

THERAPEUTICS

Drug treatment of adults with nausea and vomiting in primary care

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This is one of a series of occasional articles on therapeutics for common or serious conditions, covering new drugs and old drugs with important new indications or concerns. The series advisers are Robin Ferner, honorary professor of clinical pharmacology, University of Birmingham and Birmingham City Hospital, and Albert Ferro, professor of cardiovascular clinical pharmacology, King's College London. To suggest a topic, please email us at practice@bmj.com.

A usually healthy 25 year old man presents to you as his general practitioner at 9 am. He has had fluctuating nausea with four vomits and one loose stool overnight, associated with colicky central abdominal pain. No blood was present in the vomit or stool, and he reports that his girlfriend was recently diagnosed as having “viral gastro.” He is afebrile, intermittently uncomfortable, but otherwise well, with mild epigastric tenderness but no guarding or rebound. Clinically, you believe viral gastroenteritis is the most likely cause of his symptoms, and you consider his request for treatment that will help to stop his vomiting so that he can get to his evening shift at a factory.

What drugs are available and how do they work?

Nausea and vomiting are a common reason for patients to seek treatment in primary care, which we take here to include general practice and the emergency department. Identification and management of underlying problems are important, if these are apparent on clinical grounds. This article will focus on common causes in primary care such as gastroenteritis (usually viral), adverse drug reactions, pregnancy, vestibular disorders, and motion sickness. Other causes of nausea and vomiting such as postoperative, chemotherapy and radiotherapy associated, and specific conditions such as migraines are briefly discussed but are beyond the scope of this article.

Although still incompletely understood, nausea and vomiting are thought to follow activation of a medullary “vomiting centre,” by either afferent input from the gastrointestinal tract due to presence of local irritants or stimulation of the central chemoreceptor trigger zone by circulating emetogenic substances; however, other pathways exist. Dopamine and serotonin seem to be key transmitters both centrally and in the gastrointestinal tract.

Surveys of emergency physicians in Australia and the United States identified the most commonly prescribed agents as metoclopramide, prochlorperazine, promethazine, droperidol, and ondansetron.^{1,2} Anecdotally, cyclizine and domperidone are also commonly prescribed in the United Kingdom.

Metoclopramide and domperidone are benzamides that are thought to act through a combination of antidopaminergic and gastrointestinal tract pro-kinetic effects.³ Domperidone penetrates the blood-brain barrier poorly, so although it still has effects on the chemoreceptor trigger zone, it has min-

imal centrally mediated side effects, in contrast to metoclopramide. Droperidol (a butyrophenone compound) and the phenothiazines (prochlorperazine and promethazine) have actions mediated primarily through central antidopaminergic mechanisms. Ondansetron and tropisetron are serotonin (5-HT) receptor antagonists both centrally and peripherally, although their action is thought to be predominantly mediated in the chemoreceptor trigger zone. Cyclizine is a histamine H₁ receptor antagonist with a central antiemetic effect. Scopolamine is an anticholinergic agent that acts to inhibit vestibular input to the central nervous system.

Current approved indications for the older antiemetics in Australia and the UK are broad and non-specific. For example, metoclopramide's indications include relief of nausea and vomiting associated with infectious disease, malignant disease, uraemia, migraine, labour, cancer treatment (chemotherapy or radiation), and postoperative vomiting and to assist in small bowel intubation. Selective antagonists are preferred for nausea and vomiting associated with specific mechanisms such as motion sickness, which is mediated via histaminic receptors. The newer serotonin antagonists, such as ondansetron, are approved only for the treatment of nausea and vomiting either postoperatively or with cancer treatment,^{4,5} although this restriction is not adhered to in emergency department practice.¹

How well do antiemetic agents work?

Table 1 summarises the usual agents recommended for specific indications, with the level of evidence. Most antiemetic drug research has been in cancer treatment and postoperative nausea and vomiting. Systematic reviews have shown efficacy of serotonin antagonists in chemotherapy settings,⁶ whereas drugs have been shown to be beneficial in postoperative nausea and vomiting, but with no drug group being clearly superior to any other.⁷

For paediatric gastroenteritis, ondansetron has been shown to be somewhat more effective than placebo in reducing vomiting and intravenous fluid requirements in the emergency department, as well as hospital admissions, although at the expense of a slight increase in diarrhoea.⁸ For nausea in pregnancy, a recent narrative review article found no evidence of superiority of any agent over another.⁹ Metoclopramide, prochlorperazine, promethazine, and ondansetron all seem to be somewhat effective and have no apparent teratogenicity. For motion sickness, the presumed

