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REVIEW ARTICLE

An assessment of the effects of neurokinin$_1$ receptor antagonism against nausea and vomiting: Relative efficacy, sites of action and lessons for future drug development

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A *broad-spectrum* anti-vomiting effect of neurokinin$_1$ receptor antagonists (NK$_1$RA), shown in pre-clinical animal studies, has been supported by a more limited range of clinical studies in different indications. However, this review suggests that compared with vomiting, the self-reported sensation of nausea is less affected or possibly unaffected (depending on the stimulus) by NK$_1$ receptor antagonism, a common finding for anti-emetics. The stimulus-independent effects of NK$_1$RAs against vomiting are explicable by actions within the central pattern generator (ventral brainstem) and the nucleus tractus solitarius (NTS; dorsal brainstem), with additional effects on vagal afferent activity for certain stimuli (e.g., highly emetogenic chemotherapy). The central pattern generator and NTS neurones are multifunctional so the notable lack of obvious effects of NK$_1$RAs on other reflexes mediated by the same neurones suggests that their anti-vomiting action is dependent on the activation state of the pathway leading to vomiting. Nausea requires activation of cerebral pathways by projection of information from the NTS. Although NK$_1$ receptors are present in cerebral nuclei implicated in nausea, and imaging studies show very high receptor occupancy at clinically used doses, the variable or limited ability of NK$_1$RAs to inhibit nausea emphasizes: (i) our inadequate understanding of the mechanisms of nausea; and (ii) that classification of a drug as an *anti-emetic* may give a false impression of efficacy against nausea *vs*. vomiting. We discuss the potential mechanisms for the differential efficacy of NK$_1$RA and the implications for future development of drugs that can effectively treat nausea, an area of unmet clinical need.

KEYWORDS
anti-cancer chemotherapy, gastroparesis, motion sickness, nausea, neurokinin$_1$, substance P, vomiting

1 | INTRODUCTION

Drugs treating nausea and vomiting as disease symptoms or as adverse effects of therapy are usually classified as *anti-emetics*. However, the term *emetic* refers to a substance that causes vomiting (or retching). Emesis does not mean nausea. Further, increasing evidence indicates differential efficacy of *anti-emetic* drugs against nausea *vs*. vomiting. Seifert and Alexander[1] proposed a *rational drug class*

terminology based on a drug's pharmacological actions rather than its therapeutic orientation (e.g., anti-emetic). Applying this terminology to nausea and vomiting means that the term *anti-emetic* must be written in italics to denote the fact that efficacy against nausea and vomiting should not be assumed to be the same.[2] Here, we emphasize the importance of differentiating between nausea, a self-reported aversive sensation involving cortical and sub-cortical brain regions[3–6] and the mechanical events of retching and vomiting involving multiple brainstem nuclei.[7]

The introduction of **neurokinin$_1$ receptor** antagonists (NK$_1$RAs) further improved control of *chemotherapy-induced nausea and vomiting* (CINV) and *post-operative nausea and vomiting* (PONV).[8] In addition, a potential expansion of indications may be appropriate, to include, for example, motion sickness.[9] If confirmed, this would point towards a relatively wide spectrum of *anti-emetic* activity for the NK$_1$RAs in humans, as suggested by animal studies (see below). However, originating primarily from studies of CINV, there has been a concern that nausea is less well treated than vomiting[10] and this concern persists, as reflected in the comment by Aapro[11] that "Perhaps the greatest unmet need in CINV is the lack of complete nausea control." Accordingly, in an attempt to understand the nausea *vs*. vomiting question in relation to NK$_1$RAs, from both clinical and basic science perspectives, we identified five key questions:

1. Has the broad spectrum of activity of NK$_1$RAs suggested by animal studies of vomiting translated to humans?
2. Where do NK$_1$RAs act to inhibit vomiting?
3. To what extent do NK$_1$RAs inhibit nausea as compared to vomiting?
4. If NK$_1$RAs have a differential effect against nausea compared to vomiting, what is the explanation?
5. What are the implications of the answers to the above questions in terms of patient satisfaction and for future development of drugs to treat nausea?

Different emetic stimuli signal to the brain via different routes. This is why it is first necessary to determine if the broad-spectrum ability of NK$_1$RAs to prevent vomiting in animals translates to humans in a similar manner; such a profile directs the discussion on potential mechanism of action against vomiting and nausea. Accordingly, we begin by briefly describing the NK$_1$RA studies in animals and then review the effects of NK$_1$RAs against vomiting and nausea in different clinical indications (see below for selection criteria), identifying differences in efficacy between these different indications.

2 | ANIMAL STUDIES: SPECTRUM OF NK$_1$RA EFFECTS AGAINST VOMITING AND NAUSEA-LIKE BEHAVIOURS

In this section we consider only data from species with a vomiting reflex (ferret, dog, cat, house musk shrew [*Suncus murinus*] and least shrew [*Cryptotis parva*]). To simplify comparisons between species and between the effects of drugs on vomiting and nausea, we have not considered *nausea-like* behaviour data from rodents, which cannot vomit.[12,13]

2.1 | Vomiting

Studies in multiple animal species (Table 1) have demonstrated *broad-spectrum* effects of NK$_1$RAs, markedly reducing/blocking retching and/or vomiting induced by diverse stimuli acting via three key inputs to the brainstem (Figure 1; [7,8] for references).

2.2 | Nausea-like behaviours

Administration to animals of substances inducing nausea and vomiting in humans evoke behavioural changes (often referred to as *nausea-like*), but their significance and relevance to the human sensation of nausea is contentious (Chapter 11[7,10]). In summary, and in contrast to the clear effects of NK$_1$RA on vomiting, effects on nausea-like behaviours (as defined in individual papers) are absent or inconsistent (e.g., Table S1). Given this lack of clarity and since the relevance of these behaviours to the human experience is unknown, they will not be considered further (Chapter 11,[7,10] for detailed discussion).

3 | HUMAN STUDIES: SPECTRUM OF NK$_1$RA EFFECTS AGAINST VOMITING AND NAUSEA

It is important to determine if the broad-spectrum ability of NK$_1$RAs to prevent vomiting in animals translates to the vomiting and nausea of humans. Accordingly, we searched either the name of individual antagonists and/or the therapeutic area (e.g., motion sickness, CINV, PONV, gastroparesis and cyclical vomiting syndrome). For CINV and PONV, where there has been more extensive investigation of NK$_1$RAs *anti-emetic* efficacy, we initially reviewed systematic reviews/meta-analyses and then analysed data in selected original papers. As our focus was on the relative efficacy of NK$_1$RAs against nausea and vomiting, we included papers where data on *both* vomiting and nausea were presented and in particular where adequate information was provided in the methods about how each was quantified, with data presented in a form allowing comparison. We note that few studies have given an NK$_1$RA *alone*, *n* values can be small (e.g., in PONV the *n* value for seven studies of **aprepitant** included in a meta-analysis ranged from 30 to 55[60]) and some studies are uncontrolled. Nausea is often a secondary outcome with methodological variations in its assessment complicating inter-study comparisons (see below).

Sections 3.1 to 3.7 describe the results of studies investigating the effects of NK$_1$RAs against different emetic challenges. Section 3.8 then provides an overview of the spectrum of efficacy against nausea and vomiting.

TABLE 1 A summary of pre-clinical studies investigating the efficacy of neurokinin$_1$ receptor antagonists against retching/vomiting induced by a range of stimuli across multiple species. The studies show the *broad-spectrum* effect of the neurokinin$_1$ receptor antagonists against stimuli acting via the vestibular system, area postrema or abdominal vagal afferents. See text for discussion of mechanisms.

Species	Neurokinin$_1$ receptor antagonist	Stimulus details	References
		Cytotoxic anti-cancer drugs	
Acute phase of cisplatin			
Ferret	CJ-11974 CJ-17493 CP-99994 CP-122721 GR203040 L-742694 L-741671 Netupitant SCH 619734	Given either i.p or i.v.	14–19 20
Dog	FK886 Maropitant		21–24
Suncus	GR203040		25
Doxorubicin emesis (5 days)			
Dog	Maropitant	i.v.	26
Delayed phase of cisplatin			
Ferret	CJ-11974 Netupitant SCH619734	Given either i.p or i.v.	14,16,27
Cyclophosphamide			
Ferret	GR203040 GR205171	Given i.p.	25,28
		Pharmacological agents	
Apomorphine			
Dog	CP-99994 FK886 Maropitant	Given s.c.	22,29,20
Ferret	CP-99994 Netupitant SCH619734		14,16,30,20
Brimonidine			
Cat	Maropitant	Sedative given as eye drops	31
Copper sulphate			
Dog	CP-99994	Given p.o.	32,20
Ferret	CP-99994 Netupitant	Given p.o.	16,20
Ethanol			
Suncus	CP-99994	Given i.p.	33
FPL64176			
Least shrew	Netupitant	L-type Ca^{++} channel agonist	34
GR73632			
Least shrew	CP-99994	Neurokinin$_1$ receptor agonist; given i.p.	35
Halothane/N_2O			
Suncus	GR205171	Inhaled	36

(Continues)

TABLE 1 (Continued)

