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REVIEW



New therapies to treat nausea and vomiting: clinical need, progress towards novelty and research challenges

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ABSTRACT

Introduction: Despite the availability of drugs which prevent vomiting, treatment gaps in controlling nausea and vomiting remain. New approaches are needed.

Areas covered: We identify unmet clinical needs by examining clinical reviews (last 5-years), adding our experience in drug discovery/emesis research. Mechanisms of nausea and vomiting are given. We identify emerging research and new approaches before discussing the challenges of quantifying nausea and vomiting in future trials.

Expert opinion: As single agents, drugs which prevent vomiting have efficacy in some but not all groups of patients, with NK₁ receptor antagonists possessing the widest spectrum of action. Drug combinations have improved efficacy in specific clinical settings. However, treatment gaps remain (e.g. gastroparesis, cyclic vomiting syndrome) and efficacy is lower against nausea compared with vomiting. The latter requires greater attention in trial design and regulatory assessments. The issue of nausea is difficult because in humans it is inadequately quantified (with high temporal resolution), there is a lack of clinical research into nausea, and animal models only measure 'nausea-like behaviours,' with challenges in translating to humans. In drug discovery, more systematic and critical analysis of the pharmacology of the diverse agents which induce or reduce nausea and vomiting may help identify new therapeutic mechanisms.

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1. Introduction

Vomiting is a mechanical event resulting in forceful oral ejection of gastric contents, whereas nausea is a self-reported sensation, making drug control of nausea and vomiting particularly complex. The need for these drugs covers many diseases (e.g. gastroparesis, cyclical vomiting syndrome (CVS), migraine), treatments (e.g. radiotherapy) and drug therapies where nausea/vomiting reduce quality-of-life and treatment compliance (e.g. cancer chemotherapy/immunotherapy, opioid-based drugs, glucagon-like-1 receptor agonists (GLP-1 R-agonists)) and can limit maximum tolerated doses (MTD), reducing clinical impact. Patients receiving palliative care may experience nausea and vomiting from multiple causes [1,2]. Nausea and vomiting occur with terrestrial motion sickness (MS), labyrinthine disorders [3,4], and space travel [5].

A second complexity is that these drugs are called 'anti-emetics' (Table 1), without clarifying if both nausea and vomiting are prevented (see below for discussion on this weakness). Most received regulatory approval decades ago. Some originated from natural remedies (e.g. scopolamine) or incidental observations. They include antagonists at dopamine (D₂), histamine (H₁) and muscarinic acetylcholine (mACh) receptors, with representative drugs available by 1970. Even 'recent' drugs, antagonizing at 5-hydroxytryptamine₃ (5-HT₃) and neurokinin₁ (NK₁) receptors, were identified >30 years ago, with

highly emetogenic chemotherapy driving research [6]. There are also drugs not classed as 'anti-emetics' but used 'off-label' to alleviate nausea/vomiting (e.g. the psychotropic olanzapine in chemotherapy-induced nausea and vomiting (CINV) [27]). Patterns of 'anti-emetic' drug evolution are:

- (i) After achieving efficacy in one condition, the drug is investigated elsewhere, with variable rationale. This applies to all drug classes. Using 5-HT₃ receptor antagonists (5-HT₃RA) as an example, efficacy was shown in CINV and then against post-operative nausea and vomiting (PONV), achieving regulatory approval. Smaller studies conducted in other conditions had less success (e.g. [34]). NK₁RA followed a similar pathway, with efficacy in MS also pursued (e.g. tradipitant [35]). Among older drugs, efficacy has not always been rigorously established, and mechanisms not established (e.g. the H₁RA cyclizine, used to prevent MS and vomiting in several other conditions including *hyperemesis gravidarum* [36]). Other examples where 'anti-emetic's' are used without fully understanding mechanisms include patients receiving palliative care, and patients with *hyperemesis gravidarum* (controlled trials are difficult), CVS and gastroparesis [37–39].

Article highlights

- Despite the use of anti-emetic drugs, significant groups of patients still suffer from nausea and vomiting, and when vomiting can be prevented, nausea may remain.
- In approval of new drugs to control nausea and vomiting, there should be more emphasis on the efficacy against **both** nausea and vomiting.
- For some drugs, progress includes improved delivery, long receptor occupancy to prevent prolonged nausea and vomiting, and identification of receptor mutations and patient risk factors.
- Clinical pharmacology and physiology must develop better methods to quantify nausea, understand mechanisms of nausea and evaluate agents which may reduce nausea.
- Identification of GDF-15 antibodies, GFRAL-receptor antagonists and GLP receptor agonists as agents which may inhibit vomiting, presents a new chapter in anti-emetic research.

- (ii) For CINV, 'anti-emetics' with differing pharmacological targets are used in combination. It is recommended that patients given highly emetogenic chemotherapy (>90% incidence of vomiting) may receive a 5-HT₃RA, NK₁RA, dexamethasone, and olanzapine [40]. This reflects different neurochemical changes driving different dominant pathways that change over time (acute, delayed, and long-delayed phases of nausea and vomiting). In some non-cancer patients, it may also be necessary to target multiple receptors to optimize control of nausea and vomiting, but this has not been adequately explored.

A third complexity is that drugs should prevent two different symptoms – vomiting and nausea. Here, the term 'anti-emetic' is potentially misleading as it classifies drugs which treat vomiting but implies inhibition of vomiting **and** nausea [41]. However, nausea is less effectively reduced, compared to the mechanical events of retching and vomiting [39,42,43]. This means that efficacy against nausea **and/or** vomiting should be separately defined. Failure to do so should be of concern to those involved in drug development and regulation. It also hampers the understanding of how drugs inhibit or cause nausea and/or vomiting, their correct usage and future developments. We use 'nausea' to refer to the self-reported sensation in **humans** and 'emesis' to refer to retching and/or vomiting in laboratory **animals or humans**, as in both, these are physiologically similar [44]. Translation of 'nausea-like behaviours' in animals to humans remains uncertain [45,46]. Hereon, we avoid the term 'anti-emetic' and describe drugs which only prevent vomiting unless otherwise proven.

2. Aims

The review is a critical analysis of literature (e.g. PubMed) to identify knowledge gaps, informed by our insights from extensive research in this area. We aim to: i) identify gaps in the treatment of nausea and vomiting; ii) review current developments in treatments for nausea **and/or** vomiting and in our understanding of emetic mechanisms; iii) provide considered opinion of pathways to progress this area, based upon our

combined experience of drug discovery and development (granisetron, ondansetron [47]), and preclinical/clinical studies into these drugs. We review pathways for nausea and vomiting in relation to drugs preventing or causing vomiting, before identifying treatment gaps, recent advances, potential solutions, and limitations.

3. Pathways and sites of action of drugs which cause or prevent vomiting

3.1. Pathways

Pathways leading to vomiting were identified using dogs, cats, and to a lesser extent, non-human primates [48], and more recently, ferrets [49] and shrews (house musk shrew [50,51]; least shrew [52]). Mice and rats lack a complete emetic reflex [44] but are used extensively to study behavioral responses (conditioned aversive and avoidance responses, pica, or kaolin consumption) to substances causing vomiting in humans [42]. Nausea is a human experience with pathways studied mostly by brain imaging in volunteers exposed to virtual motion and rarely, to drugs or in patients [53]. The pathways summarized in Figure 1 are:

- Initial signaling.* Occurs via the area postrema (AP), abdominal and cardiac vagal afferents, vestibular system, and ill-defined inputs from 'higher' brain areas thought to influence the sensitivity of brainstem mechanisms [43,54];
- Integration of signaling.* Achieved by the *nucleus tractus solitarius* (NTS) in the brainstem and if appropriate, the NTS signals for N&V [55–57];
- Divergent outputs from the NTS.* Nausea is signaled to 'higher' brain regions (particularly inferior frontal gyrus, anterior insula and cingulate cortex [53]), whereas vomiting and retching are signaled to the ventral brainstem, driving thoracic and abdominal muscles involved in the mechanical events of emesis [44].

3.2. Sites of action of drugs

A summary is given in Table 1, with sites of key receptors shown in Figure 1. The latter were derived largely from animal studies by overlaying activity onto known pathways of vomiting (e.g. ferrets [49]).

3.2.1. Initial signalling

- Hair cells in vestibular labyrinths [58] detect motion, releasing a transmitter (histamine) to activate the vestibular nerve projecting to the vestibular nerve nucleus. H₁RA's acting at this site reduce vomiting caused by abnormal motion [59], but this is not the only site at which H₁RA's act (see below). A recent animal study demonstrated that acetazolamide could reduce the motion-induced increase in endolymph volume and hence reduce MS [60].
- Vagal intra-ganglionic laminar endings have mechanoreceptive functions in the gut [61], with receptors

Table 1. Main pharmacology of drugs which inhibit vomiting.

