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Newest Drugs for Chronic Unexplained Nausea and Vomiting

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OPINION STATEMENT

Chronic unexplained nausea and vomiting (CUNV) refers to a symptom complex defined by nausea and/or vomiting with normal diagnostic testing, including anatomic assessments (including upper endoscopy) and measures of upper gut function (e.g. gastric emptying testing). Nausea and vomiting in this condition are postulated to result from aberrant peripheral or central neurohumoral activity. A substantial subset of patients satisfies this diagnosis as more than half of individuals referred for scintigraphic testing exhibit normal gastric emptying rates. No randomized, placebo-controlled trials of any medication treatment have been performed in CUNV. However, agents with potential therapeutic benefit in CUNV include antiemetic drugs, neuromodulatory treatments which are proposed to act by reducing gastric sensitivity, and medications with prokinetic action to stimulate upper gut propulsion. Recently approved drugs with antiemetic capability include serotonin antagonists with novel modes of delivery and neurokinin antagonists with or without additional serotonergic blocking capabilities. Existing neuroleptics and pain modifying neuromodulatory therapies with fortuitous antiemetic benefits are being considered for their benefits in this disorder. Furthermore, current investigations will define potential therapeutic actions of agents that stimulate gastric emptying via action on gastroduodenal serotonin, motilin, and ghrelin receptors. This current research may broaden the treatment options for refractory cases of unexplained nausea and vomiting.

Keywords

Antiemetic medications; prokinetic medications; neuromodulators; gastric emptying; functional gastroduodenal disorders

INTRODUCTION

Definition and Epidemiology

Chronic unexplained nausea and vomiting (CUNV) is defined as a disorder presenting with nausea with or without vomiting where appropriate diagnostic testing has failed to reveal a

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Conflict of Interest

William L. Hasler has received grant support from Medtronic, Inc. (manufacturer of SmartPill) and has served as consultant with Allergan, Plc. and Rhythm Pharmaceuticals, Inc. (regarding potential use of relamorelin in gastroparesis). Dr. Hasler has also received grant support from NIDDK and has received advisory board fees from Ironwood Pharmaceuticals.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by the author.

cause of symptoms (1). Diagnostic evaluations usually include selected blood tests to rule out metabolic disorders including uremia, hypercalcemia, and thyroid chemistries, endoscopic or radiographic studies to assess for anatomic causes including partial luminal obstructions, and methods to quantify gastric propulsion or contractility. The prevalence of CUNV has not been defined with certainty. Nausea occurring at least once per week has been observed in approximately 3% of the general population (2). Vomiting at least monthly without an underlying organic cause is reported by 2% of women and 3% of men. Among patients with typical symptoms suggestive of gastroparesis including nausea and vomiting, delays in stomach emptying are detected in only 25–40% undergoing gastric scintigraphy (3).

Gastric Function Testing

Gastric emptying testing is the most common method of excluding functional causes of symptoms in CUNV patients. In the United States, gastric emptying usually is measured using scintigraphy. A standardized method for performing solid phase scintigraphy has been advocated by the American Neurogastroenterology and Motility Society proposed which involves quantifying gastric retention up to 4 hours after ingesting a ^{99m}Tc -labelled meal of an egg substitute with toast, jam, and water (4, 5). In 2015, the US Food and Drug Administration (FDA) approved an alternative to scintigraphy for diagnosing gastroparesis, the ^{13}C -Spirulina platensis gastric emptying breath test which employs a non-radioactive ^{13}C isotope in a low fat meal that can be used in patient populations (children, pregnant women) for whom radiation exposure is relatively contraindicated. With this test, ^{13}C is liberated upon meal digestion in the upper intestine to form $^{13}\text{CO}_2$ which diffuses across the intestinal epithelium and is exhaled in the breath in time-dependent fashion. A wireless motility capsule (WMC) is the third test to quantify gastric emptying by sensing pH transitions as it passes from the stomach to duodenum (6). Emptying parameters from scintigraphy correlate closely with those from the breath test and WMC (7, 8). Performance of any of these tests can rule out gastroparesis and rule in CUNV in a patient with uninvestigated chronic nausea and vomiting.

