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REVIEW

Pharmacological Approaches to Diabetic Gastroparesis

A systematic review of randomised clinical trials

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النُهُج الدوائية لعلاج خَزَل المعدة السُّكَرِي

مراجعة منهجية للتجارب السريرية العشوائية

محمد زكي عشا و سندس فالح حسني خليل

ABSTRACT: Pharmacological interventions of diabetic gastroparesis (DG) constitute an essential element of a patient's management. This article aimed to systematically review the available pharmacological approaches of DG, including their efficacy and safety. A total of 24 randomised clinical trials (RCTs) that investigated the efficacy and/or safety of medications targeting DG symptoms were identified using several online databases. Their results revealed that metoclopramide was the only approved drug for accelerating gastric emptying and improving disease symptoms. However, this medication may have several adverse effects on the cardiovascular and nervous systems, which might be resolved with a new intranasal preparation. Acceptable alternatives are oral domperidone for patients without cardiovascular risk factors or intravenous erythromycin for hospitalised patients. Preliminary data indicated that relamorelin and prucalopride are novel candidates that have proven to be effective and safe. Future RCTs should be conducted based on unified guidelines using universal diagnostic modalities to reveal reliable and comprehensive outcomes.

Keywords: Gastroparesis; Diabetes Mellitus; Diabetes Complications; Randomized Controlled Trial; Metoclopramide; Domperidone; Relamorelin.

الملخص: تشكل التدخلات الدوائية في خَزَل المعدة السُّكَري عنصرا أساسيا لعلاج المريض. تهدف هذه المقالة إلى مراجعة منتظمة للنُهُج الدوائية المتوافرة لعلاج خَزَل المعدة السُّكري، بما في ذلك فعاليتها وسلامتها. تم تحديد ما مجموعه 24 تجربة سريرية عشوائية والتي تم التحقق من فعالية وسلامة الأدوية التي تستهدف أعراض خَزَل المعدة السُّكَري باستخدام العديد من قواعد البيانات عبر الانترنت. أظهرت نتائج هذه التجارب أن الميتوكلوبراميد كان الدواء الوحيد المعتمد لتسريع التفريغ المَعِدي وتحسين أعراض المرض. ومع ذلك ، قد يكون لهذا الدواء العديد من الآثار الجانبية على الجهاز القلبي الوعائي والجهاز العصبي، والتَي يمكن التغلب عليها عن طريق مستحضر جديد يستخدم عبر الأنف. البدائل المقبولة هما الدومبيريدون عن طريق الفم للمرضى الذين ليس لديهم عوامل خطر قلبية وعائية أو الإريثروميسين عن طريق الحقن الوريدي للمرضى المنومين في المستشفى. أشارت البيانات الأولية إلى أن الريلاموريلين والبروكالوبريد هي من الأدوية المرشحة الجديدة التي ثبتت فعاليتها وسلامة استعمالها. ينبغي إجراء تجارب سريرية عشوائية مستقبلية بناءً على مبادئ توجيهية موحدة باستخدام طرائق تشخيصية عامة للكشف عن نتائج موثوقة وشاملة.

الكلمات المفتاحية: خَزَل المعدة السُّكَري؛ داء السُّكَري؛ مضاعفات السُّكَري؛ تجربة عشوائية مُراقبة؛ ميتوكلوبراميد؛ دومبيريدون؛ ريلاموريلين.

Gastrointestinal neuropathies in patients with diabetes represent vital aspects of the chronic course of the disease. They may include oesophageal dysmotility, gastroparesis, small bowel dysmotility or diarrhoea and fecal incontinence.[1] More precisely, reduced gastric emptying (GE) has been frequently reported in diabetic patients having gastrointestinal autonomic neuropathy.[2] Delayed GE was first reported by Boas in 1925, which was subsequently termed gastroparesis diabeticorum by Kassender in 1958.[3,4] A symptom entailing contractile, functional, sensory and electrical dysfunction of the stomach was then identified and described as diabetic gastroparesis (DG).[5] This can be perceived as chronic delayed GE associated with nausea, vomiting, postprandial fullness, weight loss, anorexia and abdominal pain without evidence of mechanical obstruction. Furthermore, DG patients usually have poor quality of life and poor glycaemic control; in addition, the disease imposes a significant financial burden on healthcare systems.[6]

The prevalence of DG varies in the literature; in general, the risk of gastroparesis is higher in patients with type 1 diabetes mellitus (T1DM) compared to type 2 diabetes mellitus (T2DM). DG disease prevalence in T1DM was found to be 4.8% based on diabetes registries while tertiary medical centres have reported a prevalence of up to 64%.[7–9] In T2DM, DG is reported in 10.8–30% of patients.[10,11] Gender differences were

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observed in several publications where females had higher prevalence rates than males.[8,10,12] Poorly-controlled diabetes, higher glycosylated haemoglobin (HbA1c), long duration of diabetes and the presence of comorbidities have been consistently reported as independent risk factors of DG.[8,10] Similarly, in an epidemiological study involving 8,657 individuals in Australia, patients with poor glycaemic control had increased prevalence of upper and lower gastrointestinal symptoms.[12] Additionally, the probability of developing DG symptoms increased with advanced age, with a mean age of onset at approximately 34 years.[5]

The diagnosis of DG may remain elusive until the development of complications. To avoid this delay, a precise medical history of the timing of symptoms (i.e. vomiting and satiety) in relation to meals, diet history, symptom progression and diabetes control should be carefully assessed. Severity of DG symptoms is evaluated using the Gastroparesis Cardinal Symptom Index (GCSI), which can be utilised to rate changes in symptoms in clinical studies either by the patient or the physician on a scale ranging from zero (no symptoms) to six (very severe symptoms).[13] Furthermore, gastric obstruction can be excluded using abdominal radiography, computed tomography and magnetic resonance imaging scans. Consequently, a DG diagnosis is confirmed by means of three main diagnostic tests. The first method is gastric emptying scintigraphy (GES), which is a non-invasive method employing a radio-labelled solid meal (mostly using ^{99m}Tc-sulfur) followed by scanning the stomach at one, two and four hours after the meal.[14] The second method is the stable isotope breath test (gastric emptying breath test [GEBT]). After ingestion of meals with ^{13}C-labelled substrates, such as octanoic acid and *Spirulina platensis*, the isotope is absorbed in the small intestine and metabolised to ^{13}carbon dioxide and exhaled through the lungs. Finally, a recent diagnostic modality is a swallowed wireless motility capsule wherein a specialised sensor is used to measure pressure, temperature and pH.[15]

GE in patients with DG is challenging in terms of treatment. This is particularly evident because optimum glycaemic control should be achieved in poorly-controlled diabetic patients. Dietary modifications, such as replacing solid food with a soft and liquid diet, are required. Several pharmacologic options are available although the efficacy and safety of these medications vary. Usually, patients with mild to moderate symptoms are managed by prokinetics and antiemetics. However, disease burden in patients experiencing severe symptoms is difficult to manage. Therefore, it is necessary to determine the most appropriate therapeutic options bearing in mind the prevention of potential gastrointestinal complications in DG patients including gastroesophageal reflux disease, bacterial and fungal infections of the gastrointestinal tract and intestinal dysmotility. In this context, this article aimed to systematically review the available approaches for the pharmacotherapy of DG, including their efficacy and safety and emphasising their roles in patients with different disease severities.

