

Beilage für Gastroenterologen

GI-TELEX



Functional Gastrointestinal Diseases – Effective Treatment Using Multi-Target Therapy

Symposium on “Functional GI Disease: Solving the Therapeutic Dilemma”,
held as part of the “European Bridging Meeting in Gastroenterology”,
on 18th November 2010 in Berlin

Chairman: Prof. Dr. Peter Malfertheiner, Magdeburg

Umbruchkopie: Die Weitergabe an Dritte ist nicht erlaubt!

Solving the therapeutic dilemma

The therapeutic dilemma posed by functional gastrointestinal diseases derives from the fact of their pathophysiological multicausality. Both irritable bowel syndrome (IBS) and functional dyspepsia (FD) stem from several dysfunctions. This is why a monocausal treatment approach holds out little prospect of success. Instead, there is a need for treatment which addresses the key causes of impaired digestion, i.e. multi-target therapy. A growing understanding of the pathophysiological causes has already led to promising trials with chemically defined medications. However, there is only a phytotherapeutical remedy which so far in any way fulfils the description of a multi-target therapy, the Iberis amara combination preparation STW 5 (Iberogast®). In Germany, this is the only preparation authorised for the treatment of both FD and IBS patients.

Functional gastroenterological diseases have plagued humanity since time immemorial. Prof. Dr. Hans-Dieter Allescher, Garmisch-Partenkirchen, has traced the first historically specific reference to the symptoms back to Ancient Rome, in a description by Aulus Cornelius Celsus (25 BC to 50 AD). We have to wait until the late Middle Ages for the re-appearance of this description in the Christian west – by Paracelsus (1493 – 1541). It is to be found in Book 2: “On ailments caused by the stone”.

Varied pathogenesis

In the course of time, this still very cursory pathophysiological attribution has been expanded considerably. A distinction is now made between FD and IBS by referring to the clinical profile of the diseases. Under the ROME III Criteria, the definition of FD is now broken down into segments: postprandial disorders (e.g. abdominal fullness, stomach cramps, early satiety) and reflux disorders including heart burn.

Pathogenesis of FD

Over the past 50 years, more and more pathophysiological explanations for FD have been posited. These have ranged from mental predisposition to the effect of acid, medications and infections and ultimately to genetic susceptibility. The group headed by Prof. Michael Camilleri, Rochester/USA, has made a significant contribution to this field [1].

The modern approach is to group the pathological control variables “psychosocial irritations”, “changed motility” (stomach evacuation and accommodation) and “disordered sensibility” around FD. These may be enhanced by such factors as stress, genetic disposition and the impact of gastroenteritis in the patient’s history as well as by changes in the duodenum’s sensitivity to fats or acids. Infection with *Helicobacter pylori* as a pathogenetic factor is also addressed (Fig. 1). Overall, Prof. Allescher cites 5 causes of FD as proven: inadequate ability of the stomach to

adapt to ingested food, delayed stomach evacuation, hypersensitivity to expansion of the stomach wall, abnormal duodenojejunal motility and changes in sensitivity to fats and acids. These five causes are further modified by psychosocial factors, *H. pylori* status and acute gastrointestinal infections.

The pathogenetic role of the duodenum in the genesis of FD disorders has been substantiated only recently. As the work of Lee and Tack [2] summarises, functional disorders of the duodenum have a direct bearing on the stomach’s ability to digest. A crucial factor here seems to be the sensitivity of the duodenum to acids and fats.

Pathogenesis of IBS

The two functional gastroenterological disorders known as FD and IBS form a clinical continuum. This is the view reached, for example, by Ford and colleagues from the Löwen working team after their survey of the literature [3]. Accordingly, the risk of an FD patient contracting IBS as well is increased by a factor of eight. Depending on the particular study, the overlap ranges between 15 and 42%.

In the course of time, more and more pathogenetic factors have been identified as additional causes of IBS. During the past 50 years alone, there have been ten models that have been positively identified with greater or less success. Also, other models have been added and some deleted. As Prof. Allescher explained, the focus has shifted with the passage of the years. Motility disorders in the gut used to be regarded as the essential cause of IBS, but now disorders of the enteric nervous system are seen as the key factor. This system regulates functions in the digestive tract. The sensory nervous system could also be behind the visceral hypersensitivity that is often observed in IBS patients. It is clear that serotonin has a major part to play here. This is indicated by the fact that in the presence of the mast cell stabiliser ketotifen, which suppresses serotonin secretion, the symptoms of IBS patients improve significantly [4]. Overall, Prof. Allescher cites seven causes of functional gastrointestinal disorders as proven:

- motility disorders
- visceral hypersensitivity

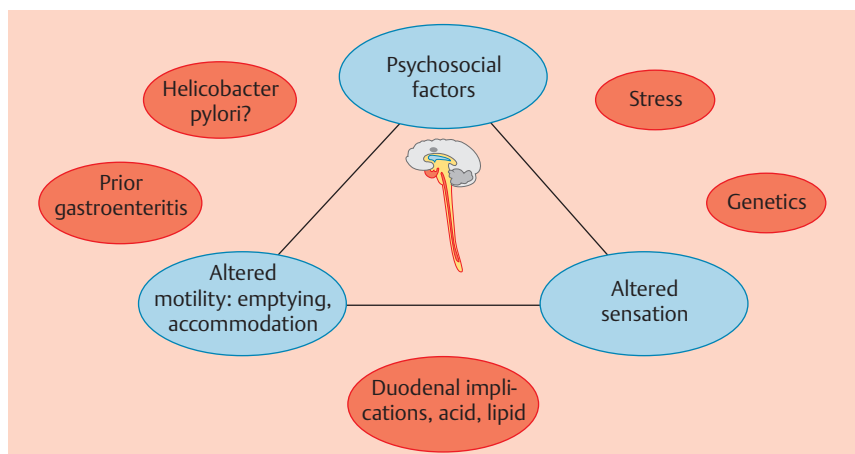


Fig. 1 Pathophysiology and mechanisms as causes of FD (Source: Allescher H-D, 2010, modified after [1]).