Other tests conducted in research settings define abnormalities of gastric function other than delayed emptying which may underlie the symptom benefits of some medications used to treat chronic nausea and vomiting. Relaxation of the gastric fundus after meal ingestion, also known as accommodation, can be quantified by barostat methods, satiety testing, magnetic resonance imaging, or single photon emission computed tomography. Gastric hypersensitivity to distention typically is measured using barostat testing.

Relating symptoms such as nausea and vomiting to abnormalities of gastric emptying, accommodation, or sensitivity has been the focus of discussion amongst experts in this field. The prevalence of nausea and vomiting is higher in functional dyspepsia patients with delayed versus normal gastric emptying, whereas rates of weight loss and early satiety are greater with impaired accommodation and weight loss and belching are more common with hypersensitivity to gastric distention (9, 10, 11). Nevertheless, substantial overlaps exist such that one cannot predict emptying delays or other functional abnormalities from a given symptom presentation. Indeed in large series of patients with presumed gastroparesis or

functional dyspepsia, correlation of gastric emptying rates to nausea and vomiting intensity is poor (1, 12). These observations have promoted conferring the diagnosis of CUNV on patients who present with symptoms indistinguishable from gastroparesis but who exhibit normal gastric function (1). CUNV has substantial overlap with some of the functional gastroduodenal disorders from the Rome foundation including functional dyspepsia and the new Rome IV diagnosis of chronic nausea vomiting syndrome (13).

MECHANISMS OF NAUSEA AND VOMITING

Several well-characterized neurotransmitter pathways participate in activation of emesis, while neurohumoral regulation of nausea is less well understood (14). Investigation of these mechanisms has permitted development of a diverse range of antiemetic therapies which may be potentially useful for managing CUNV. Serotonin 5-HT₃ and neurokinin NK₁, mechanisms are involved in coordinating emesis by several brainstem nuclei. Muscarinic M₁ and histaminergic H₁ receptor pathways mediate emesis in response to vestibular stimulation as with motion sickness or labyrinthitis. Stimuli which act on vagal afferent pathways, such as gastric irritants and selected chemotherapies (e.g. cisplatin) activate serotonin 5-HT₃ receptors. The area postrema responds to a broad range of blood borne emetic stimuli including bacteria toxins associated with food poisoning, hormonal and metabolic factors (e.g. thyroid disease, uremia, pregnancy), and many medications by stimulating 5-HT₃, M₁, H₁, and dopamine D₂ receptor mechanisms. Additional research has focused on the role of cannabinoid CB₁ pathways in the cerebral cortex and brainstem as means of reducing emesis.

MEDICATIONS USED TO TREAT NAUSEA AND VOMITING

Medications that treat chronic nausea and vomiting can be stratified into three separate categories: antiemetic agents, neuromodulators that are proposed to reduce symptoms by blunting gastric sensory function, and prokinetic drugs that stimulate gut propulsion. Established agents have been characterized for each category for a multitude of indications. Furthermore, new options are in testing as novel antiemetic, neuromodulator, and prokinetic therapies for different causes of nausea and vomiting.

Antiemetics

Established antiemetics—Medications with action on several receptor subtypes exhibit antiemetic effects in different settings. H₁ antagonists such as dimenhydrinate, meclizine, and promethazine show efficacy in vestibular processes like motion sickness as well as postoperative nausea and vomiting (PONV) and uremia. Similarly, M₁ antagonists like scopolamine are effective preventatives of motion sickness. Phenothiazine (prochlorperazine, chlorpromazine) and butyrophenone (droperidol, haloperidol) D₂ antagonists serve as antiemetics for several etiologies of vomiting including bacterial toxins associated with gastroenteritis, medications, PONV, and radiation therapy induced nausea and vomiting. 5-HT₃ antagonists such as ondansetron and granisetron are also commonly administered for diverse indications including nausea and vomiting secondary to cancer chemotherapy, after surgery, and with radiation therapy. The oral NK₁ antagonist aprepitant and the parenteral prodrug fosaprepitant are the first drugs in this class and effective at

prophylaxis of both acute and delayed chemotherapy-induced nausea and vomiting (CINV) (15). Aprepitant also shows benefits in motion sickness and PONV. CB₁ agonists like dronabinol and nabilone have been employed to prevent CINV.

Newest antiemetic research—Most recent research into antiemetic agents has focused on new 5-HT₃ or NK₁ antagonists, either alone or in combination, for preventing CINV or PONV (Table 1).

