**Drug therapies to manage nausea and vomiting:**

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**Abstract:**

This article is intended to provide an overview of the drug management of nausea and vomiting in adults. Signs/symptoms arise from a diverse range of causes and while there is consensus regarding the broad approach to clinical management, there are many opinions on the optimum approach. The main causes of acute, delayed and longer term nausea and vomiting are identified and linked to the rationale for antiemetic selection. Key therapeutics for the main classes of anti-emetic agents are discussed. Alternative and non-pharmacological treatments are not included.

Key Words:

Nausea and vomiting; antiemetics;

Key Points:

There is a plethora of antiemetic agents within and between drug classes. The rationale for use is made complex because of the complicated neural circuits and the multiple neurotransmitters involved in nausea and vomiting. Some older drugs, such as dexamethasone and cyclizine are still central to management, while more recent additions include palonosetron and novel agents e.g nabilone. The approach to effective and evidenced based use is discussed, as is the recommended staging and combination therapies for the main causes of nausea and vomiting.

There are no conflicts of interest.

**Introduction**

There are various strategies for managing nausea and/or vomiting (Na/ V), which involve a variety of drug classes (see Table 1). Na/V are typically a continuum, but nausea can also occur without vomiting, and it is possible to vomit in the absence of preceding nausea. Clearly, both are important and frequent clinical events, warranting prevention strategies where predictable, e.g cancer induced, as well as effective immediate management and, sometimes, longer term control. From the drug intervention perspective, there is little differentiation in addressing nausea, vomiting or both. The clinical scenario, will, however, influence the route of administration and formulation of the agent selected.

The precise mechanisms for Na/V are poorly defined, which means there are complexities in aligning the pathology with the drug treatment. Nonetheless, the rationale for drug selection is driven by the cause (where known). The vomiting circuitry has distinct, but overlapping pathways, so the effect of drugs acting on respective pathways can be additive, which is advantageous. There is a wide range of anti-emetic agents, within and between drug classes, and it is often the case that several drugs will be tried, and more than one anti-emetic agent may be necessary.

**Overview of Na/V pathways**

The brain stem contains three important centres which between them mediate vomiting; the vomiting centre, the chemoreceptor trigger zone (CTZ) and the nucleus tract solitaris (NTS). All the stimuli which result in vomiting are coordinated from the vomiting centre via cranial nerves, e.g glossopharyngeal and hypoglossal nerves, as well as spinal nerves. Vagal innervation in the throat signals the ‘gag’ reflex to the CTZ and on to the vomiting centre. When activated, the vomiting reflex causes expulsion of gastric contents, an event which triggers accompanying autonomic responses, such as pallor, tachycardia, excessive salivation and sweating.

The CTZ (sometimes called the area postrema) lies outside the blood brain barrier, assisting detection of toxins in the blood e.g opioids or the cerebro-spinal fluid. It communicates with the vomiting centre via dopamine controlled pathways. Also in the brain stem lies the nucleus tract solitaris (NTS). This connects sensory input from vagal afferents, the cranial nerves, e.g taste sensation from facial and glossopharyngeal nerves, and visceral inputs, such as from the heart and various areas of the gut. Circuits are formed between the multiple autonomic feeds and the vomiting centre, allowing the NTS to exert control over many reflex actions, including vomiting.

The NTS is central to stress responses, and accordingly physical and /or psychogenic stress can produce Na/V. The NTS pathways contain abundant corticosteroid (glucocorticoid) receptors responsive to cortisol (Ghosal at al 2014). These are believed to attenuate the stress response, for example, elevating mood, improving anxiety behaviours and alleviating Na/V. This has been linked to the helpful effect of cortisol analogues, such as dexamethasone, in the management of Na/V, although this is postulated from animal models (Morimoto et al 1996; Ho et al 2004)

Other key inputs into the vomiting centre are parts of the enteric nervous system, such as the vagal gastrointestinal neurons, the vestibular labyrinth, the cerebellum, and cerebral pathways. Emetogenic stimuli in the gastro-intestinal (GI) tract includes surgery, chemotherapy and some drugs, e.g NSAIDs, which are irritants sensed by enterochromaffin (EC) cells. The EC cells release serotonin (5HT) in the small intestine and**,** via the 5HT3 receptors on vagal sensory nerves**,** can induce the vomiting reflex. Vagal signalling from the gut afferents to the NTS and the CTZ is also stimulated via substance P and dopamine.

