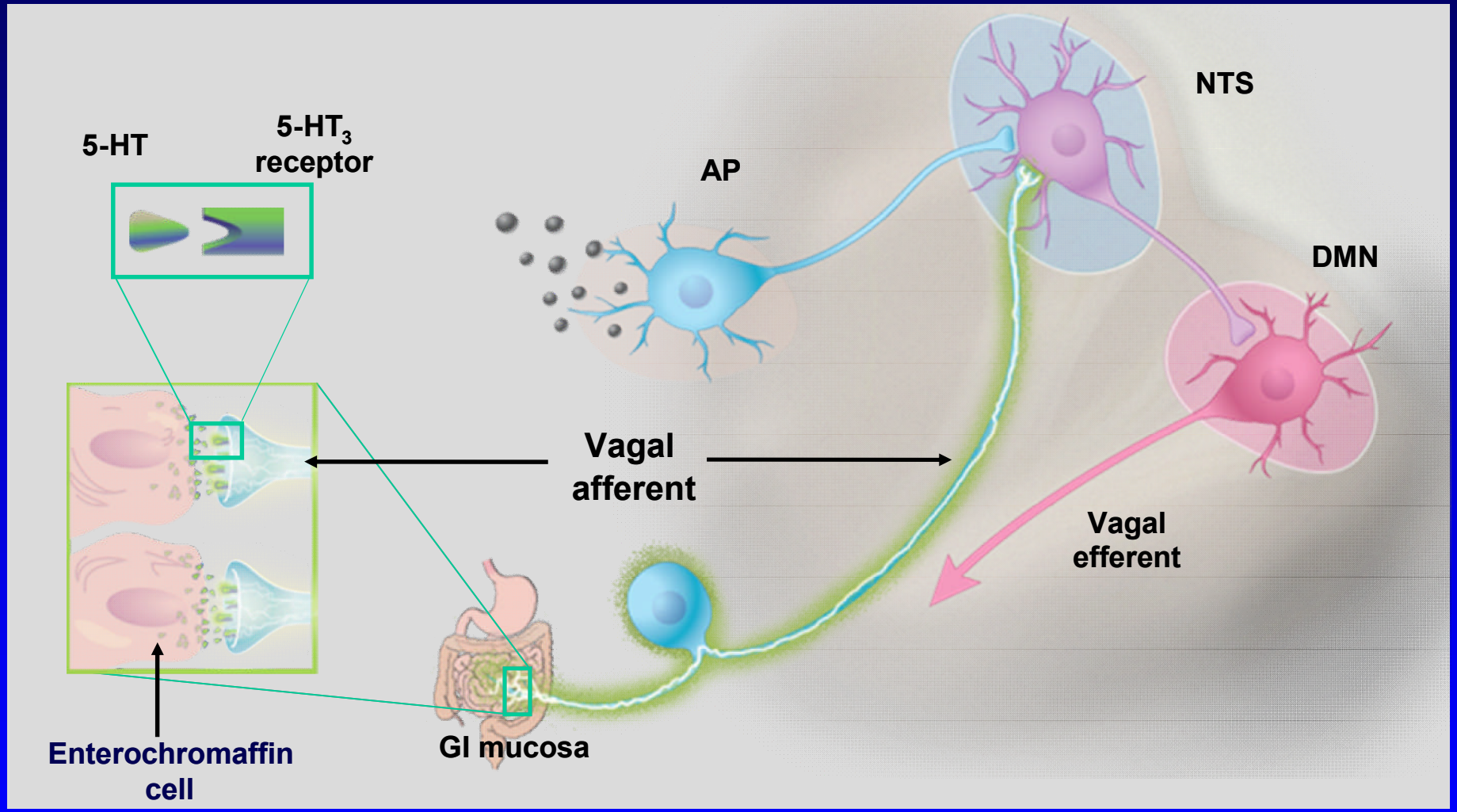
Chemotherapeutic drugs stimulate enterochromaffin cells to secrete mediators that activate vagal afferents




Adapted from:
1. Sanger GJ, Andrews PLR. *Auton Neurosci* 2006; **129**: 3–16.
2. Hesketh PJ. *N Engl J Med* 2008; **358**: 2482–2494

AP=area postrema; NTS=nucleus tractus solitarius; DMN=dorsal nucleus of the vagus; GI=gastrointestinal; 5-HT=serotonin; CCK=cholecystokinin

