Received: 23 January 2023 | First decision: 28 February 2023 | Accepted: 1 March 2023

DOI: 10.1111/apt.17466

AP&T Alimentary Pharmacology & Therapeutics WILEY

Review article: An analysis of the pharmacological rationale for selecting drugs to inhibit vomiting or increase gastric emptying during treatment of gastroparesis

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Summary

Background: Drugs which can inhibit nausea/vomiting and/or increase gastric emptying are used to treat gastroparesis, mostly 'off-label'. Within each category, they act at different targets and modulate different physiological mechanisms.

Aims: Address the questions: In gastroparesis, why should blocking one pathway causing vomiting, be more appropriate than another? Why might increasing gastric emptying via one mechanism be more appropriate than another?

Methods: Drugs used clinically were identified via consensus opinions and reviews, excluding the poorly characterised. Their pharmacology was defined, mapped to mechanisms influencing vomiting and gastric emptying, and rationale developed for therapeutic use.

Results: Vomiting: Rationale for 5-HT_3, D_2, H_1 or muscarinic antagonists, and mirtazapine, amitriptyline, nortriptyline, are poor. Arguments for inhibiting central consequences of vagal afferent transmission by NK_1 antagonism are complicated by doubts over effects on nausea. Gastric emptying: Confusion emerges because of side-effects of drugs increasing gastric emptying: Metoclopramide (5-HT_4 agonist, D_2 and 5-HT_3 antagonist; also blocks some emetic stimuli and causes tardive dyskinesia) and Erythromycin (high-efficacy motilin agonist, requiring low doses to minimise side-effects). Limited trials with selective 5-HT_4 agonists indicate variable efficacy.

Conclusions: Several drug classes inhibiting vomiting have no scientific rationale. NK_1 antagonism has rationale but complicated by limited efficacy against nausea. Studies must resolve variable efficacy of selective 5-HT_4 agonists and apparent superiority over motilin agonists. Overall, lack of robust activity indicates a need for novel approaches targeting nausea (e.g., modulating gastric pacemaker or vagal activity, use of receptor agonists or new targets such as GDF15) and objective assessments of nausea.

The Handling Editor for this article was Professor Colin Howden, and it was accepted for publication after full peer-review.

1 | INTRODUCTION

Gastroparesis is characterised by nausea and vomiting with delayed gastric emptying in the absence of mechanical gastric outlet obstruction, often coexisting with 'postprandial distress syndrome' symptoms of dyspepsia.[1,2] As discussed below (Background and Scope of Review), multiple causes are proposed (e.g., diabetes, viral infection) but the ultimate consequences appear to be damage to the enteric nerves and/or the Interstitial Cells of Cajal and/or muscle fibrosis within the stomach. Symptoms may depend on whether the ingested meal is preferentially distributed to the proximal or distal stomach,[3] potentially reflecting their different structures and functions, and how vagal signalling from these regions is interpreted within the brain.[4] The delayed gastric emptying can make it difficult to manage patients, especially those with diabetic gastroparesis, affecting the availability of ingested carbohydrate and delivery of drugs needed to optimise glycaemic control.[5] When gastric emptying of meals is within normal range, without identified cause, patients are diagnosed with chronic unexplained nausea and vomiting (CUNV), or 'gastroparesis-like'.[6] Gastroparesis and functional dyspepsia (FD) may be interchangeable.[7] FD is characterised by early satiation, postprandial fullness, epigastric pain and burning, with accessory symptoms (upper abdominal bloating, nausea, belching).[8] To date, only metoclopramide has been approved for treatment of gastroparesis by the Food and Drug Administration (but for a limited duration and not in the elderly), and other drugs are prescribed 'off label' following registration for different indications.[9] Thus, there is an unmet need for efficacious therapies.[9]

A recent network meta-analysis of 29 randomised controlled drug trials (3772 patients), including experimental compounds and drugs registered for different disorders, found that when assessing global gastroparesis symptoms, 'dopamine receptor antagonists' (particularly clebopride and domperidone) and tachykinin NK_1 receptor antagonists were the only drugs more efficacious than placebo. Nevertheless, overall confidence in the evidence was 'low to moderate'.[9] Clinical consensus opinions also agree that certain drugs can be used to treat gastroparesis.[1,2] They include drugs (5-HT_3 and NK_1 receptor antagonists) inhibiting nausea and/or vomiting evoked by specific stimuli (e.g., anti-cancer chemotherapy), drugs stimulating gastric emptying (5-HT_4 and possibly, motilin receptor agonists) and drugs which may combine both types of activities (e.g., metoclopramide). Notably, consensus was not built on positive phase III clinical trials or positive systematic reviews of individual drugs and indeed, one systematic review concluded that the evidence in favour of using domperidone is poor.[10] Thus, the evidence in favour of any drug to treat gastroparesis is generally considered to be of low quality.[9,11]

Among patients, a questionnaire found poor satisfaction with treatments that included diet modification, drugs inhibiting nausea and/or vomiting or stimulating gastric emptying, analgesic drugs, gastric pace-making and 'alternatives'.[12] Drugs which can inhibit vomiting to varying degrees, depending upon the stimulus (aprepitant, dimenhydrinate, diphenhydramine, dronabinol, granisetron, ondansetron, prochlorperazine, promethazine, scopolamine, thiethylperazine, trimethobenzamide), had satisfaction scores of 31.9%–63.4%. Drugs thought to stimulate gastric emptying (bethanechol, cisapride, metoclopramide, erythromycin, domperidone) scored 22.5%–66.7%. More recently, patients with nausea, of assumed gastrointestinal (GI) origin (mostly gastroparesis; also functional, oesophageal and other diagnoses) were found to prefer marijuana, ondansetron and promethazine. Least effective were 'neuromodulators' (amitriptyline, gabapentin, pregabalin, buspirone), complementary/alternatives, diphenhydramine, and erythromycin.[13]

Particularly striking is the absence of clear, mechanism-based evidence to support prescribing any particular 'anti-emetic' drug for patients with gastroparesis. This suggests they are given because they are effective against nausea and vomiting in other groups of patients or human volunteers. However, translation to gastroparesis patients is not guaranteed since different classes of drugs block vomiting at different parts of emetic pathways that are activated by specific and sometimes disease-specific stimuli (Figure 1). Further, different classes of drugs increase gastric emptying in different ways (Figure 1), providing advantages and disadvantages, depending on the reason for use. Confusingly, some have mixed activities, capable of directly stimulating gastric emptying and inhibiting vomiting. These include metoclopramide and clebopride, sometimes (mis)classified solely as 'dopamine receptor antagonists'[9] yet also activating 5-HT_4 receptors and antagonising at other receptors. Conversely, the term 'gastric prokinetic' has often been collectively applied to drugs with mixed abilities to increase gastric emptying by various mechanisms and/or inhibit certain emetic stimuli (e.g., botulinum toxin, domperidone, cisapride, levosulpiride and erythromycin together with metoclopramide[14]; see also a subsequent correspondence[15]) (Tables 1 and 2).

So, for gastroparesis, is there a mechanism-based rationale for using any of these drugs? To answer this fundamental question, we address the questions that lie within:

- Why use a drug to block one pathway leading to vomiting, but not another?
- Why should one class of drug stimulating gastric emptying be favoured over another?
- What do the conclusions tell us about mechanisms involved in generating the symptoms of gastroparesis and how can this inform future drug developments, particularly for nausea?

