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Phytotherapy for functional dyspepsia: A review of the clinical evidence for the herbal preparation STW 5

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Abstract

Functional gastrointestinal disorders such as functional (or non-ulcer) dyspepsia are characterized by a broad spectrum of symptoms referred to the upper abdomen without a detectable cause utilizing routine diagnostic measures. It is now believed that disordered gut function (including abnormalities like disturbances of motility such as postprandial fundic relaxation, gastric emptying and disturbed visceral sensory function) play a key role for the manifestation of these disorders. The underlying pathophysiology is not yet fully understood. However, the available data suggest that a number of factors may contribute to the manifestation of symptoms. These factors include environmental factors such as acute infections as trigger event, psychological stressors that may precede acute exacerbations and a genetic predisposition. Considering the large number of mechanisms, a treatment targeting a single mechanism is unlikely to be effective in all patients. Indeed, chemically defined treatments usually gain a 10–15% superiority over placebo. In recent years placebo-controlled studies have demonstrated superiority of a commercial multicomponent herbal preparation, STW 5, with the trade name Iberogast® for the treatment of patients with functional dyspepsia and irritable bowel syndrome. This phytopharmacon is a combination of nine plant extracts each with a number of different active constituents. Pharmacological studies have shown different effects of the single plant extracts on the (molecular) mechanisms which are discussed as underlying the manifestation of symptoms. Various well-controlled clinical trials have independently confirmed clinical efficacy and safety.

The clinically efficacy of this multicomponent herbal preparation questions the current trend of highly targeted drug molecules that usually target one single receptor population while it has not been shown that a single receptor group plays a pivotal role for the control of symptoms. Herbal medicines are obtained from various plants and contain complex extracts with a large number of different active substances. While there are only limited head-to-head comparisons with conventional chemically defined medications, the combination of extracts with various gastrointestinal active ingredients appears to be advantageous for a heterogenous condition such as functional dyspepsia.

Keywords: Medical therapy; Phytopharmacons; STW 5 (Iberogast®); Clinical study; Functional dyspepsia

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Introduction

Functional gastrointestinal disorders (i.e. functional dyspepsia or irritable bowel syndrome) are characterized by symptoms and the lack of structural lesions that can be identified utilizing routine clinical diagnostic work-up (Allescher 2006).

Based upon the predominant symptom pattern, these disorders are categorized as functional dyspepsia (symptoms including pain and discomfort early satiety, bloating and nausea centered in the upper abdomen) or irritable bowel syndrome (lower abdominal symptoms associated with alteration of bowel movements).

Therapeutic options

Functional gastrointestinal disorders and in particular dyspepsia are among the most frequently disorders seen in general practice (Gschossmann et al., 2001). A large amount of patients is suffering very strong from these symptoms which are affecting daily life routine and have a great impact on quality of life as well as ability to work. Epidemiological studies documented incidence rates in the range of 15–25% in western countries (Allescher 2006).

There is no curative treatment available to date for patients with functional dyspepsia and standard therapies are not established yet (Talley et al., 1998a, b). Substances, which inhibit acid secretion, such as proton-pump inhibitors, are frequently applicated for the treatment of functional dyspepsia. These show in clinical trials statistically significant superiority to placebo although the differences in treatment effects between placebo and verum in these studies were only approx. 10–15% (Talley et al., 1998a, b). Results for prokinetics were similar (Holtmann et al., 2002). In view of the multiple causes which are discussed as underlying the symptoms of functional dyspepsia the therapy option of combining different substances with different gastrointestinal effects seems appropriate. The herbal combination preparation STW 5 (Iberogast®) consisting of 9 plant extracts has been used for treatment of various gastrointestinal disorders for more than 40 years. It has since then been systematically evaluated in numerous open (Bleimann and Hartmann, 1983; Ohms, 1983; Steimer, 1983; Bremer et al., 1983; Brückel and Gisevius, 1984; Hölscher, 1984; Illing and Sajthy, 1984; Sporrer, 1984; Nicolay, 1984; Mac Lean and Hübner-Steiner, 1985; Mac Lean and Hübner-Steiner, 1987) and later in controlled clinical trials. From the 1990s, therapeutic use of it has been, besides the use in irritable bowel syndrome (IBS), focused on the treatment of functional dyspepsia. This review will focus therefore on the clinical evidence for the herbal medicine STW 5 for the treatment of patients with functional dyspepsia. The clinical double blind studies conducted so far as well as meta-analyses will be summarized. Supportive data from retrospective and postmarketing surveillances will be summarized especially for safety aspects.

