

# Diabetic Gastropathy and Prokinetics

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## ABSTRACT

The treatment of diabetic gastropathy, which here refers to a clinical syndrome of upper GI tract symptoms suggestive of an upper motility disturbance in diabetes whether or not there is delayed gastric emptying, remains suboptimal. New prokinetics and other motility-modifying agents may prove useful, but adequate clinical trials will be required to establish a role for them. However, diabetic gastropathy seems to represent a heterogenous syndrome in terms of pathophysiology, which potentially complicates the design of new randomized, controlled trials. This review aims to provide guidelines for future trials in this field. The evidence that delayed gastric emptying is a cause of symptoms in diabetic gastropathy is critically evaluated. The trial evidence supporting the short and long term efficacy of prokinetics is reviewed. Based on the available literature, it is concluded that improvement in gastric emptying does not equate with symptom relief in diabetic gastropathy. It is suggested that although gastric emptying should still be measured in clinical trials, it should not represent the primary outcome. The withdrawal treatment design applied in studies of diabetic gastropathy might be suboptimal. Double blind, parallel group studies remain the trial design of choice, but incorporation of validated outcome assessments and measurement of potential confounders of treatment response need attention in future trials. (Am J Gastroenterol 2003;98:264–271. © 2003 by Am. Coll. of Gastroenterology)

## INTRODUCTION

<sup>1</sup>Symptoms suggestive of upper GI tract dysmotility are common in patients with diabetes (1–3). In the past, the term “diabetic gastropathy” has been used to describe a number of potential neuromuscular dysfunctions of the stomach, including abnormalities of motor function such as antral hypomotility or gastric dysrhythmias (2). However, not all patients with neuromuscular abnormalities are symptomatic, suggesting that the terminology should be reconsidered (4, 5). Diabetic gastroparesis is a well recognized complication of diabetes that may induce not only symptoms but also greater impairment of glycemic control (4, 5). However, when delayed gastric emptying is severe enough to be labelled gastroparesis remains poorly defined, and the effi-

cacy of prokinetic therapy remains controversial (6, 7). In view of the side effects associated with the currently available agents, the use of these agents in diabetic patients with GI symptoms should be firmly evidence based. Here, a critical review of the evidence for the efficacy of prokinetic agents is presented and, in particular, the limitations of published trials are considered. The overall aim of this review is to ensure that future trials of new agents will be of the highest quality and will therefore lead to clinical advances in this important area.

## Association of GI Symptoms With Diabetes

There has been some controversy as to whether upper GI tract symptoms are more common in diabetic patients than in nondiabetic controls. Although there is evidence that GI symptoms adversely affect quality of life (8) and represent a substantial cause of morbidity in patients with diabetes (4), the available epidemiological data related to the prevalence of GI symptoms in diabetes are conflicting and can be challenged on methodological grounds.

Schvarcz *et al.* (9) evaluated the prevalence of GI symptoms in an unselected, population-based cohort of 110 young adult patients with long standing type 1 diabetes, as compared with age- and sex-matched control subjects. In the subjects with diabetes, there was an increased prevalence of upper GI symptoms, including anorexia and vomiting, whereas there was no difference in the frequency of symptoms referable to the lower GI tract. The prevalence of GI symptoms was significantly greater in women than in men and in those subjects with poorer glycemic control, as assessed by Hb A1C concentrations. Janatuinen *et al.* (10), on the hand, found that the prevalence of upper GI symptoms, abdominal pain, constipation, and diarrhea were similar in diabetic patients and controls. In that study, only middle-aged patients with type 1 or type 2 diabetes who were treated with insulin or oral hypoglycemic drugs were evaluated, and the questionnaire used to evaluate symptoms was not a validated measure. A study from Hong Kong reported higher rates of all GI symptoms in 149 patients with type 2 diabetes who were referred to a university clinic, when compared with community controls; the duration of diabetes was the only parameter independently associated with GI symptoms (11). A German study of 333 patients referred to a diabetes research institute found that only type 2 diabetic patients had more upper and lower GI symptoms than did community controls, the most common symptoms being

constipation (12). In a population-based study, Bytzer *et al.* evaluate 423 subjects with diabetes (predominantly type 2) and nondiabetic controls (3). They identified a modest but significant increased risk of upper dysmotility like symptoms as well as esophageal and colonic symptoms in patients with diabetes. However, a study from Olmsted County, MN, failed to detect an association between the presence of symptoms and diabetes in the general population (13).