PHARMACOLOGY OF DRUGS WHICH PREVENT VOMITING				SUMMARY OF CLINICAL USE
DRUG	Receptors antagonized or, where specified, activated	Most likely site(s) at which vomiting is prevented		
Hyoscine hydrobromide Promethazine	M ₁₋₄ (~0.5 log differences). Antagonism at M ₅ may explain the anti-emetic activity. H ₁ , mACh receptors	M receptor antagonism within the vestibular system and associated brainstem nuclei. H ₁ and M receptor antagonism within the vestibular system and associated brainstem nuclei, including the NTS. H ₁ RA within the vestibular system and associated brainstem nuclei, including the NTS. The role of histamine in causing N&V is unclear. For conditions other than motion sickness, we speculate that a reduction in tonic drive to the NTS by H ₁ RA may increase the threshold required for non-vestibular stimuli to sufficiently activate the NTS and induce nausea and vomiting.		Motion sickness and uses other than prevention of vomiting Nausea/Vomiting (including use to treat pregnancy sickness). Labyrinthine disorders, Motion sickness Vomiting (of known cause). Labyrinthine disorders, Motion sickness. PONV. Also used to treat Nausea/Vomiting in palliative care, and pregnancy sickness
Cinnarizine	H ₁ , H ₄ , D ₁ , D ₂ , D ₃ > M ₁ , M ₃ , M ₄ , Cav1.3	H ₁ RA within the vestibular system and associated brainstem nuclei, including the NTS. D _{2/3} RA within the AP D _{2/3} RA within the AP		Vestibular disorders, such as vertigo, tinnitus, N&V in Ménière's disease. Also used for motion sickness but no longer approved in U.S.A.. Neuroleptic Pain, agitation and nausea/vomiting in palliative care (not licensed)
Levomethoprazine (or methotrimeprazine)	D ₁ , D ₂ , D ₃ , D ₄ , 5-HT ₁ , 5-HT ₂ , H ₁ , α ₁ /α ₂ -adrenoceptors, M ₁ , M ₂			Anti-psychoctic and Anxiolytic. Vomiting (cause not specified but used to treat pregnancy sickness). Labyrinthine disorders. Nausea/vomiting with migraine
Prochlorperazine	H ₁ , D ₂ , D ₃ , 5-HT _{2A} > D ₁ > D ₄	Vestibular neuron input to vestibular nuclei D _{2/3} RA within the AP		Anti-psychoctic and Anxiolytic. Nausea/vomiting in palliative care. Used to treat pregnancy sickness
Chlorpromazine	H ₁ , 5-HT _{2A} > 5-HT _{2C} , D ₄ , 5-HT ₆ , 5-HT ₇ , α _{2B} -adrenoceptor > D ₃ , D ₂ , D ₁	Vestibular neuron input to vestibular nuclei		Anti-psychoctic and Anxiolytic. Nausea/vomiting in palliative care. Used to treat pregnancy sickness
Trifluoperazine	D ₂ > 5-HT _{2A} , D ₄ , H ₁ > 5-HT _{2C}	D ₂ RA within the AP		Anti-psychoctic and Anxiolytic. Severe vomiting (cause not specified)
Haloperidol	D ₄ , D ₂ , D ₃ , D ₁ > 5-HT _{2A}	D _{2/3} RA within the AP		Anti-psychoctic and treatment of Huntington's disease PONV. Nausea/vomiting in palliative care (not licensed)
Properidol Domperidone	α ₁ -adrenoceptors, D ₂ , 5-HT _{2A} D ₂ , D ₃	D ₂ RA within the AP D _{2/3} RA within the AP Poor brain penetration. hERG blocker		PONV (including analgesics as a cause) Vomiting (indication not specified), GI pain palliative care
Metoclopramide	D ₂ and 5-HT _{3A} (higher concentration) Also, an agonist at 5-HT ₄ receptors which facilitates gastric emptying.	D ₂ RA within the AP 5-HT ₃ RA at abdominal vagal afferent neurons		Vomiting (including migraine but otherwise, indications not specified), delayed vomiting during chemotherapy, radiotherapy-induced vomiting, PONV. Used to treat vomiting during pregnancy, in palliative care and acute migraine (not licensed)
Ondansetron (racemate) Granisetron Palonosetron	5-HT _{3A} , 5-HT _{3AB} , > 5-HT _{2B} (agonist) 5-HT _{3A} 5-HT _{3A} Binds allosterically to the receptor, with a relatively high affinity and a long plasma half-life in healthy volunteers.	5-HT ₃ RA at abdominal vagal afferent neurons 5-HT ₃ RA at abdominal vagal afferent neurons Thought to trigger receptor internalization, interacting with the NK ₁ receptor to further inhibit the functions of substance P NK ₁ RA within the NTS/CPG and their linking pathways		CINV, PONV, Radiation-induced vomiting CINV; effective in acute and delayed phases Adjunct to dexmethasone and a 5HT ₃ RA in CINV
Aprepitant	NK ₁ Also activates a mechanosensitive two-pore domain potassium channel, TRAAK			
Fosaprepitant (intravenous prodrug of aprepitant)	NK ₁	Acts within the NTS/CPG and their linking pathways		Adjunct to dexmethasone and a 5HT ₃ RA in CINV

(Continued)

Table 1. (Continued).

PHARMACOLOGY OF DRUGS WHICH PREVENT VOMITING			SUMMARY OF CLINICAL USE
DRUG	Receptors antagonized or, where specified, activated	Most likely site(s) at which vomiting is prevented	
Netupitant with Palonosetron ('NEPA,' a fixed dose combination) (also fosnetupitant and palonosetron)	Netupitant; an NK ₁ RA with long plasma half-life and long duration of receptor occupancy (see [1]). Palonosetron; a 5-HT ₃ RA (see above). Its use may lead to receptor internalization and 'crosstalk' with NK ₁ signaling pathways (see [1]).	See above for NK ₁ and 5-HT ₃ receptor antagonists.	CINV; the combination of two long-acting anti-emetic drugs may achieve a more complete block of delayed and super-delayed nausea/vomiting during repeat treatment with chemotherapy (see text for details).
Nabilone (racemate)	CB ₁ and CB ₂ receptor agonist	Acts within the NTS to suppress activation. May also be cerebral site(s).	CINV unresponsive to conventional antiemetics
Doxylamine with pyridoxine	Doxylamine: antagonizes H ₁ receptors. Pyridoxine (vitamin B6): a water-soluble vitamin.	H ₁ RA within the vestibular system and associated brainstem nuclei. May inhibit histamine-induced activation of vagal afferent neurons. Pyridoxine (and its active form, pyridoxal-5-phosphate) is a coenzyme in metabolic pathways, including those involved with hormone (e.g. related to pregnancy vomiting) and neurotransmitter metabolism. The former is hypothesized to reduce pregnancy vomiting by overcoming a deficiency of pyridoxine. The latter include 5-HT, dopamine and GABA; it is hypothesized that increased availability of GABA within the brainstem may suppress vomiting. In addition, the effects of pyridoxine of GDF-15 should be assessed in view of studies implicating this cytokine in pregnancy sickness.	Nausea/vomiting in pregnancy Pyridoxine alone may also reduce pregnancy vomiting and PONV.
Drugs used to prevent vomiting, but not categorized as anti-emetic drugs in the standard BNF			
Mirtazapine (racemate)	H ₁ , $\alpha_{2A,B,C}$ -adrenoceptor, 5-HT _{2C} , 5-HT _{2A} , 5-HT ₃	For both drugs it is uncertain why they may facilitate the anti-emetic and anti-nausea effects of combined dexamethasone, 5-HT ₃ and NK ₁ RA. Possible mechanisms include the benefits of H ₁ RA (in addition to causing somnolence this may also reduce a tonic drive to the NTS) and 5-HT _{2C} RA (increasing appetite and weight gain). See text for details.	Major depression Anti-emetic activity includes PONV and CINV Used in combination with dexamethasone, a 5-HT ₃ and an NK ₁ RA to reduce occurrence of nausea in patients receiving highly emetogenic chemotherapy.
Olanzapine	H ₁ , 5-HT _{2A} , 5-HT _{2B} , D ₂ , 5-HT _{2C} , 5-HT ₆ , 5-HT ₇ , α_{2A} -adrenoceptor > α_{2D} -adrenoceptor, D ₃ , M ₁ , M ₂ , M ₃ , M ₄ . Also, a noncompetitive, allosteric 5-HT ₃ RA inhibitor. At H ₁ , 5-HT _{2A} , 5-HT _{2B} and 5-HT _{2C} , inhibition of function may be due to inverse agonism. Pharmacokinetics suggest occupancy of the receptors expressed peripherally. Therapeutic and adverse event profiling suggests brain occupation of H ₁ (causing somnolence), D ₂ and 5-HT _{2A} (therapeutic benefit), 5-HT _{2B} and 5-HT _{2C} receptors (increasing slow wave sleep).		Anti-psychotic Used in combination with dexamethasone, a 5-HT ₃ and an NK ₁ RA to reduce occurrence of nausea in patients receiving highly emetogenic chemotherapy.

This shows the main human receptors antagonized by the different anti-emetic drugs and their likely site of action. The drugs are as listed in the British National Formulary [7], a resource to identify regulated/prescription drugs that are generally globally available, but with some exceptions given below. It should be noted that the descriptions within the BNF do not separate nausea from vomiting. This is a significant omission as nausea is less well prevented by most or all the drugs (see text for details). Not included are dexamethasone (which has anti-emetic activity but is used together with a 5-HT₃ receptor antagonist to treat CINV) and drugs used in other countries including tropisetron (antagonist at 5-HT_{3A} > 5-HT₄), metopimazine (NG101; peripherally restricted antagonist at D₂, D₃, 5-HT_{2A}, α_1 -adrenoceptor > H₁), lonaserin (antipsychotic drug antagonizing at D₂, D₃, 5-HT_{2A} and used as an anti-emetic in palliative medicine [8]) and tridipitant (NK₁ receptor antagonist recently approved by the U.S.A. Food and Drug Administration for prevention of vomiting induced by motion [9]). Information on the receptors antagonized by the drugs was obtained mostly from [6], and the IUPHAR/ BPS Guide to Pharmacology [10], with subsections for GPCRs and Ion Channels (5-HT₃). Inhibition of H₁ receptor function may be achieved by inverse agonism. For older drugs, references are provided to studies which describe their pharmacology, avoiding the reviews and databases which respectively, cite other reviews or do not provide the methodology used to define the conclusions. For these drugs, some information obtained by using animal receptors are included. Additional information is provided for hyoscine [11], promethazine [12], levomepromazine [13], levomepromazine, cinnarizine, prochlorperazine, mirtazapine [14], cinnarizine [15,16], metopimazine [17,18,28], droperidol [19], ondansetron [20], aprepitant [21], the netupitant/palonosetron combination [22–24], mirtazapine [8,25,26] and olanzapine [27,29–31]. For clinical efficacy and hypothesized mechanisms by which pyridoxine alone may inhibit vomiting see [32,33].

Abbreviations: 5-HT: 5-Hydroxytryptamine (receptor subtypes are 5-HT₁, 5-HT₂ (A, B, and C subtypes); 5-HT₃ (A-E subunits), 5-HT₄, 5-HT₆, 5-HT₇); AP: Area Postrema; Cav1.3: voltage-gated Ca²⁺ channel isoform; CB: Cannabinoid receptor (1 and 2 subtypes); CINV: Chemotherapy-induced Nausea and Vomiting; D: Dopamine receptor (1–5 subtypes); H: Histamine receptor (1–4 subtypes); M: Muscarinic ACh (mACh) receptor (1–5 subtypes); N&V: Nausea and Vomiting; NK₁: Neurokinin₁ receptor; NTS: Nucleus Tractus Solitarius; PONV: Post-Operative Nausea and Vomiting; RA: Receptor Antagonism (e.g. H₁RA).

