OSTEOPATHIC TREATMENT FOR IRRITABLE BOWEL SYNDROME

A SYSTEMATIC REVIEW

BY

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Approval Page

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Abstract

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Background: Irritable bowel syndrome (IBS) is a common and often life-long functional gastrointestinal disorder. A causal treatment for IBS is lacking.

Objectives: The aim of this thesis is a systematic review of trials on the clinical effects of an osteopathic treatment of IBS and a meta-analysis.

Methods: Computerized bibliographic databases including MEDLINE, EMBASE, COCHRANE were searched from 1-1-1999 to 2-28-2011. A manual search in relevant papers not listed in the electronic databases was supplemented. Eligible were RCT`s and controlled clinical trials (CCT). Study selection, data collection and methodological quality assessment were conducted as much as possible according to the standards of the Cochrane Collaboration. Quantitative pooling of data of "Pain" was done by calculating the overall effect size and applying a random effects model, using the Cochrane "RevMan".

Results: The search identified 9 studies. Four studies (a total of 182 patients) met the inclusion criteria.

Conclusion: Descriptive analyses of the four clinical studies considered indicate a stronger therapeutic effect of osteopathy as compared to the control groups.

The meta-analysis of three studies shows a statistically significant superiority of osteopathic interventions compared to the control group with an overall effect size of 3.49 standard mean differences (95% CI: -4.24 -0.75). There is significant heterogeneity between the trials concerning "Pain" as well as concerning the control interventions.

Future, larger studies may significantly alter the results of the meta-analysis in either direction.

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List of Abbreviations and Symbols

Abbreviation	Definition
CG	control group
CR	Cochrane review
EBR	evidence-based research
FGID	functional gastrointestinal disorders
FBDSI	functional bowel disorder severity index
GI	gastrointestinal
GID	gastrointestinal disorder
HRQOL	health-related quality of life
IG	intervention group
IBS	irritable bowel syndrome
IBSQ	irritable bowel syndrome questionnaire
IBSQOL 2000	irritable bowel syndrome questionnaire 2000
NNT	number needed to treat
NS	not significant
OG	group treated with osteopathy
PG	placebo treated group
QOL	quality of life
QOL-AD	quality of life adjusted year
RCT	randomized controlled trial
SF 36	the 36-item short form 36 health survey
SMC	standard medical care
TK	day of control examination (at the end)

Chapter 1 Background

1.1 Irritable Bowel Syndrome: The Facts

1.1.1 Methods

In order to comprehend major aspects of a common clinical problem, irritable bowel syndrome, e.g. physiopathology, epidemiology, diagnosis, therapy, prognosis, and the burden of disease, it was necessary to identify pivotal scientific communications on the problem. Since textbooks are rarely up-to-date, and individual reviews and educational articles may present a focused view, it was decided to consider only actual guidelines in the first place. A search on the topic at the National Guideline Clearinghouse (http://www.guideline.gov/) revealed one guideline issued by the United Kingdom National Institute for Health and Clinical Excellence (Nice, 2008) and another one issued by the World Gastroenterology Organisation (WGO, 2009). These two were complemented by a recently updated German National Guideline on the subject (Layer et al., 2011). Based on these three guidelines and respective bibliographies additional relevant publications were retrieved for further details.

1.1.2 The Problem

In 1944, Bargen and Peters (Peters & Bargen, 1944) probably created the term "Irritable bowel syndrome" to describe a functional gastrointestinal disorder (FGID).

Irritable bowel syndrome (IBS) is one of the most common gastrointestinal disorders. IBS (K 58) based on International Classification of Diseases (World Health Organization, 2011) is a chronic, recurrent and often lifelong persistent gastrointestinal illness which can be quite different in its symptoms and characteristics (Talley & Spiller, 2002). The symptoms of IBS are abdominal pain and discomfort associated with a change in bowel habits. Supportive symptoms of IBS include change in frequency of stool, abnormal stool form, straining during defecation, defecation urgency, feeling of incomplete defecation, passage of mucus and bloating (Jones et al., 2000). Symptoms outside the intestines e.g. back pain, headaches, dyspareunia, symptoms within the genito-urinary tract and sleep disorders are more common in IBS patients than in the

control groups. IBS also results in significant impairments in functional status, higher levels of disability and increased frequency of physician visits (Drossman et al., 1993; Whitehead, Burnett, Cook, III, & Taub, 1996). It is common that changes in bowel movement and impaired sensory- and motor functions are paired with normal bowel morphology and are unexplained by biochemical abnormalities (Drossman & Dumitrascu, 2006).

The pattern of symptoms varies between individuals (Mearin et al., 2004). Characteristic for IBS is abdominal pain which is associated with defecation, e.g.:

- Relief through defecation
- Pain onset associated with a change in defecation frequency
- Pain onset associated with a change in stool consistency (Spiller et al., 2007).

IBS symptoms include abnormal defecation (constipation, diarrhea or both) and abdominal bloating in the intestinal region (Lydiard, 2001).

IBS patients have significantly lower SF-36 values than the healthy controls (general health 62.3 vs. 85.6; $p < 0.001$). IBS patients have e.g. difficulties travelling, participating in sports and attending social gatherings (Whitehead et al., 1996).

About 10% of the population has IBS at any one time and about 200 people per 100,000 will receive an initial diagnosis of IBS over the course of a year (Choung & Locke, III, 2011). Using specific gender- and age prevalence rates (Wilson, Roberts, Roalfe, Bridge, & Singh, 2004), calculations show that the prevalence estimates for IBS are about 11% in Great Britain and ranged between 3 to 20% in the United States. IBS is more likely to be affect people from lower socioeconomic background and is more commonly diagnosed in people over 50 years of age. In most surveys there is a female predominance of approximately 2:1 up to 4:1 (Huertas-Ceballos, Logan, Bennett, & Macarthur, 2008). IBS can certainly be regarded as a common disorder (Hungin, Whorwell, Tack, & Mearin, 2003).

Pain, discomfort and limitations in quality of life through IBS account for around 12% of visits to primary care providers in America (Horwitz & Fisher, 2001) and lead to sick notes, work absenteeism, change of workplace (Leong et al., 2003), premature termination of employment and the associated economic costs (Talley, Boyce, & Jones, 1997) .

Several pathophysiological mechanisms are believed to be the basis of IBS. This includes disorders that range from intestinal motility (Farthing, 2005) to increased visceral sensitivity. Still there is no clear pathophysiology (Zhou, Zhang, & Verne, 2009; Price et al., 2009).

The standard medical treatments in IBS are only of limited value. Many of them solely aim at specific symptoms. A distinct analysis is difficult, since placebo effects in short-term trials cannot be excluded (Mertz, 2003). Therapeutic options are dominated by "Standard Medical Care" therapies but there is uncertainty about their effectiveness (Quartero, Meineche-Schmidt, Muris, Rubin, & De, 2005). Many sufferers do not, however, use conventional medicine and up to 40% of patients with IBS use complementary and alternative medicine (CAM) (Langmead & Rampton, 2001).

In summary: IBS is not a life-threatening disorder but it can have a serious effect on the patient's daily life or his quality of life in general. Today the pathophysiological mechanism of IBS is still unclear. This is the reason for the lack of a gold standard for the treatment of IBS (Lydiard, 2001).

Two newer randomized controlled osteopathic trials show good results compared to standard medical therapies and clearly provide evidence that osteopathy is effective in treating IBS (Brice & Mountford, 2000; Hundscheid, Pepels, Engels, & Loffeld, 2007).

1.1.3 Historical Remarks

As long as 3,000 years ago, Hippocrates described a patient with abdominal pain, changes in stool habits, flatulence and an urge to defecate (Lacy & Lee, 2005). Reports on dysfunctions of the gastrointestinal tract were already found on papyrus rolls from ancient Egypt. They obviously used different plants to treat indigestion and constipation (Drossman et al., 1988). They even had sanatoriums where sick people could undergo a "dream therapy" and were treated with "healing waters". It is possible that at that time the negative influence of stress on the gastrointestinal tract had already been recognized (Alander, Heimer, Svardsudd, & Agreus, 2008).

In old and recent European literature there are descriptions of gastrointestinal pathologies. In the early 19th century a description of IBS was published in English (Powell, 1818). Powell already called attention to the three cardinal symptoms of IBS:

“Abdominal pain”, “digestion disorders” and “flatulence”. In 1849, Cumming (Cumming, 1849) reported about a simultaneous presence of abdominal hypo- and hyper-motoric activities in an IBS patient. In 1892, Osler and Hurst (Maxwell, Mendall, & Kumar, 1997) described „mucous colitis“ With a discharge of mucus (mucorrhea), cell debris and „intestinal sand“. Many of these patients were characterized as hysteric, hypochondriacal or depressive and suffered from abdominal colics. The expressions „spastic colon“ or „irritable colon“ were used by in 1928 or by Jordan and Kiefer in 1929, who described a neuromuscular disorder of the colon in 30% of the gastroenterologic ambulant patients (outpatients) with stomach aches and impaired defecation (Ryle, 1928). Since then, different expressions have been used in literature. Chaudhary and Truelove (Chaudary &Truelove, 1962) described two different clinical subtypes, namely a spastic colon with abdominal pain and a variation between constipation and diarrhea or a painless diarrhea.

The systematic examination of functional gastrointestinal dysfunctions did not start until the mid-20th century. Furthermore, more scientific reports were published and TV, radio and internet passed on more information about IBS to the public.

1.1.4 Terminology

IBS is a chronic, recurrent and often life-long functional gastrointestinal dysfunction with significant morbidity. IBS is part of a group of 24 functional gastrointestinal diseases. A functional disease is generally known as an illness, where no organic changes or diseases can be diagnosed but where the patient has recurring symptoms for longer periods of time (Longstreth, 2005). IBS is a complex disorder which can trigger a wide variety of symptoms. For the first time, these symptoms were defined at the World Congress of Gastroenterology in Rome in 1988 via a globally recognized classification system, the so-called “Rome Criteria” (Drossman, Richter, & Thompson, 1994) [See Appendix A].

1.1.5 Etiology

The etiology of IBS is very complex. While research discovers ever more references for the basis of pathophysiology, for some therapists IBS is increasingly

connected to the biopsychosocial model. This means they favor a holistic view wherein single causes lose their importance and complex interactions of biological and psychosocial influences and also factors of the early life are made responsible for the development and the clinical symptoms of IBS (Gaynes & Drossman, 1999). This is why diagnostic- and therapeutic strategies, which only focus on organic etiologies, seem to be unsuitable for the majority of patients. With this point of view, it seems unlikely that only one medication can treat all IBS patients reliably. In order to treat IBS and to boost the development of effective therapies, it is very important to understand the "brain-gut axis" or respectively the communication between the intestines, the enteric nervous system and the brain (Aziz & Thompson, 1998).

On the one hand central pain sensitivity, mood and behavior are all influenced by visceral sensory information (Derbyshire, 2003) and on the other hand the psychosocial status of an individual can modulate sensibility, motility and secretion processes of the gastrointestinal tract.

1.1.6 Epidemiology

From a historical point of view, mainly the Manning pain scale (Manning, Thompson, Heaton, & Morris, 1978), Rome I- (Drossman et al., 1994) and Rome II criteria (Drossman, Corazziari, & Talley, 2000) were of use in the diagnosis and classification of IBS. Since 2003 Rome III is being used for the „IBS" diagnosis (Longstreth et al., 2006) [See Appendix B].

Under consideration of these criteria, the estimated prevalence of IBS in the US is between 14% to 25% in women and 5% to 19% in men. The estimated prevalence of IBS in Europe shows that up to 24% of women and 19% of men are affected. Based on the Rome III criteria, the prevalence of IBS has been estimated to range from 10% to 18% in the general population of Western countries. It is assumed that 13% to 20% of the Canadian population suffers from IBS (Canadian Society of Intestinal Research, 2011). The prevalence of IBS worldwide amounts to 7% to 10% (Saito, Schoenfeld, & Locke, III, 2002). However, the prevalence of IBS is strongly dependent on the classification algorithm employed (Choung & Locke, III, 2011).

1.1.7 Health Related Quality of Life (HRQOL)

IBS is associated with a significantly influenced health-related quality of life (HRQOL) (Huertas-Ceballos et al., 2008). The symptoms of IBS such as abdominal pain, flatulence, irregular defecation, etc. are often related to associated extra-intestinal symptoms. This is why:

- sleep disorders, (including sleep deprivation) and fatigue syndromes,
- anxiety, lack of wellbeing,
- pain such as back pain, headaches and symptoms in the genito-urinary tract,
- avoidance of stress-causing or socially oriented situations and
- strong symptoms or lethargy

lead to a significant reduction of life quality (National Institute for Health and Clinical Excellence, 2008).

Whitehead (Whitehead et al., 1996) showed that IBS patients have a significantly lower SF-36 evaluation than healthy controls (general health 62.3 vs. 85.6; $p < 0.001$).

In order to make an evaluation or measuring of the IBS-patient's „Health-Related Quality of Life" (HRQOL) possible, each individual's personality, activities of daily life and current (or past) stress situations (e.g. divorce, bereavement or loss of employment) cannot be disregarded and must be included in the evaluation. Possibly existing psychological disorders are of particular importance. HRQOL is a concept which evolved from the necessity of attempting to evaluate the influence of chronic illnesses such as IBS (Wong & Drossman, 2010). The calculation of the HRQOL is a conceptual construction, which tries to predict everyday functioning and wellbeing, based on subjective attitude and experiences of physical, social and emotional health.

The lack of objective parameters for the evaluation of the HRQOL, especially in IBS, was the inspiration to develop an IBS disease-specific stipulation for the HRQOL. In 1991, Drossman (Drossman et al., 1991) published a questionnaire with 25 questions, the RFIPC (Rating Form of Inflammatory Bowel Disease Patient Concerns). It was especially designed to differentiate IBS from other intestinal disorders and to allow for a better determination of the course and the prognosis for the disorder.

A specific tool is the HRQOL (IBS). The first one, the IBSQOL, was developed at UCLA (The University of California, Los Angeles) by Hahn et al. (Hahn, Kirchdoerfer,

Fullerton, & Mayer, 1997). Each of the 30 points is evaluated on a five- or six-point Likert scale and summed up to nine interim results. The IBSQOL distinguishes well between a control group with non-gastrointestinal disorders and unselected patients with IBS. A later study showed that the IBSQOL was also able to distinguish between IBS patients with different severity of illness (Hahn et al., 1997). However, no data were published on the validity of the factor reliability or the responsiveness.

The IBSQOL, a 34-point enclosing tool, developed by Patrick et al., was tested by European gastroenterologists from Great Britain, Germany, Italy and France to guarantee intercultural validity. The IBSQOL has an excellent test-retest reliability and internal consistency (Patrick, Drossman, Frederick, DiCesare, & Puder, 1998).

A third IBS-specific tool, the IBS Questionnaire (IBSQ), was developed by Wong et al. (Wong, Guyatt, Cook, Griffith, & Irvine, 1998). This 26-point enclosing questionnaire is evaluated via a seven-point Likert scale. The validation under use of factor analysis defined four domains: intestinal symptoms, fatigue, activity restrictions and emotional functions.

The "Functional Digestive Disorder Quality of Life" (FDDQL) was also developed for IBS patients. So far, no validation data has been published for IBS.

HRQOL is related to but not redundant with psychological (Lackner et al., 2006) distress, but these four disease-specific tools could possibly be useful in measuring the course of IBS.

1.1.8 The Rome Criteria

A clear and precise definition of IBS is clearly a prerequisite to progress. The Rome Criteria [See Appendix A] are the outcome of international efforts (87 experts from 18 countries) to gather data on functional gastrointestinal disorders, using a symptom-based classification system. The foundation for such a classification system is based on the premise that patients with functional gastrointestinal complaints consistently report about symptoms which comply with the clinical features (Drossman & Dumitrascu, 2006). However, the described symptoms cannot be assigned to a structural or physiological cause or be explained by a biochemical dysfunction.

Until 1992 several committees met to discuss the criteria, which finally led to the “Rome Criteria“. The definition of IBS has evolved over time, from a “diagnosis of exclusion” to the symptom-based diagnostic criteria including “The Manning Pain Scale” , “Rome I-and Rome II Criteria” (Drossman & Dumitrascu, 2006).While the third iteration (Rome III) of the Rome Consensus Conference provided yet another approach to positively diagnose functional illnesses. Nevertheless many physicians continue to see and approach IBS as a diagnosis of exclusion (Spiegel, Farid, Esrailian, Talley, & Chang, 2010).

The publication of the book "The Functional Gastrointestinal Disorders (FGID) (Rome I)” detailing the advancement and further development of the Rome I Criteria led to the publication of a second edition of the Rome Criteria (Rome II) in 2000 (Drossman, 2006). Rome III was published in 2006.

Rome III now presents a grand total of 28 adult and two paediatric functional gastrointestinal disorders FGID (Drossman et al., 2007).

The Rome III Criteria [See Appendix A] characterize IBS as follows:

- Minimum prevalence of three months (which do not have to be consecutive)
- At least three days per month recurrent abdominal discomfort or pain together with two of the following symptoms:
- Relief through defecation
- Beginning is connected to a change in defecation frequency
- Beginning is connected to a change in stool consistency
- Onset longer than six months before diagnosis was issued.

There are additional sub-classifications [See Appendix C]:

- IBS-D (constipation and / or diarrhea)
- IBS-C (flatulence or not specified)
- IBS-M (mixed C and D)
- PI-IBS (post-infectious IBS)

Population-based data imply that diarrhea-prevalent IBS (IBS-D) and mixed IBS (IBS-M) are more widely spread subtypes than constipation-prevalent IBS (IBS-C) subtypes and that a switching between subtype-groups [See Appendix C] can occur.

