



An assessment of the effects of neurokinin1 receptor antagonism against nausea and vomiting: Relative efficacy, sites of action and lessons for future drug development.

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Abstract:	<p>A 'broad-spectrum' anti-vomiting effect of neurokinin1 receptor antagonists (NK1RA), shown in preclinical 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 by NK1 receptor antagonism, a common finding for 'anti-emetics'.</p> <p>The stimulus-independent effects of NK1RAs against vomiting are explicable by actions within the central pattern generator (CPG; 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 CPG and NTS neurones are multifunctional so the notable lack of obvious effects of NK1RAs 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.</p> <p>Nausea requires activation of cerebral pathways by projection of information from the NTS. Although NK1 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 NK1RAs to inhibit nausea emphasises (a) our inadequate understanding of the mechanisms of nausea and (b) that classification of a drug as an "anti-emetic" gives a false impression of efficacy against nausea versus vomiting.</p> <p>We discuss the potential mechanisms for the differential efficacy of NK1RA and the implications for future development of drugs which can effectively treat nausea, an area of unmet clinical need.</p>

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1 **An assessment of the effects of neurokinin₁ receptor antagonism against**
2 **nausea and vomiting: Relative efficacy, sites of action and lessons for future**
3 **drug development.**

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18 **Key words:** Anti-cancer chemotherapy, gastroparesis, motion sickness, nausea, neurokinin₁,
19 substance P, tradipitant, vomiting.

20 **Abbreviations:**

21 AP: Area postrema

22 AVP: Arginine vasopressin

23 CB₁: Cannabinoid₁ receptor

24 CCK: Cholecystokinin

25 CI: Confidence Interval

26 CINV: chemotherapy-induced nausea and vomiting

27 CPG: central pattern generator for vomiting

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3 28 CUNV: Chronic Unexplained Nausea and Vomiting
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5 29 D₂: dopamine₂ receptor
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7 30 EC: Enterochromaffin cell
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9 31 EEC: Enteroendocrine cell
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11 32 GABA: Gamma amino butyric acid
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13 33 GABA_B: Gamma amino butyric acid B receptor
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15 34 GCSI: Gastroparesis Clinical Symptom Index
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17 35 GDF15: Growth differentiation factor 15
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19 36 GLP-1: Glucagon like peptide 1
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21 37 5-HT: 5-Hydroxytryptamine
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23 38 5-HT_{1A}: 5-Hydroxytryptamine_{1A} receptor
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25 39 5-HT₃: 5-Hydroxytryptamine₃ receptor
26
27 40 HEC: Highly emetogenic chemotherapy
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29 41 H₁: Histamine₁ receptor
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31 42 ICC: interstitial cells of Cajal
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33 43 i.v.: Intravenous
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35 44 MSSS: motion sickness severity scale
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37 45 mACh: Muscarinic acetylcholine receptor
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39 46 mNTS: medial nucleus tractus solitarius
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41 47 MRI: Magnetic resonance imaging
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43 48 NA: Nucleus ambiguus
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45 49 NK₁RA: Neurokinin₁ receptor antagonist
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47 50 NN: no nausea
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49 51 NSN: no significant nausea
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51 52 NTS: Nucleus tractus solitarius
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53 53 PET: Positron emission tomography
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55 54 p.o.: *Per oral*
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57 55 PONV: post-operative nausea and vomiting
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59 56 PSC: prodromal sign centre
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57 57 RGC: Retrograde giant contraction
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59 58 RR: Risk ratio
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3 59 SP: Substance P

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5 60 VRG: Ventral respiratory group

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7 61 VIMS: Visually-induced motion sickness

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11 63 **Author contribution. All authors made an equivalent contribution.**

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14
15 65 **Abstract**

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18 66 A 'broad-spectrum' anti-vomiting effect of neurokinin₁ receptor antagonists (NK₁RA), shown
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21 67 in preclinical animal studies, has been supported by a more limited range of clinical studies in
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24 68 different indications. However, this review suggests that compared with vomiting, the self-
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27 69 reported sensation of nausea is less affected or possibly unaffected by NK₁ receptor
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29 70 antagonism, a common finding for 'anti-emetics'.

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31 71 The stimulus-independent effects of NK₁RAs against vomiting are explicable by actions within
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34 72 the central pattern generator (CPG; ventral brainstem) and the nucleus tractus solitarius (NTS;
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37 73 dorsal brainstem), with additional effects on vagal afferent activity for certain stimuli (e.g.,
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39 74 highly emetogenic chemotherapy). The CPG and NTS neurones are multifunctional so the
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42 75 notable lack of obvious effects of NK₁RAs on other reflexes mediated by the same neurones
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44 76 suggests that their anti-vomiting action is dependent on the activation state of the pathway
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46 77 leading to vomiting.

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49 78 Nausea requires activation of cerebral pathways by projection of information from the NTS.

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51 79 Although NK₁ receptors are present in cerebral nuclei implicated in nausea, and imaging
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54 80 studies show very high receptor occupancy at clinically used doses, the variable or limited
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57 81 ability of NK₁RAs to inhibit nausea emphasises (a) our inadequate understanding of the
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3 82 mechanisms of nausea and (b) that classification of a drug as an “anti-emetic” gives a false
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6 83 impression of efficacy against nausea *versus* vomiting.
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9 84 We discuss the potential mechanisms for the differential efficacy of NK₁RA and the
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11 85 implications for future development of drugs which can effectively treat nausea, an area of
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13 86 unmet clinical need.
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19 88 **1. Introduction**

22 89 Drugs treating nausea and vomiting as disease symptoms or as adverse effects of therapy are
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24 90 usually classified as ‘anti-emetics’. However, the term ‘emetic’ refers to a substance which
25
26 91 causes vomiting (or retching). Emesis does not mean nausea. Further, increasing evidence
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28 92 indicates differential efficacy of ‘anti-emetic’ drugs against nausea *versus* vomiting. Seifert &
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30 93 Alexander (2022) proposed a “rational drug class terminology” based on a drug’s
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32 94 pharmacological actions rather than its therapeutic orientation (e.g., anti-emetic). Applying
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34 95 this terminology to nausea and vomiting means that the term ‘anti-emetic’ must be written
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36 96 in inverted commas to denote the fact that efficacy against nausea and vomiting should not
37
38 97 be assumed to be the same (Sanger & Andrews, 2022). Here, we emphasise the importance
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40 98 of differentiating between nausea, a self-reported aversive sensation involving cortical and
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42 99 sub-cortical brain regions (Napadow et al., 2013; Farmer et al., 2015; Ruffle et al., 2019;
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44 100 Varangot-Reille et al., 2023) and the mechanical events of retching and vomiting involving
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46 101 multiple brainstem nuclei (Stern et al., 2011).
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54 102 The introduction of NK₁ receptor antagonists (NK₁RAs) further improved control of
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56 103 ‘chemotherapy-induced nausea and vomiting’ (CINV) and ‘post-operative nausea and
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58 104 vomiting’ (PONV) (Sanger & Andrews, 2018). In addition, a potential expansion of indications
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105 may be appropriate, to include, for example, motion sickness (Polymeropoulos et al., 2020).

106 If confirmed, this would point towards a relatively wide spectrum of 'anti-emetic' activity for

107 the NK₁RAs in humans, as suggested by animal studies (see below). However, originating

108 primarily from studies of CINV including the earliest clinical studies of NK₁RAs (e.g., Navari et

109 al., 1999) there has been a concern that nausea is less well treated than vomiting (Andrews

110 & Sanger, 2014) and this concern persists, as reflected in the comment by Apro (2018, p.57)

111 that "Perhaps the greatest unmet need in CINV is the lack of complete nausea control".

112 Accordingly, in an attempt to understand the nausea *versus* vomiting question in relation to

113 NK₁RAs, from both clinical and basic science perspectives, we identified five key questions:

114 1. Has the broad spectrum of activity of NK₁RAs suggested by animal studies of vomiting

115 translated to humans?

116 2. Where do NK₁RAs act to inhibit vomiting?

117 3. To what extent do NK₁RAs inhibit nausea as compared to vomiting?

118 4. If NK₁RAs have a differential effect against nausea compared to vomiting, what is the

119 explanation?

120 5. What are the implications of the answers to the above questions in terms of patient

121 satisfaction and for future development of drugs to treat nausea?

122 Different emetic stimuli signal to the brain via different routes. This is why it is first necessary

123 to determine if the broad-spectrum ability of NK₁RAs to prevent vomiting in animals

124 translates to humans in a similar manner; such a profile directs the discussion on potential

125 mechanism of action against vomiting and nausea. Accordingly, we begin by briefly describing

126 the NK₁RA studies in animals and then review the effects of NK₁RAs against vomiting and

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3 127 nausea in different clinical indications (see below for selection criteria), identifying
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6 128 differences in efficacy between these different indications.
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9 **129 2. Animal studies: Spectrum of NK₁RA effects against vomiting and nausea-like behaviours**

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11 130 In this section we consider only data from species with a vomiting reflex (ferret dog, cat,
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14 131 House musk shrew [*Suncus murinus*] and Least shrew [*Cryptotis parva*]). To simplify
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16 132 comparisons between species and between the effects of drugs on vomiting and nausea, we
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19 133 have not considered 'nausea-like' behaviour data from rodents, which cannot vomit (Sanger
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21 134 et al., 2011; Horn et al., 2013).
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24 135 **2.1. Vomiting.** Studies in multiple animal species (**Table 1**) have demonstrated 'broad
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26 136 spectrum' effects of NK₁RAs, markedly reducing/blocking retching and/or vomiting induced
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29 137 by diverse stimuli acting via three key inputs to the brainstem (**Figure 1**) (Stern et al., 2011;
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31 138 Sanger & Andrews, 2018 for references).
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34 139 **2.2. 'Nausea-like behaviours.'** Administration to animals of substances inducing nausea and
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37 140 vomiting in humans evoke behavioural changes (often referred to as 'nausea-like'), but their
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40 141 significance and relevance to the human sensation of nausea is contentious (Stern et al., 2011,
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42 142 Chapter 11; Andrews & Sanger, 2014). In summary, and in contrast to the clear effects of
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44 143 NK₁RA on vomiting, effects on 'nausea-like behaviours' are absent or inconsistent
45
46 144 (**Supplementary Table 1**). Given this lack of clarity and since the relevance of these behaviours
47
48
49 145 to the human experience is unknown, they will not be considered further (Stern et al., 2011,
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51 146 Chapter 11; Andrews & Sanger, 2014, for detailed discussion).
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53

54 147 **3. Human studies: Spectrum of NK₁RA effects against vomiting and nausea.**

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57 148 It is important to determine if the broad-spectrum ability of NK₁RAs to prevent vomiting in
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60 149 animals translates to the vomiting and nausea of humans. Accordingly, we searched either

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3 150 the name of individual antagonists and/or the therapeutic area (e.g., motion sickness, CINV,
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6 151 PONV, gastroparesis, and cyclical vomiting syndrome). For CINV and PONV where there has
7
8 152 been more extensive investigation of NK₁RAs 'anti-emetic' efficacy we initially reviewed
9
10 153 systematic reviews/meta-analyses and then analysed data in selected original papers. As our
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12 154 focus was on the relative efficacy of NK₁RAs against nausea and vomiting we included papers
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14 155 where data on *both* vomiting and nausea was presented and in particular where adequate
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16 156 information was provided in the methods about how each was quantified, with data
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18 157 presented in a form allowing comparison. We note that few studies have given an NK₁RA
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20 158 *alone*, 'N' values can be small (e.g., in PONV the N value for 7 studies of aprepitant included
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22 159 in a meta-analysis ranged from 30-55; Cavaye et al., 2021) and some studies are uncontrolled.
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24 160 Nausea is often a secondary outcome with methodological variations in its assessment
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26 161 complicating inter-study comparisons (see below).
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33 162 Sections 3.1 to 3.6 describe the results of studies investigating the effects of NK₁RAs against
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35 163 different emetic challenges. Section 3.7 then provides an overview of the spectrum of efficacy
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37 164 against nausea and vomiting.
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41 165 **3.1. Motion sickness (MS).** Studies in humans are limited as ethical considerations usually
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43 166 dictate that vomiting endpoints cannot be used in laboratory-based studies inducing motion
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45 167 sickness in healthy human volunteers. Two laboratory-based studies employed the well
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47 168 proven method of highly provocative whole-body rotational motion with head movements to
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49 169 induce motion sickness (so-called "Cross-coupled motion"). These studies showed no
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51 170 significant efficacy of an NK₁RA (GR205171 [vofopitant]; L758,298) using the degree of motion
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53 171 exposure tolerated before onset of nausea as the endpoint; this suggests no efficacy against
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55 172 nausea (Reid et al., 1998; Reid et al., 2000). A study of healthy human volunteers using
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3 173 inescapable motion at sea investigated the NK₁RA tradipitant (VLY-686/ LY686017)
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6 174 (Polymeropoulos et al., 2020) and unlike laboratory-based trials, it was possible to measure
7
8 175 both vomiting and nausea. Tradipitant was significantly effective (placebo comparator) in
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10 176 protecting against vomiting, but less effective against nausea, using the motion sickness
11
12 177 severity scale (MSSS) as an index (**Figure 2**). Only for selected data obtained during rough seas
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15 178 did the NK₁RA provide any protection against nausea compared to vomiting in this sub-group
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17
18 179 (**Figure 2**). By contrast, well proven muscarinic acetylcholine (ACh) receptor antagonists such
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20 180 as scopolamine (hyoscine), provided protection against both nausea (Golding et al., 1997;
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22 181 2018) and vomiting (Golding et al., 2017). More detailed studies are now required,
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25 182 investigating for example, the effects of NK₁RA on the physiological changes accompanying
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27 183 motion sickness such as the reduced gastric antral contractile activity (Faas et al., 2001), a
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29 184 pathway of potential relevance to understanding the effects of NK₁RAs in gastrointestinal
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31 185 conditions associated with nausea, such as gastroparesis (see below).

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35 186 From these very limited data, we tentatively conclude that NK₁RAs are effective against
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37 187 *vomiting* induced by abnormal motion but are less effective against *nausea*.

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41 188 **3.2 Chemotherapy-induced nausea and vomiting.** We focus on NK₁RA use in the acute and
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43 189 delayed phases of highly emetogenic chemotherapy (HEC) discussing their effects against
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45 190 vomiting before effects against nausea.

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49 191 A study of CINV in seven patients given CP-122,721 *alone* showed that in the acute phase (first
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51 192 24h) of HEC five patients had ≤2 episodes v. 7 episodes of “emesis” in an historic control group
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53 193 and in the delayed phase, 6 had no emesis (Kris et al., 1997). A larger study with L-758, 298
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55 194 (the prodrug for the NK₁RA, aprepitant [L-754,030]) showed that 37% of patients (n=30) had
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57 195 no vomiting or retching in the acute phase, compared with 52% of patients in an ondansetron
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3 196 (5-HT₃RA) group (n=23; not significantly different) (Cocquyt et al., 2001). However, confining
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6 197 analysis to the first 8h following cisplatin showed 37% of patients had no vomiting or retching
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8 198 in the NK₁RA group compared to 83% in the 5-HT₃RA group ($P=0.001$) but in the delayed phase
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10 199 72% of patients were without vomiting or retching in the NK₁RA group vs 30% in the
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12 200 ondansetron group ($P=0.005$) (Cocquyt et al., 2001). This study suggests a shift in the relative
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14 201 involvement of 5-hydroxytryptamine₃ (5-HT₃) and NK₁ receptors driving retching and
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16 202 vomiting between the acute and delayed phases following cisplatin, a finding confirmed by
17
18 203 detailed time course analysis of the efficacy of aprepitant, L-758, 298, ondansetron and
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20 204 granisetron in treatment of CINV (Hesketh et al., 2003).

25 205 Recent meta-analyses demonstrate additional protection against vomiting when NK₁RAs are
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27 206 given with a 5-HT₃RA and dexamethasone during both acute and delayed phases in HEC (~15-
28
29 207 20% more complete protection), with a greater effect in the delayed phase (Jordan et al.,
30
31 208 2016; Yokoe et al., 2019; Qiu et al., 2020).

35 209 Overall, and despite an ability of NK₁RAs to further reduce the incidence of vomiting during
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37 210 the acute phase when combined with a 5-HT₃RA and dexamethasone, the incidence of nausea
38
39 211 is not further reduced during this phase. For example, an initial study with L-754,030 showed
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41 212 a clear additional effect on vomiting in the acute phase following cisplatin when added to a
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43 213 5-HT₃RA/dexamethasone regimen (Kris et al., 1997), but no difference in the median nausea
44
45 214 score. An analysis of the Phase III studies of NK₁RAs added to a 5-HT₃RA and dexamethasone
46
47 215 regime in HEC, found no consistent evidence for an improvement in the incidence of “no
48
49 216 significant nausea” (NSN) or “no nausea” (NN) in the acute phase (Bošnjak et al., 2017). For
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51 217 example, the percentage of patients experiencing “no nausea” in the NK₁RA arm v. placebo
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53 218 in the acute phase was 53.6% v. 52% (Roila et al., 2014), 65% v. 66% (Schwartzberg et al.,
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219 2015), 68% vs 61% (Study 2, Rapoport et al., 2015; statistically significant) and 73% vs 68%
220 (Study 1, Rapoport et al., 2015). A pooled analysis of studies with rolapitant showed a small
221 but statistically significant increase in the percentage of patients reporting NN (respectively,
222 64% and 70%) in the acute phase of HEC (Bošnjak et al., 2017). Saito et al., (2013) found a
223 tendency for the incidence of NSN to increase (90.2% v. 84.9%) when using intravenous
224 fosaprepitant (150mg+granisetron/dexamethasone) in patients receiving high-dose cisplatin,
225 although the difference was not statistically significant and the NN incidence was unchanged
226 (67.6% vs. 67.5%) compared to placebo.

227 Some, but not all, studies reported that during the delayed phase the addition of an NK₁RA
228 significantly increased the percentage of patients reporting NN or NSN. In the initial study
229 with L-754,030 (\pm placebo+ granisetron/dexamethasone; Navari et al., 1999) the median
230 nausea score was reduced on a 100mm VAS (higher score indicating more severe nausea)
231 from 19mm to 1mm on day 2 and over days 2-5 from 10mm to 1mm. Similarly, others
232 reported that the percentage of patients experiencing NN in the NK₁RA arm vs placebo in the
233 delayed phase increased significantly: 52.7% v. 39.9% (Poli-Bigelli et al.,2003), 53% v. 42%
234 (Study 1, Rapoport et al., 2015) and 58% v. 47% (Study 2, Rapoport et al., 2015). However,
235 some showed no statistically significant change in NN (e.g., 43.9% vs 49.1%, Roila et al., 2014;
236 71.4% v. 73%, Roila et al., 2015; 48% v. 45%, Schwartzberg et al., 2015). A pooled analysis of
237 studies using rolapitant showed a significant 12% increase in the NN percentage (44% v. 56%)
238 in the delayed phase (Bošnjak et al., 2017).

239 A recent meta-analysis investigated the addition of aprepitant to a 5-HT₃RA/dexamethasone
240 regimen in patients (only 258 in the final analysis) receiving HEC treatments for lung cancer
241 (He et al., 2021). While the overall complete response rate (no vomiting/no rescue

242 medication) was significantly better when aprepitant was given, the NN rate was not
243 statistically significantly different (although significant in two of the studies included in the
244 analysis; Dupuis et al., 2020; Yokoe et al., 2019).

245 In summary, there is insufficient data to compare different NK₁RAs, but it is possible to draw
246 general conclusions about their efficacy in HEC:

- 247 i) NK₁RAs further reduce the incidence of vomiting during the acute phase when
248 combined with a 5-HT₃RA and dexamethasone, but the effect is more marked in
249 the delayed phase of HEC.
- 250 ii) When added to a 5-HT₃RA/dexamethasone regime, any ability of NK₁RAs to further
251 reduce the incidence of nausea appears inconsistent and in one meta-analysis the
252 NN rate was not statistically significant.

253 3.3. Post-operative nausea and vomiting.