One of the older 5-HT₃ antagonists, granisetron, has been reformulated for other methods of administration to optimize delivery to patients who may have difficulties absorbing the drug due to persistent vomiting. A transdermal granisetron patch was approved by the FDA in 2008 for CINV prophylaxis and offers theoretical advantages including continuous medication absorption, bypass of the gut to avoid clearance by the liver, and improved compliance because of reduced dosing frequency (16). The patch delivers granisetron continuously at 3.1 mg every 24 hours for 7 days (17). Peak plasma levels are achieved 48 hours after patch application. In phase 3 trials in CINV, the transdermal product showed comparable efficacy to oral granisetron at 2–3 mg daily (18, 19). Tolerability of transdermal granisetron is high with loss of adhesion in only 1% and pruritus in 0.3% of patients; the main side effect is constipation (19, 20). A recent open label study of transdermal granisetron in 36 patients with a diagnosis of gastroparesis reported improvement in 18, no change in 15, and worsening of nausea and vomiting scores in 2 patients (21). Responses were similar in diabetic versus idiopathic gastroparesis and among those with delayed versus no documented delay in gastric emptying. Recently, an intranasal granisetron product was developed which may provide another means of drug delivery (22).

Palonosetron is the newest 5-HT₃ antagonist; the intravenous form was FDA approved in 2003 and oral dosing was approved in 2008. It offers advantages over older agents because of its greater potency (30 times higher than other 5-HT₃ antagonists) and longer half life (31–54 hours)(23). Palonosetron also stimulates 5-HT₃ receptor internalization with extended blockage of receptor function and also promotes NK₁ receptor internalization by 5-HT₃ receptor-dependent pathways leading to inhibition of crosstalk between the two receptor pathways (24). Likely because of these actions on NK₁ receptors, palonosetron reduces delayed nausea and vomiting after chemotherapy whereas older 5-HT₃ antagonists only are effective during the acute phase of CINV. In a recent review of phase 3 and 4 trials, palonosetron produced complete responses ranging from 57% to 84% for acute CINV and 54% to 94% for delayed CINV (25). One meta-analysis reported a favorable safety profile for palonosetron with lesser prolongation of the electrocardiographic QTc interval compared to other 5-HT₃ antagonists (26).

An oral capsule containing palonosetron combined with a new NK₁ antagonist, netupitant, was FDA approved in 2015 to treat CINV. Netupitant is potent, highly penetrant into the brain, and has a 90 hour half life versus 9–13 hours for aprepitant (27, 28). Netupitant and palonosetron have additive effects on inhibiting 5-HT₃ and NK₁ receptor crosstalk, enhancing antiemetic effects of this combination (29). In a phase 2 trial and in two phase 3 investigations, this agent produced superior rates of complete response of acute and delayed CINV for 120 hours compared to palonosetron given alone and to 3 days of a combination

of aprepitant and ondansetron (27, 30, 31, 32). Benefits were maintained over repeated courses and were associated with improved quality of life (31, 32). In pooled data from 4 trials, the most common side effects were headache and constipation while QTc prolongation was noted in 1.6% (33).

Rolapitant is the newest NK₁ antagonist, being FDA approved in 2015. It exhibits the longest half life (180 hours) in this drug class and occupies CNS NK₁ receptors for >5 days (34). In a phase 2 trial, rolapitant produced significantly better complete responses in CINV versus a regimen of ondansetron plus dexamethasone (35). In three phase 3 investigations, this agent elicited higher responses particularly in the delayed phase of CINV than control groups who received a 5-HT₃ antagonist and corticosteroid (36). A recent pooled analysis of these controlled trials reported a relative risk for complete response of 1.23 (95% CI; 1.18–1.33, P<0.00001) versus comparator regimens with relative risks of no nausea of 1.17 (95% C, 1.04–1.32, P=0.008) and no vomiting of 1.24 (95% CI; 1.18–1.31, P<0.00001)(37). As with netupitant-palonosetron, rolapitant improves quality of life in patients receiving chemotherapy (38). Furthermore in a placebo-controlled trial, the drug was effective in preventing PONV (39). Rolapitant has the additional benefit of not inducing or inhibiting with the CYP3A4 pathway, permitting safer use of other medications metabolized by this pathway including corticosteroids and 5-HT₃ antagonists (40). The most prevalent side effects with rolapitant include constipation, headache, dyspepsia, and hiccups (36).