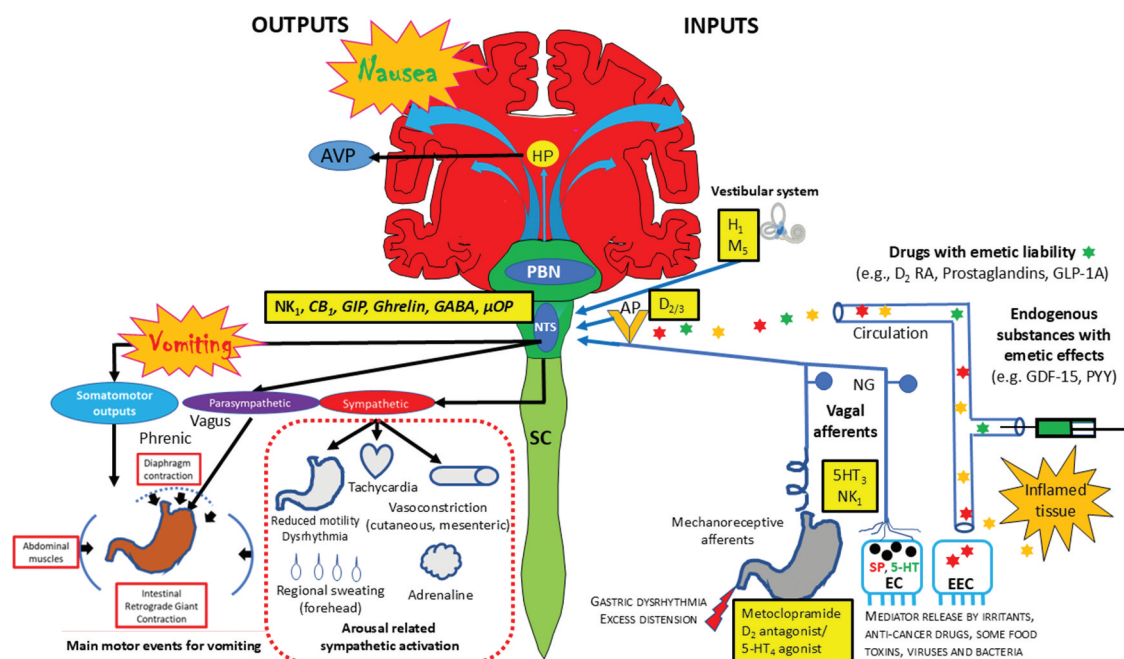


Figure 1. A summary diagram of the major pathways implicated in nausea and vomiting. The right side shows the major inputs from the vestibular system, area postrema and abdominal vagal afferents, all converging on the nucleus tractus solitarius. The descending pathways from the cerebral hemisphere by which psychological stress can induce vomiting is not shown. The left side shows the outputs of associated with nausea and vomiting including motor changes in the diaphragm and abdominal muscles, alterations in digestive tract motility and consequences of sympathetic nervous system activation associated with nausea (red dotted line box). The main receptors involved in the emetic responses are shown in yellow boxes. Agents or receptors with an agonistic anti-emetic action are shown in italics. For details see text and references (modified from [39,43,54]).

Abbreviations: AP = area postrema; AVP = arginine vasopressin; CB₁ = cannabinoid₁ receptor; D_{2/3} = dopamine_{2/3} receptors; EC = enterochromaffin cell; EEC = enteroendocrine cells; GABA = gamma amino butyric acid; GDF-15 = growth differentiation factor 15; GLP-1 = glucagon-like 1; H₁ = histamine₁ receptor; 5-HT = 5-hydroxytryptamine; HP = hypothalamus; M₅ = muscarinic₅ receptor; N&V = nausea and vomiting; NK₁ = neurokinin₁ receptor; NG = nodose ganglion; NTS = nucleus tractus solitarius; PBN = parabrachial nucleus complex; PYY = peptide YY; SC = spinal cord; SP = substance P; μ OP = μ -opioid receptor agonist.

modulating afferent activity (e.g. GLP-1, Cholecystokinin₁ [CCK₁], Neuropeptide Y₂ [NPY₂], Transient Receptor Potential Vanilloid₁ [TRPV₁] [62–64]). Thus, vagal afferents can detect changes in gut motility associated with nausea and vomiting, sometimes alleviated by gastric prokinetics [39,65]. Historical studies identified substances activating receptors on other vagal afferents projecting from digestive tract muscle and mucosa (e.g. histamine, 5-HT, prostaglandin-E₂ [66]), or reducing responses (e.g. gamma-aminobutyric acid activating GABA_B receptors [67]). Molecular studies in mice revealed a greater diversity of receptors on vagal afferent terminals [68,69], potentially identifying novel targets for prevention of vomiting.

Two examples of afferent activation and drugs preventing vomiting are:

- 5-HT₃ receptors on mucosa-terminating vagal afferents, activated and sensitized by 5-HT from enterochromaffin (EC) cells of the upper gut mucosa, to cause vomiting during the acute phase of CINV [70] and vomiting by X-radiation and rotavirus [71,72]
- Histamine from intestinal mast cells stimulate vagal afferents in staphylococcal enterotoxin A-induced emesis [73]. We speculate that a similar pathway explains the

contribution of histamine from mast cells and basophils in mechanisms of PONV [e.g. [74].

iii) Area Postrema. This region, where the blood–brain barrier is relatively permeable, is in the fourth ventricle of species with, and lacking, the ability to vomit [44]. Emesis may be evoked after stimulation of the AP by agents given intravenously or into the ventricular system (e.g. histamine, GLP-1 R-agonists, D_{2/3}-agonists, adrenaline [75,76]). Molecular studies in rodents identified neuronal clusters of surface receptor and neurotransmitter-related genes [77,78]. The AP receives some input from vagal afferents, the NTS, lateral parabrachial nucleus (LPBN), and hypothalamus, but their role in emesis is unclear. Studies need to understand how the AP encodes information based on blood concentration and exposure time of agents acting on its neurones. This will determine how the same agent can produce dose-related responses, ranging from reduced food intake to nausea and subsequently vomiting; this is critical to understanding mechanisms for MTDs. AP sensitivity is not fixed, as the threshold dose for the D_{2/3}-agonist apomorphine to cause vomiting in dogs is lowered by agents increasing intracellular cAMP [75]. Once activated, the AP signals to the NTS and LPBN [79].

Activation of AP D₂ receptors by apomorphine was a key challenge characterizing the anti-vomiting activity of metoclopramide and the more selective D₂RA domperidone [6]. D₂RAs are now widely used to prevent vomiting in different

conditions [80]. Although systemic and iontophoretic apomorphine activates AP neurones [75,81] the exact location of the relevant D₂ receptors within the heterogeneous structure of the AP is unknown. The efficacy of D₂ RAs against stimuli with no evidence for elevated plasma dopamine (e.g. [39]) suggests the site is within the AP circuitry activated by other stimuli.

3.2.2. Block or modulation at point of input into the NTS

Drugs acting at the point of input to the NTS only affect the emetic stimuli acting via that pathway and do not have a 'broad spectrum' ability to prevent vomiting. For example, the mAChRA scopolamine (hyoscine) has its primary action on afferent neurones projecting from the vestibular system to the vestibular nuclei, and H₁ RAs have one of several potential sites of action here [3,6]. There are mAChR in other locations (e.g. pre-synaptic on vagal afferents terminating in the NTS [82]), but not in critical emetic pathways as the ability of scopolamine to prevent vomiting is limited to stimuli activating the vestibular system. Peripherally-restricted mAChRA (atropine methyl nitrate) did not prevent MS in dogs [83], and centrally penetrant antagonists are not effective against stimuli acting via the AP (e.g. apomorphine [84]). 5-HT₃ RAs are another example, inhibiting the peripheral EC-vagal afferent pathway to the NTS. Although 5-HT₃ receptors are in the human brain stem, primarily the NTS [84], they do not have a major role in prevention of vomiting [71,85]. Further, 5-HT₃ RAs do not prevent MS [86] or vomiting caused by stimuli acting via the AP (e.g. morphine, apomorphine [87,88]).

3.2.3. Blocking integration of signaling for nausea and vomiting by the NTS

Little is known about how inputs to the NTS encode the outputs causing nausea/vomiting. However, a relationship to stimulus intensity is likely, with a duration element. Thus, induction of emesis by drugs and endogenous agents, ionizing radiation and motion, is 'dose'-related, with nausea at lower doses/intensities of stimulation [89–91]. For NK₁ RAs a major site of action is in the central integrative mechanisms (particularly the NTS and central pattern generator), blocking the ability of neurones to reach threshold for generation of the patterned output to motor neurones causing vomiting [43,54]. It is this ability to generate the pattern of motor activity that is blocked and not the motor activity itself, responsible for other activities involving respiratory muscles (e.g. eupnea, gag). This antagonism of a single receptor at critical point(s) in a pathway can have 'broad spectrum' ability to prevent vomiting [43,54]. However, NK₁ RAs are less effective against nausea, suggesting that other transmitters project information from the NTS to 'higher' brain regions [54]. The neurochemical complexity of the NTS is shown by recent molecular studies which also discuss models of processing within the NTS [56,92,93].

3.2.4. Blocking outputs from the NTS: the challenge of nausea

To prevent nausea, it would be necessary to block output from the NTS to the cerebral cortex [53], most likely via the

parabrachial nucleus (PBN) [94]. However, targeting the PBN is challenging because of the divergent outputs from this region. Notably, many drugs which prevent vomiting are brain penetrant, but despite good receptor occupancy in cerebral structures (e.g. NK₁, see [54]) nausea is not fully blocked. Perhaps, drug combinations are needed or drugs with multiple actions, particularly those which reduce neuronal excitability (e.g. GABA-R-agonists, anti-epileptics) (see 6.2.1).

4. Treatment gaps

Identified in key therapeutic areas primarily by examining recent clinical reviews (Table 2).

