

MENTHACARIN IN FUNCTIONAL GASTROINTESTINAL DISORDERS: A PHARMACY-BASED COHORT STUDY

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SUMMARY

Functional dyspepsia and irritable bowel syndrome (IBS) are among the most prevalent functional gastrointestinal disorders (FGID) and often treated by self-medication.

To gain insights into experienced effects and tolerability of pharmacy-supported self-medication with Menthacarin, a proprietary specified combination of essential oils from *Mentha x piperita* L. (90 mg WS[®] 1340) and *Carum carvi* L. (50 mg WS[®] 1520), in pharmacy customers suffering from FGID.

The study was designed as a prospective, observational, multicenter, pharmacy-based cohort study in pharmacy customers suffering from dyspeptic complaints, particularly with mild cramps in the gastrointestinal tract, bloating, and fullness, who were routinely recommended the commercially available preparation of Menthacarin. Occurrence and severity of 13 dyspeptic symptoms were assessed by the modified Gastrointestinal Symptoms Rating Scale (GSRS). Patient satisfaction and tolerability were evaluated.

50 customers (mean age 53.8 years) were recruited. After 3 weeks, GSRS total score was reduced from 48.6 ± 17.1 to 22.8 ± 12.3 points ($p < 0.001$). In 68.7% of the participating customers, an improvement occurred within the first week of Menthacarin administration. Greatest improvements were noted for abdominal pain, bloating, and impression of fullness. At study end, 83.3% reported general health state improvement. 44.9% rated the perceived effects as "very good" or "good", 30.6% as "satisfactory". Tolerability was rated as "very good" or "good" by 83.3% of customers and 87.7% of pharmacists.

These findings suggest the satisfactory and safe applicability of Menthacarin in pharmacy-supported self-medication of pharmacy customers suffering from dyspeptic and IBS-related complaints due to FGID.

Key words

Functional gastrointestinal disorder; Menthacarin; Peppermint oil; Caraway oil; Pharmacy-based cohort study.

Impact statement

The results of this pharmacy-based cohort study (a) show significant improvement in symptoms of functional gastrointestinal disorders, such as abdominal pain and bloating, and improved overall health status after 3 weeks of observational treatment, with improvement in pharmacy customers occurring already after one week of taking Menthacarin, and (b) suggest the satisfactory and safe applicability of Menthacarin in pharmacy-supported self-medication of pharmacy customers suffering from dyspeptic and irritable-bowel-syndrome-related complaints due to functional gastrointestinal disorders.

Abbreviations

CI: Confidence interval; FD: Functional dyspepsia; FGID: Functional gastrointestinal disorders; GSRS: Gastrointestinal Symptoms Rating Scale; IBS: Irritable bowel syndrome; NDI: Napean Dyspepsia Index; SD: Standard deviation(s); VAS: Visual analogue scale.

INTRODUCTION

Functional gastrointestinal disorders (FGID) such as irritable bowel syndrome (IBS) and functional dyspepsia (FD) are highly prevalent and currently belong to the most common gastrointestinal syndromes (1, 2). For Southern Europe, pooled prevalences are estimated, for example, as 15.0% for IBS (3) and 24% for uninvestigated dyspepsia (4).

FGID is a diagnosis of exclusion and can solely be identified by associated symptoms, among which chronic abdominal pain and bloating belong to the most common (5, 6). The treatment is symptom-based and symptoms are usually chronic and not independent of each other, with considerable overlap between the symptoms of different FGID (5).

During the last decades, there has been a considerable effort among gastroenterologists to find ways to define, evaluate and - most importantly - appropriately treat the various forms of FGID. In the course of the revision of diagnostic algorithms, the current criteria, guidelines and recommendations of the Rome foundation, recently published as the Rome IV materials (7), describe FGID as disorders of gut brain interaction and introduce a number of diagnostic specifications that - among other issues - aim to address the high rate of concomitant IBS and FD occurrence (6, 8) and the frequent overlap and variability of symptoms in FGID in general. According to Rome IV, the main symptom occurring with IBS and FD is chronic or relapsing abdominal pain. In IBS, associated symptoms also comprise a change of bowel habit, stool consistency and/or frequency, and bloating: Symptoms must have existed for at least 6 months prior to diagnosis, with pain having occurred at least once a week for at least 3 months (9). Likewise associated with chronic or relapsing abdominal pain, FD presents with symptoms located in the upper abdomen, such

as impression of fullness, early satiation and bloating (5, 7).