The vestibular nerve pathways communicate with the VC predominantly via acetylcholine and histamine and**,** when triggered**,** cause motion sickness. The higher brain centres in the cerebrum relay information about nauseating smells, sights, pain, as well as anticipatory or anxiety related Na/V, by complex neural networks via neurotransmitters including histamine and dopamine.

Neurotransmitter signalling in the pathways described above is complex. However, each pathway has primary neurotransmitters. For example, the vestibular system of the inner ear is rich in cholinergic and histamine receptors, while the role of serotonin in the gut sensory circuit has already been described. Substance P acts on the NK-1 receptors which are abundant in the gut, CTZ and NTS pathways. As a chemosensor, the CTZ has multiple inputs and output loops which function via dopamine, histamine and serotonin receptors, and respond to substance P and acetylcholine (ACh).

**Table 1. Therapeutics of the major anti-emetic drug classes**

|  |  |  |  |
| --- | --- | --- | --- |
| **Drug Class** | **Emetic pathway** | **Key therapeutics** | **Anti-emetic use** |
| 5HT3 receptor antagonists: ondansetrongranisetron palonosetron | Block peripheral GI and central 5HT3 receptor vagal input into the vomiting centre | ADR: headache, constipation\*DDI:vandetanib,apomorphineCI: congenital long QT syndromeRenal: safe in renal impairment | PONV(1st line)CINV(1st line)PINV (2nd line)(ondansetron unlicensed) |
| Antimuscarinic: hyoscine  | Anti-spasmodicReduces gastric motilityReduces afferent stimulation of vomiting centreInhibits vestibular signalling | ADR: bradycardia, dry mouth, urinary retention, anti-cholinergic syndrome esp in elderly\*DDI: other antimuscarinic drugs incl. anti-depressants;anti-histamines, metoclopramideCI:none; Cautions epilepsy | Motion sickness (1st line)PONV(used as pre-medication) |
| Dopamine receptor antagonists: metoclopramide domperidone | Block dopamine (D2) receptors centrally in the CTZ and enhance gastric motility by blocking D2 receptors peripherally in the gut | ADR: metoclopramide – extra-pyramidal effects e.g akathisia (restlessness)\*DDI: alcohol, SSRIs,antimuscarinics,ciclosporin CI:GI surgery, GI obstructionADR: domperidone can induce prolactinaemia and still carries a risk of dystonia;dry mouth, drowsiness, sudden cardiac death\*DDI:antimuscarinics,macrolides,CI: cardiac disease | PONV (2-3rd line)PINV(2nd line)Delayed CINV(2nd line)CINV(2-3 line)General nausea and vomiting |
| Anti-histamines:cyclizinepromethazine (sedating) | Block histamine receptors in the CTZ and inner ear | ADR: drowsiness, antimuscarinic effects e.g dry mouth, GI disturbance\*DDI:opioids, antimuscarinic drugsCI: acute porphyriasADR:anaphylaxis, arrhythmias, confusion, antimuscarinic effects\*DDI:opioids,antimuscarinicsCI:none | Motion sickness (1st line)PONV(1-2 line)PINV(1st line)CINV(1-2 line) |
| Anti-psychotics:First-generation e.g haloperidolSecond generation:olanzapine | Block D2 receptors in the CTZBlocks D2 receptors (and many others) and H1 receptors  | ADRs:agitation, blood dyscrasias, confusion, dystonia\*DDI: any drug which prolongs QT interval, SSRIs, antiepilepticsCI:bradycardia, CNS depression, Parkinson’s diseaseADR:GI disturbance, headache, hyperglycaemia,dystonia\*DDI: ciprofloxacinCI: none with oral administration | Na/V in palliative careCINV(2-3 line) |
| Corticosteroids: dexamethasone  | Action unknownAnti-inflammatoryBlocks ‘stress’ responses in the NTS | ADR:Hyperglycaemia, bruising, headache, increased appetite, water retention\*DDI:netupitant, rilpivarine, amphotericin, carbamazepineCI: systemic infection | PONV (1st line)CINV (1st line) |
| NK1 Antagonist;Aprepitant | Blocks the action of substance P which transmits vagal signals from the gut to the CTZ | ADR: diarrhoea, constipation, dizziness, headaches\*DDI: dexamethasone (increases levels) warfarinCI:acute porphyrias | CINV (1-2nd line) |
| Cannabinoid: nabilone | Mechanism unclear? blocks the CB1 receptors in the brain stem and/or vomiting pathways  | ADR: ataxia, drowsiness, dry mouth, dysphoria, sleep disturbance\*DDI:none knownCI:none | CINV(3rd +line) |