Investigational data for STW 5

Components and safety of STW 5

The herbal medicine STW 5 is composed of a fresh plant extract of bitter candytuft (*Iberis amara*) and drug extracts of Angelica root, milk thistle fruit, caraway fruit, celandine her liquorice root, chamomile flower, lemon balm leaf, and peppermint leaf with an ethanol content of 31%. Beside pharmacological studies elucidating the mechanisms of action, various toxicological studies have been conducted, covering all guidelines of ICH, EU, FDA, Japanese MWDH relevant for a new chemical entity (NCE), showing no observed adverse effect levels (NOAELs) of the 600-fold, in most studies of the 1200-fold of the human daily dose (Table 1). In clinical investigations the side effect rate was low and no interactions with other substances or systemic side effects have been documented yet (Saller et al., 2002).

Clinical data for STW 5

Beside its traditional use for treating various gastrointestinal disorders its therapeutical efficacy has been

Table 1. Toxicological studies conducted with STW 5

Studies in two animal species	Dose (times daily dose)	Toxicity
Acute toxicity	600–1200	None
Subchronic toxicity	1200	None
Chronic toxicity	1200	None
Genotoxicity, mutagenicity, cytotoxicity in vitro/ex vivo	up to 1200	None
Reproduction toxicity (fertility, teratogenicity, embryotoxicity, postnatal development)	300–1200	None

The studies have been conducted according to actual ICH-, ICH, EU, FDA, Japanese MWDH guidelines and fulfil the requirements for a new chemical entity (NCE).

investigated in many clinical trials according to modern guidelines and thus evidence-based confirmed.

Four double blind randomized clinical trials with STW 5 have been conducted in patients with functional dyspepsia. Data for the use and safety of the phytopharmacon in general practice and in children with an age up to 12 years were provided by postmarketing and retrospective surveillances as well as meta-analyses of pooled data.

Randomized, double blind multicenter clinical trials in patients with functional dyspepsia

In all studies a validated instrument was used to assess the Gastrointestinal Symptom Score (GIS) during treatment. The GIS comprises 10 dyspepsia specific symptoms: epigastric pain/upper abdominal pain; nausea, sickness, vomiting, bloating, abdominal cramps, early satiety, acidic eructation/heartburn, loss of appetite and retrosternal discomfort (Holtmann et al., 2004). Each symptom is rated using a 5-point Likert scale (0–4) with 0 meaning the symptom is no problem and 4 symptom intensity is affecting quality of life very strong. Highest value of the GIS is thus 40 points meaning lower values of the GIS are implicating an improvement of overall symptom intensity and quality of life.

Efficacy in overall dyspeptic symptoms and in pain specific symptoms

Following a 2-week washout phase, a total of 243 patients with non-ulcer dyspepsia (NUD) was treated daily with 3×20 drops STW 5, the research preparation STW 5 II or placebo for 4 weeks in a multicentric, randomized double-blind study. The primary outcome parameter was the change in the gastrointestinal summary score comprising the above-mentioned various abdominal symptoms as well as the symptom irregular bowel movements.

The sum score for the patient group treated with STW 5 decreased from 15.9 ± 4.46 at start of therapy to 6.8 ± 4.55 after the 4-week treatment and from 16.5 ± 4.26 to 12.6 ± 5.10 for the placebo group (Fig. 1). This difference in the therapeutic effect was statistically significant ($p < 0.0001$). A corresponding result was also seen for the pain index comprising the pain related symptoms of the main score. In the STW 5 group, the score decreased from 5.6 ± 2.2 at start of therapy to 2.5 ± 1.8 after 4 weeks of treatment and in the placebo group from 5.8 ± 1.7 to 4.4 ± 2.2 score points. The difference between the two treatment groups was also significant ($p < 0.0001$).

