#### **CASE REPORT**

Katherine Heineman, DO, FAAO

# Osteopathic Manipulative Treatment for the Management of Irritable Bowel Syndrome: A Case Report

### **Abstract**

Irritable bowel syndrome (IBS) is one of the most common disorders of the gastrointestinal system, occurring in 10-20% of the general population. <sup>1,2,3</sup> IBS is associated with heavy social and economic costs in the United States, as it results in the second highest cause of work absenteeism and accounts for 25-50% percent of all gastroenterology referrals. <sup>1,4</sup> IBS is characterized by recurrent abdominal pain or discomfort and bowel dysfunction as diarrhea, constipation or both, in the absence of any organic cause. <sup>3,5,6,7</sup> The pathophysiology of IBS appears multifactorial, although current focus for an understanding of the disease process is on alteration of gastrointestinal motility, visceral hypersensitivity and dysregulation of the brain-gut axis between the autonomic nervous system (ANS) and the enteric nervous system (ENS). <sup>6,8</sup> The lack of full understanding of the pathophysiologic processes of IBS means current management options are often ineffective and unreliable, leaving patients with frustrating and sometimes disabling symptoms. <sup>2,7</sup>

An osteopathic approach using osteopathic manipulative treatment (OMT) to address symptoms related to IBS is an under-explored treatment option. The use of OMT within a treatment plan offers the ability to address manifestations of visceral and somatic dysfunctions unique to each patient. This case report outlines a successful osteopathic manipulative treatment course for a patient suffering from IBS symptoms. Randomized controlled trials (RCTs) for the use of OMT on patients with IBS in the current literature are also reviewed below and provide further preliminary evidence that OMT may be effective in managing IBS symptoms. <sup>2,5,7,9,11</sup>

# Report of Case

# **History of Present Illness**

A 74-year-old female, G.J., presented to an Osteopathic Manipulative Medicine (OMM) Clinic for evaluation of severe abdominal pain, cramping and diarrhea for the past 5-6 years, worsening in intensity over the past 2-3 months, related to a diagnosis of irritable bowel syndrome. The patient reported severe abdominal pain and cramping following eating approximately 3/7 days of the week. Her abdominal cramping episodes would last around 3-5 minutes, after which she would often have an episode of diarrhea. She had reportedly lost 12

# **Corresponding Author**

Katherine Heineman, DO, FAAO

Email:

katherine@yourosteopathiccare.com

# **Keywords**

Irritable bowel syndrome, IBS, gastroenterology, diarrhea, constipation

| Table 1. Physical Exam. |  |
|-------------------------|--|
| Vital Signs             | Height 5ft 3in, Weight 172 lbs, BMI 30.5, Pulse 67 bpm, BP 133/77.   |
| Constitutional          | Well-nourished, although the patient's BMI put her into the obese category. No acute distress. Ambulating normally.                              |
| Psychiatric             | Normal mood and affect. Active and alert.  |
| Head                    | Normocephalic and atraumatic.  |
| ENMT                    | Ears: no lesions on external ear. Nose: no lesions on external nose. Oropharynx: moist mucous membranes.   |
| Lungs                   | Respiratory effort of respiration rhythm and depth was normal.   |
| Cardiovascular          | No edema on inspection or palpation of right or left lower extremities.  |
| Abdomen                 | Inspection and palpation: no guarding or rebound tenderness and soft throughout. Normal bowel sounds in all quadrants.                           |
| Musculoskeletal         | Motor Strength and Tone: normal tone. Right Upper Extremity: normal bulk. Left Upper Extremity: normal bulk. Normal movement of all extremities. |
| Neurologic              | Normal gait. Cranial Nerves were grossly intact.   |
| Skin                    | No rash on inspection of exposure of hands, face or abdomen.   |
|                         |  |

pounds over the past month secondary to avoiding food, so as not to experience the abdominal pain and cramping symptoms. She had previously been given a diagnosis of lactose intolerance and continued to avoid dairy. She had also been on an elimination diet for about 1 month and had eliminated coffee, leafy greens, seeds and dairy, although without significant benefit. She was otherwise trying to follow a "bland diet." Every few weeks, she stated the abdominal pain and cramping would be so severe that she would present to the emergency department (ED). Three weeks prior to her initial visit, G.J. did present to the ED after a severe episode of abdominal cramps and pain. An abdominal CT scan at the ED visit did not show organic disease although she was diagnosed with a urinary tract infection at that time. Two years prior, she had undergone an esophagogastroduodenoscopy (EGD) and a colonoscopy, which were both reportedly normal. She had had a total of four colonoscopies in the past, none of which showed organic disease. She had seen her primary care physician after the ED visit, however, did not receive any further direction or recommendations regarding her abdominal pain and cramping episodes.