**\*DDI: some key drug-drug interactions (DDI) are listed but this is not the full list**

**Joint Formulary Committee 2017**

**Mechanisms of Actions summarised from papers in main text**

**Post-operative N and V (PONV)**

PONV occurs up to 48 hours after surgery. It is common (Kehlet and Dahl 2003) and can initiate medical complications and prolong admission. Therefore, it is advised that patients be assessed for their risk using the Apfel scoring system (Apfel et al 2012) and any modifiable risk factors addressed. Numerous peri-operative interventions can trigger the Na/V pathway(s), including the anticipation of Na/V in patients who expect this as part of their surgical experience (Pierre and Whelan 2013). As part of anaesthetic induction and reversal, it can be possible to predict causes of emesis from the type of surgery, e.g intra-abdominal surgery carries a high risk of emesis, the type of anaesthesia, e.g general anaesthetic with intubation, and the drugs used before, during and after the surgery (Table 2).

The threshold for Na/V varies considerably, as do individual responses to opioids and other drugs. Some predisposing factors are known, including female gender, obesity, anxiety, a history of PONV or motion sickness (Chatterjee et al 2011), with some protection from PONV with older age (Stadler et al 2003). Surgery itself can produce emetic stimuli, such as gastric distension or intestinal ischaemia. Predictably, ophthalmic or middle ear surgery can stimulate PONV.

The drugs used to manage PONV may be used for prophylaxis and/or treatment. A popular option is the serotonin receptor antagonist class e.g ondansetron. They are selective for the serotonin receptor sub-type 5HT3, which is found on the vagus nerve peripherally in the gastro-intestinal tract and centrally in the brainstem vomiting centre. The highly selective 5HT3 receptor antagonists perform a dual anti-emetic action by blocking the gut-brain reflex arc.

Acetylcholine is a major neurotransmitter in the gut/brain axis and in the vestibular system. Hyoscine can be used as premedication in injection form or applied as a patch to avoid emesis, for example where opioid induced PONV is anticipated. Central competition for histamine and cholinergic (muscarinic) receptors by antihistamine drugs like cyclizine, inhibits communication to the vomiting centre. This can be effective if the surgery involves the vestibular pathways, but is less so if the Na/V arises because of CTZ activation.

Alternatively, the CTZ is highly responsive to dopaminergic stimuli, making dopamine receptor antagonists particularly effective at blocking emetic stimuli. Metoclopramide and domperidone can both be used in this context, e.g opioid and drug induced emesis, and both have the additional advantage of being pro-kinetic agents. However, metoclopramide crosses the blood brain barrier and can induce somnolence and some serious neurological disorders (extra-pyramidal effects), such as dyskinesias. Although this represents a major disadvantage for high dose or long-term use (see MHRA warning), metoclopramide can be used for acute PONV intervention. However, it is not usually a first line drug, because its efficacy is uncertain (this is under review) and there are safer alternatives, e.g the 5HT3 antagonists which have become less expensive. Domperidone is not associated with dystonic reactions, but its contra-indication with cardiac disease makes it problematic in the operative setting.

Prochlorperazine is licensed for treatment of acute emesis, as well as for prevention, and it may be combined with agents such as a 5HT3 antagonist at induction if there is a high risk of PONV. It is a first-generation antipsychotic drug and works in NA/V because one of its primary mechanisms of action is to block dopamine (D2) receptors. At lower doses than would be used when treating psychoses, this can assist in Na/V. Droperidol is also a first-generation anti-psychotic drug, related to haloperidol, and can be given i.v. intra-operatively.

The corticosteroid dexamethasone can be given before or at induction to offset PONV risk, but despite long-term use, the mechanism of action is unknown. As a corticosteroid, there is an anti-inflammatory action, which may exert an anti-emetic action with or without reducing pain. Less pain means less cortical stimulation and less opioid requirement. The anti-inflammatory effects cause inhibition of prostaglandin and serotonin release, which could oppose/counteract emesis. These effects will be delayed, as the dexamethasone must cross cell membranes and modulate gene transcription, for which onset is at least 1-2 hours (Sapolsky et al 2000), hence the general advantage of pre-induction administration (Waldron et al 2013).

Activation of corticosteroid receptors in the NTS could alleviate Na/V, and this may explain some of the more rapid actions as an anti-emetic, at approximately 2 hours after i.v administration (Wang et al 2000). A long half-life of 36-54 hours (SPC) provides prolonged anti-emetic peri-operative cover. Dexamethasone is considered to work well with other antiemetic agents, having an additive effect and, as such, is often used in combination (Szarvas et al 2003; Song et al 2011).

