Herbal Preparation STW 5 for Functional Gastrointestinal Disorders: Clinical Experience in Everyday Practice

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Keywords

Irritable bowel syndrome · Functional dyspepsia · Heartburn · STW 5 · Safety

Abstract

Background: The most common functional gastrointestinal disorders (FGID) are functional dyspepsia (FD) and irritable bowel syndrome (IBS), with a prevalence in the general population of 15–20% (FD) and 10% (IBS), respectively. The complexity of pathophysiologic mechanisms and limitations in therapeutic options make the management of FD and IBS patients a challenge in routine clinical practice. **Summary:** Syndromes classified as FGID frequently overlap, and coexist with gastroesophageal reflux disease (GERD). Patients with overlapping symptoms are more likely to seek medical care. The challenge for routine clinical practice is to find the best approach for treatment of multiple symptoms. STW 5, a combination of 9 herbal extracts, was shown to have multi-target effects: it normalizes the disturbed gastrointestinal motility, alleviates hypersensitivity, inhibits inflammation, suppresses gastric hypersecretion, and modulates the microbiota. Controlled randomized studies proved STW 5 to be efficacious both in FD and IBS, with control over the full spectrum of upper and lower gastrointestinal symptoms. STW 5 reduced concomitant heartburn in FD patients. STW 5 was well

tolerated in the examined populations, independent of concomitant diseases and concomitant medication. **Key Messages:** The clinical use of the herbal preparation STW 5 in FD and IBS is evidence-based. STW 5 is an example for the concept of multi-target therapy. It offers treatment opportunities in routine clinical practice with high prevalence of overlap of FGID and concomitant GERD. Considering that FD and IBS are typically chronic and recurrent conditions, the clinically observed good tolerability and safety of STW 5 is an advantage.

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Introduction

Herbal preparation STW 5 (Iberogast) is relatively a new addition to clinical practice in Russia: it was approved as a treatment option for functional dyspepsia (FD) and irritable bowel syndrome (IBS) by the latest edition of the National Recommendations [1, 2]. STW 5 contains aqueous-ethanolic extracts of *Iberis amara* total fresh plant, *Angelicae radix*, *Cardui mariae fructus*, *Chelidonii herba*, *Liquiritiae radix*, *Matricariae flos*, *Melissae folium*, *Carvi fructus*, and *Menthae piperitae folium*. This combination has been in use for 5 decades in

Germany for the therapy of functional gastrointestinal disorders (FGID) [3–6]. It is the only herbal preparation that was included in the guidelines of the Russian Gastroenterological Association for the treatment of FD and IBS. The approval process was based on an assessment of plant harvesting procedures in accordance with the standards of good agricultural and collection practice and quality assurance in accordance with good manufacturing practice [3].

Pharmacology of STW 5: Multi-Target Effects

Unlike traditional pharmacological agents that usually address one symptom, STW 5 is a multi-target medication that provides promising opportunities for FGID management. STW 5 normalizes gastrointestinal motility, alleviates hypersensitivity, inhibits inflammation, suppresses gastric over-secretion, and modulates the microbiota [4, 6]. The contribution of each individual component of STW 5 was demonstrated in pharmacological models in vitro and in vivo. These experiments also showed synergistic and multiple effects of the single extracts. For example, the components of STW 5 were shown in vitro to act via important target sites of the gastrointestinal tract including 5-HT₃, 5-HT₄, muscarinic M₃, and opioid receptors [6]. From the pharmacological findings and clinical observations, it was concluded that STW 5 could be useful in the therapy of the most common types of FGID, especially FD and IBS [3, 4, 7–9]. According to the pharmacological findings, STW 5 may provide an opportunity for the practical management of overlapping and concomitant types of FGID – an assumption confirmed in the clinical trials (see below).

STW 5 led to a significant dose-dependent reduction of the ulcerative area in the esophagus, it prevented the occurrence of ulcer perforations, normalized elevated levels of myeloperoxidase activity, tumor necrosis factor- α , and interleukin-1 β in the esophageal tissue in an experimental model of acid reflux. STW 5 has been shown to decrease acid secretion, thus potentially reducing the exposure of esophageal mucosa to acid [3, 4, 6, 10].