2 | BACKGROUND AND SCOPE OF REVIEW

Except where pertinent to drug activity, it is not our intention to examine the causes and pathophysiology of gastroparesis in detail, being well covered in other reviews (e.g., Ref. [16]). In summary, the main causes are idiopathic or associated with diabetes, surgery, Parkinson's disease, and viral infections. Damage to the stomach, differing between idiopathic and diabetic gastroparesis, has been typified by

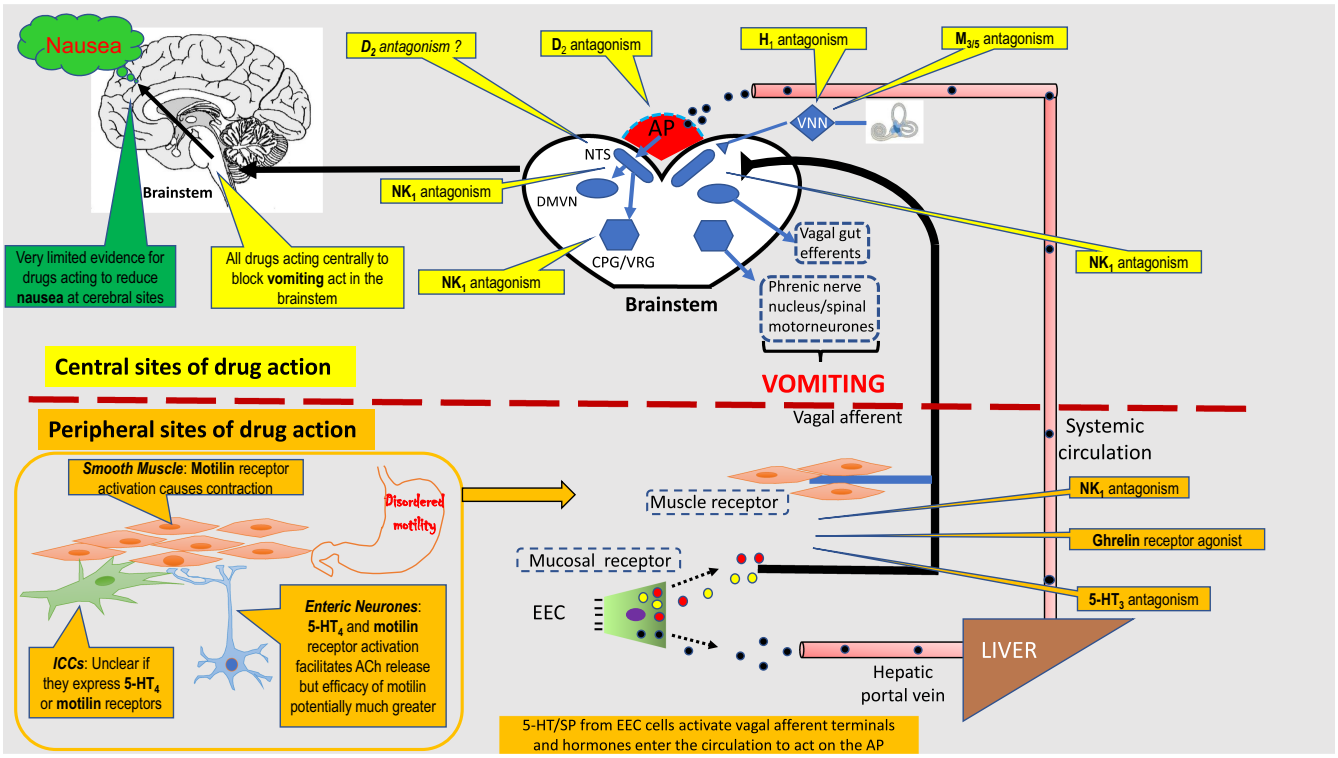

FIGURE 1 Summary of the sites of action of the drugs included in this review and which have been used to treat vomiting and delayed gastric emptying in patients with gastroparesis. It should be noted that the sites of action are based on mechanistic studies in multiple clinical contexts and not gastroparesis, as such information is not available. Motility stimulant mechanisms are based largely on in vitro pharmacological studies in humans. See text for details and references. The box on the lower left illustrates sites on the gastric smooth muscle, ICCs and enteric nervous system implicated in the gastric motility stimulant action of motilin (e.g., erythromycin) and 5-HT_4 receptor agonists (e.g., metoclopramide). Changes in gastric motor function associated with gastroparesis (electrical/ mechanical) can be signalled to the brainstem by abdominal vagal afferents – primarily receptors in the muscle but potentially epithelial receptors (EEC cell-vagal afferent) could also be involved. The vagal afferent terminals can also be activated/sensitised by locally released 5-HT/SP (from EEC) providing a potential target for 5-HT_3 and NK_1 receptor antagonism, respectively. Finally, agents capable of inducing nausea and vomiting could be released from the EEC cell to act on the AP as is proposed for the delayed phase of chemotherapy-induced nausea and vomiting; such an action could be implicated in duodenal inflammatory responses associated with gastroparesis. ACh, acetylcholine; AP, area postrema; CPG, central pattern generator for retching and vomiting; D_2, dopamine$_2$ receptor; DMVN, dorsal motor nucleus of the vagus; EEC, enteroendocrine cell; 5-HT, 5-hydroxytryptamine; 5-HT_3, 5-hydroxytryptamine$_3$ receptor; 5-HT_4, 5-hydroxytryptamine$_4$ receptor; H_1, histamine$_1$ receptor; ICC, interstitial cell of Cajal; $M_{3/5}$, muscarinic$_{3/5}$ receptor; NK_1, neurokinin$_1$ receptor; NTS, nucleus tractus solitarius; SP, substance P; VRG, ventral respiratory group.

macrophage-driven immune dysregulation (inflammatory cells around myenteric neurons with neuronal loss), oxidative stress, loss or injury to pacemaker cells (interstitial cells of Cajal; ICC) and muscle fibrosis.[16] Dysrhythmic gastric electrical activity, measured indirectly (electrogastrography), has been linked to the nausea of many conditions (e.g., gastroparesis, CUNV, FD).[17] Direct gastric electrical recording, using dense arrays of extracellular electrodes, identified conduction blocks, retrograde propagation and other anomalies in patients with gastroparesis, linked with damaged ICCs.[18] Indeed, the existence of retrograde electrical activity (and contraction) is emerging as an important characteristic of patients with gastroparesis and possibly FD.[19]

For the present mechanistic analysis, drugs used to inhibit vomiting and/or increase gastric emptying were identified from reviews on treatments for gastroparesis.[1,2,9–13,20–24] For some, there are few or no controlled studies and/or poor pharmacological characterisation, severely hampering interpretation of data.[20,23,25] They include histamine H_1 receptor antagonists (promethazine, diphenhydramine), tetrahydrocannabinol derivatives (dronabinol, nabilone), marijuana, the alpha$_2$-adrenoceptor agonist clonidine, D_2 receptor antagonists (haloperidol, trimethobenzamide, thiethylperazine, levosulpiride), and anti-psychotic drugs (prochlorperazine, chlorpromazine, fluphenazine, levomepromazine) (see Table S1). Accordingly, we examined only those drugs which have been reasonably well studied in patients with gastroparesis (but often without phase III investigations) and possess a known pharmacology. The potential for bias was mitigated by the choice of drugs finding some consistency with those discussed within recent systematic reviews, consensus clinical opinions and guidelines on treatment of patients with gastroparesis.[1,2,9,10]

For the selected drugs, we (1) examine their pharmacological actions, mapping these to physiological mechanisms, (2) look for evidence that these mechanisms might be relevant to the genesis

TABLE 1 Drugs which block nausea and/ or vomiting.