In all, 89% of the patients in the STW 5 group rates the tolerability as being excellent or good compared to 60.2% of the patients in the placebo group. A total of three adverse events were reported which were considered to have a possible causal relationship to the test medication (esophagitis, bronchitis and diarrhea). One patient in the placebo group had a deterioration of the symptom vomiting. None of these reported events were considered to be serious. There were no clinically relevant changes in the laboratory and vital parameters documented (Buchert, 1994).

Efficacy in overall dyspeptic symptoms vs. placebo

In a further multicentric, placebo-controlled, double-blind, randomized phase II study, 60 patients with functional dyspepsia underwent a 7-day washout phase followed by a 4-week treatment with daily 3×2 drops of STW 5, the research preparation STW 5-S or placebo [20]. The efficacy was assessed by means of the validated gastrointestinal symptom profile (GIS). The change in the sum score during therapy (after 14 and 28 days) was the main outcome parameter. Secondary parameter were the efficacy and tolerability assessments by the patients and physicians as well as the documentation of adverse events and vital and laboratory parameters.

A significantly larger decrease in the GIS was observed after 28 days in the STW 5 group (from 11.4 ± 2.5 to 3.3 ± 2.2) compared to the placebo group (from 10.4 ± 2.7 to 8.8 ± 2.0). This difference was significant ($p < 0.001$) (Fig. 2).

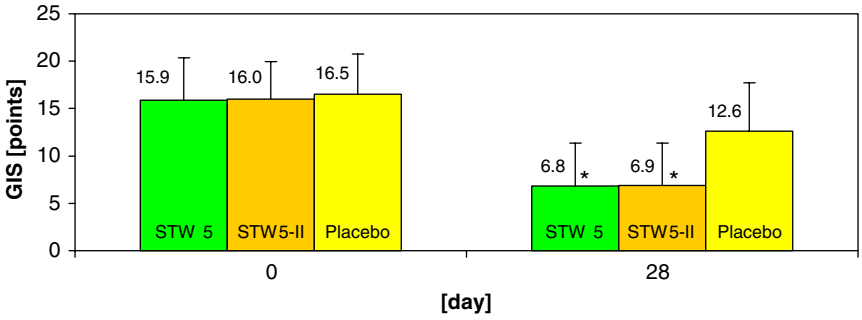

Fig. 1. Change of the gastrointestinal symptom score during 4 weeks of therapy with STW 5, STW 5 II or Placebo (Buchert, 1994).

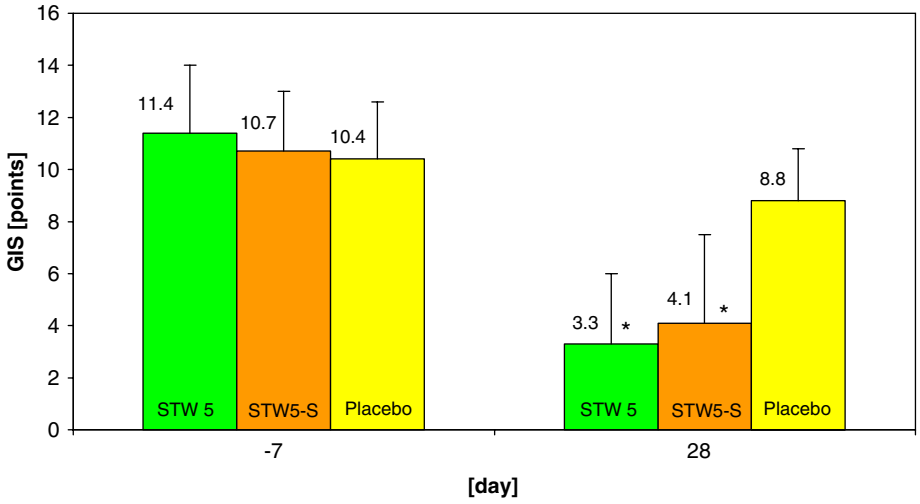

Fig. 2. Change of the gastrointestinal symptom score during 4 weeks of therapy with STW 5, STW 5 S or Placebo (Madisch et al., 2001).

