

Evidence Tables

GAST 1: In people with type 2 diabetes, can gastroparesis be effectively treated with a prokinetic drug (metoclopramide or domperidone)?

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding
T. Erbas, E. Varoglu, B. Erbas, G. Tastekin, and S. Akalin. Comparison of metoclopramide and erythromycin in the treatment of diabetic gastroparesis. <i>Diabetes Care</i> 16 (11):1511-1514, 1993.	RCT, single blind, crossover 1+	N=13	Those with diabetes (N=9 were insulin treated, N=4 taking oral hypoglycaemic agents, N=5 type 1 diabetes and N=8 type 2 diabetes), non-smokers, not taking drugs likely to interfere with GI motility. A number of participants had complications related to diabetes (peripheral neuropathy, cardiac autonomic neuropathy, diabetic nephropathy and retinopathy) The sample was not uniform for demographic and clinical data.	N=13 erythromycin 250mg TID, 30 min before each meal, crossover	N=13 metoclopramide 10mg TID, 30 min before each meal, crossover	9 weeks 3 weeks erythromycin /metoclopramide, 3 weeks washout, 3 weeks erythromycin /metoclopramide	Gastric emptying sequential images taken with a y camera (normal range had been established with an identical meal test in normal volunteers)	*Gastric emptying There were significant improvements for both erythromycin and metoclopramide for gastric emptying and meal retention at 60 and 90 minutes. However there was no significant difference found between the effects of erythromycin and metoclopramide. There was a significant difference in the symptom score after week 3 with erythromycin (2[0 to 5]) and metoclopramide (3[0-11]), p<0.05. *Adverse events No side effects of erythromycin were reported, for metoclopramide 2 patients had weakness, sedation and leg cramps, 1 palpation and 1 had drowsiness	Not stated
C. E. Farup, N. K. Leidy, M. Murray, G. R. Williams, L. Helbers, and E. M. Quigley. Effect of domperidone on the health-related quality of life of	Phase 1, single-blind Phase 2, double-blind,	N=287 N=269, single-blind domperidone, phase 1 N=208,	Inclusion criteria: insulin treated diabetes, 18-70 yrs, 6-month history of symptoms indicative of gastroparesis Exclusion criteria:	N=269 single-blind, domperidone 20mg QID		8 weeks 4 weeks single-blind treatment and 4 weeks double-blind	SF-36 to measure health-related quality of life (HRQOL)	*Patient norm comparison The HRQOL SF-36 profile was considered in respect to norms from the general population, the HRQOL scores were significantly lower than those of the general population across all 8 of the SF-36 subscales, (p<0.0001).	Janssen Research Foundation

