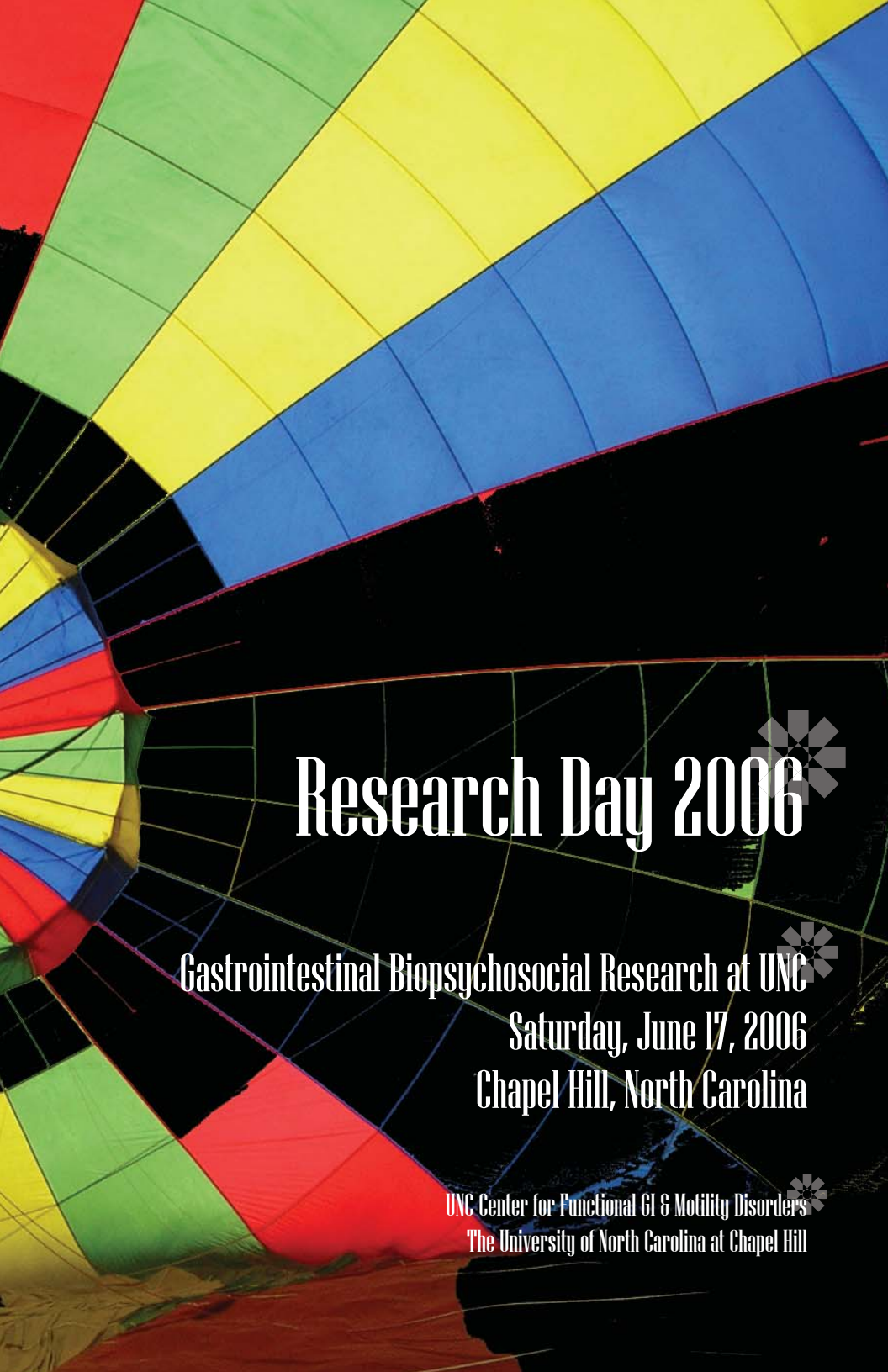

Research Day 2006

Gastrointestinal Biopsychosocial Research at UNC

Saturday, June 17, 2006

Chapel Hill, North Carolina

UNC Center for Functional GI & Motility Disorders
The University of North Carolina at Chapel Hill

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In October 2004, the UNC Center for Functional GI & Motility Disorders was awarded a grant (R24 DK067674) from the National Institutes of Health (NIH) to foster interdisciplinary research on interactions between the mind and body in health and disease, with a specific focus on the causes and treatment of functional gastrointestinal disorders. As part of this NIH grant, the Center hosted the second of what has now become an annual Research Day on June 17, 2006, on the campus of the University of North Carolina at Chapel Hill.

The program for this non-CME symposium was focused on four areas of research: (1) treatment studies, (2) questionnaire development and outcome assessment, (3) psychophysiological mechanism studies, and (4) pediatric GI disorders. The format for the day was presentations on the state-of-the-art in each of these areas by visiting senior scientists, followed by overviews of on-going studies involving UNC faculty and investigators. This booklet provides a summary of all presentations.

Research Day 2006 was held in conjunction with the Center for Gastrointestinal Biology & Disease (UNC Division of Gastroenterology & Hepatology). We appreciate the educational grants from Sucampo Pharmaceuticals and Takeda Pharmaceuticals as well as AstraZeneca Pharmaceuticals and Novartis Pharmaceuticals that provided additional support for this event.

William E. Whitehead, PhD
Co-Director

Douglas A. Drossman, MD
Co-Director

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State of the Art on Treatment Studies

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Nicholas Talley

In irritable bowel syndrome (IBS), management of this disorder has traditionally focused on diet and relieving symptoms rather than modifying the underlying pathophysiology. As of 2006, antispasmodics, antidepressants (TCAs, SSRIs), and serotonin agents (tegaserod, alosetron) are used to treat the symptoms of abdominal pain or discomfort. The symptom of bloating is treated with probiotics, antibiotics, prokinetics, and alpha galactosidase. Several products are available to treat primarily the diarrhea (loperamide, alosetron) or constipation (fiber supplements, PEG solution, tegaserod, lubiprostone) components of IBS. "Satisfactory relief" or "adequate relief" scales are used to measure symptom relief.

New data suggest that targeting disease mechanisms may be a more productive and appropriate approach as we start to unravel the underlying pathophysiological disturbances associated with IBS. Specific opportunities for investigation are infection, inflammation, serotonin, and central processing.

There are several methodological challenges to consider in developing treatment trials. (1) The placebo response in IBS is approximately 44%, but predicting and controlling the placebo response remains difficult. (2) IBS symptoms fluctuate and there is wide variation in determining what is an "episode" of IBS. (3) The mechanisms for IBS are complex and multidetermined. (4) It is difficult to avoid both physician and patient bias. (5) Contamination of the IBS treatment trial with other over-the-counter treatments for IBS symptoms or drugs taken by patients for other conditions. (6) The global (binary) endpoint may be confounded by symptom severity at baseline. (7) It is important to avoid causing harm with IBS treatments, realizing that functional GI disorders are not life threatening.

Let us evaluate the evidence for efficacy of specific treatments for IBS. (a) In terms of diet interventions, fiber is possibly no better than placebo. There is evidence, however,

N. Talley, continued

that food elimination trials may be helpful. Checking for antibody responses, such as IgG levels to certain foods, may assist in identifying what should be eliminated. This has not yet been proven to be of value and better data are needed. (b) Anticholinergics are commonly used to treat IBS, usually for symptoms that develop after meals. There are only three well-designed studies published in English, and all of them have methodological flaws. Thus, it is difficult to know for sure how effective these types of drugs are for IBS. (c) Evidence for the theory that IBS is partly an inflammatory disease and follows an infectious insult continues to grow. However, this knowledge has not yet led to effective treatment using anti-inflammatory agents. (d) There is some evidence that probiotics are superior to placebo in IBS, possibly by altering fecal flora and replacing "bad" with "good" bacteria. This leads to reduced inflammation and improved immune function. Further studies are needed to determine the exact combination and dosage that should be used. (e) There is some indirect evidence that small bowel bacterial overgrowth contributes to the development of IBS, and that this can be treated with antibiotics. However, the prevalence of bacterial overgrowth in IBS and its role in symptoms presentation remains controversial. (f) Serotonin appears to be dysregulated in IBS. A number of drugs target serotonin receptors including tegaserod, a 5HT4 agonist that is a prokinetic, and alosetron, which is a 5HT3 antagonist that slows intestinal transit. Both tegaserod and alosetron appear to be superior to placebo for constipation and diarrhea predominant IBS, respectively. (g) Antidepressants may be beneficial in treating IBS, although the results of clinical trials have been equivocal for the tricyclic antidepressants, and this probably relates to dropouts because of side effects. However, tricyclic antidepressants are commonly used with at least empiric benefit and are likely to work if the medication is taken for at least several weeks. (h) The benefit of selective serotonin reuptake inhibitors is uncertain, and these agents have not been studied enough to draw firm conclusions. The newer SNRIs (e.g., mirtazepine, duloxetine) may have the advantage of benefiting the patient without producing as many side effects. (i) Psychological therapies appear to be beneficial; a 50% reduction in symptoms with psychological therapy is achievable, according to a recent meta-analysis.

To summarize, traditional treatment options for IBS are fiber, diet, laxatives, antidepressants, smooth muscle relaxants, loperamide, psychotherapy, and anti-cholinergics. However, clinical trials of these treatments are generally of poor quality and their role in IBS management is limited.

More recently developed treatments that are currently being researched include serotonergic modulators, glutamate/tachykinin receptor modulators, CCK receptor antagonists, anti-inflammatory agents, antibiotics, and probiotics. The clinical trials for these treatments are generally high quality, using internationally approved diagnostic criteria. Of these, the 5-HT modulators are the most researched.

N. Talley, continued

More work is needed to identify the appropriate targets in IBS, so that more efficacious therapy can be prescribed. Disease modification is the goal of therapy but has not been reached. For the time being, there are some general treatment guidelines to consider: (1) make a positive diagnosis; (2) exclude other diseases by applying clinical judgement; (3) provide reassurance to the patient; (4) provide an explanation; (5) advise about precipitating factors; (6) explore psychologic issues; (7) provide dietary advice; (8) target drug therapy on the major pathophysiologic derangements; and (9) follow up with the patient at least once to determine response to treatment and reinforce the general principles.

Other considerations at this time are: (1) do not to forget the placebo response, make use of it; (2) fiber is of marginal or no benefit; (3) loperamide is efficacious for diarrhea; (4) anti-cholinergics are probably ineffective in standard doses; (5) tricyclics may show benefit if the patient can take them long enough; (6) SSRIs are of uncertain efficacy; (7) SNRI's may have promise for the future; and (8) alosetron (5HT3 antagonist) appears to be effective for D-IBS in women and men (FDA approved for women only), while tegaserod (5-HT4 agonist) is effective for C-IBS in women (constipation in men and women under age 65). The role of antibiotics and probiotics in IBS is still to be determined.

Combined Treatment of Functional Bowel Disorders with CBT and Antidepressants

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Brenda Toner

There has been a long and productive collaboration between UNC (Drossman and Whitehead) and the University of Toronto (Toner and Diamant) involving clinical trials for cognitive-behavior therapy (CBT) and desipramine for functional bowel disorders (FBD). CBT has received increased attention in light of a recent shift in the conceptualization of irritable bowl syndrome (IBS) as a disorder of brain-gut function.

A review of controlled studies of CBT for IBS shows that this treatment improves IBS symptoms and associated psychosocial distress. It is problematic to compare findings across studies, since treatment protocols and outcome measures differ. However, two groups who have developed sustained programs of research in CBT and IBS -- Blanchard and colleagues at the University of Albany and our group in Toronto and Chapel Hill.