Species	Neurokinin$_1$ receptor antagonist	Stimulus details	References
Ipecacuanha			
Ferret	CP-99994 CP-122721 GR205171 GR203040 Netupitant R116301	Given p.o.	25,28,37,38,20
Dog	GR203040 GR205171 Maropitant	Given p.o.	25,28,29
Lycorine			
Dog	Maropitant	Alkaloid from daffodils; given s.c.	39
2-methyl 5-hydroxytryptamine			
Least shrew	CP-99994	5-HT$_3$ receptor agonist; given i.p. Note no significant effect of CP-99994 given at same dose that blocked NK$_1$ agonist (GR73632; see above)	35
Naloxone			
Suncus	CP-99994	Given s.c.	40
Nicotine			
Suncus	CP-99994 CP-122721 RP67580	Given s.c.	30,40
Opiate receptor agonists			
Ferret	CP-99994	Loperamide; s.c.	41
Ferret	GR203041	Morphine; s.c.	25
Dog	Maropitant	Morphine; s.c.	42,43
Dog	Maropitant	Morphine; s.c.	44
Dog	Maropitant	Hydromorphone; i.m.	45
Dog	Maropitant	Hydromorphone; i.m.	46
Dog	Maropitant	Hydromorphone; i.m. + acepromazine; i.m.	47
Cat	Maropitant	Dexmedetomidine + morphine; i.m.	48
Phosphodieseterase IV Inhibitors			
Ferret	CP-99994	R-rolipram, CT-2450, RS14203; given p.o.	49
Prostaglandin E$_2$			
Ferret	CP-99994	Given i.p.	50
Pyrogallol			
Ferret	CP-99994	Reactive oxygen species donor; given i.p.	Andrews and Matsuki, unpublished
Resiniferatoxin			
Suncus	CP-99994	Given s.c.	51
Tranexamic acid			
Dog	Maropitant	Fibrinolytic	52
U46619			
Suncus	CP-99994	TP agonist; given i.p.	53
Xylazine			
Cat	R116301	Given s.c.	38

TABLE 1 (Continued)

Species	Neurokinin$_1$ receptor antagonist	Stimulus details	References
		Non-pharmacological stimuli	
Motion			
Cat	CP-99994	Ferris wheel	54
Dog	Maropitant	Car journey	55
Suncus	GR203040 Netupitant	Horizontal motion	25,16
Total Body Radiation			
Ferret	GR203040 GR205171	X-radiation	25,28
Ferret	CP-99994	X-radiation (3-week post-abdominal vagotomy and greater splanchnic nerve section)	Andrews and Watson, unpublished
Electrical stimulation of vagal afferents			
Dog (decerebrate)	GR205171	Stimulation either at the level of the terminal thoracic oesophagus or abdomen; fictive emesis measured in the decerebrate dog.	56,57
Ferret (urethane anaesthesia)	CP-99994		20
Parvoviral enteritis-induced vomiting			
Dog	Maropitant		58
Post-neurosurgery vomiting			
Macaca fascicularis *Macaca mulatta*	Maropitant		59

Abbreviations: i.m., intramuscularly; i.p, intraperitoneally; i.v., intravenously; p.o., orally; s.c. subcutaneously.

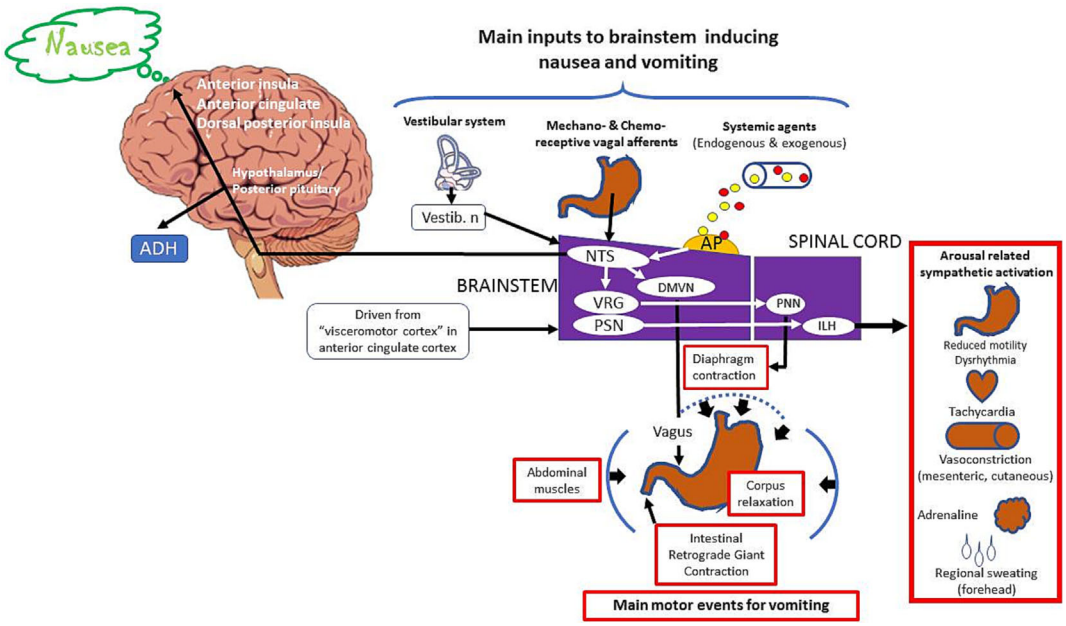

FIGURE 1 A summary of the major pathways implicated in the motor events of vomiting and the sensation of nausea. The diagram shows the major inputs (vestibular system, abdominal vagal afferents, area postrema) to the nucleus tractus solitarius (NTS) in the brainstem by which both nausea and vomiting are evoked. The mechanical events of vomiting only require activation of brainstem and spinal cord nuclei. Most notable are the dorsal motor vagal nucleus (DMVN) projecting vagal efferents to the digestive tract to induce gastric relaxation and intestinal retrograde giant contraction, and the ventral respiratory group (VRG) of neurones driving the spinal phrenic nerve nucleus (PNN) responsible for contraction of the costal diaphragm, which together with the anterior abdominal muscles (not shown) provides the main force compressing the stomach and leading to forceful oral ejection of contents. Nausea requires activation of cerebral structures and is associated with the secretion of high concentrations vasopressin (AVP/ADH) from the hypothalamic/pituitary axis but other hormones are also released (e.g., cortisol). The main sympathetic motor outputs associated with nausea are shown in the right-hand red rectangle and are a consequence of descending pathways from the *visceromotor cortex* activating the pre-sympathetic nuclei (PSN) in the brainstem, which in turn drive the pre-ganglionic sympathetic neurones in the spinal cord (ILH). For details and references see text. Adapted and modified from previous studies.[6]

3.1 | Motion sickness

Studies in humans are limited as ethical considerations usually dictate that vomiting endpoints cannot be used in laboratory-based studies inducing motion sickness in healthy human volunteers. Two laboratory-based studies employed the well proven method of highly provocative whole-body rotational motion with head movements to induce motion sickness (so-called *cross-coupled motion*). These studies showed no significant efficacy of an NK_1RA (**GR205171** [vofopitant]; L-758298) using the degree of motion exposure tolerated before onset of nausea as the endpoint; this suggests no efficacy against nausea.[61,62] A study of healthy human volunteers using inescapable motion at sea investigated the NK_1RA **tradipitant** (VLY-686/LY686017)[9] and unlike laboratory-based trials, it was possible to measure both vomiting and nausea. Tradipitant was significantly effective (placebo comparator) in protecting against vomiting, but less effective against nausea, using the motion sickness severity scale as an index (Figure 2). Only for selected data obtained during rough seas did the NK_1RA provide any protection against nausea compared to vomiting in this sub-group (Figure 2). By contrast, well proven **muscarinic acetylcholine receptor** antagonists such as **scopolamine** (hyoscine), provided protection against both nausea[63,64] and vomiting.[65] More detailed studies are now required, investigating, for example, the effects of NK_1RA on the physiological changes accompanying motion sickness such as the reduced gastric antral contractile activity,[66] a pathway of potential relevance to understanding the effects of NK_1RAs in gastrointestinal conditions associated with nausea, such as gastroparesis (see below).

From these very limited data, we tentatively conclude that NK_1RAs are effective against *vomiting* induced by abnormal motion but are less effective against *nausea*.

3.2 | CINV

We focus on NK_1RA use in the acute and delayed phases of highly emetogenic chemotherapy (HEC) discussing their effects against vomiting before effects against nausea.

A study of CINV in seven patients given CP-122721 *alone* showed that in the acute phase (first 24 h) of HEC five patients had ≤2 episodes *vs.* 7 episodes of *emesis* in an historic control group and in the delayed phase, six had no emesis.[67] A larger study with L-758298 (the prodrug for the NK_1RA, aprepitant [L-754030]) showed that 37% of patients ($n = 30$) had no vomiting or retching in the acute phase, compared with 52% of patients in an **ondansetron** (**5-hydroxytryptamine$_3$** receptor antagonist; 5-HT_3RA) group ($n = 23$; not significantly different).[68] However, confining analysis to the first 8 h following **cisplatin** showed 37% of patients had no vomiting or retching in the NK_1RA group compared to 83% in the 5-HT_3RA group ($P = .001$) but, in the delayed phase, 72% of patients were without vomiting or retching in the NK_1RA group *vs.* 30% in the ondansetron group ($P = .005$).[68] This study suggests a shift in the relative involvement of 5-HT_3 and NK_1 receptors driving retching and vomiting between the acute and delayed phases following cisplatin, a finding confirmed by detailed time course analysis of the efficacy of aprepitant, L-758298, ondansetron and **granisetron** in treatment of CINV.[69]

Recent meta-analyses demonstrate additional protection against vomiting when NK_1RAs are given with a 5-HT_3RA and **dexamethasone** during both acute and delayed phases in HEC (~15–20% more complete protection), with a greater effect in the delayed phase.[70–72]

Overall, and despite an ability of NK_1RAs to further reduce the incidence of vomiting during the acute phase when combined with a 5-HT_3RA and **dexamethasone**, the incidence of nausea is not further reduced during this phase. For example, an initial study with L-754030

