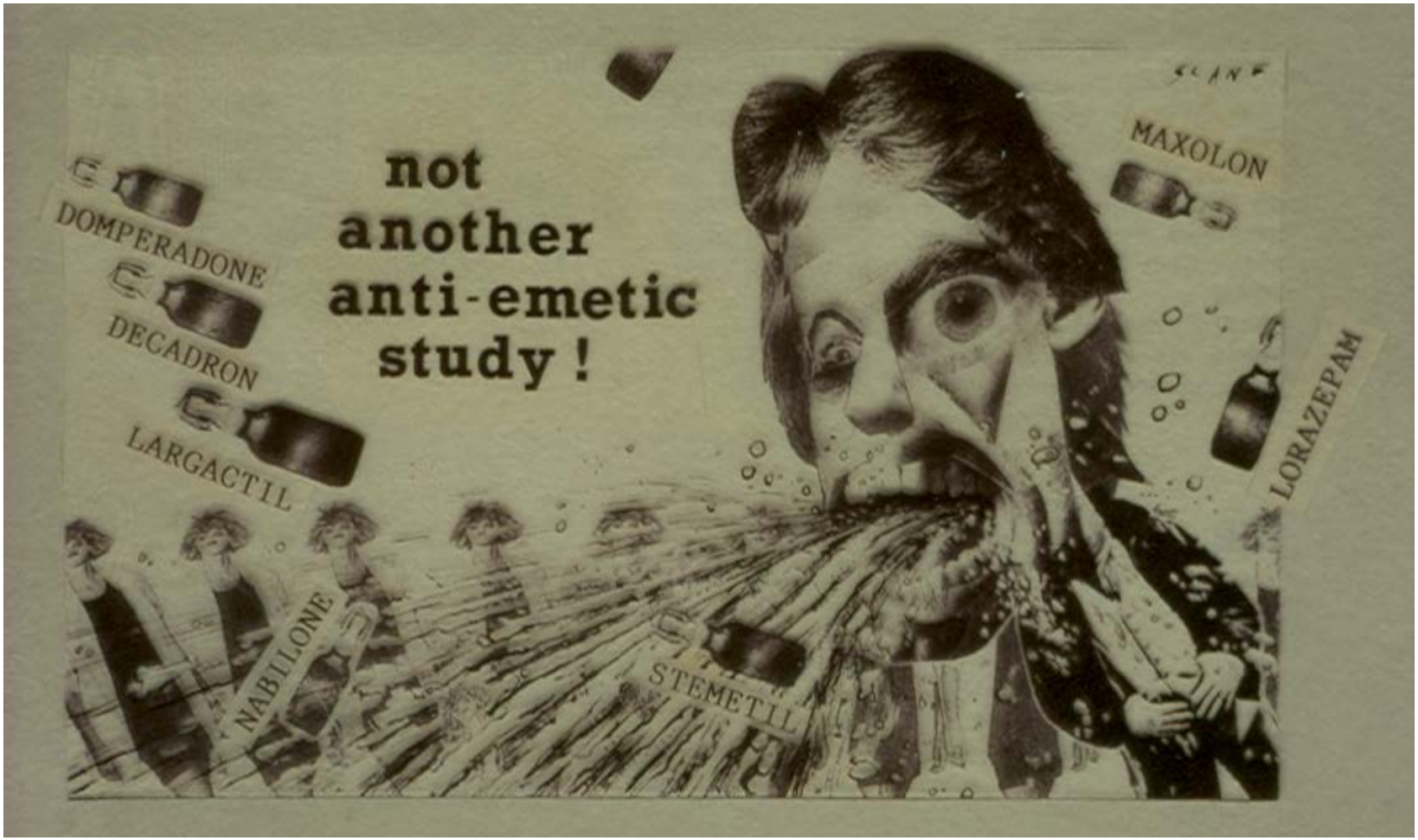
not another anti-emetic study !
DOMPERADONE
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LORAZEPAM