- psychosocial factors
- infections, inflammations or irritations of the mucous membrane
- genetic factors
- mast cell hyperactivity
- changes to bacterial flora and the influence of luminal antigens

The modern approach is to group the pathological control variables “psychosocial factors”, “changed motility” and “changed sensibility” together as the pathological triumvirate behind IBS. Linked to these main factors are other pathomechanisms, such as genetic predispositions, infections and inflammations, neurotransmitters, gas retention and dysfunctions of the pelvic floor (Fig. 2).

Some clinical studies reveal a considerable degree of overlap between these factors. For example, Prof. Camillieri’s working team working with IBS patients found that the symptoms “abnormal intestinal transit” and “increased rectal sensitivity” overlapped [5]. So it is with the genesis of IBS after gastroenteritis, which is associated with gene mutations more often than can be simply coincidental. The genes concerned are those which code for the epithelial barrier function and immune response to bacteria [6]. For their part, the team of Prof. Dr. Michael Schemann, Munich, was able to show that enteric nerve cells are stimulated by the residue after incubation of colonic biopsy material sourced from IBS patients [7].

Pathogenetically based classification

Hitherto, the practice has been to classify functional gastroenterological diseases in terms of their symptoms (roughly in terms of the Rome II/III Criteria) (Fig. 3). However, it is now recognised that all subclasses of these diseases involve different pathological mechanisms which may well be the causes of the disorders, according to Prof. Allescher. This line of thought enables the grouping of functional gastroenterological diseases in terms of their predominant pathomechanisms. The following would be important features of a grouping system based on pathogenesis: the underlying disorder and the genetic or molecular changes (immunity, hyperalgesia, permeability etc.)

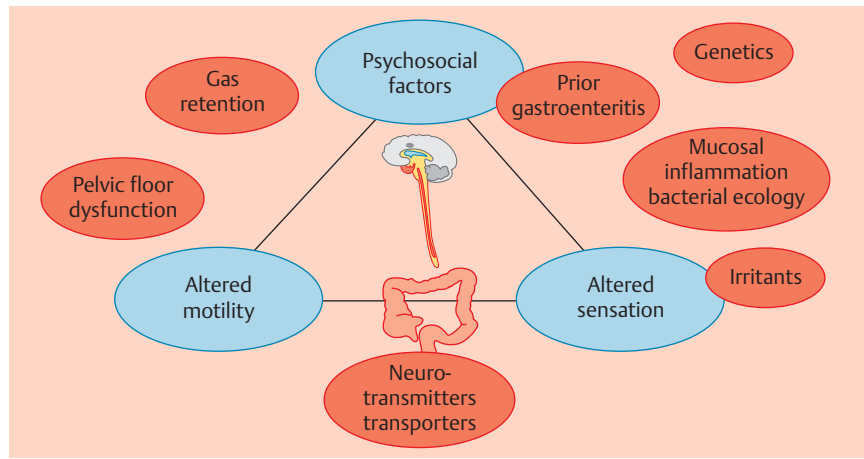


Fig. 2 Pathophysiology and mechanisms as causes of IBS (Source: modified after [1]).

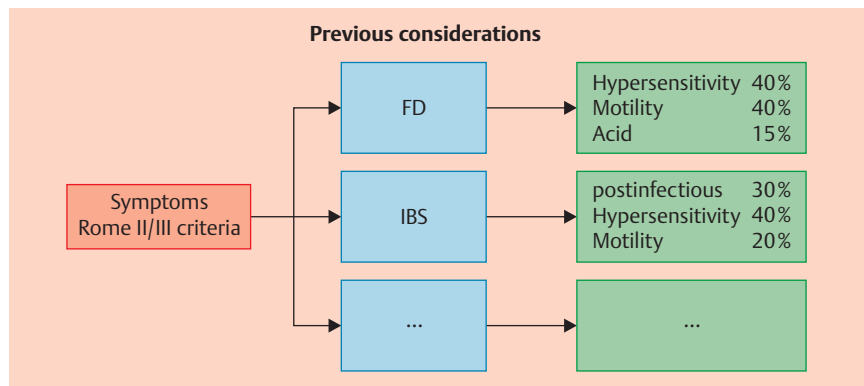


Fig. 3 Classification of functional gastroenterological diseases in terms of their predominant symptoms (Source: modified after Allescher H-D, 2010).