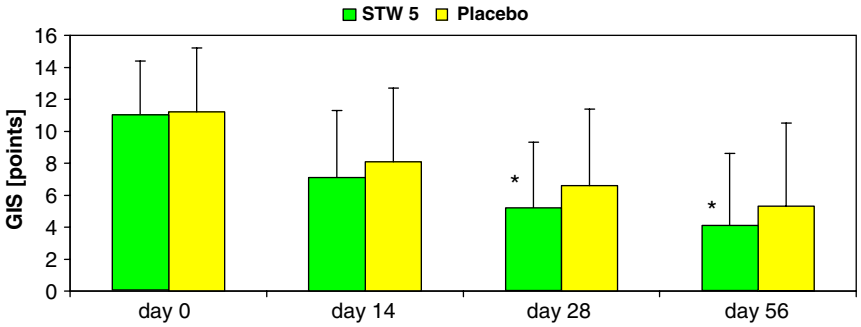

Fig. 3. Change of the gastrointestinal symptom score during 8 weeks of therapy with STW 5 or Placebo (v. Arnim et al., 2004).

In total, 80% of the physicians and 75% of the patients assessed the efficacy of STW 5 as being "very good" or "good" whereas efficacy of placebo was judged poor or very poor by 52.7% of the physicians and by 57.9% of the patients. However, 75% of the physicians and 68% of the patients assessed tolerability of STW 5 as being "good" or "very good". In the placebo group, corresponding data were 75% of the physicians and 58% of the patients. In one patient an adverse event was assessed by the investigator as to be in possible causal relationship to STW 5 (mild nausea). There were no clinically relevant changes in the laboratory and vital parameters documented (Madisch et al., 2001).

Efficacy vs. placebo in 308 patients with functional dyspepsia according to Rome II criteria

In a further randomized, placebo-controlled, double-blind study, completed in 2003, 308 patients with functional dyspepsia were enclosed according to the new Rome II criteria, and, after a 7-day washout phase, treated for 8 weeks [21]. The patients received daily 3×20 drops STW 5 or placebo. The primary outcome parameter was the change of the GIS recorded on day 0 and after 2, 4 and 8 weeks of treatment as well as twice during the 6-month follow-up.

The secondary parameters were the global assessment of the efficacy and tolerability as well as the occurrence of adverse events and changes in the laboratory and vital parameters. The mean GIS value at the start of the therapy was 11.0 ± 3.4 for the STW 5 group and 11.2 ± 4.0 for the placebo group and decreased to 4.1 ± 4.5 and 5.3 ± 5.2, respectively on day 56. This difference in the therapeutic effect was statistically significant ($p < 0.05$) (Fig. 3).

The efficacy of the therapy was rated as being "very good" by 20.6% (STW 5) and 10.8% (placebo) of the physicians. Of the patients, 92.1% (placebo) and 84.4% (STW 5) rated the tolerability as being "good" or "very good". Five adverse events were reported in the STW 5 group with a possible causal relationship to study medication (abdominal pain/gastrointestinal pain, hypersensitivity, alopecia, hypertension, pruritus). None of these events was serious. For vital and laboratory

parameters no safety relevant changes during the treatment period were documented (v. Arnim et al., 2004).

Efficacy compared to prokinetics drug cisapride

The efficacy and tolerability of STW 5 (Iberogast®) and a research preparation were evaluated and compared to the prokinetics cisapride in a double-blind, randomized study with double dummy design involving 186 patients with dysmotility-type of functional dyspepsia. After a 1-week washout phase, the patients were randomized to a treatment with either STW 5, STW 5-II or cisapride and received daily 3×20 drops of either STW 5 or STW 5-II plus 3×10 mg cisapride-placebo or 3×10 mg cisapride plus 3×20 drops of an STW 5/STW 5-II-placebo. A follow-up observation was carried out 6 months after therapy end for the patients who were symptom-free at therapy end. The change in the GIS over the course of the treatment period served as the primary study variable, and the change was tested for non-inferiority.