These efficacy and safety of these newer 5-HT₃ and NK₁ antagonists have not been evaluated in CUNV, although it is likely that at least some patients in the study of transdermal granisetron in patients with gastroparesis symptoms fit this diagnostic category (21). A placebo-controlled trial of aprepitant for relieving nausea of presumed gastric origin has just been completed and the results will be presented in late 2016 ([ClinicalTrials.gov: NCT01149369](https://clinicaltrials.gov/ct2/show/study/NCT01149369)). It is expected that nearly one third of patients in this trial have normal gastric emptying and would be considered to have CUNV. Findings of this investigation will define if this medication class has utility in this condition. However for economic reasons, prescription of any of these novel antiemetics will be quite limited for CUNV as the monthly cost of the least expensive of these medications is nearly \$2000 if used continuously.

Neuromodulators

Established neuromodulators—In the gut, neuromodulators most often are used to control functional abdominal pain. However in a small, uncontrolled cases series of patients with functional nausea and vomiting, 84% reported moderate to complete symptom control with tricyclic antidepressants like amitriptyline, desipramine, nortriptyline, doxepin, and imipramine at average daily doses of 50 mg over 5.4±1.1 months (41). In a follow-up series of diabetics with nausea and vomiting, tricyclics at a mean dose of 50 mg/day elicited at least moderate symptom control in 77% and 68% reported these drugs were their most effective therapies (42). These observations parallel the larger (also uncontrolled) experience in cyclic vomiting syndrome. In this condition, tricyclic antidepressants reduce attacks in 76% of adults and 68% of children with decreases in emetic episode frequency and duration (43). Other neuromodulatory antidepressants have shown efficacy in CUNV. In a retrospective analysis of patients with chronic idiopathic nausea or functional vomiting, 72%

reported moderate or greater symptom reductions on different drug classes including tricyclics (66 patients), selective serotonin reuptake inhibitors (5 patients), serotonin norepinephrine reuptake inhibitors (5 patients), and norepinephrine dopamine reuptake inhibitors (10 patients)(44).

Newest neuromodulator research—Because of the promise of tricyclics to reduce nausea and vomiting, investigators have increased focus on neuromodulators to prevent or treat these symptoms in several settings (Table 2).

A multicenter, placebo-controlled trial of the tricyclic drug nortriptyline was conducted in 130 idiopathic gastroparesis patients (45). The primary outcome, a 50% decrease in symptom scores on at least 2 consecutive study visits, was met similarly by 23% of patients on nortriptyline up to a daily dose of 75 mg versus 21% on placebo ($P=0.86$). When individual symptoms were measured, significant improvements were noted only for anorexia with nortriptyline whereas nausea showed no superior reductions compared to placebo. It should be recognized that subjects in this trial were not considered to have CUNV because of their gastric emptying delays and most patients were referred to tertiary centers because of refractory symptoms. Nevertheless, observations from this first blinded, controlled trial of tricyclics to treat nausea and vomiting somewhat diminish enthusiasm for this medication class as antiemetics.

Mirtazapine is a second antidepressant promoted as a potential therapy for nausea and vomiting. This agent has a complex pharmacology including acting as an indirect agonist on CNS 5-HT_{1A} receptors, an inverse agonist on both 5-HT_{2C} and H₁ receptors, and an antagonist on 5-HT₂, 5-HT₃, and α_2 receptors (46). In a controlled trial of patients receiving spinal anesthesia for orthopedic surgery, nausea and vomiting were reduced with mirtazapine versus placebo (47). Likewise among 80 women undergoing gynecologic surgery, addition of mirtazapine to dexamethasone prophylaxis decreased PONV rates (48). Other settings in which the drug has demonstrated efficacy include hyperemesis gravidarum and vomiting after gastric bypass surgery (49, 50, 51). Mirtazapine also reduced symptoms in two women with CUNV in one series (52). The drug has been reported to be effective in individual patients with idiopathic gastroparesis as well as disease secondary to diabetes, after gastropexy, and occurring as a postinfectious complication (53, 54, 55, 56).