As a change in criteria of Rome II vs. Rome III, the category "functional gastrointestinal disorders during childhood" (named category G) was divided into two categories (G and H) (Alander et al., 2008). Rome III compared to Rome II has a change in chronological criteria, different classification criteria, different criteria in general and includes two additional criteria.

In summary: Rome III is somewhat more precise and specifies that pain must have been prevalent on three or more days of the month during the past three months. For an IBS diagnosis the criteria have to be fulfilled for the past three months.

Comparable studies suggest that the subtle changes only have little influence on the prevalence (Clouse et al., 2006).

However, the current definitions like the "Manning Pain Scale",(Manning, Thompson, Heaton, & Morris, 1978) "Rome I", (Drossman et al., 1994) "Rome II" (Drossman, Corazziari, & Talley, 2000) and "Rome III" (Drossman, D., Corazziari E, Delvaux, M., Spiller, R., Talley NJ, Thompson WG et al. (2007).have fundamental weaknesses and do not sufficiently reflect the clinical reality in several aspects (Layer et al., 2011).

1.1.9 Pathology and Pathophysiological Mechanisms

An interaction between motor and sensory dysfunctions seems to explain the symptoms of the irritable bowel syndrome, but the cause of these symptoms is yet to be clarified. The effects of the luminal factors, e.g. meals, intestinal expansion, inflammation, bacteria and provocative environmental influences (e.g. psychosocial stress) on the gastrointestinal motility and visceral sensitivity seem to have an exaggerated course in IBS patients (Mertz et al., 2000). The gastrointestinal sensorimotor dysfunction can be seen as a deregulation in the neural processing between intestines and brain. This complex is termed "brain-gut-axis" (Mertz, 2003) which is a synonym for the communication between intestines with the enteric nervous system and the brain (Derbyshire, 2003). This is why medicinal therapies for IBS are generally directed at the

processing of the motor-, sensory- and central nervous system of the gastrointestinal region (Mertz, 2003; Jones, Wessinger, & Crowell, 2006).

The central pain sensitivity, the moods and the behavior are influenced by the visceral sensory (Ropert & Bouguen, 2009) information. However, conversely the psychosocial state can influence sensibility, motility and secretion processes within the gastrointestinal tract. Derived from this is the bio-psycho-social model which requires a holistic view and treatment of IBS and which considers assumed etiological factors such as gastrointestinal infections or surgery just as "triggering factors" (Jones, Koloski, Boyce, & Talley, 2011).

Psychological factors seem to be involved in the illness experience, illness behavior and the clinical consequences of IBS Epidemiologic studies show that fear and depression are more likely in IBS patients who seek medical support for their symptoms than in the control groups. (Bennett, Tennant, Piesse, Badcock, & Kellow, 1998).

Recent studies demonstrate that different lines of research in functional gastrointestinal disorders have moved away from the old psychosomatic concepts (Gwee, 2010). Studies have reported of a connection between the polymorphism of the serotonin transmitter 5-HTT and certain IBS subtypes (Spiller et al., 2007; Park & Camilleri, 2005). To date, more than 100 genetic variants in more than 60 genes from various pathways have been studied in a number of candidate gene studies, with several positive associations reported. These findings suggest that there may be distinct, as well as shared molecular underpinnings for IBS and its subtypes (Saito, 2011). But no specific genetic background for IBS could be detected. Up to now, there is no clear cause for IBS and the therapy management depends on an assured diagnosis (Brandtzaeg, 2010). But evidence for subtle inflammatory bowel disease, serotonin deregulation, bacterial overgrowth and central deregulation continue to accumulate. The underlying causes of IBS remain to be adequately identified, but post infectious IBS is a clear-cut entity (Talley, 2006). In almost 20% of the patients, IBS is clearly a post-infectious IBS as a consequence of an acute bacterial gastroenteritis (Ducrotte, 2010).

In summary: Since no single cause for IBS has been identified, a conglomerate of all regions is suspected. Visceral hypersensitivity (enhanced perception of peripheral signals), infection / inflammation, and psychological factors that alter "brain-gut axis"

function are all operative in understanding these disorders. (Drossman, Camilleri, Mayer, & Whitehead, 2002).

1.1.10 Clinical Evaluation

Pending the development of a reliable biomarker, the diagnosis of IBS rests entirely on patient history. The patient's history is paramount in diagnosis. But a symptom descriptor can mean different things to different people, and multiple terms can be applied to the same symptom, demanding interpretive skill from the practitioner (Longstreth, 2005). Furthermore, many studies attest to the unreliability of retrospective recall; patients do not lie; their memories selectively overemphasize the frequency and severity of those symptoms which distress them (Ashraf, Park, Lof, & Quigley, 1996; Chapman & Martin, 2011).

The diagnosis depends on the thorough interpretation of the temporal relationship between pain and discomfort, intestinal habits and stool consistency. Whereas pain or discomfort, regarding defecation, are probably gut-related, if the pain is influenced by recreational sport, exercise, urination or menstruation, it probably has a different origin. Special attention should be turned towards fever, gastrointestinal bleeding, weight loss, anemia, abdominal proliferation and other “alarm symptoms” or “alarm signals”, which might not be caused by but accompany IBS (De Giorgio R. et al., 2004).

For women, gynecological symptoms such as increased pain during menstruation or dyspareunia or the like can disguise IBS symptoms (Won & Abbott, 2010).

Since functional GI disorders generally are chronic, it is important to determine the immediate reason for each doctor’s visit. Yet many clinicians are concerned about overlooking alternative diagnoses (Spiegel et al., 2010). Based on this and on the severity and kind of symptoms, the patient’s physiologic- and psychosocial factors of the illness behavior and the degree of functional impairment, the therapy is then customized (Drossman & Swantkowksi, 2011). The symptoms of the disease can be divided into mild-, medium- and severe categories.

Patients with mild symptoms are usually found in the primary care unit. These patients have no pronounced impairments of their daily life and either no or only few psychological troubles. They are worried about their condition but rarely visit their

physicians. Instead, the treatment of these patients includes educational advice on their impairment and its symptoms as well as information about the correct diet, the right use of medication, their undesired side-effects and disadvantages (Abraham & Kellow, 2011).

Patients with moderate symptoms, who are generally found in primary- and secondary care units, experience alternating impairments in daily life activities. A relationship between symptoms and trigger factors (stress, travelling or dietary irregularities) can be established. This is why symptom monitoring and recording of the time of onset, severity and the existence of associated factors are important and can contribute to the detection of triggering factors. This gives the patients the feeling of having some control over their disorder. Additionally, medical therapy can be especially helpful against those symptoms, which impede daily life. A psychological therapy can help to reduce anxiety and restlessness and encourage the patient to behave in a way that improves the health.

Patients with severe symptoms have difficulties with daily life and conceive their disorder as strongly disabling. They have strongly associated psychological difficulties. The clinical complaints result in many doctors' visits.

In the latter case a long-term doctor-patient relationship is necessary. This is the only way to reach realistic treatment goals (such as achieving an improvement of quality of life rather than the complete elimination of pain). The focus for these patients must be directed towards moving away from the treatment of an illness to the handling of a chronic disorder (Drossman & Swantkowksi, 2011). Further diagnostic approaches depend on the age and the medical history of the patient (National Institute for Health and Clinical Excellence, 2008).

But most family practitioners who have been questioned have not heard of the Manning or Rome criteria or recognized the Rome II symptoms as typical of IBS (Bijkerk et al., 2003).

In summary: A verified diagnosis of IBS relies on a normal physical examination in connection with a restricted relevant diagnostic clarification. Further diagnostic examinations depend on the age and the medical history of the patient (Mertz, 2003). If

there are no „red flag“ symptoms, the diagnosis relies on the validated symptom criteria of Rome III.

1.1.11 Therapy

The basis for the treatment of functional gastrointestinal disorders is a good therapeutic patient-physician relationship (Moayyedi & Ford, 2011). This confidential patient-physician relationship seems to be important in the context that patients with functional gastrointestinal disorders have a placebo reaction rate of 30% to 80% (Kaptchuk et al., 2010, Drossman & Swantkowksi, 2011).

In IBS, the pattern and the manifestation of symptoms are different in every individual. Many patients have mild symptoms with irregular frequency and low intensity. They need no or very little medicinal treatment. Others, however, can be downright incapacitated by persistent symptoms and thus urgently seek medical advice in the hope for a lasting cure (Drossman & Dumitrascu, 2006).

In mild IBS cases, therapy can first consist of comforting support in combination with instructions for a proper diet, which is rich in fibers and bulking agents. In severe IBS, depending on the case, a medical therapy with antibiotics (Gwee, 2010), antidepressants, antispasmodics, laxatives or anti-diarrheal agents can be administered (Camilleri, Heading, & Thompson, 2002); (Kwon et al., 2011). But medicines are only good for some symptoms and only help some of the patients (Ramkumar & Rao, 2005).

The treatment depends on the type and severity of the symptoms and the kind of accompanying associated psychosocial topics. Psychological factors can change the perception and the interpretation of the symptoms. In those cases, the patient’s response to the symptoms should be considered as important. The treatment is based on a biopsychosocial approach with a trusting therapeutic patient-physician relationship as its base (Khan & Chang, 2010). Most patients show a positive response to psychological support, to a strong patient-physician relationship and to versatile treatment approaches (Spiller, 2003). The doctor should be understanding, should stay in contact with his patients and should favor simple examination and treatment methods. Unsatisfied patients possibly consult several physicians, undergo pointless and dangerous interventions, take

untested medicines and undergo unnecessary surgery (Longstreth & Yao, 2004; Longstreth, 2005; Talley, 2004).

Medicinal therapies against irritable bowel syndrome, with the exception of antibiotics, are generally directed at the motor-, sensory- or central-gastrointestinal nervous system. Conventional therapies for IBS include lactose reduction, fiber supplementation, smooth muscle relaxants / antispasmodics, antibiotics, psychological interventions and antidepressants. Some of the conventional therapies have a proven effect (e.g. smooth muscle relaxants / antispasmodics, psychological interventions and antidepressants). Others have shown little effect in randomized controlled trials but are often used (e.g. fiber supplementation, stimulating laxatives and bulking agents) (Halpert et al., 2005). However, the efficacy of these conventional therapies varies from study to study (Camilleri et al., 1999; Muller-Lissner et al., 2001).

Usual medical care for irritable bowel syndrome emphasizes education and lifestyle modification more than drugs; patients have a greater expectation of benefit from lifestyle modification than drugs (Whitehead et al., 2004). A recent review found that generally speaking the efficacy of medicinal therapies for IBS is weak (Quartero et al., 2005).

Cognitive behavior therapy, standard psychotherapy and hypnotherapy can help individual IBS patients (Drossman et al., 2003). Depressed patients, however, only occasionally respond to these therapies with their quality of life improved, but not their pain. Hypnotherapy only showed its positive effects in uncontrolled studies and there is no proof so far for the efficacy of psychological treatments (Simren, Ringstrom, Bjornsson, & Abrahamsson, 2004; Palsson, Turner, Johnson, Burnett, & Whitehead, 2002). Hypnotherapy, the most thoroughly investigated psychological treatment method, certainly normalizes the rectal sensitivity (Lea et al., 2003), 12 sessions improve the life quality, anxiety and depression in resistant patients (exception: Men with IBS and diarrhea). These advantages prevailed for five years (Gonsalkorale, Miller, Afzal, & Whorwell, 2003).

Due to the lack of reliable and effective medicines with little side-effects for IBS, there is a growing interest in complementary and alternative forms of therapy (Drossman, 1999). The number of randomized trials of complementary treatments has doubled every

five years, and The Cochrane Library includes nearly 50 systematic reviews of complementary medicine interventions (Vickers, 2000). Between 11% and 43% of the patients with gastrointestinal disorders receive alternative or complementary forms of therapies. Many consider them beneficial (Spanier, Howden, & Jones, 2003).

Alternative treatments can even have positive effects (Spiller, 2005). This phenomenon was evaluated in some of the Cochrane Reviews, e.g. acupuncture (Lim et al., 2006), psychological treatments (Zijdenbos, de-Wit, van der Heijden, Rubin, & Quartero, 2009), hypnotherapy (Webb, Kukuruzovic, Catto-Smith, & Sawyer, 2007) and herbaltherapy (Liu, Yang, Liu, Wei, & Grimsgaard, 2006).

Osteopathy is constantly gaining in popularity and acceptance in medicine for the treatment of certain illnesses and also gastrointestinal disorders and is already mentioned in the German "S3 guideline for IBS" (Layer et al., 2011). Osteopathy could establish itself as an alternative modality.

1.1.12 Economic Costs

Whitehead et al. (Whitehead et al., 1996) showed that IBS patients have significantly lower SF-36 scores than healthy controls. The symptoms of irritable bowel syndrome lead to an increased number of doctors' visits, work absenteeism, change of workplace, termination of employment and early retirement (Drossman et al., 1993). With an estimated IBS prevalence of approximately 7 to 10% in Europe, the estimated annual costs per patient for medical treatments sum up to about 1,600 Euros. In the USA, the prevalence also surpasses the 10% rate, (Choung & Locke, III, 2011) which causes about 3.5 million visits to physicians and about 2.9 million prescriptions per year. In the year 2002, the total annual direct costs per patient in the USA added up to approximately 348 to 8,750 US dollars. The total number of sick days of IBS patients on an average were between 8.5 and 21.6 days per year (Maxion-Bergemann, Thielecke, Abel, & Bergemann, 2006). This led to an estimated cost of20,000 to 40,000 US dollars per QOL-AD per patient (Bracco, Jonsson, Ricci, Drummond, & Nyhlin, 2007).

Most primary care providers believe IBS is a diagnosis of exclusion; this belief is associated with increased resource use (Spiegel et al., 2010). The available data has a

broad spectrum, however, it can be concluded that IBS causes a significant use of resources and induces a high level of work absenteeism (van Tilburg et al., 2008).

1.2 Osteopathic Context

The roots of osteopathy are in the USA and date back to the year 1847. There, „Osteopathy" was discovered by Andrew Taylor Still (1828 to 1917). Dr. Still founded a philosophy of medicine, based on ideas that date back to Hippocrates, one of the forefathers of medicine. The focal point is the inseparability of the body. Osteopathy is applied in preventative health care and also in healing ailments. Osteopathy is the manual art of healing. It is a diagnostic and therapeutic approach to cure motility restrictions of the tissue. It is a holistic concept of the connection between all tissues and organs. Herein, the lymphatic, osseous as well as the viscero-neuro-muscular skeletal system plays a major role (Liem, Sommerfeld, & Wührl, 2008).

Osteopathy is practiced in the USA, all countries of the European Union, Israel, Canada, New Zealand and Australia. Typical for osteopathy is the manual contact during the diagnosis and the treatment. The treatment benefit is based on the experience of relaxation, the normalization of inner- and outer autonomous control mechanisms and the release of stases. Osteopathy relies on the body's ability to heal itself.

One of the osteopathic principles is the interrelationship between structure and function. Free and unlimited physiological motility within all bodily structures and tissues is elementary for maintaining the body's health and essential for the "*restitutio ad integrum*" after an illness or an injury. In osteopathy, the loss of tissue motility is the cause of a disorder of the basic self-regulating forces of the human body. Osteopathy relies on manual contact during diagnosis and treatment. The osteopathic diagnosis is based on judging the body's functions, as well as carrying out soft specific movements of joints and organs. An essential component of the diagnosis is the ability to feel and evaluate the body's own rhythm (Still, Littlejohn, & Sutherland, 2009), the tissues and the flow of liquids in different tissues and regions of the body. These results are found in the areas of the musculoskeletal, neural and visceral systems. By using palpatory examinations and motility evaluations, the osteopath can feel motility restrictions and changes in texture and tone of the tissue, which could be relevant for the patient's

symptoms. Therapy includes careful stretching, mobilizing techniques and possibly, if indicated, manipulation of tissue and joints. This manual procedure is applied in the different identified body regions of tissue restrictions.

In IBS therapy, the osteopathic treatment of abdominal organs and supplying blood, lymph and nervous systems, is of special interest. The viscera itself or the peritoneal structures around the viscera might have lost their normal motility and elasticity. In this connection, the dysfunction of the „brain-gut axis“ (Mertz et al., 2000) in IBS might be of special interest. The treatment of nerves and the brain itself is a fundamental possibility in osteopathy.

The therapeutic goal of the osteopathic treatment of IBS is to improve or regenerate the motility within the environment of the organ. Another goal of visceral therapy can be the regeneration of motility deviating from physiology, i.e., the impaired motility of an organ. Of course Aristotle's quote holds true in osteopathy: "The whole is different from the sum of its parts". In the treatment of living tissue, the soul and mind are naturally influenced and treated as well. Osteopathy is therefore a holistic therapy. In osteopathy, symptoms or even illnesses are not treated but rather the entire "Person" or respectively his health. The focal point of therapy is not the illness but the health (Still et al., 2009). The goal is to free and therefore strengthen health. Osteopathic treatment of impaired tissue reestablishes motility within the body and in between different layers of tissue. The loss of tissue motility through physical and psychological kinds of trauma is improved or eliminated. The loss of motility and therefore lost health of the tissue and of the whole body is restored. Osteopathy influences the visceral and neuro-vegetative system (Barral, 1988). This fact coincides exactly with the concept of the "brain-gut axis" and the biopsychosocial model of IBS (Gaynes & Drossman, 1999). It is therefore not unlikely that the various osteopathic forms of treatment make it possible to influence the different levels of the "brain-gut axis". It can thus be assume that an osteopathic treatment is a potentially promising therapy for IBS and for the treatment of this frustrating problem.