Prevalence of FD and IBS

FGID are common. FD affects 15–20% of the global population worldwide, and IBS occurs in 10% of the general population [11–13]. The prevalence of gastrointestinal symptoms has been evaluated in epidemio-

logical studies with different age groups and ethnic populations within the Russian Federation. The prevalence of uninvestigated dyspepsia was 21% in adolescents, 26% in the age group of 25–64 years, 38% in the age group of 45–69 years, and 30% in Asian populations of Siberia (45–69 years) [14–16]. After examination, including esophagogastroduodenoscopy, there is no obvious structural cause for the digestive symptoms in more than 75% of dyspeptic patients. These patients are diagnosed as having FD, based on current consensus. The prevalence of IBS symptoms was estimated in Russia as 19% in the adult population with 2:1 female predominance [14–16]. The prevalence figures of gastrointestinal symptoms in Russia follow the same tendency towards high patient numbers as worldwide.

Helicobacter pylori Eradication

An important epidemiological consideration of dyspepsia management in Russia is the prevalence of *Helicobacter pylori* infection: 56% of adolescents and 80–92% of adults are infected [14–16]. The high level of *H. pylori* infection makes an eradication therapy an everyday practical choice. Eradication treatment should best serve the subset of *H. pylori*-associated dyspepsia, and counts as an active strategy for gastric cancer prevention [1, 17, 18]. However, dyspepsia symptom resolution after *H. pylori* eradication cannot be predicted. The number needed to treat (NNT) to cure one case of dyspepsia is 14 (95% CI 10–25) [19].

H. pylori eradication for infected dyspeptic patients is the most complicated approach in primary healthcare compared with alternative medical therapies. *H. pylori* “test and treat” is recommended more by guidelines and consensus papers than fulfilled by general practitioners. It is reasonable to indicate both FD and chronic gastritis (*H. pylori*-positive or post-eradication) in the individual diagnosis. Treatment of chronic gastritis involves eradication of *H. pylori* infection and leads to relief of dyspepsia in a minority of patients. Independent approaches for FD management are therefore needed.

Overlapping Syndromes

Another challenge in FD and IBS management is the complexity of the syndromes. The underlying pathophysiologic mechanisms are multi-factorial, variable,

and not fully understood. They include motor and sensory dysfunction, impaired mucosal integrity, dysregulation of the gut brain axis, and changes to the microbiota [1, 2, 17, 20]. A considerable degree of overlap exists for FGID and its clinical subgroups. Patients with FGID often report other physical comorbidities. The Rome IV criteria for FD states that other individual digestive symptoms or groups of symptoms, for example, from gastroesophageal reflux disease (GERD) and IBS may co-exist with postprandial distress syndrome and epigastric pain syndrome [17]. Specifically, there is a marked overlap for various bowel disorders (IBS, functional constipation, functional diarrhea, functional abdominal bloating/distension). These symptoms should rather be considered parts of a continuum rather than isolated syndromes [20].

The chances to encounter patients with a clearly identifiable gastrointestinal disorder with just one or 2 independent symptoms are slim in everyday practice. In a large US survey study ($n = 10,030$), 26.3% of the participants met the criteria for one of the diagnoses: FD, constipation-predominant IBS-C, chronic idiopathic constipation, and GERD. About 60.3% had one condition; 31.5% had 2, and 8.2% had 3 overlapping diseases. The most common was the combination of FD with GERD (16%). The combination of both IBS-C and chronic idiopathic constipation with FD gave 12%. Overall gastrointestinal symptoms were very/extremely bothersome in 28.6% of single-condition respondents, 50.7% of 2-condition, and 69.6% of 3-condition respondents. Symptom frequency and productivity losses both increased with condition overlap. The percentage of patients who sought physician's care for gastrointestinal symptoms in the past 12 months was significantly higher in patients with symptom overlap [21].