Methods

Based on the guidelines provided by the Preferred Reporting Items for Systematic reviews and Meta-analyses statement, this systematic review was conducted on investigated medications of diabetic patients with DG.[16] In the context of DG, a medication's efficacy targets the severity of symptoms and/or GE while safety deals with the reported adverse events (AEs) in the groups under investigation.

MEDLINE® (National Library of Medicine, Bethesda, Maryland, USA), EMBASE (Elsevier, Amsterdam, Netherlands), Cochrane Library (Wiley, Hoboken, New Jersey, USA) and Google Scholar (Google LLC, Menlo Park, California, USA) databases were used to search for randomised clinical trials (RCTs) that assessed the efficacy and/or safety of medications used for the management of DG. Although the last search was performed until April 2019, there was no time limit set for the included trials. The search strategy used specific keywords based on a Patient/Problem, Intervention, Comparison and Outcome strategy, utilising relevant subject headings and Boolean Operators. These databases were searched with the terms "diabetes" or "diabetic", "gastroparesis" or a combination of the two, "prokinetics" or "prokinetic", "metoclopramide" or "domperidone" or "erythromycin" or "cisapride" or "bethanecol" or "tegaserod", "Motilin agonist" or "ghrelin agonist" or "5-HT4 agonist" (5-hydroxytryptamine receptor 4) and "antiemetic" or "phenothiazine" or "serotonin 5-HT3 Receptor Antagonist" or "antihistamine". Only RCTs with the following characteristics were included in this review: (1) DG had to be diagnosed based on the exclusion of gastrointestinal obstruction; (2) studies should have allocated at least two groups for comparing the outcomes of a single medication versus placebo or another medication; (3) the allocated patients may be adults or children with T1DM or T2DM; (4) the study should be published in a peer-reviewed journal and written in English; (5) the primary outcomes of the RCT should include changes in the scores of the severity of symptoms (as indicated by the GCSI scale, visual analogue scores, etc.) in addition to changes in GE (assessed by ultrasound, GES, GEBT or the swallowed wireless motility capsule); (6) all changes should have been initially measured at

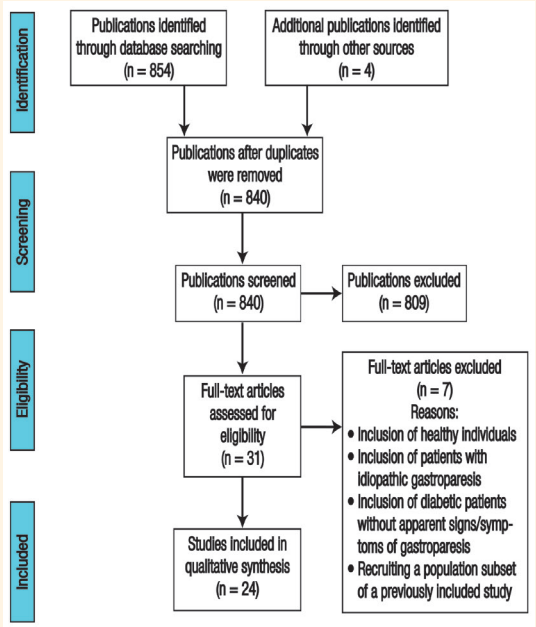

Figure 1: A flowchart of the search process used to identify randomised clinical trials investigating the efficacy and/or safety of medications targeting diabetic gastroparesis symptoms (N = 24).

baseline and reassessed during the course of the study after the administration of medication(s); (7) the AEs should have been assessed in patients in accordance with the physical examination or patient self-reported data; and (8) changes in GE as retrieved from GEBT may be reported as gastric half-emptying time (T½). Studies recruiting a population or subpopulation of healthy individuals or presenting comorbidities with serious conditions rather than diabetes were excluded. Additionally, studies were ineligible if they were non-randomised prospective investigations, retrospective studies, narrative reviews, systematic reviews and meta-analyses.

Finally, a comprehensive search for on-going clinical trials for each medication in ClinicalTrials.gov (https://clinicaltrials.gov/) was performed. A medication was considered novel when its relevant phase 2 RCT was published in 2010 or later.

Two authors independently screened the titles and abstracts obtained by the database search process. Additionally, the reference lists of the identified RCTs were screened for additional eligible studies. The obtained publications were uploaded to EndNote, Version X7 (Clarivate Analytics, Philadelphia, USA) and all duplicate publications were omitted. Decisions regarding the included studies were approached via consensus and any disagreement was resolved via discussion. All data were extracted into a specifically-designed Excel spreadsheet, Version 2016 (Microsoft Inc., Redmond, Washington, USA), that included: 1) study data (name of the first author, year of publication, study design, study duration and country); 2) patients' data (gender, total sample size, age, type of diabetes, glycaemic indicators [e.g. HbA1c] and baseline parameters used to confirm DG symptoms); 3) study groups and interventions (medication(s) used and/or placebo, dosage and methods and duration of administration); 4) the efficacy of medication(s) (changes in severity scores and/or GE in relation to other groups and baseline values when appropriate); and 5) the safety of medication(s) (reported AEs following drug administration).

The methodological quality of the included RCTs was assessed using the Cochrane's Risk of Bias Tool.[17] The domains assessed in each trial included performance bias, selection bias, detection bias, attrition bias and other biases. The results of the assessment process were either reported as "low risk", "high risk" or "unclear". Trials were labelled "unclear" when no data were available in the RCT about the domain under investigation. All data were entered and graphically presented using RevMan, Version 5.3 (Cochrane, London, England).

Results

A total of 854 publications were initially obtained in the specified databases by using the relevant keywords. Four studies were additionally identified from Google search (Google LLC). Following the removal of 18 duplicate publications, the titles and abstracts of 840 studies were screened and 809 were excluded. The full-text versions of the remaining 31 articles were thoroughly checked for eligibility. Nonetheless, seven articles were excluded due to the inclusion of healthy individuals, inclusion of patients with idiopathic gastroparesis, inclusion of patients with diabetes but without signs/symptoms of gastroparesis or a separate trial which included a population subset of an already included study.[18–24] Finally, a total of 24 RCTs were included in this qualitative review [Figure 1].

