Neurogastroenterol Motil (2009) **21,** 632–e25 doi: 10.1111/j.1365-2982.2008.01249.x

Clinical effects of STW 5 (Iberogast®) are not based on acceleration of gastric emptying in patients with functional dyspepsia and gastroparesis

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Abstract *STW 5, a herbal extract, is effective for the treatment of symptoms in patients with functional dyspepsia (FD). However, its mode of action is still unclear and a modulation of gastric motility is hypothesized. This multicentre, placebo-controlled double-blind study addressed the question of whether STW 5 accelerates gastric emptying in patients with FD and gastroparesis. One-hundred and three patients diagnosed with FD were randomly assigned to a treatment with either STW 5 or a liquid placebo for 28 days. The primary end point of the study was a change of a validated gastrointestinal symptom (GIS) score under treatment. Additionally, patients underwent a ^{13}C octanoic acid breath test for the assessment of the gastric half-emptying time ($t_{1/2}$). Patients with prolonged $t_{1/2}$ were diagnosed with gastroparesis and requested to repeat the test at the end of treatment. A change of $t_{1/2}$ was defined a secondary study end point. $t_{1/2}$ was prolonged in 48.6% of patients in the STW 5 group and in 43.8% of the placebo group. During treatment, $t_{1/2}$ increased non-significantly in patients treated with STW 5 (+23 ± 109 min; P = 0.51) and slightly accelerated among patients in the placebo arm (−26 ± 51 min; P = 0.77) (P = 0.49). The improvement of the GIS (P = 0.08) and the proportion of patients with a treatment response (P = 0.03) were more pronounced in the STW 5 group. Our findings suggest that the clinical effects of STW 5 in patients with FD and gastroparesis are not directly mediated by an acceleration of gastric emptying. A clear-cut correlation with symptom improvement is still lacking.*

Keywords *functional dyspepsia, gastric motility, herbals, octanoic acid breath test.*

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Received: 25 June 2008
Accepted for publication: 29 October 2008

INTRODUCTION

Functional dyspepsia (FD) is a gastrointestinal disorder frequently encountered in clinical practice.[1–5] As objective diagnostic criteria are lacking, FD is defined by subjective symptoms. Patients may complain of epigastric pain, heartburn, postprandial fullness, nausea and a vast range of other abdominal symptoms. The absence of a detectable organic cause is a prerequisite for the diagnosis. The pathophysiological background of FD still remains vague.[6–9] Studies on visceral sensitivity and nociception, psychological factors and gastric motility have rendered no clear-cut results.[10–19] The threshold of abdominal pain perception seems to be decreased in a considerable proportion of patients with FD.[18,20] In contrast, psychological stress may be a contributory factor, but typical psychopathologies associated with FD are lacking.[21–23] With respect to gastric accommodation and emptying, results from previous studies also failed to demonstrate a definite concept. Though up to 50% of patients have an impaired postprandial accommodation, the current workup of FD neither involves diagnostic testing with a barostat nor recommends treatment with appropriately modulating drugs.[24,25] A variety of studies have focused on the question of whether delayed gastric

emptying accounts for the symptoms associated with FD. On the other hand, only one-third of patients with FD have gastroparesis and gastric motility poorly correlates with symptoms.

The therapeutic approach most often confines to acid inhibition with proton pump inhibitors and/or prokinetics. These drugs exert positive effects in additional 10–15% of patients with FD, compared with placebo.[26–28] A herbal preparation, namely STW 5 (Iberogast, Steigerwald GmbH, Darmstadt, Germany) has been applied in the treatment of FD already for decades. The clinical efficacy of STW 5, which consists of nine plant extracts, has been shown in a considerable number of trials.[29–34] Throughout all studies, STW 5 proved superior to placebo in enhancing the symptoms of FD. Additionally, the improvement of the clinical gastrointestinal symptom (GIS) score for STW 5 was not statistically significant from cisapride.[33] These results suggested a modulating effect of STW 5 on gastric motility. Further trials described regional effects of STW 5 components on antral motility and accommodation in the fundus.[35,36] A recent study reported on the effects of STW 5 on gastric motility *in vivo*:[37] briefly, STW 5 slightly slowed gastric emptying of liquids, but improved proximal gastric accommodation and antral pressure waves substantially. In view of these results, we aimed to further elucidate whether STW 5 has an influence on gastric emptying in patients with FD and gastroparesis.