Drug	Primary activity	Additional actions
Muscarinic ACh receptor antagonism		
Scopolamine	• Inhibits motion sickness by antagonising at mACh M_5 and perhaps M_3 and M_4 receptors within vestibular nuclei.[117]	• Antagonist at human mACh M_1–M_5 receptors.[30,117]
Dopamine D_2 receptor antagonism		
Domperidone	• Acts at the AP to prevent vomiting induced by D_2 receptor activation.[30,118] • The ability of domperidone and other D_2/D_3 receptor antagonists to increase gastric emptying of solid meals has not been consistently demonstrated in humans (Table S2).	• Dopamine D_3 receptor antagonist.[119] • D_2 and D_3 receptors expressed within the AP, NTS and dorsal motor vagal nucleus.[120] In least shrews, antagonism at both might be superior to antagonism at D_2 alone.[121] • Substrate for human p-glycoprotein.[122] • Normally unable to penetrate the blood–brain barrier.[118] • *h*ERG (human ether-ago-go-related gene)/Kv11.1 channel blocker.[28] • α_{1A}-Adrenoceptor antagonist (lower affinity than for D_2/D_3 receptors)[30]
Metopimazine and NG101 (a proprietary mesylate salt form of metopimazine)[123–125]		• Dopamine D_2 receptor antagonist (IC_{50} in CHO cells: 2.2×10^{-9} M) • High binding affinity for D_2 (Ki 0.07 nM) and D_3 (Ki 0.61 nM) receptors, and α_1-adrenoceptors (Ki 1.9 nM), with lower affinity for histamine H_1 (Ki 8.4 nM) and 5-HT_2 (Ki 15 nM) and no meaningful affinity for 5-HT_3 or 5-HT_4 receptors (likely to be human receptors but not stated). • Low concentrations do not appreciably inhibit *h*ERG channels. • Did not penetrate rat brain at therapeutically relevant concentrations
Metoclopramide, clebopride, levosulpiride		• Also 5-HT_4 receptor agonists: See Table 2
5-HT_3 receptor antagonism		
Granisetron ondansetron	• Inhibits vomiting by antagonising at 5-HT_3 receptors expressed on vagal abdominal (peripheral) nerve terminals[30]	• Generally regarded as selective 5-HT_3RAs although ondansetron may act as 5-HT_{2B} receptor agonist[30]
NK_1 receptor antagonism		
Aprepitant	• Selective antagonist at the human NK_1 receptor[30] • Inhibits vomiting by antagonising at NK_1 receptors expressed on vagal abdominal (peripheral) nerve terminals[30] and within the NTS and Central Pattern Generator[126,127]	• Can activate a mechanosensitive two-pore domain potassium channel, TRAAK (encoded by the KCNK4 gene)[128]
Atypical antidepressant		
Mirtazapine	Centrally penetrant antagonist at H_1 > 5-HT_{2A}, 5-HT_3, α_2 adrenoceptor and 5-HT_{2C} receptors, the order representing declining affinity for the receptors.[30]	
Tricyclic antidepressants		
Amitriptyline nortriptyline (metabolite of amitriptyline)	• 5-HT and noradrenaline uptake inhibitors with affinity for H_1 receptor, muscarinic receptors, α_1-adrenoceptor and 5-HT_{2A} receptor (at concentrations similar to those binding 5-HT and noradrenaline transporter sites).[30]	

and/or treatment of symptoms of gastroparesis, (3) summarise their clinical activity and (4) draw conclusions about the relevance of the targeted mechanism in treatment of these patients. Finally, we look to the future, suggesting new areas of research to explore.

When discussing mechanisms, the emphasis is on the pathways of vomiting and on human studies. Thus, the mechanisms of action of 'anti-emetic' drugs are understood for vomiting but not for nausea, the mechanisms of which remain uncertain and have no universally agreed biomarkers.[27] In addition, rodents cannot vomit and compared with humans and other species capable of vomiting, rats and mice show gross differences in gastric anatomy/physiology, and brainstem pathways related to the ability/inability to vomit.[28,29]

TABLE 2 Characteristics of major drugs which increase gastric emptying/motility.

Drug	Primary activity in stomach	Additional actions
Muscarinic ACh receptor activation		
Bethanechol	• M_3 receptor activation causes muscle contraction[129] • M_2 receptor activation may stimulate ICCs and regulate slow wave electrical activity[131] • Causes non-propulsive contractions without increasing gastric emptying[132]	Full agonist at mACh M_1–M_4 receptors[130]
5-HT_4 receptor agonists		
Metoclopramide[96]	• When gastric emptying is delayed, 5-HT_4 receptor agonists increase emptying in a coordinated manner. • In humans and animals these drugs cause prolonged facilitation of ACh release from active enteric cholinergic motor neurons, without directly affecting resting muscle tone.[96] • It is not known if 5-HT_4 receptors are expressed by ICCs in human stomach, stimulation of which would increase enteric motor nerve activity. 5-HT_4 receptor immunofluorescence has been reported in ICCs of rodent intestine (e.g. Ref. [133]). • In rodents, gastric motility may also be increased via activation of 5-HT_4 receptors within the brainstem[134,135]; it is not known if a similar mechanism exists in humans. • 5-HT_4 receptors also found in the intestine, (underpinning the use of selective 5-HT_4 receptor agonists for treatment of constipation) and in some non-GI tissues, including cardiac atria and ventricles. 5-HT_4 receptor agonists are partial agonists, with good efficacy in gastrointestinal myenteric plexus (well coupled to intracellular effector pathways), but little-or-no efficacy in cardiac muscle (poorly coupled receptors)[96]	• Antagonist at D_2 and at higher concentrations, at 5-HT_3 receptors, these additional actions inhibiting different parts of pathways leading to vomiting.[96] • Brain penetrant[96]
Clebopride		• 5-HT_4 receptor agonist and a less potent D_2 and D_4 receptor antagonist.[136–138] • Brain penetrant.[139]
Cisapride[96]		• High-intrinsic activity at native 5-HT_4 receptor, at least in the guinea-pig[140,141] • Antagonist at 5-HT_{2A}, 5-HT_{2B} receptors and $alpha_1$-adrenoceptors[96,140] • Activity at *h*ERG channel, with cardiac side-effects[96]
Levosulpiride[142]		• Antagonist at D_2 and D_3 receptors and with lower potency, D_4[143]
Tegaserod[96]		• Low-intrinsic activity at native 5-HT_4 receptors[96,140] • Antagonist at 5-HT_{2B} receptors[96]
Mosapride[144]		• Low-intrinsic activity at native 5-HT_4 receptors[140,141] • Some ability to antagonise at 5-HT_3 receptors[145] • Can block Kv4.3 potassium channels[146]
Prucalopride		• Selective 5-HT_4 receptor agonist[144] • High intrinsic activity at native 5-HT_4 receptor, at least in the guinea-pig[141,147] • Brain penetrant.[148]
Inhibitors of acetylcholinesterase		
Itopride	• Inhibits aetylcholinesterase activity and stimulates GI motility[149]	D_2 receptor antagonist with minimal ability to cross the blood–brain barrier[150]
Motilin receptor agonists		
Erythromycin Azithromycin	• Full agonists at motilin receptors.[105] Relatively low concentrations facilitate cholinergic activity whereas higher contractions directly contract the smooth muscle • It is not known if ICCs within human stomach express motilin receptors, but functional studies suggest this possibility.[151]	• Antibiotic drugs • At micro-molar concentrations, may inhibit hERG/Kv11.1 channel activity[152]