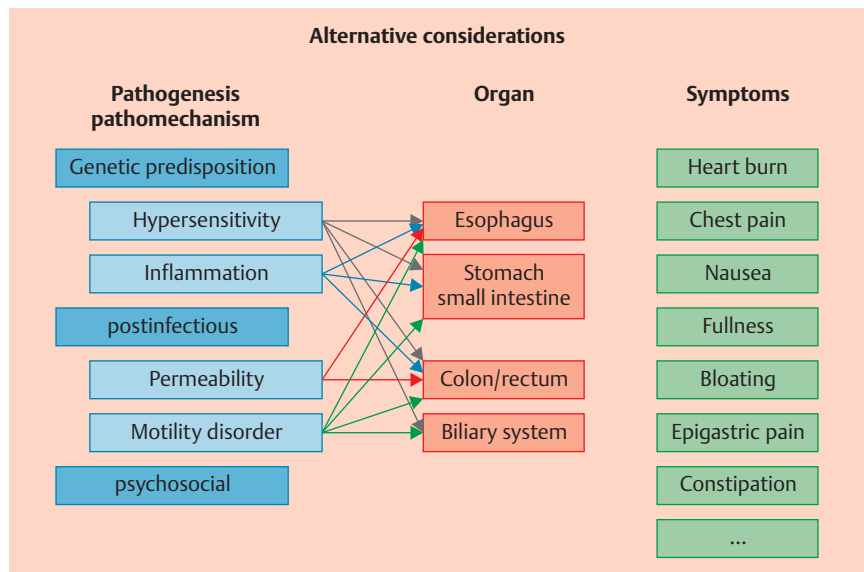


Fig. 4 Classification of functional gastroenterological diseases in terms of their predominant pathomechanisms (Source: modified after Allescher H-D, 2010).

As Fig. 4 shows, this type of classification enables the organic disorder to be deduced from the pathogenesis. Ultimately, the symptoms can be understood in the context of the organic disorders.

This way of grouping – no longer in terms of the predominant symptoms but of pathogenesis – can inform the approach to researching therapeutic alternatives with a view ultimately to deter-

mining an appropriate treatment regime. However, according to Prof. Allescher, this should obviously deal a death blow to the view that medication could affect the disease profile in the longterm by acting on just one pathomechanism.

Still no single fully effective treatment

Pharmacotherapy is faced with the dilemma that all therapies that address causes can only act on a certain spectrum of the disease profile, which often results in only inadequate, partial improvement in the symptoms. Dr. Tim Vanuytsel, Löwen/Belgium, has also commented that this inadequate improvement often comes at the price of side effects so severe that many, initially promising medications are no longer available.

Proton pump inhibitors (PPI) only partially effective

The failure of monotherapeutic approaches in the treatment of the whole FD disorder spectrum is particularly obvious in treatment approaches which depend solely on the inhibition or blockade of gastric acid. This was shown in the meta-analysis of the controlled studies with PPI conducted by Moayyedi and colleagues [8]. In patients with postprandial distress syndrome (PDS), disease activity even increased slightly (risk rate 1.02). In patients suffering only from heartburn or reflux (epigastric pain syndrome, EPS), the reflux disorders improved (risk rate 0.76) as did to a lesser degree discomfort through heartburn (risk rate 0.85). This shows that full treatment for FD patients with PPI was not possible. In patients primarily affected by dysfunctional motility, PPI proved to be no more effective than placebo.

Slight effect after *H. pylori* eradication

Following the discovery that ulcers can be caused by infection with *H. pylori*, there was research into whether colonisation of the gastric membrane by this bacterium also impacted negatively on the stomach's digestive functions and, in reverse, whether or not eradicating *H. pylori* might improve FD symptoms. And yet, even here, we must recognise that a monotherapeutic approach in an

illness as complex as FD is not very effective. As Dr. Vanuytsel has shown, analysis of studies on the efficacy of *H. pylori* eradication in FD patients reveals that the effect is zero. His own meta-analysis did show a minor degree of symptom improvement with an odds ratio (OR) of 0.92 and a "number needed to treat" of 14–16 and yet this minimal treatment success did not appear until several months had passed [9].

Prokinetics provide a heterogeneous picture

If acid blockade cannot improve FD symptoms across the board, it would be worth considering whether or not eradicating the dysfunctional motility would be a more significant pathomechanism for achieving the desired treatment outcome. But, as Dr. Vanuytsel has explained, even this treatment approach has so far not led to a convincing treatment breakthrough. Instead, relevant study data reveals a very varied picture, as is corroborated by the meta-analysis conducted by Moayyedi and colleagues [10]. All studies investigating prokinetics produce a risk rate of 0.52, though Moayyedi speaks frankly of the likelihood of bias in the publications: the evaluated studies with a larger number of patients generally produced no evidence of any positive therapeutic effect.

Vanuytsel further states that the situation is complicated by the inadequate number of available prokinetics. Some substances tested in the studies can no longer be used today, generally because of adverse side effects. Also, the prokinetics investigated (cisapride and other 5-HT₄ receptor agonists, metoclopramide and domperidone) are a heterogeneous group of substances. Each of them obviously promotes stomach evacuation by acting on different effectors. That would further complicate systematic assessment.

Search for the ideal treatment

PPI only help some patients and the eradication of *H. pylori* is only minimally effective making it difficult to assess the available prokinetics, so there remain only two treatment approaches in the search for the ideal treatment. You either have to find new, better prokinetics or pursue completely different treat-

ment options. At the present time, a range of other prokinetics is being developed. Examples are D₂ receptor agonists (itopride), another 5-HT₄ receptor agonist (tegaserod), motilin agonists (erythromycin, ABT-229, motilin) and botulinum toxin and others. Some of them deliver good treatment outcomes, according to Vanuytsel. Yet it is doubtful whether or not the conventional prokinetic-based approach intended to accelerate stomach evacuation is delivering the breakthrough. Ultimately, evacuation of the bolus is only one of the stages in digestion in the stomach. Any search for efficient medication will need to produce a solution that not only promotes stomach evacuation but also improves stomach accommodation and normalises visceral sensitivity.

