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RD 09/4

State of the Art: hypnotherapy for functional gi disorders

Peter Whorwell, MD, PhD

Franz Anton Mesmer (1734-1815) is credited as being the pioneer of medical hypnosis although unfortunately he wrongly concluded that the phenomenon was dependent on the use of magnetic fields. Subsequently, James Braid (1795-1860) refuted the idea that magnetism was essential to bring about a trance-like state and went on to coin the term hypnosis. Since that time the technique has waxed and waned in terms of its popularity and we are currently witnessing renewed interest in its therapeutic potential especially as there is increasing evidence that hypnosis can be used to influence physiological processes in addition to its well known benefits on psychological function.

These attributes of hypnosis would suggest it might have utility in disorders where there is no structural abnormality and biopsychosocial factors are important. Consequently, we developed the technique of gut focused hypnosis and undertook a small trial of its effectiveness in irritable bowel syndrome. The results were very encouraging and in subsequent studies we confirmed that hypnotherapy consistently reduces the symptoms of IBS as well as improving quality of life in approximately two-thirds of patients, with the beneficial effects being sustained for at least five years. These results have been confirmed by others although all the trials have been somewhat small in size leading to some sceptics concluding that much larger studies are required before the technique can be fully endorsed. This is an unfortunate stance to be taking as funding for a large scale trial is going to be difficult because potential sponsors are going to be reluctant to "waste" resources on a modality that many think already has a sufficient evidence base.

In addition to its positive effects in IBS, hypnotherapy has also been shown to be useful in the treatment of other functional gastrointestinal disorders such as functional dyspepsia and non cardiac chest pain. It is not entirely clear how these beneficial effects are mediated although there is reasonably good evidence that hypnosis can affect a variety of gastrointestinal physiological parameters such as motility, visceral sensitivity, gastric acid secretion, gastric emptying as well as the processing of painful stimuli by the brain.

Hypnotherapy appears to have considerable potential in the management of functional gastrointestinal disorders but there are a number of impediments to it gaining general acceptability not least of which is considerable residual prejudice. However, we also need to know what is the ideal package in terms of content and duration as well as ensuring that it is provided in a reproducible and uniform style.

For more details of the work described in this paper and the technique of gut focused hypnosis see: Miller V and Whorwell PJ, Int J Clinc Exp Hyp 2009; 57:279-92.

RD 09/5

nationwide effectiveness trial of hypnosis for ibs

Olafur Palsson, PsyD

We developed a completely standardized hypnosis treatment protocol using verbatim scripts for the treatment of irritable bowel syndrome, making it possible for clinicians to easily adopt and implement the exact treatment tested in our research studies. The protocol was designed to be usable with all patients regardless of their specific symptoms, or their pace of responsiveness to hypnosis or capacity for mental imagery. This is a seven-session treatment protocol: One scripted session is delivered by a therapist approximately every other week, and a shorter audio home exercise is used by patients at home daily, for a total treatment period of about 3 months.

This protocol was tested by our team in two published research studies (Palsson et al., Digestive Diseases and Sciences 2002;47(11): 2605-2614) and found to improve the bowel symptoms of the great majority of patients treated. Abdominal pain was shown to be reduced by about half on the average, stool consistency normalized and bloating improved as well. Additionally, there was a substantial reduction in psychological symptoms, especially in anxiety and somatization scores. In our second study, we showed that the treatment gains were well maintained at the 10-month follow-up.

In 2000, I started sharing this scripted North Carolina Protocol without charge in a protected manner with appropriately qualified clinicians, and also began teaching regular training workshops for therapists on this treatment approach. As a result, there are now more than 400 clinicians using the protocol across the U.S. , of which about 250 are listed on our national provider list on www.ibshypnosis.com. The protocol is increasingly used internationally as well, primarily in the English-speaking world but also been translation into several other languages.

The many therapists who are now using the standardized protocol generally report excellent success rate anecdotally, similar to what has been found in the publishes studies. However, it is unknown exactly how effective the protocol is, and this is the primary reason for this outcomes research project.

The U.S. Nationwide IBS Hypnosis Outcomes Project (NIHOP) is an unfunded systematic large-scale data collection and healthcare enhancement effort for IBS. It will be the first-ever evaluation of hypnosis treatment outcomes when treatment is provided with the same standardized therapy by numerous different therapists in a variety of clinical settings. The aim is for 100+ therapists to participate and complete treatment of 500+ well-characterized IBS patients, and for this data collection to be completed within 24 months.

The project will be directed and principally carried out by myself, with collaboration from co-investigators at Northwestern University, UCLA, Washington State

University and UNC, and participating therapists throughout the U.S.
The aims of this project are to: (a) quantify and characterize the effects of hypnosis treatment for IBS when delivered in routine clinical practice on a national scale in the U.S.; (b) investigate which variables modulate the effectiveness of hypnosis treatment for IBS in a far broader and better-powered way than previously possible; (c) enhance the quality of IBS care by hypnosis providers by supporting good standards for assessment, diagnosis and evaluation of treatment changes and providing simple-to-use valid tools for detailed assessment; and (d) create an effective re-usable/replicable online system for outcome tracking in large-scale electronic data collection projects in the field of clinical hypnosis and psychological treatment more generally.

These aims are all accomplished via a dedicated secure website, through which all patient evaluations and communication with therapists will be conducted. This will be done in a HIPAA-compliant manner by ensuring that therapists and patients are completely anonymous in the online system. The system is designed not to request or allow any unique personal identifiers.

Therapists with appropriate training and experience in clinical hypnosis who offer IBS treatment with the standardized protocol will be invited to participate. They will have an Internet-connected computer available in their practice where patients can complete assessments before, during and after the treatment course. Participating therapists agree to document all patients with a presenting problem of IBS in the online system during the participation period. They will use the uniform ,efficient online clinical assessment system to evaluate their IBS patients and track their progress throughout treatment and at follow-up. Assessments will be conducted pre-treatment, in every other treatment visit, at the end of treatment, and at 6- and 12-month follow-ups. Changes in bowel symptoms, non-GI symptoms, quality of life, anxiety, depression, somatization, stress, sleep, IBS medications and healthcare utilization will be tracked from baseline through follow-up. Pre-treatment assessment will additionally include demographics and clinical history.

Therapists and patients will receive automated instantly available scored summaries and graphs showing results of all evaluations completed, with interpretations and norms where appropriate, that help guide initial assessment and provide clear and comprehensive picture of therapy response and change over time. Therapists will be able to retrieve data summaries for all patients they have treated and print out evaluation summaries and graphs for documentation of treatment results.

Therapists also will receive support throughout the project via the project website in the form of monthly online chat sessions, a growing expert knowledge FAQ database, internal discussion bulletin board, and a resource library containing key publications, reference articles, handouts for patients and doctors, etc.

RD 09/7

guided imagery treatment of pediatric ibd

Emilee Colella, BA

Children and adolescents with quiescent inflammatory bowel diseases commonly experience abdominal pain, similar to patients who suffer from functional gastrointestinal disorders such as Irritable Bowel Syndrome (IBS), without the presence of physiological disease. Functional abdominal pain can decrease quality of life, but effective treatment is neither widely available nor easily accessible.

Medical treatment consists of reassurance that the pain is real but not caused by a disease such as inflammation, and medications for accompanying symptoms. This can be successful, but additional therapy is required for many patients. In pediatric patients with functional abdominal pain, guided imagery is a useful coping mechanism that is quickly learned and maintained. Previous studies have shown that patients undergoing guided imagery treatment with progressive muscle relaxation experienced fewer days of pain and missed less days of activities than patients treated with relaxing breathing exercises, exemplifying the validity of guided imagery itself rather than relaxation techniques in general (Weydert et al, 2006).

In a recent study, van Tilburg and colleagues showed the effectiveness of an audio recorded guided imagery treatment to treat functional abdominal pain in pediatric patients that is easy to use, low in cost, for use in the comfort of the patient's home and can be prescribed by any clinician without training in these techniques (van Tilburg et al., 2009). Although the study group was small, the results indicate that audio guided imagery therapy, in conjunction with regular medical treatment, is more effective than medical treatment alone. Guided imagery resulted in reduced abdominal pain, disability and number of medical visits, as well as an improvement in quality of life. Effects of the therapy were maintained at the six month follow - up. These findings in patients with functional abdominal pain suggest that guided imagery may also be a potentially effective therapy for treating abdominal pain in pediatric IBD patients who are in remission.

The aim of this pilot study is to test the feasibility of the use of guided imagery in quiescent IBD. We will collect descriptive data on changes in abdominal pain and quality of life that will be used to design a larger clinical trial. The long term goal is to reduce abdominal pain symptoms and increase quality of life in pediatric IBD patients who are in remission, while avoiding unnecessary toxicity of medical treatment often utilized when health care providers assume that pain is due to disease exacerbations.

Patients between the ages of 9-17 years who have been diagnosed by a pediatric gastroenterologist with IBD, and who are clinically determined to be in remission

but experiencing abdominal pain, are recruited from the UNC Pediatric IBD clinic. Patients are randomly selected to receive audio-recorded guided imagery treatment or placebo (listening to music of the child's choice). The following questionnaires are administered pre - and post - treatment to evaluate the treatment results: a. Pediatric Quality of Life; b. Abdominal Pain Index; c. Functional Disability Inventory. Expectation of treatment benefits was assessed pre-treatment through an adapted version by Drossman and colleagues of the Credibility scale Scale developed by Borkovec and Nau for use in patients with functional gastrointestinal disorders.

A total of 18 patients have been referred into the study, of which 8 patients were enrolled (Mean Age:14 std. 2.98; 63%F). N=5Five children received guided imagery materials and N=3three received placebo materials. Of the remaining patients approached, 5 declined participation, 1 was determined found to be ineligible due to prior experience with guided imagery, and 4 patients with a history of functional abdominal pain did not suffer from pain during the summer months. These patients will be contacted at a later date to reassess their eligibility into the study.

Recruitment is ongoing at UNC and Duke Pediatric GI clinics. Data analysis will be completed by late winter 2009 and will include patient demographics, credibility scores, and changes from baseline measurements in quality of life, pain, and disability to post-treatment measurements, comparing patients in the guided imagery and placebo groups.

RD 09/9

hypnosis for functional heartburn

Olafur Palsson, PsyD

Non-cardiac chest pain (NCCP) is a common and costly health problem. Prevalence in epidemiological surveys ranges from 24-33%. NCCP accounts for approximately 2-5% of all ER visits, and was estimated in 2003 to result in 8 billion dollars of annual costs in the United States.

The etilogy of NCCP is complex and often unclear, and may include esophageal disorders (GERD, motility disorders), Cardiac Syndrome X, musculoskeletal disorders, psychological disturbance and visceral hypersensitivity.

Gastroesophageal reflux disease (GERD) is a substantial contributor to NCCP. Approximately 40% of patients with GERD have chest pain. Abnormal pH test are seen in up to 50% of NCCP patients, and esophagitis in up to 70%. Proton-pump inhibitors (PPIs) are used both as a diagnostic and therapeutic tool for NCCP. They are highly sensitive (about 80-90%) to detect patients with NCCP related to GERD, and are the primary diagnostic and treatment approach after cardiac disease has been ruled out. Treatment options for patients who do not respond to PPIs are limited. However, Miller and colleagues (Miller V, Jones H, Whorwell PJ. Gut. 2007 Nov;56(11):1643) recently reported that chest pain and health-related quality of life improved in over 80% of NCCP patients receiving hypnotherapy in a small randomized controlled trial, compared to only 23% in the control group who received placebo medication and supportive talk therapy. This improvement was well-maintained at 2-year follow-up.

Limited availability of therapists able to deliver such specialized hypnosis treatment, as well as high costs of such therapy, limits the potential for large numbers of NCCP patients benefiting from this promising approach. We therefore decided to test a standardized home-hypnotherapy protocol, delivered entirely via audio-recordings, as a way of providing this kind of treatment for NCCP in a cost-effective and widely distributable manner.

The primary aims of the study are to develop, and test the feasibility of, a standardized CD-based home hypnosis treatment program for patients with refractory functional chest pain. Secondary aims are to obtain pilot data to assess the magnitude of the treatment effect of such treatment for this disorder for an anticipated future, larger treatment trial; to determine the stability of the treatment effect; assess the relationship between response to the home hypnosis treatment and psychological factors; and assess the relationship between response to the home hypnosis treatment and symptomatic dimensions of chest pain (severity, frequency, and duration).

Subjects will be 30 individuals age 18-80 who fulfill Rome III criteria for

Functional Chest Pain that has persisted despite PPI treatment as well as a trial of antidepressant within the past 6 months or intolerance to at least one antidepressant. Subjects must have completed a cardiac evaluation with negative findings as well as a negative GI evaluation (absence of erosive esophagitis on EGD and pH or pH-MII study negative).

This will be a randomized open-label trial. The active arm will complete 12 weeks of home hypnotherapy delivered on CDs (n=15). Subjects in the control arm will listen to an educational CD program containing general information about functional chest pain and functional gastrointestinal disorders (n=15). Subjects will be evaluated in study visits pre-treatment, mid-treatment (4-6 wks), at the end of treatment (12 wks) and at 3-month follow-up.

The hypnosis home treatment program will be adapted from previous treatment protocol developed at UNC for management of IBS, which has been shown to improve IBS when used in self-administered CD format. The hypnotic suggestions and imagery will be rewritten to address functional chest pain rather than bowel symptoms. The audio program will consist of 7 biweekly 30-40 minute audio sessions, as well as a shorter daily listening exercise.

Main outcome measure will be a 7-point Global Chest Pain Assessment question, asked at visit 2-4: “Compared to before starting this therapy, how would you rate your chest pain?” Response options range from “Much better “ to “Much Worse”. Treatment response will be defined as those responding either “Much better” or “Somewhat Better” on this assessment at the end of 12 weeks.

Other outcome measures will be a Chest Pain Symptom Diary, the SCL-90 questionnaire to measure psychological distress, the Catastrophizing subscale of the Coping Strategies Questionnaire (CSQ-C) and the SF-36 quality-of-life questionnaire.

RD 09/11

children with ibs and other functional gi pain disorders: assessment, treatment & understanding

Rona Levy, PhD, MPH, FACG, AGAF

Previous research by Dr. Levy's team and others has shown parental response to the illness behavior of children with chronic abdominal pain of unknown etiology is associated with children's symptom reports and other illness outcomes. However, studies examining the effectiveness of interventions aimed at altering symptoms by changing parent and child responses have been methodologically limited. Therefore, her group designed and tested whether a cognitive behavioral intervention based on principles of social learning theory (SLCBT) would result in greater process changes in parental response and outcome changes in pain symptoms than an attention comparison condition (ES) in children with chronic abdominal pain. Her presentation summarized the methods and results of this work.

One particularly interesting aspect of this research was the unusually large number of participants in this study and the careful attention to methodological detail, including attention to treatment fidelity, a carefully constructed comparison condition, etc. 200 children and their parents were randomly assigned to one of the two conditions.
All participants were exposed to three treatment sessions with a trained counselor.
Assessments were completed 1 week pre-treatment, 1 week, and 3 months, and one year post-treatment. Children provided responses on a variety of measures on symptoms, their response to symptoms, etc. Parents completed similar measures with respect to their children, as well as measures on their own responses to their children's symptoms.

Findings Dr. Levy presented showed that parents in the SLCBT condition reported their behaviors changed in the desired direction. Furthermore, they also found greater reductions in child GI symptoms and child pain in this group.