<p>patients with symptoms of diabetic gastroparesis. <i>Diabetes Care</i> 21 (10):1699-1706, 1998.</p>	<p>placebo controlled 1-+</p>	<p>double-blind, domperidone and placebo Insulin-treated diabetes</p>	<p>history of GI cancer, heart or liver disease, renal failure, cancer, AIDS, previous alcoholism or substance abuse. Those who had previously taken cisapride or metoclopramide had a 1 week wash out period.</p> <p>Patients showing significant improvement at the end of the single-phase were classed as responders and continued to phase 2</p> <p>Note: patients were evaluated for severity of nausea, abdominal distention/bloating, early satiety, vomiting, and abdominal on a 4 point scale. Appropriate scores had to be reported on this scale for entry to both the single-blind (minimum symptom score required) and the double-blind (decreased symptom score from baseline) phases.</p>	<p>N=105 domperidone 20mg QID</p>	<p>N=103 placebo</p>			<p>Scores for patients participating in the study were also significantly lower than norms for patients with type 2 diabetes ($p<0.0001$).</p> <p>*Single-blind phase A significant symptomatic improvement was found in the single-blind phase at the end of the 4 weeks ($p<0.001$).</p> <p>Improvements were also noted in the HRQOL outcomes across all domains ($p<0.001$, except physical functioning where $p<0.01$).</p> <p>Patients identified as responders demonstrated significant improvements in all the primary (physical component summary (PCS) and mental component summary (MCS)) and secondary HRQOL parameters.</p> <p>*Double-blind phase Symptom severity increased in both groups, this increase in symptom severity was significantly greater for the placebo compared with domperidone ($p<0.05$). Symptom severity did not return to baseline levels.</p> <p>Those in the placebo group had a significant decrease in PCS (-1.77 ± 0.75) compared with the change in the domperidone group (0.65 ± 0.71), $p=0.05$.</p> <p>*Adverse events Not reported</p>	
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J. Janssens, T. L. Peeters, G. Vantrappen, J. Tack, J. L. Urbain, Roo M. De, E. Muls, and R. Bouillon. Improvement of gastric emptying in diabetic gastroparesis by erythromycin. Preliminary studies.[see comment]. <i>New England Journal of Medicine</i> 322 (15):1028-1031, 1990.	RCT, crossover, double-blind – followed by single-dose 1+	N=10 with diabetes N=10 healthy subjects	Mean age 51 yr, insulin dependent diabetes for 5-41yrs (mean 24.4), mean HbA1c 8% (ranged from 5.3-11.6%), known prolonged gastric emptying for solids and liquids, due to diabetic gastroparesis Healthy subjects were matched for age and sex. Insufficient data to judge the compatibility of the groups Blood glucose concentrations were maintained between 5.5 and 8.3 mmol/L by combined infusions of insulin and glucose during the fast and subsequent study period.	N=10 erythromycin IV 200mg – crossover Both the erythromycin and placebo were given after a standardised meal and with a previous overnight fast N=10 patients treated for 4 weeks with oral erythromycin 250mg TID before meals	N=10 placebo IV	4 weeks and 3 days 1day IV treatment, 1 day washout, crossover and 1 day IV treatment 4 weeks oral erythromycin	Scintigraphically with a double-isotope technique to consider simultaneous gastric emptying of both solids and liquids	*Gastric emptying <i>Solids</i> – after 60 minutes IV erythromycin had significantly increased gastric emptying compared with placebo for mean % of simultaneously ingested solids; 21±5 vs 85±7, p<0.0005, this was also found after 120 mins; 4±1 vs 63±9, p<0.0005. Erythromycin IV had also increased gastric emptying compared with the healthy subjects for solids at 60 mins, p<0.05 <i>Liquids</i> – after 60 mins IV erythromycin had increased gastric emptying significantly compared with placebo for mean % of simultaneously ingested liquids 22±5 vs 54±5, p<0.0005, this was also found at 120 mins; 9±3 vs 32±4, p<0.005. Oral erythromycin – gastric emptying was significantly increased compared with placebo for the mean % of simultaneously ingested solids and liquids at 120mins (p<0.05). *Adverse events There were no side effects of erythromycin delivery *Discontinuation Not reported	Not stated

<p>R. W. McCallum, D. A. Ricci, H. Rakatansky, J. Behar, J. B. Rhodes, G. Salen, J. Deren, A. Ippoliti, H. W. Olsen, and K. Falchuk. A multicenter placebo-controlled clinical trial of oral metoclopramide in diabetic gastroparesis. <i>Diabetes Care</i> 6 (5):463-467, 1983.</p>	<p>RCT, double-blind 1+</p>	<p>N=44</p>	<p>Inclusion criteria: diabetes (all except 2 who were diet controlled all were insulin dependent), gastroparesis symptoms between 3mths – 7yrs. Groups were similar at baseline – though the distribution of those with diabetic complications such as peripheral neuropathy was not reported</p>	<p>N=18 oral metoclopramide 10mg QID</p>	<p>N=22 placebo</p>	<p>5 weeks 2 week baseline 3 week treatment phase</p>	<p>Grading diary sheets of symptoms (intolerance of meals; fullness and bloating after meals; nausea; vomiting; anorexia; early satiety)</p>	<p>*Symptom severity Mean symptom scores for anorexia, meal intolerance and early satiety were similar for metoclopramide and placebo. Symptom improvement was significantly greater for metoclopramide than placebo for nausea at week 1 (53% vs 22%, p<0.05) and week 3 (77% vs 31%, p<0.05). This was also found for fullness at week 2 (59% vs 36%, p<0.05) and week 3 (65% vs 22%, p<0.05). *Adverse events A higher number of side effects were noted in the placebo group (n=20) than with metoclopramide (n=11). The most frequently reported were restlessness (n=3), drowsiness (n=2), anxiety (n=2) and headache (n=2) *Discontinuation There were 2 discontinuations in each group – none were drug related</p>	<p>Not stated</p>
<p>D. Patterson, T. Abell, R. Rothstein, K. Koch, and J. Barnett. A double-blind multicenter comparison of domperidone and metoclopramide in the treatment of diabetic patients with symptoms of gastroparesis. <i>American Journal of Gastroenterology</i> 94 (5):1230-1234, 1999.</p>	<p>RCT, double-blind, multicentre 1+</p>	<p>N= 95 (ITT completed on N=93), 5 centres, USA</p>	<p>Inclusion criteria: ambulatory, ≥18yrs, insulin-dependent diabetes, > 3 mth history of gastroparesis, required to exhibit at least 2 of the GI symptoms of; nausea, bloating/distension, early satiety. Exclusion criteria: GI tract or major</p>	<p>N=48 domperidone 20mg QID, 15-30 mins before meals and at bedtime</p>	<p>N=45 metoclopramide 10mg QID, 15-30 mins before meals and at bedtime</p>	<p>4 weeks</p>	<p>Gastroparetic symptoms, tolerability (participants were specifically asked about CNS-associated side effects that have been noted previously</p>	<p>*Symptoms Significant reductions in gastroparetic symptoms were found with both domperidone and metoclopramide. However, there was no significant difference found between the two treatments *Tolerability At week 2 the severity of somnolence (p<0.001), akathisia (p=0.03), anxiety (p=0.02) and depression (p=0.05) were significantly greater for metoclopramide</p>	<p>Janssen Research Foundation</p>