The chronicity or frequent relapsing of the symptoms over a long time can lead to serious reductions in quality of life as well as considerable impairment of social and professional functioning (6), let alone the socioeconomic burden implied (2, 10).

Given the long-term duration of the condition as well as the great variety and overlapping of symptoms, the need for a safe and efficacious therapeutic option applicable in FGID is obvious. Self-medication is a major issue here, which, besides broad-range efficacy, implies the particular importance of safe application and tolerability of the drug as perceived by the patient. It would therefore be helpful to complement medical data derived from clinical trials by data from self-medication. For this purpose, pharmacy-based observational studies - also called naturalistic cohort studies - are a valid and helpful research tool (11, 12). They are usually conducted by physicians. In Germany, they may also be carried out by other healthcare professionals, e.g., pharmacists, if the medicinal products are marketed as over the counter products (13).

Menthacarin¹ is a proprietary combination of peppermint oil (90 mg WS[®] 1340) and caraway oil (50 mg WS[®] 1520) with specified quality. One gastro-resistant capsule, soft, contains 90 mg *Mentha x piperita* L., *aetheroleum* (peppermint oil) and 50 mg *Carum carvi* L., *aetheroleum* (caraway oil). Menthacarin is available in Germany and other European countries in pharmacies without prescription. Herbal preparations such as peppermint (*Mentha piperita*) or caraway (*Carum Carvi*) have a centuries-long successful history in gastrointestinal conditions.

1 Menthacarin[®] is the active agent of the product Carmenthin[®] bei Verdauungsstörungen (Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe).

Whereas peppermint oil was proved to act as a spasmolytic in gastrointestinal disorders and thus be effective in reducing FGID-related abdominal pain (14, 15), caraway fruit and caraway oil are acknowledged to be effective in digestive problems with regard to bloating (16), to exert antispasmodic effects (17), and to act selectively growth-inhibiting on pathogenic intestinal bacteria (18). Four double-blind, randomized trials showed that treatment of patients suffering from functional dyspepsia with 2 x 1 or 3 x 1 capsules/day Menthacarin was significantly more effective than placebo and as effective as the prokinetic agent cisapride, respectively (19-22). Favorable treatment effects similar to those found for FD patients in the primary analyses were also shown for concomitant IBS-associated symptoms in FD patients (23). The observational, prospective, pharmacy-based, cohort study presented here was conducted to gain insight into tolerability as a pharmacy-supported self-medication in patients with FGID as reported by pharmacy customers and pharmacists, as well as into patient compliance and experienced changes in symptom improvement.

MATERIALS AND METHODS

This study was conducted in 10 pharmacies in Germany. As this was a non-interventional, open, multi-center, pharmacy-based, post-authorization cohort study, this investigation was not subject to an ethics approval. In accordance with the national regulations, notification of the study was made to the Federal Institute for Drugs and Medical Devices (BfArM) and the National Association of Statutory Health Insurance Physicians prior to study start.

Pharmacy customers aged ≥ 18 years who were routinely recommended the commercially available preparation of Menthacarin due to the reason for the consultation at the pharmacy were asked whether they would participate in the cohort study. After verbal consent, they were asked about demographic data, existing diseases, medical treatment, and drug therapy in a baseline survey and the information was documented.

Pharmacy customers who reported to be suffering from dyspeptic complaints, particularly with mild cramps in the gastrointestinal tract, bloating, and fullness could be involved provided they had undergone a medical examination in the last 12 months to clarify the above-mentioned symptoms. Pharmacy customers with a medically confirmed organic cause for these symptoms, e.g., gastric ulcer, short bowel syndrome or biliary tract disease were not included. The dyspeptic complaints had to be frequently relapsing during the last 3 months prior to participation. Study eligibility required the occurrence of either 3 out of 4 pre-defined symptoms related to the upper abdomen or 2 out of 3 pre-defined symptoms related to the bowel. Regarding the upper abdomen, pre-defined symptoms were the following symptoms occurring independent of meals: frequent eructation without acid taste, impression of fullness, frequently relapsing nausea and retching impulse, and the symptom early satiation already after small meals. Regarding the bowel, pre-defined symptoms required for study eligibility were increased borborygmi, increased bloating associated with altered frequency and consistency of stool.