Secondary parameters were the efficacy and tolerability assessments by the physician and patient as well as the documentation of adverse events and laboratory and vital parameters.

The mean symptom score at therapy begin for STW 5/cisapride/STW 5-II was comparable with 14.3 ± 4.7, 14.5 ± 4.1 and 14.4 ± 4.0 score points, respectively, and after 28 days therapy with 2.3 ± 2.7, 3.6 ± 4.0 and 2.8 ± 3.9, score-points, respectively (Fig. 4). The results for the therapeutic response did thus not significantly differ and confirmed a comparable efficacy of both vera. The patients who were symptom-free at therapy end remained recurrence-free during the 6-month follow-up period without any significant differences between the groups (STW 5 16 of 21, STW 5-II 12 of 18, cisapride 12 of 15).

Since, 96.7% of the physicians and 93.5% of the patients assessed the tolerability of STW 5 as being "very good" or "good" , for STW 5-II 95.1% and 90.3%, respectively, and for cisapride 90.5% and 81%, respectively. In the STW 5 group 2 adverse events classified as in a probable relationship to study medication were reported (abdominal cramps, dizziness and nausea) in the cisapride group one adverse event (diarrhoea) was reported. None of these events was classified as serious. No clinically relevant changes in the laboratory or vital parameters were documented (Rösch et al., 2002).

Surveillances and analyses

In order to verify the clinical data, several analyses of pooled data were conducted. To assess STW 5 in daily practice, a postmarketing surveillance with 2267 patients in general practice, retrospective surveillances of the use of STW 5 in children with ages below 12 years and an epidemiologic cohort study comparing STW 5 and Metoclopramide in daily practice were conducted.

Postmarketing surveillance

Two thousand two hundred and sixty-seven patients with functional dyspepsia were enrolled into a postmarketing surveillance. Patients were assessed with the

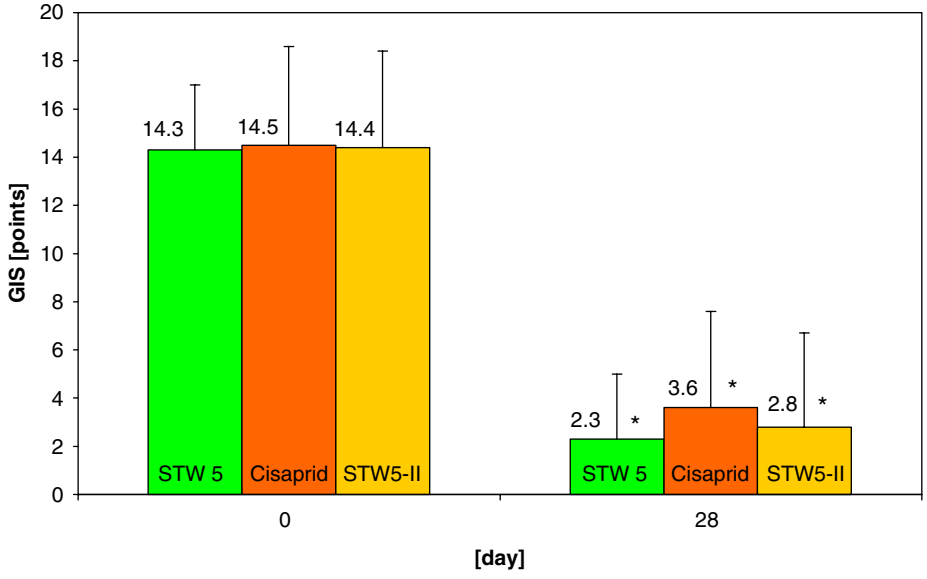

Fig. 4. Change of the gastrointestinal symptom score during 4 weeks of therapy with STW 5, Cisapride or STW 5 II (Rösch et al., 2002).