254 **Table 2** summarises the effects of NK₁RAs in PONV using the outcome from studies reporting
255 nausea and vomiting separately to illustrate the efficacy differences. Overall, several NK₁RAs
256 show efficacy against post-operative *vomiting* in a proportion of patients but the block is not
257 complete in all patients and, the efficacy against *nausea* is inconsistent (e.g., small changes in
258 incidence, inconsistent change in intensity, **Table 2**) and lower than against vomiting. A
259 Cochrane meta-analysis examined the efficacy of diverse pharmacological agents in treating
260 *vomiting* in the first 24h (Weibel et al., 2020) and concluded that *single* NK₁RAs were as
261 effective as other *drug combinations*. The analysis did not compare efficacy against nausea.
262 Assessment of the overall efficacy of NK₁RAs against PONV is complicated by the variety of
263 types or surgery (e.g., open abdomen, laparoscopic) and anaesthesia/analgesia protocols. A
264 further issue is that in studies where a range of doses has been investigated the relationship

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3 265 between NK₁RA dose and efficacy against either nausea or vomiting is not always clear (e.g.,
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5 266 casopitant, Singla et al., 2010; rolapitant, Gan et al., 2011; vestepitant, Kranke et al., 2015).
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9 267 **3.4. Cyclical vomiting syndrome.** An open-label uncontrolled trial of aprepitant in a paediatric
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11 268 population refractory to conventional treatment showed reduction in the number of cyclic
12
13 269 vomiting episodes/year and number of vomits/h (Cristofori et al., 2014). Although nausea is
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16 270 a feature of CVS it was not assessed in this study.
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19 271 **3.5. Paediatric patients with life-limiting conditions.**

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22 272 A case series showed aprepitant (2.0-2.5mg/kg, i.v.) was effective in complete resolution of
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24 273 nausea (parental reports of impact on mobility and feeding used as proxy efficacy markers) in
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26 274 paediatric patients receiving palliative care, with different diagnoses and unresponsive to at
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29 275 least two drugs classified as 'anti-emetics' (e.g., cyclizine, ondansetron, metoclopramide,
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31 276 levomepromazine; Patel et al., 2021). Additionally, aprepitant increased the ability to tolerate
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34 277 feeds as might be expected from the proposal that food refusal in children could be used as
35
36 278 a surrogate marker for nausea (Richards & Andrews, 2004), although NK₁RA-induced changes
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39 279 in gastric accommodation (Jacob et al., 2017) offers an alternative explanation.
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42 280 **3.6. Gastric distension induced sensations and gastroparesis.**

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45 281 In healthy human volunteers a single dose of aprepitant (80 or 125mg) had no effect on gastric
46
47 282 compliance or sensitivity to distension (Ang et al., 2013). Also, in healthy volunteers,
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49 283 aprepitant (125mg p.o. day 1 + 80mg p.o. days 2-5) did not affect gastric emptying of liquids
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51
52 284 or solids, intestinal or colonic transit (Madsen & Fuglsang, 2008). Using the same repeat
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54 285 dosing schedule but following a 'dyspeptogenic' meal, Jacob et al. (2017) confirmed no
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57 286 change in gastric emptying with aprepitant but found a modest increase in fasting (~10%),
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59 287 postprandial (~9%) and gastric accommodation (~5%) volumes, and a tendency to increase
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3 288 maximal tolerated volume (~25%). Interestingly, the aggregate symptoms, nausea, and pain
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6 289 scores (but not bloating or fullness) increased significantly following the 'dyspeptogenic' meal
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8 290 in the aprepitant group compared to placebo (median 36 v. 4).
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11 291 A four-week placebo-controlled study of aprepitant (125mg/day, p.o.) involving 126 patients
12
13 292 failed to demonstrate an improvement in the primary outcome measure of nausea (Pasricha
14
15 293 et al., 2018), in a population with 57% gastroparesis patients and the remainder with Chronic
16
17 294 Unexplained Nausea and Vomiting (CUNV). The study also used the Gastroparesis Clinical
18
19 295 Symptom Index (GCSI; Revicki et al., 2004) to assess symptom severity as a secondary
20
21 296 outcome and this showed significant reductions in overall symptom score (1.3 v. 0.7),
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23 297 vomiting (1.6 v. 0.5 [69% decrease]) and nausea (1.8 v. 1 [44% decrease]). The number of
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25 298 hours per day when nausea was experienced, was reduced and the proportion of nausea-free
26
27 299 days increased (~ twofold).
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33 300 A placebo-controlled trial of 152 patients with idiopathic or diabetic gastroparesis and
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35 301 moderate-to-severe nausea, investigated tradipitant (85mg orally) twice daily (daily total
36
37 302 170mg) for 4 weeks (Carlin et al., 2020). The trial met the primary outcome measure of a
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39 303 reduction in average daily diary nausea score measured using the GCSI Daily Diary with a
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41 304 difference in score reduction between placebo and tradipitant of ~10%. Nausea severity
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43 305 appeared to begin decreasing by week 2 and this was statistically significant by week 3.
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45 306 Additionally, tradipitant increased secondary outcomes of nausea free days (~14%>placebo)
46
47 307 and nausea response rate (~21%>placebo). Patients who responded to tradipitant with a
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49 308 reduction in nausea also had improved early satiety, excessive fullness, bloating and upper
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51 309 abdominal pain, compared to placebo. Two case reports involving single patients with
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3 310 gastroparesis report stoppage of previously intractable nausea (Fahler et al., 2012) or
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6 311 vomiting (Chong & Dhatariya, 2009) on administration of aprepitant.
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9 312 A recent systematic review and network meta-analysis of drugs used to treat gastroparesis
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11 313 showed that NK₁RAs were efficacious (RR=0.69) using global symptom score. When individual
12
13 314 symptoms were assessed tradipitant was more effective than placebo in treating nausea
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15 315 (tradipitant RR=0.77; 95% CI 0.65-0.91) (Ingrosso et al., 2023). By contrast, a recent phase III
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17 316 trial of tradipitant in gastroparesis showed no difference from placebo in the intensity of
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19 317 nausea over a 12 week period (Vanda, 2022).
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25 26 319 **3.7. Overview of clinical efficacy against nausea versus vomiting.**

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29 320 Summarising sections 3.1 to 3.6, NK₁RAs can block vomiting induced by HEC (± 5HT₃RA and
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31 321 dexamethasone) and PONV, and with much more limited evidence perhaps also the vomiting
32
33 322 associated with CVS and motion-induced vomiting. NK₁RAs do not block vomiting in all
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35 323 patients/subjects exposed to a given stimulus and for CINV the efficacy may depend on the
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37 324 phase (potentially, delayed>acute). When nausea is assessed, several studies report no
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39 325 significant benefit although there is some evidence that even if not completely blocking
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41 326 nausea NK₁RAs may reduce its intensity (e.g., see PONV data, **Table 2**). Overall, however, the
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43 327 NK₁RAs are less efficacious or have more variable efficacy against nausea than vomiting over
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45 328 the same range of stimuli but more quantitative data are needed.
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52 329 We now attempt to explain this differential effect by a detailed analysis of the sites at which
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54 330 NK₁RAs could act to affect vomiting (section 4) and nausea (section 5).
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3 332 **4. Potential site(s) of action of NK₁RA against retching and vomiting (Figure 3).**
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6 333 The sites at which NK₁RA block retching and vomiting have been investigated in animals
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8 334 (primarily dog and ferret). The findings of these studies are included here because the
9
10 335 afferent, integrative and motor pathways responsible for vomiting are comparable between
11
12 336 animals (e.g., dog, ferret; Onishi et al., 2007) and humans (Stern et al., 2011). For each
13
14 337 potential site of action, we will consider whether it could account for a 'broad spectrum'
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16 338 effect against vomiting or whether it can only explain an action against vomiting induced by
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18 339 a specific stimulus or pathway. This analysis also provides an essential background for
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20 340 understanding the differential effects against nausea.
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26 341 **4.1.1. Vestibular system.** The vestibular system is essential for induction of nausea and
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28 342 vomiting caused by abnormal body motion. From an evolutionary perspective the vestibular
29
30 343 system is considered a component of the mechanisms protecting the body against ingested
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32 344 toxins (see Treisman 1977, Money & Cheung, 1983, Oman, 2012; Lackner, 2014). Although
33
34 345 sensitivity to motion sickness is a predictive factor for both CINV and PONV (Gan, 2006; Warr,
35
36 346 2014) there is no evidence that the vestibular system (including vestibular nuclei) is directly
37
38 347 implicated in the induction of either. During motion sickness, the motor pathways for
39
40 348 vomiting are activated via projections of the vestibular nuclei to the medial and caudal
41
42 349 nucleus tractus solitarius (NTS) (studies in the cat; Yates et al., 1994; Sugiyama et al., 2011).
43
44 350 There is no evidence that NK₁RAs affect transmission in the pathway between the vestibular
45
46 351 system, the vestibular nuclei and the NTS, to block induction of vomiting. This contrasts with
47
48 352 the actions on this pathway of H₁ and mACh (M₃/ M₅) receptor antagonists, used to treat
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50 353 motion sickness (Soto & Vega, 2010; Golding & Stott, 1997; Golding et al., 2018). An action of
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3 354 NK₁RAs within the NTS or at a site(s) deeper in the brainstem is therefore the most likely site
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6 355 for effects against motion-induced vomiting.
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9 356 **4.1.2. Area postrema (AP).** The AP projects to neurones in the medial NTS (mNTS) which can
10
11 357 be activated by emetic stimuli applied to the AP (e.g., apomorphine, L-glutamate) and by vagal
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13 358 afferent stimulation (dog studies; Koga & Fukuda, 1992). However, the evidence that NK₁
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15 359 receptors occur within the AP is weak, and their functional relevance uncertain. For example,
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17
18 360 low levels of [³H]-substance P binding displaced by CP-99,994 (0.1nM-100nM) were found in
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20
21 361 the ferret AP, as compared to the NTS (particularly subnucleus gelatinosus) (Watson et al.,
22
23 362 1995). Ariumi et al. (2000) reported dense ³H-substance P binding in the AP and NTS of ferret
24
25 363 but displacement by an NK₁RA was not studied. Comparable evidence is available for *Suncus*
26
27 364 *murinus* and rat (Maubach et al., 1997; Andrews & Rudd, 2004). Iontophoretic application of
28
29 365 substance P (SP) activated ~50% of AP neurones tested (dog; Carpenter et al., 1988), but
30
31 366 although assumed to play a role during vomiting induced by intravenously-administered SP
32
33 367 (dog; Carpenter et al., 1984), the receptor type activated by the applied concentration of SP
34
35 368 and the link between activation and vomiting was not identified. In the ferret, application of
36
37 369 SP to the AP can evoke vomiting (Andrews & Rudd, 2004) but microinjection studies (Gardner
38
39 370 et al., 1994) suggest that this response was probably due to SP penetration to the subjacent
40
41 371 NTS as the blood-brain barrier between these two areas may have some permeability. A
42
43 372 similar explanation of leak into the NTS may account for the block in morphine (s.c.) and
44
45 373 reduction in copper sulphate (intra-gastric) induced vomiting in the ferret by administration
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47 374 of CP-99,994 or HSP-117 into the AP (Ariumi et al. 2000).
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55 375 It is a possibility that NK₁ receptors in the AP could be activated if SP (or other tachykinins)
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57 376 are released from gut enteroendocrine cells (EEC; Rezzani et al., 2022) to enter the blood
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1
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3 377 circulation in addition to acting more locally. However, the evidence for this possibility in
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5
6 378 response to emetic stimuli is weak. Thus, in patients undergoing chemotherapy, the elevation
7
8 379 of serum concentrations of SP during the delayed phase of vomiting was inconsistent (Higa et
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11 380 al., 2006, 2012; Matsumoto et al., 1999; Park et al., 2020; Takahashi et al., 2011) although this
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13 381 is the phase during which NK₁RA are most effective (see above).

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15
16 382 Another possibility is that SP could arise from neurones intrinsic to the AP following direct
17
18 383 activation by endogenous or exogenous emetic substances or by abdominal vagal afferents
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21 384 projecting to the AP. However, SP-like immunoreactivity (SP-Li) was absent in the AP of a
22
23 385 human infant (Rikard-Bell et al., 1990), consistent with the absence of SP-Li cell bodies in the
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25
26 386 AP of adult cat, rat (Newton et al., 1985) and ferret (Boissonade et al., 1996). Previously,
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28 387 extraction studies in humans found some SP in the AP (Zettler & Schlosser, 1955; Cooper et
29
30
31 388 al., 1981) and radioligand binding showed a “moderate” uptake of an NK₁RA by the human
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33 389 AP (Hietala et al., 2005). Sparse SP-Li nerve fibres have been found in the AP (cat, rat) but
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35
36 390 their origin is most likely from either vagal nerve afferents terminating there or from the NTS
37
38 391 (Newton et al., 1985); this is consistent with the finding of high-densities of SP
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41 392 immunoreactive fibres in lateral borders of the AP in the ferret (Boissonade et al., 1996).
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43 393 However, in the least shrew SP-Li fibres and puncta were present at a “moderate” level in the
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45
46 394 AP (Ray & Darmani, 2007).

47
48 395 Finally, it is worth noting that the concept of the AP as a site at which systemic agents act to
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51 396 induce nausea and vomiting was originally derived from studies showing abolition of vomiting
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53 397 induced by apomorphine (a dopamine D₂ receptor agonist), following surgical ablation of the
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56 398 AP including in humans (Lindstrom & Brizzee, 1962; Borison & Wang, 1953). Similarly, other
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58 399 exogenously administered agents (e.g., morphine, loperamide, cisplatin) can induce emesis
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3 400 via the AP (Borison, 1989; Bhandari et al., 1992; Percie du Sert et al., 2009). However, there
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6 401 is only limited evidence that systemic endogenous agents which can induce vomiting (e.g.,
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8 402 adrenaline, cholecystokinin [CCK], GDF15, vasopressin), act via the AP, with alternative sites
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10 403 of action suggested (Borison, 1989; Borner et al., 2020; Makwana et al., 2022). The above
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12
13 404 discussion suggests that SP, acting via NK₁ receptors in the AP should be added to the list of
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15 405 systemic endogenous emetic agents.

18 406 **4.1.3. Abdominal vagal afferents.**

21 407 There are two sites at which vagal afferent activation by emetic stimuli could be affected by
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23
24 408 an NK₁RA; they are not mutually exclusive (**Figure 3**).

26 409 **4.1.3.1. The peripheral transduction mechanism.** A potential ability of SP from
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29 410 enterochromaffin cells (ECs) to induce vomiting by acting on vagal afferents was hypothesised
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31 411 >30 years ago (Andrews et al., 1988; for details see Andrews & Rudd, 2004). Potentially, such
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34 412 a mechanism would be similar to that for 5-HT, which is released from ECs in response to
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36 413 chemotherapeutic agents (e.g., cisplatin) and other emetic stimuli (e.g., rotavirus), causing
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39 414 vomiting by stimulating and sensitizing abdominal vagal afferent terminals via 5-HT₃ receptor
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41 415 activation (Andrews & Rudd, 2015; Sanger and Andrews, 2018; for reviews). In rats, treatment
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44 416 with methotrexate or cisplatin increased the number of SP-containing ECs within the
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46 417 intestine, 24h after administration (Machida et al., 2017; Obara et al., 2018) but studies have
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48
49 418 not yet looked for local release of SP from ECs in response to anti-cancer chemotherapeutic
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51 419 agents or other emetic stimuli. By analogy with 5-HT (see above), any release of SP might be
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53
54 420 expected to activate vagal nerve terminals. Recently, SP (1µM)-induced depolarisation of
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56 421 human isolated vagus was shown to be blocked by aprepitant (Smith et al., 2021). However,
57
58 422 the authors used a concentration (10µM) at least 10000x the human NK₁ receptor binding
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3 423 IC_{50} , at or above the concentrations examined for selectivity of action (Tattersall et al., 2000),
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6 424 and now understood to also activate the mechanosensitive two-pore domain potassium
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8 425 channel, TRAAK (encoded by the *KCNK4* gene) (McCoull et al., 2022). Interestingly, recordings
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10 426 from abdominal vagal afferents of ferrets show an interaction between 5-HT and SP (Minami
11
12 427 et al., 2001) and 'cross talk' has been demonstrated between NK_1 and 5-HT₃ receptors in
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14 428 relation to the 'anti-emetic' effect of palonosetron (Rojas et al., 2014).

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18 429 **4.1.3.2. Vagal afferent to NTS transmission.** Abdominal vagal afferents terminate in the
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20 430 mNTS (Fukuda & Koga, 1992). There is evidence that SP is a transmitter from vagal afferents
21
22 431 to NTS neurones (cat, Baude et al., 1989; dog, Shiroshita et al., 1997) and for activation of NTS
23
24 432 neurones by iontophoretically applied SP (ferret, Saito et al., 1998; rat, Maubach & Jones,
25
26 433 1997). However, any action of NK_1RA on vagal to NTS transmission must be selective for
27
28 434 afferents involved in induction of vomiting as NK_1RA s do not block the gag reflex, the cardiac
29
30 435 or respiratory components of the von Bezold-Jarisch reflex or apnoea induced by cervical
31
32 436 vagal afferent stimulation (Watson et al., 1995; Fukuda et al., 1999). Additionally, while
33
34 437 systemic administration of the NK_1RA , CP-99,994 in the anaesthetised ferret blocked licking,
35
36 438 swallowing and retching induced by electrical stimulation of the abdominal vagal afferents,
37
38 439 the accompanying rise in blood pressure was unaffected (Watson et al., 1995). This makes it
39
40 440 unlikely that vagal to NTS transmission *per se* is blocked and suggests that the block is either
41
42 441 within the NTS integrative pathways which initiate vomiting or on the output side of the
43
44 442 system in the 'central pattern generator' (CPG) for vomiting located in the reticular formation
45
46 443 dorsomedial to the retrofacial nucleus (Böttinger complex) in the region of the NA (compact
47
48 444 region) and the associated 'prodromal sign centre' (PSC in the semi-compact area of the
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50 445 nucleus ambiguus (Fukuda & Koga, 1991, 1992; Fukuda et al., 2003). Further support for a
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52 446 specific activity on some but not all vagal functions comes from studies in the decerebrate

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3 447 dog where the NK₁RA, GR-205171 (i.v.) blocked fictive retching, the accompanying antral
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6 448 contractile response (most likely the extension of the Retrograde Giant Contraction (RGC) that
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8 449 originates in the small intestine and immediately precedes the onset of retching mediated by
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10 450 vagal efferents; see Lang et al., 1986; Lang, 1990), and reduced the hypersalivation (mediated
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12
13 451 by PSC) evoked by vagal afferent stimulation, but not the accompanying vagal efferent
14
15 452 mediated relaxation of the proximal stomach (Furukawa et al., 1998).

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18 453 It is self-evident that blockade of vagal afferent activation at a peripheral site or vagal afferent
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21 454 transmission to the mNTS would only contribute to the anti-vomiting effects of NK₁RAs when
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23 455 the primary stimulus activates the vagus (e.g., acute phase of CINV, possibly gastroparesis;
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25 456 Sanger & Andrews, 2023). Therefore, a vagal site of action would not account for block of
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28 457 stimuli acting only either via the AP or the vestibular system so additional site(s) of action
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30
31 458 need to be considered.

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33 459 **4.1.4. Brainstem integrative mechanism and the drive to the visceral and somatic motor**
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35
36 460 **outputs.** The selective effects of NK₁RA on reflex responses to vagal afferent stimulation (as
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38 461 above) show that actions of NK₁RA within the brain stem integrative pathways (i.e. NTS, CPG,
39
40 462 ventral respiratory group [VRG]) are selective to neurones involved in the 'vomiting motor
41
42 463 programme' occurring as a result of reconfiguration of the pattern of activity in the
43
44 464 multifunctional respiratory neurones (Grélot & Bianchi, 1997; Grélot & Miller, 1997) (c.f.
45
46 465 cough, yawn, sneeze). These same sets of neurones can also be driven to evoke vomiting by
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48 466 stimuli acting on the vestibular system and the AP (**Figure 4**). Thus, the effects of NK₁RAs on
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50
51 467 the brainstem pathways are 'state dependent' and this can explain the selectivity of effects
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53
54 468 against vomiting; when the brainstem is involved in baseline respiration and some respiratory
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3 469 reflexes there is little dependence on SP as a transmitter but when the pathway reconfigures
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6 470 and is highly active as occurs for vomiting then it becomes critically dependent on SP.
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9 471 Overall, there is evidence for either the presence of SP positive neurones and/or NK₁
10
11 472 receptors in the key brainstem sites implicated in vomiting.
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14 473 **4.1.4.1. Nucleus tractus solitarius.** SP-like immunoreactive neurones are present in the
15
16 474 human NTS, particularly subnucleus gelatinosus (mNTS) and this is consistent with studies in
17
18 475 both the cat and ferret (Leslie, 1985; Boissonade et al., 1996). A human brain PET study using
19
20 476 a fluorine-18 labelled NK₁RA reported 'moderate' uptake in the NTS, the nucleus ambiguus
21
22 477 and "other nuclei of the vagus" (not specified) (Hietala et al., 2005).
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25
26 478 A site of action within the NTS is supported by studies showing microinjection of CP-99,994 in
27
28 479 the "region of the NTS" inhibited, but did not completely block, cisplatin-induced acute
29
30 480 retching and vomiting in the ferret (Gardner et al., 1994; Tattersall et al., 1996). An important
31
32 481 point is that the NK₁RA was injected after retching/vomiting began showing that the
33
34 482 antagonist was blocking a pathway driven by ongoing NK₁ receptor activation. The peptide
35
36 483 NK₁RA, GR-82334 was ineffective against cisplatin-induced retching/vomiting when given
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38 484 intravenously but was effective (77% reduction) when given into the NTS (Gardner et al.,
39
40 485 1994). Rupniak et al (1997) correlated anti-emetic activity against cisplatin in the ferret with
41
42 486 central penetration using a range of NK₁RAs with differing brain penetration. These studies
43
44 487 argued strongly that central penetration (at least to the NTS) is required for the acute anti-
45
46 488 emetic effect of an NK₁RA. Further support for an action of NK₁RA in the NTS comes from
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48 489 inhibition of SP (1µM)-induced discharge in NTS slices by the NK₁RA HSP-117 (10µM), without
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50 490 affecting baseline spontaneous neuronal discharge (ferret, Saito et al., 1998).
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3 491 **4.1.4.2. Dorsal motor vagal nucleus.** NK₁ receptors are present in the dorsal motor vagal
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6 492 nucleus (DMVN; ferret, Watson et al., 1995), the site of origin of vagal efferents supplying the
7
8 493 upper digestive tract and regulating the proximal gastric relaxation and RGC prior to the onset
9
10 494 of retching and vomiting (Lang, 1990). In the rat, neurones in the DMVN responsive to gastric
11
12 495 distension±24h post-cisplatin had their baseline activity altered by CP-99,994 (5µM) (Sun et
13
14 496 al., 2017) but the results should be interpreted with caution as the efferent projection (e.g.,
15
16 497 the stomach) of the neurones was not identified (e.g., using antidromic collision, Andrews et
17
18 498 al., 1980) and the effects of CP-99,994 were not controlled for by using its less potent 2R, 3R
19
20 499 enantiomer, CP-100,263 (Watson et al., 1995). Although these studies show that the DMVN
21
22 500 is a potential target for NK₁RA it should be noted that preventing the gastric relaxation and
23
24 501 RGC will not block retching and vomiting as they can occur even in the absence of the stomach
25
26 502 (Magendie, 1813) and when the RGC is blocked by atropine (Lang et al., 1986). An action of
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28 503 NK₁RA on the DMVN is therefore unlikely to explain their anti-vomiting action.
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35 504 **4.1.4.3. Ventral brainstem.** Neurophysiological studies of fictive emesis in the dog implicate
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37 505 nuclei in the ventral brainstem (Fukuda & Koga, 1991, 1992; Fukuda et al., 2003; Onishi et al.,
38
39 506 2007). When administered systemically, the NK₁RA, GR-205171 reduces vagal afferent
40
41 507 activation (via the mNTS) of the CPG for vomiting and/or in the pathway linking the NTS to
42
43 508 the CPG via the PSC (Fukuda & Koga, 1991, 1992); immunohistochemistry has demonstrated
44
45 509 the presence of NK₁ receptors in both regions of the dog ventral brainstem (Fukuda et al.,
46
47 510 2003). The CPG connects with the VRG, the location of the neurones driving the phrenic and
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49 511 abdominal motor neurones involved in normal respiration as well as retching and vomiting
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53
54 512 **(Figure 4).**
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3 513 Total block of transmission at either the NTS or CPG is probably not required to stop induction
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6 514 of vomiting; a *reduction* in transmission at either site is likely to be sufficient as triggering
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8 515 vomiting requires a higher frequency stimulus which also lasts for an extended time (e.g.,
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10 516 ~20s of vagal afferent stimulation is required in dog [Koga & Fukuda, 1992] and ferret
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12
13 517 [Andrews et al., 1990]), presumably to prevent inappropriate triggering. It is particularly
14
15 518 notable that NK₁RAs prevent the 'wind-up' of CPG neurones induced by vagal afferent
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17
18 519 stimulation and blunts the rise in firing frequency when continuous vagal afferent stimulation
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20 520 is used, preventing the CPG reaching a threshold for induction of the oscillatory activity
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23 521 required for retching and vomiting (Fukuda et al., 1999, 2003) (**Figure 5**).