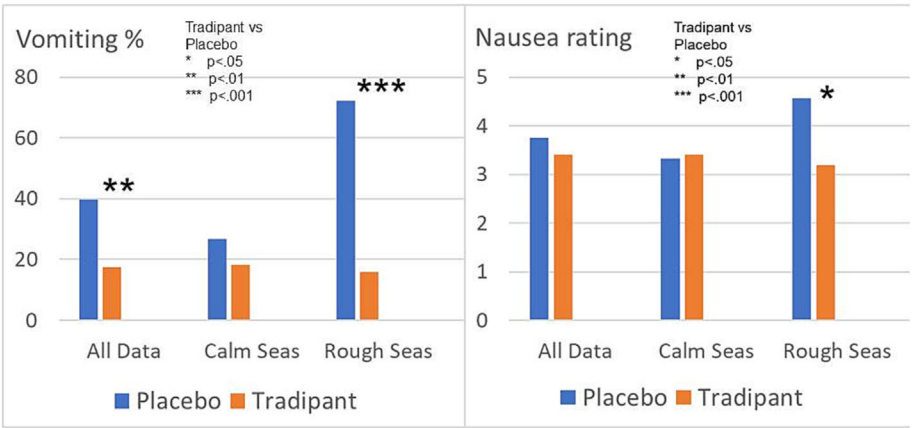

FIGURE 2 The effects of the NK_1 receptor antagonist (NK_1RA) tradipitant *vs.* placebo on motion sickness signs and symptoms, are shown for vomiting (left) and for nausea (right). Motion sickness was provoked by motion at sea. Voyages inevitably varied in terms of the weather and roughness of waves; consequently, the data are presented in terms of all data (i.e. all voyages combined) and split by lower wave motion *calm seas* and higher wave motion *rough seas*. Vomiting is shown as % incidence. Nausea is shown as the mean sickness rating scale, with higher scores indicating more severe nausea. Note the differences in levels of statistical significance for the different comparisons. Data were adapted from previous studies.[9]

showed an additional effect on vomiting in the acute phase (day 1) following cisplatin when added to a 5-HT_3RA/dexamethasone regimen,[73] but no significant reduction in nausea frequency. An analysis of the Phase III studies of NK_1RAs added to a 5-HT_3RA and dexamethasone regime in HEC, found no consistent evidence for an improvement in the incidence of *no significant nausea* (NSN) or *no nausea* (NN) in the acute phase.[74] For example, the percentage of patients experiencing NN in the NK_1RA arm *vs.* placebo in the acute phase was 53.6 *vs.* 52%,[75] 65 *vs.* 66%,[76] 68 *vs.* 61% (Study 2[77]) and 73 *vs.* 68% (Study 1[77]). A pooled analysis of studies with **rolapitant** showed a small but statistically significant increase in the percentage of patients reporting NN (respectively, 64 and 70%) in the acute phase of HEC.[74] Saito et al.[78] found a tendency for the incidence of NSN to increase (90.2 *vs.* 84.9%) when using intravenous **fosaprepitant** (150 mg + granisetron/dexamethasone) in patients receiving high-dose cisplatin, although the difference was not statistically significant and the NN incidence was unchanged (67.6 *vs.* 67.5%) compared to placebo.

Some, but not all, studies reported that during the delayed phase the addition of an NK_1RA significantly increased the percentage of patients reporting NN or NSN. In the initial study with daily L-754030 (±placebo + granisetron/dexamethasone[73]) the median nausea score was reduced on a 100 mm visual analogue scale (higher score indicating more severe nausea) from 19 to 1 mm on day 2 and over days 2–5 from 10 to 1 mm. Similarly, others reported that the percentage of patients experiencing NN in the NK_1RA arm *vs.* placebo/comparator arm in the delayed phase increased significantly: 52.7 *vs.* 39.9%,[79] 53 *vs.* 42% (Study 1[77]) and 58 *vs.* 47% (Study 2[77]). However, some showed no statistically significant change in NN (e.g., 28 *vs.* 17% days 2–7 but day 2 only, 52 *vs.* 22%,[68]; 43.9 *vs.* 49.1%,[75]; 71.4 *vs.* 73%,[80]; 48 *vs.* 45%,[76]). A pooled analysis of studies using rolapitant showed a significant 12% increase in the NN percentage (44 *vs.* 56%) in the delayed phase.[74]

A recent meta-analysis investigated the addition of aprepitant to a 5-HT_3RA/dexamethasone regimen in patients receiving HEC treatments for lung cancer.[81] While the overall complete response rate (no vomiting/no rescue medication) was significantly better when aprepitant was given, the NN rate was not statistically significantly different.

In summary, there are insufficient data to compare different NK_1RAs, but it is possible to draw general conclusions about their efficacy in HEC:

i. NK_1RAs further reduce the incidence of vomiting during the acute phase when combined with a 5-HT_3RA and dexamethasone, but the effect is more marked in the delayed phase of HEC.
ii. When added to a 5-HT_3RA/dexamethasone regime, the ability of NK_1RAs to further reduce the incidence of nausea appears inconsistent.

3.3 | Post-operative nausea and vomiting

Table 2 summarizes the effects of NK_1RAs in PONV using the outcome from studies reporting nausea and vomiting separately to illustrate the efficacy differences. Overall, several NK_1RAs show efficacy against post-operative *vomiting* in a proportion of patients but the block is not complete in all patients and, the efficacy against *nausea* is inconsistent (e.g., small changes in incidence, inconsistent change in intensity, Table 2) and lower than against vomiting. A Cochrane meta-analysis examined the efficacy of diverse pharmacological agents in treating *vomiting* in the first 24 h[95] and concluded that *single* NK_1RAs were as effective as other *drug combinations*. The analysis did not compare efficacy against nausea.

Assessment of the overall efficacy of NK_1RAs against PONV is complicated by the variety of types or surgery (e.g., open abdomen, laparoscopic) and anaesthesia/analgesia protocols. A further issue is that in studies where a range of doses has been investigated the relationship between NK_1RA dose and efficacy against either nausea or vomiting is not always clear (e.g., **casopitant**,[90] rolapitant,[96] vestepitant[88]).

3.4 | Cyclical vomiting syndrome

An open-label uncontrolled trial of aprepitant in a paediatric population refractory to conventional treatment showed reduction in the number of cyclic vomiting episodes/year and number of vomits/h.[97] Although nausea is a feature of cyclical vomiting syndrome it was not assessed in this study.

3.5 | Paediatric patients with life-limiting conditions

A case series showed aprepitant (2.0–2.5 mg/kg, intravenously) was effective in complete resolution of nausea (parental reports of impact on mobility and feeding used as proxy efficacy markers) in paediatric patients receiving palliative care, with different diagnoses and unresponsive to at least two drugs classified as *anti-emetics* (e.g., **cyclizine**, ondansetron, **metoclopramide**, levomepromazine[98]). Additionally, aprepitant increased the ability to tolerate feeds as might be expected from the proposal that food refusal in children could be used as a surrogate marker for nausea,[99] although NK_1RA-induced changes in gastric accommodation[100] offers an alternative explanation.

3.6 | Gastric distension-induced sensations and gastroparesis

In healthy human volunteers a single dose of aprepitant (80 or 125 mg) had no effect on gastric compliance or sensitivity to distension.[101] Also, in healthy volunteers, aprepitant (125 mg orally [p.o.] day 1 + 80 mg p.o. days 2–5) did not affect gastric emptying of liquids or solids, intestinal or colonic transit.[102] Using the same repeat dosing schedule but following a *dyspeptogenic* meal, Jacob et al.[100] confirmed no change in gastric emptying with aprepitant but found a modest increase in fasting (~10%), postprandial (~9%) and gastric accommodation (~5%)

TABLE 2 A summary of studies investigating the efficacy of neurokinin$_1$ receptor antagonists against post-operative nausea and vomiting (PONV). Studies are selected to show the relative efficacy against nausea and vomiting and hence only studies in which they were assessed independently are included. See text for further discussion.