# Serotonin-mediated signalling in CINV is primarily peripheral

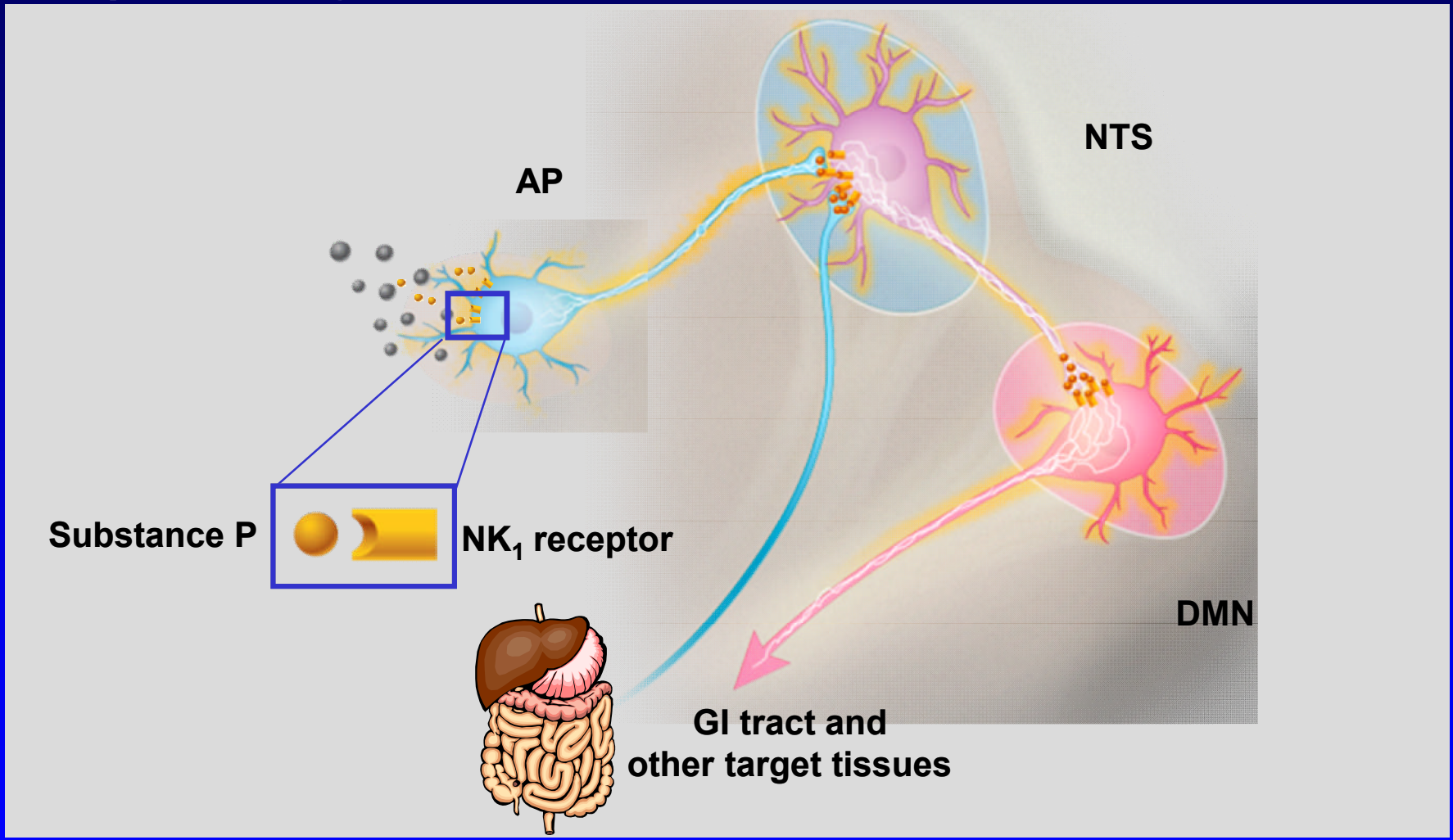



Adapted from:

1. Sanger GJ, Andrews PLR. *Auton Neurosci* 2006; **129**: 3–16.
2. Hesketh PJ. *N Engl J Med* 2008; **358**: 2482–2494

AP=area postrema; NTS=nucleus tractus solitarius; DMN=dorsal nucleus of the vagus; GI=gastrointestinal; 5-HT=serotonin

# Substance P-mediated signalling in CINV is primarily central

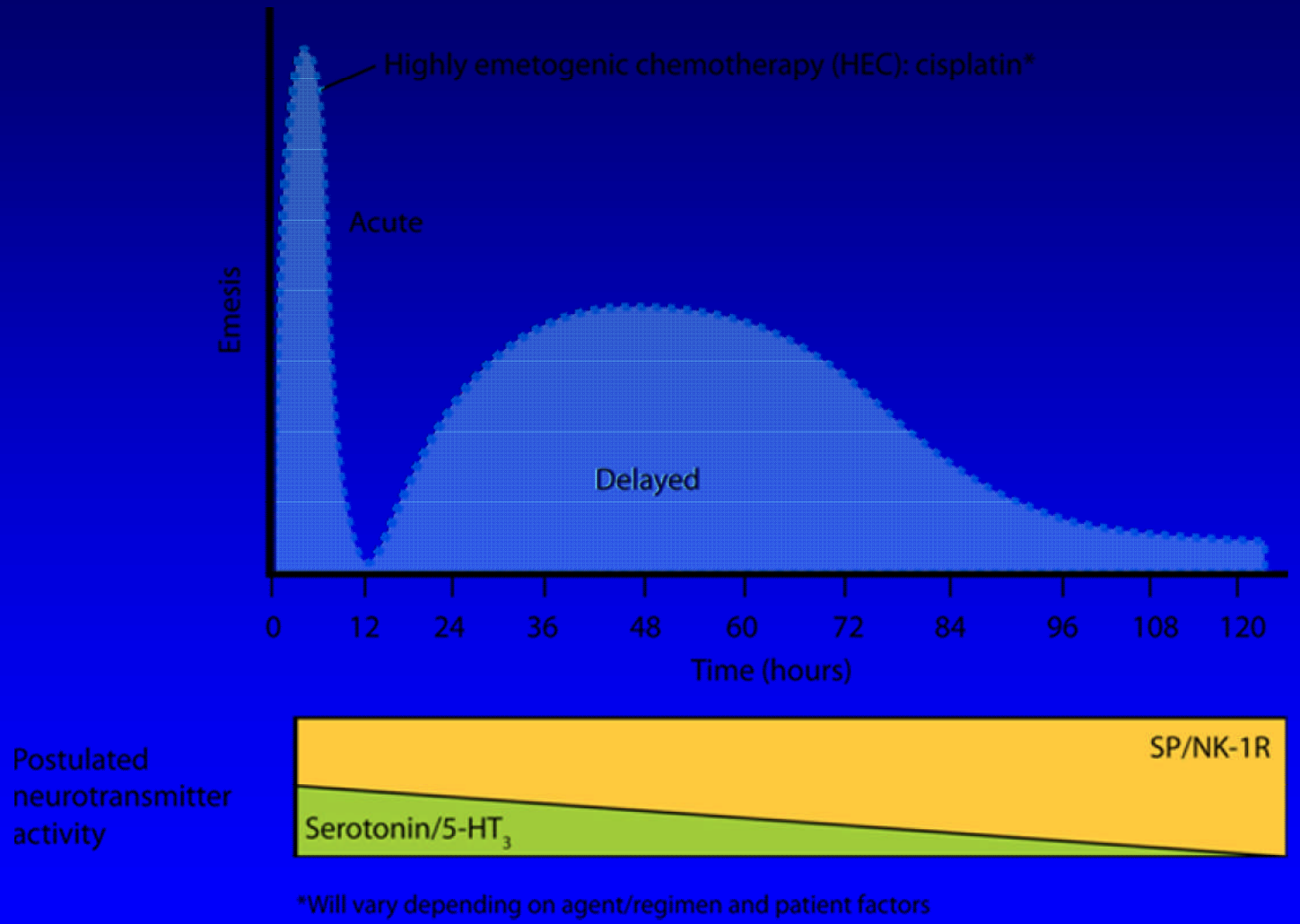



Adapted from:

1. Sanger GJ, Andrews PLR. *Auton Neurosci* 2006; **129**: 3–16.
2. Hesketh PJ. *N Engl J Med* 2008; **358**: 2482–2494

AP=area postrema; NTS=nucleus tractus solitarius; $NK_1$: neurokinin-1; DMN=dorsal nucleus of the vagus; GI=gastrointestinal