In an epidemiological study of the prevalence of gastrointestinal symptoms in Novosibirsk, one quarter of patients had multiple symptoms – the most common combination was dyspepsia and reflux symptoms (9.9%). Both dyspepsia and bowel symptoms were found in 6.3% of the population [16]. In another study performed in Moscow, the patients that met Rome III criteria for FD and IBS in primary care settings were examined by a gastroenterologist to exclude organic and metabolic diseases. Among 383 patients with a verified diagnosis of FGID, there were 34% with FD, 15% with IBS, and 51% with both syndromes [22]. The challenge for routine clinical practice is therefore to find the best treatment approach for patients with multiple symptoms.

Drug Therapy for FD and IBS

The current drug treatment strategy for FD and IBS is oriented at symptom type and severity. Multiple drug classes have been studied to treat FGID, but therapeutic options remain limited, as they provide in most cases only symptomatic benefit and/or only temporary symptomatic relief [4, 8, 9]. The choice of a suitable pharmacotherapy is therefore very difficult in primary care. General practitioners in the Moscow study prescribed 12 groups of different medications to FD and IBS patients ($n = 502$): drugs for acid suppression (31.9%), probiotics (30.3%), antispasmodics with different mechanisms of action including the peripheral opioid receptor antagonist trimebutine (88.8%), pancreatin (21.1%), laxatives (20.7%), antibiotics (not for *H. pylori* eradication; 19.5%), antacids (17.6%), antibiotics (for *H. pylori* eradication; 2.2%), prokinetic drugs (1.5%), antidiarrheal drugs (1.2%), and antidepressants (0.9%) [22].

Treatment satisfaction after exposure to drugs was studied in a group of Asian patients with functional bowel disorders ($n = 1,367$). About 75.8% received 2 or more drugs. Proton pump inhibitors were recorded in 57% of patients with an overlap of bowel disorders with epigastric pain and heartburn, 46.1% were not satisfied with their treatment, judging it ineffective in most cases [23]. FD and IBS patients frequently have experience with different medications in their medical history. Often this experience is negative, with dissatisfaction with respect to treatment results or to adverse reactions. Concurrent prescription of different types of medications for patients with simultaneous upper and lower gastrointestinal tract symptoms may lead to unpredictable results.

Efficacy Studies with STW 5

Five controlled randomized studies with STW 5 demonstrated its efficacy and safety in FD, where STW 5 was superior to placebo and equivalent or even superior to cisapride [24–28]. STW 5 was significantly better than placebo in reducing the total abdominal pain score and the IBS symptom score in a randomized controlled trial in IBS [29]. The studies in FD have also been included in meta-analyses [7–9]. The level of evidence for STW 5 in FD was considered as 1a, for STW 5 in IBS as 1b with a level “A” recommendation (Oxford Centre for Evidence-based Medicine).

The therapeutic efficacy of STW 5 in FD was demonstrated by change of the gastrointestinal symptom (GIS)

score, a validated questionnaire with 10 items on specific dyspeptic symptoms (abdominal cramps, epigastric/upper abdominal pain, early satiety, fullness, loss of appetite, vomiting, sickness, nausea, retrosternal pain, acid eructation/ heartburn). Each symptom was graded on a 5-point Likert scale, ranging from 0 (no problem) to 4 (very severe problem, markedly influencing daily activities or requiring rest) [24–28]. Changes in total abdominal pain and IBS symptom scores were measured for the assessment of STW 5 efficacy in the treatment of IBS [29]. A detailed examination of the effect against the various score items confirmed a multi-faceted effect of STW 5.

The effect of STW 5 on concomitant reflux symptoms of patients with FD was assessed in an explorative analysis of placebo-controlled trials. The primary outcome measure of the studies was the improvement of a validated GIS score consisting of 10 typical symptoms, including heartburn and acid regurgitation (not dominating the clinical picture). A total of 413 patients (mean age 48 years; female 61%) were included in the analysis. Moderate reflux symptoms (heartburn and acid regurgitation) were reported by 32.7% of all patients. The mean of the reflux symptoms score was 1.82 in both groups (active treatment and placebo) at baseline. After 4 weeks of treatment, there was a significant decrease of the GIS ($p < 0.0001$; NNT = 9) and of the reflux symptom score in the active treatment group compared to the placebo group (mean decrease: 1.06 vs. 0.70; $p = 0.0004$; NNT = 9) [30].