PATIENTS AND METHODS

Subjects

One-hundred and three patients (n = 30 male) aged 18–85 years (mean 46.8 years) participated in a double-blind, randomized, placebo-controlled, multicentre study. All patients were diagnosed with FD according to the Rome II criteria.[38] The main criteria for the diagnosis were epigastric pain and/or discomfort, centred in the upper abdomen during the preceding 12 months, with a duration of at least 12 weeks. Three or more items on a GIS Profile had to be judged at least 'moderate' (grade '2') to meet the inclusion criteria (see below). Clinically, relevant organic diseases of the upper gastrointestinal tract and abdominal organs have had to be ruled out by an abdominal ultrasound examination and an oesophagogastroduodenoscopy within the preceding 3 months. Patients with endoscopically proven oesophageal erosions, Barrett's oesophagus, gastroduodenal ulcers or erosions were excluded. Inclusion criteria also required the *Helicobacter pylori* status to be determined, but *H. pylori* positive patients were not excluded from the study. Among several other exclusion criteria, patients with diabetes mellitus, a history of abdominal surgery (apart from appendectomy and cholecystectomy) or predominant gastro-oesophageal reflux disease were not eligible for the study.

Study design

Patients were randomly assigned to either the verum group, treated with STW 5 tincture (20 drops tid for 28 days), or the placebo group. The latter group received a liquid placebo, mimicking organoleptic properties of STW 5 by the addition of flavours and colour, but lacking the active herbal extracts (20 drops tid for 28 days). None of the constituents of the placebo preparation was similar to STW 5, as approved by independent chemical analysis.

Before the treatment phase, patients were scheduled for a screening visit (visit 1, day −7 ± 2), when the diagnosis of FD and inclusion/exclusion criteria were checked. After screening, a washout-phase of 7 days preceded the beginning of the placebo-controlled treatment period (visit 2, day 0 ± 2). During this period and throughout the entire study period, patients had to refrain from drugs known to influence intestinal motility, including prokinetics, antacids, beta-blockers, calcium-antagonists, antidepressants, antibiotics and laxatives. Additionally, non-steroidal anti-inflammatory drugs were prohibited apart from a regular medication with acetylsalicylic acid for cardiovascular indications of maximum 100 mg per day. On visit 2, patients also underwent a ^{13}C octanoic acid breath test (^{13}C-OBT) for the assessment of gastric emptying. Patients with gastroparesis, defined by a prolonged gastric half-emptying time, underwent an additional ^{13}C-OBT at the end of the treatment period of 28 ± 2 days (visit 3).

^{13}C-octanoic acid breath test

After an overnight fast, patients received a standardized breakfast. The meal consisted of two slices of toast, 5 g margarine, 150 mL water and 100 mg of [^{13}C]octanoic acid (1-^{13}C, 99%; Euriso-Top SA, Saint-Aubin, France) incorporated into a baked egg. Patients were encouraged to consume the test meal within 5 min. Breath samples were collected before, every 15 min during the first 2 h and every 30 min during the following 2 h after the ingestion of the substrate. Samples were analysed for the ratio of $^{13}CO_2$ to $^{12}CO_2$ using non-dispersive isotope-selective infrared spectrometry (IRIS system; Wagner Analysentechnik,

Bremen, Germany). Gastric half-emptying time ($t_{1/2}$), lag phase (t_{lag}) and gastric emptying coefficients (GEC) were calculated using a standardized algorithm which involves a nonlinear regression formula.[39,40] The individual CO_2-production was estimated using the formula by Haycock for the calculation of the body surface area, assuming an endogenous CO_2-production of 5 mmol m^{-2} min^{-1}.[41] A half-emptying time of >150 min was considered delayed and defined gastroparesis.

Primary and secondary end points

The primary end point was a change of the 'GIS score', representing a validated combination of 10 questions, regarding different specific dyspeptic symptoms (abdominal cramps, epigastric/upper abdominal pain, early satiety, fullness, loss of appetite, vomiting, sickness, nausea, retrosternal pain, acid eructation/heartburn).[42] Each symptom was graded on a validated five-point Likert scale, ranging from 0 (no problem) to 4 (very severe problem, markedly influencing daily activities or requiring rest). Accordingly, the maximum result of the GIS was 40. A minimum of three parameters had to be judged at least 'moderate' (grade 2) by patients to be included in the study. Patients who reported higher values for the items 'retrosternal discomfort' and/or 'acid eructation/heartburn' compared with other symptoms of the GIS were excluded from the study, because non-erosive gastro-oesophageal reflux disease was suspected. The GIS score was assessed on all three scheduled visits.

On visit 3 at the end of treatment, both patients and physicians assessed the treatment efficacy on a six-point Likert scale [good (1)–very poor (6)]. Further evaluation included the proportion of responders, defined by a GIS-improvement of at least 40% from visit 2 to visit 3. The efficacy of STW 5 was characterized in different subgroups of FD. The subgroups were defined according to the Rome II criteria: ulcer-like (predominant pain), dysmotility-like (predominant discomfort, vomiting and/or postprandial fullness) and unspecific (compound symptoms without predominance). Patients with reflux-like FD had been excluded from the study.