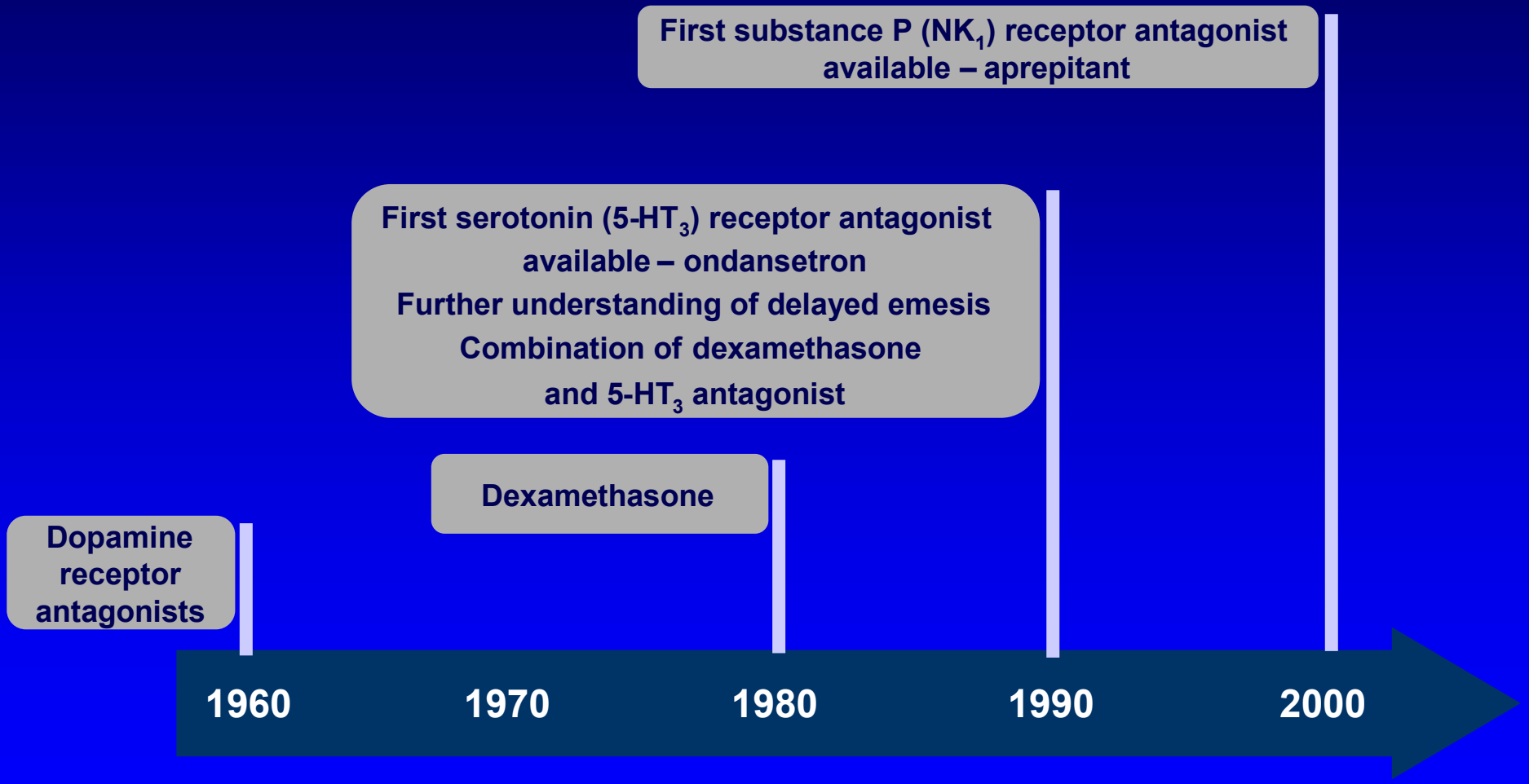
# Conceptual model of neurotransmitters activity during acute and delayed CINV




Hesketh PJ, *et al. Err J Can* 2003; **39**: 1074–1080

SP= substance P
NK-1R: neurokinin-1 receptor

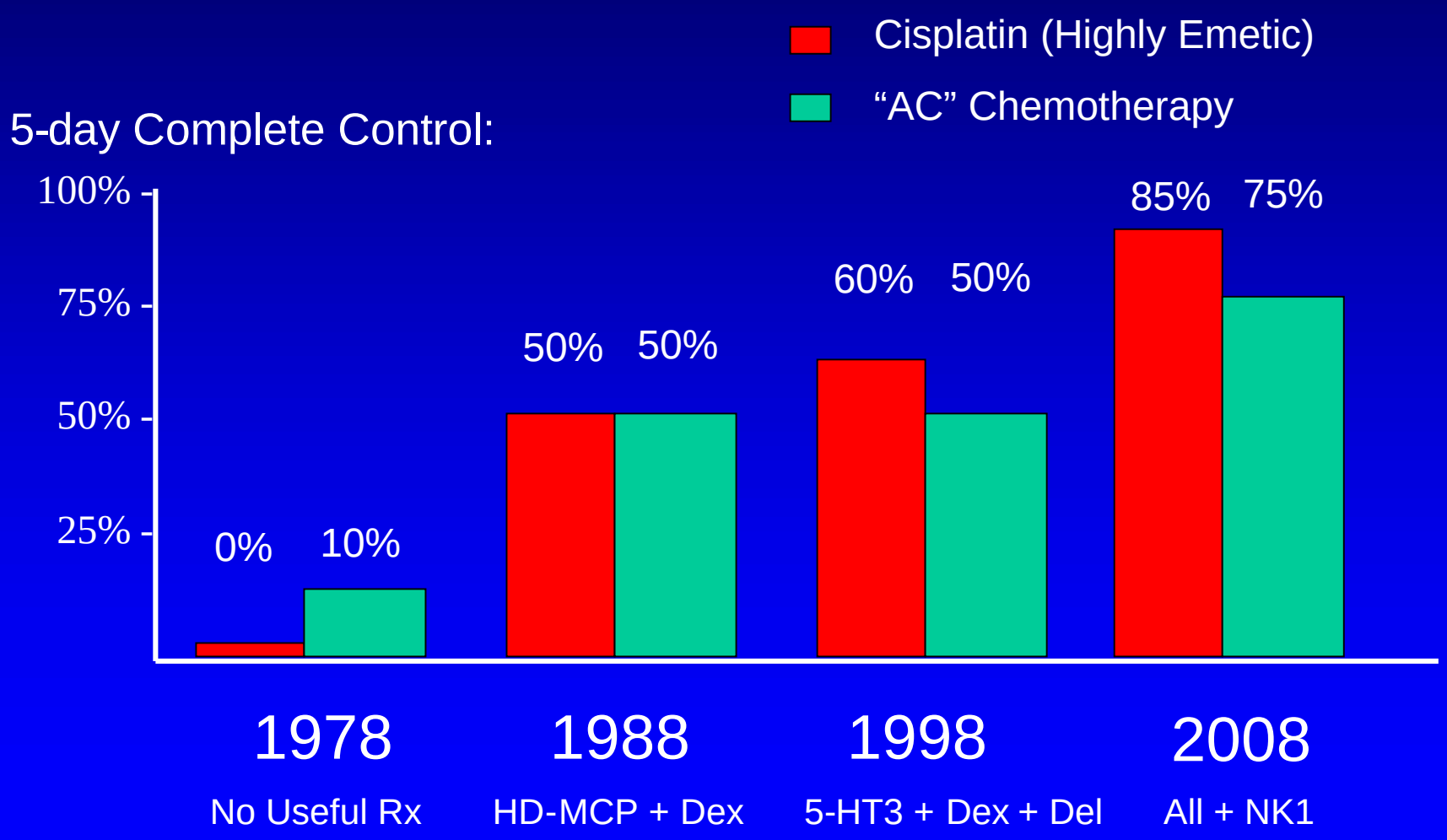
# Timeline of the evolution of antiemetics