Thus, the literature relating to the prevalence and determinants of GI symptoms in patients with diabetes is conflicting and limited, although most studies support an association. The populations studied have mainly comprised patients attending diabetic clinics in tertiary hospitals (1, 11, 12) who are unlikely to be representative of the diabetes population in general, whereas other studies have focused on subgroups of diabetic patients only (3, 9, 10, 12). Moreover, GI symptoms, particularly symptoms compatible with functional dyspepsia or the irritable bowel syndrome, occur frequently in nondiabetic populations (3) and therefore may confound any apparent association.

#### ***Prevalence of Delayed Gastric Emptying in Diabetes and Association With Upper GI Symptoms***

Gastric emptying delay is documented to be common in diabetes. In type 1 diabetes, delayed emptying has been identified in 27–58% of cases (14, 15). In long standing type 2 diabetes, the prevalence seems to be lower (approximately 30%) but still substantial (14, 16). However, a standard definition for gastroparesis in diabetes is lacking.

One key question is whether those individuals with delayed emptying have a particular pattern of symptoms that is characteristic. If this were the case, it would allow better targeting of drugs that accelerate gastric emptying for this subset of patients. In functional dyspepsia, a meta-analysis concluded that 40% of patients have delayed gastric emptying, but a link with symptoms remains controversial (17). Stanghellini *et al.* identified three risk factors that seemed to be independently associated with delayed gastric emptying in functional dyspepsia (18). These factors were female sex, relevant postprandial fullness, and severe vomiting; if all three risk factors were present, the odds ratio for delayed gastric emptying was very substantially increased. However, other studies have not been able to confirm these associations in functional dyspepsia. Talley *et al.* studied 551 patients with functional dyspepsia applying the C<sup>13</sup> octanoic acid breath test (19). The odds ratios of symptom severity for delayed gastric emptying were not significant for any upper GI tract symptom in this study. However, the breath test is less accurate than scintigraphy, and patient selection may have influenced the results.

Jones *et al.* evaluated 101 outpatients with diabetes; 79 had type 1 diabetes, and 65% of these cases had delayed gastric emptying (15). The authors identified abdominal bloating or fullness to be an independent predictor of delayed gastric emptying. Female sex, blood glucose levels,

and body mass index were also independent predictors. However, all of these predictors accounted for only 19% of the variance. Furthermore, other upper GI tract symptoms as well as age and autonomic nervous system function were not significant risk factors.

Hence, symptoms seem to be a poor predictor of delayed gastric emptying in type 1 diabetes, as is the case for functional dyspepsia. A disease can be defined as a morbid process with a characteristic train of symptoms, even if the etiology or pathophysiology is unknown or multifactorial. It is documented that even severe gastroparesis can be asymptomatic (4). Presumably this reflects the fact that delayed gastric emptying is not a disease but a multifactorial condition, and symptoms of dyspepsia may occur for reasons other than delayed gastric emptying in diabetes.

#### ***Potential Value of Prokinetics in Diabetic Gastropathy***

Diabetic gastropathy here refers to a spectrum of upper GI tract symptoms suggestive of motility disturbances in diabetes, regardless of whether there is evidence of delayed gastric emptying (as this may not be the key disturbance.) Symptoms that may be associated include postprandial fullness, upper abdominal bloating, early satiety, nausea, and vomiting, as well as epigastric discomfort or pain (2). Unlike some other diabetic complications (*e.g.*, retinopathy, nephropathy), there is no compelling clinical reason to treat asymptomatic gastric neuromuscular disturbances in diabetes; therefore, these should not be considered as relevant in diabetic gastropathy.