A RANDOMISED, OPEN LABEL STUDY OF GUIDELINE DRIVEN TARGETED ANTIEMETIC THERAPY VERSUS SINGLE AGENT ANTIEMETIC THERAPY

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In the last year of life…

- 51% of cancer patients
- 27% of patients with non malignant disease

…experience nausea and vomiting

Common causes

- GI problems
- pharyngeal irritation
- drugs
- metabolic
- toxic
- brain metastases
- psychosomatic factors
- pain

Nausea and vomiting in patients with advanced disease

- often multifactorial
- often no obvious cause

- Kennett et al, 65 pts

-mulifactorial 35 (56%)

-unknown 22 (33%)

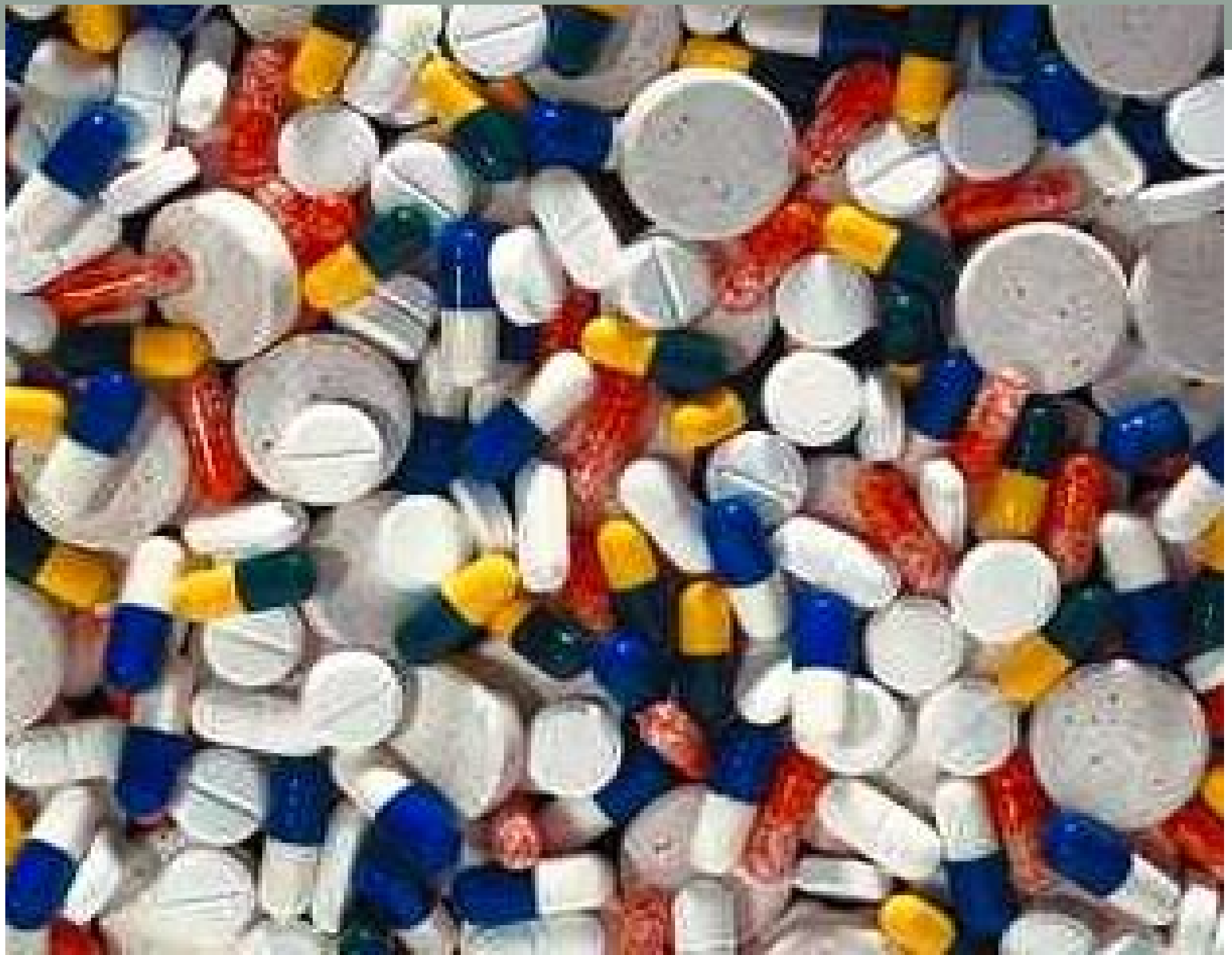
-specific cause 6 (10%)