A total of 2,309 patients, of which the majority (65.22%) were female, were included in all studies which were published between 1982 and 2017. Only one RCT recruited paediatric patients; adults were included in the remaining investigations.[25] Studies were conducted in European countries, at multiple sites in Europe and the USA or only in the USA.[25–33] Patients were diagnosed with T1DM exclusively in nine studies,[25,30,31,34–39] only T2DM in one study and both types in the remaining trials [Table 1].[40]

Figure 2 shows the summary of risk of bias assessment. Random sequence generation was generated by a computer software in eight trials and an Interactive Voice Response System was used in four trials.[27,29–33,38,40–44] Since the method of randomisation

Table 1: Summary of the included randomised clinical trials investigating the efficacy and/or safety of medications targeting diabetic gastroparesis symptoms[21,25–45,59,66]

Author and year of study	Study duration	Country	Gender			Age in years	Diabetic indicators	Gastroparesis indicators
			Male	Female	Total			
Barton *et al.*[66] (2014)	4 weeks	USA	32	47	79	18–60	N/A	• GCSI-DD score: 1.68 ± 0.38; GE was confirmed by ^{13}C-GEBT at baseline
Braden *et al.*[30] (2002)	12 months	Germany	5	14	19	56–72	HbA1c: 7.1–8.2%	• GEBT T½ >170 min
Camilleri *et al.*[42] (2017)	3 months	USA	148	245	393	20–76	HbA1c: 5.2–11.0%	• DG Symptom Severity daily e-diaries (to report vomiting frequency, GE and other symptom scores)
Desautels *et al.*[59] (1995)	NA	USA	10	0	10	26–70	HbA1c: 6.7–12.9%	• History of previous GES
Ejskjaer *et al.*[28] (2009)	10 months	Denmark	5	5	10	46–56	HbA1c: 9.5 ± 2.2 %	• GCSI scores: 3.0 ± 0.9 (moderate to severe DG); ≥29% retention 4 hours following a radio-labelled solid meal. • Gastric T½ above the normal limits for both breath test and scintigraphy
Ejskjaer *et al.*[29] (2010)	17 months	Denmark	25	51	76	18–80	HbA1c: 6.6–10.9%	• GCSI scores: 3.4-4 (moderate to severe DG) • Gastric T½ above the normal limits for both breath test and scintigraphy
Ejskjaer *et al.*[32] (2013)	13 months	18 centres in different countries	32	60	92	20–70	HbA1c: 6.5–10.2%	• GCSI-DD score: 3.3 ± 0.8 (moderate-to-severe DG) • GMBT T½ ≥150 min
Erbas *et al.*[26] (1993)	9 weeks	Turkey	4	9	13	19–68	Self-reported treatment by an oral diabetic agent and/or insulin	• A specific questionnaire for DG symptoms (patients were graded as experiencing severe symptoms) • Objective documentation of delayed GE by a radionuclide solid meal
Franzese *et al.*[25] (2002)	8 weeks	Italy	14	14	28	6–16.9	Insulin dependence for a mean of 5 years	• N/A
Hellström *et al.*[39] (2016)	4 weeks	USA	5	5	10	18–70	N/A	• A positive history of at least 3 months of DG symptoms
Lehmann *et al.*[31] (2003)	7 months	Switzerland	4	4	8	28–63	HbA1c: 8.0 ± 1.3%	• N/A
Lembo *et al.*[41] (2016)	14 months	USA	67	137	204	18–75	HbA1c: ≤11%	• GCSI-DD score ≥2.6 • Gastric T½ ≥79 min by 13C-GEBT
McCallum *et al.*[35] (1983)	3 weeks	USA	16	28	44	21–67	Insulin dependence for 12.6 years	• Patients' self-reported data (mean DG symptoms 2.5 years)
McCallum *et al.*[21] (2007)	12 weeks	USA	139	253	392	18–70	HbA1c: 7.7 ± 1.7%	• Composite TSS score: 2.38 ± 0.69
McCallum *et al.*[43] (2013)	22 months	USA	56	145	201	42–66	HbA1c: 7.8 ± 1.5%	• GCSI score: 3.4 ± 0.7 (moderate to severe DG) • The Michigan Neuropathy Screening Instrument score: 5 ± 2.6 (mild neuropathy) • Gastric T½ above the normal limits for both breath test and scintigraphy
Murray *et al.*[27] (2005)	N/A	UK	5	5	10	36–63	HbA1c: ≤11%	• Patients were recruited based on the presence of bloat plus two gastrointestinal symptoms as predictors of DG
Parkman *et al.*[33] (2014)	6 weeks	USA (in 6 centres)	41	48	89	18–82	N/A	• Mean TSS score range: 21.3–23.4 (indicating moderate to severe symptoms) • All symptoms were reported except nausea at baseline
Parkman *et al.*[44] (2015)	4 weeks	USA	83	202	285	18–75	Self-reported treatment by an oral diabetic agent and/or insulin	• GCSI-DD score: 2.74 ± 0.48
Patterson *et al.*[37] (1999)	4 weeks	USA	33	62	95	19–69	N/A	• TSS scale
Ricci *et al.*[36] (1985)	6 weeks	USA	6	7	13	24–73	Insulin dependence for 12.5 years	• Objective documentation of delayed GE by a radionuclide solid meal
Shin *et al.*[38] (2013)	6 months	USA	2	8	10	31–65	HbA1c: ≤11.3%	• GCSI-DD score: 1.66 ± 0.38 • Gastric T½: 4.9 ± 1.3 by ^{13}C-GEBT • Baseline composite NVFP score: 1.73 ± 0.39
Shin *et al.*[40] (2013)	3 months	USA	0	10	10	36–60	HbA1c: 7.2 ± 0.4%	• GCSI-DD score: 1.32 ± 0.21
Silvers *et al.*[45] (1998)	4 weeks	USA	66	142	208	19–76	N/A	• TSS scale of five symptoms (≥8 out of 15, indicating moderate to severe DG)
Snape *et al.*[34] (1982)	6 weeks	USA	5	5	10	21–49	Insulin dependence for 16.2 ± 2.4 years	• A specific questionnaire for DG symptoms • Objective documentation of delayed GE by a radionuclide solid meal

N/A = not available; GCSI-DD = The Gastroparesis Cardinal Symptom Index-Daily Diary; GE = gastric emptying; ^{13}C-GEBT = ^{13}C-spirulina gastric emptying breath test; T½ = half-emptying time; HbA1C = glycosylated haemoglobin; DG = diabetic gastroparesis; min = minutes; GES = gastric emptying scintigraphy; GMBT = gastric motility breath test; TSS = total symptom score; NVFP = nausea, vomiting, fullness, and pain.