Dr. Levy concluded by making the points that this is the first large study of children with chronic abdominal pain utilizing a methodologically solid comparison condition, with demonstrated significant changes in children's pain symptoms. Thus, this study has significant implications for treatment of children with chronic unexplained abdominal pain.

The study was supported by a grant to Dr. Levy from the National Institutes of Health, NIDDK.

RD 09/12

State of the Art: overview of basic and translational research at the unc center for fgimd

William E. Whitehead, PhD

Introduction

The Center hosts a broad spectrum of research in basic and translational science with studies falling into 4 basic science domains: (1) Genes, (2) Microbes and inflammation, (3) Gastrointestinal physiology, and (4) Psychology. The goals of this summary are to explain the rationale that has led to the choice of studies we support, to provide summaries of some of the studies not covered by other presenters at this conference, and lastly to identify gaps in our basic and translational research program.

A hallmark of the UNC Center's research program is the development and testing of integrative models to account for the multiple physiological and psychosocial factors that are known to contribute to the etiology and course of irritable bowel syndrome (IBS). The best know of these is the biopsychosocial model which holds that all these factors interact with each other to influence the development of IBS and its severity. An alternative model addressed by some of our recent research is the heterogeneity model, which holds that IBS is not one disease entity but a group of disorders which produce similar symptoms but have different etiologies that may require different treatments. Our basic science research initiatives are motivated in part by these models: we consider all new developments in the field and try to see how they fit into these two integrative models. In addition, we have an independent line of basic and applied research on pelvic floor disorders – fecal incontinence, pelvic floor dyssynergia type constipation, and chronic proctalgia.

Genes

Research programs in this domain include:

- Identification of polymorphisms that may distinguish subtypes of IBS from each other. Building on previous work which identified 4 distinct subtypes of IBS, Principal Investigator Whitehead is looking for polymorphisms that distinguish among these subtypes.
- Gene-environment interactions involved in the etiology of post-infectious IBS (PI-IBS). Investigators Reuben Wong, Robert Schulman, and Miranda van Tilburg are collecting DNA from patients with PI-IBS identified through a collaboration with the North Carolina Department of Health.
- Genetic polymorphisms and other biomarkers that could account for the comorbidity of IBS with other chronic pain disorders. In collaboration with Principal Investigator William Maixner, Dr. Whitehead seeks to identify polymorphisms that are specific to patients who have IBS plus at least one other chronic pain comorbidity.
- Polymorphisms in mitochondrial DNA that are associated with IBS. Principal Investigator Miranda van Tilburg is pursuing this quest; see her summary in this book.

Microbes and Inflammation

- Biomarkers (serum antibodies) for infection or inflammation of enteric neurons. Drs. Jack Wood and William Whitehead are investigating this.
- Fecal microbiota specific to IBS. Principal investigator is Ian Carroll.
- Abnormal immune response to enteric bacteria. Principal investigator is Yehuda Ringel.
- Probiotic treatment of IBS. Dr. Ringel's team is pursuing studies in this area.

Physiology

- Visceral hypersensitivity. Studies in this arena include Chloe Hill's efforts to improve the measurement of visceral pain sensitivity, Dr Whitehead's studies on lubiprostone's effects on visceral pain, and brain imaging studies by Drs. Ringel and Drossman.
- Gastrointestinal motility. Studies in this area include Dr. Motoyori Kanazawa's work on colon motility in IBS and clinical trials of the efficacy of biofeedback for fecal incontinence (Dr. Heymen), pelvic floor dyssynergia type constipation (Drs Heymen, Whitehead, and collaborating investigator Dr. Giuseppe Chiarioni), and chronic proctalgia (Drs. Chiarioni and Whitehead). Large randomized controlled trials have made us a referral center for pelvic floor disorders and led to the creation of a dedicated pelvic floor biofeedback clinic at UNC.

Psychology

- Learned illness behavior. Principal investigator Rona Levy and co-investigator Whitehead are completing a randomized controlled trial of a successful psychological treatment for functional abdominal pain in children based on their previous collaboration.
- Hypervigilance and somatization. Investigators are Drs. Palsson and Whitehead.
- Effects of stress and trauma. Investigators are Drs. Drossman and Lesserman.

Gaps in the Basic and Translational Research Program

Looking forward, the Center is seeking to address the following gaps: (1) Nutrition, food sensitivity, and obesity. (2) Proteomics and metabolomics, seen as a broader approach to the discovery of biomarkers. (3) In vitro research (currently non-existent in our research program) to address biological mechanisms bridging between genetics and function. (4) Animal models to validate genetic and other basic science findings.

RD 09/14

gene environment interactions in ibs: a prospective study of post-infectious ibs

Reuben Wong, MD

Post-Infectious IBS (PI-IBS) has been previously documented in studies of patients following bacterial gastroenteritis (GE) with incidences ranging from 9% to 30%. Factors favoring the development of PI-IBS include severity of the infectious episode, host factors such as female sex, and psychological factors including anxiety and the trait of somatization. There have also been several studies into the genetics of IBS which have identified a number of genes such as IL10-1082, TNF-a, and SCN5A, although there are inconsistencies between studies. A pilot project in our laboratory using a gene chip consisting 3300 SNPs across approximately 320 genes that mediate pain and inflammation, identified a number of polymorphisms that are more common in IBS patients than in healthy controls. Many of these SNPs are in genes associated with inflammation.

Our hypothesis is that in PI-IBS patients, it is a combination of the environment (in this case a pathogen that caused the inflammatory process in the GE) and predisposing genes (very likely those that mediate inflammation) that need to be present together to result in the phenotype that is PI-IBS. The aims of our study are: (1) to identify genetic markers associated with the development of PI-IBS, (2) to evaluate the concept of gene-environment interaction, and (3) to investigate whether there are other FGIDs triggered by a bacterial gastroenteritis (GE).

In collaboration with the North Carolina Department of Public Health (NCDPH), our goal is to screen 2,000 individuals with a confirmed diagnosis of bacterial gastroenteritis in order to identify 200 patients with PI-IBS and 200 controls who have had gastroenteritis but have recovered without persistence of gastrointestinal symptoms. The initial design of the study was to request NCDPH nurses to refer patients to us prospectively. However, in response to a suboptimal referral rate by these nurses, the study methodology was modified to a partial prospective model in which we would send letters of invitation to all patients with a confirmed bacterial gastroenteritis in a defined period to (a) invite them to participate and (b) request them to answer 4 screening questions which are used to identify probably cases of PI-IBS. The first retrospective sample will cover a one-year retrospective period, but subsequent samples will be drawn every 3 months.

Patients who meet screening criteria (presence of gastrointestinal symptoms consistent with IBS for cases and absence of such symptoms for controls) are invited to participate and are sent questionnaires to confirm their diagnosis and to assess psychological moderators of risk. These questionnaires address demographics, pre-existing illnesses, acute gastroenteritis characteristics, and subsequent gastrointestinal symptoms. Instruments

used include the BSI-18 (for psychological traits of anxiety, depression, and somatization), Rome III criteria (diagnosis of IBS), and the IBS Severity Scale. Subjects are also mailed saliva collection kits for extraction of DNA. Subjects will be re-surveyed at 6 and 12 months to assess the duration of PI-IBS. All aspects of the study will be conducted remotely by mail.

The outcome of primary interest is the identification of genes that may predispose to the development of PI-IBS, by comparing the prevalence rates of candidate genes in cases and controls. We will also look for moderators of the gene-environment interaction: (1) psychological characteristics, (2) host characteristics (such as gender), and (3) characteristics of the gastroenteritis (such as clinical severity and bacterium involved). Finally, we will conduct exploratory analyses: (1) comparing genes identified in PI-IBS patients with those of *de novo* IBS patients (i.e., patients whose IBS is not considered post-infectious) and (2) looking for functional GI disorders other than IBS.

RD 09/16

maternally inherited mitochondrial sequence variants and ibs

Miranda van Tilburg, PhD

Irritable Bowel Syndrome (IBS) is a disabling functional condition that affects approximately 30 million people in North America. IBS and many other functional conditions, including migraine, chornic fatigues syndrome syndrome, depression, cyclic vomiting syndrome and fibromyalgia, are multi-factorial conditions that likely have a shared genetic component in their pathogenesis based upon a high-degree of co-morbidity and responsiveness to the same treatments. We hypothesize that a significant proportion of that shared genetic component is encoded by the maternally-inherited mitochondrial DNA (mtDNA) based on:

1) Mitochondrial dysfunction has been documented in functional conditions
2) IBS and mitochondrial disease share many cardinal features, including infection and stress-triggered exacerbations
3) Multiple functional disorders are maternally inherited in some families
4) Our data demonstrates that two common mtDNA single nucleotide polymorphisms (SNPs) are highly associated with migraine and cyclic vomiting syndrome.

The aims of this study are to:

1) determine the presence and degree of maternal inheritance of functional disorders in IBS
2) determine if two specific polymorphisms predispose towards the development of IBS and other functional disorders.

To determine the degree of maternal inheritance of functional disorders we will collect questionnaire data and pedigrees on 300 subjects with IBS to determine diagnosis of IBS and several other functional disorders (e.g., migraine, major depressive disorder, cyclic vomiting syndrome) and the presence of many other functional/dysautonomic/neurological conditions. To determine polymorphisms that predispose to functional disorders saliva will be collected directly from the IBS probands. Genotyping of the two polymorphisms wil be achieved only in those belonging to haplogroup H.

RD 09/17

appetite hormones, gastric emptying and symptoms in postprandial distress syndrome: a pilot study

Kimberly Brownley, PhD

Functional dyspepsia (FD) is a disorder characterized by persistent upper abdominal pain or discomfort of undefined etiology. Impaired gastric motility is implicated in the pathophysiology of FD. Observations include both accelerated early phase gastric emptying as well as delayed overall gastric emptying in FD (Stanghellini, Tosetti et al. 1996; Delgado-Aros, Camilleri et al. 2004). Delayed gastric emptying is generally associated with symptoms of premature satiety, fullness and bloating. One subtype of FD – postprandial distress syndrome (PDS) – is defined by frequent (> 1 per week) episodes of early satiety that prevent finishing a regular meal and bothersome fullness after ordinary-sized meals.

Ghrelin is a gut-derived hormone that signals hunger and is directly involved in meal initiation. It exists in circulation in two forms: acylated ('active') and des-acylated ('inactive'). Acylated ghrelin accelerates and des-acylated ghrelin inhibits gastric emptying (Kojima, Hosoda et al. 1999; Masuda, Tanaka et al. 2000; Asakawa, Inui et al. 2005; Chen, Chao et al. 2005). Ghrelin administration increases food intake in healthy individuals (Druce, Wren et al. 2005) and to a lesser degree in individuals with FD (Akamizu, Iwakura et al. 2008). Studies have found no difference (Shinomiya, Fukunaga et al. 2005; Pilichiewicz, Feltrin et al. 2008) or lower (Takamori, Mizuta et al.; Lee, Cha et al. 2009) endogenous fasting ghrelin levels and no difference in postprandial ghrelin level (Pilichiewicz, Feltrin et al. 2008) in FD compared to healthy controls. In PDS, there has been one report of lower fasting acylated ghrelin levels compared to controls (Shindo, Futagami et al. 2009).

Peptide-YY (PYY) is a gut-derived peptide hormone that plays a key role in the achievement and maintenance of satiety in the inter-meal period (Lundberg, Tatemoto et al. 1982; Ballantyne 2006; Batterham, Heffron et al. 2006). PYY exists in circulation in two forms (PYY1-36 and PYY3-36) with PYY3-36 being the predominant form that has clear effects on food intake and appetite in humans. PYY3-36 administration reduces food intake and subjective hunger ratings in healthy individuals (Batterham, Cohen et al. 2003; Sloth, Holst et al. 2007). PYY regulation in FD has not been widely studied, with one report suggesting lower fasting and postprandial PYY in FD vs. controls (Pilichiewicz, Feltrin et al. 2008). There are no published studies of PYY in PDS.

We investigated gastric emptying rate, ghrelin, PYY, and postprandial symptoms in 8 normal weight individuals with PDS (5 female, 4 white/4 black) and 7 healthy controls who were selected to match PDS subjects on the basis of sex, race, age (± 2 yrs, range 20 – 47 yrs), and body mass index (± 2, range 19 to 26.5). PDS

status was determined using the Rome III Questionnaire for Functional GI Disorders with alarm questions, with the requirement that symptoms were present for the last 3 months with onset at least 6 months prior. Each participant was assessed under two conditions: before and after a low (25%) and a high (55%) 500 kcal test meal. Dyspepsia symptoms were assessed by visual analog scales. Gastric emptying was assessed via the 13C-Spirulina plantensis breath test. Total and acylated ghrelin and PYY3-36 were assayed in plasma. Self-report and biological specimens were obtained before and at various intervals (range 15 to 60 minutes) over 4 hours after each meal.

Compared to controls, PDS subjects reported significantly higher levels of postprandial bloating and early satiety (ps < 0.01), nausea ($p < 0.05$), and trends toward higher levels of belching and fullness (Ps < 0.10). Consistent with the distinction between PDS and epigastric pain syndrome, PDS subjects did not differ from controls in ratings of postprandial epigastric pain. PDS subjects also exhibited greater kPCD, suggesting faster gastric emptying than controls ($p < 0.04$), largely due to slower gastric emptying in controls subjects only after the high (49.6) vs. the low fat (57.1) meal. In addition, compared to controls, PDS subjects exhibited higher fasting and early postprandial total ghrelin levels (group X time, $p < 0.06$) as well as trends toward higher overall levels of acylated ghrelin ($p < 0.11$) and higher PYY ($p < 0.07$) especially one to four hours after food ingestion.

Although preliminary, these findings suggest that individuals with PDS may experience a persistent state of heightened appetite (ghrelin) and satiety (PYY) co-signaling, with this state being exacerbated during the postprandial period, possibly contributing to their increased postprandial symptoms. Further studies, with increased sample size and longer postprandial periods, are needed to better understand the pathophysiological and clinical implications of these findings. Studies that use methods to capture changes in gastric emptying in the very early postprandial period (i.e., 0 to 45 minutes after food intake) may be particularly instrumental in evaluating the role of early acylated ghrelin release and conversion to desacylated ghrelin on gastric emptying and, in turn, early changes in gastric emptying on subsequent PYY release. Whether this cascade of events directly contributes to postprandial distress in a manner that is unique to PDS warrants further examination. Also, dietary manipulations focusing on simultaneously reducing fat and glycemic load to blunt the early PYY response may be worthy of further exploration.

RD 09/19

State of the Art: bloating

Peter Whorwell, MD, PhD

Bloating is a common feature of functional gastrointestinal disorders in general and irritable bowel syndrome (IBS) in particular. It appears to be more common in females but this may partly be because men tend to describe it differently using words such as a tight or a hard feeling in the abdominal wall. Typically it evolves over the day being at its worst in the evening and subsequently subsiding over night. From the patient's point of view, it is a particularly intrusive symptom, and from the physicians standpoint it has diagnostic utility as diurnal bloating is a feature peculiar to functional gastrointestinal disorder. Only 50% of patients with a sensation of bloating experience distension defined as an actual increase in abdominal girth of up to 12cms. This has led to the suggestion that the terms bloating and distension should not really be used synonymously as they are describing different phenomena. However, in the English language, patients tend to use only the descriptor bloating. Another problem is that the word does not necessarily translate well into other languages.

One of the reasons that bloating has been so poorly understood in the past is that there have been no good methods for investigating it. However, with the development of the gas challenge technique and abdominal inductance plethysmography our understanding has improved considerably, and no doubt technologies such as CT and MR scanning will lead to further advances.

