

Pharmacological Management of Chemotherapy-induced Nausea & Vomiting (CINV)

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Patient Perceptions of the Most Severe Side Effects of Cancer Chemotherapy

Rank	1983 ¹	1993 ²	1995 ³	1999 ⁴	2008 ⁵	2011 ⁶
1.	Vomiting	Nausea	Nausea	Nausea	Fatigue	Fatigue
2.	Nausea	Fatigue	Loss of hair	Loss of hair	Nausea	Nausea/vomiting
3.	Loss of hair	Loss of hair	Vomiting	Fatigue	Taste change	Loss of hair
4.	Thought of coming for treatment	Effect on family	Fatigue	Vomiting	Fever	Taste change
5.	Length of time treatment takes	Vomiting	Having to have an injection	Taste change	Depression or Irritability	Blood counts problem

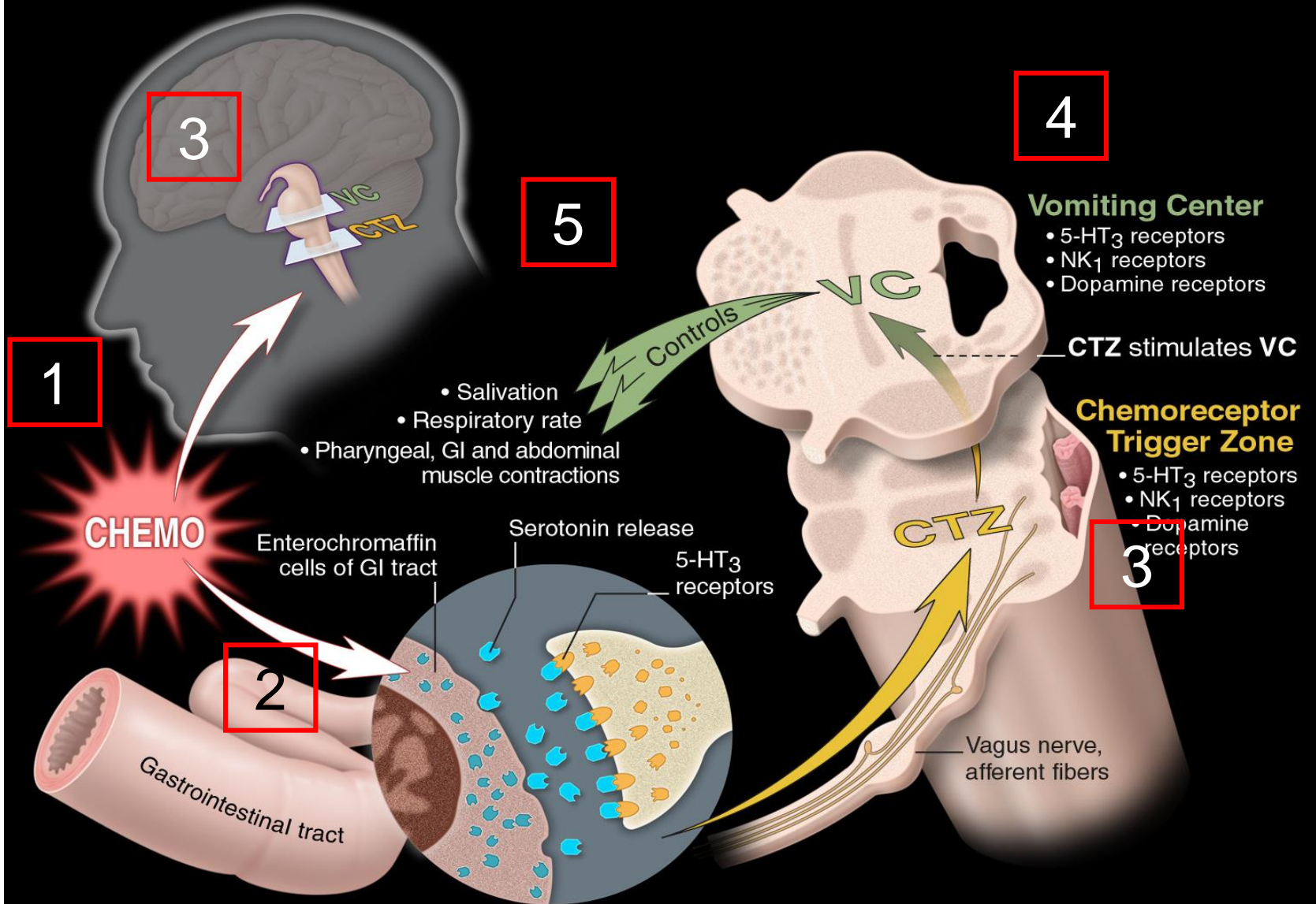
1. Coates A, et al. Eur J Cancer Clin Oncol. 1983;19:203-8. 2. Griffin AM, et al. Ann Oncol. 1996;7:189-95.
 3. De Boer-Dennert M, et al. Br J Cancer. 1997;76:1055-61. 4. Lindley C, et al. Cancer Pract. 1999;7:59-65.
 5. Dawn Hershman Arch Drug Info 2008;1:70-8. 6. 台灣癌症基金會--- 2011關懷癌友調查計畫