Pharmacy customers participating in the study were asked to follow the instructions in the package leaflet to daily swallow 1 enteric-coated soft capsule in the morning and one at lunchtime, 30 minutes before meals, and to visit the pharmacy again after 3 weeks. Occurrence and severity of 13 dyspeptic symptoms were assessed by the pharmacist at baseline and after 3 weeks of administration of the herbal medicinal product.

Outcome measure was a modified version of the Gastrointestinal Symptoms Rating Scale (GSRS) (24). Symptom severity was evaluated by a visual analogue scale (VAS) covering degrees from 0 (not present) to 10 (severe). Also, drug tolerability as well as changes of symptoms accompanying treatment were evaluated by pharmacists and pharmacy customers using a scale from 1 (very good) to 5 (poor). Patient satisfaction with the treatment was assessed on a 5-point health-state scale ranging from "much better" to "much worse". In addition,

the pharmacy customers were asked about the convenience of dosage form, compliance, and willingness of future intake of Menthacarin.

The change in severity of present symptoms was evaluated by means of the intraindividual differences between the respective values of the final visit (after 3 weeks of drug intake) and the respective values at the baseline visit. Mean values, standard deviations (SD) and 95% confidence intervals (CI) were computed for symptom severity and change. Obtained data were analyzed for significance by application of the two-sided Wilcoxon signed-rank test. Due to the descriptive nature of the analyses, statistical significance was assumed for $p < 0.05$. Adverse events were documented.

RESULTS

A total of 50 customers (mean age 53.8 ± 13.6 , 68.0% female) were recruited. A total of 48 questionnaires could be evaluated for effectiveness and 50 for safety.

The global FGID symptoms that were rated as "impairing" by most pharmacy customers at baseline were "bloating" (in 62% of the patients with a mean severity of 6.5 ± 2.8 points as as-

sessed on the GSRS), "impression of fullness" (50%, 6.1 ± 2.3), and "abdominal pain" (44%, 5.6 ± 2.6). The symptoms "early satiation" and "eructation" were initially noted in 34% and 40% of the patients, respectively. Symptoms related to defecation were reported by 26% ("liquid or soft stool") and 28% of the patients ("sudden urge to defecate"), respectively, at study start.

After 3 weeks of Menthacarin intake, the initially most impairing global FGID symptoms "abdominal pain" "bloating", and "impression of fullness" showed mean improvement rates of 3.2 ± 2.6 , 3.2 ± 3.1 , and 3.1 ± 2.6 points, respectively. Mean values of "early satiation" and "eructation" had decreased by 2.2 ± 2.5 points and 2.4 ± 2.8 points, respectively, whereas in the defecation-related symptoms "liquid or soft stool" and "sudden urge to defecate" an average decrease by 1.5 ± 1.9 points and 1.2 ± 2.0 points, respectively, was noted. The overall severity of the 13 symptoms assessed decreased during the study, which was statistically significant in 12 of the symptoms (**figure 1**). The total GSRS score significantly improved from 48.6 ± 17.1 points to 22.8 ± 12.3 points ($p < 0.0001$, two-sided, Wilcoxon signed-rank test).