A prokinetic agent may potentially be useful in diabetic gastropathy, given that it accelerates delayed gastric emptying (20). On the other hand, a prokinetic drug may be efficacious in the syndrome because it relaxes the fundus (21, 22). Fundic disaccommodation has been identified as present in up to 40% of patients with functional dyspepsia, and it has been linked specifically to early satiety as well as weight loss in this population (21). Drugs that relax the fundus despite slowing gastric emptying (*e.g.*, the 5HT<sub>1</sub> agonist sumatriptan) have been observed to improve early satiety as well as fullness, bloating, discomfort, and nausea in functional dyspepsia, although large randomized, controlled trials are unavailable (21). Cisapride is also a fundus-relaxing agent, which may partly explain its efficacy in functional dyspepsia (22). Prokinetics may also be useful in diabetic gastropathy because of acceleration of small bowel transit. Alternatively, prokinetic drugs could theoretically alter visceral sensation, which may in turn reduce symptoms (23) or alter gastric dysrhythmias, although the relevance of electrogastrographic findings is highly controversial (24–26). The effect of prokinetics on pyloric dysmotility (pylorospasm) that has been observed in diabetic patients with recurrent nausea and vomiting is uncertain (27). Finally, a prokinetic may be useful, as it further improves glycemic control and therefore might retard (or even potentially reverse) complications of diabetes, including autonomic neuropathy and delayed gastric emptying (4, 5, 28).

### **Efficacy of Prokinetics**

Prokinetics have an established role in functional dyspepsia (29). However, the overall efficacy of these agents has been modest, based on recent meta-analyses. In a Cochrane review of prokinetics, 12 trials were identified that concluded that these drugs produced a relative risk reduction of 50% (30). However, a funnel plot suggested that the positive result with the prokinetics may be explained by publication bias. Allescher *et al.* evaluated 19 prokinetic studies and reported that these drugs were significantly more effective than placebo and were also more effective than the histamine-2 receptor antagonists in functional dyspepsia (31).

There is no convincing evidence, however, that prokinetics are efficacious in functional dyspepsia because they accelerate gastric emptying. Van Zanten *et al.* reviewed the available prokinetic trials and evaluated the evidence that delayed gastric emptying was a predictor or therapeutic success in functional dyspepsia (32). Only two of nine trials in the meta-analysis assessed whether any benefit of cisapride was related to improved gastric emptying; Jian *et al.* did show a correlation but this did not reach significance although the number included was small ( $n = 17$ ) (33), whereas Kellow *et al.* measured baseline gastric emptying and observed a beneficial effect only in subjects with normal emptying (34). The authors concluded that there was insufficient evidence to determine whether accelerated gastric emptying was predictive of symptom improvement, as so few studies evaluated baseline gastric emptying or determined gastric emptying on therapy and the relationship with symptoms (32).

The data on prokinetics in diabetes have produced mixed results, and very few large, high quality, randomized, controlled trials are available (35–47). For example, McCallum *et al.* compared metoclopramide with placebo in the treatment of GI symptoms in 40 patients with diabetic gastroparesis (38). Metoclopramide (10 mg *q.i.d.*) in the 3-wk, double-blind study was superior to placebo in terms of relief of symptoms of nausea, vomiting, fullness, and early satiety; however, it is noteworthy that the differences were only significant for nausea and postprandial fullness. Mean gastric emptying assessed by radionuclide scintigraphy was significantly improved in the metoclopramide-treated group when compared with their baseline results. Feldman and Smith studied the effect of cisapride on gastric emptying of solids in nine diabetic patients, all of whom had gastroparesis (39). These investigators found that acute, *i.v.* administration of cisapride accelerated gastric emptying of indigestible solids in patients with diabetic gastroparesis. On the other hand, Havelund *et al.* tested cisapride in a placebo-controlled cross-over trial of 14 insulin-dependent diabetic patients with symptoms and signs of delayed gastric emptying; no significant differences from placebo were found in terms of overall symptomatic benefit or effects on gastric emptying of a mixed solid/liquid isotope-marked test meal (36). Patterson *et al.* studied 93 insulin-dependent diabetic patients with a history of “gastroparesis symptoms”; 48