1. Jordan K, *et al. Clin Rev Oncol/Hematol* 2007; **61**: 162–175.
2. Hesketh PJ. *N Engl J Med* 2008; **358**: 2482–2494.

# Kontrolle der Chemotherapie-induzierten Emesis: Fortschritte über 30 Jahre

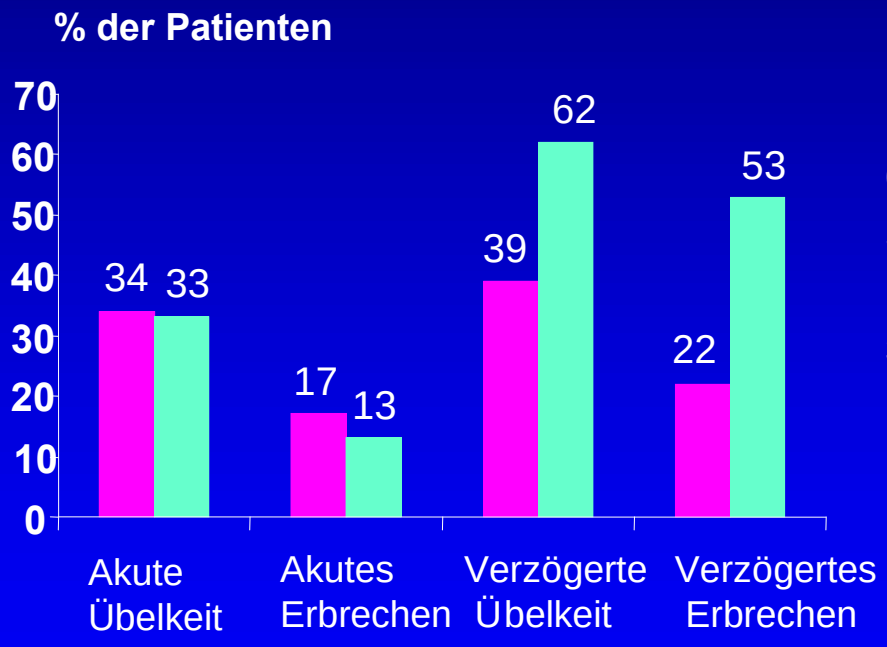


# ANCHOR Studie

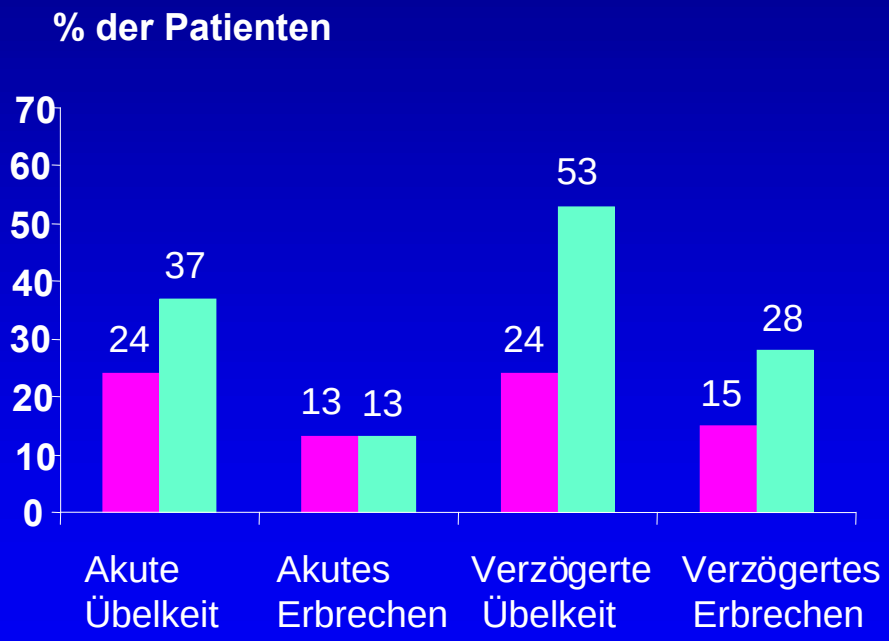
**Erwartung versus Realität bzgl. Chemotherapie-Induzierter Nausea und Emesis (CINV)**

# Erwartung versus Realität bei emetogener Chemotherapie

## Hoch emetogene Chemotherapie




## Moderat emetogene Chemotherapie




**Erwartung des Arztes/Schwester** **Realität des Patienten**

Physicians and nurses from 14 oncology practices in 6 countries

Patients: 75% women; 78% Mod emetic chemo; 50% breast cancer; 18% lung cancer

Grunberg et al. (2004). *Cancer, 100*, 261-268.