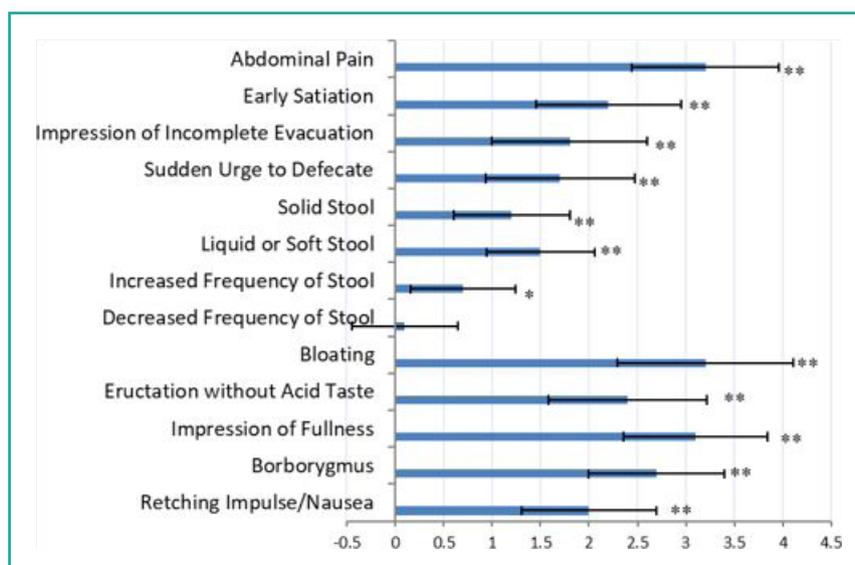


Figure 1. Improvement in gastrointestinal symptoms after 3 weeks of Menthacarin intake (mean GSRS score and 95% CI). * $p = 0.0134$, ** $p < 0.0001$; two-sided, Wilcoxon signed-rank test.

At the end of the study, 83.3% of pharmacy customers reported an improvement in their general health state compared to two weeks earlier (**figure 2**). In 68.7% of all customers participating, an improvement occurred within the first week of Menthacarin intake.

10.2% of the participants rated the effectiveness of Menthacarin as "very good", 34.7% as "good", and 30.6% as "satisfactory". This was comparable to the pharmacists' rating (10.2% "very good", 42.9% "good", 10.2% "satisfactory") (**figure 3**).

83.3% of the pharmacy customers' and 87.7% of the pharmacists' ratings for tolerability of Menthacarin were "very good" or "good" (**figure 4**).

Nearly all participating customers (96%) rated the Menthacarin dosage form in capsules as "convenient". Almost 90% of the pharmacy customers took the drug as instructed over the complete study term. 22.9% of the pharmacy customers reported to be symptom-free after 3 weeks of Menthacarin intake. 73.5% of the participating customers stated their willingness to administer the drug again in the future, and 43.8% decided to continue Menthacarin intake after the end of the cohort study.

A total of 10 adverse events in 7 pharmacy customers were documented, for 3 out of which (stomach ache) a relation to Menthacarin could not be excluded.

DISCUSSION

Cohort studies in this over-the-counter pharmacy-based setting have the advantage of being able to assess tolerability and effectiveness of a medication by means of detailed questioning of the recipient under real-world conditions (25). In this context, the results presented here show that self-medication with Menthacarin carried out under the guidance of a pharmacist leads to a relevant improvement and alleviation of FGID-related symptoms. During the cohort study, considerable improvement in 13 pre-defined symptoms under Menthacarin intake was seen. Out of these

symptoms, 12 improved significantly, especially abdominal pain, bloating, and impression of fullness.

These findings are in line with effects shown for Menthacarin reported earlier: Koch and colleagues (26) demonstrated the antifoaming and thus bloating-relieving effects of both essential oils, which are largely mediated by lowering the surface tension of the gastric or intestinal juices. In an investigation of the effects of an intraduodenal application of both essential oils on gastroduodenal motility in healthy volunteers, Micklefield and colleagues (27) demonstrated a significant decrease in frequency and duration of contractions for peppermint oil WS[®] 1340 and a significant reduction of the respective contraction amplitudes by caraway oil. These results therefore proved the contribution of both active ingredients to the spasmolytic effects of the combined preparation. A similarly relaxing effect of both peppermint oil and caraway oil on the gallbladder was shown by Goerg and Spilker (28), who suggested a synergistic action mode with both WS[®] 1340 and WS[®] 1520 contributing to the effectiveness of Menthacarin in an amplifying manner. The combination of peppermint oil and caraway oil as well as the individual substances were also tested in a model of post-inflammatory visceral hyperalgesia (29). For the combination, a significant effect on the sensitivity to pain was shown whereas neither peppermint oil nor caraway oil showed significant activity when administered individually.