Safety and tolerability were also analysed, using the documentation of adverse events, clinically relevant changes in laboratory parameters from baseline to the study end and the global assessment of tolerability on a six-point Likert scale by both patients and physicians.

The secondary target parameters comprised a change of the gastric half-emptying time ($t_{1/2}$) from baseline (visit 2) to the end of the study (visit 3) in patients in whom a delayed gastric emptying time was documented on visit 2.

Statistics

The primary objective was to prove the superiority of STW 5 over placebo during the treatment period (from day 0 to day 28). Considering a two-sided α-level of 0.05 and a power of 80%, 54 patients per study arm would have been required. In consideration of a 10% drop-out rate, the study aimed to recruit 60 patients in each treatment arm.

Originally, the study was planned as a single-centre trial. Due to the fact that the enrolment of patients proceeded slowly, the study was extended to a multicentre (n = 15) study approximately 1 year after the initiation.

For statistical analysis, different sets of patients were defined: all enrolled patients, non-randomized population (all patients enrolled into the study, but not randomized), intention-to-treat (ITT) population (all randomized patients who took any study medication) and per-protocol population (all patients from the ITT-population who essentially completed the study in compliance with the protocol).

Statistic evaluation of the primary variable GIS was performed by an analysis of variance (ANOVA). ANOVA was also applied for continuous secondary parameters, whereas a logistic regression model was used for categorical data. In cases when the assumption of normality in the linear models was not fulfilled (^{13}C-octanoic acid breath test parameters), a non-parametric Wilcoxon signed rank test was applied. For all tests, a $P \leq 0.05$ was considered significant.

Statistics were calculated using the Statistical Analysis System SAS (SAS Institute Inc., Cary, NC, USA), vers. 8.2.

The study was approved by the Ethical Committee by the Faculty of Medicine of the Johann-Wolfgang-Goethe University Frankfurt (approval No.164/02). The other participating centres obtained an approval from proper ethical committees, referring to the approval of the principal centre.

RESULTS

A total of 103 subjects were recruited. The study was terminated prematurely after more than 2 years because of a protracted recruitment. This decision was made in accordance with an expert statistical appraisal, stating that data met the requirements for a valid statistical analysis. Ten patients were not randomized due to a withdrawal of consent (n = 6), new intercurrent diseases

(n = 2), a violation of in-/exclusion criteria (n = 1) or for other reasons (n = 1). Of the remaining randomized 93 patients, 86 (92.5%) were included in the ITT population (STW 5 n = 44; placebo n = 42). In each group, 41 patients remained for the 'per protocol' analysis, whereas three patients in the verum- and one patient in the placebo group were excluded due to time frame deviations (n = 2) or a lack of compliance (n = 2).

Demographics, subgroups of FD and medical history

Comparison of demographic data showed a good homogeneity among the ITT-STW 5- and the -placebo group, regarding age, gender, body mass index, height and weight ($P > 0.05$). In both groups, about 50% of patients suffered from dysmotility-like FD (Table 1). The remainder equally distributed among the ulcer-like and the non-specific FD subgroup. *Helicobacter pylori* was positive in nine patients (20.5%) treated with verum and four patients of the placebo group (9.5%) (P = 0.16).

Gastric emptying parameters (^{13}C-octanoic acid breath test)

Sixty-seven of 86 patients (77.9%; STW 5 n = 35, placebo n = 32) performed the ^{13}C-OBT for the assessment of gastric motility on visit 2 (day 0 of the treatment phase). Mean gastric half-emptying times did not differ significantly between both groups [STW 5: 163 ± 59 min *vs* Placebo: 171 ± 138 min; P = 0.83 (mean ± SD)]. The same was observed with respect to the duration of the lag phase t_{lag} (STW 5: 104 ± 38 min *vs* Placebo: 107 ± 56 min; P = 0.81) and the GEC (STW 5: 2.97 ± 0.76 *vs* Placebo: 3.04 ± 0.629; P = 0.41).

Gastric half-emptying time was prolonged in 17/35 (48.6%) of patients in the STW 5 group and in 14/32 (43.8%) of the placebo group (STW 5: 208 ± 50 min and Placebo: 179 ± 28 min) with a t_{lag} of 128 ± 32 and 120 ± 25 min respectively. The GEC in this subgroup was 2.54 ± 0.43 (STW 5) and 2.68 ± 0.55 (Placebo).

Among patients with initially prolonged gastric half-emptying times, 13/17 participants of the verum- and 9/14 in the placebo group underwent an additional ^{13}C-OBT at the end of the treatment period (visit 3). Mean gastric half-emptying times (Fig. 1) had increased non-significantly in patients treated with STW 5 (+23 ± 109 min, P = 0.51) and slightly accelerated among patients in the placebo arm (−26 ± 51 min, P = 0.77). The differences in gastric emptying alterations under treatment between the verum and the placebo group were also not significant (P = 0.49). The t_{lag} and the GEC had also remained roughly unchanged by the end of the treatment period (17 ± 71 *vs* 7 ± 35 min, P = 0.70 and 0.03 ± 0.51 *vs* 0.14 ± 0.37, P = 0.44).