調查發現癌症病患經過化療後，最常見的三種副作用

- ✓ 疲憊(81%)。
- ✓ 噁心嘔吐(71%)。
- ✓ 落髮問題(60%)。

疲憊、嘔心噁吐、落髮
是三種常見的化療副作用

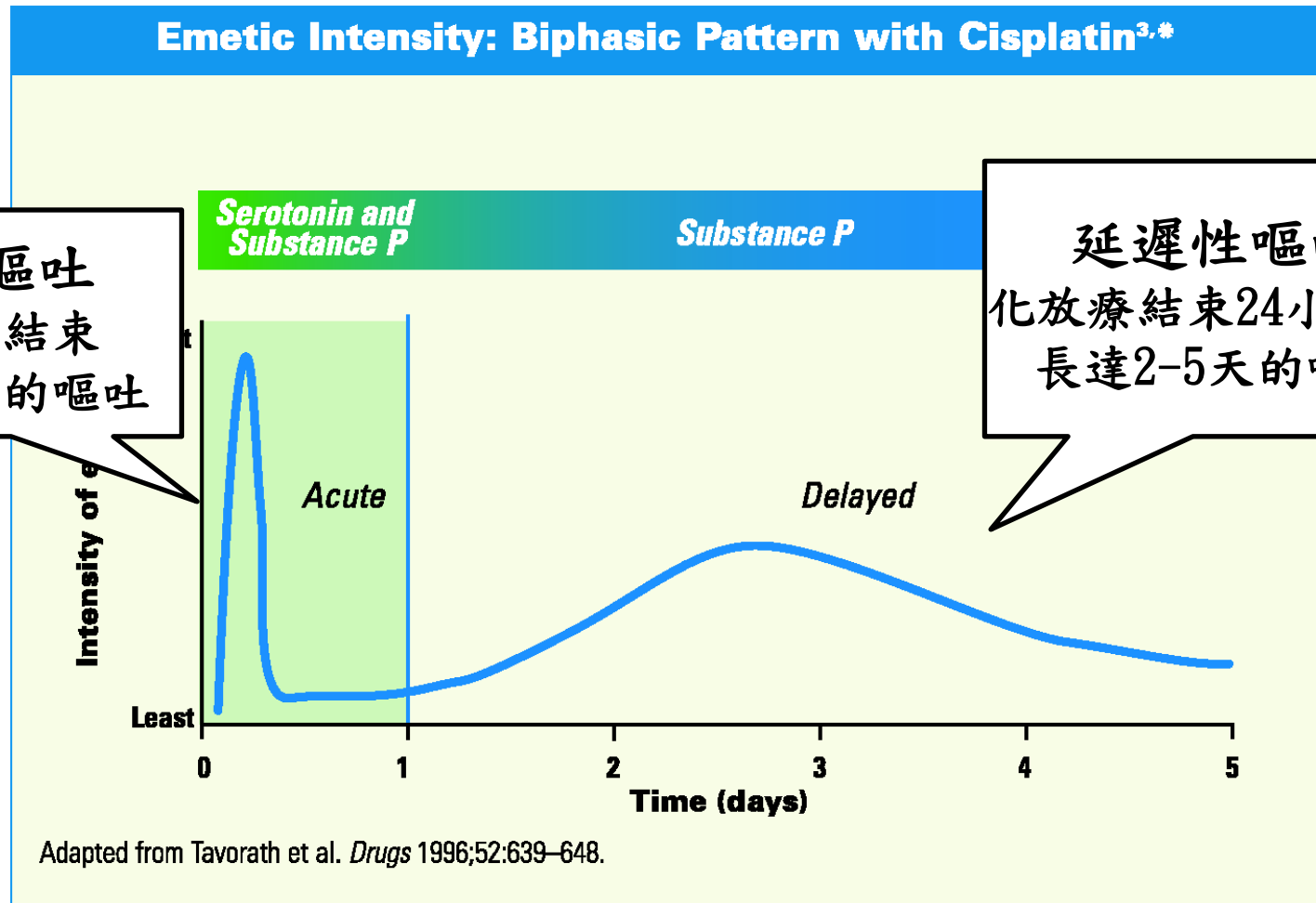
化療引起的嘔吐機轉



化學治療引起噁心嘔吐之類型及定義

- 急性噁心嘔吐 (**Acute**)
 - 使用化學治療藥物後，24小時內
- 延遲性噁心嘔吐 (**Delayed**)
 - 使用化學治療藥物後，超過24小時
 - 可能會持續至120小時(Day 5)
- 預期性噁心嘔吐 (**Anticipatory**)
 - 使用化學治療藥物開始前數天至數小時發生
- 突發性噁心嘔吐 (**Breakthrough**)
 - 已使用預防性處置，或止吐藥物，仍發生

急性及延遲性嘔吐 作用時間不同



Adapted from Tavorath R, Hesketh PJ *Drugs* 1996;52:639-648. © 1996. Used with permission from Adis International Limited.

Risk factors for CINV

Patient specific	Chemotherapy specific
Female	Emetogenic potential of a chemotherapeutic agent
History of morning sickness	Coadministration with other chemotherapeutic agents
Age <50 years	Dosage of chemotherapeutic agents
History of low alcohol intake (<1.5 oz/day)	Rate of intravenous (I.V.) infusion time
