

# Irritable Bowel Syndrome

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## Impact paragraph

Irritable bowel syndrome is a highly prevalent disorder affecting 5-15% of the population and is associated with a substantial financial and societal burden. The studies described in this thesis contribute to the long-term goal to further optimize IBS treatment.

### Impact on healthcare providers

The results from this thesis are relevant for people involved in the care of patients with IBS such as general practitioners, gastroenterologists, psychologists, and dieticians.

Treatment of cardinal IBS symptoms such as abdominal pain is exceptionally challenging. The large randomized controlled trial on the efficacy of peppermint oil in IBS, the PERSUADE study, showed that peppermint oil is a moderately, though most-likely cost-effective treatment. This allows for appropriate positioning of peppermint oil in the therapeutic arsenal and for more informed decision making. Upper GI symptoms may occur as side effects during treatment with peppermint oil. We demonstrated for the first time that belching severity decreases after three weeks of continues peppermint oil treatment. This particular finding can help healthcare providers who prescribed peppermint oil treatment to better inform patients when this highly burdensome but harmless side-effect occurs.

Although part of this thesis focused on (GI-)targeted treatment with peppermint oil, we also showed that improvement in GI symptom severity does not necessarily result in an improvement in quality of life in patients with IBS. Furthermore, we showed that a large part of the total healthcare costs in patients with IBS was spent on mental healthcare. Findings like these can inform healthcare providers about the importance of a multidimensional and integrated treatment and will eventually help them in treating IBS patients successfully.

Furthermore, results from the different studies described in this thesis are largely applicable to primary care where general practitioners diagnose and see the majority of patients with IBS. The Maastricht IBS Cohort studies included 28-33% of patients recruited from primary care. The PERSUADE study included 57.7% of patients recruited from primary care. This in itself represents the largest of such population examined with regards to peppermint oil efficacy and led to a high applicability of the results to everyday clinical practice.

## **Impact on research**

This thesis is relevant for researchers in the field of functional gastrointestinal disorders. After redefinition of the diagnostic criteria our results were one of the first to show how this affected prevalence and characteristics of IBS patient populations.

In addition, the studies included in this thesis provide a solid basis to optimize treatment response measurement in functional GI disorders by designing and describing a framework for digitalized data-collection in RCTs. This data-collection method showed excellent adherence from both patients and researchers in our PERSUADE study. In addition, future Dutch studies benefit from the national multicenter network established at the start of our peppermint oil RCT. Currently, the (slightly adapted) framework for data-collection is being used for symptom measurement in the multicenter RCT of our research group on the efficacy of face-to-face versus online hypnotherapy for patients with IBS.

This thesis has contributed to science by giving an overview of current knowledge on transient receptor potential channels and by investigating the role of the TRPM8 receptor in the human (IBS) colon. The results in this thesis showed for first time that colonic mRNA expression levels are significantly higher in patients with IBS compared to healthy volunteers and that intestinal TRPM8 activation results in a decrease of pro-inflammatory cytokines. Shedding light onto this pathophysiological mechanism may lead to the proposal of new mechanistic studies of which the outcomes can eventually lead to the development of more targeted treatment for patients with IBS.

## **Impact on patients with IBS and society**

Importantly, the research topics described in this thesis provide benefit to patients with IBS in a broad sense. By increasing knowledge on key factors involved in pathophysiology of IBS and in quality of life, more targeted treatment can be developed and investigated. This will then hopefully lead to improvements in healthcare with better health outcomes on the long-term for patients with IBS.

Although there is long-standing appreciation for the magnitude of the societal and economic burden imposed by IBS, Dutch data are still sparse. Data included in this thesis indicated that a large part of the substantial healthcare costs incurred by Dutch patients with IBS was actually driven by mental and not GI-related healthcare. In addition, it was shown that patients who improve in GI symptom severity did not necessarily have a better quality of life. These findings point to a large impact of

psychological comorbidities on total associated costs and call for a change in quality of care models for IBS. Implementing the biopsychosocial model in healthcare systems could lead to an early recognition of psychological comorbidity in IBS patients, which may further lead to significant economic benefit for the healthcare system and society in general.

In addition, this thesis provided the first trial-based data suggesting that treatment with small-intestinal release peppermint oil is cost-effective. This finding can impact clinical decision making, implementing the cost-effective peppermint oil in routine practice and hence lowering total IBS associated costs while high quality care is maintained.

### **Knowledge translation**

A prerequisite for the implementation of novel scientific knowledge is the dissemination of research findings to the scientific community, healthcare providers, policy makers, and patients. Therefore, the chapters in this thesis were or will be published in international peer-reviewed journals. Moreover, results were presented at various national and international research meetings such as the Dutch Digestive Disease Days, the European NeuroGASTRO meeting, the United European Gastroenterology (UEG) congress, and the Federation of Neurogastroenterology and Motility Meeting.

At this moment, the joint multidisciplinary clinical guideline of the Dutch College of General Practitioners (Nederlands Huisartsen Genootschap) and the Dutch society of gastroenterologists (Nederlandse Vereniging van Maag-Darm-Leverartsen) on IBS is under revision. As a result of the studies in this thesis, the novel guideline can incorporate data on prevalence after the change from Rome III to Rome IV diagnostic criteria. Furthermore, based on a meta-analysis that included data from our study<sup>1</sup>, it is expected that peppermint oil will be included as a moderately effective and low-cost first-line treatment option for IBS. Taken together with the publications on the PERSUADE study in *Medisch Contact*<sup>2</sup>, *Nederlands Tijdschrift voor Geneeskunde*<sup>3</sup> and *Huisarts en Wetenschap*<sup>4</sup>, and the publication of trial results by the Maastricht University Medical Center and Zuyderland Medical Center websites and social media accounts, the national dissemination was successful and will likely lead to further implementation throughout the Netherlands.

Results of this RCT have been picked up by the international gastroenterologist community as well. Features included an editorial about our study design and results in *Gastroenterology*<sup>5</sup>, a citation as one of the major highlights of the past decade by the

editors of *The American Journal of Gastroenterology*<sup>6</sup>, a laudatory summary in *The New England Journal of Medicine (NEJM) Journal watch*<sup>7</sup>, and a discussion and summary in the *BMJ Evidence Based Medicine*.<sup>8</sup> Most recently, our study findings have been incorporated in the *American College of Gastroenterology* clinical guideline on the management of IBS.<sup>9</sup>

With regards to knowledge distribution to patients with IBS, findings of the Maastricht IBS Cohort and PERSUADE study have been summarized and sent to patients who participated in the studies. Members of the Dutch IBS patient organization were informed about results in layman's articles published in their members magazine *Prikkels*. In addition, Maastricht University Medical Center has organized various patient information evenings to keep patients up to date with current knowledge.

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