Nowadays, case studies and personal experiences are not sufficient anymore to justify a therapy or intervention. The efficacy/effectiveness and safety of therapies must

be proven in randomized trials with clear initial instructions and in terms of evidence-based medicine.

The primary goal of the treatment of IBS is the elimination of pain and an improvement of the patient's quality of life. This may also result in fewer days of work absenteeism and thus in a reduction of the related economic costs.

1.3 Objectives

The assumption that osteopathy has a supporting influence on different gastrointestinal disorders is the inspiration for this objective summary of the findings of different clinical trials. This appears to be the first objective assessment of the efficacy of the osteopathic treatment of IBS, published by Guillaume et al. in 1998 showed a relief of the main GI-symptoms in patients (bloating, diarrhea, abdominal pain) (Guillaume et al., 1998). A newer randomized controlled study (Hundscheidet al., 2007) showed similar results. Since there was some evidence that more RCT`s might exist, a systematic review and possibly meta-analysis of all existing data on the efficacy/effectiveness of an osteopathic treatment of IBS was undertaken.

Chapter 2: Methods

2.1 Criteria for Considering Studies for this Review

2.1.1 Types of Studies

Only randomized controlled trials or controlled clinical studies (CCT) will be included. The publication must have been published or be available via internet, a library or via the authors. The search strategy will not be limited by language.

2.1.2 Types of Participants

Only intervention studies on IBS should be considered where patients were diagnosed via Rome I-, Rome II- or Rome III Criteria. The subjects had to be adults (over 18 years of age). Studies with children were not considered.

2.1.3 Types of Intervention

The study design had to be appropriate to establish causality between effect and treatment. If the osteopathic treatment was not the sole intervention in the intervention group, the same basic/additional interventions had to be applied to the control group. The nature of the intervention in the control group was not restricted, and thus placebo, standard medical or other therapies were possible.

2.1.4 Types of Outcome Measure

For this review subjective pain parameters like the visual analogue scale (VAS) or number rating scales (NRS-101) for abdominal pain or the results of functional pain questionnaires was considered as a primary outcome measure. The meta-analysis was based on the primary outcome measure.

The secondary outcome measures were determined from the other outcome measurements included in the studies. They were extracted and descriptively analyzed for all included studies.

2.2 Search Strategy for the Identification of Studies

2.2.1 Electronic Searches

The literature search for relevant studies was carried out in 2010 at different times in the following electronic databases:

- PUBMED
- EMBASE
- COCHRANE LIBRARY
- SCIENCE DIRECT
- PEDro
- OSTMED-DR
- OSTEOPATHIC WEBRESEARCH
- GOOGLE SCHOLAR

Within the specific database (PEDro, OSTMED-DR OSTEOPATHIC WEBRESEARCH) the search was sensitive, i.e., it was searched via the medical term of illness or a synonym but it was not narrowed down by the kind of therapy or study. Synonyms were derived from the entry terms to the mesh term “Irritable bowel syndrome” in Medline as well as from keywords in medical articles.

For large data bases a comprehensive strategy was developed and applied as suggested by the Cochrane Collaboration and medical writers (Higgins & Green, 2008; Kunz, Khan, Kleijnen, & Antes, 2009), based on the combination of terms of population, intervention and study design. The combination of terms followed “The rules of the rules” of Boolean algebra. The final search strategy for the systematic search in Medline (PubMed) is depicted below. [See Table 1] This search strategy was adapted to the respective syntax for searches in other databases.

Table 1: Search Strategy for the Identification of IBS Studies

#1	((functional colonic diseas*) OR(irritable bowel syndrome*, OR (syndrome*) OR (irritab* bowel*) OR (colon, irritable*) OR (irritable colon) OR (colitis, mucous) OR (colitides, mucous) OR (mucous coliti*) OR (mucous colitis) OR (irritable OR functional OR spastic) OR (bowel OR colon))	results 1869012
#2	"irritable bowel syndrome " (Mesh)	results 2662
#3	osteopath*	results 7973
#4	"osteopathic medicine" (Mesh)	results 2345
#5	"manipulation, osteopathic" (Mesh)	results 241
Search-box	(#1 OR #2) AND (#3 OR #4 OR #5)	results 662
Search-box	(#1 OR #2) AND (#3 OR #4 OR #5) limits: Clinical trial, randomized controlled trial, controlled clinical trial	results 25

2.2.2 Searching for Other Resources

In addition to the electronic searches, a manual search in the reference lists of all relevant papers, which were not listed in the electronic databases, was carried out. Personal communication was conducted with experts in the field of visceral osteopathy to identify additional studies.

2.3 Data Collection and Analysis

Citation identification, study selection and data extraction were undertaken by the reviewer.

The search results were checked for relevant studies. If no complete texts were available the abstracts were examined. For those studies without available abstracts a

possible suitability was suggested via their title. Finally the following publications were deemed relevant for further investigation.[See Table 2]

Table 2: Search results

Database	Results of Potential Interest	
	Duplicates	**New**
Pubmed Www.ncbi.nlm.nih.gov/pubmed/ Last date of search: 1-15-2011 Search strategy: Specific search strategy see at the end of this table 25 results	None	Hundscheid2007
Embase Via www.dimdi.de Last date of search: 11-15-2010 Search strategy: Irritable bowel syndrome or functional colonic disease or colon irritable or spastic colon or IBS or colitis and osteopath? (all in text fields) 18 results	Hundscheid2007	None
The cochrane library Www.cochrane.de/de/browse.htm last date of search: 10-4-2010 Search strategy: (irritable bowel syndrome or functional colonic disease or colon irritable) and (osteopath* or manipulative treatment) in (search all text) 2 results	Hundscheid2007	Muller 2002

Table 2: Search results, continued

Database	Results of Potential Interest	
Osteopathic research web Www.osteopathic-research.com Last date of search: 12-10-2010 Search strategy: Irritable bowel syndrome or Functional colonic disease or Colon irritable (all fields) 4 results	Muller 2002	Mitchell 2002 Scheuchl (In Progress) Steiner 1970
Pedro Www.pedro.org.au Date: 10-12-2010 Search strategy: Irritable bowel syndrome (abstract and title) 10 results Colon irritable (abstract and title) 1 result Colitis (abstract and title) 1 result	None	None
Ostmed.dr Www.ostmed-dr.com Last date of search: 11-20-2010 Search strategy: "irritable bowel syndrome" or (functional colonic disease" or "colon irritable" in (keyword) 90 results	None	None
Manual search In reference lists of articles in journals and books Or **Personal communication** With experts in the field Until september 2010	None	Guillaume 1998 Chiesa 2003

Table 2: Search results, continued

Database	Results of Potential Interest	
Google scholar www.scholar.google.de Last date of search: 11-15-2010 Search strategy: "Irritable bowel syndrome" osteopathic (in title) 3 results "irritable bowel syndrome" osteopathy (in title) 2 results "IBS" osteopathic or osteopathy or Osteopathie (in title) No results irritable bowel syndrome osteopathic treatment 994 results	 Hundscheid2007 Stasiuk 2004 Hundscheid2007 Stasiuk 2004	 Brice 2000 Stasiuk 2004
Total	8	9

These publications were retrieved as complete texts and their contents were then analyzed in detail according to inclusion and exclusion criteria [See Appendix D].

Data was extracted from the primary outcome measures of the patient's pain symptoms, as well as from the secondary outcome measures of the specific GI-symptoms, described under chapter 3.4.4.

For the characteristics of the study population, such as average age and gender, diagnostic method, BMI and duration of irritable bowel syndrome, a standardized form was used which was also applied in the Cochrane Reviews on IBS (Evans, Clark, Moore, & Whorwell, 2007; Lim et al., 2006; Zijdenbos et al., 2009).

If there were no data on the study design or the calculation of the effect size of the primary outcome, the authors – as far as possible – were interrogated [See Appendix C].

2.4 Assessment of Methodological Quality

It is common practice in contemporary medicine to follow stringently the scientific method in the process of validating efficacy and effectiveness of new or improved modes of treatment intervention establishing the best available evidence in complementary and alternative medicine (CAM). It follows that these complementary or alternative interventions must be validated by stringent research before they can be reliably integrated into medicine (Chiappelli, Prolo, Rosenblum, Edgerton, & Cajulis, 2006).

The methodological quality of the RCT`s was assessed by:

Chapter 1 The Jadad Score / Oxford Scale (Jadad et al., 1996), and,

Chapter 2 The Linde Internal Validity Scale, which has been used in several systematic reviews of complementary medicine (Linde et al., 1996a; Linde et al., 1996b; Linde et al., 1997; Linde et al., 2005).

The Linde Internal Validity Scale has the following six items:

1. Method of allocation to groups,
2. Concealment of allocation,
3. Baseline comparability,
4. Blinding of patients,
5. Blinding of evaluators, and,
6. Likelihood of selection bias after allocation to groups due to dropouts.

Each item is scored as:

- Criterion met……1.0 points
- Criterion partially met……...0.5 points
- Criterion not met or insufficient information provided…….....0.0 points

The Jadad or Oxford Scale (Jadad et al., 1996) evaluates the performance quality of studies, not the quality of the results. Questions about quality assurance or quality evaluation are as follows:

First question block:

1A. Was the study described as randomized? Yes = 1 point, No = 0 points 1B. If the above answer is yes: Was the method of generating the randomization sequence appropriate? Yes = 1 point, No = minus 1 point

Second question block:

2A. Was the study described as double blind? Yes = 1 point, No = 0 points 2B. If the above answer is Yes: Was the method of double blinding appropriate? Yes = 1 point, No = minus 1 point

Third question block:

3. Was there a description of dropouts and withdrawals? Yes = 1 point, No = 0 points

⇨ Add: 1A+1B+2A+2B+3 = ∑

∑ = maximum possible are 5 points Result:

∑= 0 to 2 points	⇨	low quality
∑= 3 to 5 points	⇨	high quality

With the Cochrane software RevMan, a forest plot for the primary outcome measure was calculated, based on the standardized mean difference with a confidence interval of 95% (SMD; 95% CI).

Small studies were found in the preliminary investigation. For the forest plot a random-effects model was chosen, which was designed for smaller studies with possibly higher heterogeneity (Higgins & Green, 2008; Kunz et al., 2009). In case of inconsistent study results, explanatory models were discussed.

Chapter 3: Results

3.1 Results of the Search

Sixteen studies were identified by the reviewer. [See figure 1] After duplication removing nine studies remained. After screening four studies were included [See table 3]. in the qualitative review in contrast to only three studies in the meta-analysis.

The four included studies [See Table 3] were randomized controlled trials and came from France, Great Britain, Germany and the Netherlands.

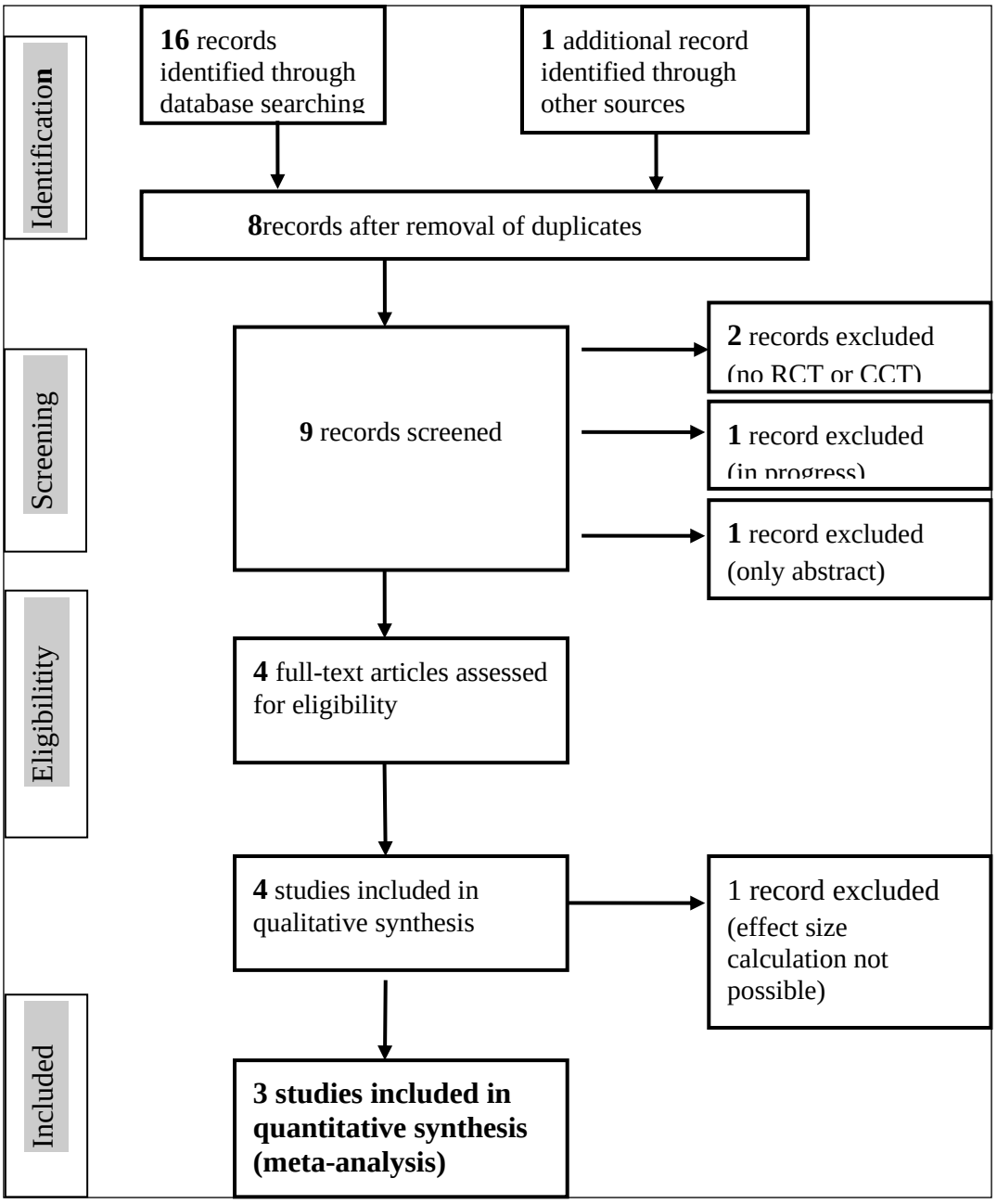
The demographic parameters [See Table 4] of the included studies were analyzed. None of the trials included children.

The included studies were characterized [See Appendix E] and the data were extracted [See Appendix F].

An overview of the data of the included studies is provided [See Table 5].

Five studies were excluded. [See Table 6]. Three studies (Stasiuk, Nicholls, & Kiatos, 2004; Steiner, 1970; Mitchell, 2002) were excluded for being a controlled, but not a randomized controlled study. Only an abstract was available for the study by Chiesa (Chiesa, Pomerantz, Shinkle, Chiesielski, & Cavalieri, 2003). At the end of the process the study by Scheuchl (Scheuchl, 2011) was still in progress.

Figure 1: Flowchart Study Selection „Osteopathic Treatment for IBS"



The flow of information is based on a diagram as recommended in the PRISMA statement (Moher, Liberati, Tetzlaff, Altman, & The Prisma Group, 2009).

Table 3: Included Studies

Name	Intervention	Control Group	Study Design
Guillaume 1998	Osteopathic Treatment	Sham Treatment	RCT
Brice 2000	Osteopathic Treatment	Standard Medical Care	RCT*
Müller 2002	Osteopathic Treatment	Sham Treatment	RCT
Hundscheid2007	Osteopathic Treatment	Standard Medical Care	RCT

* Only included for the descriptive analysis.