24 25 26 522 **4.1.5. Overview of site(s) of action against vomiting**

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28
29 523 The clinically used NK₁RAs are brain penetrant so when given systemically they can act at both
30
31 524 the central and peripheral neuronal sites involved in retching and vomiting:

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34 525 i) For vomiting induced by abnormal motion, the brainstem integrative pathways
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36 526 (NTS, CPG) are the most likely site of action.
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38
39 527 ii) For stimuli involving abdominal vagal afferents it is possible that NK₁RA can a)
40
41 528 block effects of any SP released from EEC cells onto NK₁ receptors on the
42
43
44 529 peripheral afferent nerve terminals (Minami et al., 2001); b) reduce
45
46 530 tachykininergic transmission between vagal afferents and the NTS (Fukuda et
47
48
49 531 al., 2003; Andrews & Rudd, 2004); c) modulate the brainstem integrative
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51 532 pathways (NTS, CPG) sufficiently to disrupt the signals encoding induction of
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53
54 533 vomiting (Fukuda et al., 1999, 2003; Fukuda & Koga, 1991, 1992; Watson et al.,
55
56 534 1995) . At present, the evidence for (b) and (c) is stronger.
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3 535 iii) For stimuli acting on the AP via the circulation (or cerebrospinal fluid) including
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6 536 exogenous emetics and endogenous substances released for example from the
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8 537 digestive tract because of damage/inflammation (e.g., during the delayed
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10 538 phase of CINV and chronic phases of infection) (Sanger & Andrews, 2018;
11
12
13 539 Andrews et al., 2021, 2023 for references), the brainstem integrative
14
15 540 mechanisms (NTS, CPG) are the most likely sites at which vomiting is affected
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17
18 541 as there is little evidence for an action within the AP itself.

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20
21 542 The NTS and CPG sites of action of NK₁RA are common to all stimuli inducing vomiting.
22
23 543 However, for stimuli where abdominal vagal afferent activation occurs two additional sites of
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25 544 action are implicated which, if operational, would block vagal afferent input and thereby
26
27 545 make it unnecessary for NK₁RA to act within the NTS and CPG. However, although the NK₁RA
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29 546 are highly effective against vomiting in a number of clinical settings, NK₁ receptors are not the
30
31 547 only receptors involved in all of the pathways and this may explain why they may not always
32
33 548 be fully effective in all patients. For example, SP is likely to co-transmit with a non-peptide
34
35 549 (e.g., glutamate) with the former likely to be released by a higher frequency or different
36
37 550 pattern of nerve firing (Svensson et al., 2019). Further, glutamate has been implicated in
38
39 551 abdominal vagal afferent to mNTS transmission as NBQX blocked vagal afferent-induced
40
41 552 retching in dog and ferret and the resulting mNTS activation in the dog (Furukawa et al., 2001;
42
43 553 Onishi et al., 2007). Nevertheless peptides, as co-transmitters, are known to be involved in
44
45 554 network reconfiguration with release determined by both neuronal firing pattern and time
46
47 555 (Cropper et al., 2018). Variations in the predominant transmitters in the nausea and vomiting
48
49 556 pathways, possibly as a response to disease, especially if chronic (e.g., in chronic visceral pain
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51 557 NK₁ receptor availability is downregulated; Jarcho et al., 2013), may also contribute to NK₁RAs
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53 558 spectrum of clinical efficacy.
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5. The potential site(s) of NK₁RA action against nausea

'Anti-emetics' must not be assumed to equally affect both nausea and vomiting (Sanger & Andrews, 2022). Accordingly, we discuss the relative effects of NK₁RA 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 is not available to answer all the questions raised, so some answers are speculative and hypothetical but experimentally testable.

5.1. What information reaches the mNTS from the abdominal vagal afferents in the presence of NK₁RAs?

This question is relevant to both CINV and gastroparesis where abdominal vagal afferents are implicated in genesis of nausea and vomiting (Sanger and Andrews, 2018, 2023). Regardless of whether NK₁RAs reduce vagal afferent firing by acting peripherally (e.g., Minami et al., 2001) or centrally (e.g., Fukuda et al., 2003), 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 Horn 2014 for discussion in relation to the vagus). The effects of NK₁RAs on vagal afferent activity evoked by a wide range of stimulus intensities, \pm substances which may sensitise 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 (Ottaviani et al., 2020).

5.2. Do differential effects of NK₁RAs on the NTS account for the differential effects against nausea and vomiting?

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3 582 NK₁RA modulation of the vagal afferent drive to the mNTS and/or transmission within the NTS
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5
6 583 (vagal, AP and vestibular inputs) could contribute to a *reduction* in nausea *intensity* by
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8 584 decreasing the drive from the NTS to supra-medullary structures implicated in the sensation
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10 585 of nausea. However, the evidence for such an action is poor, as discussed below.

13 586 **5.3. Are NK₁ receptors in the mid-brain and cerebral hemispheres involved in potential anti-**
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15
16 587 **nausea effects of NK₁RA?**

18 588 In contrast to vomiting, the brain pathways responsible for nausea are not well defined. The
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20
21 589 majority of brain imaging studies are in subjects reporting nausea induced by illusory-self
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23
24 590 motion (vection; visually-induced motion sickness, VIMS), with only single studies using 'real'
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26 591 motion or a pharmacological challenge (see Varangot-Reille et al., 2023) making it difficult to
27
28 592 assess whether the findings have general applicability. Cortical and sub-cortical areas
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30
31 593 consistently showing an increase in activity in healthy volunteers reporting nausea include
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33
34 594 the frontal lobe (e.g., anterior cingulate cortex), occipital lobe (e.g., posterior cingulate
35
36 595 cortex), temporal lobe (e.g., amygdala, part of the 'limbic cortex') and basal ganglia (e.g.,
37
38 596 putamen) (Varangot-Reille et al., 2023).

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41 597 NK₁RA binding in the human brain using PET shows NK₁ receptors in several brain areas
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44 598 implicated in nausea. For example, aprepitant has receptor occupancy of 50% in the caudate
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46 599 and 90% in the putamen (basal ganglia) at plasma concentrations of $\sim 2 \times 10^{-9}$ M and $\sim 2 \times 10^{-8}$
47
48 600 M respectively (Bergstrom et al., 2004). Based on the striatal occupancy levels, the authors
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51 601 concluded that the recommended 'anti-emetic' aprepitant regime of 125mg on day 1 and
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53 602 80mg on the subsequent two days in CINV would result in an occupancy of >90% (Bergstrom
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55 603 et al., 2004). Hietala et al., (2005) using the same radioligand confirmed the highest uptake in
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58 604 the caudate and putamen and levels $\sim 50\%$ in regions of the occipital lobe (e.g., posterior
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3 605 cingulate cortex), temporal lobe (e.g., amygdala [forms the 'limbic cortex' with the
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6 606 hippocampus]) and frontal lobe (anterior cingulate cortex) all of which have been implicated
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8 607 in nausea in brain imaging studies (Varangot-Reille et al., 2023).
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11 608 Pharmacological MRI studies provide additional unexpected insights. Using fosaprepitant
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13 609 (pro-drug of aprepitant) the NK₁ receptor distribution profile identified in the above PET
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16 610 studies was confirmed but in addition identified *activation* of brain areas (e.g., cerebellum,
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18 611 red nucleus) where there were thought to not be any NK₁ receptors, an effect attributed to
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21 612 "downstream pharmacodynamic effects" (Borsook et al., 2012, Fig. 2; Upadhyay et al., 2011).
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23 613 Such effects demonstrate that in identifying brain sites of drug action we should not only
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26 614 consider regions which have their activity inhibited; activation of a pathway which itself is
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28 615 inhibitory on the function under consideration should not be overlooked. Brain imaging
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31 616 studies in nausea have identified areas with both *increased* and *decreased* activity (Farmer et
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33 617 al., 2015).
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36 618 Although we focus on areas directly implicated in nausea, as nausea involves heightened
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38 619 anxiety, the potential anxiolytic effects of NK₁RA (Hoppe et al., 2018) could indirectly
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41 620 contribute to reducing nausea scores especially in chronic conditions (e.g., gastroparesis).
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44 621 Overall, NK₁RAs do not appear to have a consistent ability to reduce nausea induced by
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46 622 multiple stimuli despite high levels of NK₁RA binding in many of the relevant brain areas.
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49 623 Therefore, it is reasonable to conclude that NK₁ receptors do not have a major role in
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51 624 transmission in the 'higher' brain regions currently implicated in nausea. We note that NK₁RA
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54 625 efficacy in depression (e.g., Keller et al., 2006; Ratti et al., 2013), panic disorder (Fujimura et
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56 626 al., 2009), pain (Borsook et al., 2012) and anxiety (Hoppe et al., 2018) are also variable and
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58 627 less than might be anticipated from NK₁ receptor distribution.
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628 **5.4. Do NK₁ RA reduce vasopressin secretion?**

629 Relatively high plasma concentrations of arginine vasopressin (AVP) are associated with
630 nausea induced by stimuli activating the vestibular system, AP and abdominal vagal afferents
631 (Makwana et al., 2022). A causal link between AVP and nausea is not proven, but a credible
632 possibility in at least some clinical scenarios involves the actions of low concentrations of AVP
633 on gastric pacemaker activity (the interstitial cells of Cajal; ICC), synergising with actions of
634 other nauseagenic stimuli to disrupt motility and hence, initiate vagal afferent discharge; the
635 demonstration of synergy between two different nauseagenic stimuli (adrenaline + AVP) was
636 used to argue that antagonism of one alone (e.g., the effects of vasopressin) might reduce
637 but not prevent the symptom of nausea (Makwana et al., 2022). In dogs, following cisplatin
638 administration, the NK₁RA maropitant was without significant effect on the peak [AVP] or the
639 area under the curve whereas both were significantly reduced by ondansetron (Kenward et
640 al., 2017). In human patients treated with cisplatin the acute rise in [AVP] was blocked by
641 ondansetron (Barreca et al., 1996) as in the dog, but as far as we are aware similar patient
642 studies have not been performed with an NK₁RA.

643 **5.5. Do NK₁RA have a role in treating nausea by gastric motility modulation?**

644 The presence of SP in the digestive tract in nerve terminals and EEC (Sanger, 2004) and of NK₁
645 receptors on smooth muscle cells and Interstitial cells of Cajal (ICCs) (Lavin et al., 1998;
646 Fausson-Pellegrini, 2006; Cheng et al., 2007; Liu & Rudd, 2023) makes the digestive tract a
647 potential target for NK₁RA. However, an ability of NK₁RAs to affect nausea by a direct effect
648 on gastric motility is unlikely. Thus, in healthy volunteers there is little evidence for an effect
649 of NK₁RA on digestive tract motility (assessed by gastric emptying or compliance, or small and
650 large bowel propulsion) (Madsen & Fuglsang 2008; Ang et al., 2013; Jacob et al., 2017; Khanna

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3 651 et al., 2022). Interestingly, after a dyspeptogenic meal, aprepitant (125 mg on day 1, then 80
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5 652 mg on days 2–5) increased fasting, postprandial, and accommodation gastric volume but
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8 653 increased aggregate symptoms, nausea, and pain scores after ingestion of the maximum
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10 654 tolerated volume; the authors suggested that differences between these studies may be
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13 655 dependent on what is measured and on the application of acute- or longer-term dosing with
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15 656 aprepitant (Jacob et al., 2017) but activation of TRAAK channels (see above) should also be
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18 657 considered.

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21 658 Dysrhythmic gastric electrical activity has been associated with nausea in disorders including
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23 659 gastroparesis, CUNV, functional dyspepsia, gastro-oesophageal reflux disease, all linked with
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26 660 loss of ICCs (Koch 2014; O’Grady et al., 2021). Thus, any ability of NK₁RAs to affect ICC
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28 661 functions (see above) could, in theory, have an influence on *induction* of nausea although an
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30 662 effect on vagal afferent signalling or the NTS seems more likely based on current knowledge.

31 32 33 663 **6. Concluding comments.**

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36 664 Irrespective of the stimulus, the effects of NK₁RA against *vomiting* are explicable by a central
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39 665 action on the NTS and CPG in the brain stem with potential additional peripheral effects on
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41 666 vagal afferent activity when activated by an emetic stimulus (e.g., HEC, some ingested toxins).
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44 667 NK₁RAs are not always 100% effective against vomiting in humans (c.f., pre-clinical studies,
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46 668 **Table 1**) implicating other transmitter/receptor systems and explaining why optimal *anti-*
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48 669 *vomiting* therapy may require drug combinations (e.g., netupitant + palonosetron +
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51 670 dexamethasone) in treating complex situations such as HEC. An additional role for other
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54 671 neurotransmitters/co-transmitters (e.g., glutamate) has not yet been fully explored.
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57 672 A reduction in the projection of information from the NTS to the higher brain regions by
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59 673 suppression of NTS pathways and the drive from the abdominal vagal afferents is likely to
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3 674 contribute to any reduction of nausea by NK₁RAs, no matter how sub-optimal the current
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6 675 evidence suggests. It could be argued that the distribution of NK₁ receptors in cortical and
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8 676 subcortical structures implicated in nausea may predict efficacy against nausea, but it is also
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11 677 possible these receptors are coupled to non-nauseagenic pathways, such as those involved in
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13 678 fear and/ or anxiety (which nonetheless may contribute to the overall sensation of nausea).

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16 679 Mechanistically, vomiting is well understood and studies with NK₁RAs show that targeting the
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18 680 NTS/CPG in the brainstem is a valid approach and adverse effects on the respiratory,
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21 681 cardiovascular and digestive systems all regulated from the brainstem appear to be avoided.
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23 682 The apparent specificity of NK₁RA blockade of vomiting likely reflects the functional
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26 683 reconfiguration of the neural network to coordinate retching/vomiting where tachykininergic
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28 684 signalling becomes critical (state dependence; see Doi & Ramirez 2010 for a study of NK₁
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31 685 receptors and state dependent functions of pre-Bötzinger complex respiratory neurones). The
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33 686 NTS and CPG need investigating in emetic species using neurophysiological studies similar to
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36 687 those in rodents showing complex interaction between NK₁ receptor activation, glutamate
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38 688 and GABA release (Bailey et al., 2004) to understand how NK₁RAs are 'functionally specific'
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41 689 for vomiting.

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43 690 Nausea remains a challenge as there are major gaps in knowledge of the cerebral pathways
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46 691 involved and hence in identifying potential receptor targets to identify 'broad spectrum' anti-
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48 692 nausea drugs. As the insular cortex is the "highest" cortical region consistently activated in
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51 693 subjects reporting nausea (Varangot-Reille et al., 2023) this would be a logical place to target
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53 694 a drug to block nausea although the associated physiological changes (e.g., regional cold
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56 695 sweating, AVP secretion) may not be blocked as they involve 'lower' brain regions. An
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58 696 alternative approach is to selectively suppress transmission of 'nauseagenic' signals from the
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3 697 NTS to the mid-brain with consideration being given to the parabrachial nucleus as a potential
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6 698 target. Whilst this might be achieved by a combination of receptor antagonists the use of
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8 699 agonists (e.g., GABA_B, CB₁, 5-HT_{1A}, ghrelin, opioid) may provide a more fruitful approach as
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11 700 this makes fewer assumptions about the nature of the nauseogenic stimulus (Sanger &
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13 701 Andrews, 2006). A gastric inhibitory polypeptide-1 receptor agonist has been shown to block
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15 702 the acute vomiting induced by the chemotherapeutic agent cisplatin in the ferret (Borner et
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17 703 al., 2023), further extending the list of receptor agonists with 'anti-emetic' potential. The
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20 704 electroceutical approaches to treatment of gastrointestinal symptoms, including nausea
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22 705 (Horn et al., 2019; Ramadi et al., 2020), may provide a route by which this system may be
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24 706 controlled but further study is needed to determine the pathways and cell types involved. A
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26 707 final approach is to target the abdominal vagal afferents at a peripheral site but this would
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28 708 only be applicable when a peripheral release of SP has been demonstrated and when the
29
30 709 original signal originates from disordered upper digestive tract function (e.g., gastroparesis;
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32 710 Sanger & Andrews, 2023). Research into the development of anti-nausea drugs is further
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34 711 hampered by the paucity of human volunteer studies using stimuli other than motion. Studies
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36 712 of 'anti-emetics' have been undertaken in humans using apomorphine, ipecacuanha and
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38 713 morphine as challenges (Proctor et al., 1978; Minton et al., 1993; Soergel et al., 2014) and a
39
40 714 wider range of challenges could be identified from the side effect profile of licenced drugs
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42 715 (e.g., GLP-1 receptor agonists). The final issue is quantification of nausea. The assessment
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44 716 tools widely used in clinical trials rely on an accurate classification of nausea by the subject,
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46 717 an assumption that subjects are reporting the same sensation and reliable recollection as data
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48 718 may only be collected daily giving data with a low temporal resolution (see Varangot-Reille et
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50 719 al., 2023, Suppl. files). The heterogeneity of nausea assessment instruments was identified as
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52 720 an issue in a recent US, F.D.A. review of endpoints in CINV and PONV studies which identified
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3 721 nausea assessment as an “opportunity for continued research and development” (Gabby et
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5 722 al., 2021). A reliable, subject independent method for assessing nausea in real time is needed
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8 723 to ensure an accurate assessment of candidate drug efficacy (Andrews & Sanger, 2014).
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11 724 We close by dedicating this review to a colleague and friend Wes Miner who died while we
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13 725 were drafting this review. Wes was co-author of the first paper demonstrating the remarkable
14
15 726 anti-emetic effect of a 5-HT₃ receptor antagonist (Miner & Sanger, 1986) and spent his career
16
17 727 in the pharmaceutical industry. In a note to one of the authors (PLRA) in January 1999 Wes
18
19 728 made the following insightful comment of relevance to this review regarding the Navari et al.,
20
21 729 1999 paper reporting some of the earliest clinical data on NK₁RA: “*results are very, very good*
22
23 730 *and I think this will just about wrap it up for pharmaceutical company interest in the N+V area*
24
25 731 *for the next 20 years.*” As Wes predicted, there have indeed been no major advances in the
26
27 732 development in drugs affecting vomiting and especially nausea in the last 20 plus years and
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29 733 as this review shows the accepted dogma that ‘anti-emetics’ equally affect nausea and
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31 734 vomiting requires challenging; a view with which we are sure Wes would concur.
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1652 **Figure legends**

1653 **Figure 1.** A summary of the major pathways implicated in the motor events of vomiting and
1654 the sensation of nausea. The diagram shows the major inputs (vestibular system, abdominal
1655 vagal afferents, area postrema) to the nucleus tractus solitarius (NTS) in the brainstem by
1656 which both nausea and vomiting are evoked. The mechanical events of vomiting only
1657 require activation of brainstem and spinal cord nuclei. Most notable are the dorsal motor
1658 vagal nucleus (DMVN) projecting vagal efferents to the digestive tract to induce gastric
1659 relaxation and intestinal retrograde giant contraction, and the ventral respiratory group
1660 (VRG) of neurones driving the spinal phrenic nerve nucleus (PNN) responsible for
1661 contraction of the costal diaphragm which together with the anterior abdominal muscles
1662 (not shown) provides the main force compressing the stomach and leading to forceful oral
1663 ejection of contents. Nausea requires activation of cerebral structures and is associated with
1664 the secretion of high concentrations vasopressin (AVP) from the hypothalamic /pituitary axis

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3 1665 but other hormones are also released (e.g., cortisol). The main sympathetic motor outputs
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6 1666 associated with nausea are shown in the right-hand red rectangle and are a consequence of
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8 1667 descending pathways from the “visceromotor cortex” activating the pre-sympathetic nuclei
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11 1668 (PSN) in the brainstem which in turn drive the pre-ganglionic sympathetic neurones in the
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13 1669 spinal cord (ILH). For details and references see text. Adapted and modified from Varangot-
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15 1670 Reille et al., 2023.