4.1. Nausea: all therapeutic areas

Nausea is poorly treated, relative to vomiting (e.g. delayed CINV-induced nausea [113,114]). Patients invariably consider nausea to be more serious than vomiting (e.g. CINV [115]), ranking it as of greater concern than health-care professionals [116]. Perhaps, because nausea is 'invisible' it is not treated aggressively until progression to vomiting, particularly in emergency rooms. Nausea has been referred to as the 'neglected' symptom [117]. CINV patients considered that the absence of **both** nausea **and** vomiting should be the primary end-point of antiemetic trials [115].

This issue will be discussed later, regarding the quantification of nausea during clinical trials, and the need for regulatory recognition of nausea and vomiting, as distinct clinical end-points.

4.2. Drug–drug interactions: some therapeutic areas

For drugs preventing vomiting, drug–drug interactions are relevant for patients receiving cancer treatment [118,119], older adults receiving multiple drug therapies and patients receiving palliative care. Examples are inhibition of the cytochrome P450 enzyme CYP3A4 by the NK₁ RAs aprepitant/fosaprepitant and netupitant [119], increasing exposure to co-administered drugs such as dexamethasone, ondansetron, oxycodone, and some antineoplastic drugs (e.g. cyclophosphamide, some tyrosine kinase inhibitors [120,121]). The NK₁ RA tradipitant is metabolized by CYP3A4, increasing risk of adverse events when co-administered with drugs inhibiting CYP3A4 [122]. Some drugs which prevent vomiting increase the risk of cardiac QTc interval prolongation, hindering co-administration with drugs causing the same. The latter includes many antipsychotics, antidepressants [25], some tyrosine kinase inhibitors [123,124] and even other drugs used in combination to prevent vomiting [125]. They include ondansetron, granisetron, droperidol, prochlorperazine (moderate risk), metoclopramide, tropisetron, and olanzapine (intermediate), but not palonosetron and ramosetron. The peripherally restricted D_{2/3} RA domperidone inhibits the human ether-à-g-go-related gene (hERG) and has been largely withdrawn, leaving metopimazine in some countries as the only D_{2/3} RA which poorly crosses the blood–brain barrier (minimizing extra-pyramidal side-effects of brain-penetrant D₂ RAs) without hERG activity, albeit in a nonselective manner (Table 1). Finally, 5-HT₃ RAs can cause constipation, potentially exacerbated by co-

Table 2. Major groups of patients experiencing disease- or treatment-related nausea and vomiting and requiring anti-emetic medication but highlighting those for which these symptoms remain, despite the use of drugs which prevent vomiting. For all drug groups, precise efficacy against nausea is uncertain.

Cause of N&V	Characteristics of nausea and vomiting	Treatment	Unmet need
Chemotherapy	The risk that different anti-cancer treatments cause vomiting grouped into 'high' (>90% of patients), 'moderate' (30–90%), 'low' (10–30%) or 'minimal' (<10%). Nausea is present but not part of this assessment [40]. For 'high' and 'moderate' emetogenic drugs there is a risk that nausea and vomiting during the first 24 h after administration is followed by delayed nausea/vomiting (2–4 days) and in some patients by long-delayed (days 5–7) nausea, with some vomiting [24]. Increases risk of nausea and vomiting, compared with each treatment alone	• 'High Risk' patients receive a 5-HT₃ and NK₁RA plus dexamethasone and olanzapine. • 'Medium Risk' patients receive a 5-HT₃ and NK₁RA plus dexamethasone. • 'Low risk' patients receive a 5-HT₃RA, dexamethasone and a D₂RA	Acute, delayed and long-delayed nausea can remain, especially for drugs with 'high' or 'moderate' emetogenic potential [95]. Safe, effective drugs which prevent vomiting and nausea for pediatric patients need to be developed [96].
Radiotherapy with chemotherapy	Increases risk of nausea and vomiting, compared with each treatment alone	• The same drugs are used to prevent vomiting as used for chemotherapy.	Exploration of combinations of drugs to maximize control of vomiting [97].
Targeted cancer inhibitors	The risk that this causes vomiting mostly fall into 'moderate' (30–90%), 'low' (10–30%) and 'minimal' (<10%) groups. Nausea is present but not part of this assessment [40]. Of particular concern are some antibody drug conjugates, for which nausea and vomiting can occur separately at different times and last a week or more after each infusion (e.g. trastuzumab deruxtecan [98]). These drugs can be given in a manner which allows treatment adjustments, so the overall treatment can be continuous for 6-weeks or longer, meaning that patients experience a considerable toxic burden, greatly reducing quality of life [99,100]. Changes in anaesthetic and surgical practice and identification of higher risk groups have reduced the need for drugs to prevent vomiting [103].	• The same drugs are used to prevent vomiting as used for chemotherapy. The addition of olanzapine is a recent advance. • Publications of trials on new targeted cancer inhibitors often fail to identify the drugs used to prevent vomiting [40]	Nausea remains a significant symptom especially for the antibody-drug conjugates where this may be prolonged [24,101,102]. Drug-drug interactions limit choice of drug to prevent vomiting [see text].
Post-operative nausea and vomiting	Changes in anaesthetic and surgical practice and identification of higher risk groups have reduced the need for drugs to prevent vomiting [103].	• Prophylactic use of drugs which prevent vomiting, acting at different receptors, reduce the burden of PONV in an approximate equal effective manner, although as single agents, NK₁RA may be superior. For high-risk patients, combinations of treatments are recommended [103,104].	Overall, prevention may be incomplete and activity against nausea is uncertain, variable or not discussed (e.g [104],.). For 5-HT₃RA and NK₁RA, efficacy against vomiting is greater than against nausea [103]
Gastrointestinal diseases, exemplified by gastroparesis, but includes several other disorders (e.g. pyloric stenosis, intestinal obstruction, intra-abdominal inflammation, enteritis).	Symptoms of gastroparesis are nausea and vomiting, accompanied by delayed gastric emptying without mechanical gastric outlet obstruction, often coexisting with symptoms of dyspepsia ('postprandial distress syndrome'). Patients with 'gastroparesis-like' symptoms (also known as chronic [unexplained] nausea and vomiting) have gastric emptying of meals within the normal range, without identified cause (see [39] for references).	• Only metoclopramide approved for treatment of gastroparesis, but for a limited duration and not in the elderly. Other drugs are prescribed 'off-label' following registration for different indications [39]. These include various drugs which prevent vomiting in other groups of patients.	Patient satisfaction with current treatment outcomes is low [105,106].
Labyrinthine/ vestibular disorder (motion sickness, labyrinthitis, vestibular neuronitis, dizziness, middle ear infection)	Includes nausea with autonomous vehicles and virtual reality head-sets ('cybersickness').	• mACh and H₁RA (sometimes with additional mAChRA activity) are commonly used. • The NK₁RA tridipitant was recently approved in the U.S.A. for 'prevention of vomiting induced by motion' [9].	Orally-administered mACh and H₁RA have slow onset of activity and are not effective if symptoms have begun; they can cause drowsiness, dry mouth, blurred vision. The efficacy of tridipitant against nausea is uncertain [8,43].

(Continued)

Table 2. (Continued).

Cause of N&V	Characteristics of nausea and vomiting	Treatment	Unmet need
Pregnancy	Pregnancy-Nausea and Vomiting can be mild, moderate or severe. For the latter (<i>hyperemesis gravidarum</i>) this can prevent normal eating and drinking, severely limits daily living activities and can lead to dehydration. Complications include metabolic disorders, maternal malnutrition, preterm birth, long-term consequences for the child, and electrolyte disturbances which can be fatal [107].	Treatment of <i>hyperemesis gravidarum</i> includes the use of drugs to prevent vomiting (e.g. pyridoxine, ondansetron and if necessary, a corticosteroid). For some, combinations of these drugs are required, with nutritional support [36].	Safety concerns mean that large, controlled trials are difficult, with drug use sometimes based on 'historical' use.
Cyclic Vomiting Syndrome	Characterised by cyclical protracted episodes of intense vomiting but growing recognition that despite the name, nausea is also a major issue [108]	5-HT₃ and NK₁ RAs [109,110] - Anxiolytic, anti-epileptic/anti-migraine drugs - Very few controlled trials, particularly in paediatric population - Potential link to GDF15 [111]	Need for treatments to prevent and stop an attack in progress
Palliative	The reasons for nausea and vomiting can be complex and may be related to the illness and/or the drug treatments [2,8]	When causes of nausea/vomiting were unclear 'clinical pictures,' or categories of symptom characteristics, linked to potential causes (e.g. chemical/metabolic; gastric stasis/outlet obstruction, etc.), to help guide the choice of drug treatment [112]	Large, controlled trials are difficult.

Abbreviations: 5-HT₃: 5-Hydroxytryptamine₃ receptor; D₂: Dopamine₂ receptor; H₁: Histamine₁ receptor; mACh: muscarinic acetylcholine receptor; N&V: Nausea and Vomiting; NK₁: Neurokinin₁ receptor; PONV: Post-Operative Nausea and Vomiting; RA: Receptor Antagonism (e.g. 5-HT₃RA).

The citations are predominantly recent reviews (with some additional, supporting references), the majority published in 2025. For detailed pharmacology of the drugs see Table 1.

administration with olanzapine, an mAChRA among other activities [119] or in older adults by co-administration with drugs which inhibit intestinal motility, including opioid analgesics, drugs with anti-cholinergic activity (e.g. tricyclic antidepressants) and others [126].