Table 4: Descriptive Parameters of Included Studies

Author, Year, Country	**No. of Patients**	**Age (Years)**	**Sex**	**Weight (Kg)**	**BMI**
Guillaume 1998 France	Intervention: 23 Control: 19	Intervention: 47.1 (+/-2.74) Control : 50.8 (+/-2.52)	Intervention: M3, F20 Control: M4, F15	Intervention : 62.35 (+/-2.06) Control: 61.63 (+/-2.41)	Not Reported
Brice 2000 Great Britain	Intervention: 20 Control: 20	Intervention: 45.5 Control: 41.9	Intervention: M0, F20 Control: M1, F19	Not Reported	Not Reported
Muller 2002 Germany	Intervention: 28 Control: 25	Intervention: 50 Control: 47	Intervention: M5, F23 Control: M4, F21	Not Reported	Intervention: 23.5 Control: 25.4
Hundscheid 2007 Netherlands	Intervention: 20 Control: 19	Intervention: 46.5 Control: 41	Not Reported :	Not Reported	Not Reported

Table 5: Overview of Data of Included Studies

	Guillaume 1998	Muller et al. 2002	Hundscheid 2007	Brice 2000
Control Group	Placebo	Placebo	Standard Medical Care	Standard Medical Care
Randomization	Block of 4 Patients	External Randomization	Via Envelopes	First 20 into Intervention Group, Next 20 into Control Group
No. of Osteopaths	10	3	1	1
No. in Intervention Group	23	31	20	20
No. in Control Group	19	30	19	20
No. of Dropouts in Intervention Group	1	2	1	Not Reported
No. of Dropouts in Control Group		2		Not Reported
No. of Treatments	5	5	5	4
Endpoint	End Of Treatment	End Of Treatment	1 + 3 Months	6 Weeks
Follow-Up	2 Weeks	2 Weeks	3 Months	6 Weeks
Intervention	Defined Techniques	Defined Techniques	Custom Tailored	Custom Tailored
Assessment Instrument for: Pain/Overall Wellbeing	VAS 0mm = 0 Pain 100mm = Max Pain	VAS 0mm = 0 Pain 100mm = Max Pain As	FBDSI (110 Very Severe)	IBS Symptom Diary
Improvement of Symptoms: PAIN Intervention Group	VAS In Mm 17.26 (+/-6.55)	VAS In Mm 51.65	174 (SD +/-36) At The Beginning 74 (SD +/-64) After 6 Months	Not Reported
Improvement of Symptoms: PAIN Control Group Associated P-Value	$P < 0.0156$	$P < 0.001$	171 (Sd +/-31) At The Beginning 119 (Sd+/-48) After 6 Months	$P < 0.001$

Table 5: Overview of Data of Included Studies, continued

	Guillaume 1998	Muller et al. 2002	Hundscheid 2007	Brice 2000
Overall Wellbeing Intervention Group	Not Reported	Not Reported	- Free Of Symptoms 5% - Overall Improvement 68% - Slight Improve-ment 27% - Worsening 0%	
Overall Wellbeing Control Group	Not Reported	Not Reported	- Free Of Symptoms 0% - Overall Improvement 18% - Slight Improvement 59% - Worsening 17%	
Overall Wellbeing Associated P-Value			P < 0.006 In Favor Of Intervention	P < 0.001 In Favor Of Intervention
Jadad Score	Low (close to „High")	High	High	Low
Linde Validity Scale Score	4	5	5	3

Table 6: Excluded Studies

Name	Intervention	Control Group	Study Design
Stasiuk 2004	Osteopathic Treatment	None	Case Series
Chiesa 2003*	Osteopathic Treatment	Sham Treatment, No Treatment	RCT
Mitchell 2002	Osteopathic Naturopathic Treatment	None	Case Series
Steiner (1970)	Osteopathic Treatment	None	Case Series
Scheuchl (in progress)	-	-	

* Only abstract available

3.2 Methodological Quality of Included Studies

Methodological quality was assessed using the Linde Internal Validity Scale and the Jadad Scale [See Tables 7 and 8]. In most of the studies, the number of participants was small and the methodological quality mediocre to reasonable. All studies included in this review reported patient randomization. Two studies (Hundscheid2007, Muller 2002) described the randomization process and allocation concealment in detail. Muller (2002) randomized via a specialized electronic randomization program. Hundscheid(2007) randomized via closed envelopes which contained the allocated treatment. Guillaume (1998) quasi-randomized patients in "blocks of four". Brice (2002) quasi- randomized the first 20 persons into the osteopathic group, the second half into the standard medical care group. In some cases the data of the study were not clear.

In all studies, patients signed an informed consent; patients were regarded to be blinded.

In three studies the handling of withdrawals was described in detail. The study by Brice et al. had no statement about drop outs.

All studies described baseline characteristics of the osteopathic and the control groups. In two studies (Guillaume, 1998; Brice, 2000), the baseline characteristics showed some statistically significant differences but were altogether comparable utilizing the Mann-Whitney test.

In two studies (Guillaume, 1998; Muller, 2002), standard medical care was possible in both groups but the medication had to be stopped 48 hours before the osteopathic treatment.

Table 7: Linde Internal Validity Scale Score, Summary

	Method of Allocation to Groups	Conceal-ment of Allocation	Baseline Compara-bility	Blinding of Patients	Blinding of Evaluators	Likelihood of Selection Bias after Allocation to Groups by Dropouts	Result
Guillaume 1998	0.5	1	0.5	1	0	1.0	4.0
Brice 2000	0.5	1	0.5	1	0	0	3.0
Muller 2002.	1	1	1	1	0	1	5.0
Hundscheid 2007	1	1	1	1	0	1	5.0

Table 8: Jadad Score for Internal Validity, Summary

Study ID	Was the study Described as Random-ized?	Was the Method of Generating Randomiza-tion Sequence Appropriate?	Was the Study Descri-bed as Double Blind?	Was the Method of Double Blinding Appropriate ?	Was there a Descrip-tion of Dropouts and Withdraw-als?	∑	Quality
Guillaume 1998	1.0	0.0	0. (+1.0)*	X	1	2.0 (3.0)	Low (high)
Brice 2000	1.0 (0)	0.0	0. (+1.0)*	X	0	1.0 (2.0)	Low (low)
Müller 2002	1.0	1.0	0. (+1.0)*	X	1	3.0 (4.0)	High (high)
Hundscheid 2007	1.0	1.0	0. (+1.0)*	X	1	3.0 (4.0)	High (high)

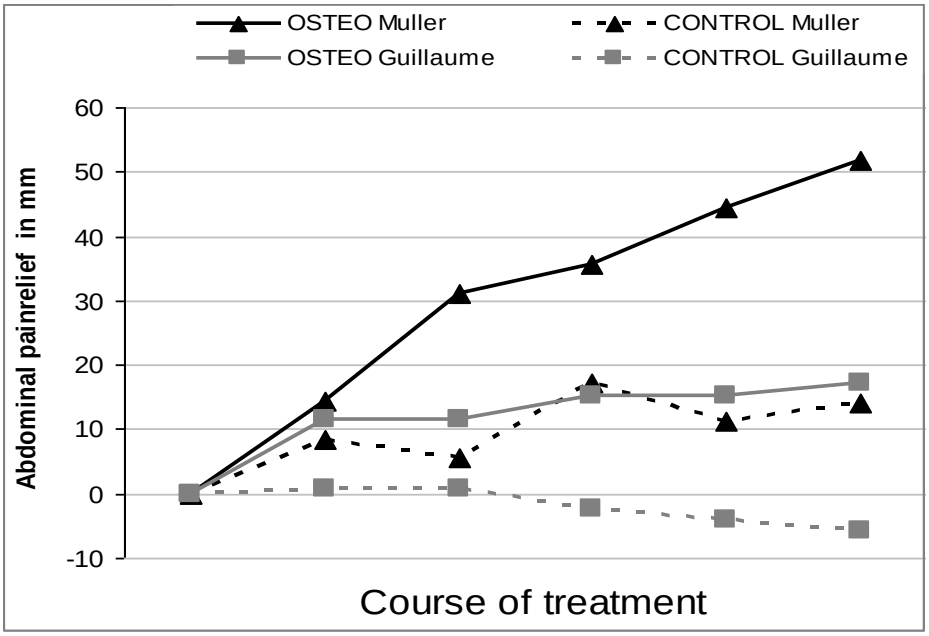
*The blinding of the osteopath is not possible. This is why all studies received a 0-point rating. If on the contrary all studies had been given a 1-point rating, only the result of the GUILLAUME study would have received a qualitative appreciation.

3.3 Descriptive Analysis of the Studies

3.3.1 Descriptive Analysis of the Studies of Guillaume (1998) and Muller (2002)

To make a descriptive analysis of the studies of Guillaume (1998) and Muller (2002) possible, the baseline values in respect to the primary outcome pain were reset to zero on the VAS (visual analogue scale).In the further course of the study, the reduction of pain (via VAS) at different times, as done in the Guillaume et al. (1998) study, was described as an "Improvement" with positive numbers in the Muller et al. (2002) study. By inverting the preceding sign of the successful study outcome in the Muller et al. (2002) study and the creation of a diagram containing the results of both studies, the basis for a descriptive comparison was established [See Figure 2].

Figure 2: Comparison of results via VAS of the studies of Guillaume (1998) and Muller (2002): Abdominal pain relief during course of treatment (Muller et al. (2002) with inverted signs)



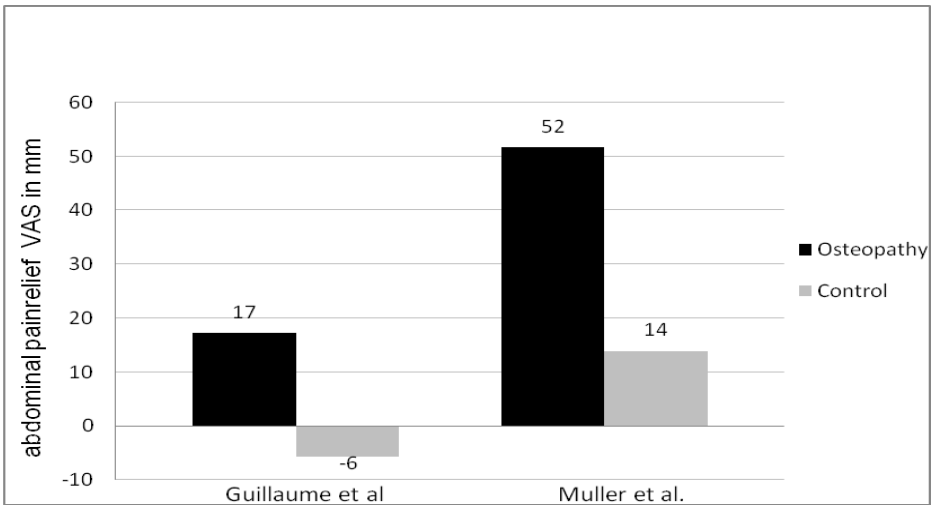
Longitudinal changes [See Figure 2] in the main outcome „PAIN" show remarkable similarities in the intervention groups of both studies, especially after the initial treatment.

While the outcomes are similar, the kinetics of changes during the course of treatment differs between the two studies. The Muller et al. (2002) intervention group shows continuous progress after the second treatment whereas the curve of the Guillaume et al. (1998) group drops clearly and starts resembling the course of its own sham group. The success after the initial treatment in the Muller (2002) sham group turns downward. After that, the curve of the sham group swings up and down and around the curve of the Guillaume 1998 intervention group, which on the average shows a continuous but shallow increase. The initial minimally positive evaluations of the Guillaume et al. (1998) sham group turn negative after the third treatment and continue the decline in comparison to the beginning of the study until the target date. The curve of the Muller et al. (2002) intervention group continuously improves with each treatment. Even the sham group of this trial showed a reduction of pain in comparison to the beginning of the trial but its course is unsteady and the positive statements were later downgraded by the patients.

In the Guillaume et al. (1998) study, “Pain” first decreased slightly after the initial sham treatment in the control group (sham treatment). After the second sham treatment a clear trend reversal could be observed. From here on, for the further course of the sham treatment, an aggravation of the primary target parameter “Pain” can be seen. A reason for this unusual development cannot be determined from this study.

The extent of improvement in both trials is clearly different in size. Nevertheless, the two groups both show a continuous and far more positive development through the interventions than the sham groups. In both trials, the group treated with osteopathy experienced an obvious advantage over that of the group with the sham treatment. [See Figure 3]

Figure 3: Comparison of studies of Guillaume (1998) and Muller (2002): Longitudinal Changes in Abdominal Pain

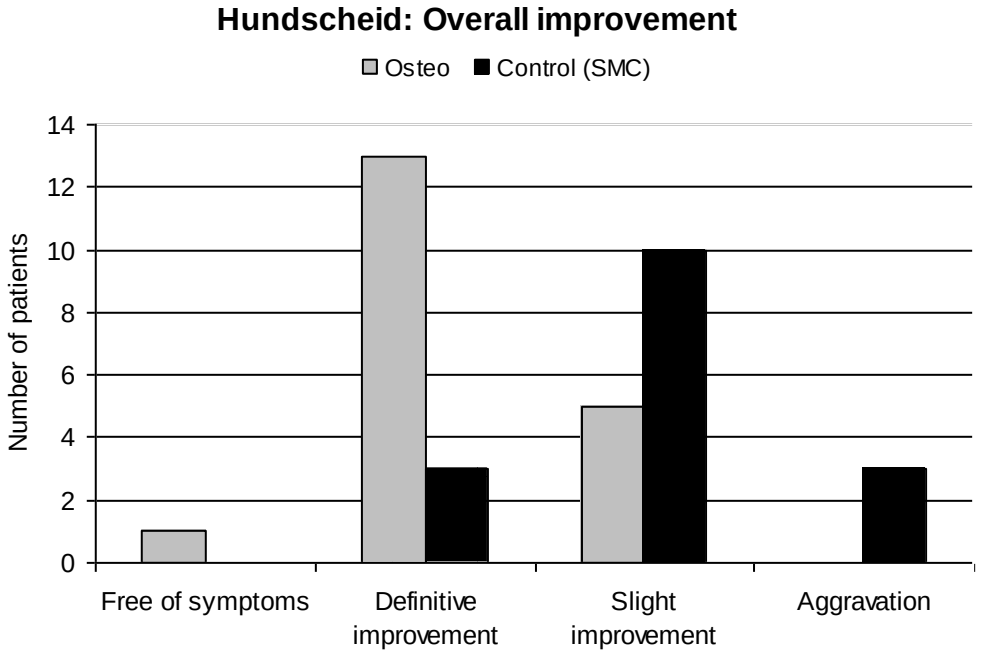


Descriptive Analysis of the Study of Hundscheid (2007)

Treatment outcome was assessed as “overall improvement”. [See Figure 4] In the osteopathic intervention group “definitive improvement” was reported by 13 patients, versus only three in of the control group, where „slight improvement“ was the most common outcome, and where three patients even reported an aggravation.

Overall, the distribution of ratings is clearly different indicating superiority of the osteopathic treatment option over standard medical care.

Figure 4: Study of Hundscheid (2007) –Overall Improvement



When dichotomizing the results [See Figures 5 and 6]. of both groups into "satisfactory results" (free of symptoms or definitive improvement) and "unsatisfactory results" (slight improvement or aggravation), the outcome is therefore also clearly in favor of the osteopathic intervention. Fourteen of the patients treated with osteopathy can be considered to have a satisfactory outcome as compared to only three patients treated with standard medical care [Figure 5]. Necessarily, the majority of patients in the control group (n=13), but less patients in the intervention group (n=4) reported an unsatisfactory outcome [Figure 6].

Figure 5: Study of Hundscheidt (2007) - Satisfying Results

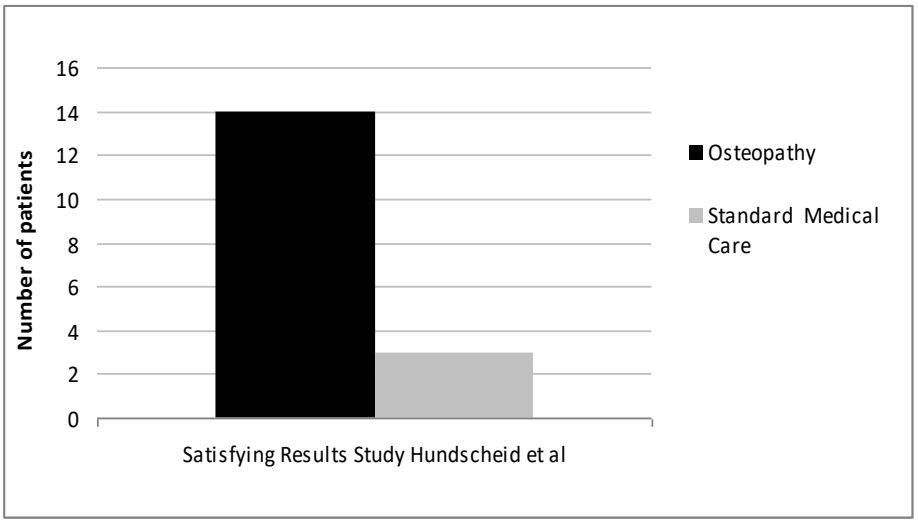
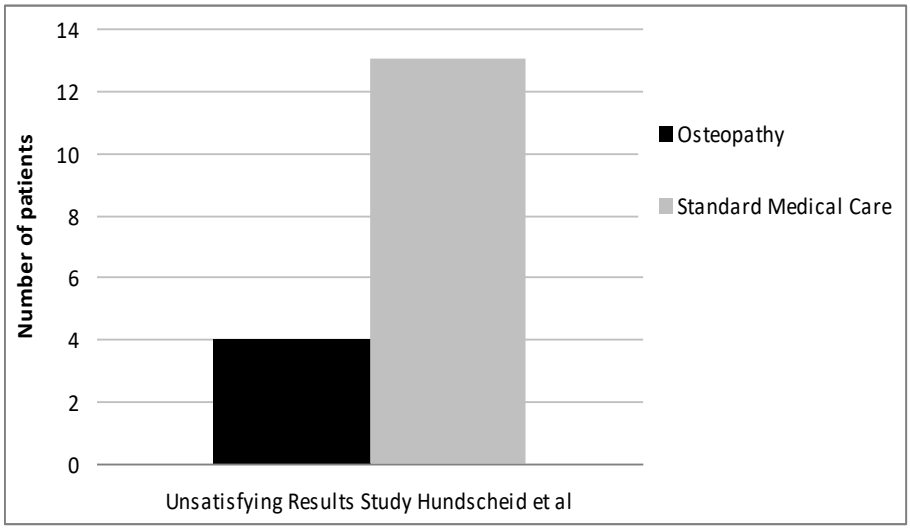


Figure 6: Study of Hundscheidt (2007) - Unsatisfying Results



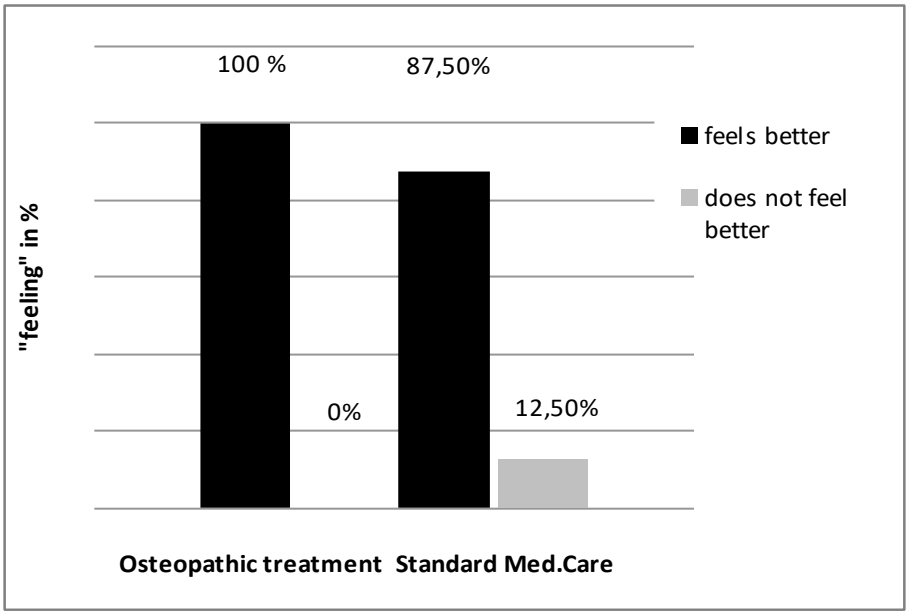
A comparison of all three studies by Guillaume (1998), Muller (2002) and Hundscheid(2007) shows a more pronounced improvement of symptoms in patients who were treated osteopathically as compared to the control groups.