GIS score

Though the GIS score decreased both under verum and placebo treatment, In STW 5-treated patients, the GIS

Table 1 Demographics, dyspepsia subtypes, medication, *Helicobacter pylori* status and gastric emptying parameters (mean ± SD)

	STW 5 (n = 44)	Placebo (n = 42)	P-value
Gender (male)	14 (31.8)	12 (28.6)	0.74
Age [(years), mean ± SD]	45.9 ± 15.2	48.6 ± 17.3	0.45
BMI [(kg m^{-2}), mean ± SD]	24.3 ± 4.5	24.7 ± 5.0	0.57
Duration of dyspepsia [(months), mean ± SD]	40.5 ± 50.3	44.2 ± 53.4	0.99
Type of dyspepsia			
Ulcer-like	13 (29.7)	10 (23.8)	0.55
Dysmotililty-like	21 (47.7)	20 (47.6)	0.99
Non-specific	10 (22.7)	12 (28.6)	0.54
GIS score (mean ± SD)	11.57 ± 4.37	12.05 ± 4.68	0.53
Medication			
PPI	6 (13.3)	4 (8.9)	0.55
Prokinetics	0 (0)	2 (4.4)	0.14
Beta-blockers	3 (6.7)	5 (11.1)	0.42
Helicobacter pylori positive	9 (20.5)	4 (9.5)	0.16
$t_{1/2}$ [(min), mean ± SD]	163 ± 59	171 ± 138	0.83
t_{lag} [(min), mean ± SD]	104 ± 38	107 ± 56	0.81
GEC (mean ± SD)	2.97 ± 0.76	3.04 ± 0.63	0.41

BMI, body mass index; GIS score, gastrointestinal symptom score; PPI, proton pump inhibitor; GEC, gastric emptying coefficient.
Values in parentheses are percentages.

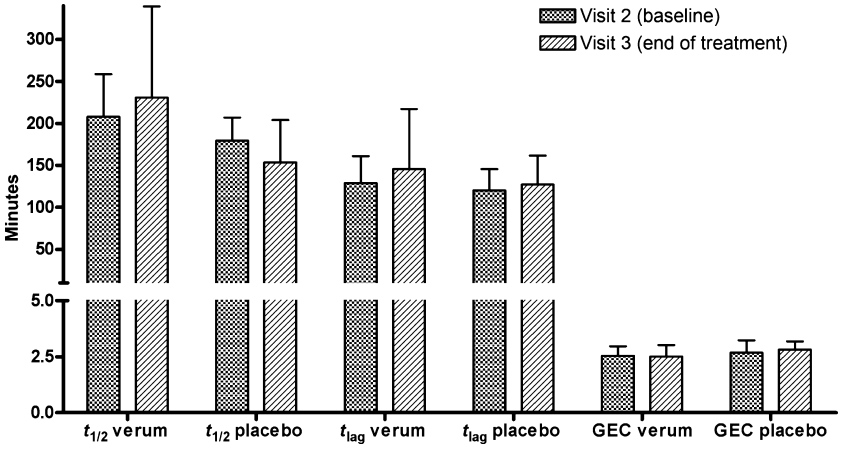

Figure 1 $t_{1/2}$, t_{lag} and gastric emptying coefficient (GEC) before (visit 2) and at the end of the treatment period (visit 3) in patients with initially (visit 2) prolonged gastric half-emptying time. $P > 0.05$ for all comparisons (mean ± SD).

score (mean ± SD) decreased from 11.6 ± 4.4 to 5.0 ± 4.3, while placebo-treated patients showed a decrease from 12.0 ± 4.7 to 7.5 ± 6.6. This improvement was more pronounced in the STW 5 group (6.5 ± 4.6) than in the control group (4.6 ± 5.5). The appropriate statistical analysis model [analysis of covariance (ANCOVA) including the factors treatment centre and covariate: baseline] showed a statistically significant difference of 2.2 points between the groups in favour of STW 5 ($P = 0.03$). An improvement of 40% or more of the GIS score was observed in 33/44 (75%) of patients treated with STW 5 and 23/42 (54.8%) patients treated with placebo ($P = 0.03$). Accordingly, the percentage improvement in the GIS score was 55.3 ± 35.0 (STW 5) and 39.8 ± 42.9 (Placebo) respectively ($P = 0.06$).

Patients with dysmotility-like dyspepsia profited most from STW 5 and reported a decrease in the GIS score of −7.8 ± 4.4 (*vs* −4.7 ± 6.7 in the placebo group). The corresponding values for patients with ulcer-like and non-specific dyspepsia were −4.5 ± 3.9 (placebo −5.1 ± 5.3) and −5.5 ± 5.0 (placebo −4.0 ± 3.4) respectively.