We now know that distension is more commonly associated with constipation and delayed transit whereas bloating without distension is more frequently observed in patients with diarrhoea or those who exhibit visceral hypersensitivity. It would seem reasonable to assume that excessive gas might be implicated in bloating but there is no evidence that this is in fact the case despite some data suggesting bacterial overgrowth and fermentation might be important in some cases. However, the handling of gas is impaired in IBS and the associated gas trapping is accompanied by symptoms such as bloating. The anterior abdominal wall and diaphragm have recently become the focus of much attention based on the assumption that there must be an accommodation reflex to allow a large meal or, in females the pregnant uterus, to be accommodated within the abdomen. It appears that patients with IBS do indeed have an abnormal accommodation reflex in terms of how the anterior abdominal muscles and the diaphragm behave.

The treatment of bloating and distension is notoriously unsatisfactory but now that we know more about the pathophysiology, it is apparent that somewhat different approaches may be necessary to achieve an optimal effect. In order to deal with poor gas handling it is reasonable to avoid gas containing drinks or foods that encourage gas production such as cereals and fermentable short chain carbohydrates and polyols such as

fructose or sorbitol. Anti-flatulents such as simethicone are also worth trying. In the presence of constipation or slow transit a prokinetic would be indicated whereas in and individual with diarrhoea and visceral hypersensitivity a trial of tricyclic antidepressant may prove useful. In the light of increasing evidence that some patients with IBS have a disturbance of gastrointestinal bacterial flora there has been interest in the therapeutic potential of probiotics and non absorbable antibiotics such as rifaximin. Interestingly, in clinic trials these agents have sometimes appeared to relieve bloating.

In conclusion, bloating and distension need to be thought of as subtly different features of the functional gastrointestinal disorders and this may explain why different treatments for this problem are effective in different patients.

For full details of the work described in this paper see: Agrawal A & Whorwell PJ, Alimentary Pharmacology & Therapeutics 2008; 27: 2-10.

RD 09/21

visceral hypersensitivity & its modulation in ibs

Motoyori Kanazawa, MD, PhD

It has been thought that the pathophysiology of IBS involves altered central processing, abnormal gastrointestinal motility and visceral hypersensitivity. Visceral pain sensitivity is studied by distending the bowel with different intensities of balloon distention and recording the intensity of pain sensations that are elicited. Patients with irritable bowel syndrome report pain at lower threshold of distention (a phenomenon called as allodynia) and they also report greater pain intensity than controls in response to distention that are above the pain threshold for both patients and controls (a phenomenon called hyperalgesia). Below I describe factors that are known to influence visceral pain hypersensitivity in IBS patients.

Bowel habit Subtypes

It has been repeatedly, confirmed that lower rectal pain thresholds are observed in most of patients with IBS compared to control subjects. We compared IBS subtypes to each other to test for differences in pain sensitivity. There were no differences in the pain threshold to colonic distention between subtypes of IBS. Furthermore, the pain threshold was significantly correlated with abdominal pain intensity and overall symptom severity on the IBS severity score (IBS-SS).
Other investigators have reported similar findings. Posserud et al. found that hypersensitive patients with IBS had more intense GI symptoms (e.g. abdominal pain, bloating) than normosensitive patients.

Perceptual response bias

By employing sensory decision theory analysis it is possible to derive independent indexes of neurosensory sensitivity (the biological ability to discriminate how painful a stimulus is) versus the perceptual response bias (which reflects cognitive and psychological influences on pain perception). We found that IBS patients have greater perceptual response bias than control but their neurosensory sensitivity scores are not different. Perceptual response bias was inversely correlated with somatization scores. Thus, colonic hypersensitivity may be influenced by a psychological tendency to report pain. On the other hand, pain discrimination was not impaired in IBS patients. It has been considered that specific brain regions may play a major role in generating pain and/or pain-related emotions in humans. IBS patients showed greater activation in the anterior cingulate cortex (ACC) and prefrontal cortex, insula and thalamus during painful rectal distension compared to control subjects.

Stress

During acute physical or psychological stress, rectal pain thresholds are significantly decreased in IBS patients but not in controls. Manipulation of attention may also influence pain perception. Pain ratings to aversive stimuli are higher when there is a warning light to draw attention to distention, and lower when the subject

is distracted. Adverse experiences during early life (e.g. sexual and physical abuse) may also increase visceral hypersensitivity. Neonatal maternal separation in an animal model induces not only more infiltration of inflammatory cells in the colonic mucosa but also pain hypersensitivity to colorectal distension.

Antidepressants

After low dose treatment with amitriptyline, there is a significant decrease in GI symptoms accompanied by a significant increase in rectal pain thresholds in IBS patients. Interestingly, a decrease in the activation of anterior cingulated cortex during rectal distention was observed in IBS patients after treatment with amitriptyline.

Inflammation

We investigated a possible low grade inflammatory marker, high-sensitive CRP (hs-CRP) in IBS. IBS with diarrhea and alternating IBS showed higher hs-CRP than normal subjects. The value for hs-CRP in IBS did not reach the level of systemic inflammation. Patients with high hs-CRP showed lower rectal pain threshold than those with normal hs-CRP.

Serotonin (5-HT)

Serotonin in the gut is released from enterochromaffin (EC) cells. It has been thought that 5-HT3 and 5-HT4 receptors may play an important role for conveying visceral sensation from the gut. After treatment with the 5-HT3 receptor antagonist alosetron, perception thresholds to colonic distension significantly increased in IBS patients with diarrhea. Another 5-HT3 antagonist, ramosetron, is now available for treatment of IBS with diarrhea in the Japanese market. No serious side effects have been observed after administration of this agent in animals or humans.

PAR-2

PAR-2 is highly expressed in the GI tract and may be activated by tryptase from mast cells but also by luminal proteases such as trypsin and possibly bacterial proteases. Increased fecal serine protease activity was observed in IBS with diarrhea and ulcerative colitis patients. Gecse et al. reported that mucosal supernatants in the colon from patients with IBS induced a significant marked discharge in afferent nerves in rats. The effect of IBS supernatants was partially prevented by the administration of serine protease inhibitors. Furthermore, the effect of IBS supernatants was not observed in PAR-2 knockout rats.

Corticotropin-releasing hormone (CRH)

Subjects treated by a CRH antagonist showed a significant decrease in rectal pain threshold. CRH receptor-1 antagonist significantly prevented an increase in gut sensitivity in rats. The non-specific CRH receptor antagonist, α-helical CRH, significantly reduced abdominal pain during gut stimulus in patients with IBS.

To summarize, visceral hypersensitivity is common in IBS patients and probably plays a major role in development of the symptoms. Stress, anticipation and inflammatory factors enhance pain hypersensitivity. However, visceral sensitivity can be pharmacologically and psychologically manipulated. In conclusion, visceral hypersensitivity is a topic of intense research and a target for the development of new drugs for the treatment of IBS. New clinical markers associated with visceral sensitivity may be required for efficient and effective treatment strategies in IBS.

RD 09/23

NHanes study of stool consistency & frequency

William E. Whitehead, PhD

The published literature on the epidemiology of constipation is filled with inconsistencies: Prevalence estimates vary from 2% to 27% of U.S. adults. Although women are consistently found to be more likely than men to report constipation, age is a risk factor in some surveys but not others. African American race and lower socioeconomic status are found to be associated with constipation in some surveys but not in all. Moreover, there is no consistent support for the role of dietary fiber and liquids in the etiology of constipation despite clinical experience suggesting that increased fiber and increased liquids may ameliorate constipation. It is likely that some of these inconsistencies are due to differences in the way constipation is defined in surveys: Many surveys have simply asked patients whether they are constipated without defining what is meant while other surveys define constipation in terms of stool frequency (less than 3 per week) or stool consistency (more than 25% of stools hard or lumpy). The aims of this study were (1) to estimate the prevalence of constipation when defined by stool frequency or stool consistency, (2) to determine whether these two definitions agree in the classification of subjects, and (3) to identify possible risk factors for constipation.

Methods

The National Health and Nutrition Examination Survey (NHANES) is an annual survey of a geographically and demographically representative sample of the non-institutionalized adult population of the United States. The survey is analyzed in two-year blocks to increase the sample size to approximately 5000 of which approximately half are males. In the 2005-2006 survey, we asked subjects (1) their average frequency of bowel movements and (2) their usual or most common stool type (rated using the Bristol Stool Scale) in the last 30 days. Data on dietary intake were analyzed for total daily fiber and liquids from all sources, and values less than one standard deviation below age and sex adjusted norms were defined as “low fiber” and “low liquids”.

Results

When constipation was defined by usual stool consistency, 9% of females and 3% of males said their usual stool consistency was hard or lumpy, but when constipation was defined by stool frequency, 5.5% of females and 0.8% of males reported less than 3 stools per week. As shown in the figure, stool consistency and frequency were poorly correlated with each other: among the 9% of women who had hard or lumpy stools most of the time, only 10% reported having fewer than 3 stools per week. Age was not found to be significantly associated with stool consistency or frequency. African Americans and Hispanics were more likely to report hard or lumpy stools, and individuals with family incomes less than 2 times the poverty index were also more likely to report hard

or lumpy stools. A diet low in fiber or liquid content was associated with an increased risk of hard or lumpy stools in univariate analyses, but the associations with fiber and liquids were not statistically significant after multivariate adjustment. Analysis of a larger sample (4 years of data) is planned.

Conclusions

Two commonly used clinical definitions of constipation, stool frequency of less than 3/week and a usual stool consistency being hard or lumpy, are poorly correlated with each other, and we recommend defining constipation by stool consistency. These data confirm a greater frequency of constipation in women compared to men (9% vs. 3% for hard or lumpy stools) and suggest that non-white race and poverty are risk factors. However, age, which is commonly thought to be a risk factor for constipation, was not significantly associated with either stool consistency or stool frequency. Dietary fiber and liquids also appear to be associated with an increased risk of hard or lumpy stools, but analyses of larger samples are awaited to confirm these univariate analyses.

This research was supported by the Plevic Floor Disorders Network and by R24 7674.

RD 09/25

the utility of the digital rectal exam amongst physicians & students

Reuben Wong, MD

Anecdotal observations suggest that the digital rectal exam (DRE), which is useful for identifying anorectal disorders, is underutilized and not thoroughly performed in clinical practice. Our aims were to comprehensively assess the role of the DRE at academic medical centers in the United States.

Academic faculty and fellows in gastroenterology (GI) and other medical subspecialties, medical residents, and final year medical students from the Universities of North Carolina, Iowa, Wisconsin and the Mayo Clinic completed a questionnaire inquiring about the use and performance of the DRE as well as prior training received for this skill. A total of 436 physicians and 196 medical students were surveyed.

A mean of 41 DREs per year were performed with a significant positive correlation with years of experience (medical students, 7.1; physicians with experience greater than 20 years, 123.0). Gastroenterologists performed the most DREs annually (172.5), followed by primary care (35.0) and internal medicine subspecialities (13.0). Refusal rates by patients were lowest among GI faculty (4.3%) and highest among primary care doctors (13.8%); there was a negative correlation between refusal rates and comfort level of the physician in performing a DRE ($p<0.001$). Most common reasons for not performing a DRE included perceived invasiveness (39.6%), a lack of indication (48.3%), concern for patient modesty (43.8%) and convenience issues (35.6%). In performing a DRE, significantly more gastroenterologists used advanced methods to detect anorectal conditions (e.g., levator contraction), and were more confident in diagnosing pelvic floor dyssynergia or levator ani syndrome. There was a significant correlation between confidence in making a diagnosis on a DRE and the number of DREs performed. A total of 93% received instruction on performing a DRE during medical school, 3.7% during residency and 1.5% during fellowship, while 1.4% had never been instructed in the DRE. 40.4% of the respondents who felt their training was completely adequate were senior doctors (10 or more yrs post-graduation) and only 23.4% were medical students.

Frequency of performance, diagnostic confidence and training adequacy on the DRE were inversely proportional to years of experience, confirming that teaching of the DRE needs to be improved during the early years of training. Incomplete steps in performing the exam and diminished confidence in diagnosing anorectal conditions suggests the need for emphasizing the role of the DRE among non-gastroenterologists. Greater use of the DRE may translate into better diagnostic confidence and comfort level in performing it, which could lead to fewer refusals.

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RD 09/26

central pain dysregulation in patients with ibs

Steve Heymen, PhD

IBS is a complex disorder of unknown etiology. Research into the pathophysiology of IBS over the last decade has demonstrated the involvement of many factors contributing to IBS symptoms. Psychological, hormonal, immunological, genetic, cardiovascular, and autonomic nervous system factors, as well as peripheral and central sensitization of pain signals are believed to be involved in the etiology and/or maintenance of IBS. Visceral hyperalgesia is often observed in IBS patients, and recent investigations have found evidence of somatic hyperalgesia, not seen in earlier studies. This new data has renewed questions of whether IBS patients suffer from a global dysregulation of central pain processing.

IBS may be part of a broader disorder of pain dysregulation that includes other chronic pain disorders such as fibromyalgia (FMS) and temporomandibular disorders (TMD). Psychophysical investigations into abnormalities in central pain processing, such as deficits in Diffuse Noxious Inhibitory Controls (DNIC) and exaggerated temporal summation have been observed in FMS and TMD, both of which have significant comorbidity with IBS. Temporal summation results in increased pain sensitivity when repetitive, brief, noxious stimuli applied to C-fiber primary nociceptive afferents increases dorsal horn neuron activity (wind-up), resulting in central sensitization of the dorsal horn neurons. DNIC are endogenous analgesic mechanisms that occur when descending serotonergic and opioidergic signals inhibit pain processing at the dorsal horn neurons in the spinal cord. A deficit in DNIC is also associated with central sensitization of dorsal horn neurons. This central dysregulation in pain inhibition (DNIC) was recently observed in IBS patients by Dr. Heymen. In a standard DNIC protocol, Heymen et al. (The Clinical Journal of Pain, in press) found that IBS patients failed to down-regulate phasic somatic stimuli of moderate pain intensity applied to one hand during counter-irritation (ice-water) applied to the patient's other hand when compared to healthy controls ($p = 0.002$, Repeated Measures ANCOVA).

Based on these data the NIDDK awarded Dr. Heymen a one-year Seed Grant (R24 DK067674-01) to further explore abnormalities in the central processing of pain in IBS patients with the following aims: 1) To determine whether IBS patients show exaggerated temporal summation resulting in a higher rate of rise (RR) of somatic pain ratings during phasic somatic heat pain testing compared to healthy controls (HC). 2) To determine whether IBS patients demonstrate somatic hyperalgesia resulting in higher average pain ratings (APR) during phasic heat pain testing compared to HC. 3) To determine whether IBS patients show compromised DNIC resulting in less reduction of APR during noxious counter-irritation compared to HC. 4) To determine whether a significant correlation exists in IBS patients between

visceral hypersensitivity, as measured by rectal pain thresholds using a barostat in an ascending method of limits (AML) protocol and; (4a) temporal summation measures, suggesting an up-regulation in ascending pain signaling as a mechanism to explain visceral hyperalgesia in IBS patients, and (4b) between visceral hypersensitivity and DNIC measures, in IBS patients, suggesting a dysregulation in descending endogenous analgesia as a mechanism to explain visceral hyperalgesia in these same IBS patients.5) To determine whether psychological variables (depression, anxiety, perceived stress, catastrophizing) found to be significantly different between IBS and healthy controls, moderate group differences in measures of (5a) temporal summation, (5b) somatic APR, and (5c) DNIC.