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18 1671 **Figure 2.** The effects of the NK₁ receptor antagonist (NK₁RA) tradipant *versus* placebo on
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20 1672 motion sickness signs and symptoms, are shown for Vomiting (left diagram) and for Nausea
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22 1673 (right diagram). Motion sickness was provoked by motion at sea. Voyages inevitably varied
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24 1674 in terms of the weather and roughness of waves, consequently the data are presented in
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26 1675 terms of all data (i.e. all voyages combined) and split by lower wave motion ‘calm seas’ and
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28 1676 higher wave motion ‘rough seas’. Vomiting is shown as % incidence. Nausea is shown as
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30 1677 the mean sickness rating scale, with higher scores indicating more severe nausea. Note the
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32 1678 differences in levels of statistical significance for the different comparisons. Data were
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34 1679 adapted from Polymeropoulos et al, 2020.

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43 1681 **Figure 3.** A diagrammatic summary of the central and peripheral sites at which NK₁RA could
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45 1682 act to reduce nausea and vomiting. Abbreviations: AP= Area Postrema; CPG= Central
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47 1683 pattern Generator for vomiting; DMVN=Dorsal Motor Vagal Nucleus EC=Enterochromaffin
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49 1684 cell; EEC=Enteroendocrine Cell; EP=Epithelial cell; HPV= Hepatic Portal Vein; ICC= Interstitial
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51 1685 Cells of Cajal; NK₁RA= Neurokinin₁ receptor antagonist; NTS= Nucleus Tractus Solitarius;
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53 1686 VNN= Vestibular Nerve Nucleus. In the periphery, NK₁ receptors located on the gastric
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55 1687 smooth muscle, the enteric neurones and possibly the ICCs could modulate motility
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57 1688 contributing to a reduction in nausea when disordered motility is implicated (e.g.,
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59 1689 gastroparesis). NK₁RA can prevent activation/sensitisation of both muscle
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3 1690 mechanoreceptors and epithelial 'chemoreceptive' vagal afferents driving nausea and
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5 1691 vomiting by locally released SP. The latter are particularly implicated in nausea and vomiting
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7 1692 induced by anti-cancer chemotherapy, gastric irritant and some infections (e.g., rotavirus).
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9 1693 NK₁ receptors are also implicated in inflammation the reduction of which by NK₁ RA could
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11 1694 also contribute to reducing afferent drive. The sites at which vomiting can be blocked all
12
13 1695 reside in the brainstem (particularly the NTS and CPG) although it is unclear if the AP is a site
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15 1696 of action other than when vomiting is induced by an NK₁ receptor agonist. Induction of
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17 1697 nausea requires activation of 'higher' brain regions and although NK₁ receptors are present
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19 1698 at multiple sites in the mid-brain and cerebral hemispheres the data implicating them in
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21 1699 anti-nausea effects is circumstantial. See text for details and references.
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23 1700

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26 1701 **Figure 4 A-D.** Diagrammatic representation of a longitudinal section through the brainstem
27 showing the key nuclei and pathways implicated in retching, vomiting and nausea.

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29 1703 Abbreviations: AP=area postrema; CPG= Central Pattern Generator responsible for the
30 generation of the oscillatory pattern of activity driving the somato-motor pathways for
31 1704 retching and vomiting in the VRG; DMVN= Dorsal Motor Nucleus of the Vagus, origin of pre-
32
33 1705 ganglionic efferents to the digestive tract; NTS= Nucleus Tractus Solitarius; VRG= Ventral
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35 1706 Respiratory Group of neurones; Ph= Phrenic nerve nucleus in cervical (C3-C-5) spinal cord;
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37 1707 Ab= Abdominal muscle motor neurones in ventrolateral thoracic and lumbar spinal cord.
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39 1708 See text for further explanation and references.
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42 1710 A: Resting state; B: Low level of activation of pathways inputting to the NTS resulting in
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44 1711 activation of NTS and ascending pathways inducing nausea including secretion of anti-
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46 1712 diuretic hormone (ADH/AVP) from the posterior pituitary; C= More intense activation of the
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48 1713 inputs results in more intense nausea and proximal gastric relaxation, a preparatory action
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50 1714 to accommodate refluxed material resulting from the Retrograde Giant Contraction
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52 1715 originating in the small intestine when the input is sufficient to exceed the threshold for
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54 1716 induction of retching and vomiting when the phrenic and abdominal motor neurones are
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56 1717 activated. Note that The CPG and the DMV outputs must be coordinated (dotted arrow) as
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58 1718 retching does not begin until the RGC reaches the gastric antrum.
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3 1720 **Figure 5.** Diagrammatic representation of the neuronal discharge pattern in the medial
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5 1721 nucleus tractus solitarius (mNTS) and the Central pattern Generator (located in the compact
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7 1722 part of the nucleus ambiguus, cAMB) in response to electrical stimulation of infra-cardia
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9 1723 vagal afferents based on neurophysiological studies in the dog reported in Koga & Fukuda,
10
11 1724 (1992), Fukuda et al., (2003), and Onishi et al., (2007). Vagal afferent stimulation results in a
12
13 1725 uniform increase in NTS firing frequency which ceases at the end of stimulation. NTS
14
15 1726 activation results in CPG activation after a lag period and is followed by a progressive
16
17 1727 increase in frequency which is due to 'wind-up'. The CPG firing frequency reaches at
18
19 1728 threshold at which the pattern becomes oscillatory with the output driving the ventral
20
21 1729 respiratory group of neurones (VRG) which in turn drive the phrenic and abdominal motor
22
23 1730 neurones responsible for the mechanical events of retching a vomiting. The CPG oscillations
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25 1731 causing retching are shorter and smaller magnitude than the ultimate burst of activity
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27 1732 resulting in vomiting and continue beyond the period of vagal afferent stimulation showing
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29 1733 a protracted effect of the initial stimulation.

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1 **An assessment of the effects of neurokinin₁ receptor antagonism against**
2 **nausea and vomiting: Relative efficacy, sites of action and lessons for future**
3 **drug development.**

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9 Kingdom.

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15 **Ethical approval:** Not required.

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18 **Key words:** Anti-cancer chemotherapy, gastroparesis, motion sickness, nausea, neurokinin₁,
19 substance P, tradipitant, vomiting.

20 **Abbreviations:**

21 AP: Area postrema

22 AVP: Arginine vasopressin

23 CB₁: Cannabinoid₁ receptor

24 CCK: Cholecystokinin

25 CI: Confidence Interval

26 CINV: chemotherapy-induced nausea and vomiting

27 CPG: central pattern generator for vomiting

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2
3 28 CUNV: Chronic Unexplained Nausea and Vomiting
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5 29 D₂: dopamine₂ receptor
6
7 30 EC: Enterochromaffin cell
8
9 31 EEC: Enteroendocrine cell
10
11 32 GABA: Gamma amino butyric acid
12
13 33 GABA_B: Gamma amino butyric acid B receptor
14
15 34 GCSI: Gastroparesis Clinical Symptom Index
16
17 35 GDF15: Growth differentiation factor 15
18
19 36 GLP-1: Glucagon like peptide 1
20
21 37 5-HT: 5-Hydroxytryptamine
22
23 38 5-HT_{1A}: 5-Hydroxytryptamine_{1A} receptor
24
25 39 5-HT₃: 5-Hydroxytryptamine₃ receptor
26
27 40 HEC: Highly emetogenic chemotherapy
28
29 41 H₁: Histamine₁ receptor
30
31 42 ICC: interstitial cells of Cajal
32
33 43 i.v.: Intravenous
34
35 44 MSSS: motion sickness severity scale
36
37 45 mACh: Muscarinic acetylcholine receptor
38
39 46 mNTS: medial nucleus tractus solitarius
40
41 47 MRI: Magnetic resonance imaging
42
43 48 NA: Nucleus ambiguus
44
45 49 NK₁RA: Neurokinin₁ receptor antagonist
46
47 50 NN: no nausea
48
49 51 NSN: no significant nausea
50
51 52 NTS: Nucleus tractus solitarius
52
53 53 PET: Positron emission tomography
54
55 54 p.o.: *Per oral*
56
57 55 PONV: post-operative nausea and vomiting
58
59 56 PSC: prodromal sign centre
60
57 57 RGC: Retrograde giant contraction
58
59 58 RR: Risk ratio
60

1
2
3 59 SP: Substance P

4
5 60 VRG: Ventral respiratory group

6
7 61 VIMS: Visually-induced motion sickness

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11 63 **Author contribution. All authors made an equivalent contribution.**

12
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14
15 65 **Abstract**

16
17
18 66 A 'broad-spectrum' anti-vomiting effect of neurokinin₁ receptor antagonists (NK₁RA), shown
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21 67 in preclinical animal studies, has been supported by a more limited range of clinical studies in
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24 68 different indications. However, this review suggests that compared with vomiting, the self-
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27 69 reported sensation of nausea is less affected or possibly unaffected by ~~the different~~
28
29 70 NK₁receptor antagonismRAs, a common finding for 'anti-emetics'.

30
31 71 The stimulus-independent effects of NK₁RAs against vomiting are explicable by actions within
32
33
34 72 the central pattern generator (CPG; ventral brainstem) and the nucleus tractus solitarius (NTS;
35
36
37 73 dorsal brainstem), with additional effects on vagal afferent activity for certain stimuli (e.g.,
38
39 74 highly emetogenic chemotherapy). The CPG and NTS neurones are multifunctional so the
40
41
42 75 notable lack of obvious effects of NK₁RAs on other reflexes mediated by the same neurones
43
44 76 suggests that their anti-vomiting action is dependent on the activation state of the pathway
45
46 77 leading to vomiting.

47
48
49 78 Nausea requires activation of cerebral pathways by projection of information from the NTS.

50
51 79 Although NK₁ receptors are present in cerebral nuclei implicated in nausea, and imaging
52
53
54 80 studies show very high receptor occupancy at clinically used doses, the variable or limited
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56
57 81 ability of NK₁RAs to inhibit nausea emphasises (a) our inadequate understanding of the
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3 82 mechanisms of nausea and (b) that classification of a drug as an “anti-emetic” gives a false
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5
6 83 impression of efficacy against nausea *versus* vomiting.
7

8
9 84 We discuss the potential mechanisms for the differential efficacy of NK₁RA and the
10
11 85 implications for future development of drugs which can effectively treat nausea, an area of
12
13 86 unmet clinical need.
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18 19 88 **1. Introduction**

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21
22 89 Drugs treating nausea and vomiting as disease symptoms or as adverse effects of therapy are
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24
25 90 usually classified as ‘anti-emetics’. However, the term ‘emetic’ refers to a substance which
26
27 91 causes vomiting (or retching). Emesis does not mean nausea. Further, increasing evidence
28
29 92 indicates with little recognition of differential efficacy of ‘anti-emetic’ drugs against nausea
30
31
32 93 *versus* vomiting. Seifert & Alexander (2022) proposed a “rational drug class terminology”
33
34
35 94 based on a drug’s pharmacological actions rather than its therapeutic orientation (e.g., anti-
36
37 95 emetic). Applying this terminology to nausea and vomiting means that in view of this the term,
38
39 96 ‘anti-emetic’ is used must be written in inverted commas to denote the fact that efficacy
40
41
42 97 against nausea and vomiting should not be assumed to be the same (Sanger
43
44 98 & Andrews, 2022). Here, and throughout we emphasise the ~~Here we also avoid using ‘anti-~~
45
46 99 ~~emetic’ and re-state the argument (Sanger & Andrews, 2022) that it is importance of not to~~
47
48
49 100 ~~blur the clinical distinction differentiating~~ between nausea, a self-reported aversive sensation
50
51
52 101 involving cortical and sub-cortical brain regions (Napadow et al., 2013; Farmer et al., 2015;
53
54 102 Ruffle et al., 2019; Varangot-Reille et al., 2023) and the mechanical events of retching and
55
56 103 vomiting involving multiple brainstem nuclei (Stern et al., 2011).
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1
2
3 104 The introduction of NK₁ receptor antagonists (NK₁RAs) further improved control of
4
5
6 105 'chemotherapy-induced nausea and vomiting' (CINV) and 'post-operative nausea and
7
8 106 vomiting' (PONV) (Sanger & Andrews, 2018). In addition, a potential expansion of indications
9
10
11 107 may be appropriate, to include, for example, motion sickness (Polymeropoulos et al., 2020).
12
13 108 If confirmed, this would point towards a relatively wide spectrum of 'anti-emetic' activity for
14
15 109 the NK₁RAs in humans, as suggested by animal studies (see below). However, originating
16
17 110 primarily from studies of CINV including the earliest clinical studies of NK₁RAs (e.g., Navari et
18
19 111 al., 1999) there has been a concern that nausea is less well treated than vomiting (Andrews
20
21 112 & Sanger, 2014) and this concern persists, as reflected in the comment by Apro (2018, p.57)
22
23 113 that "Perhaps the greatest unmet need in CINV is the lack of complete nausea control".
24
25 114 Accordingly, in an attempt to understand resolve the nausea versus vomiting question in
26
27 115 relation to NK₁-RAs, from both a clinical and basic science mechanistic perspectives, we
28
29 116 identified five key questions:

- 30
31
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33
34
35 117 1. Has the broad spectrum of activity of NK₁RAs suggested by animal studies of vomiting
36
37 translated to humans?
38
39
40 119 1.2. ~~and~~ Wwhere do NK₁RAs act to inhibit vomiting?
41
42
43 120 2.3. To what extent do NK₁RAs inhibit nausea as compared to vomiting?
44
45 121 3.4. If NK₁RAs have a differential effect against nausea compared to vomiting, what is the
46
47 explanation?
48
49
50 123 4.5. What are the implications of the answers to the above questions in terms of patient
51
52 satisfaction and for future development of drugs to treat nausea?
53
54
55 125 Different emetic stimuli signal to the brain via different routes. This is why it is first necessary
56
57 to determine if the broad-spectrum ability of NK₁RAs to prevent vomiting in animals
58
59
60

1
2
3 127 [translates to humans in a similar manner; such a profile directs the discussion on potential](#)
4
5
6 128 [mechanism of action against vomiting and nausea. Accordingly, ~~To answer these questions~~](#)
7
8 129 [w](#)~~We~~ [begin by briefly describing the NK₁RA studies in animals and then review \[\\(see below for\]\(#\)](#)
9
10 130 [selection criteria\)](#) the effects of NK₁RAs against vomiting and nausea in different clinical
11
12
13 131 indications [\(see below for selection criteria\)](#), ~~and~~ identifying ~~any~~ differences in efficacy
14
15 132 between these ~~clinical different~~ indications.

133 **2. [Animal studies: Spectrum of NK₁RA effects against vomiting and 'nausea-like behaviours'](#)**

134 ~~In this section only data from species with a vomiting reflex (i.e. not rodents) are included to~~
135 ~~In this section we consider illustrate the 'anti-emetic' effects of NK₁RAs against diverse stimuli~~
136 ~~in a range of animal species only data from species with a vomiting reflex (ferret dog, cat,~~
137 ~~House musk shrew [*Suncus murinus*] and Least shrew [*Cryptotis parva*]). To simplify~~
138 ~~comparisons between species and between the effects of drugs on vomiting and nausea, we~~
139 ~~have not considered 'nausea-like' behaviour data from rodents, which cannot vomit (Sanger~~
140 ~~et al., 2011; Horn et al., 2013).~~

141 **2.1. Vomiting.** Studies in multiple animal species (**Table 1**) have demonstrated 'broad
142 spectrum' effects of NK₁RAs, markedly reducing/blocking retching and/or vomiting induced
143 by diverse stimuli acting via three key inputs to the brainstem (**Figure 1**): ~~the vestibular system~~
144 ~~(e.g., abnormal motion); the area postrema (e.g., systemic morphine or apomorphine, and~~
145 ~~the delayed phase of cisplatin CINV); and abdominal vagal afferents (e.g., acute phase of~~
146 ~~cisplatin CINV, intragastric copper sulphate, electrical stimulation of abdominal vagal~~
147 ~~afferents)~~ (Stern et al., 2011; Sanger & Andrews, 2018 for references).

148 **2.2. 'Nausea-like behaviours.'** Administration to animals of substances inducing nausea and
149 vomiting in humans evoke behavioural changes (often referred to as 'nausea-like'), but their

150 significance and relevance to the human sensation of nausea is contentious (Stern et al., 2011,
151 Chapter 11; Andrews & Sanger, 2014).

152 ~~In reviewing the effects of NK₁RAs on 'nausea-like behaviours' we only include data obtained~~
153 ~~using species capable of vomiting (ferret dog, cat, House musk shrew [*Suncus murinus*] and~~
154 ~~Least shrew [*Cryptotis parva*]) (Supplementary Table 1). This enables direct comparison,~~
155 ~~where possible, with effects on vomiting. Rodents (e.g., rats, mice) are unable to vomit and,~~
156 ~~compared with species able to vomit, exhibit anatomical and functional differences including:~~
157 ~~brain stem neuroanatomy (Horn et al., 2013); digestive tract anatomy/physiology (Sanger et~~
158 ~~al., 2011); subtype composition of the 5-hydroxytryptamine₃ (5-HT₃) receptor (a ligand-gated~~
159 ~~ion channel; Holbrook et al., 2009); binding affinity of different NK₁RAs (Beresford et al., 1991;~~
160 ~~Andrews & Rudd, 2004). In summary, and in contrast to the clear effects of NK₁RA on~~
161 vomiting, ~~any~~ effects on 'nausea-like behaviours' are absent or inconsistent (Supplementary
162 Table 1). Given this lack of clarity and since the relevance of these behaviours to the human
163 experience is unknown, they will not be considered further (Stern et al., 2011, Chapter 11;
164 Andrews & Sanger, 2014, for detailed discussion).

165 3. Human studies: Spectrum of NK₁RA effects against vomiting and nausea.

166 It is important to determine if the broad-spectrum ability of NK₁RAs to prevent vomiting in
167 animals translates to the vomiting and nausea of humans. Accordingly, we searched either
168 the name of individual antagonists and/or the therapeutic area (e.g., motion sickness, CINV,
169 PONV, gastroparesis, and cyclical vomiting syndrome). For CINV and PONV where there has
170 been more extensive investigation of NK₁-RAs 'anti-emetic' efficacy we initially reviewed
171 systematic reviews/meta-analyses and then analysed data in selected original papers. As our
172 focus was on the relative efficacy of NK₁-RAs against nausea and vomiting we included papers

173 where data on both vomiting and nausea was presented and in particular where adequate
174 information was provided in the methods about how each was quantified, with data
175 presented in a form allowing comparison. Here the aim is not to identify optimal treatment
176 regimens but to assess the relative efficacies of NK₁RAs against nausea and vomiting.
177 ~~However, We should~~ note that few studies have given an NK₁RA *alone*, 'N' values can be
178 small (e.g., in PONV the N value for 7 studies of aprepitant included in a meta-analysis ranged
179 from 30-55; Cavaye et al., 2021) and some studies are uncontrolled. ~~Additionally, nausea is~~
180 ~~not always measured and~~ is often a secondary outcome with methodological variations in its
181 assessment complicating inter-study comparisons (see below).

182 Sections 3.1 to 3.6 describes the results of studies investigating the effects of NK₁-RAs against
183 different emetic challenges. Section 3.7 then provides an overview of the spectrum of efficacy
184 against nausea and vomiting.

185 **3.1. Motion sickness (MS).** Studies in humans are limited as ethical considerations usually
186 dictate that vomiting endpoints cannot be used in laboratory-~~based studies inducing motion~~
187 ~~sickness in healthy~~ human volunteers ~~studies~~. Two laboratory-based studies employed the
188 well proven method of highly provocative whole-body rotational motion with head
189 movements to induce motion sickness (so-called "Cross-coupled motion"). These studies
190 showed no significant efficacy of an NK₁RA (GR205171 [vofopitant]; L758,298) using the degree
191 of motion exposure tolerated before onset of nausea as the endpoint; this suggests no
192 efficacy against nausea (Reid et al., 1998; Reid et al., 2000). A study of healthy human
193 volunteers using inescapable motion at sea investigated the NK₁RA tradipitant (VLY-686/
194 LY686017) (Polymeropoulos et al., 2020) and unlike laboratory-based trials, it was possible to
195 measure both vomiting and nausea. Tradipitant was significantly effective (placebo

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2
3 196 comparator) in protecting against vomiting, but less effective against nausea, using the
4
5
6 197 motion sickness severity scale (MSSS) as an index (**Figure 2**). Only for selected data obtained
7
8 198 during rough seas did the NK₁RA provide any protection against nausea protection compared
9
10 199 to, albeit at a much lower statistical significance than the equivalent vomiting protection for
11
12 200 in this sub-group (**Figure 2**). By contrast, well proven muscarinic acetylcholine (ACh) receptor
13
14 201 antagonists such as scopolamine (hyoscine), provided protection against both nausea
15
16 202 (Golding et al., 1997; 2018) and vomiting (Golding et al., 2017). More detailed studies with
17
18 203 tradipitant are now required, investigating for example, the effects of NK₁RA on the
19
20 204 physiological changes accompanying motion sickness such as the reduced gastric antral
21
22 205 contractile activity (Faas et al., 2001), a pathway of potential relevance to understanding the
23
24 206 effects of NK₁RAs in gastrointestinal conditions associated with nausea, such as gastroparesis
25
26 207 (see below).

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32
33 208 From these very limited data, we tentatively conclude that NK₁RAs are effective against
34
35 209 *vomiting* induced by abnormal motion but are less effective against *nausea*.

36
37
38 210 **3.2 Chemotherapy-induced nausea and vomiting.** We focus on NK₁RA use in the acute and
39
40 211 delayed phases of highly emetogenic chemotherapy (HEC) discussing their effects against
41
42 212 vomiting before effects against nausea.