There occurred 17 adverse events during the study. Eight adverse events were observed in a possible or probable causal relationship to study medication (STW 5: three adverse events – stomatitis, abdominal pain and diarrhoea; placebo: five adverse events – rhinitis, diarrhoea, dyspepsia, vomiting and genitourinary tract infection). There were no clinically relevant changes in laboratory and vital parameters in both groups during study.

Global assessment of efficacy

Thirty-one patients (70.4%) and 32 physicians (72.7%) in the STW 5 group assessed the treatment efficacy as 'very good', 'good' or 'moderate'. The corresponding proportions in the placebo group were 22 (52.4%) and 26 (61.9%) respectively. Logistic regression model analysis showed a trend for a better subjective efficacy of STW 5, but this did not reach statistical significance [$P = 0.24$ (for patients) and $P = 0.15$ (for physicians)].

DISCUSSION

The therapeutic efficacy of STW 5 for the relief of symptoms associated with FD has been thoroughly demonstrated in several trials.[29–34] STW 5 showed equal efficacy to cisapride and in a retrospective cohort study a superior efficacy to metoclopramide.[43] We were also able to demonstrate the superiority of STW 5 compared with placebo in the study outlined here. The drug consists of hydroethanolic extracts of nine plants and therapy is well-tolerated without relevant adverse effects. Though the clinical effects of STW 5 have been well documented, the pathophysiological mechanisms of the therapeutic effects are still not fully elucidated.

In vitro studies of gastric motility have shown that ethanol-free lyophilisates of STW 5 exert pleiotropic effects on the muscles of different gastric regions.[35,36] Remarkably, the individual components produce differential effects on the myogenic action of the proximal and the distal stomach, i.e. that calcium-mediated actions of the constituents can be converse between the fundic and the antral region. FD has been shown to be associated with an impairment of gastric accommodation in the fundus and antral hypomotility. Consequently, STW 5 seems to improve gastric dysmotility by a relaxation of the proximal stomach and an enhancement of antral motility. An additional effect may result from a modulation of visceral nociceptive stimuli.

Data on the motility-modulating effects of STW 5 *in vivo* are scarce. A recently published study on

a limited number of healthy men confirmed that the substance increased proximal gastric volume, a surrogate marker for gastric accommodation.[37] Furthermore, antral motility improved after the oral ingestion of STW 5. Gastric emptying of liquids increased to some extent, whereas the retention of a solid meal remained unaffected.

The study design of the current trial was planned before the above mentioned results regarding the effects of STW 5 on gastric motility were available. We aimed to determine whether the substance exerts its clinical effects by an enhancement of gastric emptying. The study focused on the emptying kinetics of solid meals in FD patients with idiopathic gastroparesis, because gastric processing of solids is more complex than of fluids; therefore, gastroparesis and tachygastry primarily affect gastric emptying of solids in the majority of cases. However, our study failed to show a substantial impact of STW 5 on gastroparesis. In contrast, there was a tendency for a prolongation of gastric emptying in patients treated with STW 5, although symptoms of FD were significantly improved. How can these results be explained?

Numerous studies have shown that delayed gastric emptying is present in about 20–60% of patients with FD.[44–47] This proportion is in accordance with our study that showed a prevalence of gastroparesis in approximately 45% of patients. Subjective symptoms do not quite correlate with the degree of gastroparesis, though FD-patients with severe fullness and vomiting are more likely to suffer from gastroparesis.[48] Gastric accommodation – the adequate relaxation of the fundus region following the ingestion of a meal, thereby preserving a constant intragastric pressure – is impaired in about 40% of patients suffering from FD.[25] 5-HT_1 agonists have been deemed a promising class of drugs that modulate intestinal motility by improving gastric accommodation.[49] On the other hand, the 5-HT_4-agonist cisapride as well as the well-known dopamine D2-receptor antagonists metoclopramide and domperidone are also better than placebo.[50–59]

In the study presented here, gastroparesis did not correlate with clinical symptoms, as defined in the 'GIS score'. For this reason, acceleration of gastric emptying does not seem to be the central mechanism of action that mediates the clinical effects of STW 5. Pilichiewicz *et al.*[37] demonstrated that STW 5 did not affect the gastric emptying of solids in eight healthy controls. We can confirm these findings for patients with FD and gastroparesis. A drawback of our study is a lack of information on patients with normal or enhanced gastric emptying. Therefore, we are not able to provide further details on the effects of STW 5 in these subgroups beyond clinical efficacy data. Generally, gastroparesis appears of minor importance in FD: erythromycin, a strong motilin receptor agonist, greatly enhanced gastric emptying, but failed to improve symptoms in patients with FD.[60]

We conclude that STW 5 has the potential to produce symptomatic relief in patients with FD. In our study, this effect did not seem to be correlated to an acceleration of gastric emptying, whereas it is questionable if the velocity of gastric emptying is correlated to the symptoms of FD. In this context, differential effects of STW 5 on gastric accommodation and visceral hypersensitivity seem to be more important and need to be further investigated by future pathophysiological studies.