Finally, we cannot know with certainty if even animals capable of vomiting experience nausea, a self-reported experience in humans.[27]

3 | DRUGS INHIBITING VOMITING

The basic mechanisms of nausea and vomiting have been described, but the way(s) in which these pathways are activated in patients with gastroparesis is not known.[30] In brief, the nucleus tractus solitarius (NTS) in the dorsal brainstem receives inputs from the viscera (primarily vagus), vestibular system and the area postrema (AP). The AP, a circumventricular organ outside the blood–brain barrier, is densely vascularized and exposed to molecules released into the blood during disease, including those implicated in induction of nausea and/or vomiting (e.g., adrenaline, vasopressin, GLP-1, PYY, GDF15[31,32]). When appropriately activated the NTS can initiate retching and vomiting via additional neuronal circuitry within the ventral brainstem, whereas induction of nausea requires the NTS to influence pathways in the cerebral hemispheres.[33–35]

Different classes of drug block vomiting caused by certain stimuli, acting at different receptors on different parts of the pathways which cause vomiting (Figure 1).[30] These drugs were not developed to target the mechanisms necessarily involved in the aetiology of gastroparesis.

3.1 | Muscarinic acetylcholine (mACh) receptor antagonism

The mACh receptor antagonist scopolamine has poor selectivity for any of the five mACh receptor subtypes, but motion sickness is proposed to be prevented by antagonism at M_5 and perhaps M_3 and M_4 receptors within the vestibular nuclei (Table 1). Early recommendations for scopolamine patches to treat gastroparesis[36] were not accompanied by a mechanism-based rationale. Indeed, there is no known link between the vestibular nuclei and aetiology of gastroparesis. Further, chronic use of scopolamine and other drugs antagonising at mACh receptors (e.g., promethazine), particularly M_3, are likely to delay gastric emptying,[37,38] adding to the disrupted parasympathetic activity in severe diabetic gastroparesis.[39]

3.1.1 | Conclusions

There is no clear rationale for prescribing mACh receptor antagonists for treatment of gastroparesis, or for developing new drugs with selectivity for a particular mACh receptor subtype, acting peripherally or centrally.

3.2 | Dopamine D_2 receptor antagonism

The role of dopamine in the mechanisms of vomiting has been widely studied yet it remains one of the least understood areas of research. For example, although it is well known that exogenous dopamine receptor agonists cause vomiting (Table S2), it is difficult to find good evidence in disorders associated with vomiting, including gastroparesis, for an increase in availability of endogenous dopamine. Any role of dopamine in the aetiology of nausea, a key symptom of gastroparesis, is also unclear (Table S2). Further, there are no, widely available, selective D_2 receptor antagonists to inhibit vomiting in clinical conditions. Perhaps the best available is domperidone, also a D_3 receptor antagonist. Although restricted in its use (because of cytochrome P450 and *h*ERG interaction liabilities; Table 1), an advantage of domperidone is that it is not readily able to cross the blood brain barrier as it is returned to the blood by the P-glycoprotein transporter. This means that domperidone does not usually evoke the extrapyramidal side effects associated with D_2 receptor antagonists which do penetrate into the brain (e.g., metoclopramide, prochlorperazine; Table 1; Table S2). Other D_2 receptor antagonists are non-selective even for dopamine receptor(s) so it is sometimes difficult to draw sound conclusions from their use (Table 1). They include metoclopramide (also a 5-HT_4 receptor agonist directly stimulating gastric motility, and at higher concentrations a 5-HT_3 receptor antagonist inhibiting vomiting via a different pathway), clebopride (also a 5-HT_4 receptor agonist and D_4 receptor antagonist), and the phenothiazine drugs (e.g., prochlorpromazine, also antagonising at 5-HT_{2A} and H_1 receptors[30]).

Literature on the use of domperidone to treat gastroparesis is inconsistent. Domperidone and other D_2 receptor antagonists (metoclopramide, prochlorperazine) were among medications patients said were "*unsatisfactory*" treatments of gastroparesis,[10] yet they are commonly used (the same conundrum between poor efficacy but recommended use of D_2 receptor antagonists to control vomiting has been noted in palliative care[40]). A recent systematic review found that domperidone, and clebopride, can reduce symptoms of gastroparesis more effectively than placebo. In a subset of studies, analysis of individual symptoms ranked metoclopramide highly for efficacy against vomiting, nausea, fullness and bloating.[9] Confusingly, however, a network analysis of the three drugs using overall symptom scores concluded that 'dopamine receptor antagonists' are an effective means of treating symptoms of gastroparesis.[9] An earlier systematic review[10] concluded that the evidence for or against the use with domperidone in diabetic gastroparesis was poor, pointing out that many positive studies lacked a control arm. The recent network analysis concluded that in 13 trials of diabetic gastroparesis none of the drugs (including domperidone and metoclopramide) was superior to placebo.[9] Finally, a small study, without placebo control, found putative associations between improved symptoms in patients treated with domperidone and polymorphisms in the drug transporter gene *ABCB1* (generating P-glycoprotein), the *KCNH2* gene (encoding a subunit of voltage-gated inwardly rectifying potassium channel), and the α_{1D}-adrenoceptor *ADRA1D* gene.[41] This is a difficult study to interpret.

3.2.1 | Conclusions

It has been said that D_2 receptor antagonists (implying domperidone and metoclopramide) are the most robustly effective agents for gastroparesis, because of "central anti-nausea effects", facilitated by peripheral activity to increase gastric emptying.[42] This is a claim which raises several difficult issues, discussed above and in detail within Table S2. In brief:

1. Almost nothing is known about any ability of D_2 receptor antagonists to reduce *nausea*.
2. Conclusions about mechanisms drawn from using D_2 receptor antagonists with additional actions should be treated with caution.
3. D_2 receptor antagonists can inhibit vomiting by blocking actions of exogenously administered dopamine receptor agonists (e.g., apomorphine) within the AP, but an increase in endogenous dopamine within the blood of patients with gastroparesis, especially during episodes of vomiting or nausea, has not been demonstrated.
4. As discussed below (Section 4.3), the ability of domperidone and other D_2/D_3 receptor antagonists to increase gastric emptying of solid meals has not been consistently demonstrated and a potential source of dopamine for such an activity remains unclear.

Although the concept that D_2/D_3 receptor antagonists can effectively treat gastroparesis is currently uncertain, drug developments

in this area have continued. As there is no sound rationale for a drug which crosses the blood brain barrier (to potentially induce extrapyramidal side effects) these are all 'peripherally restricted'. Clinical trials with trazpiroben (TAK-906), a D_2/D_3 receptor antagonist with pharmacology similar to domperidone but an improved safety profile,[43] were discontinued during 2022 for an undisclosed reason (https://adisinsight.springer.com/drugs/800049598). Deudomperidone (CIN-102 or deuterated domperidone, again similar to domperidone but with improved pharmacokinetics, efficacy and tolerability), is undergoing Phase II trials in patients with gastroparesis (https://cindome.com/cin-102).[44] The phenothiazine NG101 (a proprietary salt form of metopimozide), a D_2 receptor antagonist also binding to D_3, α_1-adrenoceptors and with lower affinity to H_1 receptors, and unable to cross the blood–brain barrier or inhibit *h*ERG at therapeutically-relevant concentrations (Table 1), is undergoing Phase II trials (https://neurogastrx.com/pipeline/#section-ng101).[44] The idea that therapeutic efficacy might be achieved by combining D_2 receptor antagonism with 5-HT_4 receptor activation (as for metoclopramide and clebopride but without brain penetration) is discussed later (Section 5).