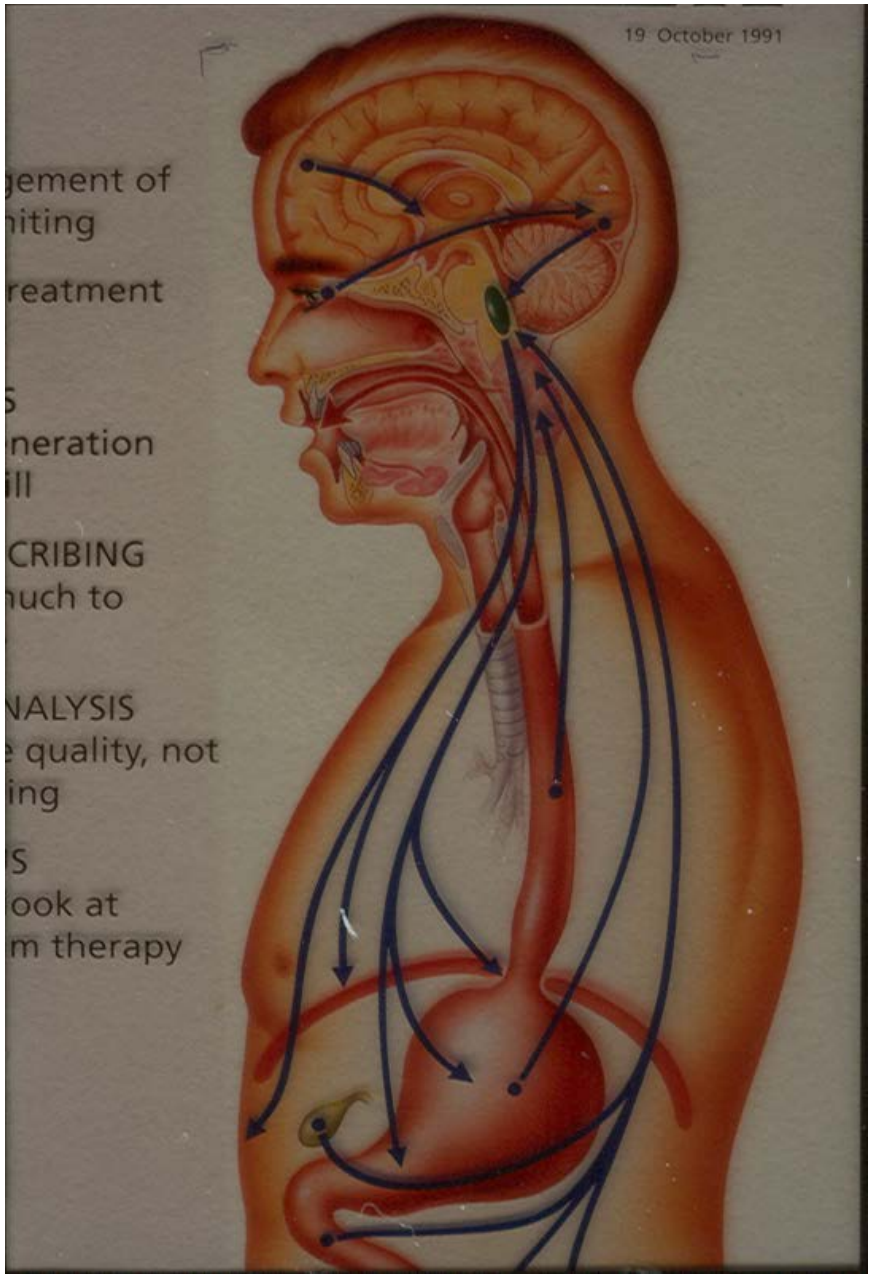
Correct reversible causes if possible

- severe pain
- infection
- cough
- hypercalcaemia
- tense ascites
- raised ICP
- stop emetogenic drugs