Targeting accommodation

Stomach accommodation is controlled centrally via excitatory and inhibitory vagal neural pathways. As Fig. 5 shows, this control offers several different avenues of approach which are also used in the development of medications. For example, studies have investigated 5-HT_{1A} receptor agonists and muscarine auto-receptor blockers (anticholinergic agents), whose fundus relaxing effect has been researched experimentally. 5-HT_{1A} receptor agonists are also used as anxiolytic agents or anti-depressants.

According to Vanuytsel, there have been clinical studies on FD patients with buspirone, R-137696 and tandospirone. Some yielded evidence of a clinical effect. However, because of the unfavourable risk/benefit profile of this substance class, no 5-HT_{1A} receptor agonist has yet been authorised for the treatment of FD. The same is true of the anticholinergic agent acotiamide.

Likewise because of side effects, i.e. an increased tendency to suicide, the relatively good clinical results obtained with venlafaxine, a 5-HT₃ receptor agonist, have not been pursued further. Finally, with asimadoline, a κ-opioid agonist, the clinical effect in studies with a relatively high number of patients disappeared. After these failures in the development of effective medications for the elimination of accommodation dysfunction in FD, Vanuytsel sees multi-target therapy as the only possible approach

for an across-the-board treatment of FD, as is possible with the Iberis amara combination STW-5.

Postulates for improved research

For pharmacological research, the fact that practically all attempts with chemically defined medications for FD have failed is a particularly unsatisfactory outcome. Vanuytsel quotes the following as reasons for this failure: the heterogeneous patient population, multiple therapy targets and the conflicting pharmacological effects of the investigational substances. Progress might be achieved if patient selection was improved, if comorbidities were taken into account better, if co-medication with PPI was regarded as a disturbance variable, if clear end points were selected and if regulatory obstacles were dismantled.

The solution is a multi-target concept

During the decades of intensive searching for a chemically defined medication for an across-the-board treatment for FD and IBS, the question has been raised of why – of all things – a phytotherapeutical remedy should be successful. Prof. Michael Schemann has responded to this by setting out the mechanism of effect of the successful Iberis amara combination STW 5.

The meaning of “multi-target”

Right at the beginning of his presentation, Prof. Schemann defines the term “multi-target” with regard to this phytotherapeutical remedy as the use of a plant-origin combination containing components with different actions to treat a multicausal gastrointestinal disease. In other words, “multi-target” is to be understood as involving action on different effectors, which produces a variety of effects. The question is whether the experimental evidence for the Iberis amara combination STW 5 confirms this approach.

During his presentation, Prof. Schemann concentrated on the four most important targets which play a crucial role for patients with FD and also those with IBS, i.e. gastro-oesophageal motility, visceral sensitivity, inflammatory processes and intestinal motility and secretion.

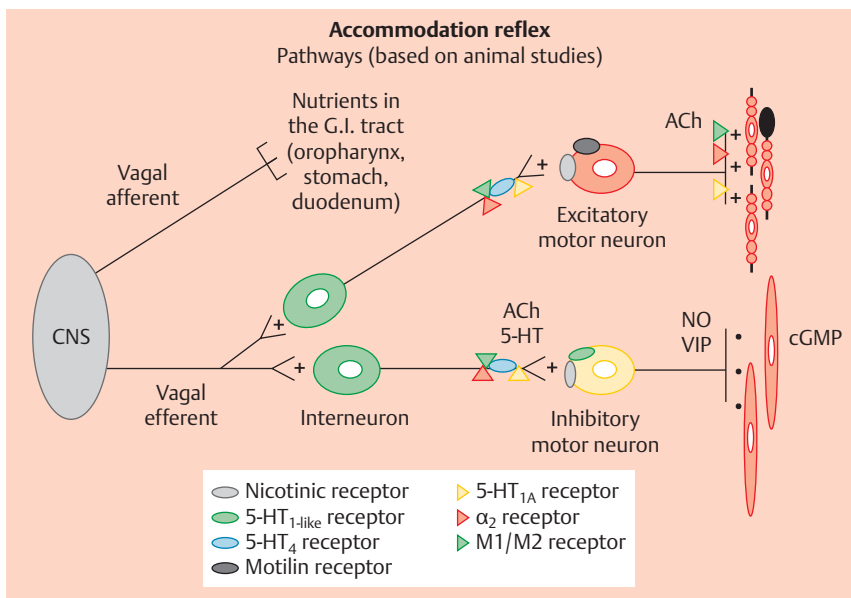


Fig. 5 Control of gastric accommodation reflex (Source: modified after Vanuytsel T und Tack J, 2010).

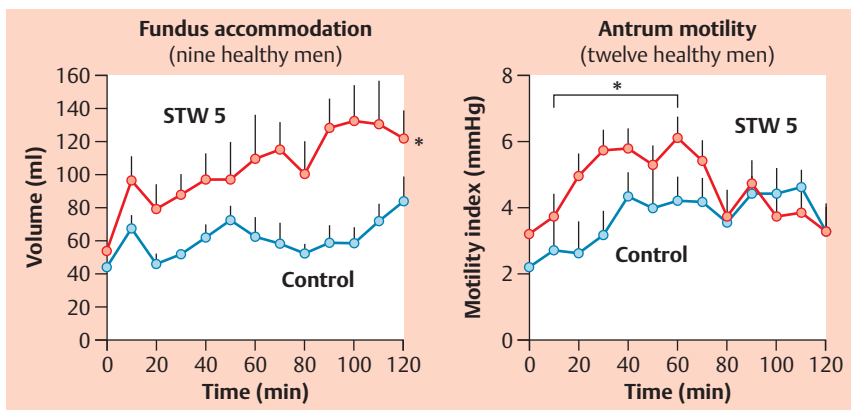


Fig. 6 Modulation of gastric motility by STW 5 (Source: modified after [12]).