Compound	Efficacy against nausea in PONV	Reference
CP-122721 (100 mg, 200 mg, p.o.)	In patients undergoing abdominal hysterectomy the maximum nausea score appeared to be reduced by CP-122721 in both dose groups compared to placebo but any effect was not statistically significant ($n = 20–24$). Visual analogue scale nausea score did not differ between ondansetron, CP-122721 and combination groups ($n = 52–53$).	[82] (abstract),[83]
Vofopitant (GR-205171) (25 mg, i.v.)	In patients undergoing major gynaecological surgery vofopitant showed superiority compared to placebo ($n = 18$ in both groups) for the percentage of patients without nausea (2-h complete control nausea: 55 *vs*. 20%) and reduced the severity of nausea over the entire 24-h post-operative observation period.	[84]
Aprepitant (L-754030) (40 mg/125, p.o.)	Peak nausea score distribution (interquartile range) was significantly lower ($P < .05$, $n = 280–293$) for both aprepitant groups (40/125 mg) compared to ondansetron (4 mg) but the percentage of patients reporting no significant nausea was only significantly higher than that ondansetron for 40-mg aprepitant (62 *vs*. 53%). For vomiting both doses of aprepitant were superior to ondansetron and blocked vomiting in ~85% of patients. Open abdominal surgery.	[85]
Aprepitant (L-754030) (80 mg p.o.)	In patients undergoing laparoscopic gynaecological surgery nausea intensity was significantly lower with aprepitant compared to palonosetron on arrival in the recovery room (11.2 ± 2.1 *vs*. 19.0 ± 2.2) and at 2 h (9.7 ± 2.1 *vs*. 19.4 ± 3.5) but not in the subsequent 46 h. The complete response rate over 48 h did not differ (74 *vs*. 77%)	[86]
Aprepitant (L-754030) (40 mg p.o.)	In patients undergoing plastic surgery compared to placebo (+ondansetron) the severity of nausea was lower ($P = .014$, $n = 75$/arm) in the aprepitant group (+ondansetron) between 0-48-h post-surgery. Vomiting incidence was also significantly lower in the aprepitant group (7/75 *vs*. 22/75).	[87]
Vestepitant (6-36 mg, i.v.)	Non-emergency surgery under general anaesthesia in patients failing prophylaxis with pre-surgery ondansetron. Nausea numerical rating scale median values did not differ between ondansetron (4 mg) alone and any dose of vestepitant ($n = 7–15$/group) given subsequently but overall vestepitant was superior to ondansetron (10.1–22.9%) improvement except at a dose of 18 mg when there was a −1.2% difference.	[88]
Fosaprepitant (150 mg, i.v.)	In patients undergoing surgery requiring general anaesthesia the percentage of patients vomiting was significantly lower with fosaprepitant ($n = 82$) than with ondansetron ($n = 89$) at 0–2 h (2 *vs*. 17%), 0–24 h (2 *vs*. 28%) and at 0–48 h (2 *vs*. 29%). However, the percentage of patients reporting nausea in the fosaprepitant was higher than for vomiting at all time points (e.g., at 0–2 h, nausea 41 *vs*. vomiting 2%).	[89]
Casopitant (GW679769) (50 100 150 mg, p.o.)	Only female patients, laparoscopic/laparotomic gynaecological procedure or laparoscopic cholecystectomy. All doses of casopitant further reduced the percentage of patients with vomiting at both 0-24 h (ondansetron 28.6 *vs*. casopitant + ondansetron 4.3–9.3%) 0–48-h time points (ondansetron 32.9 *vs*. casopitant + ondansetron 6.4–12.9%). There was no difference in the % of patients reporting nausea between ondansetron and casopitant + ondansetron groups. The % of patients experiencing nausea was higher that the % experiencing vomiting for all three doses of casopitant + ondansetron (casopitant 50 mg, nausea 70.0 *vs*. vomiting 9.3%; 100 mg, nausea 63.6 *vs*. vomiting 4.3%; 150 mg, nausea 66.4 *vs*. vomiting 7.1%). The intensity of nausea did not differ between the three casopitant doses.	[90]
Aprepitant (L-754030) (40 mg, p.o.)	Craniotomy patients. No difference between nausea scores, incidence or significant nausea between aprepitant and ondansetron (4 mg) up to 48-h post-surgery but the study may not have been sufficiently powered to see statistical differences at all time points.	[91]
Aprepitant (L-754030) (80 mg, p.o.)	In patients undergoing bariatric surgery aprepitant increased the number of patients without nausea and vomiting (42.18 *vs*. 36.67%) compared to ondansetron alone and nausea scores were unaffected by aprepitant.	[92]

TABLE 2 (Continued)

Compound	Efficacy against nausea in PONV	Reference
Aprepitant (L-754030) (80 mg, p.o.)	Laparoscopic gynaecological surgery. Significant ($P = .014$) additional reduction in nausea incidence (24 h) when aprepitant was given with ondansetron but no change in severity of nausea or incidence of vomiting.	[93]
Aprepitant/ rolapitant/ casopitant	Systematic review and meta-analysis of 14 randomized control trials of three neurokinin$_1$ receptor agonists in patients undergoing mainly either abdominal or gynaecological surgery including open abdomen approaches. Aprepitant (80 mg) showed an additional increase of 31% in the patients protected from nausea compared to placebo.	[94] Note that table 2 in this paper contains a detailed summary of results from all studies included.
Aprepitant (L-754030) (80 mg, p.o.)	Systematic review and meta-analysis of seven randomized control trials of aprepitant (80 mg) in patients undergoing laparoscopic procedures. Risk ratio for nausea 0.56 *vs.* 0.2 for vomiting compared to placebo or no anti-emetic therapy. Risk of vomiting reduced by 80% in first 2 h post-operatively *vs.* 44% for nausea.	[60] Note that table 2 in this paper contains a detailed summary of results from all studies included.

Abbreviations: i.v., intravenously; p.o., orally.

volumes, and a tendency to increase maximal tolerated volume (∼25%). Interestingly, the aggregate symptoms, nausea and pain scores (but not bloating or fullness) increased significantly following the dyspeptogenic meal in the aprepitant group compared to placebo (median 36 *vs.* 4).

A 4-week placebo-controlled study of aprepitant (125 mg/day, p.o.) involving 126 patients failed to demonstrate an improvement in the primary outcome measure of nausea,[103] in a population with 57% gastroparesis patients and the remainder with chronic unexplained nausea and vomiting. The study also used the Gastroparesis Clinical Symptom Index[104] to assess symptom severity as a secondary outcome and this showed significant reductions in overall symptom score (1.3 *vs.* 0.7), vomiting (1.6 *vs.* 0.5 [69% decrease]) and nausea (1.8 *vs.* 1 [44% decrease]). The number of hours per day when nausea was experienced was reduced and the proportion of nausea-free days increased (∼ twofold).

A placebo-controlled trial of 152 patients with idiopathic or diabetic gastroparesis and moderate-to-severe nausea, investigated tradipitant (85 mg p.o.) twice daily (daily total 170 mg) for 4 weeks.[105] The trial met the primary outcome measure of a reduction in average daily diary nausea score measured using the Gastroparesis Clinical Symptom Index Daily Diary with a difference in score reduction between placebo and tradipitant of ∼10%. Nausea severity appeared to begin decreasing by week 2 and this was statistically significant by week 3. Additionally, tradipitant increased secondary outcomes of nausea-free days (∼14% > placebo) and nausea response rate (∼21% > placebo). Patients who responded to tradipitant with a reduction in nausea also had improved early satiety, excessive fullness, bloating and upper abdominal pain, compared to placebo. Two case reports involving single patients with gastroparesis report stoppage of previously intractable nausea[106] or vomiting[107] on administration of aprepitant.

A recent systematic review and network meta-analysis of drugs used to treat gastroparesis showed that NK$_1$RAs were efficacious (risk ratio = 0.69) using global symptom score. When individual symptoms were assessed tradipitant was more effective than placebo in treating nausea (tradipitant risk ratio = 0.77; 95% CI 0.65–0.91).[108] By contrast, a recent phase III trial of tradipitant in gastroparesis showed no difference from placebo in the change of severity of nausea (prespecified primary endpoint) over a 12-week period.[109]

3.7 | Overview of clinical efficacy against nausea *vs.* vomiting

Summarizing Sections 3.1 to 3.7, NK$_1$RAs can block vomiting induced by HEC (± 5HT$_3$RA and dexamethasone) and PONV, and with much more limited evidence perhaps also the vomiting associated with cyclical vomiting syndrome and motion-induced vomiting. NK$_1$RAs do not block vomiting in all patients/subjects exposed to a given stimulus and for CINV the efficacy may depend on the phase (potentially, delayed>acute). When nausea is assessed, several studies report no significant benefit although there is some evidence that even if not completely blocking nausea NK$_1$RAs may reduce its intensity (e.g., see PONV data, Table 2). Overall, however, the NK$_1$RAs are less efficacious or have more variable efficacy against nausea than vomiting over the same range of stimuli but more quantitative data are needed.

We now attempt to explain this differential effect by a detailed analysis of the sites at which NK$_1$RAs could act to affect vomiting (Section 4) and nausea (Section 5).

4 | POTENTIAL SITE(S) OF ACTION OF NK$_1$RA AGAINST RETCHING AND VOMITING (FIGURE 3)

The sites at which NK$_1$RA block retching and vomiting have been investigated in animals (primarily dog and ferret). The findings of these studies are included here because the afferent, integrative and motor pathways responsible for vomiting are comparable between animals