Mirtazapine decreased gastric residual volumes in a diabetic on tube feedings and promoted gastric emptying in dogs with delayed emptying elicited by rectal distention (57, 58). However in another study in healthy volunteers, mirtazapine 30 mg did not affect gastric emptying or nutrient meal tolerance (59). Recently, mirtazapine was studied in 34 functional dyspepsia patients with weight loss in placebo-controlled fashion (60). Over 8 weeks, the drug decreased overall dyspepsia scores with associated improvements in early satiety, quality of life, body weight, and liquid nutrient meal tolerance versus placebo. Nausea scores showed a trend to improvement ($P=0.10$); it is possible findings would have been more robust with a larger sample. The most common side effects with this agent are sedation, constipation, and weight gain.

Another psychotropic agent with antiemetic effects, olanzapine, has properties as a 5-HT₂ and H₁ inverse agonist, and antagonist at 5-HT_{2A}, 5-HT_{2C}, 5-HT₃, 5-HT₆, M₁, M₃, D₁, D₂,

D₃, D₄, and α_1 receptors (61). Phase 3 trials have shown superiority of olanzapine in preventing delayed and overall nausea after chemotherapy versus NK₁ antagonists (62, 63). Combining olanzapine with an NK₁ antagonist provided better nausea prevention with chemotherapy compared to an NK₁ antagonist alone (62, 64). Finally in CINV, olanzapine was better than metoclopramide in reducing breakthrough nausea and vomiting (62, 65). A systematic review and meta-analysis of ten controlled trials with 1082 patients reported that olanzapine was clinically superior to comparator treatment for 4 of 6 study endpoints, with better efficacy in producing no overall vomiting with a relative risk of 1.41 (95% CI, 1.18–1.68) and no nausea with an RR of 1.53 (95% CI, 1.18–1.97)(66). In patients with duloxetine-induced nausea, addition of olanzapine reduced nausea and vomiting scores by two thirds compared to patients on duloxetine alone (67). Furthermore, olanzapine has antiemetic actions in uncontrolled studies in palliative care settings (68, 69). A case report observed improvements in a man with CUNV (70). Common side effects of olanzapine include sedation, dizziness, weight gain, increased plasma lipids, and risk of new onset diabetes (71).

Risperidone is an antipsychotic medication that acts as an antagonist on D₂, D₃, D₄, α_1 and α_2 receptors and an inverse agonist at 5-HT_{2A}, 5-HT_{2C}, and H₁ receptors. Its antiemetic actions are proposed to be secondary to antagonism of D₂ receptors. In an open label study of 20 patients with opiate-induced nausea and vomiting, risperidone reduced nausea in half of patients and vomiting in nearly two thirds (72).

The neuromodulator gabapentin, approved for chronic pain management, also exhibits antiemetic actions. This agent is postulated to act on α_2/δ subunits of voltage sensitive calcium channels to reduce calcium signaling in regions mediating vomiting including the area postrema (73). Gabapentin was observed to reduce chemotherapy-induced nausea and hyperemesis gravidarum in uncontrolled series (74, 75). Controlled data in CINV is conflicting with one phase 3 trial observing no benefits and a second reporting complete nausea and vomiting prophylaxis (76, 77). In a recent meta-analysis of 8 trials, gabapentin reduced PONV as a primary endpoint with a relative risk of 0.60 (99% CI, 0.50–0.72) including nausea with an RR of 0.34 (99% CI, 0.20–0.56) and vomiting with an RR of 0.34 (99% CI, 0.19–0.61)(78). This therapy is associated with sedation as a side effect.

As with research in novel antiemetics, little investigation has been conducted into the utility of neuromodulators in CUNV. A drawback of these neuromodulators is the significant rate of treatment limiting side effects. However, the neuromodulators studied to date as antiemetics are available in generic form and are considerably less costly than newer 5-HT₃ and NK₁ antagonists. Consequently, these drugs may be used more often for refractory CUNV than newer antiemetics.