43
44
45
46 213 A study of CINV in seven patients given CP-122,721 *alone* showed that in the acute phase (first
47
48 214 24h) of HEC five patients had ≤2 episodes vsv. 7 episodes of “emesis” in an historic control
49
50 215 group and in the delayed phase, 6 had no emesis (Kris et al., 1997). A larger study with L-758,
51
52 216 298 (the prodrug for the NK₁RA, aprepitant [L-754,030]) showed that 37% of patients (n=30)
53
54 217 had no vomiting or retching in the acute phase, compared with 52% of patients in an
55
56 218 ondansetron (5-HT₃RA) group (n=23; not significantly different) (Cocquyt et al., 2001).
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3 219 However, confining analysis to the first 8h following cisplatin showed 37% of patients had no
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5
6 220 vomiting or retching in the NK₁RA group compared to 83% in the 5-HT₃RA group ($P=0.001$)
7
8 221 but in the delayed phase 72% of patients were without vomiting or retching in the NK₁RA
9
10
11 222 group ~~vs.~~ 30% in the ondansetron group ($P=0.005$) (Cocquyt et al., 2001). This study suggests
12
13 223 a shift in the relative involvement of 5-hydroxytryptamine₃ (5-HT₃) and NK₁ receptors driving
14
15 224 retching and vomiting between the acute and delayed phases following cisplatin, a finding
16
17
18 225 confirmed by detailed time course analysis of the efficacy of aprepitant, L-758, 298,
19
20 226 ondansetron and granisetron in treatment of CINV (Hesketh et al., 2003).

21
22
23 227 Recent meta-analyses demonstrate additional protection against vomiting when NK₁RAs are
24
25 228 given with a 5-HT₃RA and dexamethasone during both acute and delayed phases in HEC (~15-
26
27
28 229 20% more complete protection), with a greater effect in the delayed phase (Jordan et al.,
29
30 230 2016; Yokoe et al., 2019; Qiu et al., 2020).

31
32
33 231 Overall, and despite an ability of NK₁RAs to further reduce the incidence of vomiting during
34
35 232 the acute phase when combined with a 5-HT₃RA and dexamethasone, the incidence of nausea
36
37
38 233 is not further reduced during this phase. For example, an initial study with L-754,030 showed
39
40 234 a clear additional effect on vomiting in the acute phase following cisplatin when added to a
41
42
43 235 5-HT₃RA/dexamethasone regimen (Kris et al., 1997), but no difference in the median nausea
44
45 236 score. An analysis of the Phase III studies of NK₁RAs added to a 5-HT₃RA and dexamethasone
46
47
48 237 regime in HEC, found no consistent evidence for an improvement in the incidence of “no
49
50 238 significant nausea” (NSN) or “no nausea” (NN) in the acute phase (Bošnjak et al., 2017). For
51
52
53 239 example, the percentage of patients experiencing “no nausea” in the NK₁RA arm v. placebo
54
55 240 in the acute phase was 53.6% v. 52% (Roila et al., 2014), 65% v. 66% (Schwartzberg et al.,
56
57
58 241 2015), 68% v. 61% (Study 2, Rapoport et al., 2015; statistically significant) and 73% v. 68%

242 (Study 1, Rapoport et al., 2015). A pooled analysis of studies with rolapitant showed a small
243 but statistically significant increase in the percentage of patients reporting NN (respectively,
244 64% and 70%) in the acute phase of HEC (Bošnjak et al., 2017). Saito et al., (2013) found a
245 tendency for the incidence of NSN to increase (90.2% v. 84.9%) when using intravenous
246 fosaprepitant (150mg+granisetron/dexamethasone) in patients receiving high-dose cisplatin,
247 although the difference was not statistically significant and the NN incidence was unchanged
248 (67.6% v. 67.5%) compared to placebo.

249 Some, but not all, studies reported that during the delayed phase the addition of an NK₁RA
250 significantly increased the percentage of patients reporting NN or NSN. In the initial study
251 with L-754,030 (\pm placebo+ granisetron/dexamethasone; Navari et al., 1999) the median
252 nausea score was reduced on a 100mm VAS (higher score indicating more severe nausea)
253 from 19mm to 1mm on day 2 and over days 2-5 from 10mm to 1mm. Similarly, others
254 reported that the percentage of patients experiencing NN in the NK₁RA arm vsv. placebo in
255 the delayed phase increased significantly: 52.7% vsv. 39.9% (Poli-Bigelli et al., 2003), 53% vsv.
256 42% (Study 1, Rapoport et al., 2015) and 58% vsv. 47% (Study 2, Rapoport et al., 2015).
257 However, some showed no statistically significant change in NN (e.g., 43.9% vsv. 49.1%, Roila
258 et al., 2014; 71.4% vsv. 73%, Roila et al., 2015; 48% vsv. 45%, Schwartzberg et al., 2015). A
259 pooled analysis of studies using rolapitant showed a significant 12% increase in the NN
260 percentage (44% vsv. 56%) in the delayed phase (Bošnjak et al., 2017).

261 A recent meta-analysis investigated the addition of aprepitant to a 5-HT₃RA/dexamethasone
262 regimen in patients (only 258 in the final analysis) receiving HEC treatments for lung cancer
263 (He et al., 2021). While the overall complete response rate (no vomiting/no rescue
264 medication) was significantly better when aprepitant was given, the NN rate was not

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3 265 statistically significantly different (although significant in two of the studies included in the
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5
6 266 analysis; Dupuis et al., 2020; Yokoe et al., 2019).

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8
9 267 In summary, there is insufficient data to compare different NK₁RAs, but it is possible to draw
10
11 268 general conclusions about their efficacy in HEC:

- 12
13
14 269 i) NK₁RAs further reduce the incidence of vomiting during the acute phase when
15
16 270 combined with a 5-HT₃RA and dexamethasone, but the effect is more marked in
17
18
19 271 the delayed phase of HEC.
20
21 272 ii) When added to a 5-HT₃RA/dexamethasone regime, any ability of NK₁RAs to further
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23
24 273 reduce the incidence of nausea appears inconsistent and in one meta-analysis the
25
26 274 NN rate was not statistically significant.

275 3.3. Post-operative nausea and vomiting.

276 ~~In contrast to CINV the mechanisms responsible for PONV are considerably less well~~
277 ~~understood, contributed to by the lack of a robust animal model (see Gardner & Perrin, 1998;~~
278 ~~Horn et al., 2012, 2014; Gupta et al., 2017).~~

279 **Table 2** summarises the effects of NK₁RAs in PONV using the outcome from studies reporting
280 nausea and vomiting separately to illustrate the efficacy differences. Overall, several NK₁RAs
281 show efficacy against post-operative *vomiting* in a proportion of patients but the block is not
282 complete in all patients and, the efficacy against *nausea* is inconsistent (e.g., small changes in
283 incidence, inconsistent change in intensity, **Table 2**) and lower than against vomiting. A
284 Cochrane meta-analysis examined the efficacy of diverse pharmacological agents in treating
285 *vomiting* in the first 24h (Weibel et al., 2020) and concluded that *single* NK₁RAs were as
286 effective as other *drug combinations*. The analysis did not compare efficacy against nausea.

287 Assessment of the overall efficacy of NK₁RAs against PONV is complicated by the variety of
288 types or surgery (e.g., open abdomen, laparoscopic) and anaesthesia/analgesia protocols. A
289 further issue is that in studies where a range of doses has been investigated the relationship
290 between NK₁RA dose and efficacy against either nausea or vomiting is not always clear (e.g.,
291 casopitant, Singla et al., 2010; rolapitant, Gan et al., 2011; vestepitant, Kranke et al., 2015).

292 **3.4. Cyclical vomiting syndrome.** An open-label uncontrolled trial of aprepitant in a paediatric
293 population refractory to conventional treatment showed reduction in the number of cyclic
294 vomiting episodes/year and number of vomits/h (Cristofori et al., 2014). Although nausea is
295 a feature of CVS it was not assessed in this study.

296 **3.5. Paediatric patients with life-limiting conditions.**

297 A case series showed aprepitant (2.0-2.5mg/kg, i.v.) was effective in complete resolution of
298 nausea (parental reports of impact on mobility and feeding used as proxy efficacy markers) in
299 paediatric patients receiving palliative care, with different diagnoses and unresponsive to at
300 least two drugs classified as 'anti-emetics' (e.g., cyclizine, ondansetron, metoclopramide,
301 levomepromazine; Patel et al., 2021). Additionally, aprepitant increased the ability to tolerate
302 feeds as might be expected from the proposal that food refusal in children could be used as
303 a surrogate marker for nausea (Richards & Andrews, 2004), although NK₁RA-induced changes
304 in gastric accommodation (Jacob et al., 2017) offers an alternative explanation.

305 **3.6. Gastric distension induced sensations and gastroparesis.**

306 In healthy human volunteers a single dose of aprepitant (80 or 125mg) had no effect on gastric
307 compliance or sensitivity to distension (Ang et al., 2013). Also, in healthy volunteers,
308 aprepitant (125mg p.o. day 1 + 80mg p.o. days 2-5) did not affect gastric emptying of liquids
309 or solids, intestinal or colonic transit (Madsen & Fuglsang, 2008). Using the same repeat

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3 310 dosing schedule but following a 'dyspeptogenic' meal, Jacob et al. (2017) confirmed no
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6 311 change in gastric emptying with aprepitant but found a modest increase in fasting (~10%),
7
8 312 postprandial (~9%) and gastric accommodation (~5%) volumes, and a tendency to increase
9
10 313 maximal tolerated volume (~25%). Interestingly, the aggregate symptoms, nausea, and pain
11
12 314 scores (but not bloating or fullness) increased significantly following the 'dyspeptogenic' meal
13
14
15 315 in the aprepitant group compared to placebo (median 36 *vs* 4). ~~These seemingly unexpected~~
16
17
18 316 ~~observations may be consistent with the recent identification of an additional ability of~~
19
20 317 ~~aprepitant to activate the mechanosensitive two-pore domain potassium channel, TRAAK~~
21
22 318 ~~(McCoull et al., 2022), which if expressed by abdominal vagal nerve terminals may also cause~~
23
24 319 ~~some reduction in the ability of aprepitant to reduce nausea and vomiting in other clinical~~
25
26 320 ~~scenarios.~~

27
28
29
30 321 A four-week placebo-controlled study of aprepitant (125mg/day, p.o.) involving 126 patients
31
32 322 failed to demonstrate an improvement in the primary outcome measure of nausea (Pasricha
33
34 323 et al., 2018), in a population with 57% gastroparesis patients and the remainder with Chronic
35
36 324 Unexplained Nausea and Vomiting (CUNV). The study also used the Gastroparesis Clinical
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38 325 Symptom Index (GCSI; Revicki et al., 2004) to assess symptom severity as a secondary
39
40 326 outcome and this showed significant reductions in overall symptom score (1.3 *vs* 0.7),
41
42 327 vomiting (1.6 *vs* 0.5 [69% decrease]) and nausea (1.8 *vs* 1 [44% decrease]). The number
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44 328 of hours per day when nausea was experienced, was reduced and the proportion of nausea-
45
46 329 free days increased (~ twofold).

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50 330 A placebo-controlled trial of 152 patients with idiopathic or diabetic gastroparesis and
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52 331 moderate-to-severe nausea, investigated tradipitant (85mg orally) twice daily (daily total
53
54 332 170mg) for 4 weeks (Carlin et al., 2020). The trial met the primary outcome measure of a

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3 333 reduction in average daily diary nausea score measured using the GCSI Daily Diary with a
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6 334 difference in score reduction between placebo and tradipitant of ~10%. Nausea severity
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8 335 appeared to begin decreasing by week 2 and this was statistically significant by week 3.
9
10 336 Additionally, tradipitant increased secondary outcomes of nausea free days (~14%>placebo)
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12
13 337 and nausea response rate (~21%>placebo). Patients who responded to tradipitant with a
14
15 338 reduction in nausea also had improved early satiety, excessive fullness, bloating and upper
16
17
18 339 abdominal pain, compared to placebo. Two case reports involving single patients with
19
20 340 gastroparesis report stoppage of previously intractable nausea (Fahler et al., 2012) or
21
22 341 vomiting (Chong & Dhatariya, 2009) on administration of aprepitant.
23
24
25 342 A recent systematic review and network meta-analysis of drugs used to treat gastroparesis
26
27 343 showed that NK₁RAs were efficacious (RR=0.69) using global symptom score. When individual
28
29 344 symptoms were assessed tradipitant was more effective than placebo in treating nausea
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31 345 (tradipitant RR=0.77; 95% CI 0.65-0.91) (Ingrosso et al., 2023). By contrast, a recent phase III
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33 346 trial of tradipitant in gastroparesis showed no difference from placebo in the intensity of
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36 347 nausea over a 12 week period (Vanda, 2022).
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44 349 **3.7. Overview of clinical efficacy against nausea vversuss vomiting.**

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47 350 Summarising sections 3.1 to 3.6, NK₁RAs can block vomiting induced by HEC (± 5HT₃RA and
48
49 351 dexamethasone) and PONV, and with much more limited evidence perhaps also the vomiting
50
51 352 associated with CVS and motion-induced vomiting. NK₁RAs do not block vomiting in all
52
53 353 patients/subjects exposed to a given stimulus and for CINV the efficacy may depend on the
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55
56 354 phase (potentially, delayed>acute). When nausea is assessed, several studies report no
57
58
59 355 significant benefit although there is some evidence that even if not completely blocking
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3 356 nausea NK₁RAs may reduce its intensity (e.g., see PONV data, **Table 2**). Overall, however, the
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6 357 NK₁RAs are less efficacious or have more variable efficacy against nausea than vomiting over
7
8 358 the same range of stimuli but more quantitative data are needed.

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11 359 We now attempt to explain this differential effect by a detailed analysis of the sites at which
12
13 360 NK₁RAs could act to affect vomiting (section 4) and nausea (section 5).
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19 362 **4. Potential site(s) of action of NK₁RA against retching and vomiting (Figure 3).**

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21
22 363 The sites at which NK₁RA block retching and vomiting have been investigated in animals
23
24 364 (primarily dog and ferret). The findings of these studies are included here because the
25
26 365 afferent, integrative and motor pathways responsible for vomiting are comparable between
27
28 366 animals (e.g., dog, ferret; Onishi et al., 2007) and humans (Stern et al., 2011). For each
29
30 367 potential site of action, we will consider whether it could account for a 'broad spectrum'
31
32 368 effect against vomiting or whether it can only explain an action against vomiting induced by
33
34 369 a specific stimulus or pathway. This analysis also provides an essential background for
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36 370 understanding the differential effects against nausea.
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41
42 371 **4.1.1. Vestibular system.** The vestibular system is essential for induction of nausea and
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44 372 vomiting caused by abnormal body motion. From an evolutionary perspective the vestibular
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46 373 system is considered **as** a component of the mechanisms protecting the body against ingested
47
48 374 toxins (see Treisman 1977, Money & Cheung, 1983, Oman, 2012; Lackner, 2014). Although
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50 375 sensitivity to motion sickness is a predictive factor for both CINV and PONV (Gan, 2006; Warr,
51
52 376 2014) there is no evidence that the vestibular system (including vestibular nuclei) is directly
53
54 377 implicated in the induction of either. During motion sickness, the motor pathways for
55
56 378 vomiting are activated via projections of the vestibular nuclei to the medial and caudal
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379 nucleus tractus solitarius (NTS) ([studies in the](#) cat; Yates et al., 1994; Sugiyama et al., 2011).

380 There is no evidence that NK₁RAs affect transmission in the pathway between the vestibular
381 system, the vestibular nuclei and the NTS, to block induction of vomiting. This contrasts with
382 the actions on this pathway of H₁ and mACh (M₃/M₅) receptor antagonists, used to treat
383 motion sickness (Soto & Vega, 2010; Golding & Stott, 1997; Golding et al., 2018). An action of
384 NK₁RAs within the NTS or at a site(s) deeper in the brainstem is therefore the most likely site
385 for effects against motion-induced vomiting.

386 **4.1.2. Area postrema (AP).** The AP projects to neurones in the medial NTS (mNTS) which can
387 be activated by emetic stimuli applied to the AP (e.g., apomorphine, L-glutamate) and by vagal
388 afferent stimulation ([dog studies](#); Koga & Fukuda, 1992). However, the evidence that NK₁
389 receptors occur within the AP is weak, and their functional relevance uncertain. For example,
390 low levels of [³H]-substance P binding displaced by CP-99,994 (0.1nM-100nM) were found in
391 the ferret AP, as compared to the NTS (particularly subnucleus gelatinosus) (Watson et al.,
392 1995). Ariumi et al. (2000) reported dense ³H-substance P binding in the AP and NTS of ferret
393 but displacement by an NK₁RA was not studied. Comparable evidence is available for *Suncus*
394 *murinus* and rat (Maubach et al., 1997; Andrews & Rudd, 2004). Ionophoretic application of
395 substance P (SP) activated ~50% of AP neurones tested (dog; Carpenter et al., 1988), but
396 although assumed to play a role during vomiting induced by intravenously-administered SP
397 (dog; Carpenter et al., 1984), the receptor type activated by the applied concentration of SP
398 and the link between activation and vomiting was not identified. In the ferret, application of
399 SP to the AP can evoke vomiting (Andrews & Rudd, 2004) but microinjection studies (Gardner
400 et al., 1994) suggest that this response was probably due to SP penetration to the subjacent
401 NTS as the blood-brain barrier between these two areas may have some permeability. A
402 similar explanation of leak into the NTS may account for the block in morphine (s.c.) and

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3 403 reduction in copper sulphate (intra-gastric) induced vomiting in the ferret by administration
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5
6 404 of CP-99,994 or HSP-117 into the AP (Ariumi et al. 2000).
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8
9 405 It is a possibility that NK₁ receptors in the AP could be activated if SP (or other tachykinins)
10
11 406 are released from gut enteroendocrine cells (EEC; Rezzani et al., 2022) to enter the blood
12
13 407 circulation in addition to acting more locally. However, the evidence for this possibility in
14
15
16 408 response to emetic stimuli is weak. Thus, in patients undergoing chemotherapy, the elevation
17
18 409 of serum concentrations of SP during the delayed phase of vomiting was inconsistent (Higa et
19
20
21 410 al., 2006, 2012; Matsumoto et al., 1999; Park et al., 2020; Takahashi et al., 2011) although this
22
23 411 is the phase during which NK₁RA are most effective (see above).
24

25
26 412 Another possibility is that SP could arise from neurones intrinsic to the AP following direct
27
28 413 activation by endogenous or exogenous emetic substances or by abdominal vagal afferents
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30
31 414 projecting to the AP. However, SP-like immunoreactivity (SP-Li) was absent in the AP of a
32
33 415 human infant (Rikard-Bell et al., 1990), consistent with the absence of SP-Li cell bodies in the
34
35
36 416 AP of adult cat, rat (Newton et al., 1985) and ferret (Boissonade et al., 1996). Previously,
37
38 417 extraction studies in humans found some SP in the AP (Zettler & Schlosser, 1955; Cooper et
39
40
41 418 al., 1981) and radioligand binding showed a “moderate” uptake of an NK₁RA by the human
42
43 419 AP (Hietala et al., 2005). Sparse SP-Li nerve fibres have been found in the AP (cat, rat) but
44
45
46 420 their origin is most likely from either vagal nerve afferents terminating there or from the NTS
47
48 421 (Newton et al., 1985); this is consistent with the finding of high-densities of SP
49
50
51 422 immunoreactive fibres in lateral borders of the AP in the ferret (Boissonade et al., 1996).
52
53 423 However, in the least shrew SP-Li fibres and puncta were present at a “moderate” level in the
54
55 424 AP (Ray & Darmani, 2007).
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3 425 Finally, it is worth noting that the concept of the AP as a site at which systemic agents act to
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5
6 426 induce nausea and vomiting was originally derived from studies showing abolition of vomiting
7
8 427 induced by apomorphine (a dopamine D₂ receptor agonist), following surgical ablation of the
9
10 428 AP including in humans (Lindstrom & Brizzee, 1962; Borison & Wang, 1953). Similarly, other
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12
13 429 exogenously administered agents (e.g., morphine, loperamide, cisplatin) can induce emesis
14
15 430 via the AP (Borison, 1989; Bhandari et al., 1992; Percie du Sert et al., 2009). However, there
16
17
18 431 is only limited evidence that systemic endogenous agents which can induce vomiting (e.g.,
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20 432 adrenaline, cholecystokinin [CCK], GDF15, vasopressin), act via the AP, with alternative sites
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22
23 433 of action suggested (Borison, 1989; Borner et al., 2020; Makwana et al., 2022). The above
24
25 434 discussion suggests that SP, acting via NK₁ receptors in the AP should be added to ~~the~~ his list of
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27
28 435 systemic endogenous emetic agents. -

30 436 **4.1.3. Abdominal vagal afferents.**

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33 437 There are two sites at which vagal afferent activation by emetic stimuli could be affected by
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36 438 an NK₁RA; they are not mutually exclusive (**Figure 3**).