Non drug treatments

- control of malodour
- calm reassuring environment
- away from sight/smell of food
- small snacks
- someone else doing cooking
- complementary therapies/acupressure bands
- counselling

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Drug approaches to emetic control

1. “mechanistic” or targeted

- use patient’s clinical picture to determine the likely pathophysiological abnormality
- select antiemetic based on understanding of neuropharmacology

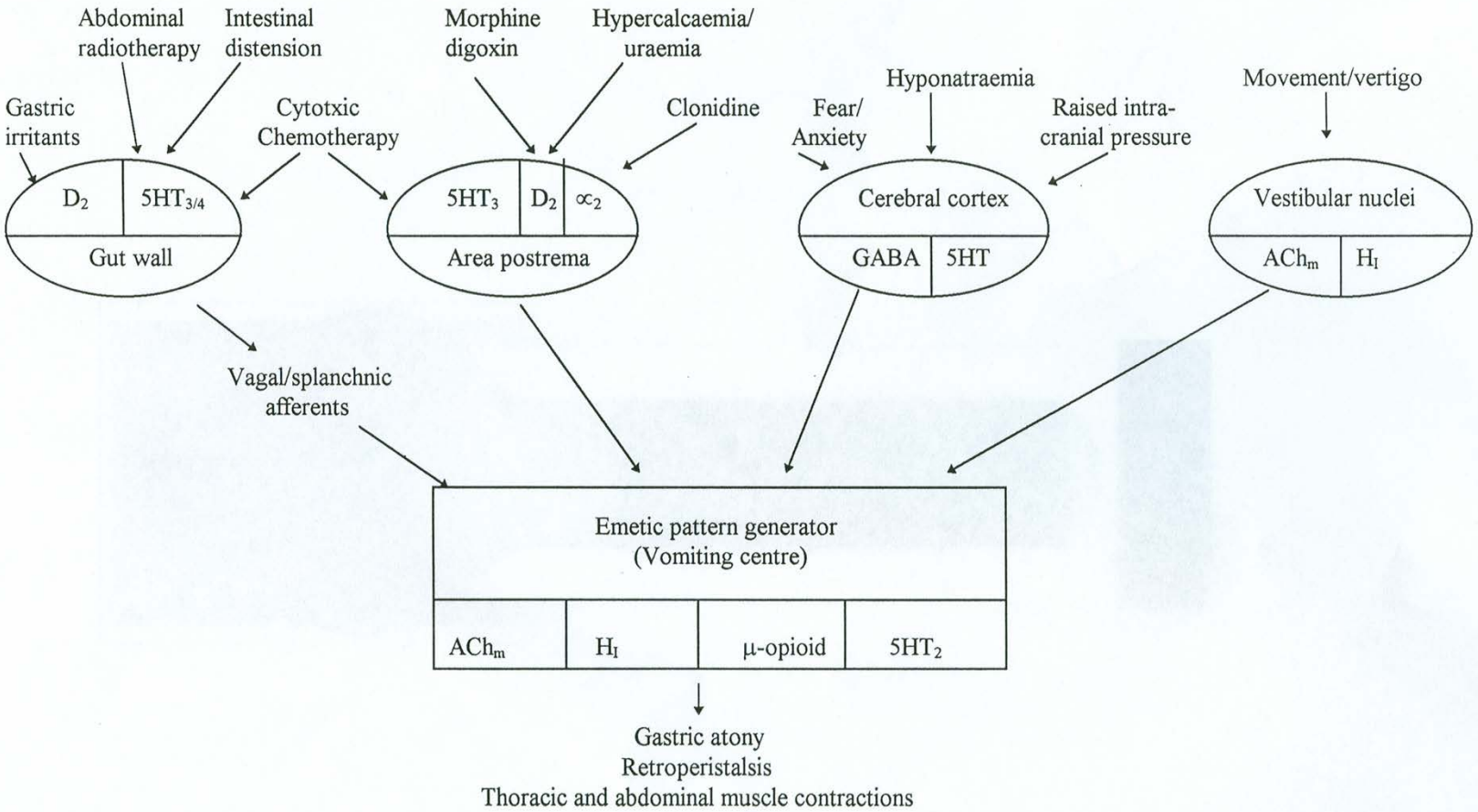

Diagram of the neural mechanisms controlling vomiting. Modified from Twycross et al 1997