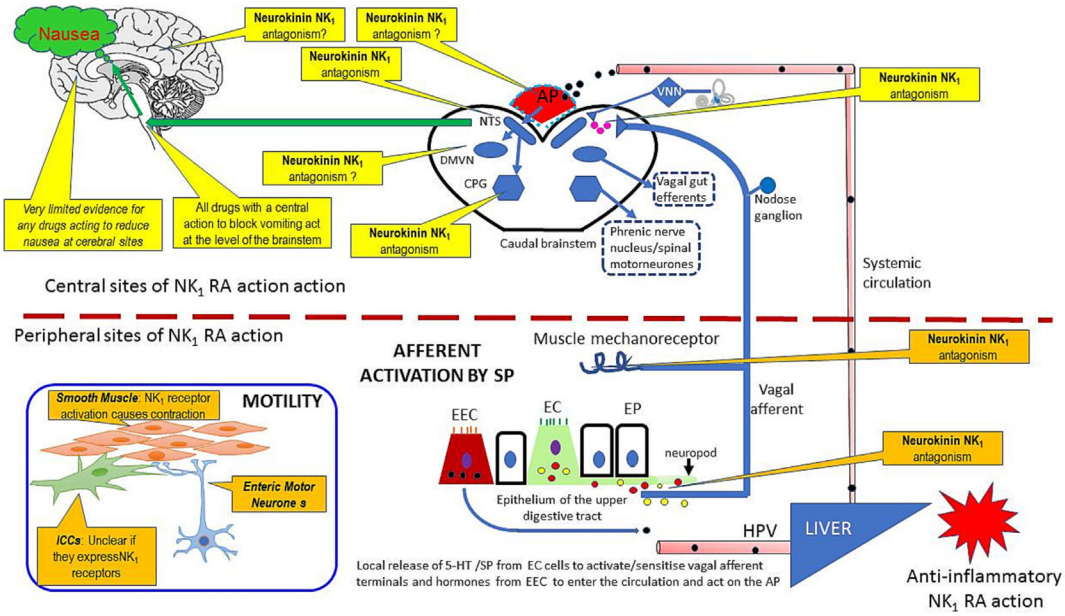

FIGURE 3 A diagrammatic summary of the central and peripheral sites at which NK_1RA could act to reduce nausea and vomiting. AP = area postrema; CPG = central pattern generator for vomiting; DMVN = dorsal motor vagal nucleus EC = enterochromaffin cell; EEC = enteroendocrine cell; EP = epithelial cell; HPV = hepatic portal vein; ICC = interstitial cells of Cajal; NK_1RA = neurokinin$_1$ receptor antagonist; NTS = nucleus tractus solitarius; VNN = vestibular nerve nucleus. In the periphery, NK_1 receptors located on the gastric smooth muscle, the enteric neurones and possibly the ICCs could modulate motility contributing to a reduction in nausea when disordered motility is implicated (e.g., gastroparesis). NK_1RA can prevent activation/sensitisation of both muscle mechanoreceptors and epithelial *chemoreceptive* vagal afferents driving nausea and vomiting by locally released SP. The latter are particularly implicated in nausea and vomiting induced by anti-cancer chemotherapy, gastric irritant and some infections (e.g., rotavirus). NK_1 receptors are also implicated in inflammation the reduction of which by NK_1RA could also contribute to reducing afferent drive. The sites at which vomiting can be blocked all reside in the brainstem (particularly the NTS and CPG), although it is unclear if the AP is a site of action other than when vomiting is induced by an NK_1 receptor agonist. Induction of nausea requires activation of *higher* brain regions and although NK_1 receptors are present at multiple sites in the mid-brain and cerebral hemispheres the data implicating them in anti-nausea effects is circumstantial. See text for details and references.

(e.g., dog, ferret[110]) and humans.[7] For each potential site of action, we will consider whether it could account for a broad-spectrum effect against vomiting or whether it can only explain an action against vomiting induced by a specific stimulus or pathway. This analysis also provides an essential background for understanding the differential effects against nausea.

4.1 | Vestibular system

The vestibular system is essential for induction of nausea and vomiting caused by abnormal body motion. From an evolutionary perspective the vestibular system is considered a component of the mechanisms protecting the body against ingested toxins (see[111–114]). Although sensitivity to motion sickness is a predictive factor for both CINV and PONV,[115,116] there is no evidence that the vestibular system (including vestibular nuclei) is directly implicated in the induction of either. During motion sickness, the motor pathways for vomiting are activated via projections of the vestibular nuclei to the medial and caudal *nucleus tractus solitarius* (NTS; studies in the cat[117,118]). There is no evidence that NK_1RAs affect transmission in the pathway between the vestibular system, the vestibular nuclei and the NTS, to block induction of vomiting. This contrasts with the actions on this pathway of **H_1** and **muscarinic acetylcholine** (M_3/M_5) receptor antagonists, used to treat motion sickness.[63,64,119] An action of NK_1RAs within the NTS or at a site(s) deeper in the brainstem is therefore the most likely site for effects against motion-induced vomiting.

4.2 | Area postrema

The area postrema (AP) projects to neurones in the medial NTS (mNTS) which can be activated by emetic stimuli applied to the AP (e.g., **apomorphine**, **L-glutamate**) and by vagal afferent stimulation (dog studies[120]). However, the evidence that NK_1 receptors occur within the AP is weak, and their functional relevance uncertain. For example, low levels of [^{3}H]-**substance P** binding displaced by CP-99994 (0.1–100 nM) were found in the ferret AP, as compared to the NTS (particularly subnucleus gelatinosus).[20] Ariumi et al.[121] reported dense ^{3}H-substance P binding in the AP and NTS of ferret but displacement by an NK_1RA was not studied. Comparable evidence is available for *S. murinus* and rat,[122,123] Iontophoretic application of substance P (SP) activated ~50% of AP neurones tested (dog[124]), but

although assumed to play a role during vomiting induced by intravenously administered SP (dog[125]), the receptor type activated by the applied concentration of SP and the link between activation and vomiting was not identified. In the ferret, application of SP to the AP can evoke vomiting[123] but microinjection studies[126] suggest that this response was probably due to SP penetration to the subjacent NTS as the blood–brain barrier between these two areas may have some permeability. A similar explanation of leak into the NTS may account for the block in **morphine** (subcutaneously) and reduction in copper sulphate (intragastric)-induced vomiting in the ferret by administration of the NK_1RAs CP-99994 or HSP-117 into the AP.[121]

It is a possibility that NK_1 receptors in the AP could be activated if SP (or other tachykinins) are released from gut enteroendocrine cells (EEC)[127] to enter the blood circulation in addition to acting more locally. However, the evidence for this possibility in response to emetic stimuli is weak. Thus, in patients undergoing chemotherapy, the elevation of serum concentrations of SP during the delayed phase of vomiting was inconsistent[128–132] although this is the phase during which NK_1RA are most effective (see above).

Another possibility is that SP could arise from neurones intrinsic to the AP following direct activation by endogenous or exogenous emetic substances or by abdominal vagal afferents projecting to the AP. However, SP-like immunoreactivity (SP-Li) was absent in the AP of a human infant,[133] consistent with the absence of SP-Li cell bodies in the AP of adult cat, rat[134] and ferret.[135] Previously, extraction studies in humans found some SP in the AP[136,137] and radioligand binding showed a *moderate* uptake of an NK_1RA by the human AP.[138] Sparse SP-Li nerve fibres have been found in the AP (cat, rat) but their origin is most likely to be from either vagal nerve afferents terminating there or from the NTS[134]; this is consistent with the finding of high densities of SP immunoreactive fibres in lateral borders of the AP in the ferret.[135] However, in the least shrew SP-Li fibres and puncta were present at a moderate level in the AP.[139]

Finally, it is worth noting that the concept of the AP as a site at which systemic agents act to induce nausea and vomiting was originally derived from studies showing abolition of vomiting induced by apomorphine (a **dopamine D_2 receptor** agonist), following surgical ablation of the AP including in humans,[140,141] Similarly, other exogenously administered agents (e.g., morphine, **loperamide**, cisplatin) can induce emesis via the AP.[142–144] However, there is only limited evidence that systemic endogenous agents which can induce vomiting (e.g., **adrenaline**, **cholecystokinin**, **GDF15**, arginine-**vasopressin**), act via the AP, with alternative sites of action suggested.[143,145,146] The above discussion suggests that SP, acting via NK_1 receptors in the AP should be added to the list of systemic endogenous emetic agents.

4.3 | Abdominal vagal afferents

There are two sites at which vagal afferent activation by emetic stimuli could be affected by an NK_1RA; they are not mutually exclusive (Figure 3).

4.3.1 | The peripheral transduction mechanism

A potential ability of SP from enterochromaffin cells (ECs) to induce vomiting by acting on vagal afferents was hypothesised >30 years ago ([147]; for details see[8]). Potentially, such a mechanism would be similar to that for 5-HT, which is released from ECs in response to chemotherapeutic agents (e.g., cisplatin) and other emetic stimuli (e.g., rotavirus), causing vomiting by stimulating and sensitizing abdominal vagal afferent terminals via 5-HT_3 receptor activation ([8,148]; for reviews). In rats, treatment with methotrexate or cisplatin increased the number of SP-containing ECs within the intestine, 24 h after administration[149,205] but studies have not yet looked for local release of SP from ECs in response to anti-cancer chemotherapeutic agents or other emetic stimuli. By analogy with 5-HT (see above), any release of SP might be expected to activate vagal nerve terminals. Recently, SP (1 μM)-induced depolarisation of human isolated vagus was shown to be blocked by aprepitant.[150] However, the authors used a concentration (10 μM) at least 10 000× the human NK_1 receptor binding half-maximal inhibitory concentration, at or above the concentrations examined for selectivity of action,[151] and now understood to also activate the mechanosensitive t-pore domain potassium channel, **TRAAK** (encoded by the *KCNK4* gene).[152] Interestingly, recordings from abdominal vagal afferents of ferrets show an interaction between 5-HT and SP[153] and *cross talk* has been demonstrated between NK_1 and 5-HT_3 receptors in relation to the *anti-emetic* effect of palonosetron.[154]

4.3.2 | Vagal afferent to NTS transmission

Abdominal vagal afferents terminate in the mNTS.[155] There is evidence that SP is a transmitter from vagal afferents to NTS neurones (cat[156]; dog[157]) and for activation of NTS neurones by iontophoretically applied SP (ferret[158]; rat[122]). However, any action of NK_1RA on vagal to NTS transmission must be selective for afferents involved in induction of vomiting as NK_1RAs do not block the gag reflex, the cardiac or respiratory components of the von Bezold–Jarisch reflex or apnoea induced by cervical vagal afferent stimulation.[20,56] Additionally, while systemic administration of the NK_1RA, CP-99994 in the anaesthetized ferret blocked licking, swallowing and retching induced by electrical stimulation of the abdominal vagal afferents, the accompanying rise in blood pressure was unaffected.[20] This makes it unlikely that vagal to NTS transmission per se is blocked and suggests that the block is either within the NTS integrative pathways that initiate vomiting or on the output side of the system in the *central pattern generator* (CPG) for vomiting located in the reticular formation dorsomedial to the retrofacial nucleus (Bötzinger complex) in the region of the NA (compact region) and the associated *prodromal sign centre* (PSC in the semi-compact area of the nucleus ambiguus).[155,159,160] Further support for a specific activity on some but not all vagal functions comes from studies in the decerebrate dog where the NK_1RA, **GR-205171** (intravenously) blocked fictive retching, the accompanying antral contractile response (probably the

extension of the Retrograde Giant Contraction [RGC] that originates in the small intestine and immediately precedes the onset of retching mediated by vagal efferents; see[161,162]), and reduced the hypersalivation (mediated by PSC) evoked by vagal afferent stimulation, but not the accompanying vagal efferent mediated relaxation of the proximal stomach.[57]

It is self-evident that blockade of vagal afferent activation at a peripheral site or vagal afferent transmission to the mNTS would only contribute to the anti-vomiting effects of NK_1RAs when the primary stimulus activates the vagus (e.g., acute phase of CINV, possibly gastroparesis[163]). Therefore, a vagal site of action would not account for block of stimuli acting only either via the AP or the vestibular system so additional site(s) of action need to be considered.