**Table 2: Examples of peri-operative drugs associated with emesis**

|  |  |
| --- | --- |
| **Drug** | **Cause of nausea and/or vomiting** |
| Opioids e.g morphine and fentanyl | Stimulate CTZ and delay gastric emptying |
| Nitrous oxide | Diffusion of gas into intestinal spaces can cause bowel distension |
| Atropine | Delays gastric emptyingLowers oesophageal tone |
| Neostigmine | Anticholinesterase action increases GI motility and secretions/high doses associated with NA/V |
| NSAIDs | GI irritation |
| Hyoscine butylbromide | Gastric stasis |

**Acute NA/V**

This has many causes (Table 3) and it is important, where possible, to establish the cause before treating the vomiting, although initial/concomitant medical support may be necessary, e.g fluid replacement. Many antiemetic drugs can be administered parenterally to avoid issues with reduced absorption and bioavailability, such as metoclopramide (i.v onset 1-3 minutes) or ondansetron (i.v onset 5 minutes).

**Table 3: Examples of acute causes of nausea and vomiting**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Gastro-intestinal** | **Endocrine** | **Medication** | **Visceral** | **Medical**  | **Psychological**  |
| Ingestion of toxins e.g viral or bacterial gastroenteritis | Diabetic ketoacidosis | Opioids | Chest pain/acute coronary syndrome | Volume depletion | Anticipatory e.g pre-chemotherapy |
| Bowel obstruction  | Hypoglycaemia | Chemotherapy e.g cisplatin | Pericarditis  | Metabolic derangement e.g lactic acidosis or hypercalcaemia | Conversion disorder (psychological problem is converted into a symptom) |
| Biliary colic | Thyroid disease | NSAIDs | Pyelonephritis  | Neurological e.g CNS tumour, infection, stroke | Eating disorders e.g bulimia nervosa |
| Cholecystitis | Pregnancy | Antibiotics | Retroperitoneal cancer | Liver metastases  |  |
| Hepatitis |  | Metformin |  | Migraine  |  |
| GI bleed |  | Theophylline  |  | Head trauma  |  |

**Motion Sickness**

A mismatch between spatial and motion sensory inputs, underlies motion sickness. However, vestibular disorders, such as vestibular neuronitis, generate Na/V via direct stimulation of the vestibular neuro-circuits. Prevention is central to effective management of motion sickness, but the same drug classes will also provide symptom control. The first-line intervention is hyoscine, which competes for acetycholine at the muscarinic receptor on vestibular neurons. This modifies the sensory input from the inner ear to the vomiting centre. It is considered an effective intervention and is widely available over the counter, for example, as a transdermal patch. As an anti-cholinergic drug, it is associated with a dry mouth, blurred vision and drowsiness, with a risk of central anti-cholinergic syndrome if used systemically. However, the patch applied behind the ear is designed to minimise side-effects, allowing steady release.

Histamine receptors are expressed in the inner ear, as well as in the NTS and vomiting centre (Housely et al 1988). Histamine signalling in the vestibular CNS pathways transmits input to the brain stem centres. The main histamine 1 (H1) receptor antagonists are cyclizine and promethazine. However, because the anti-histamine drugs used to manage emesis all have significant anti-cholinergic effects, there is uncertainty which action/combination of actions is opposing the Na/V stimuli. Both anti-histamine and anti-cholinergic actions produce sedation, with cyclizine having the least effect and promethazine the greatest. For vestibular and migraine-related Na/V, as well as vertigo, the anti-psychotic prochlorperazine blocks dopamine in the vomiting centre. The buccal tablet formulation is fast acting and less sedating than any anti-histamine.

**Cancer induced nausea and vomiting (CINV)**

The real and anticipated impact of CINV causes considerable distress, with ramifications for compliance with therapy and associated negative outcomes. Despite improvements in management, 30-60% of patients undergoing chemotherapy experience either acute (onset in minutes-hours and resolving in 24 hours) or delayed (onset 24 hours or more after therapy) CINV (Cohen et al 2007). While chemotherapeutic agents vary in the propensity to induce CINV (Box 1), great care is required to predict and manage this effectively. It is important to note that radiation and surgical treatments can induce Na/V, the degree of which depends on the target site, namely brain, gut and liver, or total body radiation being high risk.

The drugs used to shrink neoplasms do so because they are cytotoxic. While the effect is greatest on the most rapidly dividing cells, chemotherapeutic drugs have varying degrees of selectivity to the cancerous tissue, with some of the newer drugs designed to target specific tumorous sites. Many are noxious to the lining cells of the gut, as these are rapidly dividing epithelial cells. Irritation of these cells causes the release of serotonin, substance P and dopamine.