Own Clinical Examinations with STW 5

Symptom questionnaires are widely applied in clinical studies on FGID. We had positive experience with this instrument in our practical work. The Gastrointestinal Symptom Rating Scale (GSRS) questionnaire is very useful in routine clinical practice for a systematic evaluation of current gastrointestinal symptoms and their response to STW 5. This questionnaire has been translated into Russian and passed the validation procedure. The questionnaire measures 5 sub-dimensions of gastrointestinal symptoms: abdominal pain, reflux, diarrhea, constipation, and abdominal distension, eructation, flatulence. It comprises 15 separate items. The scoring is based on a 7-point Likert scale, where 1 point corresponds to minimal gastrointestinal symptoms, and 7 points to the most severe symptoms. The GSRS questionnaire covers the symptoms of the upper and lower gastrointestinal tracts. It can be used in patients with a combination of FD, IBS, and GERD.

We prescribed STW 5 for a 4-week treatment of outpatients: patients filled the questionnaire on inclusion, at days 14 and 28. In most cases, the GSRS total score and targeted sub-dimension scores decreased. The objective changes in the GSRS score reflect the clinical treatment results with STW 5 treatment, which helps reassuring the patients in a positive prognosis and the effectiveness of therapy.

The most interesting observation for us was the relief of reflux symptoms in patients with concomitant GERD through treatment with either STW 5 alone or in combination with proton pump inhibitors maintenance therapy. The clinical effect of STW 5 on heartburn and acid eructation could be based on multiple mechanisms. Enhancing the muscle tone of the lower esophageal sphincter can prevent gastroesophageal reflux. STW 5 evoked a relaxation of the proximal stomach, but increased antral motility. Both effects are myogenic. This allows better adaptation for the volume of ingested food, thus reducing the intragastric pressure. At the same time, the prokinetic effect on gastric antrum improves the gastric evacuation. It could be shown that this effect sets in within 10 minutes after oral intake of STW 5.

Safety of STW 5

Safety and tolerability are important factors for FGID patients than symptom resolution. In the clinical trials on STW 5, no serious adverse events were reported, and no relevant deviations from routine biochemical values were observed [24–29]. In a study comparing STW 5 with the 5HT-4 receptor agonist cisapride, the evaluation of tolerability by investigator and patient showed a good tolerability of both investigated treatments. The investigators rated the tolerability of STW 5 as “very good” or “good” in 96.7% of patients, versus 90.5% of patients exposed to cisapride. About 93.5% of the patients in the STW 5 group assessed tolerability as “good” or “excellent,” whereas in the cisapride group this rating was indicated by 81.0% of patients (differences not significant) [28].

The prescription of prokinetics frequently causes safety concerns in routine clinical practice. Cisapride was withdrawn from the market approximately 10 years after its introduction because of cases of severe arrhythmias. Some years ago, the use of metoclopramide and domperidone was restricted for safety reasons. In contrast, the experience with STW 5 goes back more than 5 decades, with documented safety data in large populations. Adverse central nervous or cardiac events, as occasionally report-

ed for prokinetics, have not been found with STW 5. Hypersensitivity reactions (e.g., exanthema, pruritus or dyspnea) were extremely rare [10]. STW 5 was well tolerated in the examined study populations, independent of concomitant diseases. No herb-drug interactions were observed [6–9, 30].

Conclusions

The efficacy of the herbal preparation STW 5 in FD and IBS is evidence-based. STW 5 gives new treatment opportunities in routine clinical practice with a high

prevalence of overlap of FGID and concomitant GERD. Symptoms of FGID and GERD usually require long-term treatment, where safety issues are frequently a reason for abandoning a treatment approach. The observed good tolerability of STW 5 is of particular importance when the chronic and recurring nature of the disease is taken into account.

Disclosure Statement

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