Table 1 | Commonly prescribed antiemetics for specific indications

Indication	Receptors involved	Preferred drugs	Supporting evidence
Gastroenteritis (adult)	Dopamine/serotonin	Varies by region; acceptable agents include metoclopramide, prochlorperazine, ondansetron, cyclizine	Limited evidence: few small randomised trials (see table 2)
Gastroenteritis (paediatric)	Dopamine/serotonin	Ondansetron	Systematic review of randomised controlled trials ⁸
Nausea and vomiting in pregnancy and hyperemesis gravidarum	Unknown	Metoclopramide, promethazine, ondansetron	Systematic review of randomised controlled trials (no evidence for superiority of any single agent) ⁹
Motion sickness	Incompletely understood; include histamine and acetylcholine	Scopolamine, antihistamines	Systematic review supports superiority of scopolamine over placebo and equivalence with antihistamines ¹⁰
Vestibular disorders	Histamine and acetylcholine	Antihistamines	Expert opinion ³⁰

Table 2 | Reductions in severity of undifferentiated nausea and vomiting in adult emergency department patients

Randomised controlled trial	Intravenous drug/dose (sample size)	30 minute reduction: mean mm on VAS or units on 11 point NRS
Braude 2006 ¹³	Droperidol* 1.25 mg (n=22)	55 (SD 18) mm
	Metoclopramide 10 mg (n=25)	40 (24) mm
	Prochlorperazine 10 mg (n=24)	41 (24) mm
	Saline placebo 10 mL bolus (n=26)	39 (21) mm
Egerton-Warburton 2014 ¹⁶	Ondansetron 4 mg (n=87)	27 (95% CI 22 to 33) mm
	Metoclopramide 20 mg (n=88)	28 (22 to 34) mm
	Saline placebo 10 mL bolus (n=83)	23 (16 to 30) mm
Barrett 2011 ¹¹	Ondansetron 4 mg (n=42)	40 (IQR 23-63) mm
	Metoclopramide 10 mg (n=43)	32 (20-47) mm
	Promethazine 12.5 mg (n=45)	35 (22-59) mm
	Placebo 2 mL bolus (n=41)	37 (23-56) mm
Cham 2004 ¹⁵	Metoclopramide 10 mg (n=24)	4 (95% CI 3 to 5) units
	Metoclopramide 0.4 mg/kg (max 32 mg) (n=24)	5 (4 to 6) units
Braude 2008 ¹²	Ondansetron 4 mg (n=60)	34 (SD 29) mm
	Promethazine 25 mg (n=60)	36 (28) mm
Chae 2011 ¹⁴	Tropisetron 5 mg (n=50)	25 (25) mm
	Metoclopramide 10 mg (n=50)	26 (20) mm
Ernst 2000 ¹⁷	Prochlorperazine 10 mg (n=42)	45 mm (IQR not reported)
	Promethazine 25 mg (n=42)	27 mm (IQR not reported)

IQR=interquartile range; NRS=numerical rating scale; VAS=visual analogue scale.
*Difference from placebo statistically significant.

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Previous articles in this series

- ▶ Newer agents for psoriasis in adults (BMJ 2014;349:g4026)
- ▶ Pharmacotherapy for weight loss (BMJ 2014;348:g3526)
- ▶ Procedural sedation and analgesia for adults in the emergency department (BMJ 2014;348:g2965)
- ▶ Triptans for symptomatic treatment of migraine headache (BMJ 2014;348:g2285)
- ▶ Statins for the primary prevention of cardiovascular disease (BMJ 2014;348:g280)

pathogenesis remains incompletely understood; a recent systematic review of several small controlled trials concluded that scopolamine was more effective than placebo and equivalent to antihistamines for the prevention or amelioration of nausea and vomiting in this specific setting.¹⁰

Despite the frequency of adults presenting with nausea and vomiting in primary care, surprisingly little research has been done in this setting. We were unable to locate any general practice based studies and found only seven from emergency department practice.¹¹⁻¹⁷ Study designs for research in cancer treatment and postoperative nausea and vomiting involve concurrent administration of an antiemetic drug and an emetogenic substance, with measurement of the severity of the ensuing nausea and vomiting. In emergency department based studies, designs involve antiemetic administration followed by measurement of change in severity of the already present symptoms. Although nausea and vomiting are largely mediated through the same pathways regardless of the underlying cause,³ results of research from different clinical settings may not be generalisable. The complexity of migraine and the difficulties of conducting randomised controlled trials in pregnancy have similarly left uncertainty about the effectiveness of antiemetic drugs in these more specific settings.^{18 19}