The primary objective of the investigation is to further explore the role of central sensitization in IBS pain by assessing afferent (temporal summation) as well as efferent (DNIC) central modulation of nociception in IBS patients, and to determine whether abnormalities in central pain processing is associated with visceral pain ratings using intra-rectal barostat distensions.

Central alteration in pain signaling may be important in the onset or worsening of symptoms in IBS patients. Investigations into central pain dysregulation in IBS may lead to improvements in the understanding of pain mechanisms, and ultimately, to novel therapies for patients with IBS.

RD 09/28

overlap between ibs & vulvodynia

Denniz Zolnoun, MD, MPH

Vulvar Vestibulitis (VVS) and IBS are two of the most prevalent types of idiopathic oain disorder (IDPs), affecting 10%-15% and 8%-20%, respectively, of people in the United States. Interestingly, IBS disproportionately affects women (3:1). VVS is the most common clinical diagnosis among women ages 18-64 presenting with pain on vulvar contact and is defined by a constellation of signs and symptoms including 1) severe pain upon contact to vulvar mucosa (i.e., vestibule) and pain with insertion, 2) tenderness to pressure within the vestibule, and 3) physical findings limited to erythema without other obvious pathology.

Currently, the diagnosis of both VVS and IBS is based on subjective symptoms, and relies on the absence of an "organic" pathology. Significant variability in the presentation and treatment response of patients is commonly observed in both conditions and presents a major obstacle in standardizing the care. This variability may partly be explained by differences in the underlying pathophysiology in that the symptoms may be the converging point of different clinical pathways. For example, IBS symptoms may develop in some patients after an acute episode of gastroenteritis (post-infectious IBS), while similar life long symptoms may be present in other patients without a clear precipitating event. Despite these examples of having similar symptoms and diagnoses, most clinicians empirically conceptualize the two clinical presentations differently. Any one dimensional 'symptom-based' diagnosis may not sufficiently capture the heterogeneity in unmeasured dimensions associated with persistent pain states (e.g., physiological versus environmental versus cognitive).

Thus, there is a considerable impetus to 'fine tune' diagnostic criteria and identifying distinct subgroups of IPDs. While this line of inquiry is in its infancy for VVS, research in IBS has made significant strides to incorporate clinical characteristics into the diagnosis of IBS with the advent of the ROME III criteria. Furthermore, Dr. Whitehead and colleagues at UNC have recently identified 4 distinct subgroups of IBS, differing with respect to psychological (e.g., somatization), biological (e.g., colonic motility), and neurosensory (e.g., pain) characteristics.

In this pilot study we propose to overcome existing challenges in clinical care of VVS and IBS patients by studying similarities and differences in their pathways of vulnerability. Specifically, we propose to characterize the relative contribution of pain amplification, psychological distress, and pro-inflammatory cytokine profiles in subgroups of patients with VVS and VVS concomitant with IBS.

This study is on going and plans to recruit 25 healthy controls and 70 VVS cases, of which 35 will have the diagnosis of

co-morbid IBS. To date we have enrolled 65 women (14 control, 39 VVS only, and 12 VVS +IBS). Below we describe the differences in baseline characteristics, self-reported pain intensity (VAS 0-100) and characteristics of vulvo-vaginal pain (provoked and/or unprovoked), and clinical exam findings.

We examined vulvar mucosa by a standard cotton swab palpation of mucosa; following each pressure application participants were prompted to rate the intensity of pain on a VAS scale (0= no pain and 10= worse imaginable pain). The distal pelvic floor muscles (puborectalis) were similarly examined in a structured manner at three sites. Following calibration of examiner's index finger with an algometer, approximately 2kgs of pressure were applied to each muscle site. Following individual pressure application the participants were similarly prompted to rate the intensity of pain (if any) on a 4 point ordinal scale (0= no pain, 1= mild, 2= moderate, 3= and severe).

The baseline demographic characteristics of women did not differ between the subgroups of women with and without IBS. Compared to women without IBS, those with VVS and co-morbid IBS were more likely to experience unprovoked pain ($p=0.01$) and report higher pain with intercourse ($p=0.01$). Vulvar mucosal sensitivity, however, did not differ among the subgroups of women with and without co-morbid IBS, ($p=0.25$). Lastly, women with co-morbid IBS were more likely to report moderate to severe pain in at least one of the three palpated muscle sites ($p=0.01$).

In summary, among women with VVS those with IBS are more likely to experience elevated levels of pain and muscle tenderness than those with VVS alone. Interestingly, mucosal sensitivity, which is the basis of a VVS diagnosis, did not differ in the subgroups of women with VVS and co-morbid VVS with IBS. Collectively, our observation suggests that the pathophysiology of pain in women with VVS and co-morbid IBS may be more complex, possibly due to central dysregulation. This has significant public health implications and may suggest that time honored therapies (specifically surgery) may not be as effective in women with co-morbid VVS and IBS.

RD 09/30

State of the Art: beyond tricyclics

Douglas A. Drossman, MD

At our Center for Functional GI and Motility Disorders (www.med.unc.edu/ibs), we seek new treatment methods for patients referred with painful and refractory functional GI Disorders (FGIDs), motility disturbances and high levels of emotional distress that usually have existed for many years. These patients are referred by specialists because all treatments have failed. This presentation will discuss some newer treatment methods, and their rationale which is sound since they have been tried and tested in treatments of psychiatric disorders. They are adapted here for patients with GI pain since the enteric nervous system (ENS) and the gastrointestinal pain pathways are both responsive to central treatments. More detailed treatment approaches to the psychopharmacological and behavioral care of patients with FGIDs can be found elsewhere.

General Approach

An effective physician-patient relationship is essential. It improves patient satisfaction, adherence to treatments reduces litigation and improves patient outcomes. Building upon this is the biopsychosocial, multi-component approach to patient care. We employ combinations of physiological, behavioral and pharmacological treatments that are directed toward the gut, the brain-gut axis, and the central nervous system in varying combinations.

Psychological and Behavioral Treatments

Psychological and behavioral treatments such as cognitive behavioral therapy, hypnosis and stress management are safe, effective and long lasting. There are many advantages to psychological and behavioral treatments: they can show up to 70% benefit, benefit continues after the treatment period ends, there are no medical side effects, and treatment may reduce health care costs.

Antidepressants and Psychotropic Agents

Antidepressants are being used more and more for IBS and other painful FGIDs, and based on one survey 31% of 1,966 patients reported taking an antidepressant.. These treatments are often used for patients with more severe symptoms. The 3 major antidepressant classes used include the tricyclics or TCAs (desipramine, amitriptyline and nortriptyline), the selective serotonin reuptake inhibitors or SSRIs (fluoxetine, paroxetine, citalopram, escitalopram,sertraline) and the serotonin norepinephrine reuptake inhibitors or SNRIs (duloxetine, venlafaxine, desvenlafaxine).

We initially prescribe either a TCA or an SNRI because of their enhanced pain benefit, or an SSRI when there are dominant symptoms of anxiety, obsessive features or phobic behaviors. Treatment is begun in modest dosages, increased to an

optimal level of benefit and continued for 6-12 months or longer. If co-morbid major depression is present higher dosages than typically needed for FGIDs may be needed.

We actively work with the patient to address side effects because they reduce adherence to treatment. The side effects for TCAs include sedation, constipation dry mouth/eyes, weight gain and sexual dysfunction, so the medication is usually given in the evening. The SSRIs may produce active side effects of insomnia, agitation, sexual dysfunction, diarrhea and diaphoresis and are usually given in the morning. The SNRIs such as duloxetine are more likely to produce nausea and may be taken with a meal in single or divided disages. Notably, our studies show no relationship of dosage level of a TCA with clinical benefit, and the "side effects" commonly reported after beginning treatment relate more to anxiety than to side effects of the medication. We also select medications based on the associated symptoms: a TCA when there is diarrhea, an SSRI with constipation, mirtazepine with nausea, or buspirone (an azapirone anti anxiety agent) with postprandial early satiety or fullness.

Rationale for Antidepressants, A Reappraisal

Physicians may prescribe antidepressants incorrectly, because they perceive IBS as a psychiatric problem, or give them to reduce stress; neither is correct. These medications reduce pain signals from the gut, and can improve bowel symptoms due to their effect on GI motility. Brain imaging studies also show that antidepressants act on certain areas of the brain (anterior cingulate cortex) to reduce the painful experience coming from incoming visceral signals.

In only the last few years newer ideas on the action of antidepressants have replaced older theories of the monoamine hypothesis for depression. This hypothesis relates clinical depression to reduced activity of neurotransmitters like serotonin in the brain. The new concept of neuroplasticity i.e., loss of cortical neurons with psychiatric trauma and neurogenesis, regrowth of neurons with clinical treatment, is reshaping our understanding of psychiatric and possibly functional GI disorders. We are learing that brain cells can die in key areas of the brain, such as the hippocampus after severe emotional trauma such as sexual abuse, or war trauma leading to PTSD, and fMRI studies are showing reduced cortical density in areas of the brain involved with emotional and pain regulation. In addition, antidepressant (and possibly psychological) treatments can restore lost neurons. This is evidenced by increased brain-derived neurotrophic factor (BDNF), a precursor of neurogenesis occurring after antidepressant treatment, and the longer the treatment and the greater the degree of recovery from depression[9;13] and the lower the frequency of relapse or recurrence.

So with PTSD, severe depression or chronic pain there is reduced cortical density in the anterior cingulate and prefrontal cortex and thalamus, regions that interface between emotion and pain regulation. These effects help explain the observed benefit of using psychotropic agents in reducing GI pain. In addition neural degeneration is seen with severe motility disturbances, and perhaps with proper treatments this can be reversed or slowed. One recent study has shown that 5HT4 agonists can increase enteric neurons developing from precursors and increase neurite outgrowth and decrease apoptosis.

Detoxification from Narcotics

Not infrequently clinicians may prescribe narcotics for FGI pain even though there is no evidence that they provide long term benefit. Currently up to18% of patients with IBS are inappropriately taking narcotics and US doctors are eager to prescribe it: over 80% of the world's narcotic prescriptions are prescribed in a country that represents <5% of the total population; in fact the use of oxycodone has increased over 1000% since 2002. . This overuse may be encouraged because the health care system reimburses for it, and it is a way to get patients quickly released from the hospital, ER or clinic without needing to take the time to address more comprehensive management approaches. Furthermore, patients, not knowing of other treatment options, often demand it. More important, is the evidence to suggest that these treatments are harmful, producing what has been called narcotic bowel syndrome (NBS). This complication of narcotic treatment leads to increased pain that worsens over time, and can be reduced or ameliorated when the patients are detoxified; this needs to be done before we can institute the more advanced treatments listed below.

Augmentation Treatment

If single medication treatments are not successful, we consider intensifying the treatment by using combinations of treatments because sequencing one medication after another sometimes fails, due to lack of response or side effects. The concept of augmentation is to use two or more treatments, often in lower dosages, that act upon different receptor sites or areas of the brain to enhance the therapeutic affect. This is done in addition to the continued use of peripherally acting agents used for the FGIDs (e.g., probiotics, antispasmodics, chloride channel activators, or peripheral neural agents like gabapentin). The different combinations of central treatments are described next.

Psychological Treatment and Antidepressants

Antidepressants can improve pain and vegetative signs of depression and psychological treatments improve higher levels of brain functioning such as coping, reappraising of maladaptive cognitions and cognitive adaptation to previous losses and trauma. Also, psychological treatment improves adherence to taking a medication, and taking an antidepressant increases energy to engage in the work of therapy. Brain imaging studies show that these two treatments act in different areas of the brain and provide synergistic benefit. Finally clinical trials show added benefit of combining these two treatments for depression and other psychiatric disorders and migraine headache among other disorders, and the effect-size difference for combined treatment can be 50% more than either monotherapy treatment. The Rome III committees have recommended this type of augmentation treatment for patients having more severe functional abdominal pain.

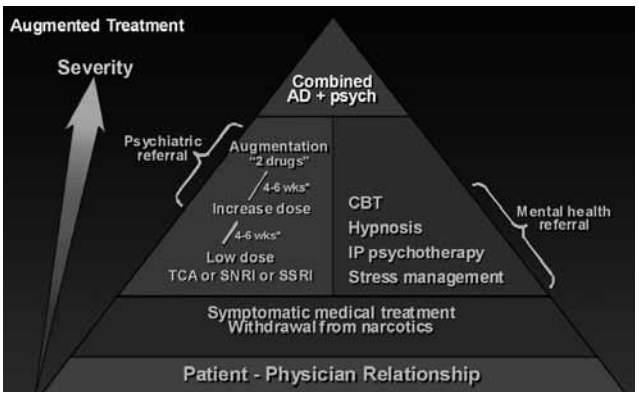
Treatment with two or more Psychotropic agents

We often employ combinations of psychotropic agents when a single treatment fails, e.g., a low dose SSRI with a low dose TCA, to address multiple symptoms such as anxiety, depression, pain and diarrhea. Another option is to add buspirone to an antidepressant to augment the antidepressant and also improve sensorimoter gut function. More recently we may combine a low dose atypical antipsychotic(e.g., quetiapine) to a TCA or SNRI to augment pain control, reduce anxiety and enhance sleep. Finally, with a musculoskeletal component to the pain, e.g., abdominal wall pain or fibromyalgia, we might add gabapentin or pregabalin to the antidepressant. We prefer to use low dosages to minimize side effects, the most concerning being the serotonin syndrome

(tremor and hyper-reflexia, spontaneous clonus and muscle rigidity with fever. This may occur with higher dosages or combinations of higher dosages of serotonin enhancing agents.

Concluding Comment

Patients presenting with severe and refractory FGIDs have been prescribed many treatments without benefit. Effective treatment requires a broader range of treatment options beginning with an effective physician-patient relationship. Building upon this are the use of antidepressants targeted toward various symptom features, and the removal of narcotic agents when prescribed. Their benefit may now extend to include reducing neuroplastic effects associated with visceral hypersensitivity and possibly increasing neurogenesis. Finally, augmentation treatments, combining behavioral interventions with antidepressants or combinations of psychotropic agents should be considered. The latter will require input from a psychopharmcologist or psychiatrist.



Legend for Figure 1
Augmentation Treatment. Beginning with an effective patient-physician relationship, treatments are added based on the severity of the symptoms. A low dose TCA or SNRI is started and after 4-6 weeks can be increased while monitoring for clinical benefit and side effects. If this is unsuccessful augmentation treatment using another antidepressant, buspirone or an atypical antipsychotic is considered and this decision may require psychiatric consultation. On occasion, the patient may first be referred to a mental health counselor for psychological treatment. With more severe symptoms, combined pharmacological and behavioral intervention is utilized. See text for further details. *Reprinted with permission*

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RD 09/34

update on severity assessment: rome foundation working team on ibs severity

Douglas A. Drossman, MD

While clinicians generally make treatment decisions in IBS related to the type of symptoms, other factors such as the perceived severity plays a major role. For this presentation I would like to provide some background as to the importance of understanding severity in IBS and the FGIDs; then I will review the existing knowledge of the data on assessing severity. Following this I will provide new data from several recent papers that gives us a deeper understanding of this concept. Finally I will make some recommendations with regard to future directions. It's a pleasure to be able to give you this presentation as I've been fortunate to be a part of the Rome Foundation Working Team on Severity and much of this information will be presented in our working team report to come out some time next year.