The considerable reduction in abdominal pain during Menthacarin intake shown in the present cohort study is of particular relevance as this symptom is considered the most common symptom in nearly all types of FGID (7). The results also show that the FGID symptoms stated by the participating pharmacy customers as particularly impairing at the beginning of the study, namely abdominal pain, bloating and impression of fullness, were among the symptoms showing the greatest improvements. These findings are in line with results from a placebo-controlled clinical trial which

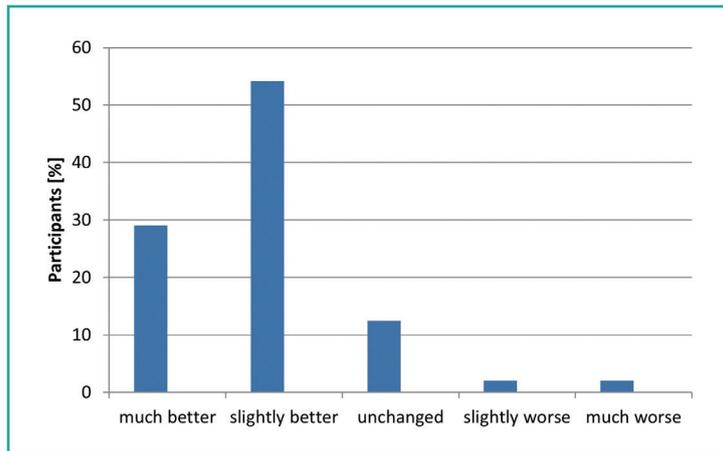


Figure 2. Change of individual health state during Menthacarin intake compared to two weeks previously as evaluated by pharmacy customers.

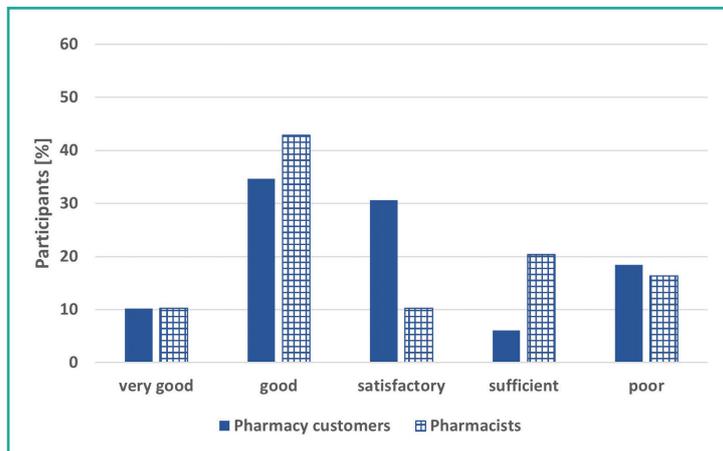


Figure 3. Effectiveness of Menthacarin as evaluated by pharmacy customers and pharmacists.

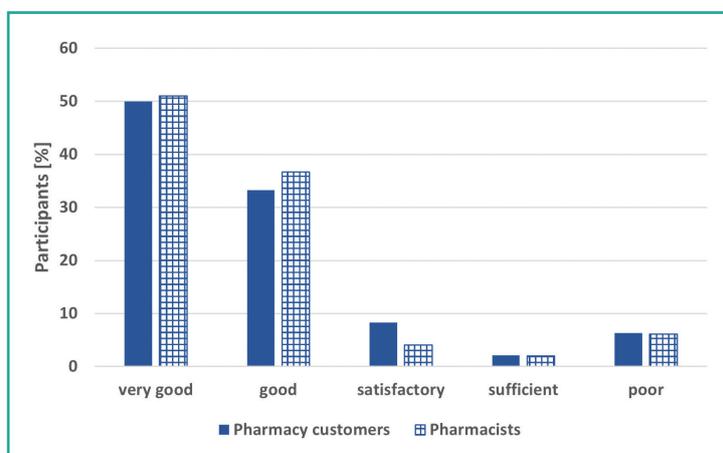


Figure 4. Tolerability of Menthacarin as evaluated by pharmacy customers and pharmacists.

show a significant reduction in FD-related pain and discomfort scores of the Nepean Dyspepsia Index (NDI) after a 4-week administration of Menthacarin (22). The findings are also consistent with results reported for a 4-week application of Menthacarin showing a reduction in pain which is comparable to that achieved under the prokinetic agent cisapride (20). Accordingly, the global effect of the reduction in FGID symptom severity as achieved by Menthacarin treatment was demonstrated to also have a considerable beneficial effect on the patients' quality of life (19, 22). These findings are supported by the results of the present study, in which nearly 85% of participating customers reported an improvement in their general health state.