3.3 | Selective 5-HT_3 receptor antagonists

Based on our understanding of the well-established mechanism by which 5-HT_3 receptor antagonists inhibit vomiting during chemotherapy and in certain other disorders,[30] there is currently no good rationale for their use in gastroparesis. To be effective these drugs must antagonise activity resulting from 5-HT released during the disorder, such as driving/sensitising peripheral vagal afferent terminals (e.g., during anti-cancer chemotherapy[45]) as there is little evidence for a central action against vomiting. However, to date, there is no evidence to suggest such a possibility for gastroparesis. In one study on patients with idiopathic gastroparesis, there were no changes in numbers of 5-HT-containing cells in mucosal biopsies (duodenum, antrum, fundus) or expression of tryptophan hydroxylase-1 (the rate limiting enzyme in 5-HT synthesis), 5-HT transport protein (SERT; involved in 5-HT reuptake), 5-HT_3 receptor subunits or the 5-HT_4 receptor.[46] The authors acknowledged that such data does not rule out the possibility of an abnormal release of 5-HT from the enteroendocrine cells but argued that the lack of change in SERT expression reflected unchanged 5-HT signalling (5-HT activity and/or release). In another small study, ondansetron did not increase gastric emptying in a small number of patients with gastric stasis, including some with gastroparesis,[47] suggesting no 5-HT release/5-HT_3 receptor activation in these patients and consistent with an inability of 5-HT_3 receptor antagonists to increase gastric emptying in healthy volunteers.[48–50] Finally, small studies with healthy volunteers have shown an ability of 5-HT_3 receptor antagonists to reduce nausea caused by gastric distension (alosetron)[51] or by proximal gastric distension during duodenal lipid infusion (ondansetron),[52] but there is currently no evidence that such mechanisms operate in patients with gastroparesis.

Finally, there are no large, controlled studies which have assessed the ability of 5-HT_3 receptor antagonists to alleviate gastroparesis, despite early recommendations.[23] In a single patient with diabetic gastroparesis on peritoneal dialysis, administration of ondansetron controlled intractable nausea and vomiting.[53] Three small open studies in patient's refractory to other drugs which increase gastric emptying and/or inhibit vomiting (including ondansetron), reported some reduction in nausea and vomiting when granisetron was given for 2 weeks as transdermal patches,[54–56] but there were no placebo controls.[57]

3.3.1 | Conclusions

There is no sound rationale for using selective 5-HT_3 receptor antagonists to treat either gastroparesis or its symptoms and as such, it is difficult to identify how changes may be made within this class of compound (e.g., in pharmacokinetic properties) to change this conclusion.

3.4 | NK_1 receptor antagonists

If gastroparesis is associated with damage to stomach functions, causing dysrhythmic gastric electrical activity and changes in muscle movements (Section 2), then a drug which inhibits the ability of vagal afferents to detect and signal these changes to the NTS might reduce symptoms. Further work is needed to characterise the contractile activity resulting from gastric electrical dysrhythmia and record from gastric afferents with receptive fields in dysrhythmic regions. However, if proven, NK_1 receptor antagonists would be expected to inhibit the vagal activity encoding induction of vomiting. This would be achieved by blocking any ability of substance P to activate/sensitise abdominal afferents (e.g., released from enteroendocrine cells),[58] but perhaps more importantly, by modulating brainstem integrative pathways (NTS, central pattern generator) involved in vomiting[59] (Table 1). Notably, however, some doubt has arisen over the consistency with which NK_1 receptor antagonists can inhibit nausea in comparison to vomiting.[27,30] If confirmed, this would suggest an ability of the above brainstem integrative pathways to activate the cortical areas involved in recognition of nausea[35] separately from the NK_1 receptor-dependent pathways leading to vomiting.

It should also be noted that in the gut, tachykinins are found in enteric neurons, with smaller amounts in immune and enteroendocrine cells, and the NK_1 receptor is expressed by enteric neurons, ICCs, epithelial cells, and the lymphocytes and macrophages of the lamina propria.[60] Accordingly it is possible that NK_1 receptor antagonists could also directly modulate any gastric immune dysregulation during gastroparesis,[16] but evidence is currently lacking.

Aprepitant is a brain penetrant NK_1 receptor antagonist, registered for prevention of vomiting in cancer patients receiving highly emetogenic therapy, when given with a 5-HT_3 receptor antagonist and dexamethasone.[30] In small studies with healthy volunteers,

gastric emptying of solid meals was not increased by aprepitant[61,62] or the development candidate tradipitant,[63] suggesting little-or-no role for tachykinins in physiological control of gastric motility. Gastric accommodation was unaffected in two studies[63,64] but increased in another, during which symptoms associated with ingestion of a maximum tolerated volume (pain, nausea) were increased by aprepitant.[62] The ability of aprepitant to activate a mechanosensitive two-pore domain potassium channel, TRAAK (encoded by *KCNK4*) (Table 1), may explain these anomalous data. A detailed pharmacology profile for tradipitant (VLY-686/LY686017) is not published.

In case reports, aprepitant reduced severe vomiting or nausea in patients with gastroparesis.[65–67] However, it did not reduce the severity of nausea in a randomised double-blind Phase II trial in patients with gastroparesis or CUNV (using a visual analogue scale); the authors argued that studies should explore different outcome measures, partly because of the lack of effective treatments for gastroparesis and partly because signs of efficacy were detected over the 4 weeks period in secondary outcomes measured using the GCSI (including nausea and vomiting).[68] More recently in a Phase II double-blind, placebo-controlled trial on 152 patients with idiopathic and diabetic gastroparesis and moderate-to-severe nausea, the experimental compound tradipitant improved nausea scores, nausea-free days and other secondary end points but this was statistically significant only after 4 weeks of treatment.[69] However, the subsequent phase III trial in gastroparesis showed no ability of tradipitant to reduce the severity of nausea from baseline at week 12 of treatment, compared with the patients receiving placebo, thereby failing to meet the primary endpoint of the study (cited by Ref. [9]).[70]

3.4.1 | Conclusions

It remains premature to draw firm conclusions about the role of NK_1 receptor antagonists for gastroparesis. A rationale exists although the data for tradipitant are disappointing. In terms of the future, drug selectivity, an understanding of the involvement of NK_1 receptors in the mechanisms of nausea and improved methods of quantifying nausea may be critical.

3.5 | Mirtazapine

Mirtazapine is a centrally-penetrant antagonist at multiple receptors (Table 1). Antagonism at H_1,[30] 5-HT_3 (see above) and α_2-adrenoceptors[71] can block vomiting, although their involvement in mechanisms of gastroparesis is unclear. Case reports (e.g., Ref. [72]) and a small study without placebo, describe reduced symptoms with mirtazapine in patients unresponsive to conventional treatments.[73] In healthy volunteers, mirtazapine did not affect gastric compliance or sensitivity to distension although gastric accommodation may be reduced.[74]

Side-effects include sedation,[75] likely explained by H_1 receptor antagonism in the cerebral cortex, hyperphagia and weight gain (likely caused by H_1 and 5-HT_{2C} receptor antagonism[76,77]). It is interesting to speculate that if appetite and nausea are interrelated,[78,79] mirtazapine could reduce nausea (a common side-effect of the 5-HT_{2C} receptor agonist lorcaserin, used to treat obesity[80]).