Many of the approaches used in treatment trials for IBS have been taken from cognitive-behavioral models developed for work with individuals who presented to mental health professionals with depressive or anxiety-related problems. There is a need to develop more relevant CBT interventions that integrate the patient's perspective and challenge societal cognitions about this stigmatized disorder. We refer to the typical patient perspective as Bowel Performance Anxiety. This consists of: (1) frequent and distressing apprehension about bowel symptoms in public, (2) avoidance of situations where this might occur or heightened state of physiological arousal both in anticipation and during public events, and (3) severe limits on daily activities and decreased quality of life. The general goal of working with individuals with bowel performance anxiety is to decrease avoidance of public situations and to help them cope with the anxiety, shame and embarrassment associated with symptoms. In addition to eliciting individual cognitions and behaviors, it is helpful to identify, acknowledge and challenge societal cognitions about bowel symptoms. Our goals are to: (1) understand the internalization of these destructive social cognitions, (2) discuss an individual's cognitions and behaviors within a larger sociopolitical

B. Toner, continued

context, and (3) use a variety of cognitive and behavioral strategies that are tailored to an individual's specific experiences and goals.

The tricyclic antidepressant, desipramine, has also been evaluated as a treatment for IBS. The rationale for desipramine is: (1) its effect of lessening pain, (2) CNS effects, and (3) central analgesia independent of reducing depression/anxiety. It is given at lower doses than for major depression and there are fewer GI side effects relative to serotonin re-uptake inhibitors. Meta-analyses show that desipramine is effective for patients with IBS, functional dyspepsia, fibromyalgia, headache, chronic fatigue, and chronic pain.

Our group published the largest randomized, controlled, multi-centered trial of CBT and desipramine in women who had moderate or severe functional bowel disorders. Four hundred thirty-one women from the University of North Carolina and the University of Toronto participated in this study. The aim was to assess the efficacy of CBT against an education control and to assess desipramine against a placebo pill control. The primary outcome was a combination (sum) of clinically meaningful endpoints: (1) satisfaction with treatment, (2) improvement in health-related quality of life, (3) improvement in global well-being, and (4) reduction in average pain severity during 14 days as assessed by diary cards. The intention-to-treat analysis showed that CBT was significantly more effective than the education control. Desipramine was not significantly better than control by intention to treat but it was more effective than placebo for those participants who were able to stay on the medication for the duration of the trial.

Our newest UNC-UT collaboration builds on findings from the NIH funded study, by testing the combination of CBT and desipramine against each of these treatments alone. The rationale for a study of combined psychological and antidepressant treatment is: (1) the benefits of each monotherapy are marginal and (2) there is a growing literature pertaining to other disorders (depression, panic, tension headache, Bulimia nervosa) showing that combined treatment is more effective than monotreatment. We have two sources of funding for this productive collaboration -- the Canadian Institute of Health Research (CIHR) agreed to fund the trial in partnership with the NIH funded mind-body grant to the Center that provides support for the Biometry Core. This study will focus on the benefit of combined treatment (CBT plus desipramine) as compared to monotherapies (CBT or desipramine alone). The primary aim of the study is to compare the outcome of combined treatment against single treatment among women with moderate or severe functional bowel disorders. Our hypothesis is that, at the end of treatment and at 6-month follow-up, combined treatment will show a statistically and clinically significant improvement over monotreatment.

Biofeedback for Fecal Incontinence

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Steve Heymen

The prevalence of fecal incontinence (FI) is about 2.2 % among U.S. adults and about 7% to 9.5% in adults over the age of 65. When conservative medical treatment is ineffective, biofeedback is often recommended for the treatment of this condition. The goal of biofeedback for treating FI is to train patients to coordinate an isolated pelvic floor muscle (PFM) contraction of increasing strength with the perception of intra-rectal distensions. Using the biofeedback display, patients develop improved perception of muscle activity and their ability to squeeze PFMs in a focused, more powerful contraction. In a review of the literature, a meta-analysis showed that the success rate of biofeedback for fecal incontinence was approximately 69% (Heymen, 2001). However, Norton et al. (2003) found no differences in the success rates among groups receiving biofeedback, Kegel exercises, education, or biofeedback plus a home trainer, with an overall success rate of 75%.

A study is underway at UNC whose primary aim is to conduct a randomized controlled trial comparing manometry biofeedback (BF) to Kegel exercises (KE) for patients with fecal incontinence. In this study, patients are first provided treatment with education and conservative medical management for a four-week run-in period and study participants are identified as run-in responders or non-responders. The non-responders then receive either biofeedback or Kegel exercises. The education component of the run-in entails: anatomical drawings and a discussion of the results of the diagnostic anorectal manometry, a discussion of the importance of stabilizing stool consistency, toileting schedules, a discussion of triggers for fecal incontinence (foods, stress, lifting, coughing), and the collection of information about symptoms on diaries for four weeks. The medical management component of the run-in entails: Metamucil or loperamide, a stool softener or Milk of Magnesia (adjusted over the phone as needed). The BF and KE treatment protocol entails: six one-hour training visits, 1 to 1, with a therapist every 2 weeks; pelvic floor muscle retraining; education and medications continued from run-in; Kegel exercise (5x/day); FI prevention strategies; and behavior modification strategies. The inclusion criteria are: at least 16 years old, FI for at least one month, and FI of more than 1 teaspoon/week. The exclusion criteria are: major medical disorder, psychotic disorder, or severe cognitive impairment.

S. Heymen, continued

From a total sample of 168, eight are in treatment, 23 withdrew consent during the run-in phase, 35 resolved their symptoms in the run-in phase and did not require further treatment, for 49 treatment was regarded as a failure (including all subjects who discontinued during treatment), and 53 were successfully treated (ITT n=110). The patient characteristics (n=168) are: average age 59.8 years; 129 female, 39 male; 148 White, 15 Black, 3 Hispanic, 2 Native American. Average symptom duration was 6.7 years, and the number of MD visits during the previous 6 months averaged 4.4 visits.

The primary outcome measure (at 3-month follow-up) was assessed by the question: "Compared to before your enrollment in this study, have you had adequate relief of your fecal incontinence symptoms?" The proportion answering this question affirmatively was 71.4% among biofeedback subjects (n=43) and 40.7% among Kegel exercise subjects (n=59) ($p = .002$, $\chi^2 = 9.33$).

Biofeedback appears to be superior to Kegel exercise training for patients with fecal incontinence who were unable to benefit from an education and medical management intervention. Data collection continues for the eight subjects who are in treatment. Our secondary aims are: to identify predictors of a successful treatment outcome; to demonstrate changes in quality of life (QOL) measures in successfully treated subjects; and to produce a treatment manual.

State of the Art: Patient reported outcomes in evaluating treatments for gastrointestinal disorders: Issues in development and application

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Donald Patrick

Dr. Patrick is a Special Government Employee working with the Food and Drug Administration on the development of patient-reported outcomes in the evaluation of medical products. This presentation represents the personal views of the author and should not be interpreted as representing an official opinion of the FDA.

Patient-reported outcomes (PROs) come directly from patients and address how they feel or function as a result of a condition or treatment. PRO measures or instruments are the methods by which these reports are captured from patients. The term 'instrument' refers to all the information and documentation that supports its use, e.g., instructions, mode of administration, scoring, and interpretation guidelines. The US Food and Drug Administration (FDA) published a guidance in early 2006 on the use of PRO measures to evaluate medical products and support labeling claims (www.fda.gov/cder/guidance/5460dft.pdf). This guidance represents the FDA's current thinking on the use of PRO measures and applies to all PRO measurement to document improvement in how a patient survives, feels or functions as a result of treatment, i.e., treatment benefit. PROs can support claims in any section of labeling or advertising, and apply to pharmaceutical interventions but also to conclusions for any trial evaluating treatment based on what the patient reports about treatment benefit. PROs are particularly important in gastrointestinal disorders, because few physiologic measures or markers exist, and survival is not usually the main outcome of interest. Even when physiological measures do exist in GI disorders, these may not reflect the outcomes of most interest to the patient, such as how she or he feels or functions. "Quality of life" is not an appropriate label for an outcome in medical product evaluations, including those for GI disorders. This concept includes elements outside health that are not the appropriate objectives for most clinical trials, i.e., housing, guaranteed income, love, respect. GI-related quality of life may be an appropriate outcome, but it is difficult to define and measure adequately in a single measure that would support a claim that this concept has been measured fully and has been affected by treatment.

Both generic and GI-specific instruments are widely used in the field. Of the generic measures, the most widely applied are the Short-Form 36-item survey and

D. Patrick, continued

the Sickness Impact Profile. Other generic measures that have been used include the EQ-5D and the CDC Health-Related Quality of Life 4-item measure. In the field of irritable bowel disorders, there are many condition-specific measures in the literature: the Irritable Bowel Syndrome Quality of Life Questionnaire (IBS-QOL), the Irritable Bowel Syndrome-Quality of Life Measure (IBS-QOL), the Irritable Bowel Syndrome Impact Scale (IBS-IS), the Gastrointestinal Symptom Rating Scale (GSRS-IBS), the IBS-36, and the Work Productivity and Activity Impairment Questionnaire for IBS (WPA-IBS).

A review of recent literature suggests that outcome measures in GI disorders focus primarily on irritable bowel syndrome (IBS). Investigators have shown that general practitioners underestimate the pain intensity of patients with IBS, and PROS are essential to take account of the patient's perspective. Bushnell and colleagues (2006) recently assessed the comparability, reliability and subject acceptability of electronic versions of IBS-specific instruments and found that the electronic versions are comparable in psychometric characteristics and are preferable to patients. Patients with a predominance of diarrhea exhibit significantly greater impairment of HRQOL in the emotional domain than IBS patients with constipation. Decrements in HrQoL were most pronounced in energy/fatigue, role limitations, body, pain and general health perceptions. Overall, most literature on GI-specific outcomes is about the instruments themselves rather than the correlates or benefits of treatments for GI disorders. Two IBS drugs have been successful in obtaining labeling using PROS -- tegaserod and alosetron. Studies supporting these labeling claims used the subject's global assessment of relief. The multi-item instruments used in studies were not part of the approved labeling.

Many challenges are present for the user of PROs in evaluating GI disorders and their treatments. Few studies include a conceptual framework for the instruments that corresponds to the study endpoint of concepts measures in the clinical trial protocol and proposed as labeling claims. The main PRO concept used in GI trials is adequate relief of pain. This concept is difficult for patients to evaluate as well as difficult for the investigator to interpret. Much more cognitive science is needed to support continued use of this concept as the primary outcome in IBS studies. These measures need to be studied in relation to all IBS symptoms, both extraintestinal and intestinal. The concept or concepts contained in the multi-item instruments are difficult to identify and use in labeling.

Recall periods for GI disorders are lengthy (up to 3 months), and little validation evidence exists to support these long recall periods. Cognitive science has shown patients' ability to recall information varies widely by person and by time. Memories are distorted when the period is long or the patient is required to "average" symptom or sign experience. Momentary pain predicts recall of weekly pain -- a consequence of the peak (or salience) memory heuristic. The appropriate recall period depends on the concept being measured and the frequency and salience of the behavior,

D. Patrick, continued

feeling, event, or burden on the patient. In bowel disorders, much more cognitive science is needed to determine the appropriateness of momentary assessments in diaries and questionnaires versus recall in questionnaires.

In the GI literature, papers contain insufficient detail to permit replication of the study, and thus study reports from authors are needed that include evidence on measurement properties and how the measure was developed and validated. Of particular concern is the target population for the evaluation: IBS in general, constipation-predominant, or diarrhea-predominant. Different measures may be required for these different conditions or alternating patterns. The measurement properties of GI instruments need to be confirmed in every trial in which they are used.