Improving gastro-oesophageal motility

As the ex vivo experiments with human material presented by Prof. Schemann show, the phytotherapeutical remedy STW 5 can, at the gastro-oesophageal level and depending on dosage, induce fundus relaxation and the required level of antrum musculature activation [11]. These experimental findings with tissue strips from the relevant areas of the stomach have also been confirmed in clinical experiments on healthy subjects (Fig. 6) [12]. The varied effect of STW 5 is obviously attributable to the fact that this combined phytotherapeutical remedy contains active ingredients which induce relaxation by inhibiting the calcium flow in fundus muscle cells where-

as in antrum muscle cells activation of the L type calcium channels promotes contractility. Schemann commented that this already indicates that this phytotherapeutical remedy has a multi-target effect in the stomach. In this way, STW 5 is capable of eliminating the two key dysfunctions involved in FD, i.e. inadequate stomach accommodation in the fundus and inadequate antral stomach pump function.

Schemann was also able to show in animal experiments that STW 5 produced increased tone of the lower oesophageal sphincter, obviously by forcing the calcium flow into the muscle cells [13]. This can in itself bring about improvement, especially to the reflux and heartburn symptoms of FD patients.

Normalisation of visceral sensitivity

The majority of symptoms in functional gastrointestinal diseases are attributable to visceral hypersensitivity. Because visceral innervation is complex, it is difficult to demonstrate experimentally the pharmacological effect of medications in this area. This did however prove possible in an animal experiment, as Schemann explained. So, in the rat model, it was possible to show that STW 5 can diminish the activation response of sensory visceral nerves to mechanical, chemical and inflammatory stimuli [14,15]. Here, too, therefore, there are indications that the clinically observed efficacy of STW 5 in patients with visceral hypersensitivity is attributable to distinct mechanisms within the context of multi-target therapy.

Anti-inflammatory effect

Inflammatory processes have long been held to be responsible for the symptoms of functional gastroenterological diseases. As regards the stomach, *H. pylori* is now known to be an important promoter of such inflammations. It is also known that when the stomach membrane is under attack it reacts particularly sensitively to acidic irritants. As

evidence of the efficacy of STW 5 on this target, Prof. Schemann cited the work of Khayyal MT et al. [16]. The studies showed that STW 5 exerts an anti-ulcerogenic and anti-inflammatory effect in the rat model.

- The **anti-ulcerogenic effect** is the consequence of reduced gastric acid formation, increased mucin secretion and delivery of the anti-inflammatory prostaglandin PGE₂ plus inhibition of inflammation-inducing leukotrienes. Here, STW 5 proved to be 50% as efficacious as the H₂ antagonist cimetidine.
- The **anti-inflammatory effect** was also detectable in the gut. Here, the team of Khayyal used the TNBS model (experimental colitis) in rats. Although the action of 5 mg/kg body weight of the phytotherapeutical remedy was shown to be prophylactic, it was still less than 300 mg/kg body weight of sulfasalazine. On the other hand, a curative application of STW 5 was almost equivalent in action to the same doses of sulfasalazine. In each case, the measured value was the rise in protective glutathione, the reduction in myeloperoxidase activity and normalisation of the inflammation mediators TNF α , IL-1 β and ICAM-1.

Intestinal motility and secretion

Finally, the action of STW 5 is also directed against mechanisms which perpetuate the often distressing symptoms of IBS patients. In this connection, Prof. Schemann referred to an experimental human study of Krüger DI et al. [17], which showed the extent to which STW 5 can normalise secretion in the intestines. Also an unpublished result in a human study points in the same direction. Accordingly, STW 5 is able to a highly significant degree to diminish colon spasms induced by carbachol [13].

Broad experimental base

Thus it can be seen that the combination of nine plant extracts (Fig. 7), continues to stand up, even against today's experimental human biology. According to Prof. Schemann, the therapeutically relevant key effects that can be confirmed experimentally are:

- desensitisation of the visceral afferent nerves
- modulation of muscle activity – spasmolytically in the stomach fundus and colon, prokinetically at the lower oesophageal sphincter and in the stomach antrum
- activation of enteric neurones
- modulation of the cytokine profile as regards anti-inflammatory activity
- modulation of secretion: in the colon, increased secretion of Cl⁻ ions, in the stomach reduced secretion of H⁺ ions

Repeated attempts have been made to ascribe these multi-target effects to only one or a few plant extracts of STW 5 – with little success, as Prof. Schemann explained. As Fig. 8 shows, it is only possible to assign a particular intensity of the observed and proven effects to each of the individual components.