History of prior CINV	Repeated cycles of chemotherapy
History of nausea/vomiting during pregnancy	
Preexisting anxiety and nausea	

1. J Support Oncol. 2003;1:89–103.
2. J Clin Oncol. 1997;15(1):116–123.
3. Ann Oncol.2006;17(1):20–28.
4. Oncologist. 1999;4:191–196.

化療藥物致吐性風險分級

單一化學治療藥物致吐風險分為四級

高致吐性	>90%
中致吐性	30%-90%
低致吐性	10%-30%
輕微致吐性	<10%

合併化學治療藥物致吐風險分級

其藥物組合中，致吐風險分級最高者為其整體組合之分級。

Commonly Used Highly and Moderately Emetogenic Chemotherapy Regimens

Cancer Type	Regimen
Breast	AC, TAC, TC, CMF, TCH
Lung	Carbo-Tax, Cis-Tax, cisplatin with vinorelbine, cisplatin with gemcitabine, cisplatin with pemetrexed
Head and neck	Cisplatin-based or carboplatin-based regimens
Hodgkin lymphoma	ABVD, CHOP with or without rituximab, CVP
Colorectal	FOLFOX, FOLFIRI, CapeOX, irinotecan
Ovarian	Carbo-Tax, IPcisplatin, cisplatin