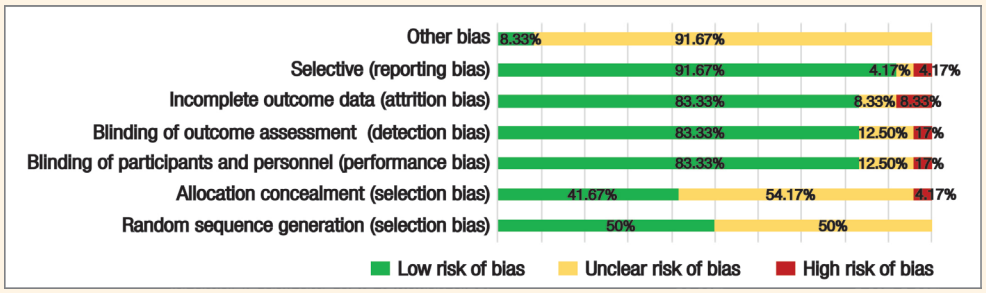

Figure 2: A summary of risk of bias assessment for the included randomised clinical trials (N = 24).

was inexplicitly mentioned in the remaining RCTs, they were assessed as "unclear". Participants' allocation was concealed from the investigators in ten trials, while selection bias was apparent in one trial, owing to the randomisation using an incomplete block method.[29,32,35,36,38–44] The method of concealment was unclear in the remaining trials. Both performance and detection biases were evident in a trial conducted by Silvers *et al.* since the investigators were not blinded to the patients receiving the intervention.[45] Intention-to-treat analysis was performed in eight trials in order to investigate the efficacy of interventions following withdrawal of a number of participants.[33,37,39,41,43–46] Patients' withdrawal had not affected the comparability between groups as explored by statistical analyses in the remaining trials [Table 2].

TRADITIONAL MEDICATIONS

Dopamine D2 receptor antagonists

Metoclopramide has dual actions on the brainstem and peripheral nerves as a dopamine D2 receptor antagonist and serotonin (i.e. 5-HT4) receptor agonist. The main effects on the gastrointestinal tract are exerted by increasing antral contraction by releasing acetylcholine from enteric neurons.[47] In DG patients, early trials indicated significant improvements in the scores of nausea, fullness and bloating after three weeks of metoclopramide oral administration as compared to the placebo.[35,36] In addition, GE improved significantly and consistently in all trials of oral regimens assessed by GES.[34–36] Therefore, it was the sole drug approved by the Food and Drug Administration (FDA) for the treatment of DG. Rather than oral administration, in terms of improving GCSI scores, more recent RCTs have shown superior efficacy of nasal spray preparations.[33,44] However, some AEs were reported in other trials, particularly in comparative ones which were conducted for more than four weeks.[26,33,37] These AEs include anxiety, depression, somnolence, headache and leg cramps. Furthermore, there are some concerns about the development of tardive dyskinesia with the chronic use of metoclopramide.[48] Diabetes itself may be independently associated with the risk of tardive dyskinesia.[49] Therefore, this medication received a 'black box warning' from the FDA. Collectively, recommendations indicate the use of metoclopramide for no longer than 12 weeks.[50]

Therefore, alternative medications with high efficacy and safety have been studied. Domperidone is another dopamine D2 receptor antagonist which is effective against nausea and vomiting with a better safety profile than metoclopramide. Patterson *et al.* showed that domperidone was associated with less frequent central AEs compared to metoclopramide.[37] Similarly, domperidone ameliorated nausea and early satiety compared to placebo in adults and cisapride in children with DG.[25,45] It can be initially administered three times daily at a dose of 10 mg, which is increased to 20 mg at bedtime. Early prospective investigations conducted almost three decades ago revealed that DG symptoms improved significantly after six months or one year of treatment.[51,52] Additionally, it improved the quality of life of patients in a subsequent retrospective analysis.[53] However, domperidone may be associated with a risk of cardiac arrhythmia and may cause QT prolongation.[54] Therefore, recommendations based on a moderate level of evidence indicate performing a baseline electrocardiogram and a cessation of treatment if the corrected QT is more than 470 and 450 ms in males and females, respectively. Moreover, a follow-up electrocardiogram along the course of treatment is advised.[55]

Ghrelin and ghrelin receptor agonists

Early studies have shown favourable implications of ghrelin in the treatment of gastroparesis as it modulates energy homeostasis and gastrointestinal motility.[27] This was evident in ten patients with DG using a test meal of rice pudding where ghrelin infusion caused a significant increase in GE independent of cardiovagal tone.[27] However, the therapeutic effects of ghrelin were limited by its relative plasma instability and short half-life.[56] Thus, several synthetic ghrelin analogues were investigated for their clinical potential.

TZP-101 (i.e. ulimorelin) is a macrocyclic ghrelin receptor analogue which has been investigated in patients with DG in a phase 1 trial in Denmark.[28] TZP-101

Table 2: The outcomes of randomised clinical trials investigating traditional and novel medications for the treatment of diabetic gastroparesis[21,25–45,59,66]