# Verbesserungspotential bei der Kontrolle der CINV

Trotz guter Kontrolle in der akuten Phase leiden 30-50% der Patienten unter verzögerte Übelkeit und Erbrechen

- Die klassische Kombination eines 5-HT3 RA und Dexamethason ist nur moderat wirksam zur Kontrolle von verzögerter Übelkeit und Erbrechen.

→ Verbesserung der Symptomkontrolle in der verzögerten Phase

- Die klassische Kombination eines 5-$HT_3$ RA und Dexamethasone kontrolliert Erbrechen besser als Übelkeit.

→ Verbesserung der Kontrolle von Übelkeit

# Incidence of CINV after HEC and MEC chemotherapy in the era of NK-1 receptor antagonists:

# Perception versus reality

*M. Majem et al., ASCO 2009*
*J Clin Oncol 27:15s, 2009 (suppl; abstr e20636)*

# Background

Physicians and nurses had underestimated the incidence CINV after both HEC and MEC.

(Grumberg, Cancer 2004;100:2261–8;
Erazo Valle, Curr Med Res Opin 2006;22:2403–10)

It was assessed if physicians and nurses' perception of CINV in their own practices after the introduction of Aprepitant was closer to reality.

*M. Majem et al., ASCO 2009*

# Results

29 physicians and nurses and 95 patients (86.3% receiving HEC, 13.7% MEC) were recruited.

| | Acute | | Delayed | |
|---|---|---|---|---|
| | Nausea | Emesis | Nausea | Emesis |
| **HEC** | 14,3 % | 2,4 % | 14,3 % | 7,1 % |
| Physicians and nurses accurately predicted the incidence of acute and delayed CINV after HEC patients receiving Aprepitant | | | | |
| **MEC** | 22,2 % | 0 % | 33,2 % | 22,2 % |
| All physicians and nurses underestimated the incidence of acute nausea and delayed nausea and emesis after MEC by | | | | |
| | 15 % | -- | 28 % | 18 % |

*M. Majem et al., ASCO 2009*

# Conclusions

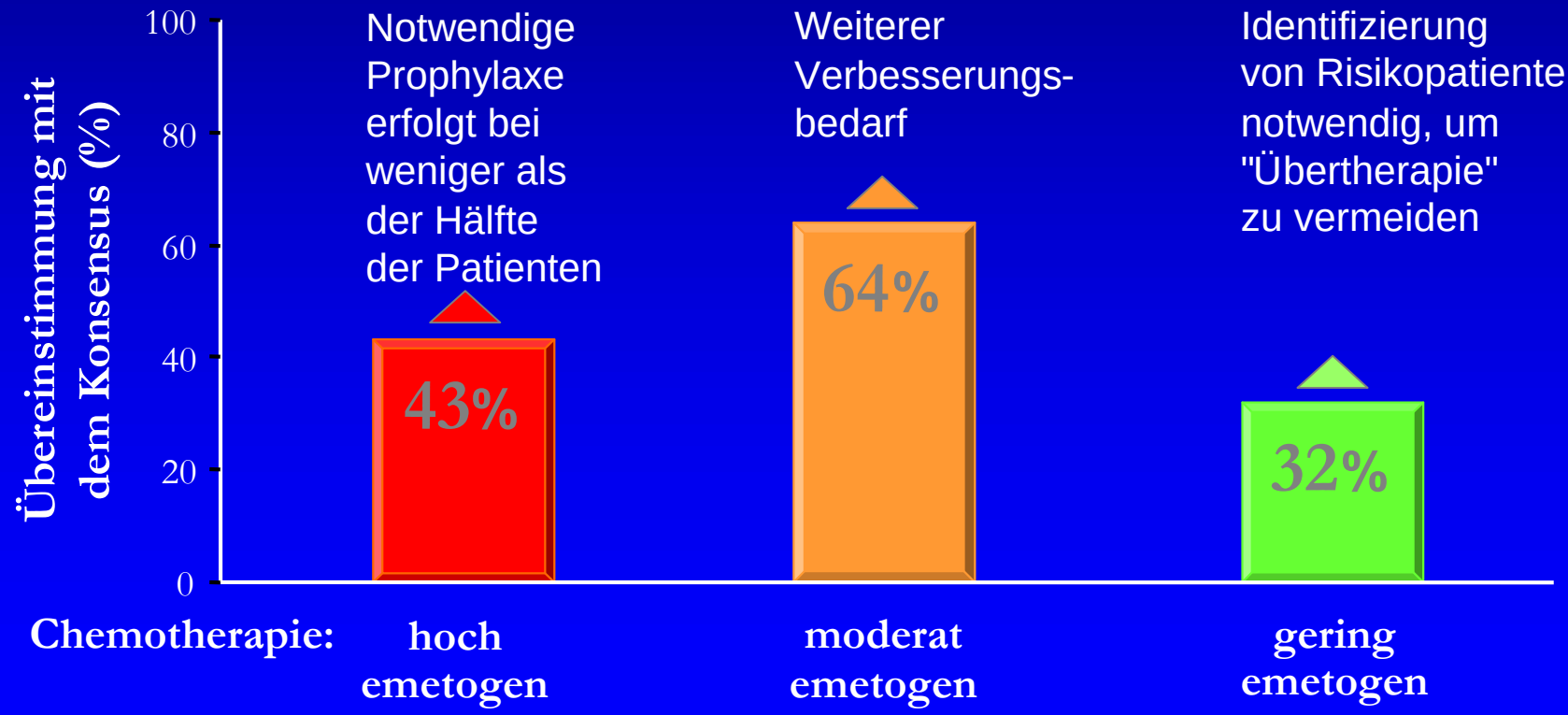
- The addition of aprepitant in the prevention of CINV after HEC allows a better control of CINV that is perceived accurately by physicians and nurses.
- By contrary, physicians and nurses continue markedly underestimating the incidence of CINV after MEC.
- CINV still remain important targets for improved therapeutic intervention and physicians and nurses must be aware about the real incidence of CINV.