			<p>illnesses, prior gastric surgery, receiving dialysis, medications which could mask the effect of domperidone or metoclopramide were not permitted</p> <p>Demographic and baseline vital signs for the groups were similar.</p>				with metoclopramide)	<p>than for domperidone. At week 4 the severity of somnolence (p=0.03) and reduced mental acuity (p=0.04) were significantly greater with metoclopramide than domperidone.</p> <p>*Adverse events The most common spontaneously reported events were vomiting (10.4% with domperidone, 4.3% with metoclopramide) and nausea (10.4% with domperidone, 4.3% with metoclopramide)</p> <p>*Discontinuation Domperidone, N=6 Metoclopramide, N=10</p>	
<p>D. A. Ricci, M. B. Saltzman, C. Meyer, C. Callachan, and R. W. McCallum. Effect of metoclopramide in diabetic gastroparesis. <i>Journal of Clinical Gastroenterology</i> 7 (1):25-32, 1985.</p>	<p>RCT, double-blind, crossover</p> <p>1+</p>	<p>N=13 (N=13 10mg IM metoclopramide 20 before standardised meal – results not reported here</p> <p>(N=7 open label oral metoclopramide arm run at the end of the study – not reported here)</p>	<p>Mean age 44.1yrs (range 24-73), six with juvenile and 7 with adult onset diabetes, mean time had had diabetes 12.6yrs (3-28 yrs), duration of gastric stasis symptoms 2.5yrs (3mths-7yrs), there was a range of other diabetes related complications in the sample.</p> <p>Groups were not similar at baseline, though symptom scores were similar.</p>	<p>N=13 oral metoclopramide 10mg 30mins before each meal and 30 mins before bedtime – crossover</p> <p>(gastric emptying determination identified 12/13 had delayed gastric emptying)</p>	<p>N=13 identical placebo</p>	<p>9 week</p> <p>2 week baseline period</p> <p>3 week treatment, followed by one week crossover</p>	<p>Graded diary cards for five symptoms (epigastric fullness, pressure and bloating; nausea; vomiting; anorexia; early satiety)</p>	<p>*Symptom score The mean symptom score during each week of oral metoclopramide therapy was significantly improved compared with placebo (p<0.05).</p> <p>The overall mean symptom score calculated for the 3 weeks of metoclopramide treatment was significantly less than the mean placebo score; 26.5±3.7 vs 45.3±7.8, p<0.01.</p> <p>*Adverse events There were individual reports of sedation and amenorrhoea, headache, agitation, mild hand tremors with metoclopramide</p>	<p>AH Robins Company & National Institute for Health</p>