For people with nausea and vomiting who might be managed in primary care, evaluation of findings in the emergency department based studies is somewhat difficult owing to relatively small sample sizes, clinical heterogeneity, inconsistent drug regimens, and emergency department based studies' use of the intravenous route, which is not routinely used in general practice. All patients in these studies received varying amounts of intravenous fluid, but four studies lacked a placebo arm.^{12 14 15 17} Table 2 summarises the primary outcome of reduction in severity of nausea at 30 minutes. The effect sizes vary between studies, probably owing to minor differences in methods; however,

within studies, results between all drug and placebo arms (where used) are similar, other than in the one small study by Braude et al in 2006, in which the now out of favour droperidol seemed to be superior to the similarly effective metoclopramide, prochlorperazine, and placebo.¹³ As all reductions in severity, whether with drug or placebo, exceeded the accepted level of clinical significance,²⁰ these studies suggest that patients' nausea and vomiting does improve, provided they receive some intravenous fluid and, where possible, treatment for their underlying condition, and that the addition of an antiemetic drug may add little. Two non-randomised, uncontrolled pre-hospital trials have suggested that oral transmucosal ondansetron is useful for nausea in the pre-hospital setting.^{21 22} However, whether these emergency department and pre-hospital results can be extrapolated to the general practice setting, where drugs usually need to be given orally or intramuscularly and intravenous fluid administration is rarely possible, remains unclear. Despite reportedly frequent use in the UK, we are not aware of any studies evaluating cyclizine as an antiemetic in the primary care setting.

How safe are these agents?

Adverse effects of antiemetic drugs are usually mild, but some adverse effects warrant consideration.

Metoclopramide and the phenothiazines—Adverse effects are relatively common, although milder symptoms are possibly under-recognised. The most common adverse events are centrally mediated extrapyramidal side effects,²³ which range from mild restlessness, agitation, and akathisia to (less commonly) overt dystonia and dyskinesia, with more distressing opisthotonus and oculogyric crises being rare (a few per thousand). Extrapyramidal effects are more common in young children and adults up to about the age of 20 years, as well as in women and older people.^{5 24}

Domperidone—This has recently been investigated by the European Medicines Agency,²⁵ owing to concerns about a small increased risk of cardiac adverse drug reactions. Although still available for the relief of nausea and vomiting, its use has been restricted for other indications.

Droperidol—Use is associated with sedation, agitation, and restlessness, but it has fallen out of favour despite evidence of efficacy, owing to concerns about prolonged QT interval and potential cardiac complications, the importance of which remains controversial.²⁶

Antihistamines—These are associated with drowsiness in clinical use.

Scopolamine—Anticholinergic side effects such as dizziness, blurred vision, and dry mouth are usually mild at therapeutic doses. It can be associated with drowsiness and occasionally causes confusion and agitation.

Ondansetron—Serious side effects are uncommon but include a risk of QT interval prolongation (including torsade de pointes) and extrapyramidal reactions. Headache is frequently reported but generally not severe.

What are the precautions?

Metoclopramide and the phenothiazines:

- Avoid in children, young adults, and patients with a previous history of extrapyramidal side effects, all of whom are at higher risk of these.

TIPS FOR PATIENTS WITH NAUSEA AND VOMITING WHO ARE WELL ENOUGH TO BE MANAGED IN PRIMARY CARE

Nausea and vomiting are common symptoms that can occur with many different underlying problems. In most cases, the nausea and vomiting component tends to resolve within the first 12-48 hours, regardless of treatment

It is not certain how much extra benefit you will get from using anti-vomiting drugs, beyond making sure you try to take enough fluids, have sufficient rest, and use simple painkillers as required

If you would like to try anti-vomiting drugs, they are reasonably safe; however, they can have unpleasant side effects. No single drug is clearly better than any other

About one in six people can get side effects from drugs such as metoclopramide and prochlorperazine. These are usually mild and will resolve so long as you stop taking the drug. If you develop worrying restlessness and agitation, muscle stiffness and limb jerking, tongue thrusting, or facial grimacing, you should see your doctor or go to a hospital emergency department

Use of regular metoclopramide for more than two weeks must be discussed with your doctor

You will need to see a doctor again if you are worried that you aren't keeping enough fluid down; if you develop new or worsening symptoms, such as blood in your vomit (or diarrhoea); or if abdominal pain becomes severe

- Use with caution in older people because of the possibility of renal dysfunction leading to increased risk of dystonic reactions.
- Avoid prolonged use owing to the risk of parkinsonism and tardive dyskinesia.
- Avoid in people with Parkinson's disease or depression, as symptoms may worsen.

When administering these agents intravenously, drugs for the management of possible dystonic reactions should be available, including diphenhydramine, benztropine, and benzodiazepines.