SEVERITY RELATES TO CLINICAL CARE

First we should consider, why should we assess severity? The primary reason is that the severity of the condition delineates different clinical profiles. Patients with mild IBS, for example, have milder and less frequent symptoms, relatively good health related quality of life and may not seek health care, or do so infrequently. They are able to self-manage their condition. Most individuals have mild severity. When the condition is in the moderate range, symptoms are more persistent and frequent, quality of life becomes impaired and there is some reduction in quality of life. These individuals are troubled enough to seek health care, perhaps first with a primary care physician and then may be referred to gastroenterologists. Finally the smaller proportion of patients with severe symptoms are more refractory to usual treatments and are often sent to referral practices or medical centers. They have notably impaired daily function and quality of life, are psychologically distressed and are coping ineffectively. Their lives are more consumed by the illness and they also may have medical and psychological co-morbidities.

In a similar fashion treatments are different depending on the patient's severity. For milder illness patients may take responsibility for their own health care and do so by using over the counter products and learning from friends and the internet. For those who go to a physician, they are aided often just when the physician makes a positive diagnosis and reassures. This has therapeutic value. In addition the physician may educate and perhaps provide dietary or lifestyle recommendations. With moderate illness the physician will often provide prescription medication and may also recommend psychological treatments. Once the pain becomes severe, it is necessary to look at combinations of treatments directed toward the gut and brain. An interdisciplinary approach is often needed and this type of approach is only provided in a few medical centers such as ours.

SEVERITY IS IMPORTANT FOR RESEARCH

Understanding severity relates to research as well. We need to understand the ways to treat our patients better. We know that patients make decisions to take medications and seek health care based on the perceived severity of their illness. Furthermore clinicians decide on what to treat based on how they perceive the severity in their patients. Finally the Food and Drug Administration has required that certain medications (e.g., Alosetron) be used only for severe IBS-D and how that is defined is open to question. Therefore because there is currently no standard method to assess severity research is needed to develop appropriate guidelines.

SYSTEMATIC REVIEW OF SEVERITY

The first and currently only published systematic review of severity was done about 3 years ago by Tony Lembo, Vanessa Ameen and myself. The results of this review are summarized as follows: 1) IBS is a chronic functional GI disorder that ranges in severity from mild to severe; 2) The published prevalence for severe IBS ranges from 3-69% (previously it was believed that only 5% of IBS patients were severe, 3) Severity has clinical implications since it affects health related quality of life (HRQOL) and health behaviors and guides diagnosis and treatment; 4) Severity is a multi-dimensional concept (more than just symptoms) that is influenced by the intensity of GI and extra-intestinal symptoms, HRQOL, co-morbidities, psychosocial factors, degree of disability and illness behaviors, and the relative contributions of each are unknown; 5) Severity is also affected by whether the patient or physician makes the assessment, and the patient remains the "gold standard", and 6) Studies are needed to assess predictors of IBS severity and to develop standardized research instruments.

EXISTING SEVERITY MEASURES IN IBS

The Lembo paper identified two standardized measures of severity:

1. Functional Bowel Severity Index (FBDSI) The FBDSI was developed by our research group along with investigators from Toronto, Canada, Manchester, UK and Binghamton NY, in anticipation of needing a severity measure for a multi-site NIH study. We evaluated a total of 270 patients, asked a variety of questions related to severity and had the treating physician rate the severity. The index was developed by creating a score of the relative weights of the factors that predicted the physicians' rating of severity. This was similar to that done for the creation of the Crohn's Disease Activity Index (CDAI). Three variables were identified: a) the rating of current pain on a 0-100 VAS scale, b) the number of physician visits in the previous 6 months X#11 and c) whether or not the patient had functional abdominal pain syndrome (if yes, score 106). Thus a linear score was created that could be broken down to mild (up to 36), moderate (37-110) and severe (>110). This measure has face validity and was validated with convergent/construct validity and has been used in a variety of other studies. The main limitation is that because the variables include number of physician visits and whether or not pain is chronic, it is not a responsive measure of change. Thus it is used primarily to assess severity at one point in time.

2. IBS Symptoms Severity Score (IBS-SSS). The IBS-SSS was developed around the same time as the FBDSI by Peter Whorwell for use in his hypnosis studies. The questions were empirically derived

and they fell into 4 general categories: a) pain (2 questions), b) bloating, c) bowel satisfaction, and d) Interference with daily function. A score was developed using visual analog scales for the four domains and then was categorized into mild (75-175), moderate (175-300) and severe (>300) based on the author's assessment which served as the gold standard. The scale has been found to have face validity, is reproducible and responsive to change. This scale is relatively easy to use and has been used by other investigators as well.

In general the two severity indices can be helpful for making treatment decisions in clinical practice and for use in clinical trials. The main limitation is that both measures are standardized to physician ratings of severity. Thus there is a need for a patient based measure of severity.

ROME WORKING TEAM ON SEVERITY

The Rome Foundation commissioned a working team to update our knowledge of this area and to make recommendations on the use of severity measures in research and clinical practice. After several months of review it was concluded that the Lembo paper was a comprehensive review of the field and any systematic review by the Working Team would not add new information. The committee recognized that the most important need would be to obtain new data on severity particularly from the patient's perspective. Accordingly, the committee's work was put on hold pending the acquisition of new data and three research initiatives were established to provide this new information.

ROME DIRECTED INITIATIVES TO BETTER UNDERSTAND SEVERITY

The three studies have been completed and have since published. They are summarized below:

1. Rome-IFFGD Focus Group. This collaborative effort studied 3 focus groups to identify the patient's perspective of IBS and, relative to this presentation, understand self-reporting of severity and identify the factors associated with severity. Some of the findings include:

a. Pain was the predominant symptom affecting severity but other symptoms also played a role,

b. The impact of IBS relates to uncertainty/unpredictability, perceived loss of daily activities, spontaneity and one's potential, emotional responses of fear, shame and embarrassment, and the feeling that family, friends and physicians don't understand the IBS or it's consequences – creating a sense of stigma,

c. The levels of response include the direct social, functional and emotional impact as well as thoughts and feelings generated that are impairing even when symptoms are not present.

d. Severity included HRQOL but had a broader conceptualization

2. UNC-IFFGD Internet Survey. This collaboration between UNC and IFFGD surveyed close to 2000 patients from the internet and had several aims. Relative to this presentation data was provided to understand the severity of IBS through various methods as well as identifying the factors contributing to self-perceived severity. This population had a larger proportion of severe IBS by self-report -- 36% (vs. 20% by FBDSI) rated themselves as severe, 42% (vs. 48% by FBDSI) as moderate, and 23% (vs. 31% by FBDSI) as mild. The top four factors affecting severity included Pain (79%), Bowel difficulties (76%), Bloating (70%) and Limitations of eating and diet (69%). In addition, the IBS

was rated as severe enough for patients to take considerable risk to obtain relief: On average patients would trade 25% of their remaining life to get complete symptom relief.

3. UCLA Clinical Survey. In the UCLA survey of 755 IBS clinical patients a multivariate model was created to predict overall severity of GI symptoms. Severity was determined by a combination of intestinal and extraintestinal symptoms:

a. Symptoms of visceral hypersensitivity (abdominal pain and bloating)

b. Outlet symptoms (straining, urgency)

c. Extra-intestinal somatic symptoms (myalgias)

d. Disease related fears and concerns ("something is seriously wrong with my body").

SUMMARY AND CONCLUSIONS

From the literature review and the use of the 3 new studies there are several conclusions that can be drawn:

1. IBS severity is based on a combination of factors:
   a. GI and non-GI symptoms
   b. Cognitive and emotional factors
   c. Limitations on activities of daily living, eating and socialization
2. Patient ratings of severity and the degree of risk that patients will take for relieve are greater than previously reported.
3. The cognitive and emotional factors that impair patient ability to manage IBS continue to exist even when the patient is not having symptoms.
4. Severity is related to but distinct from health related quality of life.

The future direction for the Rome Working team will be to make recommendations on how severity should be used in research and clinical practice, and possibly to develop an IBS severity measure using the data acquired from these recent studies.

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RD 09/38

patient satisfaction with care for functional gastrointestinal disorders

Spencer D. Dorn, MD, MPH

Irritable bowel syndrome (IBS) and other functional gastrointestinal disorders (FGIDs) are highly prevalent conditions that affect up to 15% of the U.S. population. Affected individuals may suffer marked quality of life impairment and substantial disability. With as many as one-half of these individuals seeking healthcare1 FGIDs are a leading reason for both primary care and gastroenterologist office visits at an annual cost that exceeds one billion U.S. dollars. Still, despite these exorbitant expenditures, the quality of care provided is likely variable and often sub-optimal. However, this remains largely unknown, in part because metrics for assessing quality of FGID care are not readily available.

One potentially relevant and valuable measure of the quality of FGID care is patient satisfaction. Although several theoretical models have been proposed, patient satisfaction with care can be conceptualized as how, relative to a subjective standard, a patient cognitively and affectively evaluates his or her health care experience. Although this may seem to be a relatively minor assessment measure, satisfaction is quite important because satisfied patients better understand their condition, are better able to recall medical information and physician advice, are more involved in their care, and are more adherent to therapy. Satisfied patients are also more likely to maintain a relationship with their provider and less likely to "doctor-shop. These factors have sometimes been linked to improved health outcomes and lower healthcare costs.

Thus, patient satisfaction is significant both as a measure of quality from the patient's perspective and, by extension, as a potential determinant of outcomes. However, we also know that patients with FGIDs are often dissatisfied with the care delivered. In order to identify ways to improve this care the factors that influence satisfaction must be better understood. To do so satisfaction with care must be conceptualized clearly and measured accurately. One approach is to use global assessment measures consisting of one or two simple questions. However, because satisfaction is a multi-dimensional construct, global measures are too non-specific, insensitive, and unreliable and therefore typically produce satisfaction estimates that are overly inflated, in-valid, and difficult to interpret in terms of their content. Conversely, multi-item measures that are tailored to specific patient populations are more sensitive, specific, and reliable and consequently yield more meaningful results. Along these lines, multi-item, condition specific satisfaction with treatment scales have been developed for a wide range of conditions such as diabetes (Diabetes Treatment Satisfaction Questionnaire) and physical disability (MedRisk Instrument for Measuring Satisfaction with Physical Therapy Care). Considering the high prevalence, morbidity, and costs associated with FGIDs as well as the rather specific needs of patients

with these conditions, a specific scale to measure FGID satisfaction with care is strongly necessary.

We propose to develop an FGID satisfaction with care scale using standard scale development techniques. Factors that are important for determining patient satisfaction will be identified using a qualitative research approach. First, 18 patients seen in the UNC Hospital general and functional gastroenterology clinic will be recruited to participate in 3 focus groups (6 patients/ focus group). Each subject will provide informed consent and will be compensated for their participation. A standard, written protocol will be used to guide a discussion focused on the specific aspects of care that are important to patient satisfaction. Focus groups will be tape recorded and transcribed. Transcripts will be reviewed and a set of items will be identified and then organized by content into various groups. Second, 6 non-patient experts on FGID care including nationally recognized physicians in the field, a physician assistant, and a patient advocate will be interviewed to identify additional features that may affect patient satisfaction. Third, items from a well known generic satisfaction measure (Patient Satisfaction Questionnaire III) that measure factors hypothesized to be important for satisfaction with care will be included.

These items will be used to draft a preliminary satisfaction scale. Scale items will take the form of evaluative questions with a five category response format. In order to account for "response acquiescence" (i.e., the tendency to agree irrespective of the content), both positively and negatively worded items will be used This preliminary satisfaction scale will be pilot tested on 15 patients and 5 clinicians. After they complete the scale they will undergo a cognitive debriefing interview in order to assess the measure's clarity, content validity, and responder burden. Using these interviews and a review of responses, items that are unclear will be revised and items that have either a high missing response rate or an extremely low variance will be dropped to form a second version of the scale.

This refined version will be administered to consecutive subjects (five subjects for each item on the scale) with FGIDs immediately after their gastroenterology clinic appointment. Participating patients will also complete questionnaires that assess demographic features, illness duration, illness severity, psychological stress (Brief Symptom Inventory; BSI) health related quality of life (Irritable Bowel Syndrome Quality of Life Scale; IBS-QOL), response acquiescence bias (Socially Desirable Response Scale; SDRS), general satisfaction with care (PSQ-18), whether expectations were met, and patient-provider interaction (Patient-doctor Interaction Scale; PDIS).

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RD 09/40

functional gi disorder related data collection at the point-of-care

Spencer D. Dorn, MD, MPH

BACKGROUND

Recently there has been a growing movement to encourage health care practitioners to collect and report relevant performance data, especially patient reported outcomes in relation to the clinical interaction. These data are important for several reasons. First, by measuring patient reported outcomes clinicians are better able to understand illness from the patient's perspective and, in turn, deliver higher quality, "patient-centered" care. Second, certain patient reported information may help the practitioner identify patients in need of additional evaluation. For example, the Psychosocial Committee of the Rome Foundation has suggested using "psychological red flags" to screen for patients in need of a mental health referral. This approach is similar to the use of medical "red flags" which has previously been studied to validate the Rome diagnostic criteria for IBS. However, this strategy has not yet been evaluated. Third, patient reported outcomes can be analyzed to identify which treatments and care processes work best, thereby informing both the care of individual patients as well as continuous quality improvement (CQI) initiatives. This will help identify the way treatments work in a clinical practice rather than through clinical trials. Fourth, when measured over time and appropriately risk-adjusted, changes in patient reported outcomes may be used as a surrogate of health care performance and, if combined with cost data, as a surrogate of value. If then publicly reported, this "transparent" information may motivate practitioners to improve their performance, help patients to make more informed choices about their care, and enable insurers to reward higher quality care. In a recent survey of health care opinion leaders, over three-fourths held that increasing transparency was important for improving the healthcare system's overall performance.

Despite these potential benefits, health care providers often fail to assess illness from the patients' perspective or ask patients to assess the care and treatments that they receive. Furthermore, even when done these efforts are almost never reported or quantified. This may be particularly important for patients with functional gastrointestinal disorders for which there are no "objective" measures (e.g., blood pressure or hemoglobin A1C levels) to guide therapy, track patient progress, or assess health care quality.

We therefore propose a pilot study to develop the methods and tools necessary to assess relevant, patient-centered measures at the point-of-care and over time. We will use home and tablet personal computers (PCs) to collect specific, relevant patient reported data at the point-of-care, including gastrointestinal and psychological symptoms, coping strategies, types of therapies, response to therapy, satisfaction with care, and clinical response. These data will be transformed into clear data

reports for patients and their practitioners to review during the clinic visit. This may allow patients to track their status over time and help clinicians to provide higher-quality, patient-centered care. Additionally, these patient data will be stored securely in a database and longitudinal data may then be used by providers in clinic and, once de-identified, further analyses will look at collated patient data for research studies, to assess the performance of the Center's clinical program, and for public reporting.

METHODS

We plan to study patients aged 18 years and older who newly present for treatment at the UNC Functional GI Disorders Clinic and they will be re-evaluated for up to 3 subsequent visits ending at one year after initial assessment. As summarized in the Figure, prior to the initial clinic visit recruited to enter the study. Those who agree will complete a series of user-friendly web based surveys to assess their demographics, psychosocial factors, and symptoms. All data will be uploaded to a secure, central server where surveys will be electronically processed and scored. Then, at the visit the relevant data will be presented to the clinician in a concise report. A subset of patient data will also be printed out on an easy-to-read data report for patients. We anticipate this information will help improve that quality and patient-centered nature of the visit. Subsequent to the visit both physicians and patients will be asked several brief questions regarding the process and whether they felt it was helpful. The web-based data assessment will be repeated before each follow-up visit and at one year following the initial clinic visit.