Clinical evidence favours phytotherapy

STW 5 delivers an evidence-based remedy for the treatment of FD and IBS in conformity with national and international guidelines. Priv. Doz. Ahmed Madisch, Hannover, has emphasised this, citing

- five placebo-controlled studies on a total of 897 FD patients
- two meta-analyses on the efficacy of STW 5 in FD

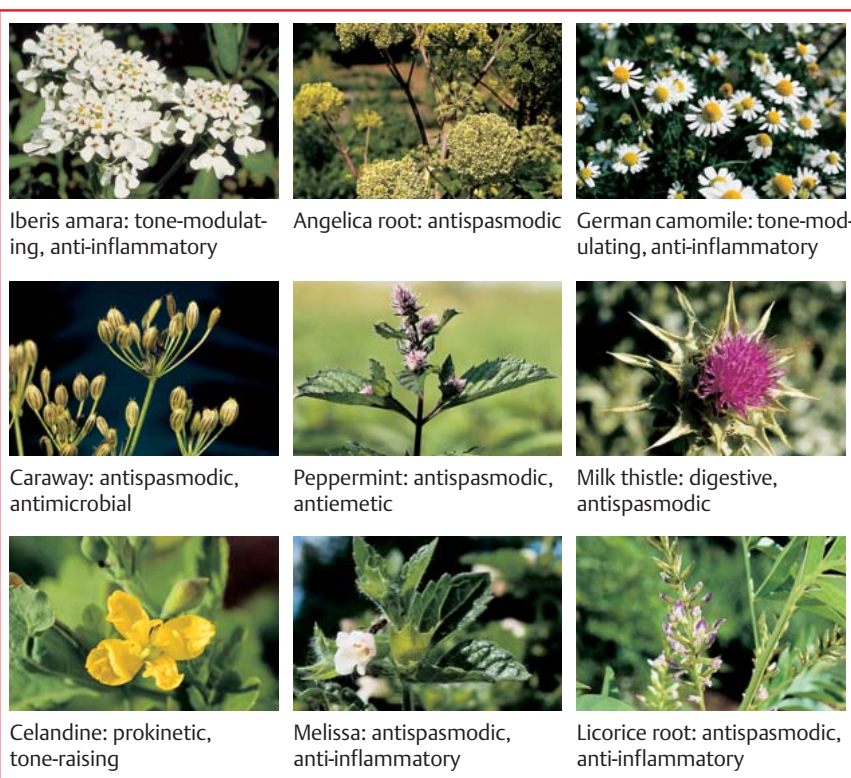


Fig. 7 Medicinal plants the extracts of which are components of STW 5 (Source: modified after [18]).

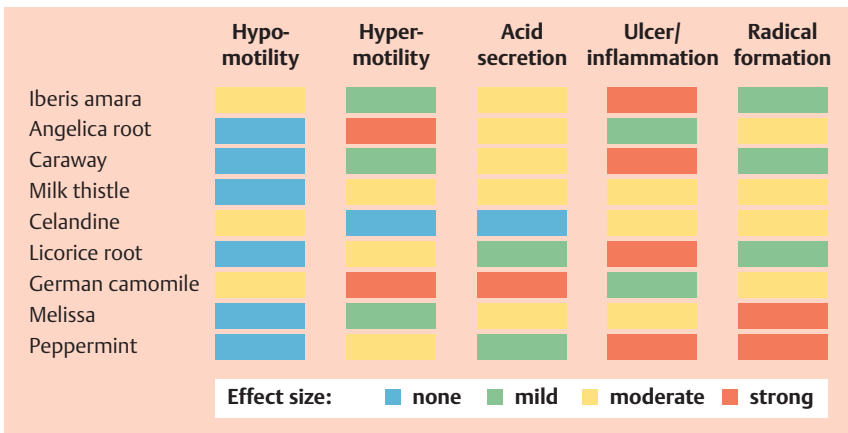


Fig. 8 Contribution of plant extracts to the multi-target effect of STW 5 (Source: modified after [18]).

- one placebo-controlled study on 208 IBS patients
- twelve partially controlled studies on FD/IBS and
- two observational studies on FD/IBS, one of which was on children.

Consequently, and thanks to its proven efficacy and outstanding tolerability, STW 5 is authorised in many countries for the treatment of patients with functional gastrointestinal diseases. In Germany, it is the only medication authorised for the treatment of both FD and IBS.

Clinical evidence for FD patients

The studies presented here measure the treatment outcome in terms of the gastroenterological symptom score (GIS). This was developed in order to cover the whole range of symptoms of functional digestive disorders [19]. The GIS covers

the following symptoms: abdominal fullness, epigastric or abdominal pain, abdominal contractions, early satiety, acid reflux or heartburn, retrosternal pain, nausea, crapulence, vomiting and loss of appetite.

The first double-blind, randomised study on STW 5 versus placebo in 234 FD patients was carried out by Buchert D et al. [20]. As their evaluation shows, after only one week's washout phase and four weeks' treatment, both the GIS and the pain score of verum patients had reduced by a highly significant degree more than those of placebo patients. Highly significant results were also obtained for verum patients in the controlled study of Madisch A et al. on 60 FD patients [21]. In a meta-analysis of the three most important controlled studies on FD patients, Melzer J et al. [22] found that on average STW 5 was 22% more effective than placebo (OR 0.22).

Another important study reaching the same conclusion is that of Arnim U et al. [23]. This study entailed eight weeks of treatment of 308 FD patients with STW 5 followed by a six-month continuous follow-up observational phase. As Fig. 9 shows, after only 14 days of STW 5 treatment, there are significantly more obvious improvements in the GIS values than with placebo. This difference remains significant even after four and eight weeks. The therapeutic effect is still detectable even after the six-month follow up observational phase.