Antihistamines and phenothiazines:

- Can have anticholinergic effects and may precipitate some conditions such as constipation in patients prone to this or urinary retention in those with prostatomegaly.
 - Can have a sedative effect, so warn about risks for driving or operating machinery.
- Scopolamine:
- Can have a sedative effect, so warn about risks for driving or operating machinery.
 - Can aggravate urinary difficulty or precipitate urinary retention in patients with bladder outflow obstruction.

Antiemetics in pregnancy:

- Metoclopramide's safety for use in pregnancy has been well established over several decades.⁵
 - Ondansetron is being increasingly used, with few side effects reported and no reports of teratogenicity to date.²⁷
- Antiemetics in breastfeeding women:

- Little information on antiemetic use in lactation is available.
- Most antiemetics are known to be excreted in breast milk, and use in breastfeeding mothers is not generally recommended.

How cost effective are these agents?

No formal cost effectiveness evaluations have been done, these being limited by lack of high quality efficacy data. The two most commonly prescribed agents are metoclopramide and ondansetron. Metoclopramide is relatively inexpensive. Each 10 mg ampoule for parenteral use

costs about \$1.85 (£1.02; €1.28; \$US1.74) in Australia and £0.30 in the UK. For oral use, a 25 tablet prescription costs about \$13.50 in Australia and a 28 tablet prescription about £0.87 in the UK. In the primary care setting, where an initial parenteral dose might be followed by a maximum of three tablets on the first day and four on the second, the total cost of acute usage over two days is about \$6 in Australia and £0.60 in the UK. In contrast, the most commonly used serotonin antagonist, ondansetron, is more expensive. Each 4 mg ampoule for parenteral use costs about \$15 in Australia and £11.39 in the UK. The 4 mg and 8 mg oral preparations cost about \$4 and \$8 per dose respectively in Australia and about £2.10 and £4.70 in the UK. So an acute regimen over two days might cost about \$70 in Australia and £25 in the UK.^{28 29}

How are they taken and monitored?

Drug selection and dosage

For nausea and vomiting in the primary care setting, no convincing evidence of efficacy exists for any drug. If drug treatment is considered necessary, evaluate possible underlying causes (table 1), costs, and precautions (see previous section) and discuss the risks versus benefits with the patient (see box). Prescribe these for the shortest period needed for symptom relief or control. Dose reductions may vary with presence and degree of renal impairment.

Route

Home use of oral antiemetics is suitable for milder or less frequent symptoms, with more than one initial parenteral dose rarely being feasible in general practice. The transmucosal route of administration, oral or rectal, may have a role in the future, but requires further evaluation in this setting. More severe or intractable vomiting often requires referral to hospital for consideration of intravenous administration of drug and fluid in the emergency department, along with assessment, monitoring, and management of the clinical consequences of the vomiting. The need for further investigation of possible underlying conditions is assessed on an individual basis.⁵

Monitoring

Monitoring requires clinical evaluation only. Checking patients' satisfaction with their progress, including effectiveness and possible side effects, usually suffices.

Outcome of hypothetical case

On examination, no evidence of any complications or dehydration, which might require hospital referral, is seen and no contraindications to any drugs exist. As the patient is keen to try an antiemetic, you administer 10 mg of intramuscular metoclopramide and advise him to continue taking oral fluids regularly. You advise him against attending work until his symptoms have resolved and issue him with a certificate to this effect.

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ANSWERS TO ENDGAMES, p 36

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ANATOMY QUIZ

Sagittal computed tomogram of the neck with bone windows

- A: Hard palate
- B: Soft palate
- C: Mandible
- D: Hyoid bone
- E: Epiglottis

STATISTICAL QUESTION

Before and after study designs

Statements *a* and *c* are true, whereas *b* is false.

CASE REPORT

A patient with type 2 diabetes and a burning sensation in his feet

- 1 The patient has painful diabetic peripheral neuropathy. Painful symptoms develop as a result of damage to, or dysfunction of, the system that normally signals pain. Doctors should examine patients with diabetes for symptoms of this condition because most patients are not aware that their symptoms are associated with diabetes.
- 2 The management of painful diabetic peripheral neuropathy includes optimal glycaemic control, drugs for pain, and psychological support. Clinical guidelines recommend tricyclic antidepressants, serotonin and noradrenaline reuptake inhibitors (duloxetine, venlafaxine), or anticonvulsants (gabapentin, pregabalin) as first line treatment.
- 3 Diabetic peripheral neuropathy is a major risk factor for foot ulceration in patients with diabetes and the main underlying cause of Charcot neuropathic osteoarthropathy (or Charcot foot).