Within the digestive tract lining reside the enterochromaffin (EC) cells, which form part of the enteric nervous system. In addition to a regulatory/homeostatic role, these cells signal to the CNS about the presence of emetic stimuli, such as the free radicals released by cytotoxic drug damage, via neurotransmitters such as serotonin. Distinct from this, the presence of abdominal toxins provokes cardiac and GI vagal afferent pathways which relay sensory information into the NTS and the vomiting centre.

Multiple emetic pathways can mean that intervening with a single drug may be inadequate, and sometimes dose and drug combination trial and error is important. In view of the many serotonin driven pathways in CINV, the 5HT3 receptor antagonists are central to management (acute and delayed), with all 3 UK agents licensed for NA/V associated with chemotherapy. The latest addition in the class is palonosetron, which binds strongly and is highly selective for the 5HT3 receptor site, as well as having the longest half-life, giving it a superior efficacy and safety profile (Navari 2013).

Other enteric pathways are also CINV targets and one of the newer drug classes was devised to block the NK-1 receptor, the natural ligand for which is substance P. Aprepitant (oral) and fosaprepitant (i.v) are both licensed specifically as adjuncts to dexamethasone for CINV (Hesketh et al 2003). Netupitant is licensed in combination with palonosetron for moderately emetogenic chemotherapy or highly emetogenic cisplatin based chemotherapy (Joint Formulary Committee 2017).

Although superseded by the 5HT3 antagonists, dopamine receptor antagonists retain a role, particularly in breakthrough or refractory emesis. Metoclopramide and the antipsychotic D2 antagonists, prochlorperazine and levomepromazine may be useful in this situation. The cannabinoid, nabilone is licensed solely for CINV, which is unresponsive to other agents. The precise mechanism of action remains unclear. It has been proposed that the EC cells in the gut might express CB1 receptors which can be blocked by nabilone (Rutkowska and Gliniak 2009). CB1 receptors are also found in the brain stem and within the dopaminergic and noradrenergic neurons involved with the main vomiting circuitry (Mackie 2005). Nabilone is a controlled drug (CD2) and is taken orally.

Various anti-psychotics agents have a role in CINV, as well as in palliative care (or both) where NA/V may be provoked by metabolic derangements such as hypercalcaemia and organ failure. In the CINV niche, olanzapine blocks a variety of dopamine sub-receptors and may be used in combination with other agents, such as dexamethasone and/or the 5HT3 antagonist palonosetron. While this is not a first line approach, this has been shown to assist with Na/V prophylaxis at all stages of chemotherapy (Navari et al 2011; Navari et al 2016). Haloperidol has a long-standing role in palliative care, as it can be used in low dose (high potency), provides sedation and can control nausea and vomiting symptoms by blocking dopamine receptors on the CTZ (CKS 2016).

**Pregnancy Induced Nausea and Vomiting (PINV)**

Multiple hormonal and metabolic factors have been implicated in this common condition, which typically does not need medical intervention. There are many stages to the appropriate assessment and management of hyperemesis gravidarum, including support, self-care advice and non-pharmacological treatments (CKS 2017). However, if these fail, and it is deemed necessary to proceed with anti-emetic treatment, the first line agents are the oral anti-histamines cyclizine or promethazine, or oral prochlorperazine (CKS 2017). Second-line agents are metoclopramide and ondansetron (CKS 2017). Specialist advice is required if these are also ineffective.

Ethical barriers prevent clinical trials on pregnant subjects, and hence all these agents are unlicensed for use in pregnancy. Nevertheless, women can be reassured that safety and efficacy evidence is available to inform use (CKS 2017). While these agents come in alternative formulations if oral intake is impractical, inability to retain oral agents may be one indication for hospital admission (RCOG 2016). It is recommended that treatment continue for the shortest possible time and regular review, e.g after 24 hours, then after one week, is implemented.

**Conclusions:**

The assortment of drugs acting on the Na/V pathways and associated neurotransmitters means there are several antiemetic choices. Efficacious selection is assisted by the current guidelines in each field and the clinician has single and combination drug class and sub-class options.

**CPD questions and reflection**

**Why is the chemotherapeutic trigger zone situated outside the blood brain barrier?**

**What role does histamine play in the central vomiting pathways?**

**Why are antimuscarinic agents useful for motion sickness?**

**How does serotonin communicate information from the gut to the brain?**

**Find the information in the BNF about the emetogenic potential for chemotherapy drugs and consider which antiemetics can be used for acute and delayed onset of cancer induced nausea and vomiting.**

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