# **Medical History**

Surgical History: Right total knee arthroplasty (9 years prior), cholecystectomy (24 years prior), appendectomy (49 years prior).

Past Medical History: Irritable bowel syndrome, lactose intolerance, hypothyroidism, osteoarthritis (right knee, cervical spine).

Family History: Father, mother, maternal grandfather and maternal grandmother with history of myocardial infarction; sister and brother with history of diabetes mellitus, type II; mother with history of osteoarthritis.

Social History: Married with 3 biologic children. Denies tobacco use, alcohol use or other substance use. Retired.

Allergies: No known drug allergies.

Medications: Levothyroxine 88 mcg 1 tab daily, ondansetron 4 mg 1 tab daily, Lactaid as needed, tramadol 50 mg 1 tab daily as needed, calcium 500 mg 1 tab daily, vitamin D3 1000 IU daily.

#### **Review of Systems**

The patient reported weight loss of 12 pounds over the past month, related to lack of eating secondary to abdominal pain. She reported abdominal pain, cramping and frequent diarrhea. No constipation. She denied history of vomiting, dyspepsia or history of gastroesophageal reflux disease. She denied history of blood in her stools. She denied fever, night sweats or pain in the night. She reported some mild anxiety, not medically treated, and increased stress, which she noted may be related in part

to her husband's recent diagnosis of Parkinson's disease and efforts to sell their 35-year homestead property. She reported no incontinence, no hematuria, no increased urinary frequency. She also denied pain with urination. She denied chest pain, palpitation, or shortness of breath. She denied swollen glands, bruising, recent injuries or trauma. She denied numbness, weakness, tingling, seizures, or dizziness.

#### **Osteopathic Structural Exam**

Notably decreased rotational motion and flexion/extension of T5-L2 with ropy tissue texture changes in the corresponding paraspinal muscles; right sacral base felt pulled anterior on a left oblique axis and motion with the primary respiratory mechanism was decreased; slowed GI physiologic clockwise motion throughout the abdomen in the coronal plane with stalled motion of the ileocecal valve, the duodenojejunal junction, the sphincter of Oddi, the pylorus and the gastroesophageal junction (no motion was appreciated of either clockwise or counterclockwise motion in these regions); thoracoabdominal diaphragm with decreased excursion of motion in anterior/posterior and superior/inferior direction; OA FSIRr.

#### **Assessment**

- 1. Abdominal cramps (R10.9: Unspecified abdominal pain)
- 2. Irritable bowel syndrome with diarrhea (K58.0: Irritable bowel syndrome with diarrhea)
- 3. Lactose intolerance (Lactose intolerance, unspecified)
- 4. Segmental and somatic dysfunction (M99.00: Segmental and somatic dysfunction of head, M99.02: Segmental and somatic dysfunction of thoracic region, M99.03: Segmental and somatic dysfunction of lumbar region, M99.04: Segmental and somatic dysfunction of sacral region, M99.09: Segmental and somatic dysfunction of abdomen)

#### Recommendations

Based on the physical examination findings, OMT was offered to address the somatic dysfunction findings (see procedure note below). The patient was instructed to continue her current elimination diet and maintain adequate hydration. She was scheduled to return for further evaluation in 1 week.