4.4 | Brainstem integrative mechanism and the drive to the visceral and somatic motor outputs

The selective effects of NK_1RA on reflex responses to vagal afferent stimulation (as above) show that actions of NK_1RA within the brain stem integrative pathways (i.e. NTS, CPG, ventral respiratory group [VRG]) are selective to neurones involved in the *vomiting motor programme* occurring as a result of reconfiguration of the pattern of activity in the multifunctional respiratory neurones ([164,206]) (c.f. cough, yawn, sneeze). These same sets of neurones can also be driven to evoke vomiting by stimuli acting on the vestibular system and the AP (Figure 4). Thus, the effects of NK_1RAs on the brainstem pathways are *state dependent* and this could explain the selectivity of effects against vomiting; when the brainstem is involved in baseline respiration and some respiratory reflexes there is probably little critical dependence on SP as a transmitter but when the pathway reconfigures and is highly active as occurs for vomiting then it becomes critically dependent on SP.

Overall, there is evidence for either the presence of SP positive neurones and/or NK_1 receptors in the key brainstem sites implicated in vomiting.

4.4.1 | Nucleus tractus solitarius

SP-like immunoreactive neurones are present in the human NTS, particularly subnucleus gelatinosus, and this is consistent with studies in both the cat and ferret.[135,165] A human brain PET study using a fluorine^{18}-labelled NK_1RA reported moderate uptake in the NTS, the nucleus ambiguus and *other nuclei of the vagus* (not specified).[138]

A site of action within the NTS is supported by studies showing microinjection of CP-99994 in the *region of the NTS* inhibited, but did not completely block, cisplatin-induced acute retching and vomiting in the ferret.[19,126] An important point is that the NK_1RA was injected after retching/vomiting began showing that the antagonist was blocking a pathway driven by ongoing NK_1 receptor activation. The peptide NK_1RA, GR-82334 was infective against cisplatin-induced retching/vomiting when given intravenously but was effective (77% reduction) when given into the NTS.[126] Rupniak et al.[17] correlated anti-emetic activity against cisplatin in the ferret with central penetration using a range of NK_1RAs with differing brain penetration. These studies argued strongly that central penetration (at least to the NTS) is required for the acute anti-emetic effect of an NK_1RA. Further support for an action of NK_1RA in the NTS comes from inhibition of SP (1 μM)-induced discharge in NTS slices by HSP-117 (10 μM), without affecting baseline spontaneous neuronal discharge (ferret[158]).

4.4.2 | Dorsal motor vagal nucleus

NK_1 receptors are present in the dorsal motor vagal nucleus (DMVN; ferret[20]), the site of origin of vagal efferents supplying the upper digestive tract and regulating the proximal gastric relaxation and RGC prior to the onset of retching and vomiting.[162] In the rat, neurones in the DMVN responsive to gastric distension ±24 h post cisplatin had their baseline activity altered by CP-99994 (5 μM)[166] but the results should be interpreted with caution as the efferent projection (e.g., the stomach) of the neurones was not identified (e.g., using antidromic collision[167]) and the effects of CP-99994 were not controlled for by using its less potent 2R, 3R enantiomer, CP-100263.[20] Although these studies show that the DMVN is a potential target for NK_1RA it should be noted that preventing the gastric relaxation and RGC will not block retching and vomiting as they can occur even in the absence of the stomach[168] and when the RGC is blocked by atropine.[161] An action of NK_1RA on the DMVN is therefore unlikely to explain their anti-vomiting action.

4.4.3 | Ventral brainstem

Neurophysiological studies of fictive emesis in the dog implicate nuclei in the ventral brainstem.[110,155,159,160] When administered systemically, the NK_1RA, GR-205171 reduces vagal afferent activation (via the mNTS) of the CPG for vomiting and/or in the pathway linking the NTS to the CPG via the PSC[155,159]; immunohistochemistry has demonstrated the presence of NK_1 receptors in both regions of the dog ventral brainstem.[160] The CPG connects with the VRG, the location of the neurones driving the phrenic and abdominal motor neurones involved in normal respiration as well as retching and vomiting (Figure 4).

Total block of transmission at either the NTS or CPG is probably not required to stop induction of vomiting; a *reduction* in transmission at either site is likely to be sufficient as triggering vomiting requires a higher frequency stimulus, which also lasts for an extended time (e.g., ~20s of vagal afferent stimulation is required in dog[120] and ferret[169]), presumably to prevent inappropriate triggering. It is particularly notable that NK_1RAs prevent the *wind-up* of CPG neurones induced by vagal afferent stimulation and blunts the rise in firing frequency when continuous vagal afferent stimulation is used, preventing the CPG reaching a threshold for induction of the oscillatory activity required for retching and vomiting[55,159] (Figure 5).

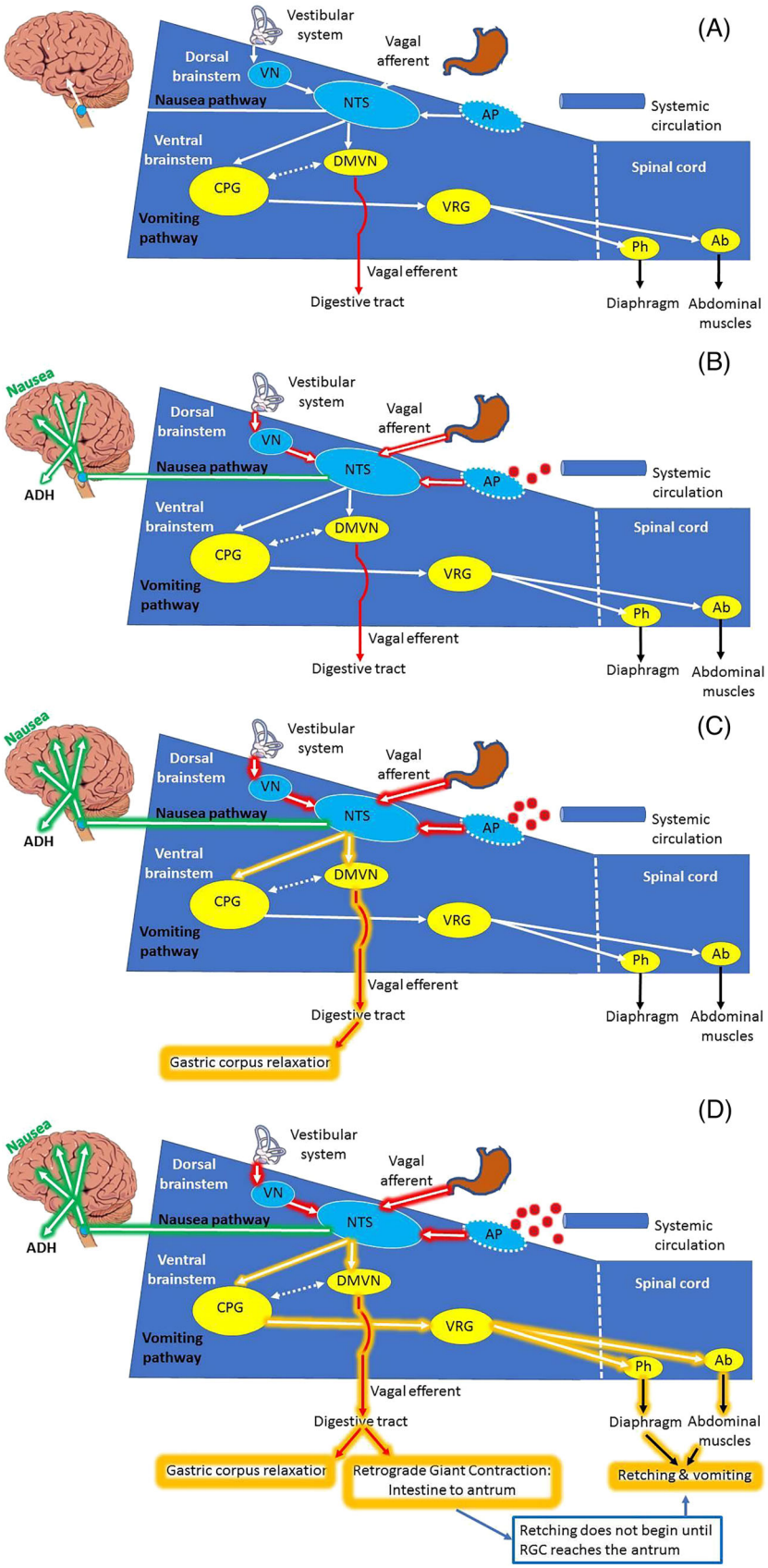

FIGURE 4 (A–D) Diagrammatic representation of a longitudinal section through the brainstem showing the key nuclei and pathways implicated in retching, vomiting and nausea. AP = area postrema; CPG = central pattern generator responsible for the generation of the oscillatory pattern of activity driving the somato-motor pathways for retching and vomiting in the VRG; DMVN = dorsal motor nucleus of the vagus, origin of pre-ganglionic efferents to the digestive tract; NTS = nucleus tractus solitarius; VRG = ventral respiratory group of neurones; Ph = phrenic nerve nucleus in cervical (C3-C-5) spinal cord; ab = abdominal muscle motor neurones in ventrolateral thoracic and lumbar spinal cord. See text for further explanation and references. (A) Resting state; (B) low level of activation of pathways inputting to the NTS resulting in activation of NTS and ascending pathways inducing nausea including secretion of anti-diuretic hormone (ADH/AVP) from the posterior pituitary; (C and D) more intense activation of the inputs results in more intense nausea and proximal gastric relaxation, a preparatory action to accommodate refluxed material resulting from the retrograde giant contraction originating in the small intestine when the input is sufficient to exceed the threshold for induction of retching and vomiting when the phrenic and abdominal motor neurones are activated. Note that the CPG and the DMV outputs must be coordinated (dotted arrow) as retching does not begin until the retrograde giant contraction reaches the gastric antrum.