Two major approaches have been proposed in the literature for interpreting effect sizes associated with PROs in clinical trials: identifying the minimum important difference (MID) and responder analysis. Using the MID, investigators propose to identify that difference between treatment groups -- e.g., placebo versus treatment or between comparators -- that could be considered "clinically meaningful". Often a patient anchor is used to identify this as a point estimate or range of estimates, such as the patient's global impression of change or the difference in the PRO observed between a rating of no change after intervention and moderate or minimal change. The point estimate of the MID may not be the most appropriate method of interpretation, particularly when patient anchors are used. Patients may not be the best evaluators of differences between groups. Instead, regulators or payers may judge if a statistically significant difference, particularly if small, is relevant for treatment and reimbursement. Instead of point estimates of the MID, it may be more meaningful to calculate the cumulative distribution curve of observed changes between treatment groups and see where in the distribution is a clear separation of placebo from treatment group, i.e., small changes versus large changes. Patients may play a more appropriate role in identifying what is a responder in a clinical trial. Using the same global impression of change, responder definitions or estimates of significant within-person change can be analyzed to compare the percentage of responders in the treatment group versus the placebo group. In GI disorders, with high placebo response, the responder definition is an important method for interpretation.

In conclusion, all evaluation of PROs when used in pharmaceutical trials should be made in the context of the claim or proposed statement of treatment benefit. Trials of non-drug interventions can follow the same logic. Methodological challenges flow from matching PROs and evidence to claims of treatment benefit in all trials. More cognitive science and epidemiology are needed in the use of PROs in evaluating GI disorders and their treatment, particularly in relation to traditional endpoints such as adequate relief of symptoms.

Comorbidity and Somatization Scale Development

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Olafur Palsson

Numerous studies have reported that functional gastrointestinal disorders (FGIDs) show excessive overlap with various somatic, visceral and psychiatric disorders. Several studies have also reported that patients with these disorders report an excess number of non-GI physical symptoms. Such co-existence/co-morbidity with other disorders and symptoms has been a topic of increasing interest in FGID research in recent years. Comorbidities and somatization in FGIDs have considerable impact and are associated with more severe GI symptoms, greater impairment in quality of life (QOL), more missed work/school due to illness, and more health care utilization and costs.

There have been no comprehensive validated measures for assessing comorbid symptoms and medical conditions in FGIDs. Typically, investigators have sampled varying subsets of symptoms or studied the co-presence of one or a few other medical conditions. This type of evidence makes it impossible to quantify the comorbidity phenomena across studies and patient groups. We aimed to remedy this lack of measures by creating empirically derived questionnaires to assess co-morbidity and somatization in IBS patients in a comprehensive, reliable and valid manner.

Our development process entailed the following: (1) reviewing the published world literature from 1965 to 2001, including DDW abstracts; (2) drafting two questionnaires – Recent Physical Symptoms Questionnaire (RPSQ) and Comorbid Medical Conditions Questionnaire (CMCQ); (3) testing readability and understandability on 20 IBS patients; (4) refinement of the two questionnaires; and (5) assessment of psychometric properties on 109 IBS patients. Study subjects met the Rome II criteria and had a physician diagnosis. Seventy-one percent were female, ranging in age from 18 to 74 (mean age 41.5 years). All completed the RPSQ, CMCQ, and non-GI physical symptoms sections of the Cornell Medical Index (CMI) twice, as well as the IBS Severity Scale and IBS-QOL. The RPSQ is a list of 26 symptoms: subjects respond on a 5-point frequency scale how often each symptom occurred in the last month. The CMCQ is a list of 17 medical diagnoses: subjects are asked whether these disorders have ever been diagnosed in them by a physician.

O. Palsson, continued

The psychometric properties of these scales were: Cronbach's alphas ranging from .70 to .88, test-retest reliability scores ranging from .86 to .95, correlations with CMI ranging from .60 to .81, and non-significant correlations with either patient age or years since the diagnosis. Intercorrelations were .44 between CMCQ & RPSQ and .90 between RPSQ-Som and RPSQ-Sev. In a preliminary assessment of clinical relevance, all three questionnaires had statistically significant correlations ($p<.01$ or better) with Overall IBS Severity, IBS-QOL, Disability Days, and Doctor Visits.

Confirmation of the clinical impact of somatization and comorbidity using the new scales was accomplished through the MAPS project (Management of Abdominal Pain Study), a large questionnaire project where 1772 respondents with IBS, abdominal pain, constipation, or diarrhea, and controls were surveyed within 2 weeks of an HMO clinic visit. Study participants were asked to complete questionnaires on Rome II criteria, IBS severity, quality of life, comorbid disorders and symptoms, and psychological symptoms. The clinical relevance of the RPSQ and CMCQ was confirmed by significance correlations with overall IBS severity, poorer IBS-QOL scores and total physician visits (6 months after the initial visit), and all were statistically significant at the $p<.01$ level. Similarly, correlations with BSI psychological scores (BSI-Depression, BSI-Anxiety, and BSI-Somatization) were all statistically significant ($p<.001$). Co-morbidity and somatization scores on the new questionnaires exhibited a fairly linear association with IBS symptom severity, poorer quality of life, and emotional symptom levels.

Conclusions: (1) The RPSQ and CMCQ are comprehensive empirically derived questionnaires which are: (a) internally consistent, (b) unaffected by age or chronicity of IBS, (c) have high test-retest reliability, and (d) are valid quantitative measures of the tendency to present with multiple somatic symptoms and diagnoses. (2) The RPSQ and CMCQ have robust associations with symptom status and poor well-being in IBS. (3) The scores on these scales appear to have predictive value for prognosis, health care costs and utilization. (4) Our validation and experience so far indicate they are useful tools for research on somatization and multiple medical co-morbidities in IBS, and they also have applicability in other functional GI disorders.

Health Related Quality of Life in Functional Bowel Disorders: Performance Features of Generic and Condition-Specific Measures

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Douglas Drossman

Health Related Quality of Life (HRQOL) measures evaluate a patient's perceptions, beliefs, experience and function in relation to illness and disease. These assessment instruments incorporate sociocultural, psychosocial and disease-related factors, and they treat the patient as the validation standard. Generic HRQOL instruments include the Sickness Impact Profile (SIP) and SF-36. Disease-specific assessment tools include the Irritable Bowel Syndrome Quality of Life (IBS-QOL), IBSQOL and GIQLI.

We studied the performance features of HRQOL instruments among female patients with moderate to severe functional bowel disorder (FBD) using a generic questionnaire (Sickness Impact Profile – SIP) and a condition-specific (IBS-QOL) quality of life (HRQOL) questionnaire at baseline and after behavioral and pharmacological treatments. The specific objectives were to: (1) profile HRQOL among patients with FBD using subscale scores, (2) determine which HRQOL subscales improved with treatment, (3) compare the responsiveness of SIP and HRQOL, (4) determine the clinically meaningful difference, and (5) determine the predictors of HRQOL.

The Sickness Impact Profile (SIP) covers 136 items of sickness related function. There are overall domains (Physical and Psychosocial) and three subscales: (1) Physical (Ambulation, Mobility, Body Care and Movement), (2) Psychosocial (Social Interaction, Altered Behavior, Emotional Behavior, Communications), and (3) Independent (Sleep and Rest, Eating, Work, Home Management, Recreation and Pastimes). The IBS-QOL, in turn, includes 34 items, uses a 5-point Likert scale, and is a "Needs - Based" model ("I worry about losing control of my bowels" or "I feel isolated from others because of my bowel problems." The IBS-QOL includes 8 subscores (Dysphoria, Interference with Activity, Body Image, and Health Worry) and has been proven reliable and valid.

For our study, 402 females with moderate to severe functional bowel disorders, (IBS, functional abdominal pain syndrome, and painful constipation) were enrolled. They

D. Drossman, continued

completed a 12-week NIH treatment trial of medication (desipramine vs. placebo) or psychological (cognitive behavioral therapy vs. education) treatment. Before and after treatment, the study subjects received a battery of psychological and clinical questionnaires including the SIP and IBS-QOL. Analyses included linear regressions for between-group and mixed models for within-group comparisons. The study population was an average of 39 years, 85% Caucasian, and 50% married. Their symptoms were 79% IBS, 10% painful constipation, 8% FAPS, and 3% unspecified FBD. We found a moderate correlation between the SIP and the IBS-QOL (Pre Rx: r=0.54; Post Rx: r=0.59; p<0.0001). There were no major differences in pre or post treatment HRQOL scores by bowel type or subset of IBS. The subjects were combined for all remaining analyses.

With regard to the pre-treatment profile of all patients with moderate to severe FBD on the SIP , the greatest functional impairments (i.e., higher scores) were in the psychosocial domains, particularly the subscales for Social Interaction (e.g., "I am going out less to visit friends", "I am avoiding social visits from others"), Alertness Behavior (e.g., "I do not finish things I start", I do not keep my attention on any activity for long"), and Emotional Behavior (e.g. "I keep rubbing or holding areas of my body that hurt", "I often moan and groan in pain"), as well as the independent domains of Home Management (e.g., "I am not doing any of the regular daily work around the house that I usually do"), Recreation and Pastimes (e.g., "I am going out for entertainment less often", and Sleep and Rest (e.g., "I spend much of the day lying down in order to rest").

With regard to the pre-treatment profile of the perceptual and attitudinal features of the FBD patients using the 8 subscales of the IBS-QOL, the greatest impairments (i.e., scores below 65) were seen with Food Avoidance (e.g., "I have to watch the amount [and kind of food] that I eat because of my bowel problems"), Dysphoria (e.g., "I feel [helpless] [losing control][depressed][angry][isolated][irritable] because of my bowel problems") , and Interference with Activities (e.g., "I am bothered by how much time I spend on the [needing to be near a] toilet", "I get less done because of my bowel problems".

To evaluate the degree to which the HRQOL questionnaires and their subscales improved with treatment, we compared the adjusted change scores from pre to post treatment for responders and non-responders to treatment. . A responder is defined as a subject having a score of >28 at the end of treatment using the Satisfaction scale (Treatment Efficacy Questionnaire). The IBS-QOL was more responsive to treatment than the SIP. With responders and non-responders combined, IBS-QOL standardized scores changed significantly more than the SIP from pre- to post-treatment (0.57 vs. 0.37, p<.0014), Additionally, IBS-QOL responders changed significantly more than SIP responders (0.90 vs. 0.49) and all non-responders (0.24 for both groups of non-responders) (p-value for all four groups: p<.0014). With the SIP, responders showed about a 50% greater change than the non-responders for most subscales, with the

D. Drossman, continued

greatest changes in the psychosocial domain, particularly Social Interaction and Emotional Behavior, as well as improvement in Home Management, and Recreation/ Pastimes. For the IBS-QOL, all subscales showed 200% to 400% greater improvement for responders over non-responders ($p<0.0001$ for all subscales) with the greatest changes in the Dysphoria, Interference with activities, Health Worry, and Social Reaction subscales. This indicates that the IBS-QOL is more responsive than the SIP to treatment effects.

With regard to changes in the IBS-QOL score for medical treatment vs psychological treatment, the medical treatment response was greater than the psychological treatment. Response was greatest for Interference with Activity, Dysphoria, Food Avoidance, and Social Reaction. Psychological treatment showed some response for Dysphoria and Health Worry. There was a greater expectancy for improvement with medical treatment -- credibility scores were higher for medical treatment pre and post treatment. This probably is explained post treatment by self selection of completers by enriching the sample with responders, and by the low credibility scores for the education arm.

To determine the magnitude of change in the SIP and IBS-QOL that is clinically meaningful, we compared the degree of change of the overall score to two independent patient-based assessments of benefit: a) the change in the averaged 2-week daily abdominal pain score, and b) end of treatment Treatment Satisfaction scores. With regard to clinically meaningful change, the clinical anchors were change in VAS pain deteriorations, Satisfaction with treatment and Meaningful change/improvement (SIP = 2.75, IBS-QOL = 14). From this analysis, the improvement in IBS-QOL score with the VAS pain anchor was 13.81 (+16.11) and for the treatment satisfaction anchor was 14.26 (+16.46), with an average of 14. Similarly, improvement with the SIP score using the VAS pain anchor was 3.08 (+ 4.77) and for the treatment satisfaction anchor was 2.43 + (5.35), with an average of 2.8. To support these findings we also used Norman's ½ s.d. of baseline values method, which identifies a statistically meaningful response for chronic medical conditions. The value for the IBS-QOL was 10.2 and for SIP it was 3.5.