TO DEVELOP AND REFINE A PATIENT REPORTED DATA COLLECTION PROGRAM

This is a pilot study to develop and refine a patient reported data collection program. Additionally, we plan to assess (1) whether this program improved patient satisfaction and quality of care; and (2) which factors predict clinical response over time.

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RD 09/42

partner burden in ibs

Reuben Wong, MD

There is the saying that disease afflicts one person but affects many. Strong anecdotal evidence suggests that the psychological, social, and physical effects of illness in a patient can have profound effects on the family. There is also increasing evidence from studies on burden of illness for family members (spouses, next of kin) and caregivers.

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder (FGID) that impacts physical and social functioning. Clinical experience suggests that IBS definitely has an effect on the partner, but no studies to date have evaluated this "effect" in the partners of IBS patients.

Our hypotheses are: (1) IBS poses a burden in the partners of patients; (2) the burden is proportional to the severity of illness and its impact; and (3) the burden affects multiple aspects of the relationship.The aims of the study are to: (1) define the degree of burden (quantify burden; compare with other studied diseases); (2) identify factors affecting the burden (disease severity; relationship characteristics; disease perception; individual factors); and (3) identify areas of relationship that are affected (daily life; sexual functioning).

As our recruitment strategy for this study, we aim to identify patients with IBS who have a "significant live-in other" partner. Patients and their partners will be surveyed using either a paper and pencil questionnaire, or via an internet survey questionnaire. Demographic data and a relationship assessment scale will be collected from both patients and partners. Patients will also complete an IBS symptom severity questionnaire (FBDSI). The questionnaire for partners consists of: (1) the Zarit Burden Interview (ZBI), (2) a questionnaire on sexual relations, and (3) a panel of questions assessing their perception of the diagnosis of IBS.

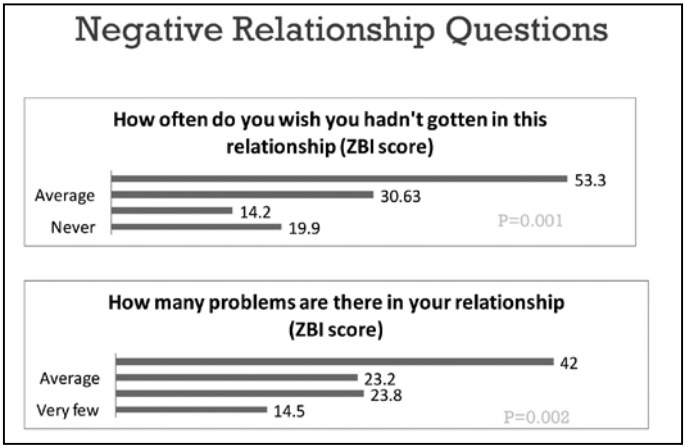
Outcomes of interest include: (1) degree of burden (comparison of ZBI score against scores for other illnesses), (2) severity of IBS relative to burden, (3) relationship characteristics relative to burden, (4) patient/partner characteristics relative to burden, (5) effects on sexual relationship, and (6) perception/attitudes towards IBS relative to burden.

67 Rome III diagnosed IBS patients and their partners have been surveyed to date. Of the participating couples, almost all were spouses (97%) who had been together for 24.1 $\pm$12.6 years. Non-IBS partners were mainly males (71%) with a mean age of 49.5 years. Relationship burden was high with an overall mean ZBI score of 22.6 (greater than caregivers of cancer patients (18.5). Those rating their relationship as more burdensome (ZBI) had IBS partners with worse disease severity (FBDSI; p=0.003). Partners' rating

of burden (ZBI) was also significantly negatively correlated with both quality of the relationship (RSS; R=-0.60, p<0.001) and sexual satisfaction (R=-0.56, p<0.0001). Demographics had no effect on burden.

Our study data strongly suggests that IBS poses a significant degree of partner burden, at least comparable to or greater than cancer. Perceived burden is increased with worsening IBS severity, and poorer sexual and relationship satisfaction.

Supported by R24 DK067674 and Takeda Pharmaceuticals



RD 09/44

narcotic bowel syndrome: assessment of outcomes & prognostic factors

Joseph Zimmerman, MD

People have used narcotics for some 4,000 years. Opioid analgesics have been the mainstay of pain treatment in cancer patients for many years. In recent years, there has been an increasing trend for prescribing narcotic agents for various nonmalignant chronic pain syndromes, such as low back pain, severe irritable bowel syndrome (IBS) or fibromyalgia. For example, in 2002, abuse of opioid pain relievers was mentioned in >119,000 Emergency Department visits. From 1994 to 2002, Emergency Department mentions of abuse of hydrocodone and oxycodone increased by 170 and 450% respectively.

Analgesia, a central effect of opioids, is frequently associated with severe side effects, mainly gastrointestinal (GI) and urinary, that result from the peripheral effects of these agents. The severe adverse GI effects result from the interaction of narcotic agents with the μ opiod receptors in the GI tract. These adverse effects which have been termed "opioid induced GI dysfunction" include severe slow transit constipation, gastroparesis and ileus.

The narcotic bowel syndrome (NBS) was first described in 19842. But by 2007, only 2 case reports and 1 editorial review appeared in the English literature. In 2007, a series of NBS patients was published, creating a flurry of interest in this syndrome. The criteria for diagnosis of NBS are: Chronic or frequently recurring abdominal pain that is treated with high-dose or chronic narcotics and all of the following:

• The pain worsens or incompletely resolves with continued or escalating dosages of narcotics.

• There is a marked worsening of pain when the narcotic dose wanes and improvement when narcotics are re-instituted (Soar and crash).

• There is a progression of the frequency, duration and intensity of pain episodes.

• The nature and intensity of the pain is not explained by a current or previous GI diagnosis.

The patient may have an organic disease (IBD, chronic pancreatitis), but the character and activity of this disease is not sufficient to explain the pain.

Additional features of NBS include worsening of pain by eating, leading to sitophobia and a mild weight loss in some patients. Abdominal radiography frequently shows features suggestive of a partial intestinal obstruction.

The NBS Study

Rationale

• NBS has recently surfaced as a significant health issue.

• The number of patients described heretofore is rather limited.

• The optimal approach to therapy is yet uncertain.

• The factors predictive of a successful detoxification have not yet been elucidated.

Study Description

Our study is a prospective, observational study of NBS patients to characterize this population according to the following features:

• Underlying physical and psychiatric comorbidity;

• Clinical features of NBS;

• Concurrent medications;

• Health related quality of life;

• Assessment of the response to detoxification using the recommended protocol and/or variations thereof.

• Assessment of the short-term (6-12 weeks) and the long-term (6 months) outcome after detoxification.

• Evaluation of the baseline predictors of a successful detoxification. These include physical illness, concurrent medications and psychiatric comorbidity.

Preliminary Results

From December 2008 to September 1, 2009, 13 NBS patients were enrolled. Of these, 85% were females. The mean age was 39±15 (SD) and ranged 21-64. After enrollment, one patient refused to further participate in the study. Duration of narcotic treatment ranged from 1 month to 23 years. (median=19 months). The daily narcotic dose (in IV morphine equivalent) ranged 10-343 mg/day. (median: 45 mg/day). 9 patients were on various codeine derivatives (± a fentanyl patch); 2 had used only a fentanyl patch. Half of the patients haD organic GI disease (Crohn's disease: 3; recurrent small bowel obstruction due to adhesions: 1; pancreatic insufficiency: 1). A functional GI disorder was present in 80% (IBS: 4; recurrent functional abdominal pain: 2; cyclic vomiting syndrome: 1; Bulimia: 1). Fibromyalgia, depression, low-back pain and chronic fatigue syndrome were also common. 68% of the patients were detoxified as inpatients, and the rest- as outpatients. Detoxification was associated with many adverse reactions. The most frequent were anxiety (36%), insomnia (27%), muscle aches (18%) and chills (18%). 91% of the patients were off narcotics at the end of the detoxification. Yet, adequate relief was reported only in 45.5% of the patients and only 27% were defined by symptom criteria to have responded to detoxification. After 3 months, 86% of the 7 patients followed up to this point said that they were not currently using narcotics. However, a review of the hospital records indicated that 4 of them actually filled prescriptions for narcotics since their detoxification.

Our preliminary conclusions are:

• Detoxification is feasible as an outpatient procedure.

• Immediate detoxification is achievable in most patients.

• A considerable proportion of patients have resumed narcotics 3 months after detoxification.

• Improvement in bowel symptoms and abdominal pain is not usually immediate, but seems to occur over time.

These conclusions are, of course, limited owing to the small sample size. The study is ongoing, and in future meetings we hope to present data on more patients, with a longer follow up.

FURTHER READING

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RD 09/46

final report on celiac disease

Spencer Dorn, MD, MPH

Background

There is considerable heterogeneity in the clinical features of celiac disease (CD) that is considered to occur in 1% of the U.S. population. Disease manifestations (i.e., the observable evidence of structural abnormalities) range widely from normal small bowel architecture to complete villous atrophy, and from normal blood counts and bone mineralization to anemia and osteoporosis. Illness severity, in terms of the individual's symptoms and subjective assessment of health, also varies considerably. Thus patients can have "silent" celiac disease in which they manifest disease (e.g., anemia, osteopenia, neuropathy etc.) but without bowel symptoms. Others experience diarrhea, bloating, and at times abdominal pain despite little or no manifestations of disease.

While it is presumed that the degree of disease activity directly correlates with both symptom features and health status, clinical observations suggest that this is not necessarily true. Our group and others have demonstrated that the severity and extent of underlying villous atrophy do not correlate with clinical presentation. Likewise, in clinical practice we have observed a group with celiac disease who report severe symptoms and frequently seek health care, yet have disease that is mild in terms of the degree of histopathology.

Thus it is possible that in celiac disease the disease activity does not always relate to the degree of illness severity and vice versa. This is also seen in patients with inflammatory bowel disease (IBD), the so-called "IBD-IBS". Also, when compared to patients with structurally based, "organic" disorders such as IBD, those with functional GI disorders who lack overt pathology can have much poorer health status.

This "disconnect" between disease activity and illness severity/health status may be explained by psychosocial factors, which in IBD and IBS predict health care utilization, disability, and health related quality of life. In IBS psychosocial more than physiological factors predict health related quality of life and health care utilizations. Therefore the primary aim of this study was to determine among patients seeking care at a celiac disease referral center the possible relationship between demographic factors, psychosocial factors (psychological symptoms, coping, abuse, and life events), and measures of disease activity (biological markers) in predicting gastrointestinal symptoms and health status (health related quality of life and health care utilization). We hypothesized that psychosocial factors more than disease activity would predict health status. We also sought to determine the degree to which psychosocial versus disease-based factors predicted GI symptoms of pain and diarrhea.

Methods

We studied consecutively 101 adults (> 18 years old) who were newly self- or physician-referred for the management celiac disease to the Columbia University Celiac Disease Center between January, 2006 and January, 2009. All had biopsy proven celiac disease (confirmed by expert review of prior and/or current histopathology) and most had moderate to severe symptoms and/or disease related features.

At initial presentation subjects who agreed to participate either released histopathologic results of prior duodenal biopsies or underwent a subsequent endoscopy with duodenal biopsies. All patients underwent a standardized health care provider assessment and laboratory testing (including IgA tissue transglutaminase levels (tTG) unless recent results were available), and completed a series of psychosocial questionnaires.

Using these data, bivariate analyses were performed to determine associations between independent variables (demographics, psychosocial factors, disease severity measures) with the following outcomes: (1) Sickness Impact Profile; (2) IBS-QOL; (3) self-report of health; (4) health care utilization; (5) abdominal pain; and (6) diarrhea (yes or no). Next, variables that were significantly associated with health status using any of the outcomes (p-value <0.2) were entered into separate multivariate regression models for each of the outcomes.

Results

In general, the study population consisted primarily of well educated, middle aged, Caucasian, females with mild-moderate underlying disease (63%). The majority had a classical presentation (79%), most had mild levels of abdominal pain (VAS 18; 0-100 range) and 40% had diarrhea (37% had diarrhea alone and 3% had diarrhea mixed with constipation). With regards to psychosocial difficulties over one-fifth had a history of prior abuse and almost one-third had significant psychological distress, though only 8% had clinically significant depression. Health related quality of life (IBS-QOL) and self rating of health were good to very good. However, almost one-half had some impairment in daily functioning and over one-third had sought care for their gastrointestinal condition at least twice over the prior six months.
In brief, the results of the six multivariate models were as follows:

1. Those with greater psychological distress (BSI) and a greater tendency to catastrophize (CSQ) (i.e., to view the illness in a pessimistic and negativistic manner) had impaired daily functioning.
2. As found with daily function, poorer health related quality of life was best explained by greater catastrophizing and psychological distress.
3. Poor coping, a longer duration of GI symptoms, lower educational attainment, and a greater weight loss were associated with poorer self rating of health.
4. Those with abnormal tTG levels and milder Marsh scores were significantly more likely to have sought treatment for their gastrointestinal condition at least twice over the prior six months.
5. The strongest predictors for greater pain reporting were higher psychosocial distress, decreased perceived ability to decrease symptoms, and greater percentage of weight loss.
6. There were borderline significant effects for both decreased perceived ability to control symptoms (p=0.06) and for psychological distress (BSI; p=0.06) to explain diarrhea.

Discussion

In summary, among 101 patients seen in a tertiary care celiac disease referral center, psychosocial factors strongly predicted health status: those with more psychological distress and/or poorer coping strategies had poorer daily function, health related quality of life, and self-reported health, greater healthcare utilization. In contrast, the disease related factors were generally not associated with these outcome variables. In fact, milder rather than more severe disease activity as measured by the Marsh histopathological classification predicted more physician visits. Furthermore we found that psychological distress –and not disease based measures – was closely associated with pain and less so diarrhea.

These findings are notable and confirmatory for a biopsychosocial model of illness where the understanding of illness and disease is based on the integrated effects of biological and psychosocial processes. The implications of these findings are broad and far reaching. They highlight the limits of the biomedical model and suggest greater utility from a biopsychosocial approach to patients with celiac disease. Treatment may include in addition to a gluten free diet, psychological support possibly to improve dietary compliance and to also reduce psychological distress and improve coping skills, thus improving overall health status. In addition, centrally acting pharmacologic agents, such as tricyclic antidepressants or selective serotonin norepinepherine reuptake inhibitors may help in reducing the GI symptoms and psychological distress.These potential treatment methods warrant to further investigation for treatment of CD.

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RD 09/49

cognitive factors predict treatment responses to medical & psychological treatment in fbd

Jane Leserman, PhD

Clinical trials in FBD are designed to measure patient responses to an intervention. While often treatments and placebos are believed to be responsible for the largest part of the treatment response, relatively little is known about what additional factors determine whether somebody responds positively to a given treatment condition. With placebo response/satisfaction rates of up to 45% common in clinical trials and a meaningful effect size difference between active and placebo responses being only 10% - what factors, specific to the treatment condition are the determinants of that response? We attempted to answer this question with a retrospective analysis of a placebo controlled treatment trial that compared active conditions of desipramine treatment and cognitive behavioral therapy to a pill placebo condition.

The primary aim of this study was to determine what baseline and post-treatment factors affect treatment response in a clinical trial for treatment of functional bowel disorders. In order to meet this aim we examined pre-treatment and post-treatment predictors that contained demographics, clinical predictors of response and psychosocial predictors of response.