It should be mentioned that the use of "Standard Medical Care" deteriorated the condition of one patient. There was no mention of any deterioration in the osteopathic trials.

3.3.2 Descriptive Analysis of Study by Brice (2000)

Since the results of this study were not presented as data but as statistical differences between groups (p-values and W-values), a direct comparison with the other studies was not possible. The communication expressed the statements of patients of the intervention and control group as the proportion who felt better six weeks after the beginning of the trial [See Figure 7]

Figure 7: Brice (2000) „Subjective Feeling after Six Weeks' Treatment"



Additionally, 19 of 20 persons of the osteopathic group (= 95%) reported a reduction of their symptoms. In the control group, this was the case in four out of eight persons (= 50%).

3.3.3 Secondary Outcome Measures

The secondary outcome measures were markedly different and inhomogeneous in the selected studies: Constipation and diarrhea were recorded in three studies. Only "Gas" was recorded in all of the studies.

Tables 9 and 10 show in summary the specific terms on which the effects of treatment focused.

Table 9: Specific items of the secondary outcome measures

Symptoms	Tested in studies*
Borborgymi	D
Consistency of stool	B
Constipation	A,C,D
Cramps	D
Diarrhea	A,C,D
Feeling of incomplete discharge of feces	B,D
Gas	A,B,C,D
Looser stools during phases of abdominal pain	B
Meteorism	D,C
More frequent stools during pain phases	B
Presence of mucous	D
Sickness	B

* A= Guillaume (1998), B= Brice (2000), C= Muller (2002), D= Hundscheid(2007

Table 10: Summary of other effects measured

Symptoms	Tested in studies*
Nausea	B
Other complaints	A,C
Over all changes	D
Patients feeling after osteopathic treatment	B,C
Side effects	A,C,D
IBSQOL 2000 (Questionnaire)	D
FBDSI (Questionnaire)	D

* A = Guillaume (1998), B = Brice (2000), C = Müller (2002), D = Hundscheid(2007)

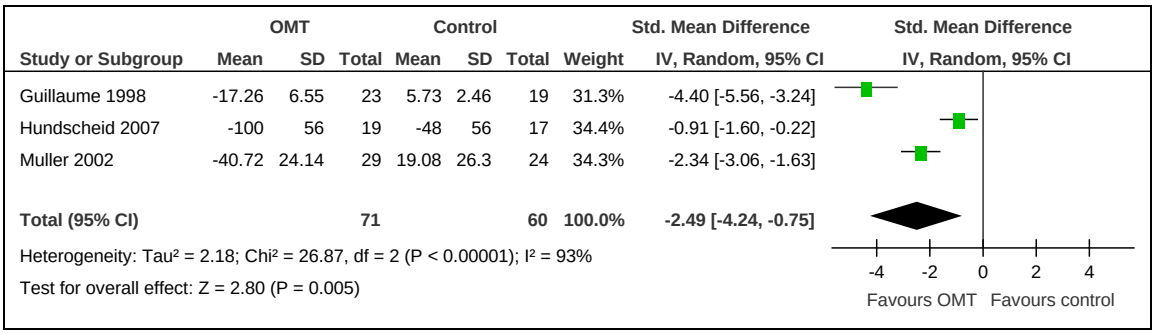
3.4 Quantitative Description of the Studies (Meta-Analysis)

The meta-analysis included three trials. Since standard deviation of the effect size was not provided by Hundscheidet al. (2007), the standard deviations of the initial values of the intervention and control groups were intercalated and used as the standard deviation of the effect size. In the Muller (2002) trial, the standard deviation of the baseline data was calculated before the initial, and after the final treatment [See Appendix G]. The trials by Guillaume (1998) and Muller (2002) are based on the VAS for abdominal pain. The basis for the Hundscheid (2007) trial was the “Functional Bowel Disorder Severity Index” (FBDSI). The FBDSI is calculated via a numerical rating scale

(NRS) for abdominal pain and includes everyday discomfort as well as the number of doctors' visits within a certain timeframe.

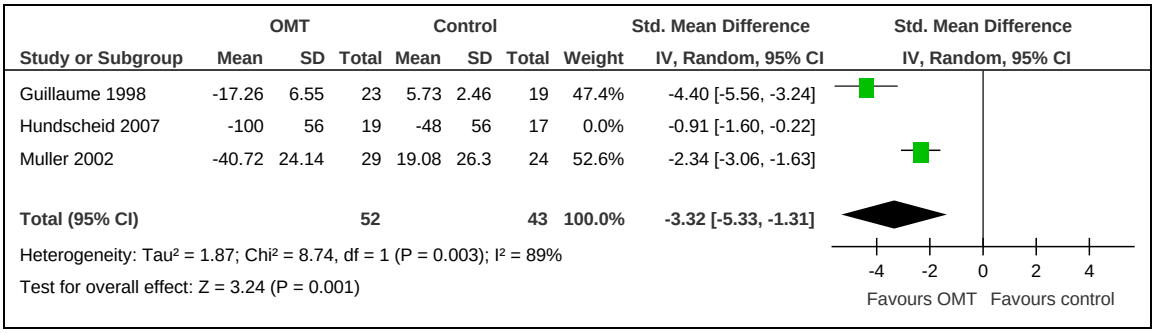
The above mentioned studies (Guillaume (1998), Muller (2002), and Hundscheid(2007)) were analyzed in a random effect model. [See Figure 8] The forest plot shows that all three trials reveal a statistically significant superiority of the osteopathic intervention compared to the control group. Heterogeneity is, however, high indicated by an I^2 of 93%.

Figure 8: Forest plot of the three studies included, in two studies based on a visual analogue scale and in one study on the Functional Bowel Disorder Severity Index (FBDSI)



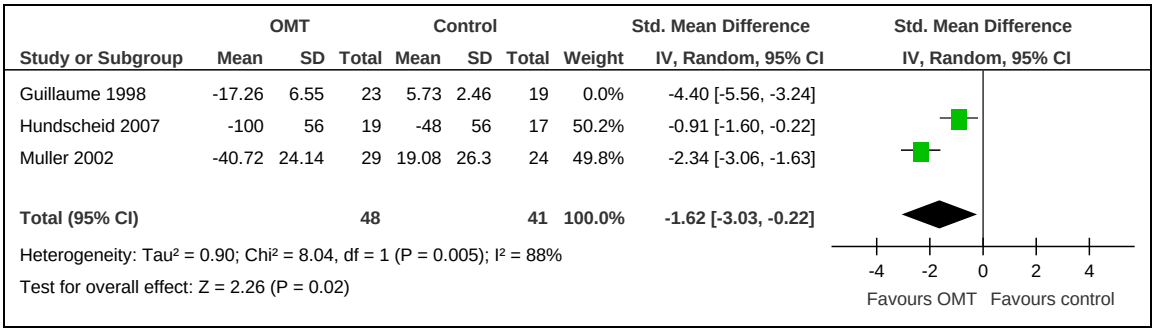
The studies of Guillaume (1998) and Muller (2002) were pooled into a meta-analysis. [See Figure 9]. Both studies had pain as their main outcome, measured at a VAS and a placebo intervention in the control group. In this analysis the effect size increased compared to the three studies from -2.49 (-4.24, -0.75) to -3.32 (-5.33, -1.31). The I2 heterogeneity value slightly improved in three of the studies from 93% to now 89%.

Figure 9: Forest plot of studies included based on visual analogue scale, compared to respective control groups



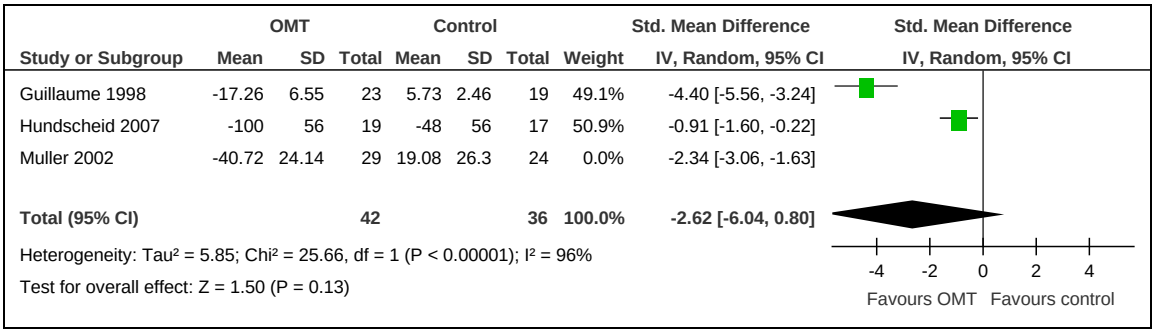
An improvement of the heterogeneity value to I2 = 88% is shown in the graph of the trials by Muller (2002) and Hundscheid(2007). However, at the same time the overall effect size decreases by an average of -1.62 (-3.03, -0.22) [See Figure 10]. Both studies have a different study design regarding primary outcome (VAS vs. FBDSI) and the intervention in the control group (placebo versus standard medical care).

Figure 10: Forest plot of studies Muller (2002) and Hundscheidt (2007). Primary outcome: osteopathic intervention is superior to control intervention.



The forest plot of the studies by Guillaume (1998) and Hundscheid(2007) indicates a marked heterogeneity between studies (I^2 = 96%). The effect size surpasses the zero line with its lower value – indicating a non-significant therapy outcome [See Figure 11]. Both studies have a different study design regarding primary outcome (VAS vs. FBDSI) and intervention in the control group (placebo versus standard medical care).

Figure 11: Forest plot of primary outcome in the studies by Guillaume (1998) and Hundscheidt (2007) showing a probable tendency towards superiority of the osteopathic intervention.



Chapter 4: Discussion

4.1 IBS: The Problem

There is convincing evidence that irritable bowel syndrome is indeed a serious illness (Huertas-Ceballos et al., 2008) which forces the affected individuals to accept enormous limitations to their quality of life (Hahn, Watson, Yan, Gunput, & Heuijerjans, 1998). IBS is one of the most common gastrointestinal illnesses with a suggested prevalence of 10 to 20% (National Institute for Health and Clinical Excellence, 2008). In standard medical therapy as well as complementary and alternative medicine, efforts are made to find explanations for the specific therapy. Research efforts are carried out in all kinds of directions in order to find the cause of IBS. The unknown pathogenesis of the disease may be the main reason (Lydiard, 2001), why only few useful drug have been developed so far (Halpert & Drossman, 2004). The recurring complaints and changing symptoms lead to frequent medical consultations (Leong et al., 2003) and high costs for medical treatment. In addition to these costs are the significant costs for workplace absenteeism (Bracco et al., 2007).

The diagnosis of IBS is not straight forward. It is mainly based on the trias: abdominal pain or discomfort, bloating, and change in bowel habit (ABC) and on the exclusion of other gastrointestinal diseases. The associated concomitant symptoms such as backache or lethargy etc. are generally unspecific.

The analysis of the literature clearly shows that currently there is no gold standard for the treatment of IBS. Currently even guidelines do not have much more to offer than advice on how to relieve the symptoms (National Institute for Health and Clinical Excellence, 2008). Besides “dietary / lifestyle advice” there is first-line pharmacological treatment such as “antispasmodic agents, laxatives for constipation or antimotility agents in case of diarrhea” and second-line pharmacological treatment based on antibiotics or “tricyclic antidepressants or selective serotonin reuptake inhibitors”. Even though medicinal treatment is not without side effects there are no suggested alternative treatments in, e.g., the NICE Guidelines.

The opposite is the case: There is explicit advise against acupuncture and reflex therapy, even though due to insufficient data in 2006, e.g., the Cochrane Review came to the conclusion that „It is still inconclusive whether acupuncture is more effective than sham acupuncture or other interventions for treating IBS" (Lim et al., 2006).

There are no recommendations for manual therapy. For the osteopathic field that might be, because even though renowned osteopaths report on the efficacy of osteopathic treatment of IBS, only five IBS studies seem to have investigated the effects of an osteopathic intervention, of which only the study by Hundscheid2007 is listed in MEDLINE. This is certainly not enough for a differentiated view of the osteopathic treatment of IBS.

4.2 Methods

In recent years investigations have shown that researching only the Medline database is not sufficient for a systematic review because it may contain only about 50% of the existing reports on randomized clinical studies (Glanville, Lefebvre, Miles, & Camosso-Stefinovic, 2006). An additional search in Embase is suggested, since theoverlapping of databases is said to be only two thirds or less (Sampson et al., 2003). This review confirms that searches in Medline and Embase are necessary and useful but not at all comprehensive for the issue of osteopathic studies on IBS.

For many years the Cochrane Collaboration has been suggesting a search within the so-called "gray literature", i.e. small, specialized databases as well as a manual search of professional journals and their bibliography of articles on the topic (Furlan, Pennick, Bombardier, & van Tulder, 2009). This method has proven more successful than the search in both large databases alone. Interestingly, the most successful method was the search in "Google Scholar", where four of five identifiable studies were found. This is possibly because Google Scholar increasingly offers publications from universities and also references to magazine articles. At the end of 2010 there were 64,000 entries in Google Scholar for "irritable bowel syndrome" alone.

Even though the US is the mother country of osteopathy, only one American clinical trial on the osteopathic treatment of IBS could be found. All available studies and all of the included studies come from European countries (Great Britain, France,

Germany, and the Netherlands). The trial by Stasiuk, which was a case study and therefore had to be excluded from further analyses, originates from Australia. Visceral osteopathy is far more popular in Europe than it is in the US, where it is clearly second to parietal osteopathy (Johnson & Kurtz, 2003). This situation is confirmed by the search results.

The Jadad Score is a globally recognized instrument for the evaluation of the internal validity of trials. This is why it was also used for this review. The Jadad Score is based on five items and one of its questions is: „Was the study described as double blind?" This is, however, problematic for studies on manual treatment modalities, because such trials can hardly be carried out in a double blind manner, and double blinding would inevitably lead to results that do not reflect any potential clinical situation. In consequence, all osteopathic studies would have to be devaluated because at best they can only be carried out single blinded. With only five items an "*a priori* devaluation" would have substantial influence on the evaluation of the quality of a study.

Thus it seems to be more sensible for a qualitative evaluation of osteopathic trials to use the Cochrane Collaboration tools, including either the risk of bias tool by the Cochrane Collaboration (Higgins & Green, 2008) or the risk of bias tool by the Cochrane Back Review Group (Furlan et al., 2009). After all, pure sum scores should be used carefully for an evaluation of internal validity (Kunz et al., 2009), and the Cochrane tools more easily differentiate studies with more items.

It is common standard to summarize studies by means of meta-analyses in order to get a quantitative estimate of the overall effect. This requires data suitable to calculate mean effect sizes and respective standard deviations, which was unfortunately not provided by all trial publications. In the Muller et al. (2002) trial the standard deviation had to be calculated from the raw data, which were provided by the authors for this purpose. Despite several requests Hundscheidet al. (2007) as well as Brice C. (2000) and Chiesa et al. (2003) failed to provide the raw data. [See Appendix D]. For the Hundscheidet al. (2007) study the standard deviation was pooled, the Brice et al. (2000) study could not be included into the meta-analysis for lack of data. This is obviously an unsatisfactory situation for the reviewer.

For future osteopathic studies it would be important and desirable to provide appropriate data for later inclusion of the studies into meta-analyses. Simple specification of the p-value as significant is not enough.

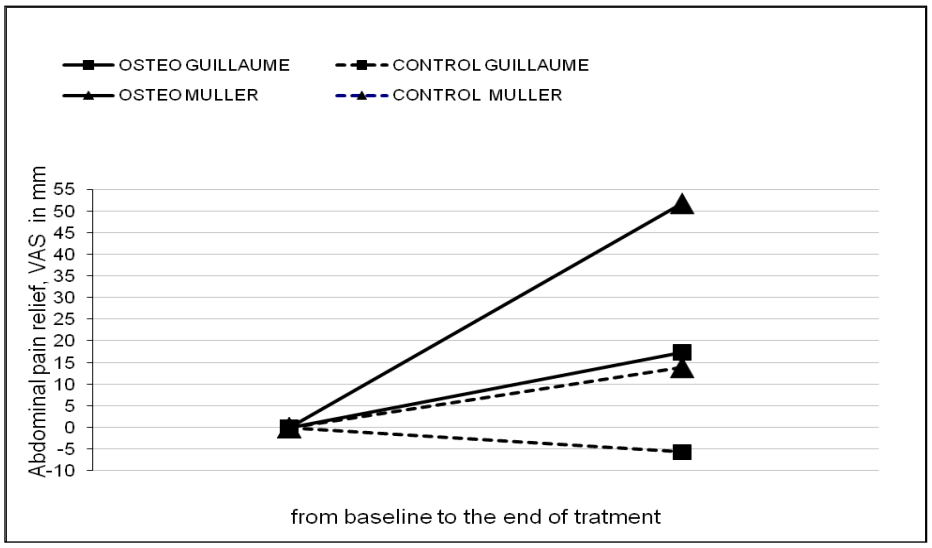
4.3 Results

In the descriptive analysis of the trials of Guillaume (1998), Muller (2002), Brice (2000), and Hundscheid (2007), the osteopathic intervention appeared to be superior to that of the control group in each study. The quantitative analysis (meta-analysis) confirmed this result for the three included trials. The overall effect size at 3.49 (-4.24 - 0.75, standard. mean difference, 95% CI) is at a high enough level to indicate the use of osteopathic treatment.