Abbr: ACH_m = muscarinic cholinergic; $\propto_2$=alpha-adrenergic type 2; D_2=dopamine type 2; GABA=gamma-aminobutyric acid; 5HT, $5HT_2$, $5HT_3$= 5-hydroxytriptamine (serotonin) type undefined, type 2, type 3; H_I-histamine type I.

Receptor site affinities of selected anti-emetics

	D_2 antag	H_1 antag	ACh antag	$5HT_2$ antag	$5HT_3$ antag	$5HT_4$ antag
Metoclopromide	++	0	0	0	(+)	++
Domperidone	++a	0	0	0	0	0
Cisapride	0	0	0	0	0	+++
Ondansetron[b]	0	0	0	0	+++	0
Cyclizine	0	++	++	0	0	0
Hyoscine hydrobromide	0	0	+++	0	0	0
Haloperidol	+++	0	0	0	0	0
Prochlorperazine	++	+	0	0	0	0
Chlorpromazine	++	++	+	0	0	0
Levomepromazine	++	+++	++	+++	**0**	**0**

Anti-emetics

Drug/Group	Dopamine (D_1) antagonist	Anti (Mu) cholinergic	Anti-(H_1) histamine	5 HT_2 antagonist
methotrimeprazine	✓	✓	✓	✓
haloperidol	✓		✓ (weak)	
cyclizine		✓	✓	
metoclopramide	✓		✓ (weak)	✓
ondansetron/ granisetron				✓

Classification of Drugs Used to Control Nausea and Vomiting

Putative site of action	**Class**	**Example**
Central nervous system		
Vomiting centre	Anticholinergic	Hyoscine hydrobromide
	Antihistaminic anticholinergic[a]	Cyclizine, dimenhydrinate, phenothiazines
	$5HT_2$-antagonist	Levomepromazine
Chemoreceptor trigger zone	Dopamine (D_2) antagonist	Haloperidol, phenothiazines, metoclopramide, domperidone
	$5HT_3$-antagonist	Granisetron, ondansetron, tropisetron
Cerebral cortex	Benzodiazepine	Lorazepam
	Cannabinoid	Nabiline
	Corticosteroid	Dexamethasone
GI tract		
Prokinetic	$5HT_4$-agonist	Metoclopramide, cisapride
	Dopamine (D_2) antagonist	Metoclopramide, domperidone
Antisecretory	Anticholinergic	Hyoscine butylbromide, glycopyrronium
	Somatostatin analogue	Ocreotide, vapreotide
Vagal $5HT_3$ receptor blockade	$5HT_3$-antagonist	Granisetron, ondansetron, tropisetron
Anti-inflammatory	Corticosteroid	Dexamethasone

a. antihistamines and phenothiazines both have H_1-receptor antagonistic and anticholinergic properties.

Mechanistic approach

- supported by 2 prospective audits

-Bently, Pall med 2001

-Lichter, J Pall Care1993

- success claimed for 80-90% pts

Approaches to emetic control

2. “empirical”

– use any antiemetic without regard to underlying cause

Empirical approach

- trying various antiemetics without regard to underlying cause
- supported by Bruera, Bruera, Mystakidou, Corli (Glare, Supp Care Cancer 2004)
- success claimed for 80-90% pts

- 2 approaches had not been directly compared

Study details

- A randomised, open label study of guideline driven targeted antiemetic therapy versus single agent antiemetic therapy (haloperidol)
- Funding: NHMRC grant
- Sponsor: PACCSC (Flinders University)
- Nausea management program (NS1-3)
- Lead Investigators : Patsy Yates, Janet Hardy

Aim

- To determine whether guideline driven aetiology based anti-emetic therapy (targeted therapy) is more effective than single agent therapy with haloperidol in patients with cancer and nausea not related to anticancer therapy.