An investigation of the long-term effects of Menthacarin was conducted as part of an open label study part over 11 months following up on a clinical trial by May and colleagues (19). During this active medication follow-up phase which followed the placebo-controlled trial phase, comparable treatment effects in both the former placebo and the Menthacarin groups after 4 months administration could be shown (30). The fact that treatment effects were comparable in both former randomization groups after 4 months suggests an overall regulating action of Menthacarin regarding FD-specific symptoms over the longer term.

Moreover, a clinical trial investigating the short-term effects of a combination preparation of caraway oil and L-menthol in FD patients (31) reported significant improvements in FD symptom severity within 24 hours as compared to placebo. These findings suggest an also short-term effectiveness of the peppermint oil-caraway oil combination which needs to be confirmed by further investigations.

With the prevailing majority of the pharmacy customers, and pharmacists' ratings for tolerability of Menthacarin being "very good" or "good" and an occurrence of only 3 adverse events for which a relation to the study medication could not be completely ruled out, the observed safety results also support for-

mer findings from randomized controlled trials (19-22).

In summary, the current study results derived from a "real-world" setting are in accordance with the current knowledge on safety and efficacy of Menthacarin from controlled clinical trials. Along with the results of the above-mentioned trials and literature reviews, the results of the present cohort study suggest Menthacarin to be a good alternative option to conventional management of abdominal pain in FGID. The high level of satisfaction with the dosage form of Menthacarin among the participating pharmacy customers, the favorable course of treatment, and the favorable tolerability ratings seen can be considered the main influential factors for the high compliance among the participating customers seen during the study. The fact that about half of the participating customers decided to continue Menthacarin intake after the end of the study and, moreover, nearly 75% of the customers considered a future use of the herbal drug is not only a statement in favor of the drug's convenience, tolerability, and safety but also for its applicability for self-medication in FGID.

CONCLUSIONS

The results of this pharmacy-based cohort study show a significant improvement in a broad range of FGID symptoms such as abdominal pain, impression of fullness and bloating, and improved overall health status after a 3-week observational treatment course with improvement onset in most participating pharmacy customers already after 1 week. Menthacarin was shown to be well applicable in pharmacy-supported self-medication of dyspeptic complaints due to FGID.

ETHICS

Fundings

The reported study and its publication were funded by Dr. Willmar Schwabe GmbH & Co.

KG. The funding source was involved in study design, data collection and interpretation. The final decision on content and submission was retained by the authors.

Conflict of interests

SN and AM have received honoraria from Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany. FAM, BS, and PF are employees of Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany.

Authors' contribution

SN was involved in interpretation of data, critical revisions related to important intellectual content, and gave final approval of the manuscript version to be published. FAM made substantial contributions to conception and design of the study, was involved in acquisition of data, analysis, and interpretation of data, critical revisions related to important intellectual content, and gave final approval of the manuscript version to be published. BS was involved in interpretation of data, drafting the article, critical revisions related to important intellectual content, and gave final approval of the manuscript version to be published. PF was involved in interpretation of data, drafting the article, critical revisions related to important intellectual content, and gave final approval of the manuscript version to be published. AM was involved in interpretation of data, critical revisions related to important intellectual content, and gave final approval of the manuscript version to be published.

Availability of data and materials

The datasets presented in this article are not readily available because raw data cannot be shared both due to ethical reasons and to data protection laws. All relevant data are within the paper. Requests to access the datasets should be directed to the corresponding author.

Ethical approval

As this was a non-interventional, open, multi-center, pharmacy-based, post-authorization cohort

study, this investigation was not subject to an ethics approval. Prior to study start, notification was made to the National Association of Statutory Health Insurance Physicians and the Federal Institute for Drugs and Medical Devices (BfArM).