The observed high level of heterogeneity (I2 = 93%) weakens the positive results of the meta-analyses to some extent, yet the cause remains unclear. One might speculate that the different control modalities may play a role. The Hundscheid (2007) study is based on a comparison between osteopathic interventions and standard care treatment while in the Guillaume (1998) and Muller (2002) studies sham interventions were applied to controls. Muller (2002) gives a precise description of the sham procedure while Guillaume (1998) just notes that the control group received an unspecific cranial, visceral and parietal therapy.

A graphical comparison of the control groups of the latter two trials seems to show different changes in pain relief in the control group. [See Figure 12]

Figure 12: Comparison of within-group changes between baseline and end of treatment in the studies of Guillaume (1998) and Muller (2002) concerning abdominal pain relief



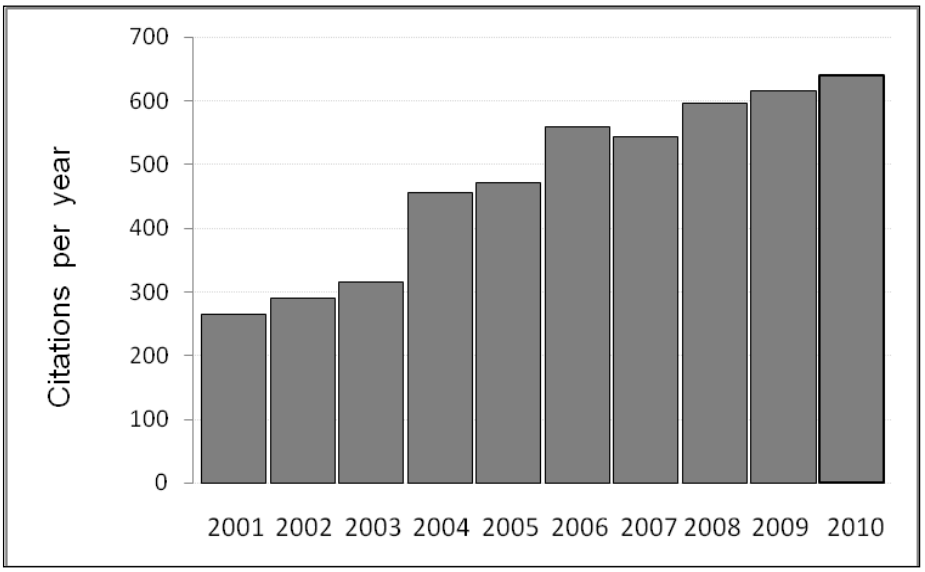
It has been stressed that there may be a chance of up to 80% of a positive placebo outcome in trials of IBS (Drossman et al., 2003). In the trial of Guillaume (1998) the sham treatment was not associated with a significant change over time. This seems noteworthy, not least because the sham treatment was similar to the intervention. For an in depth comparison of both studies as well as for the choice of sham treatments for future trials, an exact description of the control intervention would be desirable.

The main outcome parameters were similar, but not identical in the three trials. Guillaume (1998) and Muller (2002) used visual analog scales (VAS) for abdominal pain, while Hundscheid(2007) used the "Functional Bowel Disorder Severity Index" (FBDSI), which includes a VAS, but contains additional parameters. In this context it should be noted that the three studies are altogether small trials, in which despite thorough execution, incidental effects cannot be excluded. The internal validity was high for all three trials of the meta-analysis.

One factor which becomes obvious when looking at the results of the systematic searches is a continuously increasing number of trials per year. [See Figure 13]. It must be taken into account that Figure13 represents the results of an analysis performed at the beginning of January 2011, when not all articles and clinical studies published in 2010

had already been included in PubMed. In general, there is an allotted time limit for belated submissions of several months.

Figure 13: Records per year in PubMed dealing with IBS in the last ten years



Even though Guillaume et al. (1998) had already reported about the therapeutic success in their osteopathic study on IBS, only four clinical studies and a case study with particular emphasis on osteopathy have been carried out since then. Actually it was expected that the interest of osteopaths would increase with the positive outcome of the studies and the increasing importance of IBS as one of the most common gastrointestinal disorders. This was, however, not the case. No further osteopathic study on IBS could be identified since 2007, despite the fact that positive results of earlier studies seem promising to plan future trials. This development is hard to understand. Considering the low number of possible therapeutic options (dietary / lifestyle advice and / or pharmacological treatment), osteopathic treatment could be a promising choice of therapy for the patients.

Even though the meta-analysis shows a statistically significant superiority of the osteopathic intervention compared to that of controls concerning subjective pain, it should still be kept in mind that the results are based on only three trials which is the minimum number for a systematic review required by, e.g., the Cochrane Collaboration.

The number of patients in the three studies was 131 persons, and there was marked heterogeneity between studies concerning the primary outcome parameter (VAS and FBDSI score) as well as the control intervention (sham treatment versus standard care), let alone differences between patient cohorts. It is therefore possible that future, larger trials may significantly alter the results of the meta-analysis in either direction.

4.4 Conclusion

The results of this systematic review and meta-analysis are based on three RCT`s with a total of 131 patients with heterogeneity between studies concerning the primary outcome “abdominal pain” as well as concerning control interventions (sham treatment and standard care, respectively). It would therefore not be surprising if future, larger trials will essentially change the results of the meta-analysis.

Instead of using the Jadad Score for evaluating internal validity, the Cochrane Collaboration's risk of bias tool should be given preference.

In the publication of future osteopathic clinical studies more emphasis should be put on the reporting of data in order to facilitate their inclusion into reviews and meta-analyses.

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Appendices

Appendix A

History from Rome I to Rome III

Rome I	1989
Rome II	1999
Rome III	2003

ROME III Questionnaire - IBS Module

1.During the last 3 months, how often did you have discomfort or pain anywhere in your abdomen?	0 never → 1 less than one day a month 2 one day a month 3 two to three days a month 4 one day a week 5 more than one day a week 6 every day	skip remaining questions
2. For women: Did this discomfort or pain occur only during your menstrual bleeding and not at other times?	0 no 1 yes 2 does not apply, because I had a change in life (menopause) or I am a male	
3. Have you had this discomfort or pain for 6 months or longer?	0 no 1 yes	
4. How often did this discomfort or pain get better or stop after you had a bowel movement?	0 never or rarely 1 sometimes 2 often 3 most of the time 4 always	

ROME III Questionnaire - IBS Module, Continued

5. When this discomfort or pain started, did you have more frequent bowel movements?	0 never or rarely 1 sometimes 2 often 3 most of the time 4 always	
6. When this discomfort or pain started, did you have less frequent bowel movements?	0 never or rarely 1 sometimes 2 often 3 most of the time 4 always	
7. When this discomfort or pain started, were your stools (bowel movements) looser?	0 never or rarely 1 sometimes 2 often 3 most of the time 4 always	
8. When this discomfort or pain started, how often did you have harder stools?	0 never or rarely 1 sometimes 2 often 3 most of the time 4 always	
9. In the last 3 months, how often did you have hard or lumpy stools?	0 never or rarely 1 sometimes 2 often 3 most of the time 4 always	
10. In the last 3 months, how often did you have loose, mushy or watery stools?	0 never or rarely 1 sometimes 2 often 3 most of the time 4 always	

Rome III Diagnostic Criteria*

Recurrent abdominal pain or discomfort** at least 3 days / month in last 3 months associated with two or more ofCriteria #1 - #3 below:

Pain or discomfort at least 2-3 days/month (question 1 > 2)

For women, does pain occur only during menstrual bleeding? (question 2 = 0 or 2)

1. Improvement with defecation

Pain or discomfort gets better after BM at least sometimes (question 4 > 0)

2. Onset associated with a change in frequency of stool

Onset of pain or discomfort associated with more stools at least sometimes (question 5 > 0), OR

Onset of pain or discomfort associated with fewer stools at least sometimes (question 6 > 0)

3. Onset associated with a change in form (appearance) of stool

Onset of pain or discomfort associated with looser stools at least sometimes (question 7 > 0), OR

Onset of pain or discomfort associated with harder stools at least sometimes (question 8 > 0)

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis. (Question 3 = 1)

**"Discomfort" means an uncomfortable sensation not described as pain.In pathophysiology research and clinical trials, a pain / discomfort frequency of at least two days a week is recommended for subject eligibility.Pain or discomfort more than one day per week (question 1 > 4)

Criteria for Different IBS Subgroups

Criteria for IBS-C

(Question 9 > 0) and (question 10 = 0)

Criteria for IBS-D

(Question 9 = 0) and (question 10 > 0)

Criteria for IBS-M

(Question 9 > 0) and (question 10 > 0)

Criteria for IBS-U

Appendix B

Other Disease-Specific Instruments for IBS:

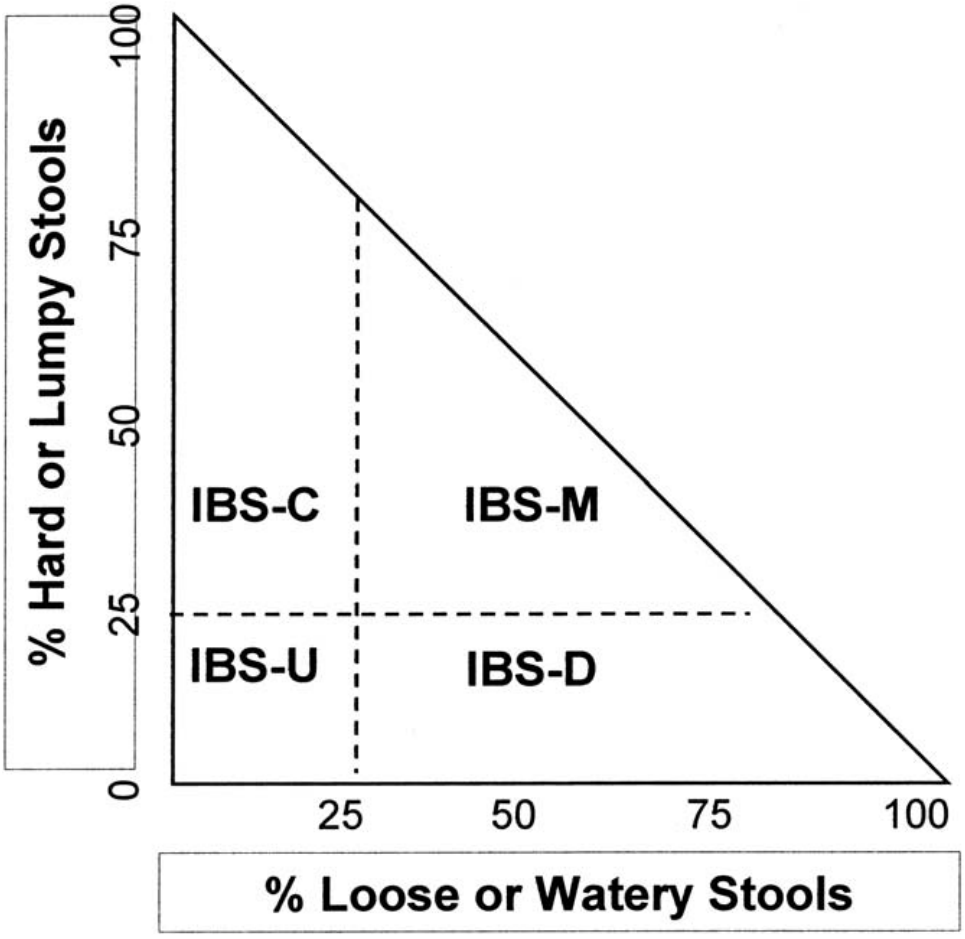
- The Manning pain scale (Manning 1978)
- RFIPC (Rating Form Of Inflammatory Bowel Disease Patient Concerns) (1991 Drossman)
- The Cleveland Clinic Questionnaire
- Zbrozek 12 Item Questionnaire
- Symptom Diary (Univ. Albany, NY)
- IBS Symptom Scale / BSS 1, 2, 3 / (Vict. Univ. Melbourne)
- IBS Module (Questionnaire) in Rome classification
- IBDQ (Inflammatory Bowel Disease Questionnaire)
- IBSQOL (The IBS Quality Of Life Questionnaire)
- FBDSI (Functional Bowel Disorder Severity Index) supplemented

Appendix C

Distribution of IBS-Subgroups

Two-dimensional display of the four possible IBS subtypes, according to bowel form at a particular point in time: IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; IBS-M, mixed IBS; IBS-U, unsubtyped period

Figure 14: Two-Dimensional Display of the 4 Possible IBS Subtypes



Appendix D

Documentation of the Correspondence with Authors Regarding

Additional Information

Ruud Loffeld (Study of Hundscheid)	x.x. 2009 (exact data lost)
	x.x. 2009 (exact data lost)
	11.2 2010
	12.4.2010
	27.1.2011
C. Brice	x.x. 2009 (exact data lost)
	x.x. 2010 (exact data lost)
Stiedl M.(Study of Muller et al)	18.2.2010
	24.6.2010
Chiesa	05.3.2011

Appendix E

Descriptions of the Studies in Detail

Study of Guillaume (1998)

Osteopathic Treatment of the Functional Colonopathy

This trial is a prospective randomized study, single-blinded against a placebo group.

Of 45 IBS patients, 42 were accepted for this study;23 of them were randomized in the verum group where patients were treated osteopathically, and 19 patients were randomly assigned to the placebo group. The patients were treated every 15 days for two months. The target parameters were measured in every session. A follow-up examination (TK) 75 days after the initial treatment completed the study. The primary target parameter was "Pain". It was measured via the visual analog scale (VAS). The results after 60 days / five treatments showed a significant analgesic effect, which still existed on the day of the TK (2 weeks after the last treatment).

The secondary target parameters were several functional symptoms, of which frequency and intensity were gathered in a table (Likert).

After 2 months of treatment (five treatments), the osteopathically treated patients showed a significant improvement in their functional conditions. This improvement persisted two weeks after the last treatment.

The osteopathic treatment was highly tolerated by the patients and they were never at risk at any point of the study. The osteopathic treatment, with its analgesic effect and impact on a series of functional ailments, should be the treatment of choice for IBS.

Inclusion Criteria:

Women and men between the age of 18 and 75

Diagnosis IBS before the age of 50

Suffering from IBS for more than a year

Last medical examination less than a month ago

The physician measured a value on the KRUIS scale of at least 44 or higher

The Rome Criteria were taken into consideration

The pain intensity on the visual analog scale (VAS) is 30 mm or more

The level of symptom A was higher or equal to four

The level of symptom B was higher or equal to four

At least 2 of the 3 zones were evaluated as one or two

(0 ≈ without finding; 1≈ medium loss of mobility (LM); 2 ≈ strong LM

- Atlanto-occipital joint
- The epigastric region
- The Colon compared to the small intestine and
- The Colon compared to the parietal layer

Participants who can read and understand French

Participants who are willing to sign the declaration of consent

Exclusion Criteria:

Treatments which are analgesic, anti-spasmodic or have a laxative or antidiarrhetic effect were allowed but their intake had to be discontinued 48 hours before the treatment.

Pregnancy.

Randomization:

The patients were not allocated separately but randomized in blocks of four in the intervention group and the control group.

The Treatment:

For two months, the patients were treated about every 15th day. The symptom intensity and frequency were measured in every session.

At a control examination (TK), 15 days after the previous treatment, both groups were asked about intensity and frequency via the VAS and a symptom table in a final inquiry.

Duration of Treatment:

The average duration of treatment (including the questioning) was about the same in both groups and lasted about 30 minutes altogether.

Treatment of the Verum Group:

A treatment depended on the findings in the following regions:

- The atlanto-occipital joint
- The epigastric region
- The colon compared to the small intestine and

- The colon compared to the parietal plane

Treatment of the Placebo Group:

Each treatment included 3 techniques

- One cranial technique
- A visceral technique
- A parietal technique

Within 2 months the patients were treated every 15 days. The target parameters were retrieved in every session. A control examination 75 days after the initial treatment concluded the study.

Results:

The secondary target parameters were a number of functional symptoms of which frequency and intensity were listed in a table (Likert scale).

After two months of treatment (five treatments) the osteopathically treated patients showed a significant improvement in their functional condition, which still existed after 75 days at the final examination.

The osteopathic treatment was highly tolerated by the patients and they were never at risk at any point of the study. The osteopathic treatment, with its analgesic effect and impact on a series of functional ailments, should therefore be the treatment of choice for IBS. Each treatments lasts about 30 minutes

The intake of medication (which had to be discontinued 48 hours before the treatment) in both groups was observed. There was no significant difference in either group.

The treatment duration was different in both groups.

Conclusion:

The osteopathic treatment was highly tolerated by the patients and they were never at risk at any point of the study. The osteopathic treatment, with its analgesic effect and impact on a series of functional ailments, should be the treatment of choice for IBS.