Prokinetics

Established prokinetics—Prokinetic medications commonly are prescribed for nausea and vomiting associated with gastroparesis. However, a systematic review of 34 controlled trials of prokinetic agents in functional dyspepsia failed to observe a relation of symptom reductions to gastric emptying acceleration (79). Furthermore, these therapies are often used for unexplained nausea and vomiting when delayed gastric emptying has not been

documented. Metoclopramide has gastric prokinetic actions and central antiemetic effects as a 5-HT₄ agonist to facilitate cholinergic transmission and as a D₂ antagonist. Domperidone is a peripheral D₂ antagonist that also has dual prokinetic and antiemetic capabilities. The drug is not approved in the United States, however the FDA permits its use under an Investigational New Drug program. Macrolide antibiotics like erythromycin and azithromycin stimulate gastric emptying by acting as motilin receptor agonists. Erythromycin likely has no central antiemetic effect, thus reductions in nausea and vomiting likely stem from its motor stimulatory properties.

Newest prokinetic research—As with new antiemetic drugs, current prokinetic research includes investigation into innovative formulations of existing agents as well as study of novel medication classes. The agents described below are still in trials and are not yet FDA approved for nausea and vomiting in the United States.

Intranasal spray preparations offer benefits because of their ability to be absorbed across nasal mucosa in patients who cannot retain oral forms due to relentless vomiting. In an open label, parallel 6 week comparison in 89 diabetics with symptoms of gastroparesis, total symptom scores after metoclopramide nasal spray were lower than with oral pills (80). In a follow-up multicenter, phase 2B study in 285 diabetics with gastroparesis, symptoms decreased ~40% only among women treated with metoclopramide nasal spray versus placebo whereas men showed no improvement (81). Symptoms in women showing significant reductions included nausea and upper abdominal pain. Gastric emptying scans were not required for either study and symptom reductions were not related to baseline emptying impairments. Thus, it is probable that some patients could be considered to have had CUNV.

Many investigational prokinetic drugs act via mechanisms of prior approved therapies including 5-HT₄ agonists like metoclopramide, cisapride, and tegaserod or motilin agonists like erythromycin. Prucalopride is a 5-HT₄ agonist approved in Europe and Canada to treat chronic constipation that accelerates gastric emptying in healthy controls and constipated patients (82, 83). In a preliminary study, prucalopride produced superior reductions in nausea and vomiting, early satiety, and bloating with associated gastric emptying acceleration versus placebo in 28 idiopathic gastroparesis patients treated for 4 weeks (84). Another 5-HT₄ agonist velusetrag also stimulates gastric emptying in healthy volunteers and patients with constipation; trials in gastroparesis are ongoing (85). Camicalin is a novel non-macrolide motilin agonist without antimicrobial activity that promotes solid food emptying in healthy volunteers and patients with type 1 diabetes and symptoms of gastroparesis (86, 87, 88). Preliminary unpublished phase 2 data observed symptom improvements in a trial in diabetic gastroparesis (89).

Another focus of prokinetic medication research has been on developing ghrelin receptor agonists. Ghrelin regulates food intake and energy balance by action on growth hormone secretagogue-1a receptors. Exogenous ghrelin accelerates gastric emptying in gastroparesis patients (90). Because of its short half life, native ghrelin is impractical for gastroparesis treatment. Relamorelin is a novel long acting ghrelin agonist with 15–130 fold greater potency than the natural peptide that increases antral contractions in healthy controls and

accelerates gastric emptying in type 1 and type 2 diabetics with gastroparesis (91, 92, 93, 94). In a multicenter, 4 week phase 2A trial in 204 diabetics with gastroparesis, relamorelin therapy produced greater gastric emptying acceleration versus placebo with associated decreases in vomiting severity and frequency (95). In 119 patients with baseline reports of vomiting from this study, relamorelin significantly reduced nausea, vomiting, abdominal pain, bloating, and early satiety versus placebo.

Although any prokinetics approved in the future will be indicated for conditions with delayed gut propulsion like gastroparesis, gastric emptying testing often is not performed in clinical practice. Existing prokinetics elicit symptom reductions in functional dyspepsia with a 30% excess probability of producing a response versus placebo (96). Even when performed, emptying rates do not correlate with symptom severity. Thus speaking practically, it is probable that many patients who receive such agents will be considered to have CUNV.