3.5.1 | Conclusions

Little evidence is available. There is no clear rationale to explore the use of mirtazapine for gastroparesis. Somnolence/weight gain may accompany treatment.

3.6 | Tricyclic antidepressants

Amitriptyline and nortriptyline (N-desmethyl metabolite of amitriptyline) are 5-HT and noradrenaline uptake inhibitors, with affinity for the H_1 receptor, mACh receptors, the α_1-adrenoceptor and 5-HT_{2A} receptor (Table 1). Both have been recommended for patients with significant dyspeptic symptoms,[23] at doses lower than used for depression to minimise impairment of GI motility by mACh receptor antagonism.

In small open-label retrospective studies in patients with chronic nausea and vomiting and in diabetic patients with unexplained vomiting resistant to treatment (including some with cyclic vomiting syndrome), there were moderate improvements of symptoms after long-term treatment with amitriptyline 50 (range 10–200) and nortriptyline 25–50 (10–75) mg/day; unfortunately, nausea and vomiting were grouped together.[81,82] In a placebo-controlled trial in patients with idiopathic gastroparesis (who could take 'prokinetics' or 'antiemetics' during the study), 15 weeks' with nortriptyline did not improve symptoms (GCSI score) or the nausea, fullness/satiety or bloating sub-scores (but decreased loss of appetite).[83]

3.6.1 | Conclusions

There is no rationale for using these drugs for treatment of gastroparesis, apart perhaps from an ability to ameliorate pain.

3.7 | Ghrelin receptor agonists

Animal studies have shown an ability to inhibit vomiting induced by cisplatin or abnormal motion, but not by nicotine or copper sulphate; the site of action is unclear but required brain penetration.[84] Animal studies have also shown that ghrelin can reduce the sensitivity of gastric muscle and mucosal vagal afferents to mechanical stimulation.[85] In contrast to rodent studies and unlike 5-HT_4 and motilin receptor agonists, ghrelin has no ability to facilitate cholinergic function in human isolated stomach.[86,87] This suggests that ghrelin increases gastric emptying in humans via the vagus nerve and/or the area postrema.[88]

To date, the development of ghrelin receptor agonists for treatment of gastroparesis has been unsuccessful. Discontinued compounds include TZP101 (intravenous infusion reduced vomiting and increased appetite in patients with diabetic gastroparesis without improving gastric emptying, and greatly reduced frequency and severity of nausea and vomiting in patients with gastroparesis and severe symptoms[89,90]), TZP-102 (oral doses did not increase gastric emptying or reduce symptoms in a Phase IIb trial; Daily Diary of Gastroparesis Symptoms Questionnaire[91]) and relamorelin[1] (peptide analogue of ghrelin given subcutaneously, accelerated gastric emptying and reduced vomiting severity in Phase II trials in diabetic gastroparesis).[92] Nevertheless, a recent network meta-analysis[7] showed that the ability of TZP-102 to reduce individual symptoms of nausea and fullness was superior to placebo, perhaps due to peripheral modulation of afferent activity and/or appetite (see above).

3.7.1 | Conclusions

There is some rationale for this approach. Thus, these are receptor agonists so are not dependent on the release of a ligand during gastroparesis. However, for future compounds, questions remain. Firstly, for optimal design, the nature of the native human ghrelin receptor(s) relevant to treatment of gastroparesis (e.g., in control of appetite and/or nausea) needs to be better understood. Thus, in different tissues the ghrelin receptor, a seven transmembrane G protein-coupled receptor (GPCR), can exist as a heterodimer with other GPCRs, can function via different intracellular coupling pathways (raising the possibility of functional or biased agonists at the receptor) and can show constitutive activity.[93] Secondly, as with all receptor agonists there is a risk that the response might fade with repeated exposure to the agonist. In designing future compounds this risk can be examined by, for example, repeat dosing in rodent models measuring changes in appetite together with a pharmacokinetic analysis. Thirdly, in humans, do these compounds cause a sustained increase in gastric emptying and reduce nausea in addition to vomiting?[88] To date, the evidence for an increase in gastric emptying is inconsistent (see above; in addition, trials with the ghrelin receptor agonist ulimorelin in patients with postoperative ileus were unsuccessful[94]). Finally, what are the long-term consequences of repeat administration (ghrelin has activity in brain, pancreatic islets, heart and other tissues, with potential to cause weight gain and change insulin sensitivity[42,88])?

3.8 | Drugs inhibiting vomiting: Overall conclusions

- To date, the pathophysiology of gastroparesis suggests that symptoms are related to changes in gastric functions, although convincing mechanistic evidence is still required and there remains a need to explore potential causal relationships between delayed gastric emptying and induction of nausea/vomiting. The consequences might be expected to be signalled to the brainstem largely by abdominal vagal afferents, although direct experimental evidence is still required. Nevertheless, theoretically, treatments which modulate vagal afferent signalling and/or the consequences on brainstem or cortical functions might be beneficial.
- NK_1 receptor antagonists can block vagal afferent nerve activity if activated by endogenous Substance P from enteroendocrine cells but perhaps more importantly, also block the consequences of vagal afferent activation in selected brainstem nuclei implicated in vomiting. However, the clinical trials in gastroparesis have been disappointing and more detailed investigation of relative efficacy against nausea is required.
- There is little rationale for use of 5-HT_3 receptor antagonists.
- There is little rationale for use of D_2 receptor antagonists.
- There is no sound rationale for treatment by antagonists at H_1 or muscarinic receptors.
- The rationale for using mirtazapine, amitriptyline, or nortriptyline is unclear.
- A future for ghrelin receptor agonists is uncertain.

4 | DRUGS INCREASING GASTRIC EMPTYING

The relationships between symptom control and drug-induced acceleration of gastric emptying are currently uncertain. A systematic review found positive correlations between drug-induced increases in gastric emptying (using validated methods, sitting positions, and drugs stated by the authors to be likely to have sustained activity: cisapride, domperidone, ghrelin receptor agonists) and reduced symptoms, in at least 75% of studies.[26] This had some consistency with an earlier systematic review (concluding that outcomes were more favourable during open-label studies, most often with erythromycin rather than domperidone, metoclopramide or cisapride[22]), but contrasted with lack of correlation between increased gastric emptying and improved symptoms in a meta-regression analysis considering different methodologies, meals and drugs (cisapride, erythromycin, domperidone, metoclopramide, levosulpiride, botulinum toxin).[14] For both studies the drugs grouped under the single description of 'gastroprokinetic therapy' hide a range of different peripheral and central activities on different molecular targets within different cell-types, sometimes with additional potential to directly influence pathways involved in mechanisms of vomiting (see commentary on the latter study[15]). Finally, a recent analysis of both studies stressed the importance of placebo-controlled trials and concluded that optimal methods for measuring gastric emptying could demonstrate symptom improvement following prokinetic therapy, in part mediated by acceleration of gastric emptying.[95]

The drugs investigated above were 5-HT_4 and motilin receptor agonists, D_2 receptor antagonists, and experimental ghrelin receptor agonists. Table 2 lists drugs, by class, which are marketed to increase gastric emptying. The older drugs are non-selective,

influencing more than one mechanism, including sometimes, a pathway leading to vomiting.[30,96] Included is the mACh receptor agonist bethanechol, sometimes given to patient's refractory to other treatments.[12,13] However, bethanechol does not induce a coordinated increase in gastric emptying, so is not discussed further. Likewise, the D_2 receptor antagonist and acetylcholinesterase inhibitor itopride is included but not discussed, since although sometimes given to patients with FD, studies in gastroparesis are limited.[1]

Do these drugs increase gastric emptying in a similar manner or are there differences favouring one class over another?