Author and year of study	Study groups and INT	Efficacy on gastroparesis symptoms	Efficacy on GE	Safety
Dopamine D2 receptor antagonist				
Snape *et al.*[34] (1982)	• Metoclopramide (10 mg orally, four times per day) • Placebo (two 3-week treatment INT with a 1-week washout period before cross-over)	• No significant changes observed in abdominal pain or bloating	• Using GES, a 24% increase in GE rate (P <0.01) was reported 3 weeks after treatment versus 5% increase in placebo	• N/A
McCallum *et al.*[35] (1983)	• Metoclopramide (10 mg orally, four times per day) • Placebo (for 3 weeks)	• A significant improvement of fullness and nausea (P <0.05) in the INT versus placebo (assessed using grading diary sheets)	• GE improved in the INT group compared to baseline values (P <0.05, assessed by GES scintigraphy) but not to placebo	• Restlessness, amenorrhea, headache, constipation and leg cramps were noted in the metoclopramide group
Ricci *et al.*[36] (1985)	• Metoclopramide (10 mg orally, four times per day) • Placebo	• Significant improvement of fullness, bloating, nausea and anorexia when compared to placebo (P <0.05) • No significant correlation between changes in symptoms and GE improvement	• GE improved significantly (isotope retention was 91% at baseline and 78.6% after metoclopramide administration)	• Mild symptoms ignore, such as sedation, headache and mild hand tremors were noted in metoclopramide-receiving patients
Parkman *et al.*[33] (2014)	• Metoclopramide (10 mg orally, four times per day; n = 18) • Metoclopramide (10 mg nasal spray, four times per day; n = 35) • Metoclopramide (20 mg nasal spray, four times per day; n = 36)	• Using TSS scores, CFB was significantly improved in the 20 mg nasal spray group compared to the oral group (P = 0.026)	• N/A	• Three subjects discontinued the study due to severe restlessness, severe drowsiness and mild headache. • Nausea was more frequently reported in the oral group
Parkman *et al.*[44] (2015)	• Metoclopramide (10 mg nasal spray, four times per day; n = 95) • Metoclopramide (14 mg nasal spray, four times per day; n = 95) • Placebo (n = 95)	• GSDD scores did not improve significantly in the INT groups as compared to placebo • Severity scores improved significantly only in women for both INT groups as compared to placebo (P = 0.02 each)	• N/A	• AEs were mild to moderate. They were more frequent in the 14 mg (8.4%, including headache, dizziness, diarrhoea, cholelithiasis, vomiting and nausea) rather than the 10 mg group (nausea, myoclonus, and memory impairment)
Patterson *et al.*[37] (1999)	The following regimens were given for 4 weeks: • Metoclopramide (one 10 mg tablet plus one placebo tablet were taken four times per day) • Domperidone (two 10 mg tablets were taken four times per day)	• No significant differences between groups in improving symptoms (improved by 41.1% with domperidone and 38.9% with metoclopramide)	• N/A	• Somnolence, anxiety, akathisia and depression were significantly more severe in the metoclopramide group after 2 and 4 weeks of treatment (P <0.001) • Severe CNS events accounted for treatment discontinuation in four patients and one patient in the metoclopramide and domperidone groups, respectively
Silvers *et al.*[45] (1998)	• Domperidone 20 mg (four times per day; n = 105) • Placebo (n = 103)	• Significant improvements were noted in the domperidone group for total symptoms (P = 0.011), nausea (P = 0.024) and early satiety (P = 0.004) compared to placebo	• N/A	• No significant differences between both groups in the tolerability profile • Headache, diarrhoea, abdominal pain, rhinitis and sinusitis were most commonly reported among patients
Franzese *et al.*[25] (2002)	• Domperidone (0.9 mg/kg three times per day; n = 14) • Cisapride (0.8 mg/kg three times per day; n = 14)	• Significant improvements in the TSS in both groups (P <0.001 each) compared to baseline	• Ultrasonography revealed significant shortening of GE time in the domperidone group compared to baseline (P <0.01). • No remarkable differences were noted in the cisapride group	• N/A
Erbas *et al.*[26] (1993)	The following regimens were given for 3 weeks, then 3 weeks washout and 3 weeks cross-over: • Metoclopramide (10 mg orally, three times per day) • Erythromycin (250 mg orally, three times per day)	• The total score of gastrointestinal symptoms significantly improved after erythromycin (0–5) compared to post-metoclopramide therapy (0–11; P <0.05)	• Gastric T½ improved significantly in both INT groups at 60 and 90 min after meal	• Two patients reported sedation, leg cramps and weakness, while one patient reported drowsiness and palpitation with use of metoclopramide
Ghrelin receptor agonist				
Murray *et al.*[27] (2005)	• The patients received either ghrelin (5 pmol/kg/min) or saline on two different occasions	• No significant differences between ghrelin and saline in the incidence of bloating, nausea and hunger during infusion as assessed by VAS	• Significant improvement of GE (from 30% to 43%) as assessed by ultrasound	• N/A
Ejskjaer *et al.*[28] (2009)	• A cross-over administration of different doses of TZP-101 infusions (80, 160, 320, or 600 g/kg) • Placebo	• No significant differences between the INT and placebo groups in the intensity of post-meal symptoms and postprandial fullness	• Gastric T½ (20%; P = 0.043) and latency times were significantly reduced compared to placebo	• No differences in AEs between TZP-101 and placebo group
Ejskjaer *et al.*[29] (2010)	• A 4-day consecutive regimen of intravenous infusion of ulimorelin at a dosage of: 20μg/kg (n = 8); 40μg/kg (n = 17); 80μg/kg (n = 13); 160μg/kg (n = 6); 320μg/kg (n = 6); 600μg/kg (n = 7); • Placebo (n = 19)	• In the group receiving ulimorelin 80 μg/kg, the severity of GCSI loss of appetite and vomiting scores was significantly improved (P = 0.034 and 0.006, respectively) • The post-prandial fullness domain of the GSA score was significantly improved compared to placebo	• No difference in gastric T½ among groups	• The frequency and severity of AEs were comparable between the INT and placebo group
Ejskjaer *et al.*[32] (2013)	• The following regimens were given once daily (oral capsules before breakfast) for 28 days: TZP-102 10 mg (n = 22); TZP-102 20 mg (n = 21); TZP-102 40 mg (n = 23); placebo (n = 26)	• All doses (combined) caused a significant decline of the GSCI total score compared to placebo	• No significant differences in GMBT T½ between INT groups and the placebo group • No correlation between GMBT T½ and the GSCI score at baseline or at 28 days	• No differences in AEs between the TZP-102 and placebo groups

INT = interventions; GE = gastric emptying; GES = gastric emptying scintigraphy; NA = not available; TSS = total symptom score; CFB = change from baseline; CNS = central nervous system; min = minutes; VAS = visual analogue score; AEs = adverse events; GCSI = Gastroparesis Cardinal Symptom Index; GSA = Gastroparesis Symptom Assessment; GMBT = gastric motility breath test; GSDD = gastroparesis symptom daily diary; CFB = change from baseline; GEBT = gastric emptying breath test; SC = subcutaneous; DD = daily diary; NVFP = nausea, vomiting, fullness and pain.

Table 2 (contd.): The outcomes of randomised clinical trials investigating traditional and novel medications for the treatment of diabetic gastroparesis[21,25–45,59,66]