4.3. Others: specific clinical areas

- Radiotherapy with chemotherapy increases the risk of nausea/vomiting, managed with the same drugs used for each treatment alone. Strategies to prevent vomiting and perhaps nausea have been slow to follow the lessons from highly emetogenic chemotherapy and combine drugs to maximize prevention of vomiting [97].
- Targeted Cancer Inhibitors (predominantly protein kinase inhibitors, monoclonal antibodies, antibody-drug conjugates) have improved the side-effect burden, but for many, nausea and vomiting occur sometimes during prolonged treatment, relative to chemotherapy [24,40]. Patients receive the same drugs used against CINV (but see above, for drug-drug interactions), but controlled trials and mechanistic studies are lacking and the impact on nausea is unclear.
- For gastroparesis, drugs which inhibit vomiting are used 'off-label' with poor rationale and unsatisfactory relief of symptoms including nausea [39,127]. Use of the 'Gastroparesis Cardinal Symptom Index' (GCSI), a collection of symptoms which define the efficacy of potential new treatments, may hamper the identification of drugs targeting one pathway to ameliorate some, but not all symptoms [127]. Perhaps this applies to drugs such as the NK₁RAs which prevent vomiting but are less efficacious against nausea (see [43] and below). Another reason may be a poor understanding of the relationship between nausea and the delayed gastric emptying characteristic of gastroparesis [128]. A recent study reported improved diagnosis of patients with chronic nausea/vomiting syndromes, gastroparesis, and functional dyspepsia when using Body Surface Gastric Mapping to identify spectral abnormalities in gastric electrical activity, together with symptom profiling [129]. Such techniques could improve the identification of patients suitable for drug treatments. This also relates to nausea/vomiting and 'gastroparesis-like' symptoms associated with GLP-1 R-agonists [130].
- For patients with CVS, 5-HT₃RAs and NK₁RAs have some efficacy [110,131,132]. For example, in a pediatric study aprepitant reduced the number of vomits/hour and number of cycles/year [109] with a similar study in adults [133]. The recent Rome V criteria identify 'unrelenting nausea' as a symptom of CVS [134], but this aspect has not been investigated in drug trials. Drugs treating migraine (sumatriptan), epilepsy (topiramate), tachycardia (propranolol) and depression (amitriptyline) are also used to treat CVS [110,131,132].
- Technical improvements have reduced PONV incidence (e.g. total intravenous anaesthesia, laparoscopic surgery). However, despite prophylactic use of drugs to prevent vomiting, single drugs or combinations are not fully effective. This includes the 5-HT₃RAs and NK₁RAs for which nausea is less well controlled than vomiting [103].
- For MS, drugs (Table 1) are available without prescription but are not fully effective and can have unwanted side-effects (e.g. drowsiness, dry mouth, blurred vision). As oral medications, they are not rapidly effective (30–45 min during fasting, or >1 h) and are ineffective if MS has begun, contributed to by the delayed gastric emptying associated with nausea. Recently, the NK₁RA tradipitant was shown to reduce the incidence of vomiting during MS [35] and approved by the U.S.A. Food and Drug Administration (FDA) for 'prevention of vomiting induced by motion' [9]. Efficacy against nausea is unclear (see [43] for discussion). Adverse reactions included somnolence (6% at 85 mg; 12% at 170 mg) and fatigue (respectively, 6% and 8%), potentially increased when co-administered with CYP3A4 inhibitors [122]. Finally, there is now concern about nausea with autonomous vehicles [135] and virtual reality head-sets ('cybersickness') [136]. In fully autonomous vehicles, the likelihood of MS is almost double that when traveling in a human-operated car [137]. Countermeasures are focussed on vehicle design (e.g. driving style, design of seats, displays, climate control, and visual, audio, olfactory cues).

5. New approaches to treat vomiting and potentially nausea

5.1. Improved formulations of existing drugs

For subjects feeling nauseous, ingesting drugs may be challenging, so convenient routes (other than intravenous) are required.

- *Sublingual.* The 5-HT₃RA ondansetron is available as a 'melt' formulation, rapidly dissolving when swallowed in saliva.
- *Intranasal.* For MS, nasal sprays provide fast onset of action and efficacy (e.g. scopolamine [138,139]), but development of a suitable formulation has ceased [140]. There is interest in aromatherapy to further alleviate CINV and PONV. This includes the higher efficacy of isopropylalcohol inhalation against nausea as compared to vomiting, in patients attending emergency departments with acute nausea/vomiting (see [8]). Nasal sprays of metoclopramide are used in the treatment of gastroparesis [141].
- *Transdermal.* Attractive for chronic conditions, but absorption rate is critical. Examples are: i) scopolamine, but onset is ~10-h, so use for MS requires pre-planning [142]; ii) the atypical antipsychotic, blonanserin (high affinity at D₂, D₃, 5-HT_{2A} receptors) [143] used in terminal care with efficacy against hydromorphone-induced vomiting [144,145]; iii) the 5-HT₃RA granisetron delivering drug over 7 days has efficacy (in combination with an NK₁RA and dexamethasone) against emesis in acute,

delayed (24–120 h) and long delayed (120–168 h) phases of high/moderately emetic chemotherapy [146].

5.2. Drugs with prolonged receptor occupancy

Long-acting 5-HT₃RA and NK₁RA may have a superior ability to prevent delayed vomiting in cancer patients. They include palonosetron, which compared with short-acting 5-HT₃RA such as ondansetron, has a longer half-life, receptor internalization, and enhanced prevention of acute and delayed CINV. A subcutaneously administered, extended-release formulation of granisetron (APF530) provided >5 days efficacy, matching or exceeding that of palonosetron, particularly for delayed vomiting during CINV [147]. The oral fixed-dose combination of the NK₁RA netupitant 300 mg and palonosetron 0.5 mg ('NEPA') has been developed [148]. The long duration of activity for both drugs (Table 1) was reasoned to provide prolonged protection against the long duration of nausea and vomiting experienced by patients receiving trastuzumab deruxtecan. Trials demonstrated superiority during the delayed and persistent delayed phases of nausea and vomiting, compared with other treatments using aprepitant; several defined 'complete response' on the basis of vomiting, but some also reported reduced occurrence of nausea (see [24] for references).

6. New therapies to treat vomiting and potentially nausea

6.1. Do current drugs show a new way forward?

- In patients receiving highly emetogenic chemotherapy, adding the antipsychotic drug olanzapine to the 'cocktail' of 5-HT₃RA, NK₁RA and dexamethasone increased the number of patients with no nausea in both acute and delayed phases [149]. It is unclear which of the many actions of olanzapine (Table 1) may reduce nausea. In rats, olanzapine reduced 'nausea-like' behavior (kaolin consumption), associated with 5-HT_{2C}RA and increased ghrelin availability [150]. Further research must determine if this translates to an emetic species. Somnolence and weight gain make olanzapine unsuitable for long-term treatment of nausea in other conditions, although use in palliative care is supported [151]. Other examples are the atypical antipsychotic blonanserin, used as a transdermal patch for patients receiving palliative care and unable to take oral medications, and the antidepressant mirtazapine (Table 1), used in palliative care and to prevent vomiting during PONV and CINV [8].
- Pyridoxine (vitamin B₆), an essential coenzyme for amino acid, lipid, and carbohydrate metabolism, is recommended for nausea/vomiting in pregnancy [36]. The mechanism of activity is unclear (see Table 1 for hypotheses).
- Thalidomide has been used for CINV [152]. Animal studies demonstrated that thalidomide has anti-epileptic and anti-convulsant effects [153–155], actions shared with some other drugs which inhibit vomiting, such as

those used to treat CVS (e.g. topiramate, zonisamide, levetiracetam [131]).

- Understanding the pharmacology of anti-epileptics/anti-convulsant's responsible for their anti-vomiting activity (e.g. modulation of Na⁺ or Ca⁺⁺ channels, action at glutamate and GABA receptors) may give insights into the regulation of excitability and the determination of the threshold for activation of emetic pathways. This applies especially to GABA_B [156], and use of baclofen (unpublished data in [70]) [157,158].
- Gabapentin is an anti-convulsant with high binding affinity to $\alpha 2\text{-}\delta$ subtypes 1 and 2 of voltage-gated calcium channels in multiple tissues. It is used to treat postoperative pain and can reduce PONV, including the risk ratio for nausea, a characteristic shared with pregabalin. Gabapentin also has efficacy in CINV, particularly delayed emesis, where unlike other agents it increased the % patients with no nausea by ~30%, compared to ~17% increase in vomiting protection [159]. This reflects an earlier report and an open-label study showing reduced nausea intensity in acute and delayed CINV [160].
- Scopolamine is one of the most effective anti-MS drugs [3,11]. Side-effects include drowsiness, dry mouth and blurred vision. Efficacy is most likely by M₃RA [11]. Given that other mAChRs may be more important in producing the unwanted side-effects of drowsiness and impaired cognition, a selective M₃RA would be an advance.
- Cyclizine, an H₁RA is primarily used for MS and Meniere's disease, acting in the vestibular system [7]. Cyclizine is also used to prevent vomiting during PONV and *hyperemesis gravidarum*, the latter not clearly linked with increased histamine availability.

6.2. Growth differentiation factor 15 (GDF-15) antibodies and GFRAL receptor antagonists

This cytokine GDF-15 is secreted in response to diverse 'stressors,' acting at the GDNF family receptor α -like receptor (GFRAL-R). The latter may be expressed only in the brainstem, particularly the AP and NTS [161,162]. Involvement of GDF-15 in mechanisms of vomiting was suggested by studies on human pregnancy and cytotoxic drug-induced emesis in animals [111]. The former included a genome-wide association study linking a single nucleotide polymorphism of GDF-15 with *hyperemesis gravidarum* [107,163] and demonstrating a rise in blood GDF-15 during pregnancy [164] with a relationship between vomiting and blood GDF-15 levels in the second trimester [165]. GDF-15 is also implicated in vomiting during CINV [166–169]. Studies using musk shrews demonstrated that GDF-15 induced emesis, and in rodents, GDF-15 caused pica, conditioned aversion and reduced food intake [167]. GDF-15-induced pica was unaffected by ondansetron, metoclopramide, dexamethasone, dimenhydrinate, exendin-9, anamorelin (brain penetrant ghrelin analogue), WIN-55 (cannabinoid-1 receptor analogue) or devazepide (CCK₁RA). However, these agents were variably effective against GDF-15-induced anorexia [170]. The effect of an NK₁RA was not investigated, but

based on their spectrum and site of anti-vomiting activity, we predict this would reduce the GDF-15-induced emesis. Elsewhere, cisplatin-induced emesis in cynomolgus monkeys was reduced by a GDF-15 neutralizing antibody [168]. In rats, peptide antagonists of the GFRAL-RET receptor complex reduced cisplatin-induced kaolin consumption [170].