patients received domperidone 20 mg *q.i.d.*, and 45 received metoclopramide 10 mg *q.i.d.* (37). It was observed that domperidone and metoclopramide were equally effective in alleviating the symptoms of diabetic gastropathy, but metoclopramide caused more central nervous system side effects, as expected. No placebo control group was included in the study.

Sturm *et al.* reviewed the efficacy of current prokinetics in gastroparesis in a formal meta-analysis (7). They identified 36 studies, but only one trial applied a validated symptom outcome measure. The study quality was generally poor. The authors concluded that the results were better in the open and single blind studies, suggesting that bias was an important factor driving treatment success. In double blind, controlled studies, cisapride produced a mean improvement in symptom score of only 8%, whereas metoclopramide produced a mean improvement in this score of 36%.

Few long term, controlled studies have been published (48–51). Abell *et al.* conducted a 12-month trial of cisapride (10 mg *t.i.d.*) in 21 patients with gastric stasis resulting from clinically and manometrically diagnosed gastroparesis (nine patients; seven because of diabetes) or chronic intestinal pseudo-obstruction (12 patients) (48). Radionuclide solid-liquid gastric emptying tests were performed at baseline and at the end of the 12-month period. For the whole group of 21 patients, gastric emptying of both solids and liquids improved significantly after 1 yr of cisapride, but patients with gastroparesis had a greater improvement in liquid emptying. The total symptom score improved significantly in the gastroparesis group but not in the chronic intestinal pseudo-obstruction patients. The long term efficacy of cisapride was also evaluated in a 1-yr open trial of 37 patients with neuropathic forms of chronic intestinal dysmotility, including 11 with diabetes (49). It was observed that the mean total symptom score was significantly reduced at the last observation relative to the entry into the trial, particularly in those patients without abdominal vagal dysfunction. Kendall *et al.* found that cisapride therapy produced long term symptomatic improvement in 42% of patients with severe gastroparesis, with sustained acceleration of gastric emptying for up to 2 yr (50). Braden *et al.* randomized 19 patients with insulin-dependent diabetes and delayed gastric emptying by breath test to cisapride or placebo for 12 months; cisapride improved symptoms and shortened gastric emptying but did not alter glycemic control (51). The small numbers and selected samples recruited limit the generalizability of all of the trials.

The side effects of metoclopramide often limit its use, and withdrawal of cisapride because of cardiac toxicity has left a void in the field. New motilin agonists have proved disappointing to date in this syndrome (47), whereas novel prokinetics including the serotonin type 4 (5HT<sub>4</sub>) agonists (*e.g.*, tegaserod) and the cholecystokinin type 1 (CCK<sub>1</sub>) antagonists (*e.g.*, deoxloxlglumide) have not yet been tested in diabetic gastropathy.

### ***Etiology of Upper GI Tract Symptoms in Diabetes***

The pathogenesis of upper GI symptoms in diabetes is likely to be multifactorial, which needs to be taken into account when designing clinical trials with new prokinetics. GI symptoms in individuals with diabetes are usually attributed to disordered neuromuscular function and the resultant modification of GI flow as a result of the autonomic (vagal) neuropathy that frequently accompanies diabetes (52). However, there is a poor correlation between symptoms and the rate of GI transit (53–55), and symptoms may occur in the fasted state; therefore, disordered transit may be only a marker of GI motility abnormalities, rather than a direct cause of symptoms.