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39 439 **4.1.3.1. The peripheral transduction mechanism.** A potential ability of SP from
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41 440 enterochromaffin cells (ECs) to induce vomiting by acting on vagal afferents was hypothesised
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44 441 >30 years ago (Andrews et al., 1988; for details see Andrews & Rudd, 2004). Potentially, such
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46 442 a mechanism would be similar to that for 5-HT, which is released from ECs in response to
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48
49 443 chemotherapeutic agents (e.g., cisplatin) and other emetic stimuli (e.g., rotavirus), causing
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51 444 vomiting by stimulating and sensitizing abdominal vagal afferent terminals via 5-HT₃ receptor
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53
54 445 activation (Andrews & Rudd, 2015; Sanger and Andrews, 2018; for reviews). In rats, treatment
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56 446 with methotrexate or cisplatin increased the number of SP-containing ECs within the
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59 447 intestine, 24h after administration (Machida et al., 2017; Obara et al., 2018) but studies have
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3 448 not yet looked for local release of SP from ECs in response to anti-cancer chemotherapeutic
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6 449 agents or other emetic stimuli. By analogy with 5-HT (see above), any release of SP might be
7
8 450 expected to activate vagal nerve terminals. Recently, SP (1 μ M)-induced depolarisation of
9
10 451 human isolated vagus was shown to be blocked by aprepitant (Smith et al., 2021). However,
11
12 452 the authors used a concentration (10 μ M) at least 10000x the human NK₁ receptor binding
13
14 453 IC₅₀, at or above the concentrations examined for selectivity of action (Tattersall et al., 2000),
15
16 454 and now understood to also activate the mechanosensitive two-pore domain potassium
17
18 455 channel, TRAAK (encoded by the *KCNK4* gene) (McCoull et al., 2022). Interestingly, recordings
19
20 456 from abdominal vagal afferents of ferrets show an interaction between 5-HT and SP (Minami
21
22 457 et al., 2001) and 'cross talk' has been demonstrated between NK₁ and 5-HT₃ receptors in
23
24 458 relation to the 'anti-emetic' effect of palonosetron (Rojas et al., 2014).

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30 459 **4.1.3.2. Vagal afferent to NTS transmission.** Abdominal vagal afferents terminate in the
31
32 460 mNTS (Fukuda & Koga, 1992). There is evidence that SP is a transmitter from vagal afferents
33
34 461 to NTS neurones (cat, Baude et al., 1989; dog, Shiroshita et al., 1997) and for activation of NTS
35
36 462 neurones by iontophoretically applied SP (ferret, Saito et al., 1998; rat, Maubach & Jones,
37
38 463 1997). However, any action of NK₁RA on vagal to NTS transmission must be selective for
39
40 464 afferents involved in induction of vomiting as NK₁RAs do not block the gag reflex, the cardiac
41
42 465 or respiratory components of the von Bezold-Jarisch reflex or apnoea induced by cervical
43
44 466 vagal afferent stimulation (Watson et al., 1995; Fukuda et al., 1999). Additionally, while
45
46 467 systemic administration of the NK₁RA, CP-99,994 in the anaesthetised ferret blocked licking,
47
48 468 swallowing and retching induced by electrical stimulation of the abdominal vagal afferents,
49
50 469 the accompanying rise in blood pressure was unaffected (Watson et al., 1995). This makes it
51
52 470 unlikely that vagal to NTS transmission *per se* is blocked and suggests that the block is either
53
54 471 within the NTS integrative pathways which initiate vomiting or on the output side of the

1
2
3 472 system in the 'central pattern generator' (CPG) for vomiting located in the reticular formation
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6 473 dorsomedial to the retrofacial nucleus (Böttinger complex) in the region of the NA (compact
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8 474 region) and the associated 'prodromal sign centre' (PSC in the semi-compact area of the
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10 475 nucleus ambiguus (Fukuda & Koga, 1991, 1992; Fukuda et al., 2003). Further support for a
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13 476 specific activity on some but not all vagal functions comes from studies in the decerebrate
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15 477 dog where the NK₁RA, GR-205171 (i.v.) blocked fictive retching, the accompanying antral
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18 478 contractile response (most likely the extension of the Retrograde Giant Contraction (RGC) that
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20 479 originates in the small intestine and immediately precedes the onset of retching mediated by
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22
23 480 vagal efferents; see Lang et al., 1986; Lang, 1990), and reduced the hypersalivation (mediated
24
25 481 by PSC) evoked by vagal afferent stimulation, but not the accompanying vagal efferent
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27
28 482 mediated relaxation of the proximal stomach (Furukawa et al., 1998).

29
30 483 It is self-evident that blockade of vagal afferent activation at a peripheral site or vagal afferent
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32
33 484 transmission to the mNTS would only contribute to the anti-vomiting effects of NK₁RAs when
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35 485 the primary stimulus activates the vagus (e.g., acute phase of CINV, possibly gastroparesis;
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37
38 486 Sanger & Andrews, 2023). Therefore, a vagal site of action would not account for block of
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40 487 stimuli acting either only via the AP or the vestibular system so additional site(s) of action
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42
43 488 need to be considered.

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45
46 489 **4.1.4. Brainstem integrative mechanism and the drive to the visceral and somatic motor**
47
48 490 **outputs.** The selective effects of NK₁RA on reflex responses to vagal afferent stimulation (as
49
50 491 above) show that actions of NK₁RA within the brain stem integrative pathways (i.e. NTS, CPG,
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52
53 492 ventral respiratory group [VRG]) are selective to neurones involved in the 'vomiting motor
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55 493 programme' occurring as a result of reconfiguration of the pattern of activity in the
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57
58 494 multifunctional respiratory neurones (Grélot & Bianchi, 1997; Grélot & Miller, 1997) (c.f.
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3 495 cough, yawn, sneeze). These same sets of neurones can also be driven to evoke vomiting by
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6 496 stimuli acting on the vestibular system and the AP (**Figure 4**). Thus, the effects of NK₁RAs on
7
8 497 the brainstem pathways are 'state dependent' and this can explain the selectivity of effects
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10 498 against vomiting; when the brainstem is involved in baseline respiration and some respiratory
11
12
13 499 reflexes there is little dependence on SP as a transmitter but when the pathway reconfigures
14
15 500 and is highly active as occurs for vomiting then it becomes critically dependent on SP.

18 501 Overall, there is evidence for either the presence of SP positive neurones and/or NK₁
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20
21 502 receptors in the key brainstem sites implicated in vomiting.

23
24 503 **4.1.4.1. Nucleus tractus solitarius.** SP-like immunoreactive neurones are present in the
25
26 504 human NTS, particularly subnucleus gelatinosus (mNTS) and this is consistent with studies in
27
28 505 both the cat and ferret (Leslie, 1985; Boissonade et al., 1996). A human brain PET study using
29
30 506 a fluorine-18 labelled NK₁RA reported 'moderate' uptake in the NTS, the nucleus ambiguus
31
32
33 507 and "other nuclei of the vagus" (not specified) (Hietala et al., 2005).

35
36 508 A site of action within the NTS is supported by studies showing microinjection of CP-99,994 in
37
38 509 the "region of the NTS" inhibited, but did not completely block, cisplatin-induced acute
39
40 510 retching and vomiting in the ferret (Gardner et al., 1994; Tattersall et al., 1996). An important
41
42 511 point is that the NK₁RA was injected after retching/vomiting began showing that the
43
44 512 antagonist was blocking a pathway driven by ongoing NK₁ receptor activation. The peptide
45
46 513 NK₁RA, GR-82334 was ineffective against cisplatin-induced retching/vomiting when given
47
48 514 intravenously but was effective (77% reduction) when given into the NTS (Gardner et al.,
49
50 515 1994). Rupniak et al (1997) correlated anti-emetic activity against cisplatin in the ferret with
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52 516 central penetration using a range of NK₁RAs with differing brain penetration. These studies
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54 517 argued strongly that central penetration (at least to the NTS) is required for the acute anti-
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3 518 emetic effect of an NK₁RA. Further support for an action of NK₁RA in the NTS comes from
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6 519 inhibition of SP (1µM)-induced discharge in NTS slices by the NK₁RA HSP-117 (10µM), without
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8 520 affecting baseline spontaneous neuronal discharge (ferret, Saito et al., 1998).
9

10
11 521 **4.1.4.2. Dorsal motor vagal nucleus.** NK₁ receptors are present in the dorsal motor vagal
12
13 522 nucleus (DMVN; ferret, Watson et al., 1995), the site of origin of vagal efferents supplying the
14
15 523 upper digestive tract and regulating the proximal gastric relaxation and RGC prior to the onset
16
17 524 of retching and vomiting (Lang, 1990). In the rat, neurones in the DMVN responsive to gastric
18
19 525 distension±24h post-cisplatin had their baseline activity altered by CP-99,994 (5µM) (Sun et
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21 526 al., 2017) but the results should be interpreted with caution as the efferent projection (e.g.,
22
23 527 the stomach) of the neurones was not identified (e.g., using antidromic collision, Andrews et
24
25 528 al., 1980) and the effects of CP-99,994 were not controlled for by using its less potent 2R, 3R
26
27 529 enantiomer, CP-100,263 (Watson et al., 1995). Although these studies show that the DMVN
28
29 530 is a potential target for NK₁RA it should be noted that preventing the gastric relaxation and
30
31 531 RGC will not block retching and vomiting as they can occur even in the absence of the stomach
32
33 532 (Magendie, 1813) and when the RGC is blocked by atropine (Lang et al., 1986). An action of
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35 533 NK₁RA on the DMVN is therefore unlikely to explain their anti-vomiting action.
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43 534 **4.1.4.3. Ventral brainstem.** Neurophysiological studies of fictive emesis in the dog implicate
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45 535 nuclei in the ventral brainstem (Fukuda & Koga, 1991, 1992; Fukuda et al., 2003; Onishi et al.,
46
47 536 2007). When administered systemically, the NK₁RA, GR-205171 reduces vagal afferent
48
49 537 activation (via the mNTS) of the CPG for vomiting and/or in the pathway linking the NTS to
50
51 538 the CPG via the PSC (Fukuda & Koga, 1991, 1992); immunohistochemistry has demonstrated
52
53 539 the presence of NK₁ receptors in both regions of the dog ventral brainstem (Fukuda et al.,
54
55 540 2003). The CPG connects with the VRG, the location of the neurones driving the phrenic and
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2
3 541 abdominal motor neurones involved in normal respiration as well as retching and vomiting
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5
6 542 (Figure 4).

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9 543 Total block of transmission at either the NTS or CPG is probably not required to stop induction
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11 544 of vomiting; a *reduction* in transmission at either site is likely to be sufficient as triggering
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13 545 vomiting requires a higher frequency stimulus which also lasts for an extended time (e.g.,
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15 546 ~20s of vagal afferent stimulation is required in dog [Koga & Fukuda, 1992] and ferret
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17
18 547 [Andrews et al., 1990]), presumably to prevent inappropriate triggering. It is particularly
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20
21 548 notable that NK₁RAs prevent the 'wind-up' of CPG neurones induced by vagal afferent
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23 549 stimulation and blunts the rise in firing frequency when continuous vagal afferent stimulation
24
25 550 is used, preventing the CPG reaching a threshold for induction of the oscillatory activity
26
27
28 551 required for retching and vomiting (Fukuda et al., 1999, 2003) (Figure 5).

31 552 4.1.5. Overview of site(s) of action against vomiting

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33
34 553 The clinically used NK₁RAs are brain penetrant so when given systemically they can act at both
35
36 554 the central and peripheral neuronal sites involved in retching and vomiting:

- 37
38
39 555 i) For ~~motion-induced~~ vomiting induced by abnormal motion, the brainstem
40
41 556 integrative pathways (NTS, CPG) are the most likely site of action.
42
43
44 557 ii) For stimuli involving abdominal vagal afferents it is possible that NK₁RA can a)
45
46 558 block effects of any SP released from EEC cells onto NK₁ receptors on the
47
48
49 559 peripheral afferent nerve terminals (Minami et al., 2001); b) reduce
50
51 560 tachykininergic transmission between vagal afferents and the NTS (Fukuda et
52
53
54 561 al., 2003; Andrews & Rudd, 2004); c) modulate the brainstem integrative
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56 562 pathways (NTS, CPG) sufficiently to disrupt the signals encoding induction of
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1
2
3 563 vomiting ([Fukuda et al., 1999, 2003](#); [Fukuda & Koga, 1991, 1992](#); [Watson et al.,](#)
4
5 [1995](#)). At present, the evidence for (b) and (c) is stronger.
6
7

8 565 iii) For stimuli acting on the AP via the circulation (or cerebrospinal fluid) including
9
10 566 exogenous emetics and endogenous substances released for example from the
11
12 567 digestive tract because of damage/inflammation (e.g., during the delayed
13
14 568 phase of CINV and chronic phases of infection) (Sanger & Andrews, 2018;
15
16 Andrews et al., 2021, 2023 for references), the brainstem integrative
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18 569 mechanisms (NTS, CPG) are the most likely sites at which vomiting is affected
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20 570 as there is little evidence for an action within the AP itself.
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24
25 572 The NTS and CPG sites of action of NK₁RA are common to all stimuli inducing vomiting.
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27 573 However, for stimuli where abdominal vagal afferent activation occurs two additional sites of
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29 574 action are implicated which, if operational, would block vagal afferent input and thereby
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31 575 make it unnecessary for NK₁RA to act within the NTS and CPG. However, although the NK₁RA
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33 576 are highly effective against vomiting in a number of clinical settings, NK₁ receptors are not the
34
35 577 only receptors involved in all of the pathways and this may explain why they may not always
36
37 578 be fully effective in all patients. For example, SP is likely to co-transmit with a non-peptide
38
39 579 (e.g., glutamate) with the former likely to be released by a higher frequency or different
40
41 580 pattern of nerve firing (Svensson et al., 2019). Further, glutamate has been implicated in
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43 581 abdominal vagal afferent to mNTS transmission as NBQX blocked vagal afferent-induced
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45 582 retching in dog and ferret and the resulting mNTS activation in the dog (Furukawa et al., 2001;
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52
53 583 Onishi et al., 2007). Nevertheless, peptides, as co-transmitters, are known to be involved in
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55 584 network reconfiguration with release determined by both neuronal firing pattern and time
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57 585 (Cropper et al., 2018). Variations in the predominant transmitters in the nausea and vomiting
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59
60 586 pathways, possibly as a response to disease, especially if chronic (e.g., in chronic visceral pain

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3 587 NK₁ receptor availability is downregulated; Jarcho et al., 2013), may also contribute to NK₁RAs
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5
6 588 spectrum of clinical efficacy.
7

8 589 **5. The potential site(s) of NK₁RA action against nausea**

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11 590 'Anti-emetics' must not be assumed to equally affect both nausea and vomiting (Sanger &
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14 591 Andrews, 2022). Accordingly, we discuss the relative effects of NK₁RA against nausea and
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16 592 vomiting by considering specific questions about the pathways involved; this also informs
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18
19 593 directions for development of novel drugs (section 6). Direct experimental data is not
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21 594 available to answer all the questions raised, so some answers are speculative and hypothetical
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23
24 595 but experimentally testable.
25

26 596 **5.1. What information reaches the mNTS from the abdominal vagal afferents in the** 27 28 29 597 **presence of NK₁RAs?**

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31
32 598 This question is relevant to both CINV and gastroparesis where abdominal vagal afferents are
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34
35 599 implicated in genesis of nausea and vomiting (Sanger and Andrews, 2018, 2023). Regardless
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37 600 of whether NK₁RAs reduce vagal afferent firing by acting peripherally (e.g., Minami et al.,
38
39 601 2001) or centrally (e.g., Fukuda et al., 2003), the degree of activation, and the pattern,
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41
42 602 frequency and duration of abdominal vagal afferent activity required for induction of nausea
43
44 603 as compared to vomiting is unknown. It is, nevertheless, a reasonable assumption that nausea
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46 604 requires less intense activation of afferent pathways than vomiting (see Horn 2014 for
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48
49 605 discussion in relation to the vagus). The effects of NK₁RAs on vagal afferent activity evoked by
50
51 606 a wide range of stimulus intensities, ± substances which may sensitise the afferents (e.g., 5-
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53
54 607 HT, prostaglandins), need to be investigated directly to answer the above question. The
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56 608 development of vagal afferent recording techniques in humans may eventually allow direct
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59 609 testing of this hypothesis (Ottaviani et al., 2020).
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3 610 **5.2. Do differential effects of NK₁RAs on the NTS account for the differential effects against**
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6 611 **nausea and vomiting?**

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9 612 NK₁RA modulation of the vagal afferent drive to the mNTS and/or transmission within the NTS
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11 613 (vagal, AP and vestibular inputs) could contribute to a *reduction* in nausea *intensity* by
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13 614 decreasing the drive from the NTS to supra-medullary structures implicated in the sensation
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15 615 of nausea. However, the evidence for such an action is poor, as discussed below.

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19 616 **5.3. Are NK₁ receptors in the mid-brain and cerebral hemispheres involved in potential anti-**
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21 617 **nausea effects of NK₁RA?**

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24 618 In contrast to vomiting, the brain pathways responsible for nausea are not well defined. The
25
26 619 majority of brain imaging studies are in subjects reporting nausea induced by illusory-self
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28 620 motion (vection; visually-induced motion sickness, VIMS), with only single studies using 'real'
29
30 621 motion or a pharmacological challenge (see Varangot-Reille et al., 2023) making it difficult to
31
32 622 assess whether the findings have general applicability. Cortical and sub-cortical areas
33
34 623 consistently showing an increase in activity in healthy volunteers reporting nausea include
35
36 624 the frontal lobe (e.g., anterior cingulate cortex), occipital lobe (e.g., posterior cingulate
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38 625 cortex), temporal lobe (e.g., amygdala, part of the 'limbic cortex') and basal ganglia (e.g.,
39
40 626 putamen) (Varangot-Reille et al., 2023).

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45
46 627 NK₁RA binding in the human brain using PET shows NK₁ receptors in several brain areas
47
48 628 implicated in nausea. For example, aprepitant has receptor occupancy of 50% in the caudate
49
50 629 and 90% in the putamen (basal ganglia) at plasma concentrations of $\sim 2 \times 10^{-9}$ M and $\sim 2 \times 10^{-8}$
51
52 630 M respectively (Bergstrom et al., 2004). Based on the striatal occupancy levels, the authors
53
54 631 concluded that the recommended 'anti-emetic' aprepitant regime of 125mg on day 1 and
55
56 632 80mg on the subsequent two days in CINV would result in an occupancy of >90% (Bergstrom
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3 633 et al.,2004). Hietala et al., (2005) using the same radioligand confirmed the highest uptake in
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5
6 634 the caudate and putamen and levels ~50% in regions of the occipital lobe (e.g., posterior
7
8 635 cingulate cortex), temporal lobe (e.g., amygdala [forms the 'limbic cortex' with the
9
10 636 hippocampus]) and frontal lobe (anterior cingulate cortex) all of which have been implicated
11
12
13 637 in nausea in brain imaging studies (Varangot-Reille et al., 2023).

14
15
16 638 Pharmacological MRI studies provide additional unexpected insights. Using fosaprepitant
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18 639 (pro-drug of aprepitant) the NK₁ receptor distribution profile identified in the above PET
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20
21 640 studies was confirmed but in addition identified *activation* of brain areas (e.g., cerebellum,
22
23 641 red nucleus) where there were thought to not be any NK₁ receptors, an effect attributed to
24
25 642 “downstream pharmacodynamic effects” (Borsook et al., 2012, Fig. 2; Upadhyay et al., 2011).
26
27
28 643 Such effects demonstrate that in identifying brain sites of drug action we should not only
29
30 644 consider regions which have their activity inhibited; activation of a pathway which itself is
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32
33 645 inhibitory on the function under consideration should not be overlooked. Brain imaging
34
35 646 studies in nausea have identified areas with both *increased* and *decreased* activity (Farmer et
36
37
38 647 al., 2015).

39
40
41 648 Although we focus on areas directly implicated in nausea, as nausea involves heightened
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43 649 anxiety, the potential anxiolytic effects of NK₁RA (Hoppe et al., 2018) could indirectly
44
45 650 contribute to reducing nausea scores especially in chronic conditions (e.g., gastroparesis).

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48
49 651 Overall, NK₁RAs do not appear to have a consistent ability to reduce nausea induced by
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51 652 multiple stimuli despite high levels of NK₁RA binding in many of the relevant brain areas.
52
53 653 Therefore, it is reasonable to conclude ~~that~~ that NK₁ receptors do not have a major role in
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55
56 654 transmission in the ‘higher’ brain regions currently implicated in nausea. We note that NK₁RA
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58 655 efficacy in depression (e.g., Keller et al., 2006; Ratti et al., 2013), panic disorder (Fujimura et
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2
3 656 al., 2009), pain (Boorsook et al., 2012) and anxiety (Hoppe et al., 2018) are also variable and
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6 657 less than might be anticipated from NK₁ receptor distribution.
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8 658 **5.4. Do NK₁ RA reduce vasopressin secretion?**

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10
11 659 Relatively high plasma concentrations of arginine vasopressin (AVP) are associated with
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14 660 nausea induced by stimuli activating the vestibular system, AP and abdominal vagal afferents
15
16 661 (Makwana et al., 2022). A causal link between AVP and nausea is not proven, but a credible
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18
19 662 possibility in at least some clinical scenarios involves the actions of low concentrations of AVP
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21
22 663 on gastric pacemaker activity (the interstitial cells of Cajal; ICC), synergising with actions of
23
24 664 other nauseogenic stimuli to disrupt motility and hence, initiate vagal afferent discharge; the
25
26 665 demonstration of synergy between two different nauseogenic stimuli (adrenaline + AVP) was
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28
29 666 used to argue that antagonism of one alone (e.g., the effects of vasopressin) might reduce
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31
32 667 but not prevent the symptom of nausea (Makwana et al., 2022). In dogs, following cisplatin
33
34 668 administration, the NK₁RA maropitant was without significant effect on the peak [AVP] or the
35
36 669 area under the curve whereas both were significantly reduced by ondansetron (Kenward et
37
38
39 670 al., 2017). In human patients treated with cisplatin the acute rise in [AVP] was blocked by
40
41 671 ondansetron (Barreca et al., 1996) as in the dog, but as far as we are aware similar patient
42
43 672 studies have not been performed with an NK₁RA.
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46 673 **5.5. Do NK₁RA have a role in treating nausea by gastric motility modulation?**

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48
49 674 The presence of SP in the digestive tract in nerve terminals and EEC (Sanger, 2004) and of NK₁
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51
52 675 receptors on smooth muscle cells and Interstitial Cells of Cajal (ICCs) (Lavin et al., 1998;
53
54 676 Faussonne-Pellegrini, 2006; Cheng et al., 2007; Liu & Rudd, 2023) makes the digestive tract a
55
56 677 potential target for NK₁RA. However, an ability of NK₁RAs to affect nausea by a direct effect
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58
59 678 on gastric motility is unlikely. Thus, in healthy volunteers there is little evidence for an effect
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3 679 of NK₁RA on digestive tract motility (assessed by gastric emptying or compliance, or small and
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6 680 large bowel propulsion) (Madsen & Fuglsang 2008; Ang et al., 2013; Jacob et al., 2017; Khanna
7
8 681 et al., 2022). Interestingly, after a dyspeptogenic meal, aprepitant (125 mg on day 1, then 80
9
10 682 mg on days 2–5) increased fasting, postprandial, and accommodation gastric volume but
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12
13 683 increased aggregate symptoms, nausea, and pain scores after ingestion of the maximum
14
15 684 tolerated volume; the authors suggested that differences between these studies may be
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17
18 685 dependent on what is measured and on the application of acute- or longer-term dosing with
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20 686 aprepitant (Jacob et al., 2017) but activation of TRAAK channels (see above) should also be
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22
23 687 considered.