For the regression analyses predicting baseline HRQOL, variables were entered in four steps: (1) Demographic variables (age, education, marital status, race, site); (2) abuse history (physical and sexual abuse, rape), (3) Clinical variables (MD visits, VAS pain, stool frequency, stool consistency, pain thresholds), and (4) psychosocial (SCL-90, BDI, IMIQ, Coping – CSQ, DIS diagnosis, NEO, Social support questionnaire.The most robust predictors of Baseline HRQOL were: (1) psychological distress – SCL-90 (SIP/IBS-QOL); (2) Cognitions - IMIQ (Severity-SIP/ Controllability-IBS-QOL); (3) Catastrophizing - CSQ (SIP/IBS-QOL); (4) Depression – BDI (SIP); (4) Perceived control - CSQ (IBS-QOL); (5) Stool Frequency (IBS-QOL); (6) race (SIP); (7) age (IBS-QOL); and (8) abuse and pain effects..

D. Drossman, continued

Prediction of improvement after treatment in HRQOL was analyzed in six steps: (1) baseline HRQOL (SIP or IBS-QOL); (2) Demographic variables (age, education, martial status, race, site); (3) abuse history (physical and sexual, rape); (4) treatment (CBT/EDU or DES/PLA); (5) clinical variables (Δ pain (VAS), Δ stool freq/consist., Δ tracking pressure); (6) psychosocial (SCL-90 (global), IMIQ, NEO, DIS diagnosis, Social support questionnaire, change in CSQ, Beck Depression Index. Predictors of improved HRQOL following medication were: (1) Desipramine treatment (IBS-QOL), (2) decrease in pain (IBS-QOL), (3) reduced psychological distress and depression (IBS-QOL/SIP), (4) increased sense of control over the illness (IBS-QOL), (5) lower perception that illness is severe/constant (IBS-QOL/SIP), (6) no Axis I psychiatric diagnosis (IBS-QOL), and (7) younger age (SIP). Predictors of improved HRQOL following psychological treatment were: (1) reduced psychological distress and depression (IBS-QOL/SIP), (2) greater sense of control over the illness (IBS-QOL), (3) decrease in catastrophizing (IBS-QOL), (4) greater sense of ability to decrease symptoms (IBS-QOL), (5) less change in stool frequency (IBS-QOL), and (6) Caucasian (IBS-QOL).

In conclusion, we have analyzed the performance features of a generic and a condition specific HRQOL measure in a sample of women with moderate to severe FBD. The results indicate a clinical profile that characterizes patients who experience fatigue, emotional irritability, impairments in daily functioning, home management and recreation and a need to focus activities to be near a toilet and to adjust their eating habits. Of the two measures, the IBS-QOL is preferred because of its greater responsiveness to treatment effects. Improvement is predicted primarily by psychosocial rather than physical domains Medication treatment is associated with greater change scores than psychological treatment, possibly due to selection that enriches responders in the per protocol analysis, and patients having greater expectation of benefit for a pill. Finally, HRQOL is best predicted by psychosocial correlates to these conditions, and in part these factors appear to mediate the effects of abuse and pain on these outcomes. This information provides new clinical information as the impact of FBD on HRQOL and the ways in which patients improve in response to medication and psychological treatments.

Satisfactory Relief as an Outcome Measure in IBS Treatment Trials

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William Whitehead

The aims of the study were to compare a binary Satisfactory Relief measure identical to one used in pivotal trials of alosetron and cilansetron to: (1) a 7-point rating of improvement, (2) an IBS symptom severity questionnaire, and (3) a disease-specific quality of life scale (IBS-QOL). The objective was to determine whether initial IBS symptom severity influences the sensitivity of these outcome measures. For this study, 641 patients meeting Rome II criteria for IBS were prospectively identified from an HMO database. Study subjects completed questionnaires at baseline and after 6 months of treatment. Treatment was usual medical care and was at the discretion of the physician.

The Satisfactory Relief question was: "In the past 7 days, have you had satisfactory relief of your bowel symptoms?" The response alternatives were: (a) "No, I have not had satisfactory relief," (b) "Yes, I have had satisfactory relief," or (c) "I have not had bowel symptoms in the last 7 days." The words 'bowel symptoms' were defined as including abdominal pain and discomfort, as well as bloating, constipation, diarrhea, or other symptoms that that subjects believed to be related to their bowels. A Responder was defined as anyone who claimed satisfactory relief or no bowel symptoms.

The rating of improvement question was: "Please indicate how your bowel symptoms have changed since you saw your doctor about 6 months ago. Please take into account your overall well-being and symptoms of abdominal pain and discomfort, as well as bloating, constipation, or diarrhea." The response alternatives were: (a) markedly better; (b) somewhat better; (c) a little better; (d) no change; (e) a little bit worse; (f) somewhat worse; and (g) markedly worse.

For the IBS Symptom Severity Scale, the score was the sum of five equally weighted questions: (1) severity of abdominal pain; (2) frequency of pain in last 10 days; (3) abdominal distention/tightness; (4) dissatisfaction with bowel habits; or (5) interference with life in general. A Responder was defined as anyone with 50% reduction in total score.

The results were as follows: (1) With regard to the percent of patients reporting satisfactory relief, it was found that patients with severe IBS (a) show the greatest reductions

W. Whitehead, continued

in symptoms but (b) are least likely to report satisfactory relief. (2) Comparing a Responder as someone who is "Somewhat or Markedly Better" vs. "50% reduction in IBS symptoms," it was found that defining responders by ratings of symptom improvement is less influenced by initial severity of IBS, and a 50% reduction of IBS symptoms is not influenced by initial symptom severity.

The magnitude of placebo response is an important consideration in choosing an outcome measure, but it was not evaluated in this study. In a meta-analysis of placebo response in IBS, it was found that the placebo response rate was higher for a global improvement scale than for a pain-specific endpoint.

To summarize, satisfactory relief – the current standard for defining responders in clinical trial – is (a) strongly influenced by initial symptom severity and (b) weakly correlated with the magnitude of symptom change. A 50% reduction in IBS symptom severity is less sensitive to bias by initial severity. These findings suggest that the choice of a primary outcome measure in clinical trials should be re-assessed. However, replication in a randomized control trial is needed.

Development and Validation of the Bloating Severity Questionnaires

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Abdominal bloating is an ambiguous and poorly understood symptom, but it is a fairly common problem in the general population, affecting 10-30% of people. It is even more common among people with functional GI disorders. Among those with IBS, 70-90% report bloating or distention, and the majority report it to be their most bothersome symptom -- even more bothersome than abdominal pain. The high incidence and bothersomeness of bloating make it an important target for study in FGID research. However, we found no reliable tool to assess the severity of abdominal bloating. We therefore developed a Bloating Severity Questionnaire (BLSQ), which quantifies bloating in a simple self-report format. The BLSQ was designed to discriminate mild versus severe cases of bloating, and to be suited to detect changes in bloating over time and in response to treatment.

The process for developing and validating the BLSQ entailed the following steps: (1) literature review of bloating and bloating assessment, (2) three focus groups conducted with adults suffering from bloating, (3) development of a preliminary BLSQ with 8 questions, (4) first administration of the BLSQ to 58 adults with bloating problems, (5) analysis of pilot results, (6) expansion of the BLSQ to 13 questions with both a 24-hour scale and a general scale, (7) second administration of the BLSQ to 149 adults with bloating problems, administered twice two weeks apart, (8) data analysis, which resulted in the elimination of one item and the creation of short versions of the BLSQ, (9) psychometric analysis that included assessment of test-retest reliability, internal consistency, and relationship with QOL impairment, and finally (10) performance assessment of the ability of the new questionnaire to discriminate between groups with different types of bloating, and to show reactivity to changes in bloating.

The 3-item general BLSQ asks: 1. How severe is your bloating typically? 2. When you have pain with your bloating, how severe is your pain typically? 3. How often do you have discomfort other than pain along with the bloating? The 24- hour BLSQ asks: 1. How severe was your bloating, in terms of its effects on you, in the past 24 hours? 2. How much pain that was related to the bloating did you have in the past 24 hours? 3. How much discomfort other than pain did you have related to your bloating in the past 24 hours?

The 2-week test-retest reliability of the subscales of the BLSQ ranged from .55 to .88, internal consistency (Cronbach's alpha) from .66 to .85, and the correlation with bloating QOL impairment ranged from .56 to .69. Both the 24-hour and general BLSQ performed well in the discrimination of bloating groups: (1) in a comparison of 29 study subjects with menstrual bloating and 85 GI bloaters, the BLSQ scores were significantly greater among the GI bloaters ($p < .01$), and (2) in a comparison of 40 post-prandial GI bloaters to 78 non-meal bloaters, post-prandial bloaters had significantly more severe bloating.

O. Palsson, continued

The 24-hour BLSQ also performed well in quantifying reactivity to lactose consumption in 26 breath-test- confirmed lactose intolerant adults.

Conclusions: (1) the two severity scales of the new 12-question BLSQ have good psychometric properties; (2) they measure both general and 24-hour bloating severity in a way that is highly reliable; (3) they appear valid based on correlations with QOL impact of bloating and ability to discriminate severity of bloating between subgroups of bloaters, and detect reactivity to experimental bloating manipulation; and (4) the shortened 3-question versions also have satisfactory test characteristics and their brevity may prove useful in some research applications. However, the validity of these scales needs further confirmation.

State of the Art: Why Mast Cells are Important in Functional Gastrointestinal Disorders

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Jack Wood

Mast cells play a key role in the gastrointestinal secretory and motor function, and they appear to be important to an understanding of altered gastrointestinal function in irritable bowel syndrome (IBS). Evidence for their involvement in IBS etiology is as follows: (1) patients with diarrhea-predominant IBS have increased numbers of mast cells, and (2) there is enhanced release of histamine and tryptase from mast cells in IBS patients as compared to healthy controls.

Mast cell signaling can be divided into three targets or signaling pathways: (1) they secrete chemo-attractants to cause migration of lymphycytes to an area of inflammation; (2) they act as paracrine signals to enteric secretoromotor neurons, and (3) they act as paracrine signals to post-ganglionic sympathetic fibers.

The communication of mast cells with enteric neurons occurs primarily through histamine release. Histamine triggers volleys of action potentials in enteric neurons in the submucosal plexus, showing that it is excitatory to these neurons. Histamine also acts on the sympathetic axons arising from the sympathetic ganglia and is inhibitory to the release of norepinephrine by these axons. Since these sympathetic neurons are themselves inhibitory for secretion and contraction, the net effect of inhibiting these inhibitory pathways is an excitation of secretion and motility.

Histamine applied directly to the submucosal plexus has effects on sensory neurons, interneurons, and secretomotor neurons. It produces rhythmic, coordinated cycles of contraction and secretion, and increased regional blood flow. At the clinical level of observation, the response to mast cell activation includes power propulsion contractions which migrate through the colon and increased secretion leading to symptoms of diarrhea and abdominal pain.

J. Wood, continued

These effects of mast cells on gastrointestinal function can be triggered by antigen-induced activation of mast cells. This can be studied experimentally by inducing an allergic reaction to milk or other proteins, after which exposure to the antigen triggers a cascade involving histamine release and excitation of motility and secretion.

What have been described up to this point are the effects of mast cells on the enteric nervous system. Mast cells are also affected by nerves: electrical stimulation of spinal afferents in the mesentery leads to volleys of action potentials in intestinal submucosal neurons. The stimulation of mast cells by these nerves is mediated by substance P and CGRP. Serotonin released by enterochromafin cells in the intestinal mucosa also stimulates mast cells to release histamine. Thus, mast cells are involved in a two-way interaction with the nervous system and participate importantly in the coordination of responses to both local inflammation and CNS-mediated cognitive and psychological events.