CONFLICT OF INTEREST DISCLOSURE

Dr Vinson is an employee of the Steigerwald Arzneimittelwerk GmbH, Darmstadt, Germany. The other authors (B.B., W.C., N.B., A.S.) do not have conflicts of interest to declare.

REFERENCES

1 Lu CL, Lang HC, Chang FY *et al.* Prevalence and health/social impacts of functional dyspepsia in Taiwan: a study based on the Rome criteria questionnaire survey assisted by endoscopic exclusion among a physical check-up population. *Scand J Gastroenterol* 2005; **40**: 402–11.
2 Mahadeva S, Goh KL. Epidemiology of functional dyspepsia: a global perspective. *World J Gastroenterol* 2006; **12**: 2661–6.
3 Shaib Y, El-Serag HB. The prevalence and risk factors of functional dyspepsia in a multiethnic population in the United States. *Am J Gastroenterol* 2004; **99**: 2210–6.
4 El-Serag HB, Talley NJ. Systemic review: the prevalence and clinical course of functional dyspepsia. *Aliment Pharmacol Ther* 2004; **19**: 643–54.
5 Locke GR III. Prevalence, incidence and natural history of dyspepsia and functional dyspepsia. *Baillieres Clin Gastroenterol* 1998; **12**: 435–42.
6 Allescher HD. Functional dyspepsia – a multicausal disease and its therapy. *Phytomedicine* 2006; **13**(Suppl. 5): 2–11.
7 Camilleri M, Thompson DG, Malagelada JR. Functional dyspepsia. Symptoms and underlying mechanism. *J Clin Gastroenterol* 1986; **8**: 424–9.
8 Jebbink HJ, Smout AJ, van Berge-Henegouwen GP. Pathophysiology and treatment of functional dyspepsia. *Scand J Gastroenterol Suppl* 1993; **200**: 8–14.
9 Smith ML. Functional dyspepsia pathogenesis and therapeutic options – implications for management. *Dig Liver Dis* 2005; **37**: 547–58.
10 Thumshirn M. Pathophysiology of functional dyspepsia. *Gut* 2002; **51**(Suppl. 1): i63–6.
11 Aoki S, Haruma K, Kusunoki H *et al.* Evaluation of gastric emptying measured with the 13C-octanoic acid breath test