The above identifies the potential use of antibodies to prevent vomiting during pregnancy sickness, CINV or other situations in which GDF-15 is implicated (e.g. CVS, see [111]). Thalidomide is hypothesized to modulate GDF-15 production, contributing to its anti-vomiting activity [152]. We are not aware of published clinical investigations into the effect of a GDF-15 antibody in emesis. However, a study of ponesegromab, an antibody inhibiting GDF-15 activity, given in combination with chemotherapy, reported a lower incidence of nausea (2% v. 16%) and vomiting (4% v. 13%) in the ponesegromab group, compared with placebo; notably, the use of drugs to prevent vomiting was not reported despite use of platinum-based chemotherapy [171].

6.3. Glucose-dependent insulinotropic peptide (GIP) receptor agonists

An ability of GIP-R-agonists to prevent vomiting was disclosed in a 2018 patent [172]. This described novel peptides activating GIP-Rs and their use to prevent vomiting induced by diverse stimuli, including acute/delayed cisplatin-emesis in ferrets, morphine-induced vomiting, and emesis evoked in dogs by Peptide YY (PYY). Subsequent studies [173–175] investigated long- (GIP-085) and short- (GIP-532) acting GIP-R-agonists. In *Suncus murinus*, GIP-085 prevented emesis, not other beneficial activities of a GLP-1 R-agonist [174]. GIP-085 also reduced the magnitude of c-Fos expression induced by the GLP-R-agonist in the AP and NTS. In ferrets, systemically administered GIP-532 blocked the acute (8 h) emetic response to cisplatin and in *Suncus*, GIP-085 reduced (>50% over 2-hour) the number of emetic episodes induced by cisplatin, increasing the latency [173]. In rats, GIP-085 reduced the increased kaolin consumption (pica) induced by cisplatin, most markedly over the first 3 h compared to 8–72 h. A GIP-R-agonist reduced cisplatin-induced increase in c-Fos immunoreactivity within the AP and especially the medial NTS [173]. In mice, GIP-085 suppressed conditioned taste aversion to saccharine paired with a PYY-R-agonist, but only reduced taste aversion caused by lithium chloride or GDF-15 [176]. The authors concluded that the anti-aversive effect of GIP-R-agonism may be effective only against meal-related factors driving nausea-like behaviors, acting via neural pathways separate from those activated by lithium and GDF-15. This suggests that GIP-R-agonists may not be effective against all emetic stimuli, although more studies are needed in emetic species. Notably, GIP and PYY (NPY2R) receptors colocalise in AP neurones of mouse, rat and cynomolgus monkey [176].

Nausea and vomiting are side-effects of GLP-1 R-agonists. Preclinical studies show an ability of GIP-R-agonists to reduce GLP-1 R-agonist-induced emesis and nausea-like behaviors [173], acting on GIPR⁺ AP neurones. Unlike GLP-1 R-agonists, a phase 1 volunteer study with a long-acting GIP-R-agonist (LY3537021) reported no nausea or vomiting [177]. This

suggested that the co-administration of a GLP-1 R-agonist with a GIP-R-agonist, or a molecule with both actions [173] may have less nausea/vomiting in clinical use. The latter may be exemplified by tirzepatide, a full agonist at GIP receptors and G-protein biased agonist at GLP-1 receptors [178], with a greater ability to promote weight loss and achieve glycemic control compared with GLP-1 R-agonists alone [179]. However, tirzepatide dose-dependently causes gastrointestinal adverse events, including nausea and vomiting, of ‘mild-to-moderate severity’ [180,181] and does not appear to have an obviously lower odds ratio for reporting nausea or vomiting [182]. Additionally, whilst administration of a GIP-R-agonist with the GLP-1 R-agonist liraglutide in healthy volunteers significantly reduced the total number of gastrointestinal adverse events, the percentage of participants with nausea/vomiting was not significantly reduced, although gastro-esophageal reflux was [183]. These observations suggest two possibilities. Firstly, a species difference (rodent vs human) in interaction between the two receptors. A second possibility arises from a large genome-wide association study of treatment response to GLP-1 R-agonist drugs [184]. This identified a missense variant in GLP-1 R, likely to reduce cell surface receptor density, and associated with differential weight loss and medication-related nausea/vomiting. A GIP-R variant was also identified, likely to cause partial loss of function. The authors suggested that nausea and vomiting in tirzepatide-treated patients, may therefore, result from diminished ability of the GIP-R-agonism to inhibit the nausea-inducing effects of GLP-1 R-activation. It should also be noted that clinical studies involving a GIP-R-agonist [182] are reporting data on the % of patients reporting nausea and vomiting and not the magnitude or duration, so more subtle inhibitory effects of GIP-R-agonism may not have been detected.

GIPR⁺ AP neurones also express ghrelin receptors [77]. Ghrelin or ghrelin-R-agonists reduce the acute phase of cisplatin-induced emesis in ferrets [185], motion and cisplatin-induced emesis in musk shrews [51] and cisplatin-induced pica in rats [186].

6.4. Electroceuticals

There is increasing interest in alleviating nausea and vomiting by electroceuticals [187,188], targeting the auricular (AVS) [189,190], or cervical vagus [191–194], and also by direct gastric stimulation, possibly involving the abdominal vagus [195–197]. We do not comment on efficacy but give examples to illustrate how this could help understand mechanisms and inform on optimal treatments. A working hypothesis is that vagal stimulation (VS) targets the NTS [198], potentially activating endogenous pathways which inhibit emetic pathways or disrupting signal processing between the NTS and the cerebral cortex. An electrocardiography study showed reduced peak theta-wave density (variability index) induced by AVS, correlating with reduced nausea severity during MS [199]. Meta-analysis [200] of brain imaging studies of VS showed changes in activity of several areas (e.g. cingulate gyrus) implicated in the genesis of nausea [53]. The time to develop nausea by off-axis rotation in healthy volunteers was increased by transcranial direct current stimulation of the left parietal cortex [201]. Electrical stimulation of the dorsal prefrontal cortex (dlPFC)

markedly reduced nausea induced by sinusoidal galvanic vestibular stimulation in humans [202]. The insula cortex has previously been implicated in nausea [53], receiving inputs from both vestibular afferents and the dlPFC, leading to the proposal that modulation of vestibular processing in the insula was responsible for nausea reduction [203]. A functional magnetic resonance imaging study supported this proposal but also showed decreased NTS activity [202].

Abdominal vagal stimulation could resynchronize disrupted signaling of the 3cpm gastric electrical rhythm to the brain [204]. The latter is generated by rhythmical depolarization of the ‘pacemaker’ cells (Interstitial Cells of Cajal; ICCs) of the stomach which are disrupted during nausea [205]. Such activity could be centrally mediated or local on the ICCs. An indirect action via modulation of gut peptides should not be overlooked, as gastric electrical stimulation in patients with intractable vomiting increased plasma leptin, correlating with reduced vomiting and decreased postprandial levels of PYY [206].

7. Understanding causes of nausea and vomiting

7.1. Network pharmacology

Nausea and vomiting are side-effects for many, diverse drugs [207,208] (Table 2), potentially impacting new drug development [89,209] and/or becoming dose-limiting, reducing compliance and increasing trial withdrawal (e.g. GLP-1 R-agonists [116]). For certain G-protein-coupled receptors allosteric modulation may be an approach to reduce GI adverse events associated with receptor agonists [210].

Drug discovery continues to externalize biological innovation and use reductive techniques in investigate toxicology (e.g. high content imaging to assess cell biology, genomics, organs-on-chips, gene editing, human cells, and tissue-specific microRNA profiles) [211]. However, these cannot easily predict complex ‘gut-brain axis’ mechanisms such as nausea, involving multiple brain areas and interconnections. Indeed, a reductionist strategy is argued to contribute to the diminishing number of new approved drugs [212]. To address this weakness, the nausea liability of drugs was investigated in animals by examining clusters of gastrointestinal adverse events, achieving a 90% successful prediction [209]. It is not known if this model has achieved more widespread use.

7.2. Interrogation of emetic hormones

The nausea and vomiting associated with GLP-1 R-agonists has renewed interest in the emetic potential of other endogenous hormones. Historically, evidence came from endocrine tumors (e.g. pheochromocytoma) and intravenous administration of hormones such as CCK, oxyntomodulin and endogenous opioid receptor ligands to animals or humans. However, there was always concern about the relevance of such findings to physiological vs pharmacological effects; the actions of a hormone may also be potentiated by the presence of another stimulus. Nevertheless, these studies demonstrated that several endogenous hormones could induce vomiting. ‘Why?’ Since many, if not all, reduce food intake, we could hypothesize that nausea and then vomiting are at one end of a spectrum of dose-related effects from satiety to reduction of food intake to nausea and then vomiting [213]. This

topic is outside the current review. However, we highlight arginine-vasopressin and peptide YY, both long implicated in nausea and vomiting (e.g. [205,214–218]). Additionally, and conversely, other hormones may prevent vomiting (e.g. ghrelin [185], GIP [173]).

7.3. Lessons from specific diseases and the role of clinical pharmacology

The link between *hyperemesis gravidarum* and GDF-15 contributed substantially to the identification of GDF-15 as an emetic agent in other areas. Other conditions in which nausea and vomiting are prominent include gastroparesis [39] the AP syndrome [219] CVS [108] and cannabinoid hyperemesis syndrome [220]. Their study may inform emetic mechanisms as in each case the nausea/vomiting is protracted and/or intense.

In terms of clinical pharmacology, human volunteer studies previously investigated the efficacy of 5-HT₃RA [221] and NK₁RA [222] and is now characterizing cybersickness and nausea associated with autonomous vehicles (see below). Areas for clinical pharmacology might now include:

- (i) *Motion*. Sea trials [35], rotating chairs [11,222], illusory self-motion/vection [223] and galvanic vestibular stimulation [203], in addition to virtual reality headsets [224], and autonomous vehicle passengers [135];
- (ii) *Direct stimulation of digestive tract*. Gastric distension, particularly antrum [225], intraduodenal lipid administration ± gastric distension [226], maximal tolerated volume of ingested liquid meals [227];
- (iii) *Systemically administered drugs*. Acting primarily via the AP: apomorphine [228], dihydroergotamine (migraine patients [229]), exendin-4 [230], morphine [231]. Previously this included arginine-vasopressin, but new studies suggest activity within the stomach may be more involved [214].