Heterogeneity of IBS: Preliminary Results of Cluster Analysis

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There are multiple etiologies proposed for IBS, but none is present in more than 60% of the patients. This diversity of possible causes, as well as the variability in the expression of IBS (e.g., diarrhea predominant, constipation predominant, pain predominant) is puzzling and does not fit a traditional biomedical model. The bio-psychosocial model is the most widely accepted explanation for this diversity: it holds that there are multiple interacting causes for IBS with none being necessary or sufficient. Although this model accommodates all of the data, it is not easily tested and does not provide specific guidance on treatment. An alternative hypothesis to explain this heterogeneity is the possibility that IBS is not a single entity but a group of different disorders with distinctly different etiologies. The importance of the heterogeneity hypothesis is that, if IBS does have multiple independent etiologies, they may require different treatments.

The overall aims of our study are: (1) to determine whether there are distinct IBS subtypes; (2) to identify variables or mechanisms that distinguish IBS subtypes (e.g., pain sensitivity, motility, psychological distress); (3) to link subtypes to clinical symptoms; and (4) to link the subtypes to distinct etiologies (e.g., post-infectious, bacterial overgrowth).

This is a preliminary report on an ongoing study. We tested more than 30 variables in a large group of IBS patients to identify variables that separate IBS from control. We then compared these variables to see whether they were correlated with each other and classified IBS patients in the same way. Finding that they were poorly correlated, we next used cluster analysis to identify distinct groups of IBS patients and to characterize these groups. The tests include physiological, clinical history, and psychological measures. The physiological measures were: (1) pain sensitivity by the ascending method of limits (AML) and signal detection; (2) phasic contractions (motility) measured both fasting and postprandially; (3) smooth muscle tone measured both fasting and postprandially; (4) small bowel bacterial overgrowth; (5) lactose malabsorption; (6) CBC and CRP as nonspecific measures of inflammation; (7) IgG & IgA, IgE measured as markers for celiac disease; (8) serotonin measured both fasting and postprandially, VIP, and Substance P; (9) heart rate variability; (10) cortisol, epinephrine, norepinephrine, and acetylcholine; and (11) genetic polymorphisms in SERT. The clinical history measures were: (a) the Rome criteria for IBS, chronic functional abdominal pain, and functional dyspepsia; (b) predominant bowel habits; (c) onset following gastroenteritis; (d) somatization measured by the Comorbid Medical Conditions Questionnaire and the Recent Physical Symptoms Questionnaire; (e) IBS Severity Index; (f) disease specific quality of life measured by the IBS-QOL; and (h) demographics including age, gender and ethnicity. The psychological measures

W. Whitehead, continued

were: (1) the BSI-18; (2) NEO Personality Inventory; (3) Prime MD; (4) SCID Somatization Module G; (5) Pain Coping Inventory (catastrophizing scale); (6) Trauma Symptom Checklist – 40; (7) Sexual and Physical Abuse Checklist; (8) Family Inventory of Life Events (stress scale); and (9) Perceived Stress Scale.

In a preliminary analysis (which we presented last year) of the first 88 IBS patients and the first 20 controls who were tested, we reported that the key variables of motility, visceral pain threshold measured by AML, and overall psychological distress measured by the BSI-18 each differentiated IBS patients from controls, but these scores were poorly correlated with each other: Pain thresholds and psychological distress correlated rho=.11 (not significant), and gastrointestinal motility and pain sensitivity correlated rho=.19 (not significant). These findings suggest that motility, pain sensitivity, and psychological distress are independent mechanisms for symptoms in IBS patients.

At this time, we are able to present further preliminary analyses employing cluster analysis to test for independent subgroups. We have now tested 198 IBS patients and 53 controls, and we have complete data scored for 122 of the IBS patients. The analyses presented here were based on a subset of the patients tested so far. We identified five clusters of IBS patients, differentiated along the dimensions of motility, psychological distress, and pain sensitivity. The characteristics of these five clusters are as follows: Group 1 (n=29) -- sensitivity to pain and urge; Group 2 (n=5) -- high motility reactivity; Group 3 (n=33) -- low pain sensitivity, low IBS severity, low psychological symptoms; Group 4 (n=11) -- high psychological distress; and Group 5 (n=10) – overlap between groups 1 and 4, characterized by both pain sensitivity and psychological distress.

We examined the association of these five groups with individual variables in the data analysis and confirmed that the groups differ on the dimensions of motility, pain sensitivity, and psychological distress. We also examined differences between these groups in clinical symptoms and found the following: (1) Group 5: Significantly greater symptoms of urgency to defecate and trend towards more frequent stools and looser stools. (2) Groups 4 and 5: Significant elevations in pain frequency and intensity, and in urge intensity during the sensory test procedure. (3) Group 2: When the distribution of SERT polymorphisms was examined, this high motility group showed a trend towards increased incidence of the short allele.
To summarize, our preliminary analysis suggests: (1) IBS patients sort into five distinct clusters; (2) key variables differentiating clusters are psychological distress, pain sensitivity, and motility; (3) clusters differ in clinical symptoms of IBS; and (4) SERT polymorphisms may be linked to clusters. The next steps are to expand the sample, confirm our findings in a new sample, and test the linkage to independent etiologies.

Association of Psychosocial Factors and Disease Markers with Health Status in Celiac Disease

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Spencer Dorn

Celiac disease is a subject of increased medical attention in part because of the availability of more sensitive screening measures and the recognition that the disease occurs in up to 1% of the population. The disease ranges in terms of histopathological severity from normal small bowel architecture to complete villous atrophy. Clinical presentations are equally diverse: some patients are debilitated by severe illness while others remain relatively asymptomatic. Accordingly, patients can be broadly sub-divided into classical celiac disease, in which diarrhea is the predominant symptom, and silent celiac disease, which includes patients with atypical symptoms and those who are asymptomatic.

While it may be assumed that illness severity and health status (pain, quality of life impairment) are strongly correlated with disease measures (histopathology, inflammatory markers), this association has not been determined for celiac disease. Thus, it is possible that more active celiac disease pathology does not necessarily predict more severe illness, and more severe illness does not necessarily predict more active celiac disease. Along these lines, the health status of patients with functional GI disorders such as IBS that have no overt pathology can be worse than patients with structurally based "organic" disorders such as inflammatory bowel disease (IBD).

Psychosocial factors (e.g., sexual and physical abuse history, depression) might explain a possible disconnect between disease activity and illness severity. For example, it is commonly recognized that patients with IBD with marked disease activity (i.e., inflammation) may function well, with little or no symptoms of pain or impaired quality of life. In these patients, psychosocial factors are better than disease-based measures at predicting health care seeking behavior. Similarly, we have found that in IBS psychosocial factors are stronger influences than physiological factors, such as visceral hypersensitivity, on patient perception of illness severity as well as their health status and health outcome (in terms of pain, quality of life impairment and health care utilization). For all GI disorders psychosocial factors increase pain,

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reduce quality of life and increase health care seeking behavior. These effects may override traditional celiac disease classifications such as classical or silent disease, but that is yet to be determined.

Thus, it is relevant to evaluate the relationship of psychosocial factors, compared to biological components of disease activity, on health status in celiac disease. We propose to assess the mutually predictive effects of demographic factors, psychosocial factors (psychological distress, depression, life stress, abuse history, and coping), and disease activity (histopathology, serum TTG, albumin, hemoglobin and cholesterol) on health status (pain levels, quality of life and health care utilization). This is a pilot study designed to generate hypotheses and data, and has both cross-sectional and longitudinal components. Our specific aims are to: (1) determine whether psychosocial factors and disease measures predict HRQOL and health care utilization; (2) identify subsets of patients whose poor health status is explained primarily by high psychosocial distress and disease based measures; (3) identify baseline patient characteristics that are associated with a response to therapy; and (4) assess the prevalence of irritable bowel syndrome (IBS) among patients treated at a celiac disease referral center.

This study will take place at both the Celiac Disease Center at Columbia University, New York, NY (recruitment of patients, study administration, data collection) and the University of North Carolina Center for Functional GI and Motility Disorders, Chapel Hill, NC (data management, quality control, data analysis). Study subjects will include adults with biopsy proven celiac disease that have been on a gluten free diet for > 6 weeks and have no history of other structural GI disease, bowel resection or gastrectomy. Since this is a hypothesis generating pilot study, there has been no "power analysis". However, based on our previous studies, we anticipate that 85 patients will be needed. At an anticipated recruitment rate of 1-5 patients/week, we expect that patient enrollment will take 30 weeks. With expected attrition at 25%, we anticipate complete data collection (both baseline and 12-week data) for 63 patients. Based on the results of this pilot study, we anticipate future studies that: (1) test any hypotheses that are generated; (2) assess antidepressant or behavioral intervention for refractory patients with high psychosocial distress; and (3) assess the correlation of cytokines with disease activity and psychosocial distress.

The Exacerbation of IBS Symptoms during Menses is Associated with Increased Prostaglandin (PGE2) Levels

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For IBS patients, pain and diarrhea symptoms often increase during menses when estrogen and progesterone levels are lowest. However, IBS symptoms often decrease after menopause when estrogen and progesterone levels are also low, indicating that estrogen levels are poorly correlated with IBS symptoms. Estrogen and progesterone effects on IBS may be indirect and mediated through the rapid drop in these hormones at menses that indirectly causes a rise in prostaglandins. The aim of our pilot study was to determine whether women who report exacerbation of IBS symptoms during menses (IBS-X) have higher levels of prostaglandins (PGE2 and PGE2 metabolite) in menstrual fluid and in serum, compared to women with IBS that is not exacerbated during menses (IBS-noX) and compared to healthy controls.

Seventeen IBS-X, 22 IBS-noX, and 18 healthy controls were evaluated on their first day of menstrual bleeding for measurement of serum and menstrual fluid levels of PGE2. Subjects had an average age of 29.6 years and included 48 White, 7 Black, 1 Asian, and 1 Hispanic subjects. Following a blood draw (8ml), a previously prepared tampon, made from dialysis tubing and containing Dextran-40 (10ml), was inserted into the vagina of the study subject. The subject then rested quietly on her back for 60 minutes while the concentration of PGE2 from menstrual fluid came into equilibrium with the concentration of PGE2 in the Dextran within the dialysis tubing. Blood and menstrual fluid were analyzed by radioimmunoassay for levels of PGE2 and PGE2 metabolite, which were then compared among the three groups.

Our results were as follows. (1) PGE2 was significantly elevated in the serum of the IBS-X group compared to the IBS-noX group ($p=.008$, Mann-Whitney), with a trend favoring IBS-X compared to the healthy controls ($p=.089$, Mann-Whitney). (2) Similar trends were seen in the menstrual fluid levels of PGE2 (Mann-Whitney). However, these differences were not significant. (3) Serum levels of PGE2 metabolite were significantly higher in the IBS-X group than in the IBS-noX group ($p<.001$, Mann-Whitney). However, the control group was not significantly different from the IBS-X group. (4) Also, in menstrual fluid, similar trends were seen in the levels of the metabolite of PGE2, but the differences were not statistically significant (Mann-Whitney).

We conclude that IBS patients whose symptoms worsen with menses show elevated PGE2 in serum and menstrual fluid compared to IBS patients whose symptoms do not worsen with menses and compared to healthy controls. These elevations in the pro-inflammatory mediator, PGE2, may contribute to the abdominal pain associated with IBS. Further investigations are needed to confirm these findings using larger sample sizes.

Caesarian Delivery upon Maternal Request: A Systematic Review of Evidence Focusing on Anal Incontinence

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Anthony Visco

Cesarean delivery (CD) rates are increasing in the United States. The contribution of Cesarean Delivery on Maternal Request (CDMR) to this trend is unclear, because providers are reluctant to list CDMR as an indication for CD as well as a lack of available coding for CDMR. The balance of risks and benefits is unknown: maternal and neonatal, short and long term, and first and subsequent pregnancies. In this study of CMDR, the focus was on primary cesarean delivery, singleton pregnancy, at term, with no maternal or neonatal indications.