Author and year of study	Study groups and INT	Efficacy on gastroparesis symptoms	Efficacy on GE	Safety
McCallum *et al.*[43] (2013)	• The following regimens were given once per day (oral capsules) for 12 weeks: TZP-102 10 mg (n = 69); TZP-102 20 mg (n = 66); Placebo (n = 66)	• GSDD improved significantly in all groups, but no difference was reported versus placebo (CFB: -1.1 versus 0.98 for INT groups and placebo groups)	• No statistical difference in CFB of GEBT among all groups	• AEs occurred in 57%, 58% and 67% in the 10 mg, 20 mg and placebo groups, respectively without remarkable differences
Shin *et al.*[38] (2013)	• Relamorelin 100 µg SC once per day (n = 5) • Patients crossed over with a 7-day washout period • Placebo (n = 5)	• Relamorelin significantly reduced GCSI-DD (P = 0.041) and NVFP (P = 0.041) scores compared to placebo	• GE was significantly accelerated in eight patients relative to the placebo (P = 0.005)	• No serious AEs were reported • Only hunger was almost significant with relamorelin use (P = 0.063)
Shin *et al.*[40] (2013)	• A single dose of relamorelin 100 µg SC (n = 5) • Patients crossed-over with a 7-day washout period • Placebo (n = 5)	• Since it was a single-dose study, it was not powered to investigate DG • GCSI scores were similar in both groups.	• Gastric T½ of solids, but not liquids, reduced by relamorelin versus placebo (P = 0.011) • Significant effects were noted also in GE at 2 and 4 hours (with percent differences of 48% and 19%, respectively)	• Relamorelin led to a large GE acceleration
Lembo *et al.*[41] (2016)	• Relamorelin 10 µg once per day (n = 67) • Relamorelin 10 µg twice per day (n = 68) • Placebo (n = 69)	• The twice-daily regimen reduced vomiting severity and frequency by 60% compared to placebo, while it had no effects on abdominal pain and satiety	• Significant improvement of GE (P <0.03) with twice-daily regimen	• In the INT group ≥5% of patients experienced headache and worsening of glycaemic control
Camilleri *et al.*[42] (2017)	• The following SC injections were given twice per day: Relamorelin 100 µg (n = 82); Relamorelin 30 µg (n = 109); Relamorelin 10 µg (n = 98); Placebo (n = 104)	• Relamorelin reduced the frequency of vomiting by 75% compared to baseline, but not compared to placebo • Different doses of relamorelin decreased all composite symptoms of DG compared to placebo (P <0.05)	• GE was significantly accelerated in the 10 and 30 µg groups by 12% (P <0.05) compared to placebo after 12 weeks	• In the INT group, 14.5% of patients experienced dose-related deteriorations of glycaemic control; this was resolved by drug dosage adjustments
Motilin receptor agonist				
Desautels *et al.*[59] (1995)	• Erythromycin base 250 mg • Erythromycin base 1000 mg • Placebo	• N/A	• Significant improvements of GE were reported between erythromycin groups and placebo (P = 0.0007) • No differences were present between erythromycin 250 and 1000 mg groups	• Diarrhea was reported in one patient in the erythromycin 1000 mg group
McCallum *et al.*[21] (2007)	• The following regimens were given for 12 weeks twice per day: Mitemcinal 5 mg (n = 131); Mitemcinal 10 mg (n = 130); Placebo (n = 131)	• No significant effects were noted over 12 weeks among groups • In a subset of the population under study (those having 75% positive weekly responses), mitemcinal 10 mg produced a significant improvement in total symptoms during the study period (P <0.05) compared to placebo	• N/A	• Severe AEs were reported in 18.8%, 15.9% and 20.0% of patients in the placebo, mitemcinal 5 mg, and mitemcinal 10 mg groups, respectively • There were non-significant differences among groups
Barton *et al.*[66] (2014)	• The following regimens were given once per day for 4 weeks: Camicinal 10 mg (n = 18); Camicinal 50 mg (n = 18); Camicinal 125 mg (n = 22); Placebo (n = 21)	• The most significant improvements occurred at 2–4 weeks for fullness and satiety for 10 mg (53%) and 50 mg (65%) groups • No or little effect was reported for the highest dose	• GEBT T½ decreased significantly with increasing dose (P <0.05) as assessed by swallowed wireless motility capsule	• There were similar frequencies of AEs among different groups (urinary tract and gastrointestinal symptoms)
Hellström *et al.*[39] (2016)	• Each patient participated in three single oral INT (out of four INT) with a 7-day washout period in-between. The groups were: Camicinal 50 mg; Camicinal 125 mg; Placebo	• No symptomatic improvement was observed	• GEBT T½ decreased by 65% (P <0.05) by 125 mg camicinal compared to placebo • There was a non-significant trend of reduced GEBT T½ with 25 and 50 mg doses • A dose-response relationship was apparent	• Headache, vomiting and decreased blood glucose were reported in a similar frequency in all groups
5-HT4 receptor agonist				
Braden *et al.*[30] (2002)	• Given thrice per day: Cisapride 10 mg (n = 9); Placebo (n = 10)	• N/A	• GEBT T½ decreased significantly in the INT group after 12 months compared to baseline (P = 0.03); the placebo group showed no changes from baseline • No effects were noted on glucose control in both groups	• N/A
Lehmann *et al.*[31] (2003)	• The following treatments were given for 3 months, then 4 weeks washout and 3 months cross-over: Cisapride 20 mg twice per day; Placebo	• N/A	• GE improved significantly at 120 min in the INT group (P = 0.025), while gastric T½ did not differ between the INT and placebo groups (P = 0.09) • No apparent improvements in glycaemic control	• No serious AE • Patients with prolonged QTc were excluded at the initial recruitment phase

INT = interventions; GE = gastric emptying; GES = gastric emptying scintigraphy; NA = not available; TSS = total symptom score; CFB = change from baseline; CNS = central nervous system; min = minutes; VAS = visual analogue score; AEs = adverse events; GCSI = Gastroparesis Cardinal Symptom Index; GSA = Gastroparesis Symptom Assessment; GMBT = gastric motility breath test; GSDD = gastroparesis symptom daily diary; CFB = change from baseline; GEBT = gastric emptying breath test; SC = subcutaneous; DD = daily diary; NVFP = nausea, vomiting, fullness and pain.

infusion (given at 80, 160, 320, or 600 µg/kg in a cross-over manner) caused 20% reduction in gastric T½ of solids compared to a placebo; however, no apparent effects were noted on postprandial symptoms.[28] A phase 2 trial conducted by the same team revealed that the infusion of 80 µg/kg TZP-101 caused a significant reduction in severity of several symptoms including vomiting, loss of appetite and reduction of the GCSI scores (25% versus 8% among patients allocated to placebo), although no differences were reported in gastric T½.[29]

Table 3: Ongoing clinical trials which investigate candidate medications for diabetic gastroparesis

Candidate drug	Mechanism of action	Disease	Intervention	Clinicaltrials.gov identifier
Prucalopride (Resotran™ [Janssen Pharmaceutica, Beerse, Belgium])	5-HT4 agonist	DG	2 × 2 mg tablets of prucalopride or placebo given once daily for 28 days	NCT02031081
Velusetrag (TD-5108)	5-HT4 agonist	DG and IG	Velusetrag 5, 15, 30 mg capsules once daily versus placebo for 12 weeks	NCT02267525
RQ-00000010	5-HT4 agonist	Gastroparesis	The intervention will be given once daily at doses of either 10, 50, 100 µg orally for 2 weeks versus placebo	NCT02838797
TAK-906	Dopamine D2 receptor antagonist	DG and IG	TAK-906 5, 25, and 100 mg capsules versus placebo for 9 days	NCT03268941
Sitagliptin (MK-0431-075)	DPP-4 inhibitor	DG	100 mg sitagliptin once daily for 2 days versus placebo	NCT02324010
VLY-686 (Tradipitant)	Neurokinin 1 antagonist	Gastroparesis	VLY-686 oral capsule once daily for 4 weeks versus placebo	NCT02970968
Relamorelin (RM-131)	Selective ghrelin receptor agonist	DG	Relamorelin 10 µg SC injection twice daily for 12 weeks versus placebo	NCT03285308
			Relamorelin 10 µg SC injection twice daily for 52 weeks versus placebo	NCT03383146

5-HT4 = 5-hydroxytryptamine receptor 4; DG = diabetic gastroparesis; IG = idiopathic gastroparesis; DPP-4 = dipeptidyl peptidase-4; SC = subcutaneous.