#### First Treatment

Procedure Note: After careful consideration of history and physical findings, osteopathic manipulation was offered to the patient as a modality to potentially improve the above areas of somatic dysfunction. The somatic dysfunctions present were found to be related to the patient's symptoms/condition. Following appropriate verbal consent, the patient was treated with gentle osteopathic manipulation to the above-mentioned areas of somatic dysfunction. Treatment techniques included: balanced ligamentous tension (BLT) and myofascial release (MFR) in a supine position to the thoracic region, lumbar region, sacrum, abdomen and head. Dysfunctional GI sphincter motion was found as 'no motion appreciated' for the listed abdominal sphincters. This was addressed with direct MFR by using a small amount of pressure to fascially engage and load the dysfunctional sphincters individually, taking each in a clockwise direction. Once the sphincter motion appeared to move in a smooth and clockwise motion, fascial engagement was released, and inherent motility was reassessed. General GI motion, palpated initially as slowed clockwise motion throughout the abdomen, was found to improve following treatment of all abdominal sphincters. The patient tolerated the treatment well without complication. Somatic dysfunctions were improved as evidenced by an increased range of motion. The patient was advised regarding post-treatment concerns (usually experienced as a transient increase in soreness/achiness) and encouraged to increase hydration and rest for the next 24-48 hrs. She was to return to her usual activity following that time.

#### **Continued Course of Treatment**

The patient returned 1 week after the initial visit for further evaluation. She stated she had only one episode of acute abdominal pain and cramping since the initial visit. She reported she was drinking lots of water and continuing her bland diet. She was continuing with 4 bowel movements daily, generally described as loose stools. She denied pain in the night, but occasionally would wake with dull, abdominal pain in the morning. No other new symptoms.

#### **Second Treatment**

Osteopathic structural exam findings at the second visit revealed persistent ropy tissue texture changes with

no rotational motion or flexion/extension of T7-L2; slowed ileocecal valve motion in a clockwise direction, lack of connected physiologic motion between the pyloric and duodenal regions, also lack of physiologic connection with the primary respiratory mechanism along the mesenteric root (the mesenteric root is found along a diagonal line from the umbilicus to the right ASIS in the coronal plane, lack of physiologic connection with the primary respiratory mechanism was palpated as no motion along this diagonal line or motion in an uncoordinated fashion); left sacral base anterior; OA FRISr. Somatic dysfunctions were treated to an end point of improved motion using BLT and MFR to the thoracics, lumbars, abdomen, sacrum and head. The patient was again instructed to continue her dietary regimen and increased hydration.

#### **Additional Treatments**

The patient returned for a third visit, 2 weeks after the initial evaluation. She again reported good improvement through the past week with only one episode of abdominal pain and cramping, followed by diarrhea, which had occurred after eating a spicy meal. Osteopathic structural exam findings at the third visit revealed decreased flexion/ extension of T10-L2; improved physiologic clockwise motion throughout the GI system, including all sphincter motion; an improved physiologic connection along the mesenteric line (palpated as inherent motion moving in a smooth, connected fashion in a superior-to-inferior and inferior-to-superior direction along this diagonal line); slight rotation of the sacral base to the left on a left vertical axis; T1 RrSr; OA FRISr. Somatic dysfunctions were again treated to an end point of improved motion using BLT and MFR to the thoracics, lumbars, abdomen, sacrum and head. The patient was again instructed to continue hydration and was allowed to try a slow return of reintroducing some foods, although not dairy.

The patient returned for a fourth visit, 1 month after the initial evaluation. She stated was doing notably better with abdominal pain and cramping occurring only "once in a great while." She had also had good improvement in her loose stools. She was cautiously introducing some additional foods, although still avoiding dairy. Osteopathic structural exam findings at the fourth visit revealed slightly decreased rotation and flexion/extension of T9-L2, although improved motion from the prior visit; counterclockwise motion of the gastroesophageal (GE) junction only; good physiologic motion with the

primary respiratory mechanism through all other sphincters and along the mesenteric root; sacral base rotated right; OA preferred flexion. Somatic dysfunctions were again treated to an end point of improved motion using BLT and MFR to the thoracics, lumbars, abdomen, sacrum and head. The patient was again instructed to continue hydration and to continue a slow return of reintroducing some foods, except dairy.

The patient returned for a fifth visit, 2 months after her initial evaluation. She had experienced 1 episode the week prior of significant abdominal pain and cramping after eating peanuts. She said the morning after eating the peanuts, she experienced severe cramps in the lower abdomen at a level of a 10/10. The waves of pain and cramping lasted 3-5 minutes, which were relieved following a bowel movement. The following 2-3 mornings, she again had abdominal pain and cramping, which then resolved. She currently reported 2-3 bowel movements per day, which were not loose in nature. She states she also had a stressful month, as she and her husband completed the sale of their home and finished a move to a townhome. Osteopathic structural exam findings at the fifth visit revealed acute facilitation of T5-L2 with decreased rotation and flexion/extension; counterclockwise motion of gastroesophageal (GE) junction and pylorus; acute facilitation of the superior linea alba at the region of the celiac ganglion; left sacral base posterior; OA FSrRl. Somatic dysfunctions were again treated to an end point of improved motion using BLT and MFR to the thoracics, lumbars, abdomen, sacrum and head. The patient was again instructed to continue hydration and to continue a slow return of reintroducing some foods, except dairy and other known aggravating foods.