4.1 | 5-HT_4 receptor agonists

When gastric emptying is delayed 5-HT_4 receptor agonists can increase gastric emptying. This occurs mostly by prolonged facilitation of acetylcholine (ACh) release from active enteric cholinergic motor neurons of the stomach, without directly affecting resting muscle tone (see Table 2 for references to this and other potential peripheral and central pathways).

The early drugs, subsequently found to be 5-HT_4 receptor agonists, were developed before this receptor was identified (in 1988[30]) and consequently, were poorly characterised, possessing additional but then unknown actions and/or low-intrinsic activity at the receptor. They include metoclopramide, clebopride, cisapride, levosulpiride, mosapride and tegaserod (Table 2). For example, metoclopramide is also a D_2 and 5-HT_3 receptor antagonist, inhibiting different parts of pathways leading to vomiting. The drug is registered by the FDA for short-term treatment of gastroparesis, but with a black box warning of a risk of tardive dyskinesia (because metoclopramide is brain-penetrant and can antagonise at D_2 receptors within the basal ganglia).[97] Clebopride is a 5-HT_4 receptor agonist derived from metoclopramide and also a D_2 and D_4 receptor antagonist. These drugs are not discussed further.

Two selective 5-HT_4 receptor agonists with high-intrinsic activity at the receptor have provided limited encouragement that in some patients with gastroparesis, symptoms may be improved by increasing gastric emptying; these are prucalopride (Table 2) and the now discontinued development compound velusetrag.[42,98–100] The phase 2B study with velusetrag (abstract only[98]) found improved GCSI scores and gastric emptying (scintigraphy) over a 4–12 weeks period, in diabetic and especially, idiopathic gastroparesis. In a small group of patients with mostly idiopathic gastroparesis, 4 weeks of prucalopride (2 mg daily) improved the GCSI and Patient Assessment of GI Symptoms (PAGI-SYM) subscales of fullness/satiety, bloating/distension, nausea/vomiting, reflux, improved quality of life, and enhanced gastric emptying of a solid meal.[99] However, in a smaller study in diabetic or connective tissue disease-related gastroparesis, prucalopride (4 mg daily for 4 weeks) accelerated gastric emptying (solid meal) without affecting the GCSI or PAGI-SYM subscales; the authors recommended further study and possible off-label use of prucalopride (the drug is marketed for chronic idiopathic constipation) in idiopathic rather than diabetic gastroparesis.[100] Other compounds in development include felcisetrag, which in a small trial increased gastric emptying when given intravenously daily for 3 days to patients with gastroparesis.[101] By contrast, a small placebo-controlled trial with the now-discontinued selective 5-HT_4 receptor agonist, revexpride (given orally three times daily over 4 weeks), in patients with symptoms suggestive of gastroparesis, did not improve gastric emptying or suggest an improvement in symptoms.[102]

4.1.1 | Conclusions

Although there is limited data to support a beneficial action of selective 5-HT_4 receptor agonists not all trials with different compounds show the same outcome. The reasons for the differences are unclear. As with all 5-HT_4 (and motilin; see below) receptor agonists which act directly on the stomach to increase gastric emptying, the question of a fading response to repeat administration must be considered (caused by receptor tachyphylaxis and/or by stomach muscle fatigue). In addition, the reasons for the different clinical outcomes for the above-mentioned compounds need to be explored. These include an examination of differences in intrinsic activities and/or off rates from the human 5-HT_4 receptor, the need for brain penetration (prucalopride can cross the blood–brain barrier; Table 2) and the overall pharmacokinetics of unbound compound and/or dosing schedules.

4.2 | Motilin receptor agonists

Erythromycin, azithromycin and perhaps some other macrolides are antibiotics and motilin receptor agonists (Table 2); they are used 'off-label' to increase gastric emptying.[103] Motilin receptor agonists act in a similar manner to 5-HT_4 receptor agonists, facilitating ACh release from active enteric cholinergic motor neurons. In addition, motilin receptor agonists directly contract the stomach muscle, most obvious at higher concentrations. It is not known if ICCs within human stomach express motilin receptors, but this has been suggested (Table 2). There is no evidence for a central mechanism by which motilin can affect gastric emptying.[103]

The ability of motilin receptor agonists to increase enteric cholinergic activity in vitro and increase gastric emptying is considerably greater than for 5-HT_4 receptor agonists.[103] This means that relatively high doses (e.g., motilides when used as antibiotic drugs) can cause rapid, powerful gastric emptying, dumping and slowing of small intestinal transit when high-nutrient contents enter the lumen.[88,103,104] Such stimulation may fade[105] and tolerance to repeat dosing has been observed.[106] In addition contraction of the stomach muscle by the higher concentrations is thought to contribute to early satiety, nausea and stomach cramps.[103]

The ability of erythromycin to reduce symptoms of gastroparesis remains equivocal and is based on small, sub-optimal

studies without selection of an optimal dose.[24,42,103,106] The latter is important because relatively low doses (compared to antibiotic doses) are needed to cause a sustained increase in gastric emptying over repeat dosing without adverse events or fade of the response.[103] It is possible that the motilin receptor agonist ABT229 failed in clinical trials for dyspepsia or gastroesophageal reflux disease because the dose selected was too high for a compound with a 20 h half-life dosed b.i.d.[103] Nevertheless although low doses of the small molecule, selective motilin receptor agonist camicinal, showed increased gastric emptying in healthy volunteers after repeat dosing[107] and some improvements in symptoms of diabetic gastroparesis, the lack of clear dose-dependency prevented further development.[108] The macrolide mitemcinal also increased gastric emptying and showed some ability to improve symptoms of gastroparesis but curiously, only in a sub-group of patients with BMI < 35 kg/m^2 and haemoglobin A1c < 10%.[109] Further progression of both compounds has stopped.

4.3 | D_2/D_3 receptor antagonists

There is no convincing evidence that domperidone or other D_2/D_3 receptor antagonists can increase gastric emptying in healthy volunteers (Table S2). Some evidence exists for an ability to increase gastric emptying in patients with gastroparesis, but positive studies are inconsistent. If gastric emptying is increased, the mechanism is unclear (e.g., no direct activity of domperidone on gastric functions; no evidence for increased dopamine availability affecting the stomach; Table S2). It may be possible that domperidone can increase gastric movements indirectly, by reducing nausea, early satiety and abdominal bloating.[27,31] Accordingly, the pharmacology of D_2 receptor antagonists has been discussed in more detail above (Section 3).

4.4 | Ghrelin receptor agonists

An ability of ghrelin receptor agonists to cause a sustained increase in gastric emptying in humans remains uncertain although they can inhibit vomiting[84] and nausea.[9] Accordingly, their effects in patients with gastroparesis are discussed above (Section 3). Development of these compounds for treatment of gastroparesis have been discontinued.[1]

4.5 | Drugs increasing gastric emptying: Overall conclusions

In idiopathic gastroparesis, some encouraging data has been reported with selective, high-efficacy 5-HT$_4$ receptor agonists, including prucalopride. This suggests that some improvement of symptoms can be achieved by increasing gastric emptying in a coordinated manner.