ABVD—doxorubicin + bleomycin + vinblastine + dacarbazine; AC—doxorubicin + cyclophosphamide; CapeOX—oxaliplatin + capecitabine; Carbo-Tax—carboplatin + paclitaxel; CHOP—cyclophosphamide + doxorubicin + vincristine + prednisone; Cis-Tax—cisplatin + paclitaxel; CMF—cyclophosphamide + methotrexate + fluorouracil; CVP—cyclophosphamide + vincristine + prednisone; FOLFIRI—irinotecan + leucovorin + 5-fluorouracil; FOLFOX—oxaliplatin + leucovorin + 5-fluorouracil; IP—intraperitoneal; TAC—docetaxel + doxorubicin + cyclophosphamide; TC—docetaxel + cyclophosphamide; TCH—doxorubicin + carboplatin + trastuzumab

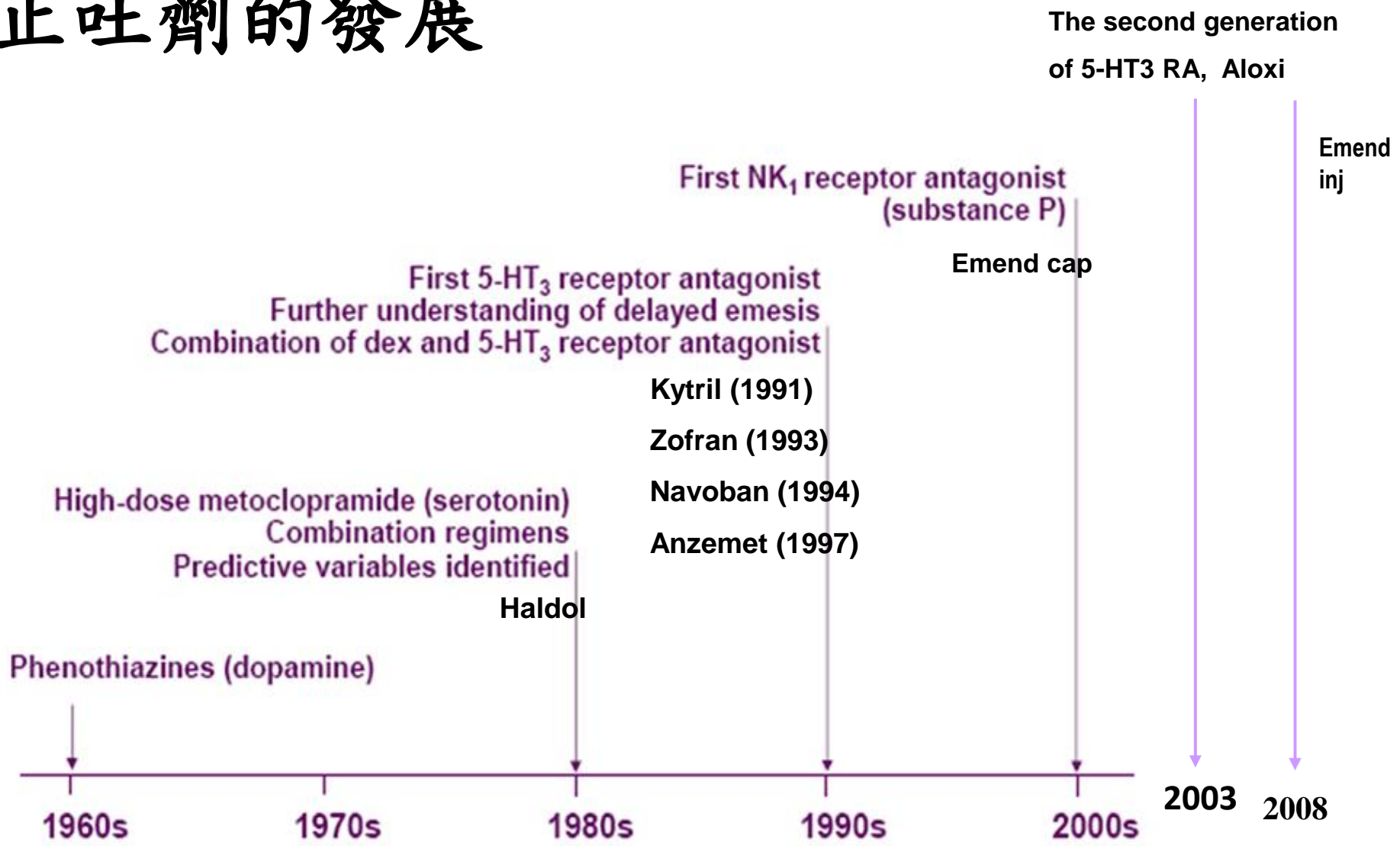
止吐藥物使用原則

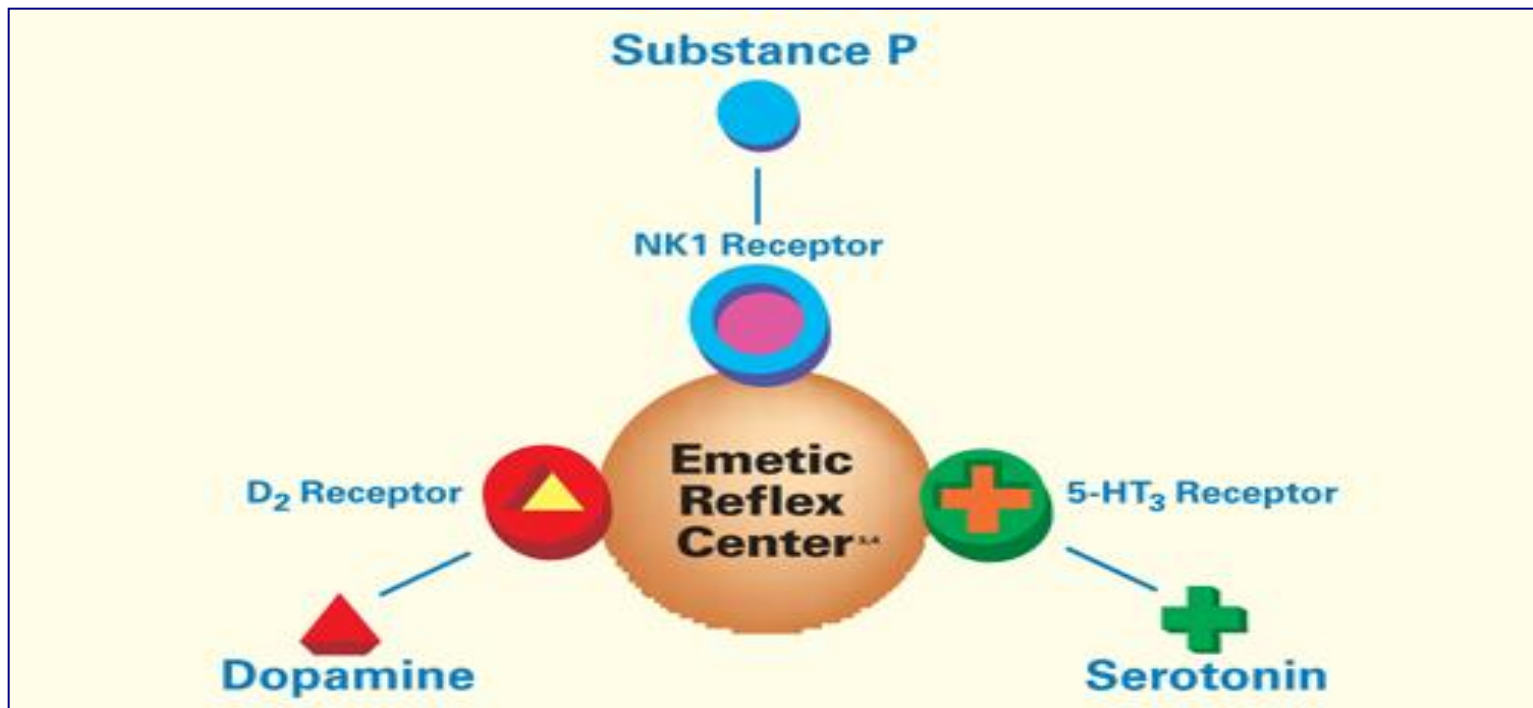
1. 以預防噁心嘔吐為目標
2. 病人開始接受化學治療藥物前即給予止吐藥物，以達到最大止吐效果
3. 止吐藥物的選擇須考量化學治療藥物致吐風險、病人之前使用止吐藥物的反應、病人個人因子、個別止吐藥物之毒性
4. 口服與靜脈給藥之止吐效果相當（口服可以為第一選擇）
5. 止吐藥物的使用期間必須考慮化學治療藥物引起噁心嘔吐作用期間
6. 病人接受高度致吐性化學治療藥物，考慮其致吐風險至少為3天；中度致吐性藥物，致吐性風險至少為2天；於整個風險期間，必須實施嘔吐預防