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25 688 Dysrhythmic gastric electrical activity has been associated with nausea in disorders including
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28 689 gastroparesis, CUNV, functional dyspepsia, gastro-oesophageal reflux disease, all linked with
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30
31 690 loss of ICCs (Koch 2014; O'Grady et al., 2021). Thus, any ability of NK₁RAs to affect ICC
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33 691 functions (see above) could, in theory, have an influence on *induction* of nausea although an
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36 692 effect on vagal afferent signalling or the NTS seems more likely based on current knowledge.

37 38 693 **6. Concluding comments.**

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41 694 Irrespective of the stimulus, the effects of NK₁RA against *vomiting* are explicable by a central
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43
44 695 action on the NTS and CPG in the brain stem with potential additional peripheral effects on
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46
47 696 vagal afferent activity when activated by an emetic stimulus (e.g., HEC, some ingested toxins).
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49 697 NK₁RAs are not 100% effective against vomiting in humans (c.f., pre-clinical studies, **Table 1**)
50
51 698 implicating other transmitter/receptor systems and explaining why optimal *anti-vomiting*
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53
54 699 therapy may require drug combinations (e.g., netupitant + palonosetron + dexamethasone)
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56 700 in treating complex situations such as HEC. An additional role for other neurotransmitters/co-
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58
59 701 transmitters (e.g., glutamate) has not yet been fully explored.
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3 702 A reduction in the projection of information from the NTS to the higher brain regions by
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6 703 suppression of NTS pathways and the drive from the abdominal vagal afferents is likely to
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8 704 contribute to any reduction of nausea by NK₁RAs, no matter how sub-optimal ~~and~~
9
10 705 ~~disappointing~~ the current evidence suggests. It could be argued that the distribution of NK₁
11
12
13 706 receptors in cortical and subcortical structures implicated in nausea may predict efficacy
14
15 707 against nausea, but it is also possible these receptors are coupled to non-nauseagenic
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17
18 708 pathways, such as those involved in fear and/ or anxiety (which nonetheless may contribute
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21 709 to the overall sensation of nausea).

22
23 710 Mechanistically, vomiting is well understood and studies with NK₁RAs show that targeting the
24
25
26 711 NTS/CPG in the brainstem is a valid approach and adverse effects on the respiratory,
27
28 712 cardiovascular and digestive systems all regulated from the brainstem appear to be avoided.
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30
31 713 The apparent specificity of NK₁RA blockade of vomiting likely reflects the functional
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33 714 reconfiguration of the neural network to coordinate retching/vomiting where tachykininergic
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36 715 signalling becomes critical (state dependence; see Doi & Ramirez 2010 for a study of NK₁
37
38 716 receptors and state dependent functions of pre-Bötzinger complex respiratory neurones). The
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41 717 NTS and CPG need investigating in emetic species using neurophysiological studies similar to
42
43 718 those in rodents showing complex interaction between NK₁ receptor activation, glutamate
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45
46 719 and GABA release (Bailey et al., 2004) to understand how NK₁RAs are 'functionally specific'
47
48 720 for vomiting.

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50
51 721 Nausea remains a challenge as there are major gaps in knowledge of the cerebral pathways
52
53 722 involved and hence in identifying potential receptor targets to identify 'broad spectrum' anti-
54
55
56 723 nausea drugs. As the insular cortex is the "highest" cortical region consistently activated in
57
58 724 subjects reporting nausea (Varangot-Reille et al., 2023) this would be a logical place to target
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1
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3 725 a drug to block nausea although the associated physiological changes (e.g., regional cold
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6 726 sweating, AVP secretion) may not be blocked as they involve 'lower' brain regions. An
7
8 727 alternative approach is to selectively suppress transmission of 'nauseagenic' signals from the
9
10 728 NTS to the mid-brain with consideration being given to the parabrachial nucleus as a potential
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12
13 729 target. Whilst this might be achieved by a combination of receptor antagonists the use of
14
15 730 agonists (e.g., GABA_B, CB₁, 5-HT_{1A}, ghrelin, opioid) may provide a more fruitful approach as
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17
18 731 this makes fewer assumptions about the nature of the nauseagenic stimulus (Sanger &
19
20 732 Andrews, 2006). A gastric inhibitory polypeptide-1 receptor agonist has been shown to block
21
22 733 the acute vomiting induced by the chemotherapeutic agent cisplatin in the ferret (Borner et
23
24 734 al., 2023), further extending the list of receptor agonists with 'anti-emetic' potential. The
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26 735 electroceutical approaches to treatment of gastrointestinal symptoms, including nausea
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28 736 (Horn et al., 2019; Ramadi et al., 2020), may provide a route by which this system may be
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31 737 controlled but further study is needed to determine the pathways and cell types involved. A
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33
34 738 final approach is to target the abdominal vagal afferents at a peripheral site but this would
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36
37 739 only be applicable when a peripheral release of SP has been demonstrated and when the
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39
40 740 original signal originates from disordered upper digestive tract function (e.g., gastroparesis;
41
42 741 Sanger & Andrews, 2023). Research into the development of anti-nausea drugs is further
43
44 742 hampered by the paucity of human volunteer studies using stimuli other than motion. Studies
45
46 743 of 'anti-emetics' have been undertaken in humans using apomorphine, ipecacuanha and
47
48 744 morphine as challenges (Proctor et al., 1978; Minton et al., 1993; Soergel et al., 2014) and a
49
50 745 wider range of challenges could be identified from the side effect profile of licenced drugs
51
52 746 (e.g., GLP-1 receptor agonists). The final issue is quantification of nausea. The present
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54
55 747 assessment tools widely used in clinical trials rely on an accurate classification of nausea by
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57
58 748 the subject, an assumption that subjects are reporting the same sensation and reliable
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3 749 recollection as data may only be collected daily giving data with a low temporal resolution
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5
6 750 (see Varangot-Reille et al., 2023, Suppl. files). The heterogeneity of nausea assessment
7
8 751 instruments was identified as an issue in a recent US, F.D.A. review of endpoints in CINV and
9
10 752 PONV studies which identified nausea assessment as an “opportunity for continued research
11
12
13 753 and development” (Gabby et al., 2021). A reliable, subject independent method for assessing
14
15 754 nausea in real time is needed to ensure an accurate assessment of candidate drug efficacy
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17
18 755 (Andrews & Sanger, 2014).

19
20
21 756 We close by dedicating this review to a colleague and friend Wes Miner who died while we
22
23 757 were drafting this review. Wes was co-author of the first paper demonstrating the remarkable
24
25 758 ‘anti-emetic’ effect of a 5-HT₃ receptor antagonist (Miner & Sanger, 1986) and spent his
26
27
28 759 career in the pharmaceutical industry. In a note to one of the authors (PLRA) in January 1999
29
30 760 Wes made the following insightful comment of relevance to this review regarding the Navari
31
32 761 et al., 1999 paper reporting some of the earliest clinical data on NK₁RA: “*results are very, very*
33
34 762 *good and I think this will just about wrap it up for pharmaceutical company interest in the N+V*
35
36 763 *area for the next 20 years.*” As Wes predicted, there have indeed been no major advances in
37
38 764 the development in drugs affecting vomiting and especially nausea in the last 20 plus years
39
40 765 and as this review shows the accepted dogma that ‘anti-emetics’ equally affect nausea and
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43 766 vomiting requires challenging; a view with which we are sure Wes would concur.
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51 768 **References**

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39 1682 shrew (*Cryptotis parva*). *Neurochemistry International*, 122, 106-119.

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42 1684 **Figure legends**

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45 1685 **Figure 1.** A summary of the major pathways implicated in the motor events of vomiting and
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47 1686 the sensation of nausea. The diagram shows the major inputs (vestibular system, abdominal
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49 1687 vagal afferents, area postrema) to the nucleus tractus solitarius (NTS) in the brainstem by
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51 1688 which both nausea and vomiting are evoked. The mechanical events of vomiting only
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53 1689 require activation of brainstem and spinal cord nuclei. Most notable are the dorsal motor
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55 1690 vagal nucleus (DMVN) projecting vagal efferents to the digestive tract to induce gastric
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3 1691 relaxation and intestinal retrograde giant contraction, and the ventral respiratory group
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6 1692 (VRG) of neurones driving the spinal phrenic nerve nucleus (PNN) responsible for
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8 1693 contraction of the costal diaphragm which together with the anterior abdominal muscles
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10 1694 (not shown) provides the main force compressing the stomach and leading to forceful oral
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13 1695 ejection of contents. Nausea requires activation of cerebral structures and is associated with
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15 1696 the secretion of high concentrations vasopressin (AVP) from the hypothalamic /pituitary axis
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18 1697 but other hormones are also released (e.g., cortisol). The main sympathetic motor outputs
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20 1698 associated with nausea are shown in the right-hand red rectangle and are a consequence of
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23 1699 descending pathways from the “visceromotor cortex” activating the pre-sympathetic nuclei
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25 1700 (PSN) in the brainstem which in turn drive the pre-ganglionic sympathetic neurones in the
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28 1701 spinal cord (ILH). For details and references see text. Adapted and modified from Varangot-
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30 1702 Reille et al., 2023.

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33 1703 **Figure 2.** The effects of the NK₁ receptor antagonist (NK₁RA) tradipant *versus* placebo on
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35 1704 motion sickness signs and symptoms, are shown for Vomiting (left diagram) and for Nausea
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37 1705 (right diagram). Motion sickness was provoked by motion at sea. Voyages inevitably varied
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39 1706 in terms of the weather and roughness of waves, consequently the data are presented in
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41 1707 terms of all data (i.e. all voyages combined) and split by lower wave motion ‘calm seas’ and
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43 1708 higher wave motion ‘rough seas’. Vomiting is shown as % incidence. Nausea is shown as
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45 1709 the mean sickness rating scale, with higher scores indicating more severe nausea. Note the
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47 1710 differences in levels of statistical significance for the different comparisons. Data were
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53 1711 adapted from Polymeropoulos et al, 2020.

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3 1713 **Figure 3.** A diagrammatic summary of the central and peripheral sites at which NK₁ RA could
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5 1714 act to reduce nausea and vomiting. Abbreviations: AP= Area Postrema; CPG= Central
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7 1715 pattern Generator for vomiting; DMVN=Dorsal Motor Vagal Nucleus EC=Enterochromaffin
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9 1716 cell; EEC=Enteroendocrine Cell; EP=Epithelial cell; HPV= Hepatic Portal Vein; ICC= Interstitial
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11 1717 Cells of Cajal; NK₁RA= Neurokinin₁ receptor antagonist; NTS= Nucleus Tractus Solitarius;
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13 1718 VNN= Vestibular Nerve Nucleus. In the periphery, NK₁ receptors located on the gastric
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15 1719 smooth muscle, the enteric neurones and possibly the ICCs could modulate motility
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17 1720 contributing to a reduction in nausea when disordered motility is implicated (e.g.,
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19 1721 gastroparesis). NK₁ RA can prevent activation/sensitisation of both muscle
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21 1722 mechanoreceptors and epithelial 'chemoreceptive' vagal afferents driving nausea and
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23 1723 vomiting by locally released SP. The latter are particularly implicated in nausea and vomiting
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25 1724 induced by anti-cancer chemotherapy, gastric irritant and some infections (e.g., rotavirus).
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27 1725 NK₁ receptors are also implicated in inflammation the reduction of which by NK₁ RA could
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29 1726 also contribute to reducing afferent drive. The sites at which vomiting can be blocked all
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31 1727 reside in the brainstem (particularly the NTS and CPG) although it is unclear if the AP is a site
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33 1728 of action other than when vomiting is induced by an NK₁ receptor agonist. Induction of
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35 1729 nausea requires activation of 'higher' brain regions and although NK₁ receptors are present
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37 1730 at multiple sites in the mid-brain and cerebral hemispheres the data implicating them in
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39 1731 anti-nausea effects is circumstantial. See text for details and references.

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43 1733 **Figure 4 A-D.** Diagrammatic representation of a longitudinal section through the brainstem
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45 1734 showing the key nuclei and pathways implicated in retching, vomiting and nausea.
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47 1735 Abbreviations: AP=area postrema; CPG= Central Pattern Generator responsible for the
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49 1736 generation of the oscillatory pattern of activity driving the somato-motor pathways for
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51 1737 retching and vomiting in the VRG; DMVN= Dorsal Motor Nucleus of the Vagus, origin of pre-
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53 1738 ganglionic efferents to the digestive tract; NTS= Nucleus Tractus Solitarius; VRG= Ventral
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55 1739 Respiratory Group of neurones; Ph= Phrenic nerve nucleus in cervical (C3-C-5) spinal cord;
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57 1740 Ab= Abdominal muscle motor neurones in ventrolateral thoracic and lumbar spinal cord.
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59 1741 See text for further explanation and references.
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3 1742 A: Resting state; B: Low level of activation of pathways inputting to the NTS resulting in
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5 1743 activation of NTS and ascending pathways inducing nausea including secretion of anti-
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7 1744 diuretic hormone (ADH/AVP) from the posterior pituitary; C= More intense activation of the
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9 1745 inputs results in more intense nausea and proximal gastric relaxation, a preparatory action
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11 1746 to accommodate refluxed material resulting from the Retrograde Giant Contraction
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13 1747 originating in the small intestine when the input is sufficient to exceed the threshold for
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15 1748 induction of retching and vomiting when the phrenic and abdominal motor neurones are
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17 1749 activated. Note that The CPG and the DMV outputs must be coordinated (dotted arrow) as
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19 1750 retching does not begin until the RGC reaches the gastric antrum.
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23 1752 **Figure 5.** Diagrammatic representation of the neuronal discharge pattern in the medial
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25 1753 nucleus tractus solitarius (mNTS) and the Central pattern Generator (located in the compact
26
27 1754 part of the nucleus ambiguus, cAMB) in response to electrical stimulation of infra-cardia
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29 1755 vagal afferents based on neurophysiological studies in the dog reported in Koga & Fukuda,
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31 1756 (1992), Fukuda et al., (2003), and Onishi et al., (2007). Vagal afferent stimulation results in a
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33 1757 uniform increase in NTS firing frequency which ceases at the end of stimulation. NTS
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35 1758 activation results in CPG activation after a lag period and is followed by a progressive
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37 1759 increase in frequency which is due to 'wind-up'. The CPG firing frequency reaches at
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39 1760 threshold at which the pattern becomes oscillatory with the output driving the ventral
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41 1761 respiratory group of neurones (VRG) which in turn drive the phrenic and abdominal motor
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43 1762 neurones responsible for the mechanical events of retching a vomiting. The CPG oscillations
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45 1763 causing retching are shorter and smaller magnitude than the ultimate burst of activity
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47 1764 resulting in vomiting and continue beyond the period of vagal afferent stimulation showing
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49 1765 a protracted effect of the initial stimulation.
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Species	Neurokinin ₁ receptor antagonist	Stimulus details	References
Cytotoxic anti-cancer drugs			
Acute phase of cisplatin			
Ferret	CJ-11,974 CJ-17, 493 CP-99,994 CP-122,721 GR203040 L-742,694 L-741,671 Netupitant SCH 619734	Given either i.p or i.v.	Duffy et al., 2012; Lau et al., 2005; Rudd et al., 2016; Rupniak et al., 1997; Shishido et al., 2008; Tattersall et al., 1996 Watson et al.,1995;
Dog	FK886 Maropitant		De la Puente -Redondo et al., 2007; Furukawa et al.,2013; Kenward et al., 2017; Vail et al., 2007
Suncus	GR203040		Gardner et al.,1995
Doxorubicin emesis (5 days)			
Dog	Maropitant	i.v.	Rau et al., 2010
Delayed phase of cisplatin			
Ferret	CJ-11, 974 Netupitant SCH619734	Given either i.p or i.v.	Duffy et al., 2012; Rudd et al., 2016; Tsuchiya et al., 2002
Cyclophosphamide			
Ferret	GR203040 GR205171	Given i.p.	Gardner et al., 1995, 1996
Pharmacological agents			
Apomorphine			
Dog	CP-99, 994 FK886	Given s.c.	Furukawa et al.,2013; Sedlacek et al., 2008; Watson et al., 1995

	Maropitant		
Ferret	CP-99,994 Netupitant SCH619734		Duffy et al., 2012; Rudd et al., 2016; Tattersall, et al., 1994; Watson et al., 1995.
Brimonidine			
Cat	Maropitant	Sedative given as eye drops	Kanda et al., 2020
Copper sulphate			
Dog	CP-99,994	Given p.o.	Andrews et al., 2001; Watson et al., 1995
Ferret	CP-99,994 Netupitant	Given p.o.	Rudd et al., 2016; Watson et al., 1995
Ethanol			
Suncus	CP-99,994	Given i.p.	Chen et al., 1997
FPL64176			
Least shrew	Netupitant	L-type Ca ⁺⁺ channel agonist	Zhong et al., 2018
GR73632			
Least shrew	CP-99,994	NK ₁ receptor agonist; given i.p.	Darmani et al., 2011
Halothane/N₂O			
Suncus	GR205171	Inhaled	Gardner & Perren, 1998
Ipecacuanha			
Ferret	CP-99,994 CP-122,721, GR205171, GR203040 Netupitant R116301	Given p.o.	Gardener et al., 1995, 1996; Gonsalves et al., 1996; Megens et al., 2002; Watson et al., 1995
Dog	GR203040 GR205171 Maropitant	Given p.o.	Gardner et al., 1995, 1996; Sedlacek, et al., 2008
Lycorine			
Dog	Maropitant	Alkaloid from daffodils; given s.c.	Kretzing et al., 2011

2-methyl 5-hydroxytryptamine			
Least shrew	CP-99,994	5-HT ₃ receptor agonist; given i.p. Note no significant effect of CP-99, 994 given at same dose that blocked NK ₁ agonist (GR73632; see above)	Darmani et al., 2011
Naloxone			
Suncus	CP-99,994	Given s.c.	Rudd et al.,1999
Nicotine			
Suncus	CP-99,994 CP-122,721 RP67580	Given s.c.	Rudd et al., 1999; Tattersall et al., 1995
Opiate receptor agonists			
Ferret	CP-99,994	Loperamide; s.c.	Zaman et al., 1999
Ferret	GR203041	Morphine; s.c.	Gardner et al., 1995
Dog	Maropitant	Morphine; s.c.	Lorenzutti et al., 2016, 2017
Dog	Maropitant	Morphine; s.c.	Koh et al., 2014
Dog	Maropitant	Hydromorphone; i.m.	Claude et al., 2014
Dog	Maropitant	Hydromorphone; i.m.	Hay Kraus 2014
Dog	Maropitant	Hydromorphone; i.m. + acepromazine; i.m.	Johnson, 2014
Cat	Maropitant	Dexmedetomidine +morphine; i.m.	Martin-Flores et al., 2016
Phosphodiesterase IV Inhibitors			
Ferret	CP-99,994	R-rolipram, CT-2450, RS14203; given p.o.	Robichaud et al., 1999
Prostaglandin E₂			
Ferret	CP-99,994	Given i.p.	Kan et al., 2006
Pyrogallol			
Ferret	CP-99,994	Reactive oxygen species donor; given i.p.	Andrews & Matsuki, unpublished.
Resiniferatoxin			
Suncus	CP-99,994	Given s.c.	Andrews et al., 2000
Tranexamic acid			
Dog	Maropitant	Fibrinolytic	Kantyka et al., 2020
U46619			
Suncus	CP-99,994	TP agonist; given i.p.	Kan et al., 2003

Xylazine			
Cat	R116301	Given s.c.	Megens et al., 2000
Non- pharmacological stimuli			
Motion			
Cat	CP-99,994	Ferris Wheel	Lucot et al., 1997
Dog	Maropitant	Car journey	Conder et al., 2008
Suncus	GR203041 Netupitant	Horizontal motion	Gardner et al., 1995 Rudd et al., 2016
Total Body Radiation			
Ferret	GR203040 GR205171,	X-radiation	Gardner et al., 1995, 1996
Ferret	CP-99, 994	X-radiation (3 weeks post abdominal vagotomy and greater splanchnic nerve section)	Andrews & Watson, unpublished observations
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.	Fukuda et al., 1999; Furukawa et al., 1998
Ferret (urethane anaesthesia)	CP-99,994		Watson et al., 1995
Parvoviral enteritis-induced vomiting			
Dog	Maropitant		Yalcin & Keser, 2016
Post-neurosurgery vomiting			
<i>Macaca fascicularis</i> , <i>Macaca mulatta</i>	Maropitant		Steinbach et al., 2018

Compound	Efficacy against nausea in PONV	Reference
Neurokinin₁ receptor antagonist given alone and compared to a placebo or active comparator		
CP-122,721 (100mg, 200mg, p.o.)	In patients undergoing abdominal hysterectomy the maximum nausea score appeared to be reduced by CP-122, 721 in both dose groups compared to placebo but any effect was not statistically significant (N=20-24). VAS nausea score did not differ between ondansetron, CP-122, 721 and combination groups (N=52-53).	Gesztesi et al., 1998 (abstract), 2000.
Vofopitant (GR-205171) (25mg, 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 (2h complete control nausea: 55% v. 20%) and reduced the severity of nausea over the entire 24h post-operative observation period.	Diemunsch et al., 1999.
Aprepitant (L-754,030)	Peak nausea score distribution (interquartile range) was significantly lower ($P<0.05$, N=280-293) for both aprepitant groups (40 /125mg) compared to ondansetron (4mg) but the percentage of patients	Diemunsch et al., 2007.