CONCLUSIONS

Chronic unexplained nausea and vomiting is managed by diverse medication therapies. Drugs with antiemetic actions on several receptor subtypes are beneficial in selected clinical settings and are commonly employed for CUNV based on limited evidence. Research into novel antiemetics has focused on new 5-HT₃ and NK₁ antagonists. Emerging investigation suggests antiemetic and antinausea benefits of neuromodulators in the neuroleptic (tricyclics, mirtazapine, olanzapine, risperidone) and pain modulator (gabapentin) classifications. Although typically indicated for gastroparesis, prokinetic agents are considered for some cases of CUNV given the poor relation of symptom responses to gastric emptying acceleration by these drugs. A novel metoclopramide nasal spray may have advantages over oral forms of this medication. New prokinetics in testing include 5-HT₄ agonists without cardiac arrhythmogenic potential, motilin agonists without antimicrobial effects, and ghrelin agonists which may also have utility for weight control. Expansion of investigation into these three broad medication classifications may identify novel treatments for patients with refractory chronic unexplained nausea and vomiting.

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Table 1

NEWEST ANTIEMETIC MEDICATIONS

Medication (approval date)	Mechanism(s) of Action	Indication	Other Conditions Where Benefits Have Been Reported	Advantages Over Older Agents	Side Effects
Transdermal scopolamine (2008)	5-HT ₃ receptor antagonist	CINV	Diabetic and idiopathic gastroparesis	Transdermal patch delivers drug continuously even in patients with severe vomiting; less cardiac toxicity	Constipation Headache Loss of adhesion Skin irritation
Palonosetron (2003-IV, 2008-oral)	5-HT ₃ receptor antagonist	CINV	Radiotherapy-induced nausea and vomiting PONV Opioid-induced nausea and vomiting Idiopathic intracranial hypertension	Greater potency an longer half life; less cardiac toxicity	Constipation Headache
Netupitant-palonosetron (2015)	Combined NK ₁ and 5-HT ₃ receptor antagonist	CINV	—	Netupitant has longer half life than aprepitant; palonosetron has longer half life than older 5-HT ₃ antagonists; combination is synergistic as antiemetic	Constipation Headache Fatigue Dyspepsia
Rolapitant (2015)	NK ₁ receptor antagonist	CINV	PONV	Longest half life in class, prolonged central nervous system penetration	Constipation Headache Dyspepsia Headache

CINV—chemotherapy-induced nausea and vomiting

PONV—postoperative nausea and vomiting

Table 2**NEUROMODULATORY MEDICATIONS TO TREAT NAUSEA AND VOMITING**

Medication(s)	Mechanism(s) of Action	RCTs Demonstrating Efficacy for Nausea and Vomiting	Open Series, Case Reports Suggesting Benefits	Side Effects
Tricyclic antidepressants (amitriptyline, nortriptyline, desipramine)	Norepinephrine reuptake inhibitors with variable serotonin (and dopamine) reuptake inhibition	—	Functional nausea and vomiting Diabetics with nausea and vomiting Functional dyspepsia Cyclic vomiting syndrome	Sleep disturbance Constipation Lightheadedness Palpitations Cardiac arrhythmias
Mirtazapine	CNS 5-HT _{1A} inverse receptor agonist, HT _{2C} , H1 inverse receptor agonist 5-HT ₂ , 5-HT ₃ , α_2 receptor antagonist	PONV Functional dyspepsia (trend to reduced nausea)	Hyperemesis gravidarum Vomiting after gastric bypass surgery Gastroparesis CUNV	Sedation Weight gain Constipation
Olanzapine	5-HT ₂ and H1 inverse receptor agonist, 5-HT _{2A} , 5-HT _{2C} , 5-HT ₃ , 5-HT ₆ , M ₁ , M ₃ , D ₁ , D ₂ , D ₃ , D ₄ , α_1 receptor antagonist	CINV Duloxetine-induced nausea and vomiting	Nausea and vomiting in palliative care CUNV	Weight gain Sedation Peripheral edema Tremor Dizziness
Risperidone	5-HT _{2A} , 5-HT _{2C} , H1 inverse receptor agonist, D ₂ , D ₃ , D ₄ , α_1 , α_2 receptor antagonist	—	Opiate-induced nausea and vomiting	Sedation Weight gain Fatigue Movement disorders Tremor Dizziness Dyspepsia
Gabapentin	Acts on $\alpha_2\delta$ subunits of voltage-sensitive calcium channels to reduce calcium signalling	PONV CINV (conflicting data)	Hyperemesis gravidarum	Sedation Dizziness Peripheral edema

CINV—chemotherapy-induced nausea and vomiting

PONV—postoperative nausea and vomiting

CUNV—chronic unexplained nausea and vomiting