The key questions in the meta-analysis were: (KQ1): What is the trend and incidence of cesarean delivery over time in the US and in other developed countries? (KQ2): What is the effect of approach to delivery (i.e. cesarean delivery on maternal request compared to planned vaginal delivery), on maternal and infant short-term and long-term outcomes? (KQ3): What are the factors affecting the magnitude of the benefits and harms in KQ2? (KQ4): What future research is needed to make appropriate decisions regarding CDMR versus planned vaginal delivery? The specific challenges in addressing these issues were: (a) minimal data are available on CDMR for outcomes, (b) the evidence relies on proxies for CDMR (comparisons are made by actual routes of delivery and not planned routes of delivery, where maternal and fetal indications result in confounding), and (c) comparison groups result in variable relevance to CDMR.

The search methods for this meta-analysis were electronic databases (MEDLINE, Cochrane Collaboration and EMBASE) and hand searching, limited to articles published in or after 1990 and studies conducted in developed countries. 1406 abstracts were reviewed, 490 articles were identified, and the number of relevant articles narrowed down to 69: (KQ1) 13 on Trends and Incidence, (KQ2) 54 on Outcomes, and (KQ3) 5 on Modifiers. The purpose of this review was to address CDMR. The literature contains ambiguous and non-standardized terms – primary, elective, scheduled, planned, labored/unlabored, urgent/emergent/emergency, and

A. Visco, continued

operative vaginal delivery. The strength of available evidence was graded as strong, moderate, weak, or no evidence.

In this presentation, only the evidence related to KQ2 -- "What is the effect of approach to delivery (CDMR compared to planned vaginal delivery) on maternal long-term outcomes" -- is addressed. The majority of the evidence was weak with regard to urinary incontinence, anorectal function, and sexual function, and there was an absence of evidence regarding pelvic organ prolapse. There was also weak evidence favoring planned compared to unplanned cesarean delivery or instrumental vaginal delivery.

Regarding anorectal function, there was evidence of reduced risk of anal incontinence in planned cesarean deliveries compared with unplanned cesarean or instrumental vaginal deliveries. However, the evidence was inconsistent about differences between planned cesarean and spontaneous vaginal delivery. The two articles pertaining to term breech trials were rated poor for a variety of reasons.

The evidence on anal incontinence has clear limitations: limited sample sizes, comparison by actual routes of delivery, lack of consistent direction, non-validated questionnaires, multiple languages, inconsistent time points (long-term follow-up), preexisting symptoms, and definitions (inclusion of flatal incontinence). Future research requires: (1) intent to treat analysis, (2) consistent terminology for mode of delivery, (3) controls for confounders and modifiers of outcomes, and (4) assessment of utility of outcomes.

Increased Colonic Sensitivity in IBS is the Result of Increased Perceptual Response Bias rather than Increased Perceptual Sensitivity

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It has been repeatedly observed that patients with IBS report pain at lower pressures and volumes of rectal and colonic distention. These lower pain thresholds have been interpreted to represent visceral hypersensitivity and have been attributed to biological differences in subjects with IBS. In fact, lower pain thresholds have even been labeled a "reliable biological marker" for IBS (Mertz, et al. 1995). However, it is impossible to attribute lower pain thresholds solely to biological factors, since threshold measurement techniques are affected by psychological factors that result in a perceptual response bias.

Sensory Decision Theory (SDT) is an alternative sensory testing paradigm that allows the separate quantification of the biological and psychological components of the threshold. In SDT, stimuli are presented in an unpredictable order and subjects rate the intensity of each stimulus. Decision theory is then used to separately quantify the individual components of the threshold: (1) Discriminatory Function (P(A)), a measure of perceptual sensitivity (biological) that is immune to psychological manipulations but affected by anesthetics and analgesics; and (2) Response Criterion (B) a measure of response bias (psychological) that is susceptible to psychological manipulations (e.g. placebo, suggestion).

The primary aim of the study was to determine whether differences in pain thresholds between patients with IBS and healthy controls are explained primarily by (1) differences in perceptual sensitivity (biological differences) versus (2) differences in perceptual response bias (psychological differences). The secondary aim was to explain differences in urge thresholds. We hypothesized that, compared to healthy controls, IBS patients have: (1) lower AML determined pain thresholds; (2) similar levels of perceptual sensitivity; (3) higher levels of perceptual response bias; and (4) higher levels of psychological distress.

This study included 132 IBS patients with IBS (35 years old, 84% female) and 31 healthy controls (30 years old, 71% female). All subjects were admitted to the General Clinical Research Center where they first underwent psychological evaluations with the Brief Symptom Inventory (BSI-18; global, depression, somatization), Trauma Symptom Checklist (TSC-40; anxiety), and Recent Physical Symptoms Questionnaire (RPSQ; somatization). Sensory testing in the descending colon was then performed using two paradigms. First, the Ascending Methods of Limits (AML) protocol involved 30-second phasic distentions that progressively increased in 2mmHg steps. The AML threshold was equal to the pressure which produced moderate pain (or urge). Then, the Sensory Decision Theory (SDT) protocol involved twenty-four 30-second phasic distentions that were presented in an unpredictable order (30mmHg, 32 mmHg, and

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34 mmHg). The subject rated the intensity of each stimulus on a six-point scale and decision theory was used to compute the P (A) and B values.

We found that compared to healthy controls, IBS patients had a lower AML pain threshold [median: 28mmHg vs. 40mmHg; p=0.0002], similar pain neurosensory sensitivity [42.6% of IBS patients vs. 42.9% of healthy controls had P (A) >0.5 (chance); p=0.98], and higher perceptual response bias [1/B: 0.25 vs. 0.19; p=0.003]. There was a strong inverse correlation between AML pain threshold and perceptual response bias to pain (1/B) [r=-0.67 p<0.0001] and a non-significant, inverse correlation with neurosensory sensitivity (P (A)) to pain [r=-0.13; p=0.14]. There were modest correlations between pain perceptual response bias (1/B) and BSI global score [r=0.18; p=0.035], BSI somatization [r=0.26; p=0.001], and TSC-40 anxiety [r=0.29; p=0.001].

There were similar findings with regards to urge. Compared to healthy controls, IBS patients had a lower AML urge threshold [median: 18mmHg v. 34mmHg; p=0.002], similar urge neurosensory sensitivity [63.1% of IBS patients vs. 46.4% of healthy controls had urge p (A) >0.5 (chance); p=0.10], and a higher perceptual response bias [1/B: 0.33 vs. 0.24; p=0.006] (table 2). There was a strong inverse correlation between AML urge thresholds and response bias to urge [r=-0.68; p<0.001] and a weak, significant inverse correlation with neurosensory sensitivity to urge [r=-0.22; p=0.002].

In conclusion, we found that lower pain thresholds in subjects with IBS are due to increased perceptual response bias rather than increased neurosensory sensitivity: colonic sensitivity in IBS is due to psychological factors rather than biological factors.

Genetics of Irritable Bowel Syndrome

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Tope Keku

IBS affects approximately 45 million Americans, roughly 10-15 percent of the US population. It is associated with indirect health care cost of about 20 billion dollars. It is characterized by symptoms such as cramping, pain, bloating, gas, diarrhea and constipation. Symptoms result from altered interactions between the gut, brain and nervous system leading to dysregulation of functions. IBS overlaps with other somatic and psychological disorders such as fibromyalgia, temperomandibular joint disorder (TMJ,) and chronic fatigue syndrome. It is predominantly a functional disorder with no known underlying structural abnormalities. A conceptual model for IBS shows how genetics and the environment affect psychosocial factors (coping, social support, stress) and physiology (motility sensation, inflammation, altered flora) and, in combination, result in IBS (symptoms, behavior).

With regard to the genetics of IBS, we know that IBS tends to cluster in families and that there is a higher concordance for IBS diagnosis in monozygotic (identical) twins compared to dizygotic (fraternal) twins. This may reflect a combination of genetic and environmental factors. Serotonin antagonists are among the IBS treatment options. Serotonin is an important neurotransmitter released by enterochromaffin cells in the gut, and it regulates gut motility and sensation. Elevated serum levels are found in IBS patients. Polymorphisms in serotonin transporter genes regulate serotonin reuptake from the synapse and influence the clinical response to serotonin antagonists used to treat IBS, particularly IBS-D. The SERT short-allele polymorphism is less common in IBS-C. There are inconsistent reports in the literature and a problem with small study samples. Studies with a larger sample size are necessary.

The aim of our study is to evaluate the association between genetic variants in key IBS-related pathways and IBS diagnosis or subtypes. We hope to generate preliminary data to secure additional funding for a larger study. Working with several collaborators, we have access to 774 IBS patients and 547 controls and will investigate the following IBS-related pathways: Inflammation (IL-10, TNF- a), Serotonin (SERT), Norepinephrine (a and β Adrenergic receptors), Dopamine receptors, and G protein translation (GN β3).

The Effect of the Atkins Diet on Diarrhea-Predominant IBS: A Prospective Pilot Study

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The prevalence of IBS in adult U.S. population is 10-15 percent. Despite the disorder being so common, relatively little is known about diet and IBS. Observational studies demonstrate patients identify foods as triggers. In one study, 209 (63%) of 330 IBS patients related GI symptoms (abdominal pain, bloating, etc.)to meals. Foods rich in carbohydrates, as well as fatty foods, coffee, alcohol and hot spices were most frequently reported to cause symptoms. However, there is very little published data on which to base dietary recommendations or guidelines. Some elimination diets suggest a role for carbohydrate ingestion. There is only anecdotal evidence on the effect of a very low carbohydrate diet in IBS, but this evidence suggests it may be specific for IBS-D. There is evidence for a role related to the post-prandial release of 5-hydroxytryptamine (5-HT, i.e. serotonin) in IBS, but it is unclear how diet may affect this release. 5-HT is a significant mediator of intestinal motility and sensation. Tegaserod, a 5-HT4 agonist, has been shown to increase gastrointestinal motility and has been effective in the treatment of patients with IBS-C. Alosetron, a 5-HT3 antagonist, was shown to improve symptoms in patients with IBS-D.

Study questions for the pilot study were: (1) Does a very low carbohydrate diet improve the symptoms (abdominal pain, stool frequency and consistency) associated with IBS-D and does it improve quality of life? (2) If a very low carbohydrate diet does improve symptoms of IBS-D, is this effect mediated through alterations in post-prandial release of 5-HT? The study will enroll 30 individuals with at least moderately severe IBS-D. Symptoms (abdominal pain, stool frequency and consistency) related to their IBS will be assessed for 2 weeks on a standard carbohydrate-rich diet followed by 4 weeks on a very low carbohydrate diet. We will also measure the post-prandial release of 5-HT and 5-HIAA in response to both carbohydrate-rich and very low carbohydrate test meals. Inclusion criteria are: (1) age 18-70 years old, male or female; (2) meets Rome II Criteria for IBS-D; (3) body mass index > 25 kg/m2; (4) desire to use a very low carbohydrate diet for weight loss; (5) score of > 36 on the FBDSI; (6) ability to understand consent form, and; (7) in stable health by screening

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history, physical examination performed by a study physician, laboratory tests (normal kidney function tests, liver tests, cholesterol panel, and negative celiac serology). Exclusion criteria are: (1) history of IBD; (2) history of any GI surgery that preceded the onset of IBS symptoms; (3) pregnancy or breastfeeding; (4) diabetes requiring medications; (5) chronic narcotic use for any reason; (6) use of any weight loss medications; (7) any chronic/unstable diseases that may put the subject at increased risk from the intervention; and (8) any of the following baseline abnormalities: (a) Cr >1.5 in men or >1.3 in women; b) AST > 2 times the ULN or T. bili >1.6mg/dL; c) Blood pressure > 160/100 mm Hg; d) fasting triglycerides > 600 mg/dL.or e) LDL > 190. Antidepressants are allowed if the patient has been on a stable dose for at least 4 weeks.