止吐劑類別

- Corticosteroids
- Dopamine antagonists
- Serotonin (5-HT₃) antagonists
- NK-1 receptor antagonists
- Cannabinoids (ex : dronabinol 、 nabilone 、 levonantradol)
- Others

止吐劑的發展





Histamine (H₁) receptors play a role in nausea and vomiting caused by the vestibular system (ie, motion sickness) but not CINV¹; no role for histamine (H₂) receptors in CINV²

Dopamine is no longer thought to be a key neurotransmitter responsible for CINV, now that the roles of serotonin and substance P are better understood²

1. Diemunsch P, Grélot L. *Drugs*. 2000;60:533–546.

2. Berger AM et al. In: *Cancer: Principles & Practice of Oncology*. Lippincott Williams & Wilkins; 2001:2869–2880.

常用現有止吐藥物的作用機轉

藥物分類	Drugs	作用機轉
5HT ₃ antagonist	Ondansetron, Granisetron, Tropisetron, Dolasetron Palonosetron	CTZ & peripheral 5HT ₃
NK-1 antagonist	Aprepitant(Emend)	CTZ substance-P
Corticosteroid	Dexamethasone	Prostaglandin
BZD	Lorazepam, Diazepam	Sedative & anxiolytic
Antihistamines	Diphehydramine	Vestibular nucleus
Dopamine & 5HT ₃ receptor	Metoclopramide	Dopamine antagonist