(40mg/125, p.o.)	reporting no significant nausea was only significantly higher than that of ondansetron for 40mg aprepitant (62% v. 53%). For vomiting both doses of aprepitant were superior to ondansetron and blocked vomiting in ~85% of patients. Open abdominal surgery.	
Aprepitant (L-754,030) (80mg 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 v. 19.0±2.2) and at two hours (9.7±2.1 v. 19.4±3.5) but not in the subsequent 46hours. The complete response rate over 48h did not differ (74% v. 77%)	Moon et al., 2014
Aprepitant (L-754,030) (40mg p.o.)	In patients undergoing plastic surgery compared to placebo the severity of nausea was lower ($p=0.014$, $N=75/arm$) in the aprepitant group between 0-48h post-surgery. Vomiting incidence was also significantly lower in the aprepitant group (7/75 v. 22/75, $p=0.003$).	Vallejo et al., 2012
Vestepitant (4-36mg, 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 (4mg) alone and any dose of vestepitant ($N=7-15/group$) given subsequently but overall vestepitant was superior to ondansetron (10.1-22.9% improvement	Kranke et al., 2015

	except at a dose of 18mg when there was a -1.2 % difference.	
Fosaprepitant (150mg, 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 0-2h (2% v. 17%), 0-24h (2% v. 28%) and at 0-48h (2% v. 29%). However, the percentage of patients reporting nausea in the fosaprepitant was higher than for vomiting at all time points (e.g., at 0-2h, nausea 41% v. vomiting 2%).	Murakami et al., 2017
Neurokinin₁ receptor antagonist given in addition to a standard treatment and compared to identify any additional benefit		
Casopitant (GW679769) (50,100,150mg, p.o.)	Only female patients, laparoscopic /laparotomic gynecological procedure or laparoscopic cholecystectomy. All doses of casopitant further reduced the percentage of patients with vomiting at both 0-24h (ondansetron 28.6 % v. casopitant + ondansetron 4.3%-9.3%) 0-48 h time points (ondansetron 32.9 % v. 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 than the % experiencing vomiting for all three doses of casopitant + ondansetron (casopitant 50 mg, nausea	Singla et al., 2010

	70.0% v. vomiting 9.3%; 100mg, nausea 63.6% v. vomiting 4.3%; 150mg, nausea 66.4% vs vomiting 7.1%). The intensity of nausea did not differ between the three casopitant doses.	
Aprepitant (L-754,030) (40mg, p.o.)	Craniotomy patients. No difference between nausea scores, incidence or significant nausea between aprepitant and ondansetron (4mg) up to 48h post-surgery but the study may not have been sufficiently powered to see statistical differences at all time points.	Habib et al., 2011
Vestepitant (4-36mg, i.v.)	Given to patients with breakthrough emesis; Nausea scores did not differ between patients with either complete response (no vomiting) or treatment failure and between vestepitant and ondansetron groups.	Kranke et al., 2014.
Aprepitant (L-754,030) (80mg, p.o.)	In patients undergoing bariatric surgery aprepitant increased the number of patients without nausea and vomiting (42.18% v. 36.67%) compared to ondansetron alone but this was not significant and nausea scores were unaffected by aprepitant.	Sinha et al., 2014.
Aprepitant (L-754,030) (80mg, p.o.)	Laparooscopic gynaecological surgery. Significant ($p=0.014$) additional reduction in nausea incidence (24h) when aprepitant was given with ondansetron but no change in severity of nausea or incidence of	Ham et al., 2016.

	vomiting.	
Systematic review and Meta-analysis		
Aprepitant/rolapitant/casopitant	Systematic review and meta-analysis of 14 randomised control trials of three NK ₁ RAs in patients undergoing mainly either abdominal or gynaecological surgery including open abdomen approaches. Aprepitant showed an additional increase of 31% in the patients protected from nausea compared to placebo with an overall incidence of 76.1%.	Liu et al., 2015. Note that Table 2 in this paper contains a detailed summary of results from all studies included.
Aprepitant (L-754,030) (80mg, p.o.)	Systematic review and meta-analysis of 7 randomised control trials of aprepitant (80mg) in patients undergoing laparoscopic procedures. RR for nausea 0.56 v. 0.2 for vomiting compared to placebo or no anti-emetic therapy (see supplementary Figure 2,). Risk of vomiting reduced by 80% in first two hours post-operatively vs. 44% for nausea.	Cavaye et al., 2021. Note that Table 2 in this paper contains a detailed summary of results from all studies included.

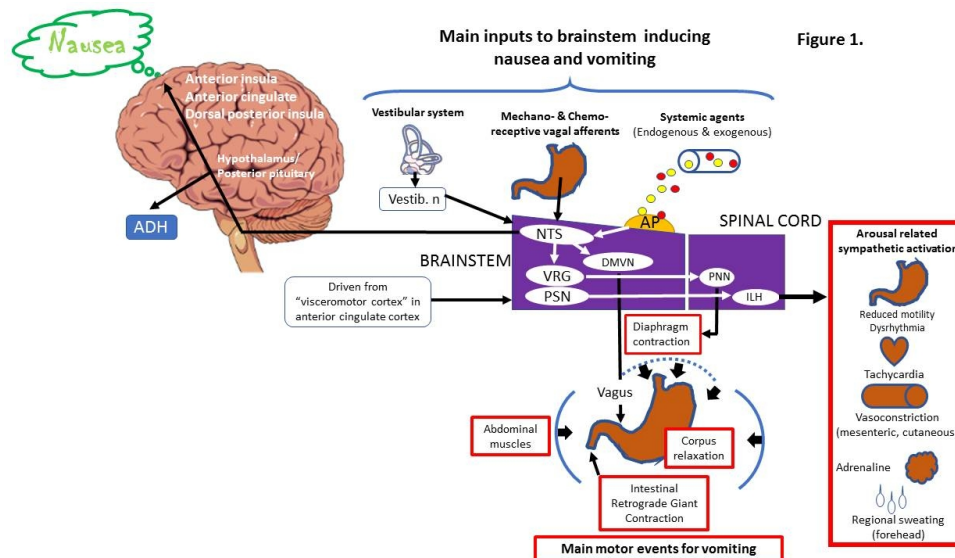


Figure 1. A summary of the major pathways implicated in the motor events of vomiting and the sensation of nausea. The diagram shows the major inputs (vestibular system, abdominal vagal afferents, area postrema) to the nucleus tractus solitarius (NTS) in the brainstem by which both nausea and vomiting 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) 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 Varangot-Reille et al., 2023.

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Figure 2

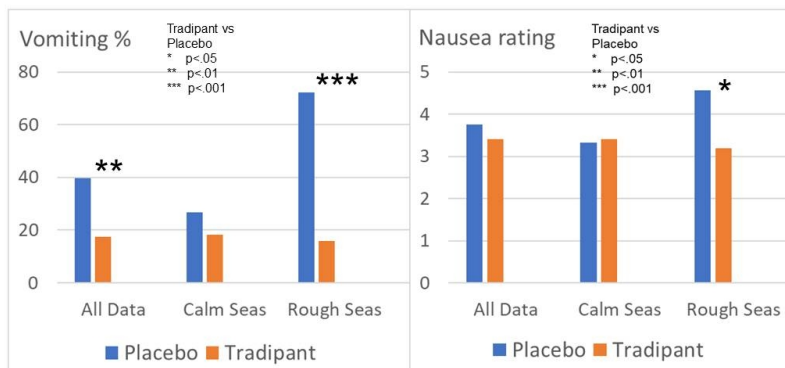


Figure 2. The effects of the NK1 receptor antagonist (NK1RA) tradipant versus placebo on motion sickness signs and symptoms, are shown for Vomiting (left diagram) and for Nausea (right diagram). Motion sickness was provoked by motion at sea. Voyages inevitably varied in terms of the weather and roughness 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 Polymeropoulos et al, 2020.

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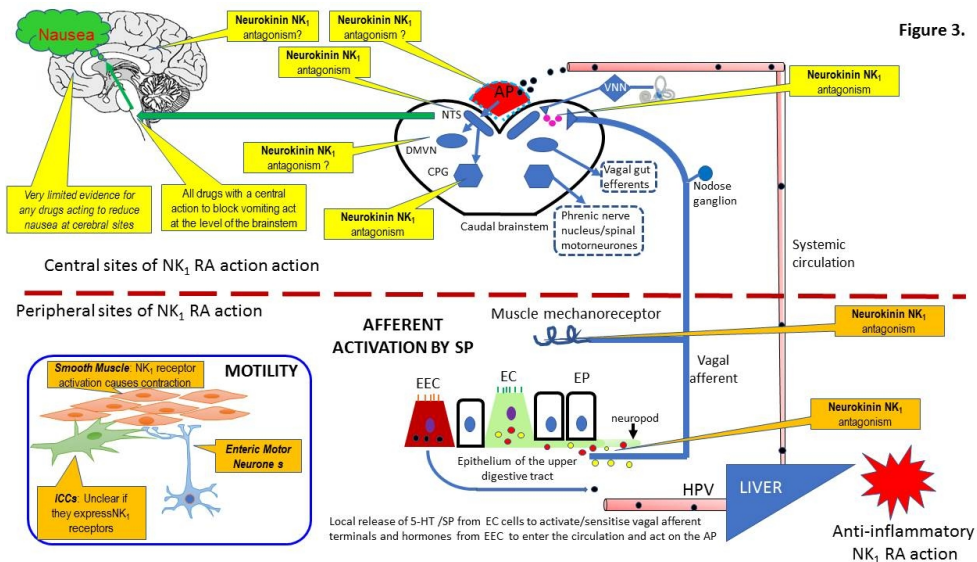
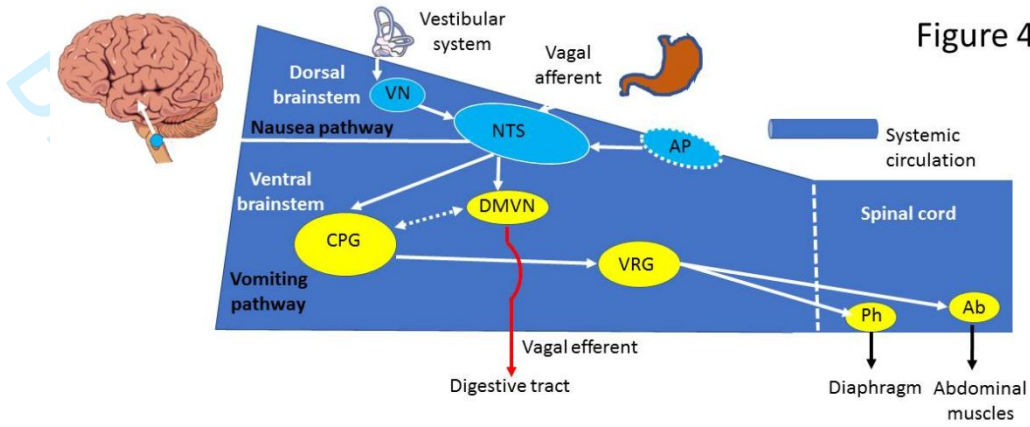


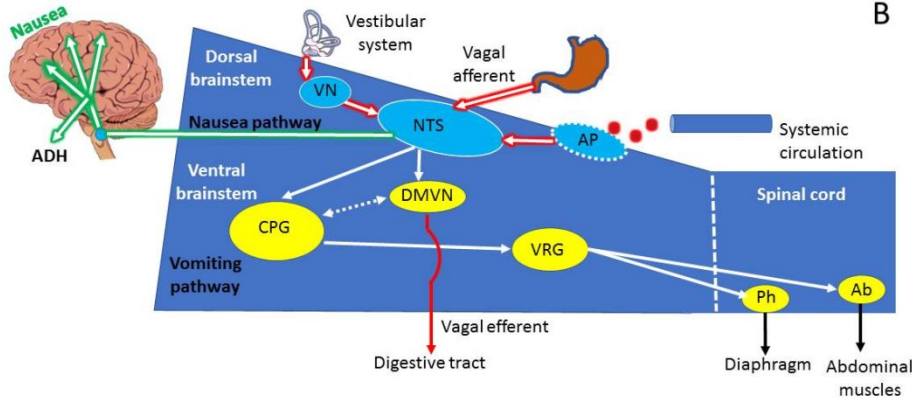
Figure 3. A diagrammatic summary of the central and peripheral sites at which NK₁RA could act to reduce nausea and vomiting. Abbreviations: AP= Area Postrema; CPG= Central pattern Generator for vomiting; DMVN=Dorsal Motor Vagal Nucleus EC=Enterochromaffin cell; EEC=Enteroendocrine Cell; EP=Epithelial cell; HPV= Hepatic Portal Vein; ICC= Interstitial Cells of Cajal; NK₁RA= Neurokinin1 receptor antagonist; NTS= Nucleus Tractus Solitarius; VNN= Vestibular Nerve Nucleus. In the periphery, NK₁ 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). NK₁RA 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). NK₁ receptors are also implicated in inflammation the reduction of which by NK₁RA 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 NK₁ receptor agonist. Induction of nausea requires activation of 'higher' brain regions and although NK₁ 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.

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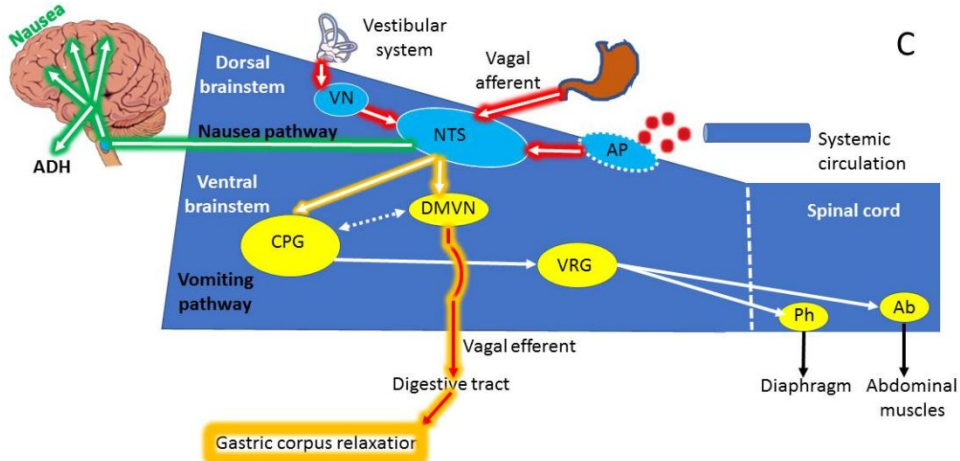
Figure 4 A



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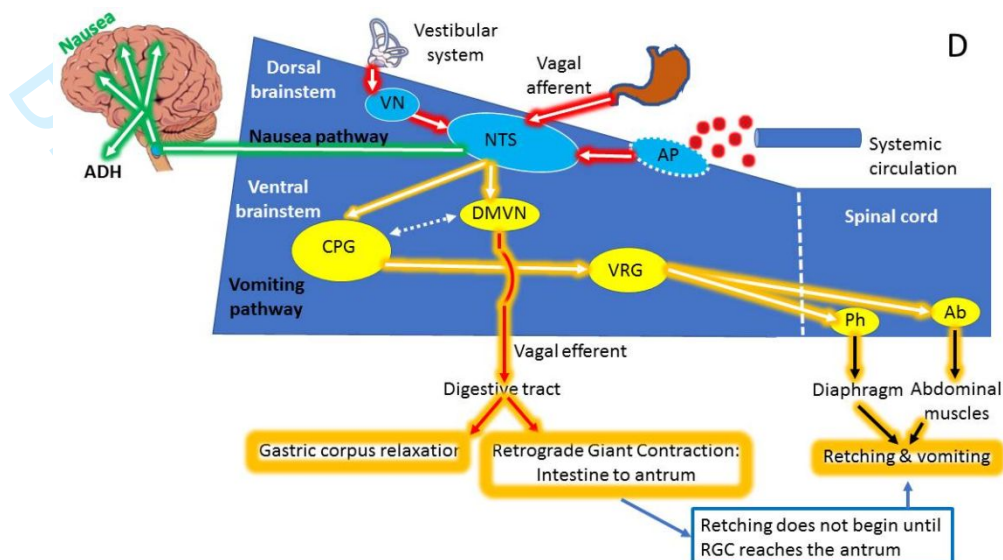


Figure 4 A-D. Diagrammatic representation of a longitudinal section through the brainstem showing the key nuclei and pathways implicated in retching, vomiting and nausea.

Abbreviations: 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= 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 RGC reaches the gastric antrum.

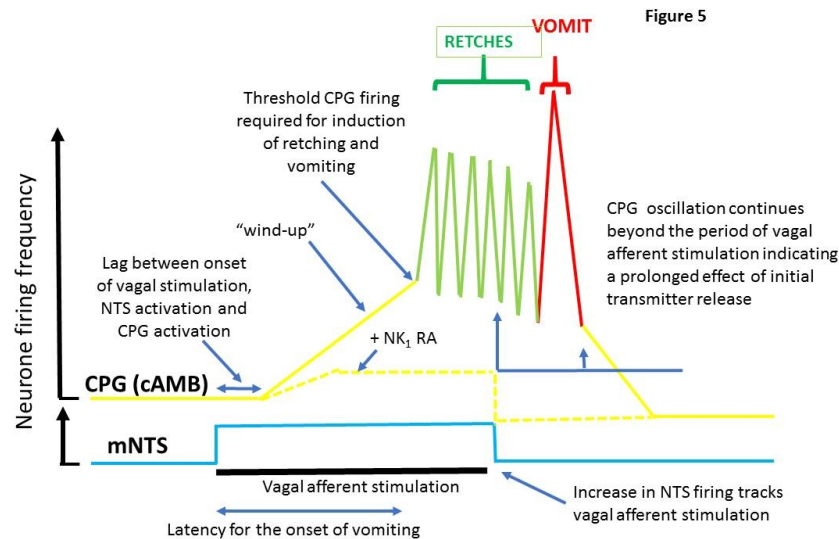


Figure 5. Diagrammatic representation of the neuronal discharge pattern in the medial Nucleus Tractus Solitarius (mNTS) and the Central pattern Generator (located in the compact part of the Nucleus Ambiguus, cAMB) in response to electrical stimulation of infra-cardia vagal afferents based on neurophysiological studies in the dog reported in Koga & Fukuda, (1992), Fukuda et al., (2003), and Onishi et al., (2007). Vagal afferent stimulation results in a uniform increase in NTS firing frequency which ceases at the end of stimulation. NTS activation results in 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 and 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.

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Species	Neurokinin ₁ receptor antagonist (route)	Effect on “nausea-like behaviour” as defined by authors	Behaviour(s) measured	Additional details of stimulus	Comment	Reference
Cisplatin (low dose)						
Dog	Maropitant (i.v.)	Onset of signs of nausea delayed and VAS scores reduced at three time points between 3.7 and 4.5h post cisplatin but AUC over 7h not significantly reduced.	Composite score of lip licking, lethargy, restlessness or turning /circling signalling that vomiting is imminent.		Also showed that vasopressin secretion was reduced by maropitant.	Kenward et al., 2017
Doxorubicin (5 days)						
Dog	Maropitant (s.c.)	No effect	Appetite, protracted salivation, lip smacking		No effect on appetite	Rau et al., 2010
Opiate receptor agonists						
Dog	Maropitant (s.c.)	No effect	Ptyalism, lip licking, increased swallowing	Morphine(s.c.)	Salivation incidence unaffected; metaclopramide also no effect on “nausea-like behaviours”	Lorenzutti et al., 2016, 2017
Dog	Maropitant(s.c.)	No significant effect but reduction in incidence	Excessive lip licking and swallowing, hunched posture	Hydromorphone (i.m.)	No effect on increased panting; maropitant	Claude et al., 2014

					increased ptyalism-salivation not included in nausea score	
Dog	Maropitant (s.c.)	Significantly decreased with 60 min pre-dose	Salivation, lip-licking	Hydromoprphone (i.m.)	Effect on "N" only seen with 60min pre-dose	Hay Kraus 2014
Cat	Maropitant (s.c.)	No effect	Sialorrhea, lip licking	Dexmedetomidine +morphine (i.m.)		Martin-Flores et al., 2016
Tranexamic acid						
Dog	Maropitant (i.v.)	No significant effect on severity	Visual analogue scale	Fibrinolytic		Kantyka et al., 2020
Brimonidine						
Cat	Maropitant(p.o.)	No effect	Sialorrhea, lip licking	α_2 agonist sedative given as eye drops		Kanda et al., 2020
Motion						
Cat	CP-99,994 (s.c.)	No effect	Suri et al., 1979 symptom scale	Ferris Wheel		Lucot et al., 1997
Lycorine (s.c.)						
Dog	Maropitant (s.c.)	No effect	Increased salivation, lip licking, frequent/exaggerated swallowing motions, lethargy, restlessness and /or panting	Alkaloid from daffodils		Kretzing et al., 2011

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3 **Supplementary Table 1.** A summary of the results of preclinical studies reporting the effects of neurokinin₁ receptor antagonists on the
4 “nausea –like behaviours” in response to a range of emetic stimuli in species capable of vomiting.
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