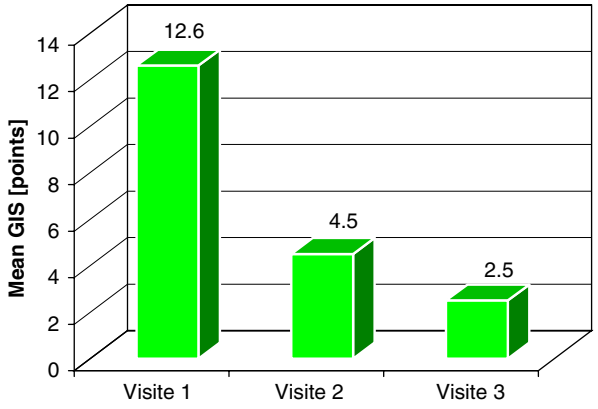

Fig. 5. Mean GIS for the patients during treatment with STW 5 at visit 1 (baseline) after 1 week (visit 2) and after 4 weeks (visit 3) of treatment.

GIS for symptom change during therapy after 2 weeks and if applicable after 4 weeks of therapy. An occurrence of adverse events as well as interactions with other medications was assessed.

There was a marked improvement of symptoms of the GIS. In all, 27% of the patients were symptom free after 1 week of therapy and did not need any further therapy (Fig. 5). Average improvement of summary score of symptoms was 78%. In all, 84% of the physicians assessed efficacy to be good or very good and 95% for tolerability. There was no adverse event or interaction with other medications reported (Sassin and Buchert, 2000).

Pharmacoepidemiologic Cohort study – STW 5 compared to Metoclopramide in daily practice

The retrospective surveillance comprised data of 961 patients with functional dyspepsia, who were administered STW 5 or mostly liquid Metoclopramide in the recommended dose.

The main outcome variable was the number of symptom-free patients after therapy. Secondary targets were duration of inability to work during therapy, assessment of tolerability and reported adverse events during therapy.

There were significantly more symptom free patients after therapy with STW 5 (71.6%) compared to Metoclopramide (62.8%), $p<0.05$ (Fig. 6). Duration of inability to work was significantly less with therapy with STW 5 (median 1 day) than with Metoclopramide (median 3 days) $p<0.001$. However, 90.0% of the physicians rated tolerability of STW 5 as very good compared to 70.6% for Metoclopramide. During therapy of STW 5 no adverse event was reported. During therapy with Metoclopramide in 5 patients adverse events mostly related to central nervous system (vertigo, dizziness) were reported (Hanisch et al., 2005).

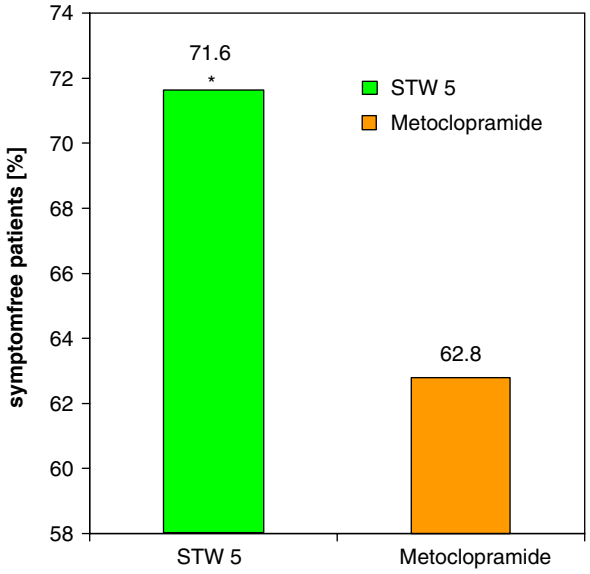

Fig. 6. Patients who were symptom free after treatment with STW 5 (Iberogast®) or Metoclopramide; $p<0.05$.

Retrospective Surveillances – treatment of children up to 12 years

During 2 retrospective surveillances data of more than 42,000 children aged up to 12 years were evaluated concerning efficacy, tolerability and dosage as well as interactions and adverse events.

Efficacy was assessed by the physicians to be very good or good by 96.8% and 87.5%, respectively. Tolerability was assessed as good and very good by the physicians for the total of 98% of the children. Children were administered STW 5 for most in the users instructions recommended dosage dependent on age. There were no adverse events documented with possible or probable causal relationship to study medication. There were no interactions reported [25].