in patients with functional dyspepsia: comparison with ultrasonography. *Scand J Gastroenterol* 2002; **37**: 662–6.
12 Berstad A, Hauksen T, Gilja OH *et al.* Gastric accommodation in functional dyspepsia. *Scand J Gastroenterol* 1997; **32**: 193–7.
13 Camilleri M. Does delayed gastric emptying really cause symptoms in functional dyspepsia? *Gut* 2006; **55**: 909–10.
14 Jebbink HJ, Van Berge-Henegouwen GP, Bruijs PP, Akkermans LM, Smout AJ. Gastric myoelectrical activity and gastrointestinal motility in patients with functional dyspepsia. *Eur J Clin Invest* 1995; **25**: 429–37.
15 Kairemo KJ, Koskenpato J, Korppi-Tommola ET, Farkkila M. A dual-tracer method for studying intragastric distribution and gastric emptying of solids and liquids in functional dyspepsia. *Nucl Med Commun* 1998; **19**: 143–7.
16 Kusunoki H, Haruma K, Hata J *et al.* Real-time ultrasonographic assessment of antroduodenal motility after ingestion of solid and liquid meals by patients with functional dyspepsia. *J Gastroenterol Hepatol* 2000; **15**: 1022–7.
17 Lorena SL, Tinois E, Brunetto SQ, Camargo EE, Mesquita MA. Gastric emptying and intragastric distribution of a solid meal in functional dyspepsia: influence of gender and anxiety. *J Clin Gastroenterol* 2004; **38**: 230–6.
18 Salet GA, Samsom M, Roelofs JM, van Berge Henegouwen GP, Smout AJ, Akkermans LM. Responses to gastric distension in functional dyspepsia. *Gut* 1998; **42**: 823–9.
19 Tack J, Bisschops R, Sarnelli G. Pathophysiology and treatment of functional dyspepsia. *Gastroenterology* 2004; **127**: 1239–55.
20 Coffin B, Azpiroz F, Guarner F, Malagelada JR. Selective gastric hypersensitivity and reflex hyporeactivity in functional dyspepsia. *Gastroenterology* 1994; **107**: 1345–51.
21 Hamilton J, Guthrie E, Creed F *et al.* A randomized controlled trial of psychotherapy in patients with chronic functional dyspepsia. *Gastroenterology* 2000; **119**: 661–9.
22 Haug TT, Wilhelmsen I, Ursin H, Berstad A. What are the real problems for patients with functional dyspepsia? *Scand J Gastroenterol* 1995; **30**: 97–100.
23 Holtmann G, Kutscher SU, Haag S *et al.* Clinical presentation and personality factors are predictors of the response to treatment in patients with functional dyspepsia; a randomized, double-blind placebo-controlled crossover study. *Dig Dis Sci* 2004; **49**: 672–9.
24 Tack J. Functional dyspepsia: impaired fundic accommodation. *Curr Treat Options Gastroenterol* 2000; **3**: 287–94.
25 Tack J, Piessevaux H, Coulie B, Caenepeel P, Janssens J. Role of impaired gastric accommodation to a meal in functional dyspepsia. *Gastroenterology* 1998; **115**: 1346–52.
26 Nyren O. Functional dyspepsia: bye-bye to PPIs. *Gut* 2002; **51**: 464–5.
27 Peura DA, Kovacs TO, Metz DC, Siepman N, Pilmer BL, Talley NJ. Lansoprazole in the treatment of functional dyspepsia: two double-blind, randomized, placebo-controlled trials. *Am J Med* 2004; **116**: 740–8.
28 Wang WH, Huang JQ, Zheng GF *et al.* Effects of proton-pump inhibitors on functional dyspepsia: a meta-analysis of randomized placebo-controlled trials. *Clin Gastroenterol Hepatol* 2007; **5**: 178–85. quiz 140.
29 Gundermann KJ, Godehardt E, Ulbrich M. Efficacy of a herbal preparation in patients with functional dyspepsia: a meta-analysis of double-blind, randomized, clinical trials. *Adv Ther* 2003; **20**: 43–9.
30 Madisch A, Melderis H, Mayr G, Sassin I, Hotz J. A plant extract and its modified preparation in functional dyspepsia. Results of a double-blind placebo controlled comparative study. *Z Gastroenterol* 2001; **39**: 511–7.
31 Melzer J, Rosch W, Reichling J, Brignoli R, Saller R. Meta-analysis: phytotherapy of functional dyspepsia with the herbal drug preparation STW 5 (Iberogast). *Aliment Pharmacol Ther* 2004; **20**: 1279–87.
32 Rosch W, Liebregts T, Gundermann KJ, Vinson B, Holtmann G. Phytotherapy for functional dyspepsia: a review of the clinical evidence for the herbal preparation STW 5. *Phytomedicine* 2006; **13**(Suppl. 5): 114–21.
33 Rosch W, Vinson B, Sassin I. A randomised clinical trial comparing the efficacy of a herbal preparation STW 5 with the prokinetic drug cisapride in patients with dysmotility type of functional dyspepsia. *Z Gastroenterol* 2002; **40**: 401–8.
34 von Arnim U, Peitz U, Vinson B, Gundermann KJ, Malfertheiner P. STW 5, a phytopharmacon for patients with functional dyspepsia: results of a multicenter, placebo-controlled double-blind study. *Am J Gastroenterol* 2007; **102**: 1268–75.
35 Schemann M, Michel K, Zeller F, Hohenester B, Ruhl A. Region-specific effects of STW 5 (Iberogast) and its components in gastric fundus, corpus and antrum. *Phytomedicine* 2006; **13**(Suppl. 5): 90–9.
36 Hohenester B, Ruhl A, Kelber O, Schemann M. The herbal preparation STW5 (Iberogast) has potent and region-specific effects on gastric motility. *Neurogastroenterol Motil* 2004; **16**: 765–73.
37 Pilichiewicz AN, Horowitz M, Russo A *et al.* Effects of Iberogast on proximal gastric volume, antropyloroduodenal motility and gastric emptying in healthy men. *Am J Gastroenterol* 2007; **102**: 1276–83.
38 Drossman DA. The functional gastrointestinal disorders and the Rome II process. *Gut* 1999; **45** (Suppl .2) : II 1–5.
39 Braden B, Enghofer M, Schaub M, Usadel KH, Caspary WF, Lembcke B. Long-term cisapride treatment improves diabetic gastroparesis but not glycaemic control. *Aliment Pharmacol Ther* 2002; **16**: 1341–6.
40 Ghoos YF, Maes BD, Geypens BJ *et al.* Measurement of gastric emptying rate of solids by means of a carbon-labeled octanoic acid breath test. *Gastroenterology* 1993; **104**: 1640–7.
41 Haycock GB, Schwartz GJ, Wisotsky DH. Geometric method for measuring body surface area: a height-weight formula validated in infants, children, and adults. *J Pediatr* 1978; **93**: 62–6.
42 Adam B, Liebregts T, Saadat-Gilani K, Vinson B, Holtmann G. Validation of the gastrointestinal symptom score for the assessment of symptoms in patients with functional dyspepsia. *Aliment Pharmacol Ther* 2005; **22**: 357–63.
43 Raedsch R, Hanisch J, Bock P, Sibaev A, Vinson B, Gundermann KJ. Assessment of the efficacy and safety of the phytopharmacon STW 5 versus metoclopramide in functional dyspepsia – a retrolective cohort study. *Z Gastroenterol* 2007; **45**: 1041–8.
44 Caballero-Plasencia AM, Muros-Navarro MC, Martin-Ruiz JL *et al.* Gastroparesis of digestible and indigestible solids in patients with insulin-dependent diabetes