397 females aged 18-70 with Functional Bowel Disorder described as having moderate or severe abdominal pain for six months or more, at least 2 days/week engaged in a 12-week, 4-arm randomized NIH treatment trial comparing Desipramine to Cognitive-behavorial therapy and pill placebo. An educational placebo condition was not examined as it was believed to be present in all three of the other treatment arms. Baseline and post-treatment. A "Responder" was defined as a patient who obtained a score greater than 3.5 (on a 5 point scale) on an 8-item Satisfaction with Treatment questionnaire (Treatment Efficacy Questionnaire).

Variables for examination were selected a priori based on previous research conducted by our center. An initial subset of variables that maintained a correlation of r=0.20 with satisfaction with treatment were used in the regression analysis. Baseline and post-treatment logistic regressions were preformed for each treatment condition to predict satisfaction with treatment. Variables entered the regression equation in the order they were believed to have a determining effect on the outcome variable of treatment satisfaction. Demographic variable were entered first, followed by clinical variables (pain intensity, bowel habit, barostat visceral sensitivity), psychosocial trait variables followed by psychosocial state variables and finally modifying variables were entered into the regression equation.

The mean age of our population was 39

with an average of 15 years of education. 58% reported a history of sexual/physical abuse. The cognitive behavioral therapy group evidenced the largest number of responders with 70% responding positively to treatment. 60% of the Desipramine treatment group responded to treatment and 47% of the placebo group was classified as responders to treatment.

Similar cognitive features predisposed participants to being satisfied with their treatment across all conditions. If subjects had confidence in the treatment or study personnel at baseline, if subjects had a sense of being in control over their GI symptoms (at baseline or after treatment) and if there were improvements in quality of life and maladaptive cognitions or worries during treatment then subjects reported an increased likelihood of responding to treatment.

Treatment specific effects that predicted responder status were a reduction in stool frequency with Desipramine treatment. Also the pill placebo worked better in patients who did not have a significant history of abuse (patients with abuse histories likely had more entrenched illness). Finally, demographic and clinical variables examined were not predictive of responder status.

Overall, factors that predisposed patients to respond to treatments were a sense of confidence in the treatment and a positive evaluation of study personnel. Helping the patient develop a sense of control over the condition, improvement in quality of life and maladaptive cognitions during treatment also resulted in increased odds of responding to treatment. Factors that did not predict treatment response were changes in pain or severity of functional bowel disorder symptoms (except for the Disipramine groups).

Paying attention to cognitive factors that might affect patients, as well as how study personnel interact with participants is critically important. In addition, this study provides additional evidence for using “satisfaction with treatment” as an outcome variable, given that satisfaction is correlated with improvement in quality of life and GI symptoms.

RD 09/51

Keynote: functional dyspepsia - then and now

Nicholas Talley, MD, PhD

Functional dyspepsia [FD] was a term first coined by Walter Alvarez, a gastroenterologist, writer and Mayo Clinic physician who wrote about the condition in 1917. However, major interest in the entity has peaked since publication of the first Rome criteria.

Dyspepsia affects about 15-30% of people world-wide, and the majority have FD. A U.S. survey identified early satiety and fullness as common symptoms in the population rivaling the prevalence of heartburn; these symptoms often overlap, which makes distinguishing gastroesophageal reflux disease (GERD) from FD problematic in some cases (and in some the entities may reflect a common underlying condition).

The Rome III criteria subdivide FD into the epigastric pain syndrome (EPS) and the postprandial distress syndrome [PDS or meal related functional dyspepsia]. There is accumulating evidence that this subdivision is useful and may identify different pathophysiological entities.

In terms of diagnosis, the current criteria [Rome III criteria] represent a diagnosis of exclusion [i.e. a normal upper endoscopy is required to make the diagnosis]. With the increased recognition of the relationship of FD symptoms to meals, it may be possible in the future to positively identify the syndrome by a specific meal stimulus although much more data are needed to confirm this concept.

The pathogenesis of FD remains elusive. Gastric emptying is delayed in about 25% of patients with FD but the abnormality while a biomarker correlates very poorly with symptoms. Impaired fundic accommodation occurs in up to 40% of patients with functional dyspepsia and this does appear to be linked to early satiety. Balloon sensitivity in the stomach and duodenum also occurs in about a third of patients with FD, and this abnormality may be related to epigastric pain. Peripheral pain pathways in FD appear to be abnormal based on positron emission tomography [PET] imaging of the brain during distention. A genetic component may be important in a subset. The first gene to be identified was GNβ3, with the CC polymorphism being linked to FD. Other work has now linked the TT polymorphism to FD, and both polymorphisms may be relevant. FD can also follow infection. Bacterial gastroenteritis can be followed by the new onset of irritable bowel syndrome [IBS], FD or both. H. pylori also appears to be linked to a very small subset of FD. Duodenal sensitivity is abnormal in FD as is abnormal duodenal motility and hold up of acid in this area. Furthermore, duodenal eosinophilia based on specific morphometric criteria appears to be associated with a subset of FD, and may reflect acid bathing the duodenal mucosa or exposure to allergens in food.

In terms of management, acid suppression

therapy is first-line treatment but only a minority respond. The responders appear to be predominately the epigastric pain group. Bismuth and sucrulfate are of no benefit. Prokinetic agents appear to be helpful and probably most often work in the postprandial distress grouping although this has not been well characterized. The multi herbal product STW5 [IberogastR] appears to relax the gastric fundus and may provide a small benefit in FD. There is a major interest in the role of anti-depressants in FD but very limited data. Amytriptyline in one small study appeared to be beneficial, while venlafaxine in another trial was disappointingly no better than placebo. An NIH funded FD treatment trial is currently underway assessing whether amytriptyline and escitalopram is superior to placebo in this condition, and mechanisms that may underlie any benefit. Please refer to the website http://clinicaltrials.gov/ct2/show/nct00248651 or email silvernail.vickie@mayo.edu.

In summary, FD is a common syndrome but remains a diagnosis of exclusion. Other causes of endoscopy negative dyspepsia do need to be excluded before a definitive diagnosis of FD can be made; these other causes include medications, gastroesophageal reflux disease, and uncommonly pancreatico-biliary pathology. The Rome III criteria dividing FD into epigastric pain syndrome and postprandial distress syndrome appears to be useful. H pylori gastritis is an established cause of FD but only in a small minority and most on healing of their gastritis will still have FD symptoms. The relationship between FD and peptic ulcer remains uncertain but on healing an ulcer FD may be present.

Acid suppression is first line therapy for FD but often fails and appears to only be beneficial in the epigastric pain syndrome. Abnormal gastric emptying, gastric accommodation and gastroduodenal hypersensitivity affect subsets of patients with FD (and can overlap); the role of prokinetics needs further study in these subsets. Antidepressants are of unknown benefit but can be considered in clinical practice. An NIH trial is testing the efficacy of antidepressants as well as mechanisms and pharmacogenomics, and patient referrals are very welcome (contact silvernail.vickie@mayo.edu).

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RD 09/53

State of the Art: translation of research instruments into other languages & validation of the translation

Ami Sperber, MD

Research projects often involve study populations in more than one cultural or population group. This is due to the need for very large study populations, for example in clinical drug trials, and the increasingly recognized value of cross-cultural research, which involves studies among different ethnic groups in the same country or in different countries. Cross-cultural research has been applied for years in the social sciences and its importance has gained recognition in the health sciences, especially with the growing role of health-related quality of life research. It has also been used in epidemiological studies, the study of health-related beliefs, attitudes and behaviors across cultures, health administration, health economics and other areas of interest.

Cross-cultural studies are often multi-disciplinary. Because of the unique complexities of this form of research it is important for physicians, nurses and other health care providers to gain an understanding of the basic concepts, considerations and methodological problems entailed. The purpose of this talk is to outline the rationale and methodology of translation and validation of questionnaires and other instruments for use in cross-cultural research.

Cross-cultural research is methodologically problematical, with specific technical problems, most relating to translation quality and the comparability of results in different cultural/ethnic groups. These technical traps may lead to erroneous research conclusions, which, although due to methodological flaws, are undetectable as such and considered to be substantive in nature.

It is not enough to translate a questionnaire literally. The additional challenge is to adapt it in a culturally relevant and comprehensible form, while maintaining the meaning and intent of the original items. To this end advanced planning is essential so that the dual processes of translation and adaptation will be as effective as possible.

Unfortunately, translation of a study instrument such as a questionnaire is often an afterthought, treated as an unimportant part of the study protocol and implemented without attention to the critical issues involved. There are several explanations for this. Many clinicians and researchers are unaware that a problem exists. Even those who are aware of the problem find its solution daunting. The process of translating and adopting a questionnaire for a different cultural group can be arduous and requires a considerable investment of time and money. However, unless this process is adopted and successfully implemented the validity of the research results is suspect. Unfortunately, it is not always clear from the methods section of scientific publications if the requisite effort was made.

The translation process requires skill, knowledge and experience. There are critical translation problems that adversely affect many studies, even with professional translators. Some translators are not sufficiently aware of the rigorous requirements of translation for cross-cultural research. They may spend too much time on literal translation, without devoting enough attention to cultural nuances. Colloquial phrases, slang and jargon, idiomatic expressions and emotionally evocative terms may be particularly difficult to handle.

There are potential cultural differences in the interpretation of many terms. For example, the term family may be interpreted in a similar manner across cultures, but the term adolescence may not. However, even the term family entails potential difficulties. In some cultures family may refer primarily to first-degree relatives, while in other cultures the interpretation may be much broader. Female and male are universal concepts, but the closely related terms femininity and masculinity may be interpreted very differently in some cultures.

Translators are not always sufficiently knowledgeable in the specific subject area of the instrument. Specialized medical subjects are an example of this type of difficult content area. Good professional translators are often incapable of translating medical material. Unfortunately not all of them are aware of this failing.

The back translation technique is most often used even though it is time consuming and can be expensive. Paradoxically, good translators can achieve a back translation that is similar to the source even though the original translation is not good. This "accomplishment" provides a methodological disservice. It can occur because translators may intuitively make sense of poorly written language, in effect, correcting it. They also may retain the grammatical form of the original language in the translation, making back translation grammatically easy but at the same time masking the critical differences between the two versions because the two source language versions appear similar. For example, the item "Do you sometimes feel fed up?" is translated as "Do you sometimes feel that your stomach is full?" The back translator, who is aware of the subject area of the questionnaire, immediately identifies the mistake. However, instead of pointing it out to the researchers he/she simply "corrects" it by back-translating it into the original phrasing. The researchers who are presented with two identical English versions can only conclude that the translation is excellent and leave the critically faulted target language version as is.

When the translation process is complete, many researchers go directly to implementation of the study. However, the proper next step is validation of the translation.

There are several methods that can be used to validate the translation; none is fail-safe. One method is evaluation by teams of experts, bilinguals or focus groups of potential research subjects. The reviewers go over the translated questionnaire and compare their interpretations of the items. Another approach is equivalency testing. In one variation, the instrument in its two versions is given to bilingual persons in alternating language order and assessed accordingly. The use of bilingual subjects for pre-testing can also create methodological problems. The translated instrument is intended ultimately for monolingual subjects. Bilingual individuals often adopt some of the concepts, values, attitudes, and role expectations of the culture of the second language that they have mastered. Thus, bilinguals represent a separate population whose responses cannot be automatically generalized to the monolingual target population.

Two colleagues from UNC (Drs. Boehlecke and DeVellis) and I have developed and published an innovative method for validating the translated instrument and have used it to validate translated questionnaires on IBS, IBD, health-related quality-of-life and others. We find it very useful in identifying problem questions that can then be revised. We do this by introducing a new step into the translation validation process in which we formally compare the original source language version with the back-translated source language version. Each item in the two versions is ranked in terms of comparability of language and similarity of interpretability by means of Likert scales. This enables us to identify potentially problematic items, and reassess and retranslate them until we are as confident as possible that the item would be interpreted in the same manner in both languages.

We use two measures of comparison to evaluate the success of the translating process. These are comparability of language and similarity of interpretability. Likert scales ranging from 1 (extremely comparable/extremely similar) to 7 (not at all comparable/not at all similar) are used. Table 1 shows the rating sheet used for this evaluation. Comparability of language refers to the formal similarity of words, phrases and sentences. If the questions are judged to be identical or extremely comparable in language they are scored 1. Similarity of interpretability refers to the degree to which the two versions engender the same response even if the wording is not the same.

In theory, back-translated items may differ from their counterparts in the original questionnaire in at least two ways: the meaning they convey and the linguistic form they assume. Form may be intentionally varied to generate items that are equivalent in meaning. In this way idiosyncrasies of language are less problematic. One means of guaranteeing that items across versions tap into the same construct is by comparing items in the back-translated version to their original counterparts, item by item. Having both similar meanings and similar forms for corresponding items is ideal. Similarity of meaning, even at the expense of similarity of form, is much more desirable than the opposite. Accordingly, we assess perceived similarity of form and meaning separately, because we believe that asking raters to assess these dimensions separately enhances the distinctness of the dimensions.

In conclusion, translation is the most common method of preparing instruments for cross-cultural research. It has pitfalls that threaten validity. Some of these problems are very difficult to detect and may have a detrimental effect on the study results. Identification of the problems and their correction can enhance validity. Guidelines for cross-cultural translation and validation have been prepared by several organizations, most recently by the Rome Foundation. Although a specific method of validation was presented in this talk, the decision as to the validation method to use is less important than the recognition that the translation process must be culturally appropriate and the validation process must be rigorous.

RD 09/56

functional gi disorders in latin america: population-based initiatives in nicaragua

Douglas Morgan, MD, MPH

Purpose

Existing epidemiologic studies of the Functional Gastrointestinal Disorders (FGIDs) and Irritable Bowel Syndrome (IBS) focus upon homogenous cohorts in the U.S., Western Europe, and Asia. Studies in Latin America and the Developing World are limited. Summarized is the first population-based study to delineate the epidemiologic profile of FGIDs and IBS in the Latino population, utilizing an epidemiology surveillance system which is unique in Spanish-speaking Latin America.

Methods

The study design is a cross-sectional survey, using household interviews. The University of Nicaragua, in the municipality of León maintains a computerized population database for Western Nicaragua, population 200,000, facilitating rigorous systematic sampling. The population is Hispanic mestizo. The Rome II Modular Questionnaire serves as the core instrument, with translation and validation per Rome Committee standards.

Results

The sampled population ranged in age from 18 to 66 with a median age of 39. Total enrollment was 1,624. The overall prevalence of IBS in the population-based cross sectional study was 13.2% -- 5.9% in females and 9.3% in males (Table 1).

The prevalence of functional dyspepsia was 10.3%, with a non-significant female predominance. Proctalgia fugax was surprisingly common, potentially reflecting differences in physiology, cultural expression, and/or language.

There was not a significant association between having an FGID diagnosis and socioeconomic status, as measured by the validated United Nations poverty index. In the households of the study population, 67.8% had their basic needs met, 28.3% lived in poverty, and 4.0% lived in extreme poverty. Nearly all subjects lived in poverty by developed nation standards.

The relationship of IBS to intimate partner violence (IPV) was also examined within this study cohort. There were nearly one thousand women (n=962) enrolled in the current investigation, with complete data available on 960 participants. There were 151 cases of IBS (15.7%) identified. Over half (56.1%) were either married or in a stable relationship.