*M. Majem et al., ASCO 2009*

# Unzureichende Befolgung der Leitlinien in der Praxis

**Multizentrische Studie (N=149)**

**Ziel: Überprüfung der Übereinstimmung der antiemetischen Therapie mit den Richtlinien der Perugia-Konsensus-Konferenz**




Fabi A et al. Support Care Cancer 2003; 11: 156-161

# Bekanntheitsgrad und Verwendung der Supportive Care Guidelines

| Supportive Care Guidelines | US (N=153) | | Europa (N=404) | |
|---|---|---|---|---|
| | etwas oder sehr vertraut mit den Guidelines | häufig oder immer in der Praxis angewendet | etwas oder sehr vertraut mit den Guidelines | häufig oder immer in der Praxis angewendet |
| MASCC | 22,2 % | 7,2% | 27,7% | 11,3% |
| ASCO | 88,9% | 56,9% | 81,4% | 47,3% |
| NCCN | 94,8% | 68,6% | 43,3% | 18,8% |
| ESMO | 15,0% | 9,9% | 55,9% | 25,7% |
| EORTC | 20,3% | 5,9% | 69,8% | 34,9% |

# Reduction in nausea and vomiting through adherence to MASCC (Multi-national Association of Supportive Care in Cancer) Antiemetic Guideline for platinum chemotherapy

O'Kane et al., MASCC 2009

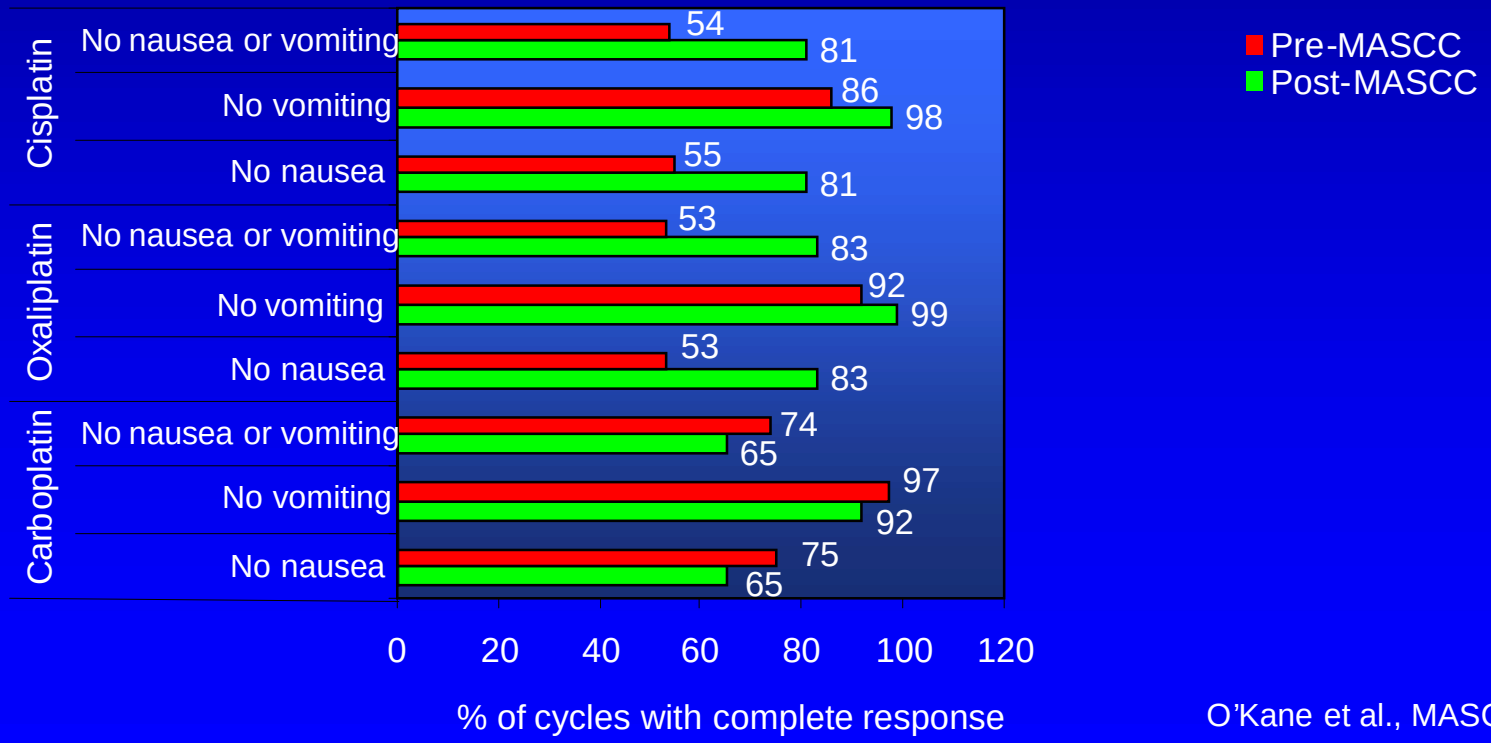
# Methodology

- Each patient completed a daily diary card recording toxicity for the duration of CTx.
- 20 patients with oxaliplatin, 20 with carboplatin, 60 with cisplatin
- Each regimen was assessed for compliance with MASCC guidelines.
- All oncologists agreed to change all regimens to complete adherence with guidelines and these were implemented.
- New patients undergoing first line treatments which followed guidelines completed the daily toxicity diary card and the results were reviewed.