Treatment schedule:

- Guideline driven antiemetic therapy, given orally or parenterally (subcutaneous or intravenous), according to presumed cause of nausea using freely available PBS listed antiemetics in a 3 step dose escalation schedule

- ***or***

- Haloperidol, in a 3 step dose escalation schedule from 1mg/24 hours to 3mg/24hours orally or parenterally (subcutaneously).

Definition of response:

- A minimum two point improvement from baseline and end score <3 on an 11 point NRS for average nausea for the previous 24 hours, measured 72 hours after the first study antiemetic administered.

Primary endpoint:

- Response to treatment, defined as at least a two point improvement from baseline and a score < 3 for average nausea over the preceding 24 hours, measured at 72 hours using an 11-point (0-10) numeric rating scale.

Secondary endpoints

- best and worst nausea scores
- vomiting
- number of rescue antiemetic doses
- adverse events
- number treated at each dose level
- refractory nausea

Null hypothesis:

- For cancer patients with nausea, the response at 72 hours to aetiology based guideline driven antiemetics and haloperidol do not differ

Study population

Patients who:

- are >18 years
- have a clinical diagnosis of cancer
- have nausea with an average score of ≥3 on an 11 point NRS
- are not currently receiving antiemetics

or are already receiving antiemetics

but these are inappropriate as defined by the antiemetic guidelines

or are at a suboptimal dose

- are able to comply with all trial requirements
- are able to provide fully informed consent

Study population exclusions:

- nausea related to the treatment of cancer where acute treatment with 5HT3 antagonists is indicated
- nausea for which a specific antiemetic is indicated and randomisation to haloperidol would not be appropriate (e.g. dexamethasone for acutely raised ICP)
- undergone a procedure with the potential to affect nausea within 2 days prior to study or are likely to undergo a procedure or intervention with the potential to affect nausea during the 3 day study period

Exclusions (contd)

- unstable corticosteroids, within 48 hours prior to study
- definite contraindication to any of guideline drugs (Parkinson's disease, QTc prolongation, uncontrolled seizures)
- prior serious adverse event following any of the guideline drugs (dystonic reaction, neuroleptic malignant syndrome)

Clinical practice guidelines for the management of nausea

(Modified from the original Glare CPGs according to expert consensus)

3 step treatment as determined by cause

Code	Dominant cause
A	Central/ CTZ stimulation
B	CNS disease
C	Vestibular involvement
D	Gastric stasis
E	Ileus
F	Mechanical obstruction
G	Gastritis
H	Cause undetermined (or multifactorial)

1. Glare P et al. Systematic review of the efficacy of antiemetics in the treatment of nausea in patients with far advanced cancer. Support Care Cancer 2004; 12:432-40