Study of Brice(2000)

Brice C., Mountford R. A Study into the Efficacy of Osteopathic Treatment of Irritable Bowel Syndrome. British Osteopathic Journal Vol. XXII 2000: Page 23

Abstract

The primary purpose of the research was to compare the efficacy of osteopathic and allopathic treatment of irritable bowel syndrome (IBS) in a hospital environment.

FortyIBS patients, diagnosed by a gastroenterological consultant using the accepted Rome Criteria, received either allopathic or osteopathic treatment. Via a symptom diary, the symptoms were assessed before treatment and again six weeks and three months after the treatment.

The patients received four osteopathic treatments. In a quasi-randomization the first 20 patients were randomized into the osteopathically treated group, the rest of the patients received allopathic treatment. Results indicate that the osteopathic treatment was effective in the treatment of irritable bowel syndrome in both, short and long term. Additionally, the osteopathic treatment was significantly more effective than the allopathic treatment of irritable bowel syndrome.

Summary

The Research Question

Primary Purpose:

- Was the osteopathic treatment effective in the treatment of IBS?
- Was the allopathic treatment effective in the treatment of IBS?
- Was the allopathic or osteopathic treatment more effective in the treatment of IBS?
- Does the osteopathic treatment have a sustainable effect on IBS syndromes?

Secondary Purpose:

- Did the patients feel better after osteopathic and allopathic treatment?

- Was there any difference in how well patients felt after osteopathic and allopathic treatment?
- Was there any relationship between symptoms and compliance in undertaking exercises with osteopathic treatment?
- Was there any relationship between the patient's age and the effect of osteopathic and allopathic treatment?
- **Case Criteria:**

Rome II and Manning symptom scale.

Inclusion Criteria:

Participants, 20 to 80 years of age, English speaking, male or female, additional treatment:

Standard medical care group (SMC):

- Advice concerning life-style was appropriate
- In osteopathic group:
- Handouts for exercises at home
- **Randomization:**

The first 20 patients were quasi-randomized into the osteopathic group (OG) and received osteopathic treatments, whereas the rest was quasi-randomized into the standard medical group and received allopathic treatments.

Osteopathic Treatment:

- Number of osteopaths: One
- The patients received four osteopathic treatments.
- The osteopathic treatments were carried out individually, i.e., manipulation and soft tissue techniques. Additionally, the patients were given a list of instructions for physical exercises.

The patients were questioned on their symptoms before the treatments via a symptom diary. This was done again after 6 weeks and for a third time after four treatments (after 3 months).

Allopathic Treatment:

Individualized drug treatment. e.g.:

- Bulking agent (Fybogel),
- Antispasmodic drug (Mebevebrine), and,
- In resistant cases, a small dose of a tricyclic antidepressants was prescribed.

Data Evaluation:

- Between and within group analysis,
- the patients were unevenly allocated to groups and were subjected to non-parametric statistics (Mann-Whitney tests), and,
- the two groups were not equal but comparable.

Results:

The symptoms of bloating, pain, frequency of discharge and nausea all showed a statistical improvement, except for the “consistency”. Statistically, the patients felt better after six weeks of treatment in the osteopathic group. The effects of the osteopathic treatments lasted up to three month after the treatments ended.

Study of Muller (2002)

Abstract

Goals:

Examination of the hypothesis, if the osteopathic treatment concerning the primary parameter “Pain” and the secondary parameters “Flatulence, constipation, diarrhea and other medical discomfort” can specifically contribute to the treatment of irritable bowel syndrome (IBS). The goal is to find a scientifically based evaluation of the therapeutic efficiency of an osteopathic treatment concept.

Design:

Prospective, randomized, controlled, patient-blinded study.

Setting:

The study was carried out between October 2000 and January 2002 by three osteopaths of the European College Of Osteopathy C.O.E. Munich after their exams in 1999.

Patient Selection:

The patients were found through newspaper ads, colleagues and doctors and with specific selection criteria.

Method:

61 patients randomized into two groups.

Group 0	verum treatment	31 patients
Group 1	sham treatment	30 patients

Efficiency test of an osteopathic treatment concept.

Performance of an exploratory trial with all patients of the sham group.

Treatments:

- Five osteopathic interventions (T1-T5) every 14th day.

Primary Target Parameters:

- Reduction of the pain intensity (VAS).

Secondary Target Parameters:

- additional parameters according to the Rome Criteria regarding the development of intensity and frequency (VAS), treatment tolerance, osteopathic examination results.

Results:

The osteopathic treatment shows a statistically significant improvement regarding the primary target parameter compared to the sham treatment and achieves a clinically relevant specific effect.

Conclusion:

The study proves that osteopathy can contribute to the treatment of irritable bowel syndrome. It therefore is to be considered as a therapeutic option.

Study of Hundscheid(2006)

Abstract

Background and Aim:

An effective treatment for irritable bowel syndrome (IBS) is not yet available. Osteopathy is a manual treatment which relies on mobilizing and manipulating procedures in order to relieve the patients' complaints. In the present study, a randomized controlled trial was carried out to evaluate the effects of osteopathic treatments for IBS.

Methods:

Eligible IBS patients were randomized into osteopathic and standard care groups.

A follow-up examination was performed after six months, only using validated means.

After one, three and six months, an overall assessment of symptoms was done and a symptom score was obtained on a five-point Likert scale. The quality of life (QOL) was determined with standardized IBSQOL 000 questionnaires and the functional bowel disorder severity index was used.

Results:

Twenty patients were randomized into the osteopathic group (OG) and 19 patients into the standard care group (SCG). Sixty-eight percent of the patients in the OG noted definite overall improvement of symptoms and 27% showed slight improvement. One patient (5%) was free of symptoms at the end of the study. In the SCG, 18% noted definite improvement, 59% slight improvement and 17% a worsening of symptoms. A difference of the overall symptomatic improvement was statistically significant in favor of osteopathic treatment ($p < 0.006$). The mean functional bowel disorder severity index (FBDSI) score of the OG decreased from 174 to 74 after 6 months ($p < 0.0001$). A significant decrease was also noted for the SCG from 171 to 119 ($p < 0.0001$). However, the decrease in the OG was significantly higher compared to that of the SCG ($p = 0.02$). The mean symptom score in the OG decreased from 9.1 to 6.8 but it did not reach statistical significance. In the SCG, there was no change in symptom score (8.7 vs. 10). After 6 months, the score in the OG was significantly lower (6.8 vs. 10; $p = 0.02$). The

QOL score increased in the OG (111 vs. 129; $p < 0.009$). In the SCG, an increase was also noted, but it was not statistically significant (109 vs. 121).

Conclusion:

Osteopathic therapy is a promising alternative in the treatment of patients with IBS. Patients treated with osteopathy showed an overall improvement of the symptom score.

Allopathic Treatment:

- Individualized drug treatment, e.g.:
- Antidiarrheals (N = 2)
- Antispasmodic drug (Mebevebrine) (N = 14)
- Fiber (N = 5)
- Laxatives (N = 5)

Appendix F

Summary of Characteristics of the Included Studies

Study of Guillaume(1998)

Osteopathy versus Placebo;

Study Design: RCT

Table 11: Characteristics of the Study

Single blinding	YES
Double blinding	NO
Attempt to confirm patient blinding	not stated
Total duration	approximately 75 days (from baseline)
Type of analysis reported	available IBS clients, 18 to 75years of age
Participant setting	IBS patients treated in private practices
Number of osteopaths	10
Recruitment method	call for bulletin
Duration of IBS symptoms before enrollment	IBS diagnosis before the 50th birthday with a duration of a minimum of 1 year
Diagnosis of IBS required for eligibility?	Rome II criteria were used Kruis pain scale values of more than 44mm more than four GI symptoms
Examination to rule out organic gastrointestinal diseases	yes, medical opinion less than 1 month before study baseline
Were people with a history of osteopathic treatment excluded?	not stated
Other important inclusion criteria	Osteopathic dysfunction - Atlanto-occipital joint - Epigastric region - Between colon and pelvic - Between colon and small intestine
Symptom score	abdominal pain, diarrhea,constipation, meteorism
Important exclusion criteria	Pregnancy
Statistical analysis	U-Mann-Whitney test for pain, because patients were allocated unevenly to both groups. For the symptom score the t-student test was used. ”Intention to treat” analyze.

Table 12: Osteopathic Intervention of the Study

Intervention	osteopathic techniques applied at: - Atlanto-occipital joint - epigastric region - between colon and pelvic - between colon and small intestine
Style of osteopathy	functional, non-manipulative
Number of participants allocated to osteopathy	23
Total length of treatment period	approximately 60 days
Number of targeted sessions	Five
Distribution of treatments	two per month
Duration (min) of treatment	approximately 30 min
Time between follow-up examinations	15 days
Additional interventions in any of the groups	medical intervention was possible but had to be stopped 48 h before treatment

Table 13: Control Group Intervention of the Study

Interventions sham group	treatment with 3 unspecified cranial-, parietal- and visceral osteopathic techniques
Number of participants allocated to sham	19
Total length of treatment period	approximately 60 days
Number of targeted sessions	five
Distribution of treatments	two per month
Time between follow-up examinations	14 days
Any additional interventions in all groups	medical intervention was possible but had to be stopped 48 h before treatment

Table 14: Demographic Parameters of Both Groups

	Osteopathic Group	Sham Group	P-Value
Age	47.1 (+/-2.74)	50.8 (+/-2.52)	0.332 NS
Number of Participants	23	19	0.782 NS
Male	3	4	
Female	20	15	
Weight	62.35 (+/-2.06)	61.63 (+/-2.41)	0.821 NS
Height	163.8 (+/-0.97)	165.6 (+/-1.76)	0.352 NS

Table 15: Dropouts of Both Groups

	Osteopathic Group	Sham Group	P-Value
Dropout		1	

Table 16: Jadad Score for Internal Validity

Was the study Described as Randomized ?	Was the Method of Generating Randomization Sequence Appropriate ?	Was the Study Described as Double Blind?	Was the Method of Double Blinding Appropriate ?	Was there a Description of Dropouts and Withdrawals ?	∑	Quality
1.0	0.0	O (+1.0)	X	1	2.0 (3.0)	low (high)

Table 17: Linde Internal Validity Scale Score

Method of allocation to groups	Concealment of allocation	Baseline comparability	Blinding of patients	Blinding of evaluators	Likelihood of selection bias after allocation to groups due to dropouts	Result
0.5	1	0.5	1	0	1.0	4.0

Outcomes Abstracted for Systematic Review

Check-up intervals: After each treatment (Day 15/30/45/60/75)

Overall general well-being: Not stated

Table 18: Abdominal Pain Outcome

Period	Treated with Osteopathy	Treated with Sham	Probability	Significant?
Between Baseline and 1st Session	9.65 (+/-1.98)	1.21 (+/-1.22)	P = 0.0028	YES
Between Baseline and 2nd Session	11.48 (+/-3.53)	0.72 (+/-3.01)	P = 0.153	NO
Between Baseline and 3rd Session	15.17 (+/-4.79)	-2.44 (+/-3.55)	P = 0.015	YES
Between Baseline and 4th Session	15.3 (+/-5.75)	-3.94 (+/-2.45)	P = 0.006	YES
Between Baseline and 75th Day	17.26 (+/-6.55)	-5.73 (+/-2.46)	P = 0.0156	YES

Table 19: Gas Outcome

Period	Treated with Osteopathy	Treated with Sham	Probability	Significant ?
Between Baseline and 1st Session	0.26 (+/-0.14)	0.42 (+/-0.16)	P = 0.458	NO
Between Baseline and 2nd Session	0.69 (+/-0.18)	0.57 (+/-0.19)	P = 0.663	NO
Between Baseline and 3rd Session	1.09 (+/-0.165)	0.26 (+/-0.15)	P = 0.0008	YES
Between Baseline and 4th Session	1.04 (+/-0.15)	0.05 (+/-0.14)	P = 0.0001	YES
Between Baseline and 75th Day	01.17 (+/-0.19)	0.21 (+/-0.12)	P = 0.0001	YES

Table 20: Diarrhea Outcome

Period	Treated with Osteopathy	Treated with Sham	Probability	Significant?
Between Baseline and 1st Session	0.43 (+/-0.16)	0.26 (+/-0.15)	P = 0.226	NO
Between Baseline and 2nd Session	0.43 (+/-0.18)	0.27 (+/-0.19)	P = 0.253	NO
Between Baseline and 3rd Session	0.39 (+/-0.16)	0.37 (+/-0.11)	P = 0.456	NO
Between Baseline and 4th Session	0.43 (+/-0.16)	0.16 (+/-0.09)	P = 0.083	NO
Between Baseline and 75th Day	0.48 (+/-0.18)	0.05 (+/-0.14)	P = 0.037	YES

Table 21: Defecation Difficulties (Constipation)Outcome

Period	Treated with Osteopathy	Treated with Sham	Probability	Significant?
Between Baseline and 1st Session	0.48 (+/-0.17)	0.21 (+/-0.19)	P = 0.149	NO
Between Baseline and 2nd Session	0.61 (+/-0.19)	0.48 (+/-0.26)	P = 0.333	NO
Between Baseline and 3rd Session	0.913 (+/-0.19)	0.58 (+/-0.22)	P = 0.126	NO
Between Baseline and 4th Session	1.09 (+/-0.21)	0.46 (+/-0.19)	P = 0.019	YES
Between Baseline and 75th Day	2.09 (+/-0.97)	0.32 (+/-0.23)	P = 0.056	NO

Type of Outcome Data Reported:

There are significant differences in post-treatment values between the osteopathic- and control group in:

- Abdominal pain
- Gas / bloating
- Diarrhea

Study Conclusion:

- Therapeutic benefit of osteopathy in IBS was clearly shown.
- Neither sham nor true osteopathy worsened any of the patient's symptoms and no additional adverse effects were reported.

Limitations:

- Few treatment sessions
- Small group size
- Time span between follow-up treatment and previous treatment was only 15 days
- No follow-up treatment after day 75

Risk of Bias:

- The sham treatment was not absolutely neutral. “Unspecific osteopathic techniques” were used as sham treatment. Maybe this was already a therapeutic component.
- Standard medication was allowed but had to be stopped 48 hours before treatment. The effects were not evaluated.
- Medication had to be stopped 48 hours before treatment. The reason of this was not reported.
- Randomization: “Blocks of four patients”.

Study of Brice(2000)

Osteopathy versus Standard Medical Care (SMC)

Study Design: RCT

Table 22: Characteristics of the Study

Single blinding	NO (SMC vs. osteopathy!)
Double blinding	NO (SMC vs. osteopathy!)
Total duration	18 months
Type of analysis reported	Available IBS clients from Dr. Mountford's gastroenterological outpatient clinic
Duration of IBS symptoms before enrollment	minimum of 6 months
IBS diagnosis required for being eligible?	Rome Criteria (I / II) were used
Other important inclusion criteria?	20 to 80 years of age
Important criteria	The groups did not include patients receiving or intending to receive new additional treatments for IBS. If a patient received further medication, he was excluded and received allopathic treatment
Were people with a history of osteopathic treatment excluded?	Not stated
Total length of treatment period	6 weeks
Number of targeted sessions	4
Distribution of treatments	1 every 2 weeks
Duration (min)	30 minutes
Measuring of IBS symptoms	3 times At study baseline After 6 weeks of treatment After 3 months
Times measured	before and after the treatment
Total follow-up period	6 months
Follow-up visits	6 months
Symptom score	IBS symptom diary, Likert scale and VAS
Statistical analysis	Mann-Whitney test, two tailed Wilcoxon test, and, Spearman rank test.

Table 23: Demographic Parameters of Both Groups

	Osteopathic treatment	Standard medical care
Average age (years)	45.5	41.9
Average duration of symptoms	6.26 years	3.84
Women (n/n):	20	1
Men (n/n):		19
Evaluated	20	20
Both groups are not equal but comparable W = 360, P = 0.08		

Table 24: Osteopathic Group Intervention

Intervention	osteopathy / black box method
Participants Setting in OG	IBS patients were treated with osteopathy in Dr. Mountford's outpatient clinic with manipulation and soft tissue technique and were given handouts with exercises
Recruitment method	clients of Dr. Mountford's outpatient clinic
No. of patients allocated to osteopathy	20
Dropouts / withdrawals	not stated
Total length of treatment period	6 weeks
Number of targeted sessions	4
Duration (min)	30 min
Additional interventions	no medication from standard medical care allowed, handouts with exercises in the osteopathic group
Distribution of treatments	every 2 weeks
Follow-up visits	1 every 3 months
Total follow-up period	3 months

Table 25: Standard Medical Care Intervention

Intervention	standard medical care: - bulking agent (Fybogel) - antispasmodic drug (Mebevebrine) - in resistant cases a small dose of a tricyclic antidepressant
Additional interventions	advice on life style changes were appropriate
Participant setting in SMC	treated in Dr. Mountford's outpatient clinic
Recruitment method	patients of Dr. Mountford's outpatient clinic
Number of patients allocated to SMC	20
Dropout rate	not stated

Table 26: Jadad Score for Internal Validity

Was the study Described as Randomized ?	Was the Method of Generating Randomiza-tion Sequence Appropriate?	Was the Study Describ-ed as Double Blind?	Was the Method of Double Blinding Appropriate?	Was there a Descrip-tion of Dropouts and Withdraw-als?	∑	Quality
1.0 /but quasi randomiza-tion	0.0	O (+1.0)	X	X	1	low (high)

Table 27: Linde Internal Validity Scale Score

Method of allocatio n to groups	Concealment of allocation	Baseline comparabili-ty	Blind-ing of patient s	Blinding of evaluators	Likeli-hood of selection bias after alloca-tion to groups due to dropouts	Result
0.5	1	0,5	1	0	0	3.0

Outcomes Abstracted for Systematic Review

Check-up intervals:

- Before treatment,
- After 6 weeks,
- After 3 months.