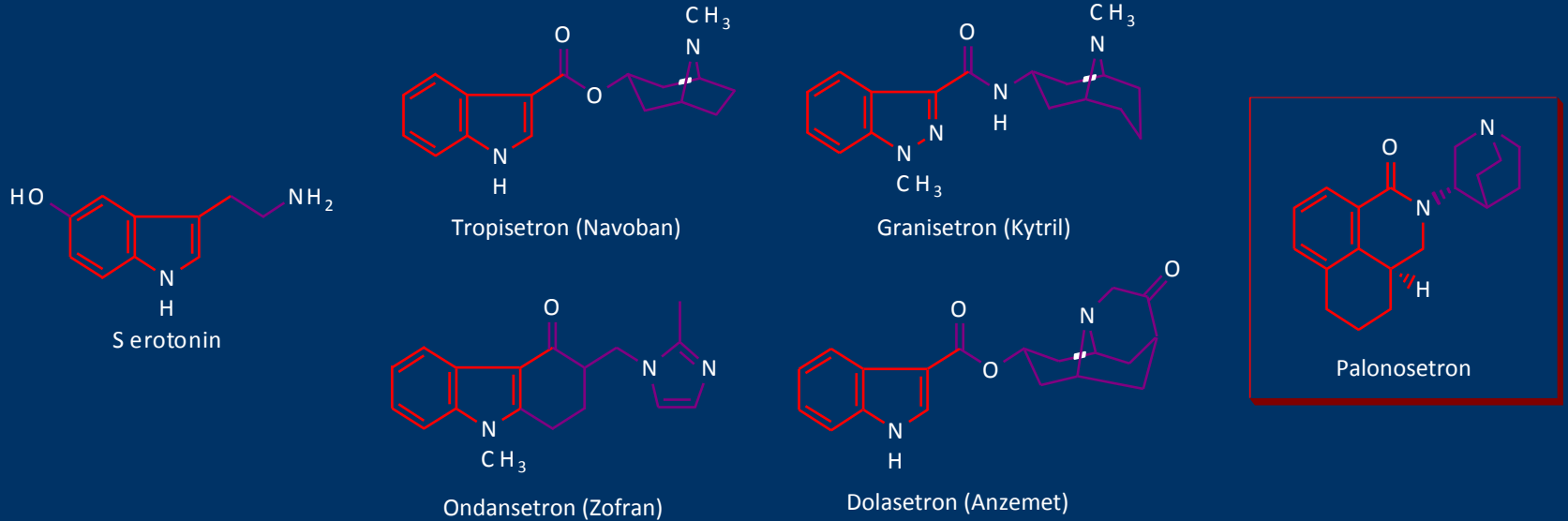
5-HT₃ 受體拮抗劑

- 所有的5-HT₃ 受體拮抗劑皆可以有效地控制化學治療藥物引起之急性嘔吐
- 併用Dexamethasone 可增加含有5-HT₃ 受體拮抗劑的治療藥物組合之止吐效用
- 靜脈注射Palonosetron可以有效地預防中致吐性化學藥物所引起之急性與延遲性嘔吐
- 每日單次之劑量為佳
- 等效治療劑量下，口服與靜脈給藥之止吐療效與安全性相當
- 副作用：constipation, diarrhea, dry mouth, and fatigue.

5-HT₃ RA : chemical structure

第一代 5-HT₃ RA

第二代



First generation 5-HT₃ antagonists resemble serotonin;
palonosetron is structurally distinct

Mechanism of Action Conclusions

All 5-HT3 RAs structures resemble serotonin...

	PALO	OND	GRAN	TROP	RAMO
Potency (NHI cost 元)	0.25mg/vial (1107)	4mg/8mg/vial; 8mg/tab (219/296;225)	1mg/3 mg/vial; 1mg/tab (450/959;259)	5mg/vial; 5mg/tab (425;428)	0.3 mg/vial (525)
Half Life (hrs)	40	4	9	8	5.8~9
Binding Affinity	10.45	8.39	8.91	8.81	10.23
Allosteric binding & Positive Cooperativity	YES	NO	NO	NO	NO
Inhibition of Receptor Function	Long Lasting	Short Lasting	Short Lasting	Short Lasting	Short Lasting
Receptor Internalization	YES	NO	NO	NO	NO
Inhibition of 5-HT3 & NK1 receptor cross-talk	YES	NO	NO	NO	NO

皮質類固醇 (Corticosteroids)

- 單一藥物適用於低致吐性化學治療藥物所引起之嘔吐
- Dexamethasone併用5-HT₃受體拮抗劑與aprepitant，對於高度或中度致吐性化學治療藥物所引起之嘔吐效果特別有價值
- 等效治療劑量下，皮質類固醇之止吐效果與安全性相當
- 已含皮質類固醇的化學治療藥物組合，避免另加入dexamethasone作為止吐之用
- 併用aprepitant時，口服皮質類固醇劑量降為原劑量之50%，而靜脈注射劑量則下降為75%

NK-1 receptor antagonist

- Aprepitant(PO); Fosaprepitant (IV),
 - PO : 125 mg on Day 1 of chemotherapy, then 80 mg daily on days 2 and 3,
 - IV : 150 mg on Day 1 only as an infusion over 20 to 30 minutes initiated approximately 30 minutes before chemotherapy.
- **combined with a regimen of dexamethasone (3 ~ 4 days) and a 5HT3 antagonist(only Day 1)**
- Common adverse effects: hiccups (4.6%), asthenia/fatigue (2.9%), increased ALT (2.8%), constipation (2.2%), headache (2.2%), and anorexia (2.0%)..