The correlation of GI symptoms and measures of cardiovascular autonomic neuropathy is weak (52, 53). It is possible that this is attributable to a differential effect of diabetes on the heart and the gut, and it is therefore conceivable that autonomic neuropathy plays a dominant role in the etiology of GI symptoms (52). However, even when abdominal vagal afferent function is severely impaired, GI symptoms may be absent (56). Clouse and Lustman (52), in their study of 114 type 1 and type 2 diabetic patients, reported that GI symptoms were poorly related to neuropathic complications once the coexistence of psychiatric illness was taken into account. Ko *et al.* (11) found that rates of GI symptoms in diabetic patients with and without peripheral neuropathy were similar.

Poor glycemic control may be an important cause of symptoms. It is now recognized that variations in the blood glucose concentration have a major influence on neuromuscular function throughout the gut (54, 56, 57) and perception of sensations arising from the gut (54, 58–63). For example, in the esophagus, the threshold for perception of balloon distension is reduced (61), and the amplitude of cortical evoked potentials induced by rapid balloon distension increased during hyperglycemia (62). Acute hyperglycemia (blood glucose 16–19 mmol/L) has been shown to reduce postprandial antral contractions in type 1 diabetes (64). In the stomach, perception of nausea and fullness, both in the fasted state and during intraduodenal lipid infusion, were increased during acute hyperglycemia when compared to euglycemia (63). Even more modest elevations of blood glucose within the normal postprandial range affect gut sensation (57, 65). In patients with type 1 diabetes, the sensation of postprandial fullness was related to blood glucose concentration (54). Because there seems to be a close correlation between chronic and acute glycemic control in diabetes (53, 66), it is not surprising that Schvarcz *et al.* (9) found that GI symptoms occurred more frequently in type 1 subjects with poor glycemic control as assessed by Hb A1C levels. Bytzer *et al.* also found that upper dysmotility-like symptoms were significantly more prevalent in individuals with self-reported poor glycemic control than in those reporting good or average glycemic control (3). Moreover, there was a dose-dependent relationship between poor glycemic control and an increasing prevalence rate of GI symp-

toms. Acute changes in the blood glucose concentration may affect autonomic nerve function (67); therefore, the relationships may be even more complex than currently appreciated. The importance of chronic hyperglycemia remains uncertain; but most studies of prokinetics have not measured glycemic control, which may have confounded their results (47).

The type of diabetes may influence symptom status. Type 2 diabetes predictably deteriorates over time, which may in turn influence outcome (5). The presence of other diabetic complications such as nephropathy might also alter GI symptom perception in diabetes (68).

Other data suggest that psychological distress is linked to GI symptoms in diabetes, and this may confound treatment trial outcomes. Wreding *et al.* (69) observed that women with type 1 diabetes had more anxiety and depression and a lower quality of life than men, but appropriate controls were lacking. Talley *et al.* reported that anxiety and depression, as measured by the Hospital Anxiety and Depression Scale, were increased in diabetic patients with GI symptoms (70). Increased levels of neuroticism were also observed in subjects with diabetes who reported GI symptoms (70). However, it is uncertain whether psychiatric comorbidity (which is distinct from underlying personality characteristics or psychological distress) accounts for GI symptoms in type 1 or 2 diabetes, as this has not been systematically studied. Clouse and Lustman (52) found that psychiatric disturbances were much more strongly related to GI symptoms in diabetes than autonomic neuropathy. Furthermore, there is evidence in patients with diabetes that “well-being” is related to glycemic control (71). Hypoglycemia can induce profound mental changes. Hence, there may be an association between psychological function and poor glycemic control, although this has not been carefully evaluated. Finally, the type of treatment prescribed for diabetes may be related to GI symptoms. For example, metformin has been associated with diarrhea and fecal incontinence in diabetes (72). However, there does not seem to be an association between the type of treatment and upper GI tract symptoms. The role of *Helicobacter pylori* in upper GI symptoms in diabetes has been controversial, but most data fail to support an association (73). The relevance of environmental factors, such as smoking or alcohol, in the genesis of GI symptoms in diabetes is unknown but probably is of minor or no importance (74).