REFERENCES

- Holtmann G, Schrenk D, Madisch A, Allescher HD, Ulrich-Merzenich G, Mearin F, et al. Use of evidence-based herbal medicines for patients with functional gastrointestinal disorders: A conceptual framework for risk-benefit assessment and regulatory approaches. *Dig Dis.* 2020;38(4):269-79. doi: 10.1159/000504570.
- Camilleri M, Choi M-G. Review article: irritable bowel syndrome. *Aliment Pharmacol Ther.* 1997;11(1):3-15. doi: 10.1046/j.1365-2036.1997.84256000.x.
- Manzoli L, Flacco ME, Marzuillo C, Lopetuso L. Prevalence of severe irritable bowel syndrome among Italian adults. A meta-analysis. *Eur Rev Med Pharmacol Sci.* 2017;21(24):5751-64. doi: 10.26355/eur-rev_201712_14022.
- Ford AC, Marwaha A, Sood R, Moayyedi P. Global prevalence of, and risk factors for, uninvestigated dyspepsia: a meta-analysis. *Gut.* 2015;64(7):1049-57. doi: 10.1136/gutjnl-2014-307843.
- Schmulson MJ, Drossman DA. What is new in Rome IV. *J Neurogastroenterol Motil.* 2017;23(2):151-63. doi: 10.5056/jnm16214.
- Tack J, Talley NJ, Camilleri M, Holtmann G, Hu P, Malagelada J-R, et al. Functional gastroduodenal disorders. *Gastroenterology.* 2006;130(5):1466-79. doi: 10.1053/j.gastro.2005.11.059.
- Drossman DA, Hasler WL. Rome IV-Functional GI Disorders: Disorders of Gut-Brain Interaction. *Gastroenterology.* 2016;150(6):1257-61. doi: 10.1053/j.gastro.2016.03.035.
- Talley NJ, Dennis EH, Schettler-Duncan VA, Lacy BE, Olden KW, Crowell MD.

- Overlapping upper and lower gastrointestinal symptoms in irritable bowel syndrome patients with constipation or diarrhea. *Am J Gastroenterol.* 2003;98(11):2454-9. doi: 10.1111/j.1572-0241.2003.07699.x.
9. Lacy BE, Mearin F, Chang L, Chey WD, Lembo AJ, Simren M, et al. Bowel disorders. *Gastroenterology.* 2016;150(6):1393-407.e5. doi: 10.1053/j.gastro.2016.02.031.
 10. Lacy BE, Weiser KT, Kennedy AT, Crowell MD, Talley NJ. Functional dyspepsia: the economic impact to patients. *Aliment Pharmacol Ther.* 2013; 38(2): 170-7. doi: 10.1111/apt.12355.
 11. Weingärtner U. Die Anwendungsbeobachtung in der Apotheke - Methodik und Evaluierung. Eschborn: Govi;2005.
 12. Schulz M, Hämmerlein A, Hinkel U, Weis G, Gillissen A. Safety and usage pattern of an over-the-counter ambroxol cough syrup: a community pharmacy-based cohort study. *Int J Clin Pharmacol Ther.* 2006;44(9):409-21. doi: 10.5414/cpp44409.
 13. Bekanntmachung über die Zulassung und Registrierung von Arzneimitteln. Empfehlung zur Planung und Durchführung von Anwendungsbeobachtungen. *Bundesanzeiger.* 1998; (229):16884-5.
 14. Chumpitazi BP, Kearns GL, Shulman RJ. Review article: the physiological effects and safety of peppermint oil and its efficacy in irritable bowel syndrome and other functional disorders. *Aliment Pharmacol Ther.* 2018;47(6):738-52. doi: 10.1111/apt.14519.
 15. Layer P, Andresen V, Allescher H, Bischoff SC, Claßen M, Elsenbruch S, et al. Update S3-Leitlinie Reizdarmsyndrom: Definition, Pathophysiologie, Diagnostik und Therapie des Reizdarmsyndroms der Deutschen Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS) und der Deutschen Gesellschaft für Neurogastroenterologie und Motilität (DGNM). awmf online 2021: AWMF-Registriernummer 021/16.
 16. Assessment report on *Carum carvi L.*, fructus and *Carum carvi L.*, aetheroleum [Internet]. European Medicines Agency. 2015. Available from: https://www.ema.europa.eu/en/documents/herbal-report/final-assessment-report-carum-carvi-l-fructus-carum-carvi-l-aetheroleum_en-0.pdf. Last accessed: Mar 23, 2017.
 17. Al-Essa MK, Shafagoj YA, Mohammed FI, Afifi FU. Relaxant effect of ethanol extract of *Carum carvi* on dispersed intestinal smooth muscle cells of the guinea pig. *Pharm Biol.* 2010;48(1):76-80. doi: 10.3109/13880200903046161.
 18. Hawrelak JA, Cattley T, Myers SP. Essential oils in the treatment of intestinal dysbiosis: A preliminary in vitro study. *Altern Med Rev.* 2009;14(4):380-4.
 19. May B, Köhler S, Schneider B. Efficacy and tolerability of a fixed combination of peppermint oil and caraway oil in patients suffering from functional dyspepsia. *Aliment Pharmacol Ther.* 2000;14(12):1671-7. doi: 10.1046/j.1365-2036.2000.00873.x.
 20. Madisch A, Heydenreich C-J, Wieland V, Hufnagel R, Hotz J. Treatment of functional dyspepsia with a fixed peppermint oil and caraway oil combination preparation as compared to cisapride. A multicenter, reference-controlled double-blind equivalence study. *Arzneimittelforschung.* 1999;49(11):925-32. doi: 10.1055/s-0031-1300528.
 21. May B, Kuntz H-D, Kieser M, Köhler S. Efficacy of a fixed peppermint oil/caraway oil combination in non-ulcer dyspepsia. *Arzneimittelforschung.* 1996;46(12):1149-53.
 22. Rich G, Shah A, Koloski N, Funk P, Stracke B, Köhler S, et al. A randomized placebo-controlled trial on the effects of Menthacarin, a proprietary peppermint- and caraway-oil-preparation, on symptoms and quality of life in patients with functional dyspepsia. *Neurogastroenterol Motil.* 2017;29:11. doi: 10.1111/nmo.13132.
 23. Madisch A, Miehlke S, Labenz J, Stracke B, Köhler S. Effectiveness of Menthacarin on symptoms of irritable bowel syndrome. *Wien Med Wochenschr.* 2019;169(5-6):149-55. doi: 10.1007/s10354-018-0635-1.