Consequently, TZP-102 was developed as an oral preparation. A phase 2a trial was performed in 2013 to assess the impact of a 28-day TZP-102 regimen for doses ranging between 10 and 40 mg versus a placebo. Ejskjaer *et al*. found that all doses (combined) significantly alleviated DG symptoms, but with no remarkable effects on GE indices.[32] Similarly, a phase 2b trial, which administered TZP-102-CL-G003 and TZP-102-CL-G004 for 12 weeks, emphasised the lack of improving effects on the Gastroparesis Symptom Daily Diary scores as well as GE analysis compared to a placebo.[43] In addition, the investigations of TZP-102-CL-G004 were terminated at an early stage due to lack of efficacy in DG patients.

Motilin receptor agonists

Erythromycin has been well-established for its prokinetic action since its introduction six decades ago.[57] Its motilin agonistic action promotes peristaltic movement and enhances GE through the induction of phase III contractions of the migrating motor complex. Thus, it increases gastric antral contraction. Early studies revealed that acute intravenous and chronic oral administration for four weeks led to a significant reduction in the total symptom score in DG patients, which may be superior to the effect of metoclopramide.[26,58] Desautels *et al*. reported significant GE acceleration via a single dose of 250 mg with no apparent side effects in diabetic patients.[59] However, subsequent studies have shown that erythromycin was associated with tachyphylaxis, whereby its prokinetic effect may be lost after 48 hours of treatment.[60] In addition, its venous administration may be associated with serious AEs such as ventricular arrhythmia and can interact with other medications due to inhibition of cytochrome P450 C3A4.[61,62]

Additional medications without antibiotic activities and avoiding the previously-mentioned AEs need to be developed. Mitemcinal is another motilin agonist which has been tested in a 12-week double-blind RCT.[46] Although there was evidence of GE improvements in patients with non-delayed GE, the results showed no significant differences in the symptoms of DG.

5-hydroxytryptamine receptor 4 agonists

Cisapride is a traditional non-selective 5-HT4 receptor agonist which causes increased muscular contraction through cholinergic pathways. Two RCTs have shown that the chronic use of this medication (for at least seven months) reduces GE time in patients with DG with no remarkable effects on their glycaemic control.[30,31] However, both trials excluded patients with prolonged QTc at the initial recruitment. Given that cisapride administration can activate the *Human ether-a-go-go-related* gene (*hERG*) potassium channels and may consequently lead to QT prolongation, ventricular arrhythmias and syncope, it has been withdrawn from the market in several countries.[63] Similarly, the use of tegaserod (another 5-HT4 agonist) has been suspended since 2007 owing to its association with ischaemic cardiovascular events.[64]

NOVEL AND INVESTIGATIONAL MEDICATIONS

Ghrelin and ghrelin receptor agonists

RM-131 (i.e. relamorelin), the most recently investigated member of the ghrelin analogue family, has provided promising outcomes. Initially, Shin *et al*. tested the efficacy of subcutaneous injections of RM-131 in 10 patients with T1DM in a double-blind,

cross-over, placebo-controlled RCT and assessed the symptoms of DG using the GCSI score and GE using scintigraphy.[38] Results revealed that gastric T½ was significantly accelerated at one and two hours after meals compared to a placebo along with significant improvements in the average symptoms scores. Similar results were reported by Shin *et al.* in an RCT conducted among female patients with T2DM.[40] More recent data from placebo-controlled RCTs indicated that subcutaneous injection of RM-131 twice daily had the most remarkable impact on reducing the frequency and severity of DG symptoms besides GE acceleration.[41,42] Additionally, these regimens were safe and well-tolerated in all trials. Phase 3 clinical trials are on-going concerning this novel medication [Table 3].

Motilin receptor agonists

Camicinal (i.e. GSK962040) is a novel small-molecule motilin agonist which causes GE acceleration in healthy individuals.[65] The pharmacokinetic characteristics of camicinal in the latter populations were similar to those in patients with T1DM, causing a significant reduction of gastric T½ (65% improvement) following a single dose of up to 125 mg compared to a placebo (52 versus 147 minutes; P <0.05) despite a lack of remarkable symptomatic improvements.[39] However, in a double-blind, phase 2 RCT, Barton *et al.* found a significant amelioration of fullness and early satiety after camicinal administration (10 and 50 mg) for four weeks.[66]

5-hydroxytryptamine receptor 4 agonists

There are multiple on-going investigations concerning new 5-HT4 receptor agonists that exert beneficial outcomes on the gastrointestinal tract without prominent AEs on cardiac muscle. However, these trials are either performed on patients with idiopathic gastroparesis or their outcomes have not been published yet. Revexepride is a specific agonist that has been tested in an RCT on diabetic and non-diabetic patients with gastroparesis.[22] There were no significant improvements in GCSI scores, GE or quality of life of patients allocated to the intervention group versus a placebo.[22] Prucalopride is a selective 5-HT4 agonist which significantly reduced GEBT T½ compared to a placebo (P <0.050) as well as GSCI scores of bloating/distension (P <0.001), nausea/vomiting (P = 0.010) and fullness (P <0.001) when it was given at a dose of 2 mg once a day for four weeks.[67] A phase 2 trial in DG patients was completed with no reported results so far [Table 3]. Likewise, velusetrag, which has been proven for its GE-accelerating effects in patients with constipation, is being investigated in patients with gastroparesis.

Discussion

DG is a relatively common complication among diabetic patients. Nevertheless, there is no consensus on the optimal management approach. Hence, several medications have been tested to relieve the symptoms in individuals with an established health burden. The current article aimed to review the best level of evidence, namely RCTs, which tested the efficacy and safety of medications targeting DG. Results showed multiple safety concerns of the currently used drugs. While metoclopramide is the only FDA-approved drug, other traditional drugs have been withdrawn from the markets of several countries owing to risky complications, mostly cardiovascular, in diabetic patients. Current efforts are aimed at developing novel medications and/or new safe preparations of traditional drugs.