The study duration is 6 weeks: 2 weeks of a standard carbohydrate-rich diet, followed by 4 weeks of very low carbohydrate diet (pre-post design). GCRC nutritionists will conduct nutrition screening questionnaires to assess ability to adhere to diet, food preferences, and exercise habits. All meals will be prepared for the participants by the GCRC during both phases of the study. Carbohydrate diet: 55% carbohydrates, 30% fat and 15% protein. Fiber content per recommended daily allowance from U.S. Dietary Guidelines. Very low carbohydrate diet: 4% carbohydrates, 51% fat, and 45% protein. Carbohydrates will be limited to 20 grams/day. Participants will complete several questionnaires: (1) Functional Bowel Disorder Severity Index (FBDSI), (2) Demographic/Medical History (DEM/MED), (3) IBS-Quality of Life (IBS-QOL), (4) Sickness Impact Profile (SIP), (5) Daily Diary Cards, (6) Weekly Assessment of Adequacy of Relief, (7) Treatment Efficacy Questionnaire (TEQ).

The primary outcome measure is "Adequate IBS Symptom Relief" (Yes or No); a responder is defined as a person who scores "yes" on at least two of four weeks of the treatment trial. Secondary outcomes are: (a) change in post-prandial release of 5-HT, (b) change in IBS-QOL score, (c) change in stool frequency and consistency, (d) average daily abdominal pain rating, (e) change in weight/BMI, (f) change in Sickness Impact Profile, and (g) Treatment Efficacy Questionnaire score. Data analysis will include the following: Univariate analyses of race, gender, age, and BMI will be calculated to characterize the study population. Paired t-tests will be used to analyze changes in the SIP, IBS-QOL, and post-prandial release of 5-HT. Appropriate adjustments will be made for repeated measures. Regression analysis will be used to assess changes in average abdominal pain rating, stool frequency, and stool consistency.

State of the Art: Pediatric GI

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Carlo DiLorenzo

This is an exciting time in pediatric functional gastrointestinal disorders (PFGIDs). There is new pediatric data on the epidemiology of PFGIDs in primary care and subspecialty clinics, and new insights into the genetic predisposition for and pathophysiology (visceral hyperalgesia, changes in tone, gastrointestinal transit, rectal compliance) of these disorders. Animal models of early life stress have been described, and there are new diagnostic techniques (barostat, nuclear medicine, water load test). There are also new studies on the impact of these disorders on quality of life and treatment outcomes.

The pediatric FGIDs are common: (1) 20% of 4-month old infants regurgitate at least four times/day; (2) infant colic affects 5-19% of infants; (3) cyclic vomiting affects 1.9% of school age children; (4) aerophagia affects 9% of the institutionalized mentally disabled population; (5) functional dyspepsia affects 5-20% of school age children; (6) IBS is found among 14% of high school children; (7) abdominal migraine affects 1-2% of children; and (8) fecal incontinence affects 2% of 11 year olds. PFGIDs are prevalent not only in the United States but in other countries, as well. It is also clear that pediatric Recurrent Abdominal Pain (RAP) has adult outcomes. In a UK cohort of adults born in 1946, 2% had abdominal pain at age 7, 11 or 15. RAP was associated with an increased risk of a psychiatric disorder, but was not associated with an increased risk of abdominal pain or headache after controlling for presence of a psychiatric disorder.

Why do children develop a FGID? One theory is genetic predisposition. In a study of 6060 twin pairs, concordance for IBS was significantly greater in monozygotic (17.2%) than in dizygotic twins (8.4%). However, logistic regression analysis showed that having a mother or father with IBS was an independent predictor of IBS status and was a stronger predictor than having a twin with IBS. Early life events have also been identified as possible causes of PFGIDs. Previous studies suggest: (1) neonatal maternal separation results in stress-induced visceral hyperalgesia in rats; (2) severe IBS in adults is associated with a history of abuse in childhood; and (3) gastric suction at birth is associated with long-term risk for FGID in later life. Finally, there is the

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issue of psychiatric disorders. In a study of pediatric chronic abdominal pain (CAP) in primary care, there was a statistically significant difference between CAP patients (n=24) and controls (n=38) with regard to depressive disorder, anxiety disorder, internalizing disorder, and externalizing disorder.

How do we make a diagnosis of PFGID? Is there a biologic marker? If we use rectal barostat testing, studies have shown that only 60-70% of patients with IBS have visceral hyperalgesia. This procedure is also invasive and expensive, and provides questionable specificity. SPECT imaging provides a method of assessing gastric emptying, but it is not available in most centers. Another technique is the water load test. In a validation of the water load test as a symptom provocation test for laboratory studies of abdominal pain in children, 100 children with CAP and 120 healthy school children were studied. The pain patients completed questionnaires describing symptoms associated with their typical abdominal pain episodes. The water load test produced significant increases in the children's GI symptoms, which were similar to their naturally occurring GI symptoms. Moreover, pain patients reported significantly greater increases in GI symptoms as compared to well children.

The Rome III criteria for PFGIDs cover infant regurgitation, infant rumination syndrome, cyclic vomiting syndrome, infant colic, functional dyspepsia, irritable bowel syndrome, functional abdominal pain, abdominal migraine, aerophagia, adolescent rumination syndrome, functional diarrhea, infant dyschezia, functional constipation, and non-retentive fecal incontinence. However, the sensitivity and specificity of the Rome III criteria for pediatric FGIDs has not yet been established. In a study of 213 children with encopresis and 198 children with defecation disorders, 16% of the patients fulfilling the pediatric constipation criteria were not recognized by the Rome constipation criteria. In another study on inter-rater agreement, the percentage of agreement coefficient was 45%, and anything less that 70% agreement is considered inadequate.

What are the treatments for pediatric FGIDs? It is important to understand that children are different from adults; they need to be seen as a unit with their parents and issues of how to interview them and of parent "enmeshment" have to be considered. Mothers of children with CAP have been found to have higher levels of anxiety, depression and somatization symptoms, and parental anxiety, as well as physician insecurity, which may determine the extent of the diagnostic work-up ("my aunt had exactly the same symptoms and…"). Traditional treatments for children include: anticholinergics for abdominal pain and bloating; acid suppression for abdominal pain; serotonin agents for altered stool form, altered stool passage and urgency; and bulking agents for all of the above except bloating and only rarely for abdominal pain. Tricyclic antidepressants and serotonin reuptake inhibitors are also used for abdominal pain, but rarely. In one study, the combination of PEG plus

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tegaserod was more effective than PEG alone for treating constipation-associated IBS in adolescents. However, the quality of evidence for all of these is problematic. Cognitive behavioral therapy (CBT) in children and their parents may prove to be an effective alternative or adjunct to traditional treatments for pediatric CAP. Children and mothers who were taught coping skills had higher rates of complete elimination of pain and fewer relapses at 6 and 12 months. In another study, the CBT treated group improved more quickly, children returned to school faster, and a larger group was pain-free after three month. In an interesting therapy analog study, Walker and colleagues used a water load test to provoke symptoms in children with CAP and then instructed the mothers of these children to show "sympathy" or to distract the child. The children in the distraction conditioned mentioned their pain significantly less than the group who were shown sympathetic attention. However, all of the mothers believed "distraction" had a greater potential for negative impact on their children, suggesting they might be reluctant to respond to the child's pain in this way.

For encopresis associated with constipation, there is good evidence that laxatives such as PEG can improve symptoms. However, as the child ages, laxatives are used less often and appear to be less beneficial. Fortunately, however, beginning around age 9 there is a steady improvement in this condition. Non-retentive fecal soiling is challenging to treat, but it also improves with age and has resolved in 90% of children by age 9.

Medical Presentation of Abdominal Pain and Co-morbid Diagnoses from Childhood to Adulthood in a Population-based Birth Cohort

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Denesh Chitkara

Functional abdominal pain (AP) in children is a common disorder that accounts for a high proportion of visits to pediatric practitioners. Both children and adults who present with abdominal pain frequently present with other somatic pain conditions such as back pain, headache and limb pain. In addition, psychological conditions such as anxiety and depression are also frequently observed in children and adults with chronic, functional, recurrent abdominal pain. These conditions have been referred to as co-morbid diagnoses that occur with functional abdominal pain. However, the pattern of medical presentation for functional abdominal pain and these somatic and psychological conditions, as well as maternal factors that may influence the presentation for abdominal pain and co-morbid conditions from childhood to adulthood, remain unknown.

To examine this, we utilized a birth cohort of all children born between January 1, 1976 and December 31, 1982 to mothers residing in Olmsted County, Minnesota. The vital status for each member of the birth cohort was confirmed retrospectively using medical, school and Department of Health records. It was determined that of the individuals who resided in the area at 5 years of age, 80% continued to stay in the community until age 19. (The medical records of all individuals living in Olmsted County who do not deny research authorization are available for retrieval for research purposes using the database of the Rochester Epidemiology Project (REP). The REP collects all diagnoses made within Olmsted County medical facilities, which include Mayo Clinic and Olmsted Medical Center. This enables tracking of all medical encounters of the individuals, as the area is relatively geographically isolated. Previous studies have demonstrated that Olmsted County medical facilities provide 98% of the healthcare to residents.) This resource was used to search for diagnoses using the Mayo Clinic adaptation of the international classification of disease diagnostic billing codes (HICDA codes) of all birth cohort members who had previously presented with symptoms of abdominal pain of unknown origin. In

addition, HICDA codes for all birth cohort members with somatic (back pain, head ache, limb pain) and psychological (anxiety and depression) conditions were also examined.

Of the 5347 birth cohort members, 1358 or 25% of the population had a medical visit for abdominal pain between 5 and <21 years of age. 60% had one visit only, while the remainder had multiple visits for AP. Children who presented with AP were significantly more likely to present for each of the co-morbid somatic and psychological conditions examined. Children were just as likely to first present for either AP or the co-morbid condition, and the average time between the diagnoses was approximately 5 years. The risk of presenting for each of the somatic co-morbid conditions appeared to increase with individuals who had multiple presentations for AP compared to controls who had no visit for AP. Furthermore, the risk of presenting for each of the psychological conditions examined appeared to increase in individuals with multiple presentations for AP.

Since children are usually brought to medical care by their parents, we examined if maternal functional bowel disease presentation (FBD) was associated with the presentation for AP and somatic and psychological conditions in their children from childhood to adulthood. We determined that 47% of mothers of children who presented with AP presented with FBD, compared to 31% of mothers of children who did not present with AP. We also found that a child's likelihood for having a mother with a FBD diagnosis from the time their child was between birth to <21years progressively increased as the number of medical visits for AP increased in the child (compared to children with no visit for AP).
The child's likelihood for presenting for AP and each of the somatic and psychological conditions seemed to increase in the mothers with a FBD presentation. The odds of a child with AP having a visit for each of the somatic and psychological conditions who had a mother with a FBD diagnosis is significantly greater compared to a children without AP (with odds ratio ranging from 2.7-4.6). The odds of a child with AP having each of the somatic and psychological conditions who have a mother with a FBD diagnosis remained significantly high even when compared to children who presented with AP without a maternal FBD diagnosis (odds ratio ranged between 1.3-1.7).

This preliminary study suggests that childhood AP is associated with the presentation of somatic and psychological co-morbid presentation from childhood (age 5) to early adulthood (<21 years of age). Maternal FBD presentation and childhood AP presentation frequently co-occur. Maternal FBD is associated with co-morbid medical complaints in the child who presents with AP. Future studies will involve examining additional childhood risk factors that may contribute to the manifestation, medical presentation, and direct and indirect medical costs of adults with functional gastrointestinal disorders.