24. Svedlund J, Sjödin I, Dotevall G. GSRS - a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. *Dig Dis Sci*. 1988; 33(2):129-34. doi: 10.1007/BF01535722.
25. Hasford J, Moore N, Hoyer K. Safety and usage pattern of low-dose diclofenac when used as an over-the-counter medication: results of an observational cohort study in a community-based pharmacy setting. *Int J Clin Pharmacol Ther*. 2004;42(8):415-22. doi: 10.5414/cpp42415.
26. Koch E, Brauch S, Treffinger H, Herrmann J. Beitrag schaumhemmender Effekte von Pfefferminz- und Kümmelöl zu den karminativen Wirkungen von Menthacarin. *Z Phytother*. 2015;36(S 01):S34. doi: 10.1055/s-0035-1565972.
27. Micklefield G, Jung O, Greving I, May B. Effects of intraduodenal application of peppermint oil (WS® 1340) and caraway oil (WS® 1520) on gastroduodenal motility in healthy volunteers. *Phytother Res*. 2003;17(2):135-40. doi: 10.1002/ptr.1089.
28. Goerg KJ, Spilker T. Effect of peppermint oil and caraway oil on gastroduodenal motility in healthy volunteers: a pharmacodynamic study using simultaneous determination of gastric and gall-bladder emptying and oro-caecal transit time. *Aliment Pharmacol Ther*. 2003;17(3):445-51. doi: 10.1046/j.1365-2036.2003.01421.x.
29. Adam B, Liebrechts T, Best J, Bechmann L, Lackner C, Neumann J, et al. A combination of peppermint oil and caraway oil attenuates the post-inflammatory visceral hyperalgesia in a rat model. *Scand J Gastroenterol*. 2006;41(2):155-60. doi: 10.1080/00365520500206442.
30. Storr M, Stracke B. Behandlungseffekt und Verträglichkeit von Menthacarin bei Patienten mit funktioneller Dyspepsie – ein 11-monatiges Follow-up. *Z Gastroenterol*. 2017;55:e220. doi: 10.1055/s-0037-1605148.
31. Lacy BE, Chey WD, Cash BD, Epstein M, Shah SM. A caraway oil/menthol combination improves functional dyspepsia (FD) symptoms within the first 24 hours: Results of a randomized controlled trial, which allowed usual FD treatments. *Gastroenterology*. 2017;152(5).