The use of metoclopramide, clebopride and erythromycin also have some, albeit inconsistent, clinical support. These drugs also increase gastric emptying (via 5-HT$_4$ or motilin receptor activation). However, compared with prucalopride there are important differences. For erythromycin the increase in gastric motility is potentially much greater and muscle tone can be directly increased, perhaps explaining both a preference and a dislike of this drug, depending on the dose. For metoclopramide and clebopride, an additional ability to inhibit certain stimuli causing nausea and/or vomiting (via 5-HT$_3$ and/or D_2 receptor antagonism) also adds a risk of extrapyramidal side-effects (central D_2 receptor antagonism).

5 | FUTURE

For many drugs discussed above, there is no mechanism-based rationale for their use in the treatment of gastroparesis and accordingly, no basis for improvement. Nevertheless, early trials with NK$_1$ receptor antagonists and 5-HT$_4$ receptor agonists have shown signs of efficacy. Thus, it remains possible that further trials with existing or new compounds could achieve significant benefit, although for the 5-HT$_4$ receptor agonists, any enthusiasm may be hampered by the near-complete patent life of prucalopride and its potential for 'off label' use. Perhaps a 5-HT$_4$ receptor agonist which also acts as a peripherally restricted D_2 receptor antagonist (unlike metoclopramide and clebopride which are centrally penetrant) would be worth exploring, given the existence of some encouraging data for these drugs.[9] In addition, the use of drugs in combination may improve treatment efficacy (note that some drugs already act on multiple receptors; Table 1). For example, a combination of a selective 5-HT$_4$ receptor agonist such as prucalopride and the NK$_1$ receptor antagonist aprepitant would utilise the peripheral prokinetic actions of 5-HT$_4$ activation and the peripheral and central antagonism of NK$_1$ receptors for effects against vomiting.

Notwithstanding the need to further examine the efficacy of NK$_1$ receptor antagonists, 5-HT$_4$ receptor agonists and the drug combinations discussed above, it is also necessary to develop new approaches which target the gastroparesis patient rather than simply rely on drugs which inhibit vomiting (as proven in different conditions) or increase gastric emptying. A first step would be to develop more objective methods of measuring nausea. This is important to improve diagnosis, to distinguish between one symptom and another (e.g., nausea versus early satiety[30]) and because drugs which inhibit vomiting are generally less effective at inhibiting nausea.[27,30,110] Perhaps the recent findings with tradipitant in patients with gastroparesis (Section 3) now means that the NK$_1$ receptor antagonists should be added to this list of drugs. Thus, the mechanisms of vomiting and nausea need to be considered separately (vomiting is a motor reflex, but nausea is an experience, and each are governed by different brain regions[27,35]). However, measures of nausea are not standardised (limiting accuracy of data[27]) and have only recently been applied to gastroparesis. For example, in one study, a questionnaire characterised nausea in 3 dimensions: somatic, GI and emotional distress,[79] finding 96% of gastroparesis patients (idiopathic

and diabetic) experienced nausea, often related to meals, whereas 65% experienced vomiting (more in diabetic gastroparesis).[6] Thus, a quantitative method for measuring nausea independent of patient reports needs to be developed, to provide a more sensitive, real-time assessment of drug efficacy than provided by current methods.[27] Notably, a recent systematic review of brain imaging in subjects reporting nausea identified relatively few studies, with most involving visually induced motion sickness as compared to stimuli that are arguably more relevant to gastroparesis (acting via the vagal afferents and/or area postrema).[35] Pharmacological MRI studies are required to explore the pathways activated, for drug targets.

New approaches to novel drug design are also needed. Gastric electrical activity (regulated by ICCs) is dysrhythmic during nausea (including patients with gastroparesis),[18] providing incentive to find ways of restoring ICC function, perhaps by modulating key ion channels affecting slow wave electrical activity.[111] It is worth noting that gastric electrical pacing has some ability to regulate gastric dysrhythmia,[18] potentially providing a model whereby novel drug targets can be identified to improve on the effects of electrical stimulation.

If the gastroparesis symptoms of vomiting, nausea, fullness and bloating originate from the stomach (Section 2), this is likely to be signalled via vagal afferents to the brainstem. Thus, strategies to modulate vagal afferent activation becomes an important target for future drug research.[112] NK_1 and 5-HT_3 receptor antagonists are examples of drugs which inhibit vagal afferent activation driven by substance P and 5-HT. However, in the case of gastroparesis where the driving stimulus is currently unidentified and appears to 'escape' from blockade of vagal activity by NK_1 receptor antagonists (Section 3), different approaches are needed. One possibility is to identify receptor agonists that reduce vagal afferent activity without regard to the initiating stimulus. Ghrelin receptor agonists have been explored (Section 3) but another example is $GABA_B$ receptor activation, exemplified by baclofen.[113] A second possibility is to mine new targets from models such as the mouse nodose ganglion, recently the subject of molecular characterisation.[114] Finally, novel targets to treat nausea and vomiting may be found by better understanding of the actions of existing drugs. For example, a recent analysis of thalidomide's effects against nausea and/or vomiting in pregnancy and anti-cancer chemotherapy identified modulation of $K_{Ca}1.1$ or $GABA_A$/glutamate and reducing functions of GDF15 as potential mechanisms.[32] GDF15 is a divergent member of the TGF-β superfamily acting on the glial-derived neurotrophic factor-family receptor α-like (GFRAL) receptor and linked to mechanisms of vomiting, anorexia and weight loss.[115,116]

As with all new mechanisms a test-model must be found that is relevant to gastroparesis and not, for example, chemotherapy-induced vomiting or drug-induced delay in gastric emptying, so that efficacy can be assessed before the expense of speculative clinical trials. The development of a non-rodent model which examined the consequences of damaged ICC activity within the stomach in vivo might be a beginning, perhaps combined with/informed by in vitro studies of the pharmacology of human gastric motility.

Finally, and in conclusion, it is argued that future treatments of patients with gastroparesis must depend on a more rational mechanism-based approach, supplemented by improved symptom assessment methodology, rather than, for example, simply 'trying' the latest drug for treating vomiting and nausea in anti-cancer chemotherapy, or a new way to stimulate gastric motility.

AUTHOR CONTRIBUTIONS

Gareth John Sanger: Conceptualization (equal); data curation (equal); formal analysis (equal); project administration (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). **Paul Andrews:** Conceptualization (equal); data curation (equal); formal analysis (equal); validation (equal); writing – review and editing (equal).

ACKNOWLEDGEMENTS

Declaration of personal interests: There was no specific funding for this publication, but the authors thank all funders who to date, have enabled the authors to conduct research into the mechanisms discussed within this review, along with our many past and present colleagues who have engaged in fruitful discussions on these mechanisms. Within the last three years GJS received research funding from Bowel Research UK and Takeda Pharmaceuticals North America.

CONFLICT OF INTEREST STATEMENT

GJS advises BYOMass, Nurix, Fauna Bio and Viwit. PLRA has no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

How to cite this article: Sanger GJ, Andrews PLR. Review article: An analysis of the pharmacological rationale for selecting drugs to inhibit vomiting or increase gastric emptying during treatment of gastroparesis. Aliment Pharmacol Ther. 2023;00:1–17. https://doi.org/10.1111/apt.17466