Table 28: Analysis of Osteopathic and Standard Medical Care After 6 Weeks

	Treated with Osteopathy and Exercises (20 Subjects)	Significant	Treated with Standard Medical Care (20 Subjects)	Significant
Bloating	P = 0? W = 148	YES	P = 0.295 W = 16.0	YES
Pain	P = 0.001 W = 161	YES	P = 0.173 W = 17.5	YES
Frequency	P = 0.001 W = 72	YES	P = 0.016 W = 21	YES
Consistency	P = 0.88 W = 365	NO	P = 0.036 W = 0.0	YES
Sick	P = 0.02 W = 79.5	YES	P = 0.418 W = 11	YES

Table 29: Analysis between Osteopathic Treatment and Standard Medical Care

	Difference between Osteopathic Treatment and Standard Medical Care after 6 Weeks	Significant
Bloating	P = 0.16 W = 318	NO
Pain	P = 0.07 W = 325.5	NO
Frequency	P = 0.52 W = 277	NO
Consistency	P = 0.03 W = 332	NO
Sick	P = 0.41 W = 295	NO

There is no statistically significant difference between osteopathic treatment and allopathic treatment after 6 weeks.

Table 30: Analysis of Treatment Effects of the Osteopathic Group after 3 Months

	Treated with Osteopathy and Exercises after 3 Months (20 Subjects)	Significant
Bloating	P = 0.004 W = 66.0	YES
Pain	P = 0.002 W = 143	YES
Frequency	P = 0.025 W = 100	YES
Consistency	P = 0.889 W = 43	NO
Sick	P = 0.004 W = 76.5	YES

All symptoms, with the exception of “Consistency”, showed a statistically significant improvement 3 month after completing osteopathic treatment.

Secondary Questions:

Table 31: Analysis of "How good did the patients feel after 6 weeks?"

	Osteopathic Treatment	Significant	Treated with Standard Medical Care	Significant
How good did the patients feel after 6 weeks?	P = 0.001 W = 79.5	YES	P = 0.55 W = 10	NO

⇨ The answer to the question "how good did the patients feel after 6 weeks" was statistically significant in favor for osteopathy.

Table 32: Analysis of "How good did the patients feel after 6 eeks in a comparison between osteopathic and allopathic groups?"

	Osteopathic Treatment Compared to Allopathic Treatment	Significant
How good did the patients feel after 6 weeks?	P = 0.016 W = 242.5	YES, in favor for osteopathy

⇨ The answer to the question "how good did the patients feel after 6 weeks in a comparison between osteopathic and allopathic groups" showed a statistically significant difference in favor of osteopathy in both groups

Table 33: Analysis of "How Good Did the Patients of the Osteopathic Group Feel After 3 Months?"

	Osteopathic Treatment	Significant
How good did the patients feel after 3 months?	P = 0.002 W = 21	YES

⇨ The answer to the question "how good did the patients of the osteopathic group feel after 3 months" was statistically significant.

Type of Outcome Data Reported:

- After treatment, there was a significant difference in general well being between the groups treated with osteopathy and standard medical care.
- The effect of the osteopathic treatment was statistically significant after 3 months.

Adverse Effects:

- No patient in either group reported any side effects. The osteopathic treatment proved to be safe.
- No additional adverse effects were reported.

Author's Conclusion:

- Therapeutic benefit of osteopathy in IBS was clearly shown.
- In the study there was no report about additional adverse effects of the osteopathic treatment or the worsening of the patients' symptoms.

Weak Points:

- Small number of treatment sessions.

Risk of Bias:

- Pseudo randomization.
- Small group size.
- At the beginning of the study both groups were not equal but comparable via the Mann – Whitney test.

Study of Muller (2002)

Osteopathy versus Placebo

Study Design: RCT

Table 34: Characteristics of the Study

Single blinding:	YES
Double blinding:	NO
Attempt to confirm patient blinding	not stated
Total duration	2 years
Total length of treatment period	approximately 60 days
Type of analysis reported	available IBS clients
Participants Setting	IBS Patients treated in private practice
Number of evaluators	3
Recruitment method	call for bulletin
Duration of IBS symptoms before enrollment	minimum of 1 year
IBS diagnosis required for eligibility	Rome II criteria were used Kruis pain scale value more than 44mm more than 4GI symptoms
Examination to rule out organic gastrointestinal disease?	yes, medical opinion less than 1 month before study baseline
Were people with a history of osteopathy treatment excluded?	not stated
Other important inclusion criteria	osteopathic dysfunction at : - Atlanto-occipital joint - epigastric region - between colon and pelvic - between colon and small intestine
Important exclusion criteria:	Pregnancy
Symptom score	abdominal pain, diarrhea, constipation, meteorism, other symptoms
Statistical analysis	ANOVA

Table 35: Demographic Parameters of Both Groups

	Osteopathic Group	Standard Error	Sham Group	Standard Error	P-Value
Age	50	2.736	47	2.926	0.4097
BMI	23.5	0.841	25.4	0.985	0.1407
Male	5		4		
Female	23		21		
Sex	0.226	0.076	0.154	0.072	0.5017

Table 36. Subjects and pain intensity of both groups

	Osteopathic Group	Standard Error	Sham Group	Standard Error	P-Value
No. of Subjects	28		25		
Pain Intensity/mm (VAS)	64.03	2.758	63.20	3.196	0.8451

Table 37. Description of the osteopathic group intervention

Intervention	4 defined osteopathic techniques - Suture occipito-mastoidea - epigastric region - between colon and pelvic - between colon and small intestine
Style of osteopathy	functional, non manipulative
No. of patients allocated to osteopathy	31
Total length of treatment period	approximately 60 days
Number of targeted sessions	5
Distribution of treatments	approximately 2 per month
Duration of treatment (min)	up to 40 minutes
Time between follow-up examinations	approximately 15 days
Additional intervention in any of the groups	medical intervention was possible but had to be stopped 48 h before treatment

Table 38. Description of the control group intervention

Interventions in the sham group	explorative osteopathic examination at column, thorax and pelvis
No. of patients allocated to sham	30
Total length of treatment period	approximately 60 days
Number of targeted sessions	5
Number of treatments	approximately 2 per month
Time between follow-up examinations	approximately every 15 days
Additional intervention in any of the groups	medical intervention was possible but had to be stopped 48 h before treatment

Table 39. Jadad Score for internal validity

Was the study Described as Randomized?	Was the Method of Generating Randomization Sequence Appropriate?	Was the Study Described as Double Blind?	Was the Method of Double Blinding Appropriate?	Was there a Description of Dropouts and Withdrawals?	∑	Quality
1.0	1.0	0. (+1.0)*	X	1	3.0 (4.0)	High (high)

Table 40. Linde Internal Validity Scale Score

Method of allocation to groups	Conceal-ment of allocation	Baseline comparabi-lity	Blinding of patients	Blinding of evaluators	Likelihood of selection bias after allocation to groups due to dropouts	Result
1.0	1.0	1	1	0	1	5

Outcomes Abstracted for Systematic Review:

Times of check-up:

- after each treatment (approximately day 14/28/42/56/75)

Overall general well-being:

- not stated

Table 41. Difference of "Pain" from T0 (First Treatment) up to the Follow-Up

	Mean	Mean	
T0 (First Treatment)	64.517	63.667	P = 0.8451
TK (75 Days after First Treatment)	12.862	49.708	
P-Value	P < O.001	P < 0.017	P < 0.0001 in favor for osteopathy

Type of Outcome Data Reported:

A significant difference in post-treatment values between the osteopathic and control group for:

- abdominal pain
- gas / bloating
- diarrhea

Study Conclusion:

- Therapeutic benefit of osteopathy in IBS was clearly shown.
- Neither sham nor true osteopathy worsened any of the patients' symptoms and no additional adverse effects were reported.

Weak Points:

- Few treatment sessions (5).
- Short time span between treatments (approximately every 2 weeks).

- No follow-up examinations after final examination on day 75.

Risk of Bias:

- Sham treatment was not absolutely neutral. Even if it was only an evaluation, it was still done manually and with mobilization techniques. Maybe this was already considered a therapeutic component.
- Medication had to be stopped 48 hours before treatment.

Study of Hundscheid(2007)

Osteopathy (in private practice) versus Standard Medical Care (SMC)

Study Design: RCT

Table 42. Characteristics of Study

Single blinding	NO (SMC vs. osteopathy!)
Double blinding	NO (SMC vs. osteopathy!)
Total duration	6 months
Type of patients	available IBS clients from Maasland Hospital
Duration of IBS symptoms before enrollment	longer than 1 year
IBS diagnosis required for eligibility?	Rome II criteria were used - severity moderate
Examination to rule out organic gastrointestinal diseases	medical opinion of a gastroenterologist from Maasland Hospital
Other important inclusion criteria?	complaints had to be present at least three days a week
Important exclusion criteria	concomitant renal / liver disease, alcoholism, psychiatric illness, etc
Were people with a history of osteopathic treatment excluded?	not stated
Total length of treatment period	?
Number of targeted sessions	5
Distribution of treatments	2 per month
Duration (min)	30 to 60 minutes
Time between follow-up examinations	6 months
Follow-up visits	after 1, 3 and 6 months
Symptom score	abdominal pain, cramps, borborygmi, diarrhea, constipation, meteorism, feeling of incomplete discharge of feces, presence of mucous, IBSQOL 2000, FBDSI
Statistical analysis	Chi-square test for contingency tables and t-test

Table 43. Demographic parameters of both groups

	Osteopathic Treatment	Standard Medical Care
Average age (years)	46.5	41
Smoker	6	6
Use of alcohol	9	9
Mean quality of life score	111 (max 160)	109 (max 160)
Mean symptom score	9.1	8.7
Mean FBDSI score	174 (above 110 = severe)	171 (above 110 = severe)
Women (n/n):		
Men (n/n):		

Table 44. Characteristics of osteopathic intervention group

Intervention	Osteopathy / black box method
Participant setting in OG	IBS Patients treated with osteopathy in private practice
Recruitment method	Clients of the outpatient clinic at Maasland Hospital
No. of patients allocated to osteopathy	23
Dropouts / withdrawals	1
Total length of treatment period	6 months
Number of targeted sessions	5
Duration of treatment (min)	30 to 60 minutes
Additional intervention in any of the groups	No medication of standard medical care allowed, no advice for rich-in-fiber diet
Distribution of treatments	Every 2 or 3 weeks
Follow-up visits	After 1, 3 and 6 months
Time between follow-up examinations	6 months
Intervention	Standard medical care Antidiarrheals (n = 2) - Fiber (n = 5) - Mebevebrine (n = 14) - Laxatives (n = 5)
Participant setting in SMC	Patients treated at the gastroenterology outpatient clinic of the Maasland Hospital
Recruitment method	Patients from the outpatient clinic at Maasland Hospital
No. of patients allocated to SMC	19
Dropout	2
Additional intervention in SMC	Only prescribed drugs and extra fiber, taken thru the entire study period

Table 45. Statistical parameters of both groups

	Osteopathic Treatment	Standard Medical Care
Evaluated	19	17
Lost to follow-up	1	2

Table 46. Linde Internal Validity Scale Score

Method of Allocation to Groups	Concealment of Allocation	Baseline Comparability	Blinding of Patients	Blinding of Evaluators	Likelihood of Selection Bias after Allocation to Groups by Dropouts	Result
1	1	1	1	0	1	**5.0**

Table 47. Jadad Score for Internal Validity

Was the study Described as Randomized?	Was the Method of Generating Randomization Sequence Appropriate?	Was the Study Described as Double Blind?	Was the Method of Double Blinding Appropriate?	Was there a Description of Dropouts and Withdrawals?	∑	Quality
1.0	1.0	0. (+1.0)*	X	1	3.0 (4.0)	High (high)

Outcomes Abstracted for Systematic Review

Times of check-up: After 1, 3 and 6 months

Table 48.Overall improvement in symptoms in %

	Treated with Osteopathy (19 subjects)	Treated with Standard Medical Care (17 Subjects)	Probability	Significant
Free of Symptoms	5% = 1 client	O		
Definite Overall Improvement in Symptoms	68% = 13 clients	18% = 3 clients		
Slight Improvement in Symptoms	27% = 5 clients	59% = 10 clients		
Worsening of Complaints	0	17% = 3 clients		
Difference of Change in Overall Symptoms			P < 0.006	YES, in favor of osteopathy

Table 49. Mean FBDSI Score

	Treated with Osteopathy (19 Subjects)	Treated with Standard Medical Care (17 Subjects)	Probability	Significant
Mean FBDSI	174 (SD +/-36) at the beginning 74 (SD +/-64) after 6 months		P < 0.0001	YES
Mean FBDSI		171 (SD +/- 31) at the beginning 119 (SD+/- 48) after 6 months	P < 0.0001	YES.
Mean FBDSI Osteopathy vs. SMC			P < 0.02	YES, in favor of osteopathy
Mean symptom score	6.8 after 6 months	10 after 6 months	P < 0.02	YES, in favor of osteopathy

Table 50. Mean Symptom Score

	Treated with Osteopathy (19 Subjects)	Treated with Standard Medical Care (17 Subjects)	Probability	Significant
3 months	9.1 (+/-SD 4 To 7.6 (+/-SD 4.5	8.7 (+/-SD 4) to 10 (+/-SD 4	P = NS	NO
6 month	6.8 (+/-SD 4)	10 (+/-SD 4)	P = 0.02	YES, in favor of osteopathy

Table 51. Quality of Life Score

	Treated with Osteopathy (19 Subjects)	Treated with Standard Medical Care (17 Subjects)	Probability	Significant
Quality of Life Score At the Beginning		109 (+/-SD 20)		
Quality of Life Score After 3 Months		111 (+/-SD 18)		
Quality of Life Score After 6 Months		121 (+/- SD 25)		NO
Quality of Life Score At the Beginning	111 (+/-SD 22)			
Quality of Life Score After 3 Months	125 (+/-SD 20)			
Quality of Life Score After 6 Months	129 (+/-SD 19)		P < 0.009	YES, in favor of osteopathy

Type of Outcome Data Reported:

A significant difference in post-treatment values between the osteopathic- and control group for:

- Abdominal pain,
- Gas / bloating,
- Diarrhea.

Author's conclusion:

- The therapeutic benefit of osteopathy in IBS was clearly shown.

Adverse Effects:

- No patient in either group reported any side effects. The osteopathic treatment proved to be safe, even though all patients reported a slight increase in symptoms severity after the first treatment. This wore off quickly. No additional adverse effects were reported.

Study Conclusion:

- It was concluded that osteopathy is a promising alternative in the treatment of patients with IBS. Patients treated with osteopathy showed an overall improvement, with respect to the symptom score and quality of live.

Weak Points:

- Few treatment sessions.
- Small group size

Risk of Bias:

- Only one Osteopath.
- The osteopath spends more time with the patient than the medical doctor(Psychological benefit).

Appendix G

Calculation of Effect Size, Mean- and Standard Deviation

Calculation of the Standard Deviation for the Effect Size of the Study by Muller (2002)

Table 52. Calculation of the Standard Deviation for the Effect Size of the Study

Proband	Group (0=Cntrl, 1=Iv)	VAS baseline	VAS after last treatment	Difference
RD/b-01	0	51	62	11
RD/b-02	0	45	61	16
RD/b-06	0	65	13	-52
RD/b-07	0	38	29	-9
RD/b-10	0	88	51	-37
RD/b-13	0	16	3	-13
RD/b-16	0	36	3	-33
RD/b-18	0	53	15	-38
RD/b-20	0	65	44	-21
RD/b-21	0	64	3	-61
RD/a-01	0	72	50	-22
RD/a-05	0	72	52	-20
RD/a-06	0	75		
RD/a-07	0	50		
RD/a-08	0	83	0	-83
RD/a-09	0	42	0	-42
RD/a-13	0	47		
RD/a-14	0	0	28	28
RD/a-17	0	58	0	-58
RD/c-02	0	60	61	1
RD/c-03	0	48	50	2
RD/c-05	0	50	50	0
RD/c-08	0	49	50	1
RD/c-09	0	93	77	-16
RD/c-11	0	68	61	-7
RD/c-13	0	65	48	-17
RD/c-14	0	85	80	-5
RD/c-17	0	71	xx	
RD/c-19	0	57	55	-2
RD/c-20	1	58	20	-38

Proband	Group (0=Cntrl, 1=Iv)	VAS baseline	VAS after last treatment	Difference
RD/b-03	1	23	20	-3
RD/b-04	1	16	12	-4
RD/b-05	1	72	30	-42
RD/c-18	1	48	15	-33
RD/b-08	1	10	6	-4
RD/b-11	1	66	xx	
RD/b-12	1	44	41	-3
RD/b-14	1	28	4	-24
RD/b-15	1	34	xx	
RD/b-17	1	46	15	-31
RD/b-19	1	26	5	-21
RD/b-22	1	89	4	-85
RD/a-02	1	78	0	-78
RD/a-03	1	47	6	-41
RD/a-04	1	87	7	-80
RD/a-10	1	52	0	-52
RD/a-11	1	54	17	-37
RD/a-12	1	55	0	-55
RD/a-15	1	0	0	0
RD/a-16	1	92	28	-64
RD/a-18	1	65	0	-65
RD/a-19	1	48	0	-48
RD/c-04	1	62	5	-57
RD/c-01	1	35	5	-30
RD/c-06	1	72	6	-66
RD/c-07	1	70	5	-65
RD/c-10	1	64	3	-61
RD/c-12	1	94	80	-14
RD/c-15	1	66	10	-56
RD/c-16	1	42	18	-24
	Group	**Mean**	**SD**	
	Intervention	**-19,08**	**26,31**	
	Control	**-40,72**	**25,14**	