Clinical evidence for IBS patients

Approximately 80% of IBS patients also suffer from FD symptoms, as Madisch recalled. It was therefore not improbable that the multi-target effect of STW 5 should also extend to IBS. It was possible to attest this clinically, even though there is not such a broad clinical evidence base for the Iberis amara combination STW 5 in IBS patients than in FD patients.

A double-blind, randomised study with STW 5 versus placebo on 208 IBS patients designed on the model of controlled studies on FD patients produced evidence of the efficacy of STW 5 for these patients. As can be seen from Fig. 10 and 11, after only one week's washout phase and four weeks' treatment, both the overall symptoms and the pain score of verum patients had reduced by a highly significant degree versus those of placebo patients [24].

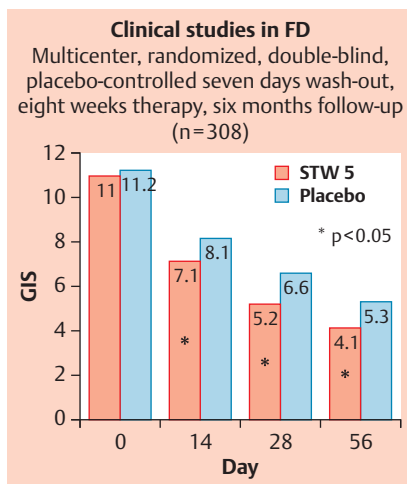


Fig. 9 Effect of eight weeks of treatment with STW 5 versus placebo on the gastroenterological symptoms (GIS) of FD patients (Source: modified after [23]).

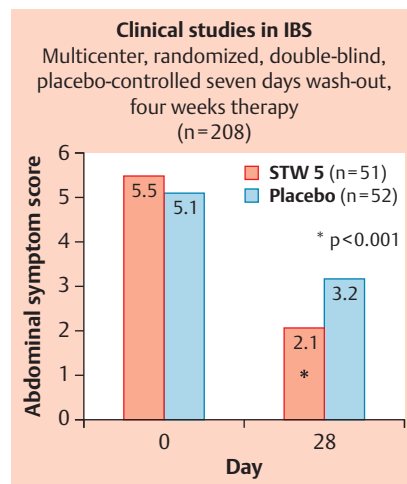


Fig. 10 Effect of four weeks of treatment with STW 5 versus placebo on the overall symptoms of IBS patients (Source: modified after [24]).

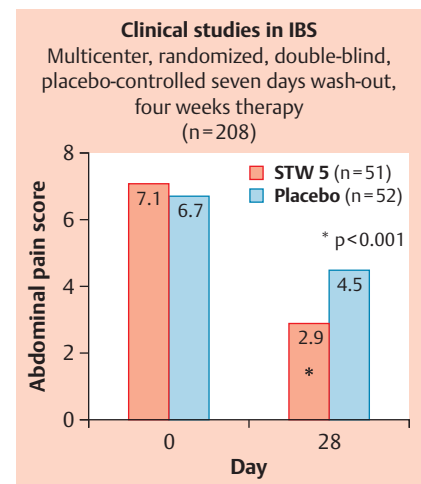


Fig. 11 Effect of four weeks of treatment with STW 5 versus placebo on the pain symptoms of IBS patients (Source: modified after [24]).

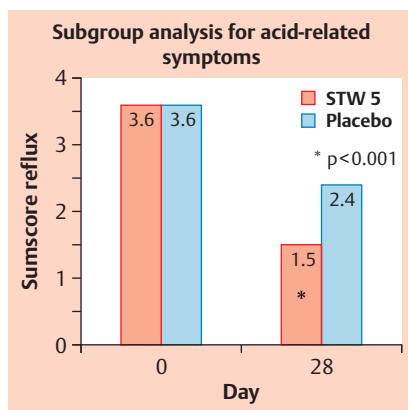


Fig. 12 Improvement in acid-related symptoms in STW 5 treatment in controlled studies on FD patients (Source: modified after [25]).

Effective for dyspeptic heartburn

In treatment with STW 5, the fundus area of the stomach can adapt to ingested food, which is a favourable indication that this medication can improve the symptoms usually associated with the "excess" gastric acid such as heartburn, acid reflux and retrosternal pain. This might also indicate a therapeutic connection between non-erosive reflux disease (NERD) and FD, as Madisch has explained.

In fact, a subgroup analysis of 306 patients included in the controlled FD studies and who also suffered, amongst other things, from symptoms typical of acid confirmed a highly significant improvement of these "acid symptoms" in STW 5 treatment [25]. As Fig. 12 shows, the value for reflux symptoms improves from 3.6 at the start of treatment in both groups to 2.4 with placebo and 1.5 with verum ($p < 0.001$). The result is unequivocal even though this is a subgroup analysis which does not have the same evidential strength as the original end point studies, says Madisch.

Summary

Functional gastrointestinal diseases have many causes. An ideal treatment would be multi-target therapy directed at the whole symptom spectrum and the underlying disorders. Monotherapies are generally only able to alleviate some of the symptoms.

The Iberis amara combination STW 5 composed of nine plant extracts approaches the ideal multi-target therapy because it

- normalises dysfunctional gastrointestinal motility
- tones the lower oesophageal sphincter
- reduces visceral hypersensitivity
- can reduce the production of gastric acid and
- has anti-inflammatory properties.