8. Challenges in quantifying nausea and vomiting and developing novel drugs

8.1. Quantification

Pharmacokinetic-pharmacodynamic modeling relies on overcoming the challenges posed by defining and quantifying nausea and vomiting. This is also required to rank the nausea/vomiting liability of drugs (to inform patients and develop guidelines for treatment) and for more precisely defining the efficacy of drugs which prevent vomiting and perhaps nausea [42,45,232,233].

8.1.1. Definitions

Nausea and vomiting are rarely defined, and there is no agreed definition of nausea. It is assumed, perhaps wrongly, that patients accurately report **both** Nausea and Vomiting, without confusion with symptoms such as early satiety, loss of appetite, fullness, regurgitation, or gastroesophageal reflux. Literature contains multiple definitions of nausea, some

defining in relation to vomiting, and some by the nature of the sensation (see Table 1 within [45]). Until objective measurements are developed, studies should define Nausea **and** Vomiting.

8.1.2. Incidence

This is the number of individuals who report nausea **and/or** vomiting during a given time, which could be one or more cycles of cancer chemotherapy, or a long trial, which for some GLP-1 R-agonists has been >1 year. Data are usually expressed as % or a probability in the form of odds ratio or risk ratio, relative to placebo. Taking chemotherapy as an example, the risk of vomiting based on incidence may be 'high' (>90%), 'medium' (30–90%), 'low' (10–30%), or 'minimal' (<10%) [234,235]. However, the intensity or duration of vomiting is not included, and nausea is not considered. Incidence increases with dose of cytotoxic drugs [102,234,235] and other drugs (e.g. GLP-1 R-agonists [182]). Based on incidence alone, comparison of emetic/nauseagenic liabilities between diverse agents is problematic. For example, the incidence of nausea/vomiting with some GLP-1 R-agonists or polyagonists [182,236] can be in the lower end of the 'medium emetogenic chemotherapy' range (i.e. 30–90%) depending on dose. However, this does not reflect the different intensities and durations of nausea and vomiting.

8.1.3. Dimensions

To accurately quantify nausea **and** vomiting and obtain precise measures of an ability to prevent vomiting and perhaps nausea, short of complete block (assessed by incidence), **both** need to be quantified **throughout** their entire duration. Without this, it is hard to identify differences between novel pharmacological approaches. Selected examples are discussed below.

- a. *Quantification of vomiting.* Retching and vomiting are easily definable, externally visible, and can be quantified separately by patients or observers. However, this is rarely done. Instead, they are often combined into an 'emetic episode.' Data on vomiting may be collected by a diary asking the patient to recall the number of events in the previous 24 h, then converted into a categorized score. These include the Pregnancy-Unique Quantification of Emesis and nausea (PUQE [237]), the Rhodes index [238], the Morrow Assessment of Nausea and Emesis scale (MANE [232] used in CINV), or a grade, as used in Common Terminology Criteria for Adverse Events [239]. The GCSI questionnaire asks patients to recollect the severity of nausea and vomiting in the last 2 weeks from none to very severe [240].
- b. *Quantification of nausea.* The main challenge is that nausea is a self-classified, self-reported sensation, relying on a patient's translation of intensity into a scale. This could be mitigated by defining nausea and accounting for confounding events (e.g. reduced appetite, fullness), but magnitude remains an issue. Scales with the upper anchor as, 'worst possible nausea' [241], 'nausea as bad as it could be' [242] or 'very

severe' [243], rely on comparison with previous, individual experiences. Other scales quantify nausea severity in relation to impact on life (e.g. several studies with GLP-1 R agonists, mild nausea = transient, tolerated, not interfering with daily life [244]), but inter-patient variabilities are likely. When a 100-point visual analogue scale (VAS) is used to assess nausea, some studies classify a VAS of <25 as 'no significant nausea', a trial end-point in combination with no emesis [245]; thus, patients can still have nausea but be scored as having a 'complete response.' Other scales, such as the 7-point Motion Sickness Severity Scale (MSSS) used to assess tradipitant [35], include 'stomach awareness or discomfort' as the first score-point on the scale between 'no nausea' (0) and 'mild nausea' (2), reflecting increased abdominal visceral awareness accompanying onset of nausea and progression to vomiting.

8.1.4. Approaches to improving nausea quantification

A 2021 FDA perspective on end-point assessments for CINV and PONV identified nausea as 'an opportunity for continued research and development due to the large heterogeneity of instruments used' [96]. Methodology independent of self-reporting needs developing, but there is no agreed biomarker. Combined measurements of physiological changes such as plasma arginine-vasopressin and adrenaline [214], gastric myoelectrical activity [69], regional skin blood and conductance [11,246], heart rate variability [199,247], electroencephalogram [136], and facial expression [248] may provide an approach.

8.2. Recognition of nausea and vomiting as separate end-points

Separation of drug efficacy against nausea and vomiting, particularly when taken for extended periods, helps manage patient expectations, differentiates between drugs and highlights unmet clinical needs.

The British National Formulary lists the different classes of 'anti-emetic' drugs and uses under 'Nausea and Labyrinth Disorders' (with links to individual drugs, prescribing during palliative care and to cytotoxic drugs, with subheadings for pregnancy, PONV, motion sickness, Ménière's disease, migraine) [7]. However, the narrative discusses nausea and vomiting without distinction. The Anatomical Therapeutic Chemical classification used by the World Health Organisation [249], classifies 'anti-emetics and anti-nauseants' under the same heading (A04A). FDA approval letters for use of the NK₁RA aprepitant in patients receiving cancer chemotherapy (in combination with other drugs which prevent vomiting) and for the prevention of PONV use the term 'nausea and vomiting' without discussing the possibility that efficacy may not be similar for each [e.g. [250,251]. A later analysis of studies with aprepitant and other NK₁RAs concluded that excellent efficacy against vomiting was not replicated by similar efficacy against nausea [43,54]. An FDA-sponsored review

of endpoint assessments for CINV and PONV treatments found that a 'complete response' was often defined by emetic episodes, sometimes with the inclusion of 'no significant nausea' (on a VAS) and no use of rescue medication [96]. The recent FDA approval of tradipitant for '*prevention of vomiting induced by motion in adults*' [9] may signal a move toward more precise acceptance of patient experiences.

8.3. Patient factors

Individual risk factors and gene polymorphisms should guide drug prescribing.

- (i) *Motion sickness.* Sensitivity to MS is a risk factor for CINV, PONV, and pregnancy sickness [248,252–254]. A genome-wide association study showed PONV and migraine phenotypes shared underlying genetic factors with MS [255]. These observations suggest that the vestibular system and vestibular nucleus complex modulate the sensitivity of the NTS to other emetic inputs.
- (ii) *Sex and age.* Females have a higher risk of MS, CINV (including anticipatory nausea/vomiting) and PONV [248,252–254], but there are interactions as sensitivity to MS and pregnancy sickness increases the risk of PONV and CINV. For PONV, female sex was the strongest patient-specific predictor [253]. Younger age (<50 years) is also a risk predictor [248,252,255–258]. Limited evidence from animal studies of MS suggests that younger age and female sex increase susceptibility [50,259]. Females with type-2 diabetes mellitus are at a higher risk of nausea and vomiting from GLP-1-R-agonists [260]. Sex also needs to be considered in assessing drug efficacy. A subgroup analysis of cancer patients treated with oxaliplatin showed that the 'no nausea,' 'no vomiting' and 'complete control' rates were higher in females given fosaprepitant as part of a triple drug combination (NK₁+5-HT₃RAs+dexamethasone) compared to controls. Additionally, the 'no-nausea' rate over days 1–5 was higher in females vs. males (61.6% vs 37.5%) [40].
- (iii) *Genetic polymorphisms.* Relationships between polymorphisms of genes potentially influencing CINV and its treatment are discussed in [261,262]. Examples include individual variations in cytochrome P450 isoenzyme CYP2D6, which more rapidly metabolize certain 5-HT₃RAs, reducing efficacy against CINV and PONV. These include dolasetron, ondansetron, and tropisetron, but not granisetron [263]. CYP2D6 polymorphisms may also influence responses to amitriptyline during the treatment of CVS [264]. Complete control rates (no emetic episode, no rescue medication, no more than mild nausea) during the first 24 h after chemotherapy were higher after receiving granisetron, compared with ondansetron or tropisetron, if patients had the drug efflux transporter ABCB1 TT genotype [265]. Other studies have

investigated transport protein gene polymorphism and efficacy of different drugs which prevent vomiting, but not all agree, perhaps because of small sample size and heterogeneity, and ethnicity [261]. The 5-HT₃ receptor itself is a ligand-gated pentameric ion channel which in humans is constructed by 5-HT_{3A-E} subunits [266]. Polymorphisms of 5-HT_{3C} and 5-HT_{3D} have been linked to increased incidence of acute vomiting during chemotherapy, but not all investigators agree [261]. Polymorphisms of 5-HT_{3B} may be linked to small variations in the efficacy of 5-HT₃RAs, but again, not all investigators agree [261]. This form of polymorphism has also been associated with CVS [267]. Evidence is emerging for pharmacogenetic predictors for NK₁RA efficacy, based on variants of the TACR1 gene encoding the NK₁ receptor [268].

9. Conclusions

An ideal 'anti-emetic' should have the following characteristics:

- Ability to fully block **both** nausea and vomiting in a high proportion of a defined clinical population or preferably, block both irrespective of cause (i.e. effective against both disease and drug-induced nausea and vomiting).
- Suitable for rapid administration **after** nausea and vomiting have started.
- Long duration of action.

No current agent meets these criteria, although 5-HT₃RAs and NK₁RAs can abort vomiting after it has started [43,269] and fixed-dose combination of netupitant and palonosetron ('NEPA') are achieving impressive results in cancer patients [24], so our criteria may be attainable in at least these patients.

The pharmacological targets for drugs which prevent vomiting were identified ~30–80 years ago. However, despite major advances provided by 5-HT₃ and NK₁RAs, nausea remains less effectively treated and both are relatively poorly treated in different patient groups (e.g. CVS, gastroparesis, targeted cancer therapy, MS, palliative care). Present advances include improvements in existing drugs (drug combinations, delivery routes, extending receptor occupancy in the treatment of cancer patients and the assessment of patient risk factors including pharmacogenetics). After a research hiatus, two novel targets involved in emetic pathways (GFRAL receptor/GDF-15 and GIP receptors) have now been identified. There is also progress in the development of electroceuticals to control nausea and vomiting in defined groups of non-cancer patients. Finally, the abilities of endogenous hormones such as PYY and GLP-1R-agonist drugs to cause nausea and vomiting are stimulating research into the pathways of nausea and vomiting.