Dominant cause	Treatment Step 1	Treatment Step 2	Treatment Step 3
A: Central/CTZ stimulation	Prochlorperazine 5mg tds po or 25mg PR then 5mg tds po or 12.5mg bd IM/iv	Haloperidol 1.5mg/24hrs po or sc	Haloperidol 3mg/24hrs po or sc
B: CNS disease	Dex 8mg/24hrs po/sc/iv	Dex 12mg/24hrs po/sc/iv	Dex 16mg/24hrs po/sc/iv
C: Vestibular involvement	Prochlorperazine 5mg tds po or 25mg PR then 5mg tds po or 12.5mg bd IM/iv	Prochlorperazine 10mg tds po or 25mg PR then 10mg tds po or 12.5mg tds IM/iv	Promethazine 25 mg tds po or 12.5mg sc then 10mg tds po
D: Gastric stasis	Metoclopramide 10mg qid po/sc/iv	Metoclopramide 10mg Q4h po/sc/iv	Metoclopramide 10mg Q4h po/sc/iv Dex 8mg/24hrs po/sc/iv
E: Ileus	Metoclopramide 10mg qid po/sc/iv	Metoclopramide 10mg Q4h po/sc/iv	Metoclopramide 10mg Q4h po/sc/iv Dexamethasone 8mg/24hrs po/sc/iv
F: Mechanical obstruction	Haloperidol 1.5mg/24hrs po/sc Dex 8mg/24hrs po/sc/v	Haloperidol 3mg/24hrs po/sc Dex 8mg/24hrs po/sc/iv	Haloperidol 3mg/24hrs po/sc Dex 8mg/24hrs po/sc/iv Hyoscine butylbromide 80mg/24hrs sc *or* Ranitidine 200mg/24hrs sc
G: Gastritis	Metoclopramide 10mg qid po/sc/iv PPI min dose	Metoclopramide 10mg qid po/sc/iv PPI max dose	Metoclopramide 10mg Q4h po/sc/iv PPI max dose
H: Cause undetermined (or multifactorial)	Metoclopramide 10mg qid po/sc/iv	Metoclopramide 10mg qid po/sc/iv Haloperidol 1.5mg/24hrs po/sc	Metoclopramide 10mg Q4h po/sc/iv Haloperidol 3mg/24hrs po/sc

Sample size

- a sample size of 75 per arm, after attrition, to detect a statistically significant difference in response of 25% between haloperidol and standard guidelines, with 90% power

Results (preliminary)

- 185 recruits between Oct 2010 and April 2014
- 124 F (69%)
- median age 70 yrs (28-91)
- most common cancers : breast, GI tract, lung, prostate
- median average nausea score at baseline: 5/10
- median worst nausea score at baseline : 8/10
- median baseline nausea interference score : 5/10 (range 0-10)

Results (preliiminary)

- 185 randomised
- 181 commenced study medication
- 152 participants (84%) completed the 3 planned days of treatment
- 7 withdrew because of unacceptable toxicty

Results –preliminary, subject to change

- Randomisations

Pre screened	Randomised	Completed
727	185	152

- Therapy arm distribution

Therapy arm	Guideline	Haloperidol	TOTAL
Randomised	95	90	185
Completed	75	77	152

Results – preliminary data

- Dominant cause selected (missing data = 1)

A	B	C	D	E	F	G	H	TOTAL
43	1	6	22	13	9	7	83	*185**
23.2%	*0.5%*	*3.2%*	*11.9%*	*7.0%*	*4.9%*	*3.8%*	*44.9%*	*100%*

Dominant cause	
A	Central/ CTZ stimulation
B	CNS disease
C	Vestibular involvement
D	Gastric stasis
E	Ileus
F	Mechanical obstruction
G	Gastritis
H	Cause undetermined (or multifactorial)

CPG interim data

- If randomised to guideline therapy, which category?

Category	A	B	C	D	E	F	G	H	TOTAL
Randomised	27	0	4	12	7	4	4	37	95
	28.4%	0.0%	4.2%	12.6%	7.4%	4.2%	4.2%	38.9%	100.0%

Dominant cause	
A	Central/ CTZ stimulation
B	CNS disease
C	Vestibular involvement
D	Gastric stasis
E	Ileus
F	Mechanical obstruction
G	Gastritis
H	Cause undetermined (or multifactorial)

Response rate

- all randomised patients: 54%
  (targeted 55.8%, single agent 53.3%)

- completed 3 days: 65.1%
  (targeted 66.7%, single agent 63.5%)

Conclusion

- the response to antiemetic therapy was high in both arms
- guideline driven therapy did not result in greater control of nausea than single agent therapy with haloperidol
- regular use of currently available PBS-listed antiemetics results in good nausea control in the majority of patients

Nausea study 3

- Nausea study 2 – refractory N/V
- Nausea study 3 : Methotrimeprazine vs haloperidol
- 3 day study
- response: 2 point reduction in nausea score
- complete response: 2 point reduction in nausea score and final score <3/10
- End point: response end day 3
- Recruiting well