Metoclopramide can interfere with emesis through its action on the central nervous system and increase gut motility via its prokinetic effect. Due to the risk of AEs such as tardive dyskinesia, it has been traditionally prescribed at the lowest effective dose for short periods of time. The novel intranasal preparation is seemingly more practical due to the intolerability of oral medications in DG patients with severe nausea and vomiting. For those who are unable to use metoclopramide, domperidone has recently been granted FDA's expanded access investigational new drug application in adults with gastroparesis.[68] This drug should be prescribed to manage severe symptoms in patients whom the potential benefits of the medication may justify its potential risks. Although the impact on the central nervous system is not apparent, domperidone still has cardiovascular risks owing to its tendency of causing a prolonged QTc interval. Seemingly, intravenous erythromycin is warranted in hospitalised patients who need intravenous therapy as they are continually monitored for any AEs.[69]

Recent trials showed promising effects of the novel ghrelin receptor agonist relamorelin, the motilin receptor agonist camicinal and the 5-HT4 agonist prucalopride. Subcutaneous relamorelin has been effective and safe in healthy individuals and in DG patients has been shown to accelerate GE and induce antral contraction.[42,70] The most effective doses are 10 and 20 μg while the on-going RCTs use the smaller dose to assess its efficacy in managing gastroparesis symptoms. Camicinal can be considered an attractive candidate for the treatment of DG as it showed GE acceleration in a dose-dependent manner in healthy and diabetic patients at a minimum dose of 125 mg.[39,71] Owing to small sample sizes and its administration at a

single dose, the conducted RCTs failed to demonstrate significant effects on DG symptoms. As such, further trials are warranted giving due consideration to using multiple-dose regimens and recruiting larger samples. Prucalopride is approved in many countries for the treatment of chronic constipation and its preliminary favourable actions on patients with gastroparesis may be attributable to its high affinity to 5-HT4 receptors with no effects on *hERG* channels.[67,72]

The efficacy of prokinetics in diabetic patients may be affected by other factors which can decrease GE. For instance, the patient's diabetologist should be consulted regarding the use of GLP-1 analogues such as liraglutide and exenatide as well as incretin-based drugs (e.g. pramlintide) as they may interfere with GE.[73,74] Furthermore, while there is no confirmative evidence of the relationship between long-term improved glycaemic control, the symptoms of DG and the rates of GE, studies have shown that acute hyperglycaemia can slow GE in diabetic patients.[75,76] It is worth noting that a diet rich in both fibre and fat can delay GE. As such, the main essence of dietary interventions should be consuming small and frequent meals which are low in fat and fibre.[50,77] Additionally, a recent RCT has indicated the significance of small-particle size diets in reducing the severity of key symptoms of DG including postprandial fullness, nausea/vomiting and bloating.[78]

Ethnic-based differences in disease presentation have been reported in a retrospective analysis of adult patients in the National Institutes of Health Gastroparesis Consortium registries, where non-Hispanic blacks with DG had more severe symptoms (nausea/vomiting) and more frequent hospitalisation rates compared to non-Hispanic whites.[79] The increased severity of DG symptoms in non-whites was also reported in other cross-sectional studies.[80,81] Additionally, Hispanics were more likely to develop gastroparesis secondary to diabetes than non-Hispanic whites who experienced idiopathic gastroparesis.[79] Therefore, domperidone treatment and peripherally inserted catheters were less used in Hispanics compared to non-Hispanic whites. Nonetheless, the therapeutic effects based on racial differences were not exclusively investigated in RCTs. Studies employing a large proportion of white patients of Caucasian heritage (>80%) showed acceptable efficacy and safety outcomes after using ulimorelin, relamorelin and domperidone.[29,41,45]

The use of antiemetics predominantly focuses on symptomatic management. Antihistamines (i.e. promethazine) and phenothiazines (i.e. prochlorperazine) are frequently prescribed, yet they may interact with the prokinetics particularly if the medications are metabolised through the CYP450 pathway. Serotonin 5-HT3 receptor antagonists, such as ondansetron and dolasetron, may be used in emergency settings when other therapies fail to relieve nausea; little is known about their efficacy in gastroparesis secondary to diabetes.[82] Moreover, patients with profound nausea and vomiting may benefit from synthetic cannabinoids, including dronabinol and nabinol, although they showed variable pharmacokinetic profiles.[83] They may be associated with a risk of hyperemesis on withdrawal and were not previously tested in DG patients.[84]

Recently, aprepitant, a neurokinin 1 (NK-1) receptor antagonist, has shown encouraging outcomes. While it was originally used for managing chemotherapy-induced nausea and vomiting, a 4-week, double-blind multicentre trial revealed that aprepitant ameliorated the severity of nausea, vomiting and all GCSI symptoms in patients with all-cause gastroparesis.[85,86] Moreover, Fountoulakis *et al.* found that this medication was effective in the long-term management of severe symptoms in two cases of DG refractory to treatment with first-line medications.[87] Currently, the efficacy of a 4-week regimen of tradipitant, another NK-1 receptor antagonist, is being investigated to manage gastroparesis.

This review provides an updated overview of the currently used medications and their therapeutic effects on patients with gastroparesis secondary to diabetes in RCTs. Other systematic reviews have summarised pharmacological and other management approaches to DG, such as nutritional support, glycaemic management, surgical techniques, intrapyloric *botulinum* toxin injection and gastric electrical stimulation.

However, the current review was subject to some limitations. The impact of antiemetics was not assessed due to a lack of relevant RCTs. Furthermore, the design of included RCTs might have impacted the results. For example, there were conflicting outcomes between phase 2a and phase 2b studies of TZP-102 which included variations in breath test methods (a 6-hour ^{13}C-octanoate test and a 3-hour ^{13}C-*Spirulina platensis* test, respectively).[32,43] Therefore, unified guidelines should be implemented and carefully employed for future trials. The FDA has provided several recommendations regarding this aspect, which include conducting double-blind, placebo-controlled trials with a 2-week screening period, a 12-week treatment period and an at least 2-week withdrawal period.[88] RCTs of longer durations should be performed for at least 12 months. Importantly, patients with diabetic and idiopathic gastroparesis should be studied in separate trials. Finally, efficacy assessment should primarily be based on the signs and symptoms of gastroparesis.

Conclusion

There is a significant unmet need for patients with DG who require effective medications to manage their symptoms with optimal levels of safety. Patients with mild to moderate symptoms are traditionally managed with metoclopramide or domperidone taking into consideration their cardiovascular consequences. In an endeavour to develop novel drugs, relamorelin, camicinal and prucalopride have shown the best outcomes; however, further investigations are required prior to approval for use in a healthcare setting. Future trials should be conducted based on unified guidelines such as those implemented by the FDA in order to enable comprehensive and reliable assessment of their outcomes.

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