The patient returned for a sixth and final visit, three and a half months after her initial evaluation and treatment. She stated she was feeling "better than I have in years!" Her last bout of abdominal cramps was a week and a half prior after eating popcorn. She noted that the osteopathic treatments had helped significantly, and she was continuing to have more regular bowel movements without diarrhea or constipation. Alleviating factors were reported as "a visit here," aggravating factors included "eating wrong." Her primary complaint at this visit was pain over the dorsum of her right 3<sup>rd</sup> metatarsal of insidious onset, 2 weeks duration. She denied trauma or injury to the foot. The foot was evaluated by her PCP and she received an x-ray, which was negative for fracture or notable osteoarthritis. Osteopathic structural exam findings at the sixth

and final visit revealed great physiologic motion through the thoracic spine, lumbar spine, sacrum and GI system; thoracoabdominal diaphragm preferred flexion in an anterior/posterior plane; right 3<sup>rd</sup> and 4<sup>th</sup> metatarsal heads dropped, decreased internal/external rotation through the right 3<sup>rd</sup> and 4<sup>th</sup> metatarsal bones; OA SrRl with good flexion/extension motion. Somatic dysfunctions were again treated to an end point of improved motion using BLT and MFR to the lower extremity, abdomen and head. The patient was instructed to continue hydration and return of reintroducing foods, except dairy and other known aggravating foods. She was told to return on an as-needed basis.

#### Discussion

Irritable bowel syndrome is a highly prevalent functional gastrointestinal disorder, accounting for 10 to 15 percent of primary care visits and 25 to 50 percent of gastroenterology referrals.<sup>2,3</sup> IBS is defined by chronic abdominal pain and/or discomfort with bowel dysfunction for recurring periods.<sup>3,5,7</sup> Bowel dysfunction includes a change in frequency of stool, change in stool formation, strain with defecation or incomplete defecation, presence of mucus, and abdominal bloating and/or distension.<sup>5,7</sup> IBS is diagnosed using Rome III criteria after excluding other organic disease. 5,7,8 IBS is not associated with increased mortality or serious disease development, although it does cause significant morbidity, such as depression and inability to work, as well as quality of life impairment, and increased economic burden on the health care system.<sup>8,9</sup> The underlying pathophysiology of IBS is not fully elucidated, although dysregulation of the brain-gut axis is thought to perpetuate functional bowel disorders, including IBS.<sup>6,10</sup> Effective management options for IBS remain scarce and disappointing with only minor clinical benefit, despite high prevalence rates.<sup>7,9</sup> In the current case, osteopathic manipulation notably improved the severity of IBS symptoms and the patient's quality of life. Several reports in the osteopathic literature provide further support and preliminary evidence that OMT may be effective for management of IBS symptoms as outlined below.

# Management

Conventional treatment for IBS is targeted at the motor, sensory and gastrointestinal nervous system, as well as psychological support.<sup>2,7,9</sup> The target for treatment has been to affect gastrointestinal motility and visceral hypersensitivity.<sup>6</sup> Common recommendations and pharmacologic

treatments include a fiber-rich diet, lactose reduction, other bulking agents, laxatives, antispasmodics, antibiotics, antidiarrheal agents, and antidepressants.<sup>2,11</sup> Antispasmodics, antidepressants and other psychological interventions have shown some improvements in the management of IBS symptoms, although fiber supplements, laxatives and bulking agents have shown little therapeutic value through RCTs, despite their frequent use for disease management.<sup>2,7</sup> Due to a lack of effective and reliable treatment options for IBS, patients frequently pursue complementary and alternative treatments to pharmacologics, including pre- and probiotics, exclusion diets, acupuncture, herbal medicines, hypnosis, meditation, and manipulative-based body practices.<sup>2</sup> Despite growing interest in these modalities, alternative care has rarely been studied for IBS.<sup>5,9</sup> IBS patients would likely have increased interest in osteopathic manipulation for treatment if it could be made available to them and if it was further shown to be an effective option.9