The phytotherapeutic remedy consistently targets all the important symptoms of both FD and IBS:

- heartburn
- stomach pain
- abdominal fullness
- flatulence
- stomach cramps
- nausea and vomiting

The effectiveness of the Iberis amara combination STW 5 has been examined in studies and surveys on more than 50 000 patients. In Germany, this phytotherapeutic remedy is the only medication authorised for the treatment of patients with FD and IBS. It is listed in the guidelines of the DGVS (German Association of Digestive and Metabolic Diseases) and other national professional associations for these indications.

Excellent tolerability

Compared with all medicinal alternatives, STW 5 is extremely well tolerated. Although the preparation has been in use for 50 years, the data reveals hardly any systemic side effects. In the 403 controlled studies on patients treated with verum, there were 14 adverse drug effects (ADE) which were possibly to probably causally connected with the medication. Among the 6143 patients included in open studies, there were 19 cases with a possible to probable causal connection. The same number was found in the reports on more than 20 million patients treated in Germany with STW 5. No ADEs were found in the retrospective subgroup analysis for reflux symptoms, nor were any found in the 2 retrospective observational studies on children ($n = 43\,311$).

References

- ¹ Camillieri M et al. *Neurogastroenterol Motil* 2005; 17: 311–316
- ² Lee KJ, Tack J. *J Neurogastroenterol Motil* 2010; 16: 251–257
- ³ Ford AC et al. *Clin Gastroenterol Hepatol* 2010; 8: 401–409
- ⁴ Klooker TK et al. *Gut* 2010; 59: 1213–1221

- ⁵ Camillieri M et al. *Clin Gastroenterol Hepatol* 2008; 6: 772–781
- ⁶ Villani AC et al. *Gastroenterology* 2010; 138: 1502–1513
- ⁷ Buhner S et al. *Gastroenterology* 2009; 137: 1425–1434
- ⁸ Moayyedi P et al. *Gastroenterology* 2004; 127: 1329–1337
- ⁹ Moayyedi P et al. *Cochrane Database Syst Rev* 2005; 1: CD002096, Update 2006; 2: CD002096
- ¹⁰ Moayyedi P et al. *Aliment Pharmacol Ther* 2003; 17: 1207–1214
- ¹¹ Hohenester B et al. *Neurogastroenterol Motil* 2004; 16: 765–773
- ¹² Pillichiewicz AN et al. *Am J Gastroenterol* 2007; 102: 1276–1283
- ¹³ Schemann M (unpublished results)
- ¹⁴ Liu CY et al. *Neurogastroenterol Motil* 2004; 16: 759–764
- ¹⁵ Müller MH et al. *Phytomedicine* 2006; 13 (Suppl. 5): 100–106
- ¹⁶ Khayyal MT et al. *Phytomedicine* 2006; 13 (Suppl. 5): 56–66
- ¹⁷ Krüger DJ et al. *Neurogastroenterol Motil* 2009; 21: 1203–e110
- ¹⁸ Schemann M. Zit. in: Buchroither B, Kongressbericht "Neurogastroenterologie & Motilität 2008", *Z Gastroenterologie* 2009; 47: Beilage in Heft 2, 4–6
- ¹⁹ Adam B et al. *Aliment Pharmacol Ther* 2005; 22: 357–363
- ²⁰ Buchert D et al. *Z Phytother* 1994; 15: 24–25
- ²¹ Madisch A et al. *Z Gastroenterol* 2001; 39: 511–517
- ²² Melzer J et al. *Aliment Pharmacol Ther* 2004; 20: 1279–1287
- ²³ von Arnim U et al. *Am J Gastroenterol* 2007; 102: 1268–1275
- ²⁴ Madisch A et al. *Aliment Pharmacol Ther* 2004; 19: 271–279
- ²⁵ Madisch A et al. *Gut* 2007; 56: Suppl. III, A 336

Impressum

Beilage zur Zeitschrift für Gastroenterologie
49. Jahrgang, Heft 2, Februar 2011

Die Beilage erscheint außerhalb des Verantwortungsbereichs der Herausgeber der Zeitschrift für Gastroenterologie.

Redaktion: Dr. rer. nat. Till U. Keil, München

Titelbild: Steigerwald Arzneimittelwerk GmbH, Darmstadt
Eine Sonderpublikation unterstützt von der Firma Steigerwald Arzneimittelwerk GmbH, Darmstadt.

Für Angaben über Dosierungsanweisungen und Applikationsformen kann vom Verlag keine Gewähr übernommen werden. **Jeder Benutzer ist angehalten**, durch sorgfältige Prüfung der Beipackzettel der verwendeten Präparate und ggf. nach Konsultation eines Spezialisten festzustellen, ob die dort gegebene Empfehlung für Dosierungen oder die Beachtung von Kontraindikationen gegenüber der Angabe in dieser Beilage abweicht. Eine solche Prüfung ist besonders wichtig bei selten verwendeten Präparaten oder solchen, die neu auf den Markt gebracht worden sind. **Jede Dosierung oder Applikation erfolgt auf eigene Gefahr des Benutzers.**

© 2011 Georg Thieme Verlag KG
Rüdigerstraße 14, 70469 Stuttgart

Chairman and Speakers



Prof. Dr. Peter Malfertheiner, Magdeburg (Chairman)



Prof. Dr. Hans-Dieter Allescher, Garmisch-Partenkirchen (Speaker)



PD Dr. Ahmed Madisch, Hannover (Speaker)



Prof. Dr. Michael Schemann, München (Speaker)



Dr. Tim Vanuytsel, Löwen/Belgium (Speaker)