Overall, all forms of intimate partner violence were common: nearly 15% of the women reported having experienced physical violence, 4.4% reported sexual violence, and 7.5% reported childhood sexual abuse. One fifth of women (19.4%) reported at least one form of violence. Nearly all of the women (90.5%) who reported sexual intimate partner violence also reported physical intimate partner violence.

Table 1. Prevalence of selected Functional Bowel Disorders in Nicaragua.

Functional GI Disorder	Overall Prevalence	Female Prevalence	Male Prevalence
Globus	4.7%	4.9%	4.4%
Chestpain, Esophageal	4.9	5.0	4.7
Dyspepsia	10.3	12.4	8.3
IBS	13.2	*15.9	9.3
Abdominal pain syndrome	2.4	2.2	**2.7
Functional fecal incontinence	7.4	*9.0	5.0
Proctalgia Fugax	13.1	*16.1	8.8

Table 1 Notes

1. Reported prevalence is based upon the population-based FGID cross-sectional survey with household interviews, within the University of Nicaragua HDSS population surveillance system with 1,642 participants.
2. * Suggests significantly increased prevalence among females ($p<0.05$).
3. ** Suggests significantly increased prevalence among males ($p<0.05$).

Table 2. IBS and Intimate Partner Violence (IPV) in Latina Women

Risk Factor	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Physical IPV	2.08 (1.36, 3.18)	2.08 (1.35, 3.21)
Sexual IPV	2.85 (1.46, 5.55)	2.85 (1.45, 5.59)
Sexual abuse prior to age 12	1.74 (0.98, 3.09)	1.82 (1.02, 3.25)
Any type of violence above	2.18 (1.47, 3.22)	2.22 (1.50, 3.32)

*Adjusted by age, poverty index, and marital status

A strong relationship was observed between IBS and prior exposure to violence, which was relatively consistent across the types of violence. A significantly higher percentage of women with IBS (23.8%) had experienced physical intimate partner violence, versus women without IBS (13.1%, p=0.001). In parallel, 9.3% of women with IBS versus 3.5% of women without IBS had experienced sexual intimate partner violence (p=0.001). Those who had experienced physical intimate partner violence had 2.1 (95% CI: 1.35, 3.2) times the odds of IBS after adjusting for sociodemographic factors: age, poverty index, and marital status (Table 2). Those who had experienced sexual intimate partner violence had 2.85 (95% CI: 1.45, 5.6) times the odds of IBS, after adjustment.

Conclusions

The first population-based studies of IBS and the FGIDs in the Latino population and Latin America are reported using Rome II based validated instruments. IBS and functional dyspepsia are common, 13% and 10%, respectively, with a female predominance. In addition, in this study cohort, women who had experienced physical intimate partner violence had significantly increased risk of IBS, as did those who had experienced sexual intimate partner violence. These findings may argue for intimate partner violence screening among Latina women with IBS. In sum, this ongoing effort, now with Rome III instruments, will help further delineate FGID prevalence and risk associations in Latino populations.

RD 09/58

sleep impairment in female patients with ibs

Ami Sperber, MD, MSPH

Health-related quality of life (HRQOL) is severely impaired in patients with IBS. One of the putative causes of this effect is disrupted sleep. It has been suggested that extra gastrointestinal factors might be more important than specific GI symptoms in predicting reduced HRQOL in IBS. The physical and mental components of HRQOL are affected by variables related to chronic stress and vital exhaustion. These include tiring easily, being low in energy, and having sleep difficulties.

Latency to sleep in adults is about 15-25 minutes, sleep efficiency is >90%, and only a few, brief nocturnal arousals and/or awakenings are recorded. Sleep is composed of several cycles of 90 minutes duration. The first 1-2 cycles are predominantly comprised of slow-wave (restorative) sleep (SWS), representing about 25% of sleep time. Rapid eye movement (REM) sleep appears at the end of each sleep cycle and represents 20-25% of sleep time. The last 2 sleep cycles are predominantly REM and the SWS stage is not present. Close to 45% of sleep is stage 2 and only 1-5% is spent in stage 1.

Impairment of sleep can lead to a decline in daily activities and productivity, excessive daytime sleepiness (EDS), mood changes and reduction in HRQOL. By subjective patient report poor sleep quality is associated with exacerbation of IBS symptoms. IBS patients report taking more time to fall asleep, waking up repeatedly from sleep, and excessive daytime sleepiness.

The results of objective sleep studies in IBS patients have been contradictory. In a previous study we conducted, IBS patients spent more time in bed, slept less efficiently, had longer duration to sleep onset, spent more time in shallower sleep stages, had a lower percentage of SWS, and had severe sleep fragmentation (i.e., double amount of arousal and awakenings) than a comparison group. Moreover, lower sleep efficiency was associated with more severe IBS symptoms, while reduced sleep efficiency and an increased arousal and awakenings index were associated with a lower HRQOL. Although this study provided solid evidence of sleep fragmentation in IBS it's methodological limitations suggested the need for a more comprehensive follow-up study enabling us to strengthen the results and further elaborate on them.

The study described here has been funded by the Bi-national US-Israel Science Foundation (BSF) with Drs. Sperber, Drossman, and Tarasiuk (an Israeli sleep physiologist) as co-PIs. It is now getting started. It is designed to reveal the role of sleep on symptoms and HRQOL in IBS. The overall hypothesis of the study is that women with IBS have sleep impairment manifested primarily

as sleep fragmentation. The latter, spontaneous or experimentally induced, causes excessive daytime sleepiness, an exacerbation of IBS symptoms and a reduction in HRQOL. Moreover, alterations in nocturnal melatonin levels may affect sleep and GI tract function. It is possible that patients with sleep impairment and severe GI symptoms have reduced nocturnal melatonin levels. Since one of the putative causes of impaired HRQOL in IBS is disrupted sleep, clarifying the effect of sleep on symptom severity and HRQOL in IBS, particularly in a real-life, at-home setting is of great potential therapeutic benefit.

The specific objectives of the study are:

1) To characterize sleep impairment in IBS by assessing: a) sleep fragmentation, b) REM sleep duration and density, c) excessive daytime sleepiness (subjective and objective), and d) nocturnal melatonin levels;
2) To assess the effect of sleep fragmentation (spontaneous and induced) on IBS symptoms and HRQOL;
3) To determine associations between sleep impairment, IBS symptoms and psychosocial variables. These associations can result from the direct effect of impaired sleep on IBS symptoms, or as an effect of impaired sleep mediated by psychosocial variables, e.g., demographics, coping skills, psychological co-morbidity, etc.

The study uses multiple robust approaches to the investigation of sleep function, thereby minimizing or even obviating methodological pitfalls inherent in studies that use subjective reporting or sleep lab monitoring alone. It includes ambulatory sleep monitoring by actigraph and peripheral arterial pulse tone tonometry (PAT tonometry). It will strengthen the comparison of subjective versus objective data collection and analyses, and facilitate extraction of the significant parameters of sleep impairment in IBS. It is the first study to use an interventional technique to induce fragmented sleep in IBS patients when they have relatively mild symptoms and assess whether this intervention has a short-term negative effect on IBS symptom severity and HRQOL.

All patients and controls for the study will be recruited in Beer-Sheva where data entry will also be conducted. All data handling and statistical analyses will be conducted in UNC-CH. Inclusion criteria for the prospective, controlled study are women aged 18-60 years who were previously diagnosed with IBS by Rome III criteria without an organic GI disorder. Healthy controls are women matched by age (±3 years) who do not have GI symptoms or diseases.

The study has three phases. In phase 1, 60 IBS patients and 30 paired controls will undergo 1-night, at-home PAT tonometry and 5-night actigraphy. The PAT tonometry and the actigraphy will be repeated in a sub-group of patients in Phases 2 and 3. The paired results will be compared by the Cronbach alpha statistic of test-retest reliability to assess data stability over time. The results from this sub-group will add important information regarding data reproducibility over time, an aspect that has not been studied in IBS patients previously. Overnight urine production will be collected from 80 patients and controls to determine nocturnal melatonin levels.

In phase 2, 13 IBS patients and 13 paired controls will undergo 2-night studies in the sleep lab (polysomnography). The results of the 1st night will serve to demonstrate the presence of a “first-night effect” (i.e., alteration of the sleep structure

in the unfamiliar environment of a sleep laboratory) and to exclude primary sleep disorders, the 2nd-night data will be used for sleep and urine melatonin analyses. We will also determine if the REM stage is different in duration and/or density in IBS and whether the differences are associated with symptom severity. PAT tonometry, which will be conducted on the 2nd PSG night, will provide us with important information regarding PSG vs. PAT data comparisons.

In phase 3, 20 IBS patients from Phase 1 will be assessed for the effects on sleep and IBS symptoms of induced sleep disruption. Ten patients will be randomized to undergo sleep deprivation and 10 patients will serve as non-sleep deprived controls. Participants will wear an actigraph and PAT some of the nights, and will complete symptom and sleepiness VAS scales beginning 3 days before the intervention and ending 2 weeks after it. The study is expected to take 3-4 years to complete.

RD 09/61

natural history of ibs symptom episodes

Olafur Palsson, PsyD

This was a diary study conducted entirely online. It was sponsored by McNeil Consumer Healthcare. The general goal of the study was to characterize the natural history of IBS with respect to day-to-day variations (and bowel movement-to-bowel movement variations) in bowel habits and symptoms, with special emphasis on diarrhea. An additional goal was to provide data needed to design a Phase III study to evaluate the efficacy of Imodium for the treatment of diarrhea episodes in patients with IBS.

Participants were recruited via the Center's research participant registry, advertisement on IBS websites, and a mass e-mail at UNC. Potential subjects were screened online. Qualified participants were enrolled via mail. They received a package with their study ID, a pocket diary book, a consent form and release of information to allow us to contact their physicians to verify their clinical status. Subjects were instructed to access a secure study website, and used their unique ID to set their own password, and completed an initial questionnaire set online. Then they used the diary book to rate every bowel movement (BM) throughout each day for 90 days, and transferred those ratings each evening to a secure web form, where they also rated their global daily symptoms. Subjects were contacted next day via e-mail if they failed to enter diary data, and they could then enter data for the previous day, but not for more than one missed day.

206 IBS patients (Rome III criteria + physician diagnosis) 18 years or older were enrolled in the study. Of these, 185 provided sufficiently complete data (at least 21 continuous days of diaries) for analysis. The characteristics of patients included in analyses were: Mean age 36.6 years (range 18-70); 88.6% females; Rome III IBS subtype distribution 31.9% IBS-D, 55.1% IBS-M, and 12.4% IBS-C, 0.5% IBS-U; and 94.1% of subjects were White/Caucasian. Analyzable continuous diary record length per subject was 72.9 days on the average.

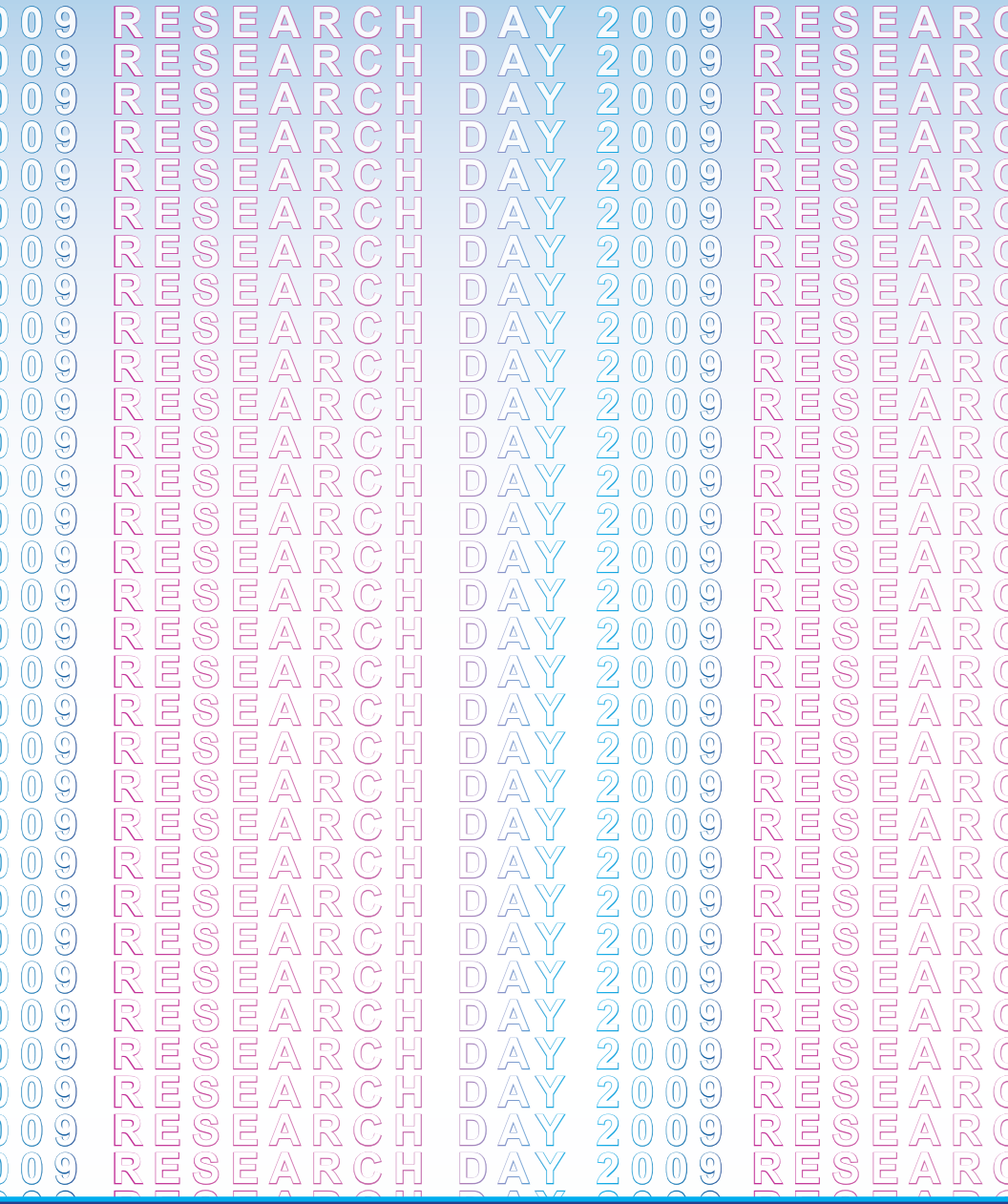
The main findings of the study so far are as follows:

- Approximately 60.8% of BMs in IBS are of normal consistency, whereas 21.6% are diarrhea and 21.3% are constipation (Bristol definitions).
- The majority of BMs of patients of all IBS subtypes are normal consistency.
- IBS patients have a mean bowel movement frequency of 1.8 BMs a day, and only 17% of days are without a bowel movement on the average.
- Most individuals with IBS fluctuate between diarrhea and constipation 2-3 times per month. This is independent of IBS subtype, demographics or clinical characteristics. Such fluctuations therefore appear normal for the disorder in general and may be one of the defining features of IBS.

• Diarrhea and constipation episodes can both be defined in simple terms as a series of at least two diarrhea/constipation BMs with no more than 1 normal consistency BM between them – this captures most of diarrhea/constipation activity (75-80%).

• The concordance between Bristol-defined and patient self-defined diarrhea is good (>70% agreement), suggesting that patient-defined diarrhea reports may be used in many situations as a valid proxy for loose/watery stool consistency measured with the Bristol Scale

• IBS-C patients have significantly greater severity of abdominal pain and bloating in diaries compared to IBS-D patients.



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