# Irritable Bowel Syndrome in the Osteopathic Literature

To date, 5 RCTs using OMT on adult IBS patients diagnosed with Rome III criteria have indicated beneficial results, including reduction of abdominal pain, constipation, and diarrhea and improved general well-being, as compared to standard medical treatment or sham interventions. 204 patients were included among the 5 studies and no adverse events were reported.<sup>2,5,7,9,12</sup>

Brisard et al (1998) and Muller et al (2002) showed a drop in a visual analog scale (VAS) for pain from 64.5 to 12.9 and from 50.7 to 33.4 respectively after 10 weeks for an OMT intervention group, while sham control group VAS levels went from 63.7 to 49.7 and from 56.5 to 62.3 respectively after 10 weeks.<sup>7,12</sup>

Hundscheid et al (2007) in the Netherlands completed a study of 39 total patients and found improvement of a Functional Bowel Disorder Severity Index (FBDSI) score. The OMT group FBDSI score improved from 174 to 74 following five OMT sessions in 2-3 weeks, while the control group of standard medical care (including dietary recommendations, laxative/antidiarrheal and antispasmodic medications) decreased from 171 to 119. The FSDSI score included symptoms of abdominal pain, cramps, borborygmi, diarrhea, constipation, flatulence, feeling of incomplete evacuation and presence of mucous. Both decreases of the FBDSI were significant, however, the decrease in the OMT group was significantly

higher compared to the control arm. Overall symptom improvement, quality of life and IBS severity conferred by the OMT group in the study was sustained after 6 months.<sup>2,7</sup>

Florance et al (2012) in a study in France also found that OMT decreased IBS symptoms and improved quality of life as compared to a sham treatment. This study of 30 patients used an IBS severity score and observed an improvement of symptoms after 2 OMT sessions in a 7-day interval, as well as sustained improvement in the OMT arm after 3 weeks of follow up as compared to the sham arm (300 to 196 and 275 to 244, respectively). Other improved secondary outcomes included quality of life and psychological factors.<sup>7,9</sup>

In a fifth study, Attali et al (2013) enrolled 31 refractory IBS patients who had failed to improve following various drug therapies and were dissatisfied about their care related to IBS treatment. The study utilized a RCT crossover design and submitted an OMT group and a sham group to a series of six treatment sessions separated by 2-week intervals. They found a statistically significant decrease in VAS score for abdominal pain for both groups after the initial short-term 12-week period; however, only the OMT group maintained a statistically significant long-term decrease in symptoms after one year of follow up (3.50 to 2.49; sham 3.02 to 3.06).<sup>5,7</sup>

The patient in this case presented with classic features of irritable bowel syndrome, including chronic abdominal pain and altered bowel habits. She also reported symptoms consistent with mild anxiety related to stress from her husband's recent medical diagnosis and the physical and emotional toll from having to sell their 35-year homestead, both of which may have contributed to her IBS flare. Initial osteopathic structural findings were consistent with visceral-somatic pathology. These findings included chronic facilitation of the mid-thoracic region to the upper lumbar segments (T5-L2) as the sympathetic innervation to the gastrointestinal tract (stomach T5-9,

# References

- Wald A. Clinical manifestations and diagnosis of irritable bowel syndrome in adults. Talley N, ed. UpToDate. Waltham, MA: UpToDate Inc. https://www.uptodate.com/ (Accessed on April 10, 2020).
- Hundscheid H, Pepels M, Engels L, Loffeld R. Treatment of irritable bowel syndrome with osteopathy: results of a randomized controlled pilot study. *J Gastrointestin Hepatol*. 2007;22(9):1394- 1398.
- 3. Choung RS, Locke GR III. Epidemiology of IBS. Gastroenterol Clin