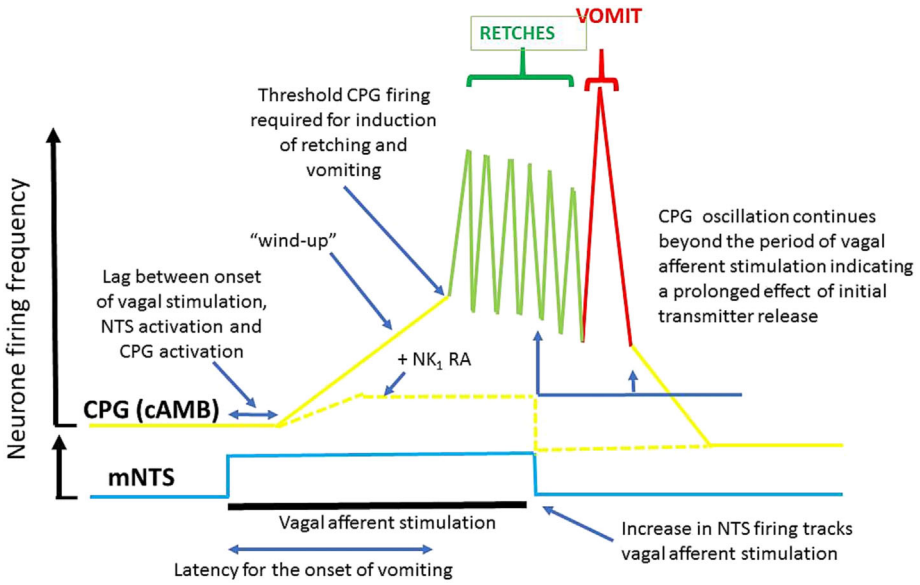

FIGURE 5 Diagrammatic representation of the likely neuronal discharge pattern in the medial nucleus tractus solitarius (mNTS) and the central pattern generator (located in the compact part of the nucleus ambiguus, cAMB) in response to electrical stimulation of infra-cardiac vagal afferents based on neurophysiological studies in the dog reported in previous works.[110,155,160] Vagal afferent stimulation results in a uniform increase in NTS firing frequency, which ceases at the end of stimulation. NTS activation results in central pattern generator (CPG) activation after a lag period and is followed by a progressive increase in frequency which is due to *wind-up*. The CPG firing frequency reaches at threshold at which the pattern becomes oscillatory with the output driving the ventral respiratory group of neurones (VRG) which in turn drive the phrenic and abdominal motor neurones responsible for the mechanical events of retching a vomiting. The CPG oscillations causing retching are shorter and smaller magnitude than the ultimate burst of activity resulting in vomiting and continue beyond the period of vagal afferent stimulation showing a protracted effect of the initial stimulation.

4.5 | Overview of site(s) of action against vomiting

The clinically used NK_1RAs are brain penetrant so when given systemically they can act at both the central and peripheral neuronal sites involved in retching and vomiting:

i. For vomiting induced by abnormal motion, the brainstem integrative pathways (NTS, CPG) are the most likely site of action.
ii. For stimuli involving abdominal vagal afferents it is possible that NK_1RA can: (a) block effects of any SP released from EEC cells onto NK_1 receptors on the peripheral afferent nerve terminals[153]; (b) reduce tachykininergic transmission between vagal afferents and the NTS[123,160]; or (c) modulate the brainstem integrative pathways (NTS, CPG) sufficiently to disrupt the signals encoding induct vomiting.[20,123,155,159,160] At present, the evidence for (b) and (c) is stronger.
iii. For stimuli acting on the AP via the circulation (or cerebrospinal fluid) including exogenous emetics and endogenous substances released for example from the digestive tract because of damage/inflammation (e.g., during the delayed phase of CINV and chronic phases of infection; [8,170,171] for references), the brainstem integrative mechanisms (NTS, CPG) are the most likely sites at which vomiting is affected as there is little evidence for an action within the AP itself.

The NTS and CPG sites of action of NK_1RA are common to all stimuli inducing vomiting. However, for stimuli where abdominal vagal afferent activation occurs two additional sites of action are implicated, which, if operational, would block vagal afferent input and thereby make it unnecessary for NK_1RA to act within the NTS and CPG. However, although the NK_1RA are highly effective against vomiting in a number of clinical settings, NK_1 receptors are not the only receptors involved in all of the pathways and this may explain why they may not always be fully effective in all patients. For example, SP is likely to co-transmit with a non-peptide (e.g., glutamate) with the former likely to be released by a higher frequency or different pattern of nerve firing.[172] Further, glutamate has been implicated in abdominal vagal afferent to mNTS transmission as **NBQX** blocked vagal afferent-induced retching in dog and ferret and the resulting mNTS activation in the dog.[110,173] Nevertheless peptides, as co-transmitters, are known to be involved in network reconfiguration with release determined by both neuronal firing pattern and time.[174] Variations in the predominant transmitters in the nausea and vomiting pathways, possibly as a response to disease, especially if chronic (e.g., in chronic visceral pain NK_1 receptor availability is downregulated[175]), may also contribute to NK_1RAs spectrum of clinical efficacy.

5 | THE POTENTIAL SITE(S) OF NK_1RA ACTION AGAINST NAUSEA

Anti-emetics must not be assumed to equally affect both nausea and vomiting.[2] Accordingly, we discuss the relative effects of NK_1RA against nausea and vomiting by considering specific questions about

the pathways involved; this also informs directions for development of novel drugs (Section 6). Direct experimental data are not available to answer all the questions raised, so some answers are speculative and hypothetical but experimentally testable.

5.1 | What information reaches the NTS from the abdominal vagal afferents in the presence of NK_1RAs?

This question is relevant to both CINV and gastroparesis where abdominal vagal afferents are implicated in genesis of nausea and vomiting.[8,163] Regardless of whether NK_1RAs reduce vagal afferent firing by acting peripherally (e.g.,[153]) or centrally (e.g.,[160]), the degree of activation, and the pattern, frequency and duration of abdominal vagal afferent activity required for induction of nausea as compared to vomiting is unknown. It is, nevertheless, a reasonable assumption that nausea requires less intense activation of afferent pathways than vomiting (see[176] for discussion in relation to the vagus). The effects of NK_1RAs on vagal afferent activity evoked by a wide range of stimulus intensities, ± substances that may sensitize the afferents (e.g., 5-HT, prostaglandins) need to be investigated directly to answer the above question. The development of vagal afferent recording techniques in humans may eventually allow direct testing of this hypothesis.[177]

5.2 | Do differential effects of NK_1RAs on the NTS account for the differential effects against nausea and vomiting?

NK_1RA modulation of the vagal afferent drive to the NTS and/or transmission within the NTS (vagal, AP and vestibular inputs) could contribute to a *reduction* in nausea *intensity* by decreasing the drive from the NTS to supra-medullary structures implicated in the sensation of nausea. However, the evidence for such an action is poor, as discussed below.

5.3 | Are NK_1 receptors in the mid-brain and cerebral hemispheres involved in potential anti-nausea effects of NK_1RA?

In contrast to vomiting, the brain pathways responsible for nausea are not well defined. The majority of brain imaging studies are in subjects reporting nausea induced by illusory-self motion (vection; visually induced motion sickness), with only single studies using *real* motion or a pharmacological challenge[6] making it difficult to assess whether the findings have general applicability. Cortical and sub-cortical areas consistently showing an increase in activity in healthy volunteers reporting nausea include the frontal lobe (e.g., anterior cingulate cortex), occipital lobe (e.g., posterior cingulate cortex), temporal lobe (e.g., amygdala, part of the *limbic cortex*) and basal ganglia (e.g., putamen).[6]

NK_1RA binding in the human brain using PET shows NK_1 receptors in several brain areas implicated in nausea. For example, aprepitant has receptor occupancy of 50% in the caudate and 90% in the putamen (basal ganglia) at plasma concentrations of $\sim 2 \times 10^{-9}$ M and $\sim 2 \times 10^{-8}$ M respectively.[178] Based on the striatal occupancy levels, the authors concluded that the recommended *anti-emetic* aprepitant regime of 125 mg on day 1 and 80 mg on the subsequent 2 days in CINV would result in an occupancy of >90%.[177] Hietala et al.,[138] using the same radioligand confirmed the highest uptake in the caudate and putamen and levels ~50% in regions of the occipital lobe (e.g., posterior cingulate cortex), temporal lobe (e.g., amygdala [forms the limbic cortex with the hippocampus]) and frontal lobe (anterior cingulate cortex) all of which have been implicated in nausea in brain imaging studies.[6]

Pharmacological MRI studies provide additional unexpected insights. Using fosaprepitant, the NK_1 receptor distribution profile identified in the above PET studies was confirmed but in addition identified *activation* of brain areas (e.g., cerebellum, red nucleus) where there were thought to not be any NK_1 receptors, an effect attributed to *downstream pharmacodynamic effects*[206] (see fig. [179]). Such effects demonstrate that in identifying brain sites of drug action we should not only consider regions that have their activity inhibited; activation of a pathway that itself is inhibitory on the function under consideration should not be overlooked. Brain imaging studies in nausea have identified areas with both *increased* and *decreased* activity.[3]

Although we focus on areas directly implicated in nausea, as nausea involves heightened anxiety, the potential anxiolytic effects of NK_1RA[180] could indirectly contribute to reducing nausea scores especially in chronic conditions (e.g., gastroparesis).