<p>A. P. Braun. Domperidone in the treatment of symptoms of delayed gastric emptying in diabetic patients. <i>Advances in Therapy</i> 6 (2):51-62, 1989.</p>	<p>Phase 1 – open label 12 week, no placebo – not reported here</p> <p>Phase 2 – RCT, double-blind, crossover</p> <p>Phase 3 – open label, no placebo, not reported here</p> <p>1-</p>	<p>N=20 – phase 1</p> <p>N=13 – phase 2</p> <p>N=13</p>	<p>Diabetic patients with at least one symptom of delayed gastric emptying at moderate to severe intensity, pre-study GI radiographic studies that were negative for other GI diseases.</p> <p>No concurrent medications that could mask GI symptoms or otherwise compromise the efficacy assessment were allowed</p> <p>NOTE: entry into phase 2 required a 30% or more reduction in symptoms on either 10mg domperidone before each meal and at bedtime or 20mg domperidone QID</p>	<p>N=13 10mg domperidone (N=9) or 20mg domperidone (N=4) QID crossover</p>	<p>N=13 placebo</p>	<p>Phase 2 – 2 months</p> <p>1 month domperidone or placebo, Crossover, 1 month domperidone or placebo</p>	<p>Symptom change</p>	<p>*Symptoms Significant mean differences favouring domperidone compared with placebo ($p \leq 0.03$) were detected in both the frequency and intensity of the symptom early satiety and in the total symptom frequency and intensity scores</p> <p>*Discontinuation One participant in phase 2 did not adhere to correct dose of medication</p>	<p>Not stated</p>
<p>M. Samsom. Effects of oral erythromycin on fasting and postprandial antroduodenal motility in patients with type I diabetes, measured with an ambulatory manometric technique. <i>Diabetes Care</i> 20 (2):129-134, 1997.</p>	<p>Double-blind, crossover</p> <p>1-</p>	<p>N=12, all type 1 diabetes, selected from 2 hospital sites in the Netherlands</p>	<p>Patients with type 1 diabetes with dyspeptic symptoms with no mechanical cause, all participants had one or more complications of diabetes.</p> <p>All medication known to influence GI motility (except insulin) was discontinued for the duration of the trial.</p>	<p>N=12 oral erythromycin (250mg TID)</p>	<p>N=12 placebo – crossover study</p>	<p>5 week study</p> <p>14 days erythromycin or placebo, 1 week wash out, crossover 14 days with erythromycin or placebo</p>	<p>Antroduodenal motility using a calibrated, solid state manometric catheter, pressure transducers used to identify the phases of the migrating</p>	<p>*Antroduodenal motility Fasting: The total number MMC cycles, the phase III total number and % with antral counterpart increased with erythromycin compared with placebo this difference was not significant. No differences were seen in the duration of phase I. The increase in duodenal phase III frequency resulted in a decrease in the length of MMC with erythromycin compared with placebo (96.2 ± 25.3 vs 118.9 ± 46.0 min, $p = 0.03$). With the</p>	<p>Diabetes Fonds, Nederland</p>

			<p>NOTE: on gastric emptying studies gastric emptying rates were considered to be normal in 7 participants and delayed in 5 participants.</p> <p>Groups were not broadly similar at baseline with diabetic duration ranging from 9-41 yrs and HbA1c from 6.0-14.3%</p>			<p>motor complex (MMC). The interdigestive phases were defined as: Phase I: motor quiescence starting at the end of phase III Phase II: pressure waves >2kPa occurring at a rate higher than two per 10min and less than the maximum frequency of the antrum (3 contractions/min) or the duodenum (10-12 contractions/min), Phase III: rhythmic contractile activity at the maximum frequency (3</p>	<p>shorter MMC, phase III length was increased (6.3±1.7 vs 5.2±1.4 min, p<0.05) and the phase II length was decreased (48.5±19.4 vs 68.7±23.5, p<0.05).</p> <p>Postprandial: erythromycin significantly decreased the duration of the postprandial motor pattern, however this was not analysed in comparison with placebo. After dinner the number of distal antral contractions (p<0.01) and motility index (p<0.03) were significantly increased by erythromycin compared with placebo.</p> <p>*Symptom score The mean symptom score during erythromycin treatment did not improve compared with placebo</p> <p>*Discontinuation All 12 patients completed the study and no adverse events were recorded that were attributed to the erythromycin or placebo.</p>	
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