### ***Trial Design Options for Prokinetics in Diabetic Gastropathy***

There have been two different types of trial designs applied to test the hypothesis that prokinetic agents are efficacious in diabetic gastropathy. The withdrawal design treats all suitable patients with a prokinetic agent for an initial period and then randomizes only responders to active therapy or placebo. This design aims to enrich the study population with active drug responders. By applying this type of design, Silvers *et al.* evaluated patients aged 18–70 yr who had

insulin dependent diabetes with chronic symptoms suggestive of gastroparesis (46). In the initial phase, patients were treated with domperidone for 1 month, and then responders were randomized to domperidone or placebo for 4 wk. In the initial phase, mean symptom scores decreased significantly on domperidone by the end of 4 wk of therapy. However, symptom scores were similar regardless of baseline gastric emptying rates. In the withdrawal phase, symptoms in both the domperidone and placebo groups deteriorated significantly from the levels achieved in phase I. However, symptoms deteriorated more on placebo than with domperidone. Changes in gastric emptying on therapy, and the relationship with symptom change, were not reported. Although the authors concluded that domperidone was a successful treatment for diabetic gastropathy, it is difficult to support this conclusion based on the study design applied. The single blind, initial phase results could well be the result of bias (7), and the withdrawal phase results are at best equivocal. Furthermore, the withdrawal design depends on the assumption that the disease relapses and remits, which may not be the pattern in diabetic gastroparesis.

The alternative approach to assessing the value of a prokinetic in diabetic gastropathy is to apply a standard double blind, randomized, placebo-controlled, parallel group trial design. For example, the motilin agonist ABT-229 was compared with a placebo in a large randomized, controlled trial in patients with insulin-dependent diabetes who were evaluated in the United States (47). The study was a phase II dose-ranging trial, and there were 269 patients in the intention-to-treat population who were evaluated. There was a significant improvement in the primary outcome, which was based on a combination of upper GI symptoms measured using visual analog scales. However, similar symptom reductions were identified for all doses of ABT-229 and placebo. Furthermore, improvement in total abdominal symptom severity scores over baseline in those with delayed gastric emptying compared with those with normal gastric emptying were similar and tended to be best with placebo. The outcomes were blinded and the groups comparable. Symptom assessment was also comprehensive and the results were consistent. Glycemic control was assessed and was found not to correlate with symptom change in this study. Autonomic neuropathy and gastric emptying at baseline were considered when interpreting the results. However, there were weaknesses of the study. Autonomic neuropathy was not assessed objectively but was based on the impression of the attending endocrinologist, which may have been inadequate. Other confounders that were not controlled for in the study included psychological distress, diabetic complications, and disease duration. Gastric emptying was also measured by breath test rather than scintigraphy, and this may have led to some misclassification error (75). Furthermore, gastric emptying was not measured on therapy, and, therefore, whether the drug effectively accelerated gastric emptying in this population was not documented.

The reasons that ABT-229 was disappointing in diabetic gastropathy remain controversial (20). It may be that gastric emptying is not relevant and that prokinetics of the motilin class in fact are not useful. Indeed, it is possible that this class of drugs has an adverse effect on fundic relaxation. Failure of fundic relaxation has been documented with the motilin agonist erythromycin, which may in turn explain the aggravation of symptoms (76). An alternative explanation is that the drug is subject to tachyphylaxis. ABT-229 has a long half-life and, therefore, may have induced receptor down-regulation, although multiple doses were tested in the study. Finally, there may have been confounding by other disease factors such as underlying autonomic neuropathy that influenced the results. All of these factors need to be measured, if possible, and their impact considered in the design of future studies.