Meta-analyses

Significant superiority for the treatment of functional dyspepsia: overall efficacy and efficacy in the most bothersome symptom

A number of independent controlled trials have shown clinical efficacy of STW 5 (Iberogast®).

However, to determine the overall therapeutic efficacy of STW 5 for the treatment of functional dyspepsia two metaanalyses were conducted. Gundermann et al. (2004a, b) analysed the pooled data of the controlled studies with STW 5 and the results confirmed a significant superior overall efficacy for all studies

Table 2. Number of adverse events assessed to be in possible or probable causal relationship to STW 5 for the clinical trials, retrospective evaluations and spontaneous reports during market launch

Clinical trial/surveillance (Indication)	Number of patients treated with STW 5	Number of adverse events assessed to be in possible or probable causal relationship to STW 5
4 controlled studies (*functional dyspepsia*)	320	10
12 open clinical trials, one postmarketing surveillance (*gastrointestinal diseases, functional dyspepsia*)	2554	10
2 retrospective surveillances with children up to 12 years (*functional gastrointestinal diseases, functional dyspepsia*)	42,003	–
1 retrospective cohort-study (*functional dyspepsia*)	490	–
Treated patients in Germany, adverse events (spontaneous reports) since market launch	>20,000,000	18

($p<0.0001$) vs. placebo for the treatment of patients with functional dyspepsia (Gundermann et al. (2004a, b)). The second metaanalysis focused on the therapeutic effect of STW 5 on the most bothersome symptom complex of the patients. In this analysis, Melzer et al. (2004) confirmed a significant superior efficacy of STW 5 vs. placebo for the improvement of the most bothersome symptom complexes (Melzer et al., 2004). Thus both analyses delivered a further evidence-based confirmation of the efficacy of the Phytopharmacon for the treatment of functional dyspepsia.

Tolerability and safety

Tolerability of STW 5 has been documented as being very good. In all placebo controlled studies tolerability of STW 5 was assessed as being "good" or "very good" in more than 80% of the patients and showed no difference compared to placebo. There were no relevant changes of laboratory and vital parameters documented in these studies during treatment with STW 5 and the documented adverse events gave no rationale for the assumption of systemic side effects or interactions, respectively for STW 5. The documentation of spontaneous reports since market launch further confirmed a very good tolerability and safety profile of STW 5 (Table 2).

Conclusions

Based on these data, it can be concluded that the herbal medicine STW 5 is an efficacious and safe therapy option to treat symptoms of functional dyspepsia. It is thereby noteworthy that the herbal medicine has demonstrated its efficacy very consistently in all studies, which was confirmed additionally with the results of two metaanalyses. Contrasting a trend towards trials enrolling several hundred of patients, it is noteworthy that the sample size per treatment arm usually did not exceed 200. Besides the statistical significance, this can serve as an argument towards the clinical relevance of the treatment effects.

Herbal medicines are obtained from various plants and contain complex extracts with a large number of different active substances. While there are only limited head-to-head comparisons with conventional chemically defined medications, the combination of extracts with various gastrointestinal active ingredients appears to be advantageous for a heterogenous condition such as functional dyspepsia. The clinically efficacy of this multicomponent herbal preparation questions the current trend of highly targeted designer drugs that usually target one single receptor population while it has not been shown that a single receptor group plays a pivotal role for the control of symptoms.

The herbal medicine STW 5 has been used for more than 40 years for the treatment of patients with gastrointestinal disorders. There is a general trend towards drug molecules designed to target a specific receptor. Head to head comparison of STW 5 (Iberogast®) with the most recent drug developments are lacking. However, it is noteworthy that all trials with reasonable sample sizes demonstrated a robust efficacy. In contrast, many new chemically defined developments have failed to yield consistent superiority and the gain over placebo was usually very small necessitating large sample sizes to yield statistical significance. The explanation might be that a disease such as functional dyspepsia with most likely a number of various mechanisms involved is more likely to respond to a multitarget treatment than to a single target treatment.

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