liver and gallbladder T9, pancreas T5-11, small intestine T9-11, ascending and transverse colon T10-12, descending colon and rectum L1-2); somatic dysfunction of the collateral sympathetic ganglion as a prevertebral sympathetic ganglion pathway to the abdominal organs; decreased motility of the abdominal sphincters, an inherent expression of the sphincter tone at transitional areas through the GI tract; somatic dysfunction of the thoracoabdominal diaphragm, a key player in lymphatic drainage of and oxygen supply to the GI tract; decreased sacral motion, affecting parasympathetic innervation to the descending colon and rectum; and occipitoatlantal (OA) dysfunction, impacting normal neural flow of the vagus nerve as it supplies parasympathetic innervation to the GI tract from the stomach to the transverse colon. 13,14 Unlike one-dimensional pharmacologic treatment, an osteopathic approach utilizing OMT can systemically help to address the dysregulation of the autonomic nervous system (ANS), the enteric nervous system (ENS), the musculoskeletal system and nociceptive drive (pain fibers). 8,13,14 By normalizing autonomic activity in the GI tract, by promoting healthy lymphatic flow, nerve flow, and oxygenation to the tissues, by normalizing motion of the spine and innominate/sacral regions, osteopathic treatment is able to support the body's self-regulatory mechanisms and restore a homeostatic balance. 8,13,14

#### Conclusion

IBS is a complex, common and frequently lifelong functional gastrointestinal disorder that often goes unor undertreated in part because the pathophysiology of IBS remains unclear. Recent studies show promising evidence that OMT may help manage IBS symptoms. Outcomes from this case report further recommend the use of an osteopathic approach to help in treatment of patients with IBS. Additional studies are needed to further explore how osteopathic treatment may potentially improve dysregulation of altered neural connections between the ANS and ENS found in irritable bowel syndrome. Research

- North Am. 2011;40(1):1-10.
- Sandler RS, Everhart JE, Donowitz M, Adams E, Cronin K, Goodman C, Gemmen E, Shah S, Avdic A, Rubin R. The burden of selected digestive diseases in the United States. *Gastroenterology*. 2002;122(5):1500.
- 5. Attali TV, Bouchoucha M, Benamouzig R. Treatment of refractory irritable bowel syndrome with visceral osteopathy:

- short-term and long-term results of a randomized trial. *J Dig Dis.* 2013 Dec;14(12):654-61.
- 6. Wald A. Pathophysiology of irritable bowel syndrome. Talley N, ed. UpToDate. Waltham, MA: UpToDate Inc. https://www.uptodate.com/ (Accessed on April 10, 2020).
- 7. Müller A, Franke H, Resch KL, Fryer G. Effectiveness of osteopathic manipulative therapy for managing symptoms of irritable bowel syndrome: a systematic review. *J Am Osteopath Assoc.* 2014 Jun;114(6):470-9.
- Collebrusco L, Lombardini R. What about OMT and nutrition for managing the irritable bowel syndrome? An overview and treatment plan. Explore (NY). 2014 Sep-Oct; 10(5):309-18.
- Florance BM, Frin G, Dainese R, Nébot-Vivinus MH, Marine Barjoan E, Marjoux S, Laurens JP, Payrouse JL, Hébuterne X, Piche T. Osteopathy improves the severity of irritable bowel syndrome: a pilot randomized sham-controlled study. *Eur J Gastroenterol Hepatol*. 2012 Aug;24(8):944-9.

- Piche T, Pishvaie D, Tirouvaziam D, Filippi J, Dainese R, Tonohouhan M, DeGalleani L, Nébot-Vivinus MH, Payrouse JL, Hébuterne X. Osteopathy decreases the severity of IBS-like symptoms associated with Crohn's disease in patients in remission. *Eur J Gastroenterol Hepatol*. 2014 Dec;26(12):1392-8.
- 11. Wald A. Treatment of irritable bowel syndrome in adults. Talley N, ed. UpToDate. Waltham, MA: UpToDate Inc. https://www.uptodate.com/ (Accessed on April 10, 2020).
- Müller A, Salomon J, Stiedl M. Osteopathy as a Promising Short-term Strategy for Irritable Bowel Syndrome: Randomized Controlled Trial. *German Academy of Osteopathy*; 2002. https://www.osteopathicre-search.org/s/afo/item/2534. Accessed April 12, 2020.
- 13. Kuchera ML, Kuchera WA. Osteopathic Considerations in Systemic Dysfunctions, 2e, (pgs. 112-120). Greyden, 1994.
- 14. Willard, F. Chapter 10: Autonomic Nervous System. Chila, A., ed. Foundations for Osteopathic Medicine, 3e, Wolters Kluwer, Lippincott Williams & Wilkins: 2010.