mellitus or functional dyspepsia. *Dig Dis Sci* 1994; **39**: 1409–15.
45 Quartero AO, de Wit NJ, Lodder AC, Numans ME, Smout AJ, Hoes AW. Disturbed solid-phase gastric emptying in functional dyspepsia: a meta-analysis. *Dig Dis Sci* 1998; **43**: 2028–33.
46 Sarnelli G, Caenepeel P, Geypens B, Janssens J, Tack J. Symptoms associated with impaired gastric emptying of solids and liquids in functional dyspepsia. *Am J Gastroenterol* 2003; **98**: 783–8.
47 Caballero-Plasencia AM, Muros-Navarro MC, Martin-Ruiz JL *et al.* Dyspeptic symptoms and gastric emptying of solids in patients with functional dyspepsia. Role of *Helicobacter pylori* infection. *Scand J Gastroenterol* 1995; **30**: 745–51.
48 Stanghellini V, Tosetti C, Paternico A *et al.* Risk indicators of delayed gastric emptying of solids in patients with functional dyspepsia. *Gastroenterology* 1996; **110**: 1036–42.
49 Tack J, Coulie B, Wilmer A, Andrioli A, Janssens J. Influence of sumatriptan on gastric fundus tone and on the perception of gastric distension in man. *Gut* 2000; **46**: 468–73.
50 Van Outryve M, De Nutte N, Van Eeghem P, Gooris JP. Efficacy of cisapride in functional dyspepsia resistant to domperidone or metoclopramide: a double-blind, placebo-controlled study. *Scand J Gastroenterol Suppl* 1993; **195**: 47–52.
51 Hiyama T, Yoshihara M, Matsuo K *et al.* Meta-analysis of the effects of prokinetic agents in patients with functional dyspepsia. *J Gastroenterol Hepatol* 2007; **22**: 304–10.
52 Dumitrascu DL, Ungureanu O, Verzea D, Pascu O. The effect of metoclopramide on antral emptying of a semi-solid meal in patients with functional dyspepsia. A randomized placebo controlled sonographic study. *Rom J Intern Med* 1998; **36**: 97–104.
53 Veldhuyzen van Zanten SJ, Jones MJ, Verlinden M, Talley NJ. Efficacy of cisapride and domperidone in functional (nonulcer) dyspepsia: a meta-analysis. *Am J Gastroenterol* 2001; **96**: 689–96.
54 Van de Mierop L, Rutgeerts L, Van den Langenbergh B, Staessen A. Oral domperidone in chronic postprandial dyspepsia. A double-blind placebo-controlled evaluation. *Digestion* 1979; **19**: 244–50.
55 Englert W, Schlich D. A double-blind crossover trial of domperidone in chronic postprandial dyspepsia. *Postgrad Med J* 1979; **55**(Suppl. 1): 28–9.
56 Arts E, Anthoni H, de Roy G, D'Hollander J, Verhaegen H. Domperidone in the treatment of dyspepsia: a double-blind placebo-controlled study. *J Int Med Res* 1979; **7**: 158–61.
57 Yeoh KG, Kang JY, Tay HH *et al.* Effect of cisapride on functional dyspepsia in patients with and without histological gastritis: a double-blind placebo-controlled trial. *J Gastroenterol Hepatol* 1997; **12**: 13–8.
58 Wood SF, Penney SC, Cochran KM. Cisapride in functional dyspepsia: a double-blind, placebo-controlled randomized trial in general practice patients. *Scand J Gastroenterol Suppl* 1993; **195**: 5–10.
59 Holtmann G, Gschossmann J, Mayr P, Talley NJ. A randomized placebo-controlled trial of simethicone and cisapride for the treatment of patients with functional dyspepsia. *Aliment Pharmacol Ther* 2002; **16**: 1641–8.
60 Arts J, Caenepeel P, Verbeke K, Tack J. Influence of erythromycin on gastric emptying and meal related symptoms in functional dyspepsia with delayed gastric emptying. *Gut* 2005; **54**: 455–60.

APPENDIX

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