O'Kane et al., MASCC 2009

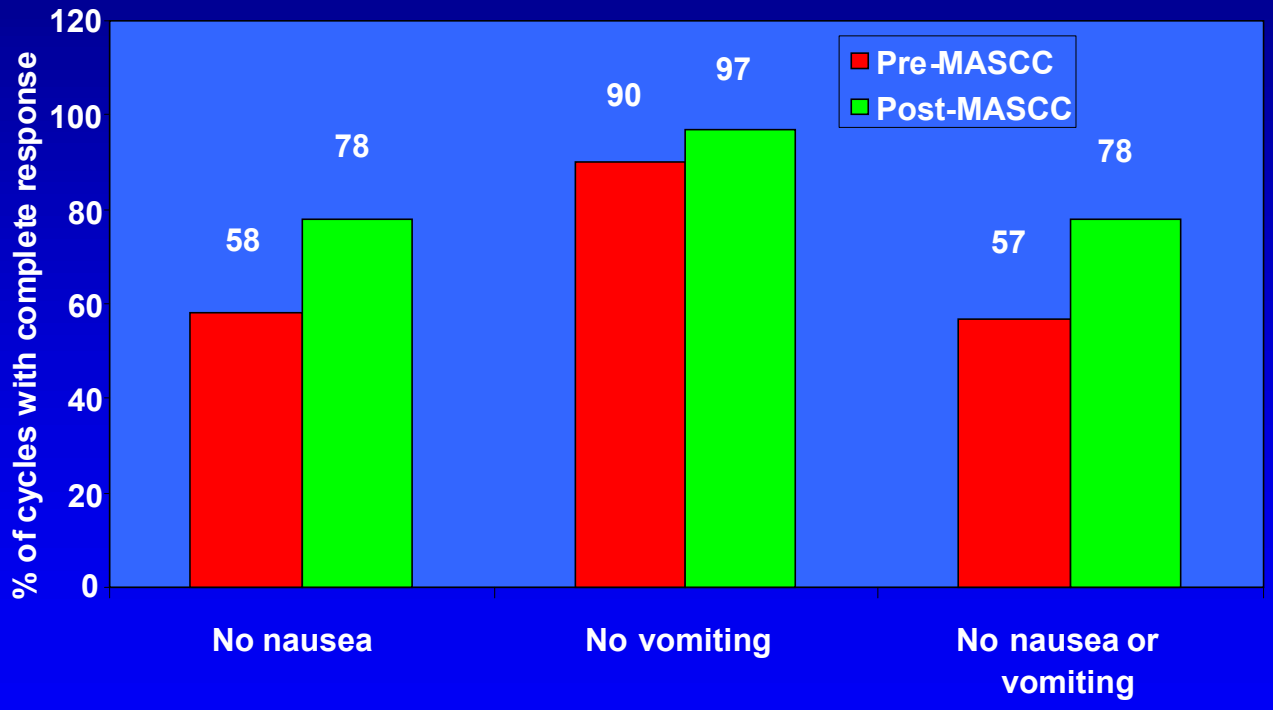
# Results

- Only 32% of a total of 90 regimens complied with MASCC guidelines for anti-emetics.




O'Kane et al., MASCC 2009

# Results




O'Kane et al., MASCC 2009

# Discussion and Conclusion

- Implementing the MASCC Antiemetic guideline improved the proportion of cycles with complete response from 57% to 78% (P=0.023 ).
- Both nausea and vomiting were significantly improved by strict adherence to the MASCC Antiemetic Guideline.
- A more marked reduction in nausea and vomiting was seen with regimens containing cisplatin or oxaliplatin than with carboplatin.
- These results reinforce the value of close adherence to the MASCC guidelines.

O'Kane et al., MASCC 2009

MASCC

INTERNATIONAL SOCIETY of ORAL ONCOLOGY

**MASCC / ISOO**
**2009 International Symposium**
**Supportive Care in Cancer**
**June 25 – June 27, 2009 / Rome, Italy**

# 2009 UPDATE OF ANTIEMETIC GUIDELINES

# PERUGIA INTERNATIONAL CANCER CONFERENCE VIII (June 20-21, 2009):

## -ANTIEMETIC GUIDELINES -

## Under the Sponsorship of:

### MULTINATIONAL ASSOCIATION OF SUPPORTIVE CARE IN CANCER

### EUROPEAN SOCIETY OF MEDICAL ONCOLOGY

**Organizing and Overall Meeting Chairs:**

Richard J. Gralla, MD
Jørn Herrstedt, MD
Fausto Roila, MD
Maurizio Tonato, MD

# STUDIES WITH A POTENTIAl TO CHANGE THE GUIDELINES

| Reference | Question |
|---|---|
| Saito et al.<br>Lancet Oncol 2009 | Palonosetron in AC? |
| Warr et al. JCO 2005 | Aprepitant in AC? |
| Rapoport et al.<br>Support Care Cancer (accepted) | Aprepitant in MEC? |
| Yeo et al.<br>Breast Cancer Res Treat 2009 | Aprepitant in AC? |

# PERUGIA 2009 ANTIEMETIC GUIDELINES

## ANTIEMETIC TREATMENT GUIDELINES

- Committee I (1/5): The Four Emetic Risk Groups -

| | |
|---|---|
| **HIGH** | Risk in nearly all patients (> 90%) |
| **MODERATE** | Risk in 30% to 90% of patients |
| **LOW** | Risk in 10% to 30% of patients |
| **MINIMAL** | Fewer than 10% at risk |

## Perugia MASCC/ESMO Guidelines 2009 - Committees II-III

# Prevention of nausea and vomiting following chemotherapy of high emetic risk

- To prevent acute and delayed vomiting and nausea following chemotherapy of high emetic risk, a multiday drug regimen including a 5-$HT_3$ receptor antagonist, dexamethasone, and a $NK_1$ receptor antagonist beginning before chemotherapy is recommended

- --- MASCC level of consensus: high
- --- MASCC level of confidence: high

- ---ESMO level of evidence: I
- ---ESMO grade of recommendation: A

Patients are at risk for delayed emesis and must receive prophylactic antiemetics for two to three days following chemotherapy (see table)

# DOSAGES AND SCHEDULES OF $NK_1$ ANTAGONISTS IN CISPLATIN-INDUCED EMESIS (Table 2)

| | |
|---|---|
| Acute Emesis | - Aprepitant 125 mg orally, once on the day of CT<br>- Fosaprepitant 115 mg IV, once on the day of CT |
| Delayed Emesis | - Aprepitant 80 mg orally, once daily for the 2 days after CT |

# Committees II-V
# Combined Statement #2 – "AC"

**Prevention of nausea and vomiting following "AC", a combination of an anthracycline plus cyclophosphamide in women with breast cancer**

To prevent acute and delayed vomiting and nausea following "AC" chemotherapy in women with breast cancer, we recommend a multiday drug regimen including a 5-$HT_3$ receptor antagonist, dexamethasone, and a $NK_1$ receptor antagonist beginning before chemotherapy

- MASCC level of consensus: high
- MASCC level of confidence: high
- ESMO level of evidence: I
- ESMO grade of recommendation: A

Patients are at risk for delayed emesis and must receive prophylactic antiemetics for two to three days following chemotherapy (see table)

# Committees II-V
# Combined Statement #3 – Moderate*

**Prevention of nausea and vomiting following chemotherapy of moderate emetic risk**

To prevent acute and delayed vomiting and nausea following chemotherapy of moderate emetic risk, we recommend a regimen of palonosetron and multiday dexamethasone beginning before chemotherapy

- MASCC level of consensus: high
- MASCC level of confidence: low
- ESMO level of evidence: II
- ESMO grade of recommendation: A