One key issue in any future trials of diabetic gastropathy will be to ensure the reliable measurement of symptom change on therapy (77). It has been suggested for the functional GI disorders that a global assessment that integrates all of the key symptoms should be the primary outcome measure in future clinical trials (77). In view of the variable symptoms present in diabetic gastropathy, a similar approach seems reasonable. Visual analog scales have been shown in diabetic gastropathy to be responsive to change and to provide results consistent with Likert scales but either method seems acceptable (47). Another issue is appropriate assessment of quality of life in this syndrome. In a withdrawal trial in diabetes, domperidone was shown to maintain quality of life scores compared with a significant deterioration on placebo (46). Improvement of quality of life indexes should be a key goal of prokinetic therapy, in addition to symptom relief. Specific quality of life tools are available for dyspepsia that presumably will also be of value in diabetic gastropathy (78–80), although no disease specific instrument has been designed to assess the impact of GI disorders in diabetes. A list of design issues to consider in future trials is presented in Table 1.

## CONCLUSION

Overall, available prokinetic agents in diabetic gastropathy seem, at best, to provide only modest efficacy. Furthermore, there seems to be lack of connection between improvement in gastric emptying and symptom relief, although surprisingly few studies have been conducted to directly test this hypothesis. In the future, investigators will need to select appropriate symptom targets and to apply these as the primary outcome in prokinetic trials. Assessment of gastric emptying, both before and while on therapy, and using an appropriate method, remains important. A prokinetic agent may be subject to tachyphylaxis; therefore, it will be important to confirm that the drug is active in terms of its prokinetic action during the trial. However, improvement of gastric emptying should not be the primary outcome, as it is unlikely that this will explain symptom relief even in the

**Table 1.** Recommendations for Evaluation of Prokinetics in Diabetic Gastropathy

1. Goal of the study: it must be stated whether the study primarily addresses the issue of symptom relief or alteration of neuromuscular function.
2. Patient population: type 1 and/or type 11 diabetics should be included and the study adequately powered to evaluate these populations separately. In multicenter studies, compatibility of patients among centers needs to be evaluated. Where patients are recruited from primary *versus* secondary or tertiary care, this may affect outcome and needs to be considered in the analysis.
3. Architecture of the trial: a placebo control group is usually essential, as no gold standard therapy exists. Compliance needs to be measured.
4. Randomization: a randomized parallel group trial is the design of choice; a crossover design is not considered suitable because of carryover effects despite a washout period, and a withdrawal design may be difficult to interpret. The randomization method needs to be adequate.
5. Blinding: patients and research personnel must be adequately blinded. Concealed allocation is essential.
6. A period of baseline symptom observation is recommended. A placebo run-in period should be avoided.
7. Assessment of neuromuscular function at baseline and at the end of the trial is recommended. Studies of neuromuscular function may be very useful as predictors of any therapeutic effect.
8. Comorbid diabetic complications and disease duration need to be assessed as potential confounders. Glycemic control must be assessed regularly throughout the trial. Psychological status measurement is recommended, as this may be an important modifier of outcome.
9. Follow-up after conclusion of treatment is recommended for both active and placebo arms.
10. Both short and long term efficacy need to be assessed, depending on the trial's goal.
11. Outcomes: use of validated outcome measures is recommended. Both symptoms and quality of life should be assessed. A global primary symptom endpoint is preferred. Symptom assessment should be done by the patient rather than the investigator. The study protocols needs to define *a priori* the definition of a responder or response, and also needs to ensure that this definition is clinically meaningful.

subset with delayed gastric emptying. The optimal dose will also need to be chosen, and this may be different in patients with diabetic gastropathy compared with other patient groups because of comorbid diabetic complications.

Currently, the trial design of choice is the double blind, parallel group study; the withdrawal design might be sub-optimal because of difficulties in interpreting the outcome. Multiple validated outcome measures can be used, which are likely based on current evidence to give consistent results. Assessing both the overall impact of therapy as well as quality of life will be important in future trials. Neuro-

muscular function should be assessed at baseline and on therapy, because an understanding of the link between pathophysiological disturbances and symptoms with new therapeutic agents is a key to progress in the field.

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