Overall, NK_1RAs do not appear to have a consistent ability to reduce nausea induced by multiple stimuli despite high levels of NK_1RA binding in many of the relevant brain areas. Therefore, it is reasonable to conclude that NK_1 receptors do not have a major role in transmission in the *higher* brain regions currently implicated in nausea. We note that NK_1RA efficacy in depression (e.g.,[181,182]), panic disorder,[183] pain[179] and anxiety[180] are also variable and less than might be anticipated from NK_1 receptor distribution.

5.4 | Do NK_1 RA reduce vasopressin secretion?

Relatively high plasma concentrations of arginine vasopressin (AVP) are associated with nausea induced by stimuli activating the vestibular system, AP and abdominal vagal afferents.[146] A causal link between AVP and nausea is not proven, but a credible possibility in at least some clinical scenarios involves the actions of low concentrations of AVP on gastric pacemaker activity (the interstitial cells of Cajal; ICC), synergising with actions of other nauseagenic stimuli to disrupt motility and hence, initiate vagal afferent discharge; the demonstration of synergy between two different nauseagenic stimuli (adrenaline + AVP) was used to argue that antagonism of one alone (e.g., the effects of vasopressin) might reduce but not prevent the symptom of nausea.[146] In dogs, following cisplatin administration, the NK_1RA maropitant was without significant effect on the peak AVP concentration

or the area under the curve whereas both were significantly reduced by ondansetron.[23] In human patients treated with cisplatin the acute rise in AVP concentration was blocked by ondansetron[184] as in the dog, but as far as we are aware similar patient studies have not been performed with an NK_1RA.

5.5 | Do NK_1RA have a role in treating nausea by gastric motility modulation?

The presence of SP in the digestive tract in nerve terminals and EEC[185] and of NK_1 receptors on smooth muscle cells and interstitial cells of Cajal (ICCs)[186–189] makes the digestive tract a potential target for NK_1RA. However, an ability of NK_1RAs to affect nausea by a direct effect on gastric motility is unlikely. Thus, in healthy volunteers there is little evidence for an effect of NK_1RA on digestive tract motility (assessed by gastric emptying or compliance, or small and large bowel propulsion).[100–102,190] Interestingly, after a dyspeptogenic meal, aprepitant (125 mg on day 1, then 80 mg on days 2–5) increased fasting, postprandial and accommodation gastric volume but increased aggregate symptoms, nausea and pain scores after ingestion of the maximum tolerated volume; the authors suggested that differences between these studies may be dependent on what is measured and on the application of acute- or longer term dosing with aprepitant[100] but activation of TRAAK channels (see above) should also be considered.

Dysrhythmic gastric electrical activity has been associated with nausea in disorders including gastroparesis, chronic unexplained nausea and vomiting, functional dyspepsia, gastro-esophageal reflux disease, all linked with loss of ICCs.[191,192] Thus, any ability of NK_1RAs to affect ICC functions (see above) could, in theory, have an influence on *induction* of nausea although an effect on vagal afferent signalling or the NTS seems more likely based on current knowledge.

6 | CONCLUDING COMMENTS

Irrespective of the stimulus, the effects of NK_1RA against *vomiting* are explicable by a central action on the NTS and CPG in the brain stem with potential additional peripheral effects on vagal afferent activity when activated by an emetic stimulus (e.g., HEC, some ingested toxins). NK_1RAs are not always 100% effective against vomiting in humans (c.f., pre-clinical studies, Table 1) implicating other transmitter/receptor systems and explaining why optimal *anti-vomiting* therapy may require drug combinations (e.g., netupitant + **palonosetron** + dexamethasone) in treating complex situations such as HEC. An additional role for other neurotransmitters/co-transmitters (e.g., glutamate) has not yet been fully explored.

A reduction in the projection of information from the NTS to the higher brain regions by suppression of NTS pathways and the drive from the abdominal vagal afferents is likely to contribute to any reduction of nausea by NK_1RAs, no matter how sub-optimal the current evidence suggests. It could be argued that the distribution of NK_1 receptors in cortical and sub-cortical structures implicated in nausea may predict efficacy against nausea, but it is also possible that these receptors are coupled to non-nauseagenic pathways, such as those involved in fear and/or anxiety (which nonetheless may contribute to the overall sensation of nausea).

Mechanistically, vomiting is well understood and studies with NK_1RAs show that targeting the NTS/CPG in the brainstem is a valid approach and adverse effects on the respiratory, cardiovascular and digestive systems all regulated from the brainstem appear to be avoided. The apparent specificity of NK_1RA blockade of vomiting probably reflects the functional reconfiguration of the neural network to coordinate retching/vomiting where tachykininergic signalling becomes critical (state dependence; see[193] for a study of NK_1 receptors and state dependent functions of pre-Bötzinger complex respiratory neurones). The NTS and CPG need investigating in emetic species using neurophysiological studies similar to those in rodents showing complex interaction between NK_1 receptor activation, glutamate and **GABA** release[194] to understand how NK_1RAs are *functionally specific* for vomiting.

Nausea remains a challenge as there are major gaps in knowledge of the cerebral pathways involved and hence in identifying potential receptor targets to identify broad-spectrum anti-nausea drugs. As the insular cortex is the highest cortical region consistently activated in subjects reporting nausea,[6] this would be a logical place to target a drug to block nausea, although the associated physiological changes (e.g., regional cold sweating, AVP secretion) may not be blocked as they involve *lower* brain regions. An alternative approach is to selectively suppress transmission of *nauseagenic* signals from the NTS to the mid-brain with consideration being given to the parabrachial nucleus as a potential target. While this might be achieved by a combination of receptor antagonists the use of agonists (e.g., **$GABA_B$**, **CB_1**, **5-HT_{1A}**, **ghrelin**, **opioid**) may provide a more fruitful approach as this makes fewer assumptions about the nature of the nauseagenic stimulus.[195] A gastric inhibitory polypeptide-1 receptor agonist has been shown to block the acute vomiting induced by the chemotherapeutic agent cisplatin in the ferret,[196] further extending the list of receptor agonists with *anti-emetic* potential. The electroceutical approaches to treatment of gastrointestinal symptoms, including nausea,[197,198] may provide a route by which this system may be controlled but further study is needed to determine the pathways and cell types involved. A final approach is to target the abdominal vagal afferents at a peripheral site but this would only be applicable when a peripheral release of SP has been demonstrated and when the original signal originates from disordered upper digestive tract function (e.g., gastroparesis[163]). Research into the development of anti-nausea drugs is further hampered by the paucity of human volunteer studies using stimuli other than motion. Studies of *anti-emetics* have been undertaken in humans using apomorphine, ipecacuanha and morphine as challenges[199–201] and a wider range of challenges could be identified from the side effect profile of licenced drugs (e.g., **GLP-1 receptor** agonists). The final issue is quantification of nausea. The assessment tools widely used in clinical trials rely on an accurate classification of nausea by

the subject, an assumption that subjects are reporting the same sensation and reliable recollection as data may only be collected daily giving data with a low temporal resolution (see[6] Supporting Information). The heterogeneity of nausea assessment instruments was identified as an issue in a recent US Food and Drug Administration review of endpoints in CINV and PONV studies, which identified nausea assessment as an "opportunity for continued research and development".[202] A reliable, subject independent method for assessing nausea in real time is needed to ensure an accurate assessment of candidate drug efficacy.[10]

We close by dedicating this review to a colleague and friend Wes Miner who died while we were drafting this review. Wes was co-author of the first paper demonstrating the remarkable anti-emetic effect of a 5-HT_3 receptor antagonist[203] and spent his career in the pharmaceutical industry. In a note to one of the authors (P.L.R.A.) in 1999 Wes made the following insightful comment of relevance to this review regarding the paper[73] reporting some of the earliest clinical data on NK_1RA: "results are very, very good and I think this will just about wrap it up for pharmaceutical company interest in the N + V area for the next 20 years". As Wes predicted, there have indeed been no major advances in the development in drugs affecting vomiting and especially nausea in the last 20 plus years and as this review shows the accepted dogma that *anti-emetics* equally affect nausea and vomiting requires challenging; a view with which we are sure Wes would concur.

AUTHOR CONTRIBUTIONS

All authors made an equivalent contribution.

CONFLICT OF INTEREST STATEMENT

P.L.R.A. has no conflict of interest; J.F.G. advises DefenderPharma; G.J.S. advises BYOMass and Neurix.

DATA AVAILABILITY STATEMENT

Not applicable.

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