Mechanisms for the Intergenerational Transmission of Functional GI Disorders

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Rona Levy

There is a 10 year history of collaboration between Dr. Levy's research group at the University of Washington and the UNC Center. Dr. Levy reviewed the published studies that have resulted from this collaboration. The first study included 631 children of parents with IBS (fathers included) and a control group of 646 children of parents without IBS. This study showed that children whose parents had IBS were more likely than control children to be brought to the doctor for gastrointestinal symptoms. This was interpreted as supporting a social learning mechanism for the intergenerational transmission of illness behavior. The children of IBS parents also incurred more health care visits and more health care costs for non-gastrointestinal symptoms.

A limitation of the first study was that parents decided whether to bring the child to the doctor, so it was possible that the increased utilization of health care by the children of IBS parents was not related to the symptom complaints of the children. To address this concern, we obtained a grant (RO1 HD36069) and carried out a second study in 296 children of 208 mothers with IBS and a control group of 335 children of 241 mothers without IBS. Children were interviewed separately from parents regarding symptoms. Visits and health care costs from automated records were analyzed. This study showed that case children reported more severe gastrointestinal symptoms when interviewed separately from their mothers. This shows that the children of IBS parents exhibited illness behaviors independently of their parents.

In another study, evidence of social learning of illness behavior was studied using data on twins and mothers of twins. The concordance for IBS diagnosis was greater in monozygotic twins than in dizygotic twins ($p=.03$), supporting a genetic contribution to IBS.—the risk of developing IBS was increased by about 9% for monozygotic twins if one twin had IBS. This study also showed that the concordance for IBS diagnosis between mother and child was as great as the concordance in monozygotic twins. This finding could not be explained by shared genes and was interpreted as evidence for

a social learning contribution to illness behavior. Thus, there appears to be a strong social learning component to the manifestation of gastrointestinal disorders.

Illness behavior (IB) refers to the ways people perceive and react to somatic sensations that may be associated with disease; it is on a continuum ranging from denial to over-reaction. Research on IB focuses on excess somatic complaints and disability. Our research investigates whether social learning is the mechanism accounting for increased illness behavior in the families of patients with IBS. Specifically, we investigated whether children of parents who are more solicitous experience more severe gastrointestinal symptoms? We found that a child's perception of the seriousness of stomachaches is related to parental reinforcement of illness behavior. Reinforcement and modeling of illness behavior increase school absences for stomachaches as well as medical clinic visits for stomachaches. We inferred that higher levels of parental solicitousness in response to their children's illness behavior appear to be related to higher levels of children's symptoms.

Three new papers arising from this collaboration were recently accepted for publication. The first is titled "Decision to take a child to the clinic for abdominal pain is related to maternal psychological distress." The objective in this study was to determine the relative contributions of the mother's psychological symptoms, the child's psychological symptoms, severity of the child's abdominal pain, and family stress, to the decision to consult a doctor for the child's abdominal pain. The study participants included 275 mothers of 334 children who had abdominal pain in the past two weeks, as per child self-report. The sample included 39 children who had been taken to the clinic for GI symptoms at least once in the past 3 months (consulters) and 295 who were non-consulters. Mothers completed the following questionnaires: (1) SCL-90R subscales for depression, anxiety and somatization in themselves, and (2) the child's self-reported school absences, medication use, and the Child Behavior Checklist. Children also completed the Pain Beliefs Questionnaire to assess perceived pain severity. Logistic regression analyses revealed that both the child's self report of perceived pain severity and maternal psychological symptoms predicted consultation ($p < .01$). Although children who consulted physicians had significantly more psychological symptoms, this was not a significant predictor of consultation after adjusting for maternal psychological symptoms. Family stress did not predict consultation. The decision to take a child to the clinic for abdominal pain is best predicted by maternal psychological distress and the child's perceived pain severity.

The second in-press paper is "Validation of a measure of protective parent responses to children's pain." The objective was to assess the validity of the Protect Scale of the Adult Responses to Children's Symptoms (ARCS) Questionnaire with regard to mothers' responses to their children's abdominal pain. Mothers with High ($n = 32$) and Low ($n = 35$) Protect scores on the ARCS questionnaire were recruited from

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participants in a larger study of family illness behavior. Mothers completed a 28-day diary report of responses to their children's abdominal pain episodes. Records of their children's annual health service utilization and costs were obtained from their health maintenance organization (HMO). The results showed that mothers' scores on the ARCS Protect Scale were significantly correlated with their subsequent diary reports of protective responses to their children's abdominal pain (rho =.614, p<.001). Compared to children of mothers in the Low Protect group, children of mothers in the High Protect group made significantly more health care visits for gastrointestinal symptoms (Z=1.956, p=.05; 0.14 + 0.43) and had significantly higher GI health care costs (Z=1.956, p=.05; $16.47 + $53.18 per year). Results supported the validity of the Protect Scale of the ARCS and demonstrated that mothers' protective responses to children's abdominal pain complaints at home predicted subsequent health service use for gastrointestinal symptoms.

The third in-press paper is "Predictors of maternal protectiveness in response to children's abdominal pain symptoms." There are established links between parental protectiveness and symptoms, reduced activity, and disability. Protectiveness, also termed solicitousness, means supporting and encouraging illness behavior. This study sought to examine demographic and psychosocial predictors of protectiveness. 450 mother/child dyads were included in the study. Questionnaires completed by mothers included: (1) Adult Responses to Children's Symptoms, to measure protectiveness -- "When your child has a stomachache, how often do you let him/her stay home from school?" (2) Pain Beliefs Questionnaire, to measure perceived symptom severity -- "My child's stomachaches mean s/he has a serious illness". (3) Symptom Checklist 90 (mother's psychological distress). (4) Child Behavior Checklist (child's psychological distress). Significant predictors of maternal protectiveness were: (a) male child gender, (b) maternal non-Caucasian race, (c) maternal lower educational status, (d) no father in the home, (e) perceived symptom severity, and (f) the interaction between child gender and perceived severity. The implications are that physicians and nurses should be aware when risk factors for protectiveness exist and, where appropriate, encourage parents to maintain normal child responsibilities (school, household chores). Clinicians might recognize that a non-Caucasian, less educated or single mother, for example, or a mother who perceives her child's condition as severe or damaging, is at greater risk for solicitousness.

We were able to competitively renew RO1 HD36069 to carry out an intervention study based on the results of our earlier mechanistic studies on social learning in recurrent abdominal pain. This study compares cognitive behavior therapy (CBT) to an educational placebo intervention.

Parental Worries about Recurrent Abdominal Pain

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Miranda Van Tilburg

Functional gastrointestinal disorders (FGIDs) run in families and this appears to be partly due to social learning of inappropriate illness behaviors. However, there is often miscommunication between parents and medical care providers with regard to how and why parents respond in certain ways to their children when they do not feel well. Within this context of miscommunication, physician recommendations to parents about parental responses -- such as focusing less on the child's symptoms -- can foster a belief that the doctor does not understand the child or his/her symptoms. It can also lead to poor adherence to medical advice and/or (self) referral to other physicians.

This obstacle to effective interventions for children with FGIDs might be overcome if we could identify the fears and beliefs of parents that motivate reinforcement of illness behavior. This understanding would allow us to address parental concerns rather than their behaviors. Acknowledging parental worries and explaining why these fears may not be rational could be far less threatening to parents than showing disapproval of their health behaviors. To date, there is no data on the specific fears and worries of parents associated with reinforcement of inappropriate illness behavior.

The aims of the study were: (1) to determine the primary parental worries surrounding chronic abdominal pain in children that are associated with reinforcement of inappropriate illness behavior and (2) to develop and validate a questionnaire assessing these worries.

To address the first aim, we interviewed 15 parents of children suffering from chronic abdominal pain (CAP) of functional origin to determine parental fears, worries and cognitions about CAP. Six domains of parental worries or perceptions were identified: (1) cognitions about CAP that revolve around their fear of a disease, (2) desire for diagnosis and effective treatment; (3) worries about the pain and the effects of pain on their child's life, (4) perception of their children as not complaining easily, (5) feeling helpless in knowing how to deal with the child's suffering, and (6)

exacerbating factors such as heredity, stress and eating habits.

Based on the findings from these interviews, 51 items were developed for a Parental Worries of Abdominal Pain questionnaire (PAWAP). We then sought to determine the dimensions of worrying about CAP and to reduce the number of items in the PAWAP. An online sample of 537 parents (94.8% mothers) of children with CAP (3-18 yrs, M=8.3; 66.3% girls) completed the 51-item questionnaire. "Understandability" (on a 5-point scale) ranged from 4.29 to 4.92. Although some items were somewhat positively or negatively skewed, all items had minimums and maximums of 1 and 5 similar to the 5-point scale. There was no kurtosis. Thus, there was no basis to delete items on grounds of understandability or skewness.

Principal Component Analyses yielded four factors: (1) Fear of Ignoring pain – focused on the meaning of symptoms (10 items, Cronbach's alpha Cα=.77); (2) Desire for Care -- dealt with a need for and frustration with physician care (8 items, Cα=.86); (3) Worry about Coping -- expmressed coping difficulties with the child's stomachaches (8 items, Cα=.75); and (4) Exacerbating Factors -- such as stress and family (5 items, Cα=.63).

To determine concurrent validity of the PAWAP, worries of families who consult a physician (CF) were compared to worries of families who do not consult a physician (NCF) for their child's abdominal pain. In the online sample, CF (N=147) scored higher on the "Fear of Ignoring Pain" and "Desire for Care" subscales as compared to NCF (N=390). These analyses were replicated in a community sample. From among 566 middle school children in North Carolina, 81 children were identified as suffering from CAP and matched on age and gender with 36 pain-free children (PFC). CAP subjects scored higher on the "Worry about Coping" and "Exacerbating Factors" subscales than PFC. Consulters (N=41) scored higher on the "Desire for Care" and "Fear of Ignoring Pain" subscales as compared to non-consulters (N=40).

To determine predictive validity, we explored whether worries as measured with the PAWAP were associated with reinforcement of illness behavior as measured by the Adult Response to Child Symptoms questionnaire (ARCS). "Fear of Ignoring Pain" and "Desire for Care" of the PAWAP correlated significantly with "Monitoring & Distracting" and "Solicitousness" of the ARCS. Significant correlations were also found between "Worry about Coping" and "Monitoring & Distracting" as well as between "Exacerbating Factors" and "Minimizing".

Although we found that the PAWAP possessed good concurrent and predictive validity, we concluded the face validity of the scale was low, since fear of underlying disease is not a separate subscale. We therefore explored hypochondriacal concerns of parents about their child's health in a new sample of 134 consulting versus 43 non-consulting families recruited on-line. We developed a new questionnaire -- the Illness Attitude Scale (IAS) by Proxy -- which was derived from the original IAS and

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measured concerns not about one's own health but about one's child's health. Contrary to our hypothesis, Health Anxiety was similar in consulters and non-consulters. When we tested 6 of the 11 Health Anxiety items that focus on disease conviction, we found that consulting families did not differ from non-consulting families on worry about: (1) child's health, (2) pain being caused by a serious illness, (3) cancer, (4) heart disease, or (5) another serious illness. The only item differentiating the two groups was a worry about a physical disease. These findings suggest that parents may be sufficiently reassured that their child's symptoms are not caused by a serious disease like cancer but may continue to worry about a relatively benign condition, such as lactose intolerance.

In conclusion, initial tests reveal good reliability and validity of the PAWAP. The number of items was reduced by almost half to 31. The PAWAP provides an opportunity to address parental fears rather than behavior in clinic and therapy. Several studies are currently underway to further validate the PAWAP. In collaboration with Dr. Rona Levy, we are assessing whether cognitions as measured by PAWAP change after cognitive behavioral therapy aimed at reducing parental reinforcement of illness behavior. In collaboration with Dr. Nader Youssef, we aim to determine differences in parental worries between mothers and fathers, as well as parental worries about organic as compared to functional chronic abdominal pain.

Notes

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