	Geometric mean	
	Aprepitant (125 mg)	Fosaprepitant (115 mg)
AUC _{0 - ∞} , ng·h/ml	27,759	29,611
C _{max} , ng/ml	1,354	3,095
C ₂₄ , ng/ml	494	504
t _{max} , h	4	0.25
t _{1/2} , h	14	13.6

Precaution (1)

- Aprepitant, is a moderate cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitor. Because fosaprepitant is rapidly converted to aprepitant, neither drug should be used concurrently with pimozide, terfenadine, astemizole, or cisapride.
 - Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions.
- In clinical trials, EMEND increased the AUC of dexamethasone(CYP3A4 substrate), by 2.2-fold on Days 1 and 5;
 - the dexamethasone dose should be reduced by approximately 50% when coadministered with EMEND.

Precaution (2)

- Aprepitant with warfarin may result in a clinically significant decrease in international normalized ratio (INR) of prothrombin time.
 - In patients on chronic warfarin therapy, the INR should be closely monitored in the 2-week period, particularly at 7 to 10 days, following initiation of the 3-day regimen of EMEND with each chemotherapy cycle.
- The efficacy of hormonal contraceptives may be reduced during coadministration with Aprepitant and for 28 days after the last dose of Aprepitant.

Dopamine 受體拮抗劑

- 適用於對5-HT₃ 受體拮抗劑、NK-1 受體拮抗劑、dexamethasone等止吐藥無法耐受或無療效的病人
- Phenothiazine (如：prochlorperazine, thiethylperazine)；Dopamine antagonist，(如：metoclopramide)；butyrophenones (如：haloperidol 和 droperidol)。
- 副作用：muscle spasms and restlessness.

Benzodiazepine

- Lorazepam在致吐藥物組合中為輔助性角色，不建議單獨使用
- Lorazepam可以協助預防與治療預期性嘔吐

2009 台灣癌症化學治療引起 之噁心嘔吐處理規範

急性嘔吐的預防

藥物致吐性分級	於第一天(day 1)使用化學治療藥物前
高致吐性 併用anthracycline 與 cyclophosphamide	<u>5-HT₃ 受體拮抗劑併用dexamethasone 與 aprepitant</u>
中致吐性	<u>5-HT₃ 受體拮抗劑併用dexamethasone</u>
低致吐性	<u>使用dexamethasone</u>
輕微致吐性	<u>無須常規性使用止吐用藥</u>

延遲性嘔吐的預防

藥物致吐性分級	使用方法
高致吐性	<u>Corticosteroids (於第二至第四天使用)</u> <u>併用 aprepitant (於第二至第三天使用)</u>
併用 anthracycline 與 cyclophosphamide	<u>Corticosteroids (於第二至第三天使用)</u> <u>併用 aprepitant (於第二至第三天使用)</u>
中致吐性	<u>使用 Corticosteroids 或 5-HT₃ 受體拮抗劑 (於第二至第三天使用)</u>
低或輕微致吐性	無須常規性使用止吐用藥

預期性嘔吐的預防

- 最佳預防方法為儘力控制病人的急性與延遲性嘔吐
- 預期性嘔吐應用心理性方式處理
- 考慮benzodiazepines為心理性方式之外加或替代治療

突發性嘔吐的治療-1

- 突發性嘔吐之治療原則為加上不同作用機轉之止吐藥物；各類止吐藥物對於突發性嘔吐之控制效果差別不大
- 應考量以固定時間且固定間隔方式給予止吐藥物，不建議以PRN方式處理
- 以靜脈或直腸給藥較口服給藥適當，因為病人可能正處在嘔吐狀態
- 確認病人無脫水現象，並考量其電解質之平衡

突發性嘔吐的治療-2

- 於下一次化學治療療程前，重新評估病人狀況，且需注意無關於本次化學治療引起突發性嘔吐之因素，其因素如下：
 - (1) 腫瘤之腦部轉移
 - (2) 體內電解質不平衡
 - (3) 腫瘤之腸胃道
 - (4) 其他疾病

化療不必吐
止吐藥緩解噁心感

台灣癌症基金會