The future must develop an objective quantification of nausea efficacy. The translational significance of animal 'nausea-like behaviours' needs to be understood, perhaps in

conjunction with increased clinical pharmacology and physiology studies, combined with brain imaging, to directly study nausea in humans.

10. Expert opinion

The current armamentarium for prevention of vomiting primarily antagonizes at dopamine ($D_{2/3}$), acetylcholine ($M_{3/5}$), H_1 , $5-HT_3$ and NK_1 receptors with contributions from the anti-inflammatory actions of the glucocorticoid dexamethasone, anti-psychotic drugs such as olanzapine antagonizing at multiple receptors, and the gastric prokinetic/anti-emetic drug metoclopramide (D_2 RA and $5-HT_4$ R-agonist, and $5-HT_3$ RA at higher doses). As single agents, most prevent

vomiting in some but not all groups of patients with N&V, with NK_1 RA possessing the widest spectrum of anti-vomiting activity. Combinations of these drugs have improved overall efficacy in specific clinical settings (e.g. CINV). However, gaps remain. This includes the lack of registered, modern-day treatments for disorders such as gastroparesis and CVS. An additional, more wide-ranging gap is that for all drug classes efficacy appears to be lower against nausea compared with vomiting. Arguably, the separation in efficacy between nausea and vomiting has been given insufficient recognition in trial endpoint measurements and, hence, the regulatory process. A similar lack of attention is illustrated by the omission of information on the drugs used to prevent vomiting in some studies of targeted cancer drugs including

Table 3. A summary of key knowledge gaps within the area of nausea and vomiting, which limit progress in understanding and the development of new treatments. Potential approaches are briefly outlined in the comments. For full references see text.

Knowledge gap	Comment
Nausea measurement - All methods rely on patient self-classifying and self-reporting nausea. - Methods for quantification of nausea do not currently provide sufficient measurement of magnitude or temporal resolution, so the efficacy of drugs may not be fully defined. - Data from current drugs may not have sufficient resolution to provide mechanistic insights into new approaches with improved efficacy. - Current methods make it difficult to investigate correlations between nausea and other symptoms (e.g. reduced food intake).	- Investigate the potential for real-time reporting of symptoms using smart phone apps to improved temporal resolution of data collection and facilitate correlation between symptoms. - Investigate the potential of combined measurement of facial expression, regional skin color, temperature and resistance (forehead), heart rate variability, electrogastrogram, arginine vasopressin and adrenaline to develop methodology for quantification of nausea, independent of self-reporting.
Encoding nausea and vomiting - How do the abdominal vagal afferents and area postrema encode the signals leading to reduced food intake, satiety, and then nausea and eventually vomiting? - Delayed gastric emptying (gastroparesis) and dysrhythmia of gastric myoelectric activity (particularly tachygastria) are associated with nausea; how are these signaled to the brain?	Simplistically, the responses relate to stimulus intensity (e.g. blood concentration of glucagon like peptide-1 receptor agonists or degree of gastric distension) encoded in neurone firing frequency, but this simplistic model has not been experimentally tested in relation to nausea and vomiting.
Cerebral pathways for nausea - Brain imaging studies in humans are predominantly from motion sickness, with very limited data from area postrema or abdominal vagal afferent activation - The nucleus tractus solitarius has a major role in processing the inputs leading to nausea and vomiting and although knowledge of its molecular biology and connectivity (including in humans) has increased this is not paralleled by neurophysiological studies.	- Brain imaging studies are needed using graded pharmacological stimulation (e.g. growth differentiation factor -15, peptide YY and glucagon like peptide 1 receptor agonists) of the area postrema to investigate changes in cerebral activity in relation to stimulus concentration. - Imaging techniques can now resolve the nucleus tractus solitarius. - Insights into changes in the nucleus tractus solitarius during nausea could be probed by using the read out of physiological functions it modulates.
Neurotransmitters and receptors Dopamine $D_{2/3}$ receptor agonists (e.g. apomorphine) induce vomiting by an action on the area postrema and a number of drugs which prevent vomiting are antagonists at D_2 receptors in the area postrema and possibly nucleus tractus solitarius. However, the role (if any) of endogenous dopamine in activating the $D_{2/3}$ receptors is not known.	- The distribution of dopamine and $D_{2/3}$ receptors in the human nucleus tractus solitarius and area postrema should be investigated using modern techniques. - The clinical and preclinical literature on the ability of dopamine receptor antagonists to prevent vomiting is considerable, so a systematic analysis of the spectrum of activity may provide novel insights which could be more formally tested.
Endogenous mechanisms modulating nausea and vomiting - Evidence for endogenous mechanisms capable of modulating the sensitivity of the emetic pathways comes in particular from studies of agonists suppressing vomiting (see Figure 1) and antagonists or enzyme inhibitors increasing the sensitivity to emetic stimuli. - The digestive tract hormones ghrelin and glucose-dependent insulinotropic peptide (GIP) can prevent vomiting (animal studies), but the reason why gut hormones should have such actions is unclear.	- The anatomical substrate of an endogenous pathway modulating nausea and vomiting needs investigation, since when defective it could be implicated in conditions with protracted nausea and vomiting such as cyclical vomiting syndrome. - The possibility that gut hormones which prevent vomiting (GIP, ghrelin) interact with gut hormones which cause vomiting (PYY), needs to be understood in relation to how the area postrema integrates detection of the complex mixture of hormones in health and disease.
Human models to investigate nausea physiology and pharmacology - Animal models of nausea use 'nausea-like behaviours' but interpretation is contentious, in relation to translation to humans for investigation of potential therapies. - Models for the study of nausea in humans that are not reliant on motion stimuli are needed to investigate basic mechanisms of nausea and test novel approaches to treatment.	- A systematic analysis of 'nausea-like behaviours' is needed to inform a consensus view of the relevance of such measurements to nausea in humans and the extent to which such data can be translated to humans, particularly in relation to 'anti-emetics.' - Publications on methods used to induce and study nausea in humans should be re-examined for their potential to be developed into models to investigate nausea mechanisms and potential 'anti-nausea' drugs.

the highly emetogenic antibody-drug conjugates [40], hampering the identification of optimal anti-emetic strategies.

The issue of identifying new drugs to treat nausea is complicated.

- Firstly, nausea is a self-identified and self-reported sensation [45] so animal models, usually in rodents which cannot vomit [44], only measure 'nausea-like behaviours' in response to stimuli which cause vomiting in humans (e.g. pica, conditioned aversions and avoidance, taste reactivity). However, these have not been rigorously translated to humans, especially problematic when considering their predictive capability for new chemical entities. It should also be noted that a number of pre-clinical publications include 'nausea' in the title, but on closer examination they are reporting data on 'nausea-like behaviours,' potentially giving the impression that our understanding of nausea is better than actually is the case. A consensus needs to be reached on the relationship of the various 'nausea-like behaviours' in rodents to the sensation of nausea in humans, combined with a systematic analysis of the efficacy of drugs which prevent vomiting in humans and 'nausea-like' behaviours in rodents.
- Secondly, even in humans there is no universally agreed definition or biomarker, so quantification can be inadequate. Quantification with high temporal resolution is needed to accurately identify the presence of nausea during short or long trials. This would help define clinical outcomes, provide evidence for regulatory authorities and give mechanistic insights.
- Thirdly, there is a lack of focused research into the pharmacology and physiology of nausea despite being consistently recognized by patients as an issue of concern. This should be integral during the assessment of the clinical potential of new ideas such as those generated by the discovery of GDF-15.

What is the future? There are several outstanding questions limiting the development of novel approaches to the treatment of nausea, in particular. These are summarized in Table 3. Identification of an agreed biomarker(s) for nausea would facilitate diagnosis of certain gastrointestinal conditions and improve treatment and research into mechanisms of nausea, which in the longer-term, would improve treatments. Here, the clinical pharmacologist has an important role to play. The tools are available, but progress is slow.

Improvements in existing therapies are happening now. Most impressive is the recognition that in cancer patients at least, CINV may be better controlled by using drugs which achieve prolonged antagonism of 5-HT₃ and NK₁ receptors. Does this thinking need to be extended to gastrointestinal and other conditions?

For some groups of patients (e.g. cancer patients and the elderly) advances over existing therapies may be achieved by minimizing drug-drug interactions which restrict the use of optimal treatments. It is not clear if this is happening. In terms of new drug targets for the treatment of nausea, the process begins with the wider recognition that nausea is a

huge unmet clinical need affecting diverse patient groups. Here, those involved in the design of clinical trial endpoints and in the labeling of new drugs ('does it prevent only vomiting or both vomiting and nausea?') have important roles to play. The next step is to identify a drug target, but this has not yet happened. This is why research into its mechanisms is so important. Today, we are understanding more about how drugs cause nausea and vomiting, exemplified by GDF-15 and the GLP-1 R-agonists. Would synergy be achieved by studying nausea together with mechanisms of appetite and satiety? If so, this must be done in a species capable of vomiting, with agreed measures of nausea.

We have emphasized that nausea is a relatively neglected symptom and overall, drugs are less efficacious in treating it as compared to vomiting. The use of the term 'anti-emetic' has been deliberately avoided in this review because we believe it gives the impression that drugs classified as such are equally efficacious against both nausea and vomiting. This terminology contributes to the impression that fully effective treatments for nausea, irrespective of cause, exist. In our opinion, the terminology needs revision [41] and such a change may focus attention on finding better treatments for nausea. By definition, an 'anti-emetic' is a drug which affects vomiting as it derived from *emetikos* (Greek) and *emeō* (Latin) 'medicine that causes vomiting,' hence an 'anti-emetic' is 'against vomiting.' We suggest that 'anti-emetic' is used for agents with primary efficacy against vomiting (in effect this is currently the case) and 'anti-nauseant' is used when the primary efficacy is against nausea. A new term will be needed to replace both when we finally have a drug that is equally and fully effective against both nausea and vomiting.

Author contributions

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