*Does not include “AC” given its higher risk of nausea and vomiting

# Committees II-V
# Combined Statement #4: Principles of 5-HT3

**Consensus principles of 5-$HT_3$ receptor antagonists used to prevent acute and delayed nausea and vomiting**

1. Use the lowest tested fully effective dose
2. No schedule better than a single dose beginning before chemotherapy
3. Intravenous and oral formulations are equally effective and safe
4. Adverse effects of these agents are comparable
5. Give with dexamethasone
6. For high emetic risk and women with breast cancer given “AC”, give with an $NK_1$ receptor antagonist beginning before chemotherapy

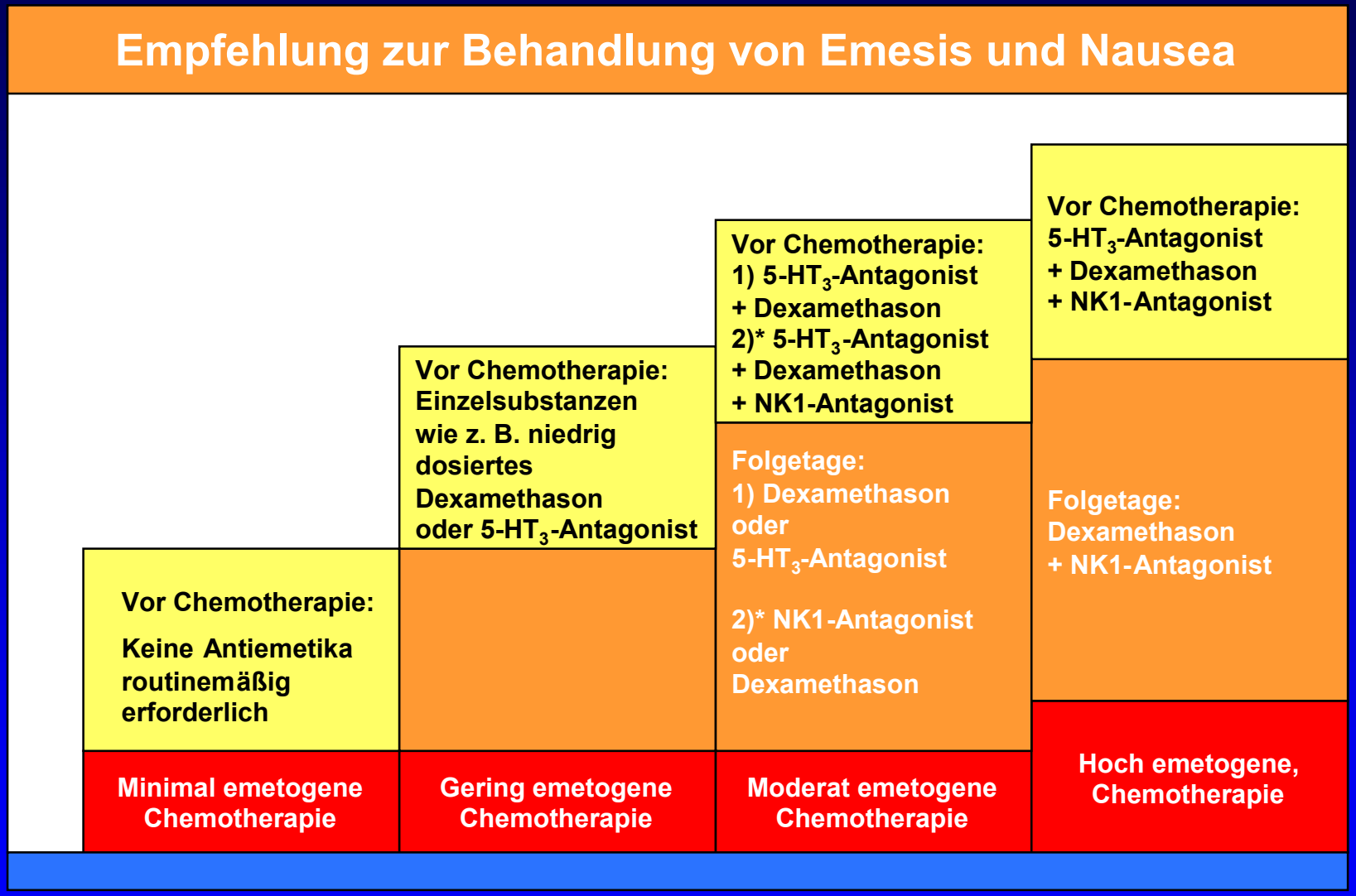
- MASCC level of consensus: high
- MASCC level of confidence: moderate
- ESMO level of evidence: I
- ESMO level of recommendation: A

# AC Recommended Dexamethasone and $NK_1$ Receptor Antagonist Dosing

| | Dose and Schedule |
|---|---|
| **DEXAMETHASONE** | 8 mg prechemotherapy |
| **APREPITANT (PO)**<br>**FOSAPREPITANT (IV)** | 125 mg PO or 115 mg IV<br>Prechemotherapy<br>than 80 mg once daily for 2 days |

# MASCC / ESMO Guidelines 2009 Update

## Empfehlung zur Behandlung von Emesis und Nausea




*bei Patientinnen mit einer Kombination aus Antrazyklin + Cyclophosphamid*

# Benefits of “Guideline-Recommended” Prophylaxis for CINV

Effective treatment can promote high adherence which may:[2-4]

- Decrease indirect costs (absenteeism, presenteeism)
- Reduce switching of medications and associated costs
- Decrease hospitalizations and emergency department visits


1. Poli-Bigelli S, et al. *Cancer*. 2003;97:3090-3098.
2. Joshi AV, et al. *J Asthma*. 2006;43:521-526.
3. Lerman I. *Arch Med Res*. 2005;36:300-306.
4. Singh M, Kansra S. *Indian Pediatr*. 2006;43:1050-1055.

# Optimizing antiemetic treatment

- Awareness must be increased for:
  - Current guidelines
  - Evidence supporting guideline recommendations
  - Incidence of and risk factors for nausea and vomiting
- Antiemetic treatment must be individualized based on emetogenic potential of the therapy and patient-specific factors

# Zukünftige Strategien der Antiemese

**Neue Substanzen und neue Wirkmechanismen**

1. Potentere 5-$HT_3$–Antagonisten
2. $NK_1$-Antagonisten
3. Single dose all in one

Erhöhte Effektivität der 5-HT3-Antagonisten
Bessere Kontrolle der verzögerten Emesis

# **Perspective** antiemetic therapy **?**

**Triple therapy** a new standard .