

## Treatment of Functional Bowel Disorders

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Good morning. Let's get started.

Now, when we have abstracts, they are really kind of a "promise." We have to go to the oral presentations or to the posters to ask some of the tough questions, to really find out if is this something that's really going to help us take care of our patients. I'm going to use evidenced based medicine o evaluate the studies. The reference for this is *JAMA* 1994; 270:2598. There's also a monograph called Evidence Based Medicine and one of the editors is Gordon Guyatt from McMaster. These are really great teaching tools for when you are working with medical students, residents, and fellows. I've also found it to be very helpful as I review the medical literature in deciding whether or not this is a study that's worth considering. So, these are some of the criteria we're going to look at. While the study does not have to meet all the criteria, you have to ask, "Is there enough evidence here for me to support this study and potentially apply it to my patients?"

First of all, were the patients randomized? Were all the subjects accounted for at the end of the study? Do we know what happened to all 100 patients that were initially enrolled? Was the follow-up complete? Were the individuals analyzed in the group that they were originally assigned to or did they crossover halfway through because they didn't respond to the initial treatment? Was it blinded? Were the patients blinded? Were the persons administering the therapy, the medicine, the endoscopy blinded to what was going on? Sometimes that's not possible, but if it is possible, that certainly increases the validity of a particular study. When it was analyzed, were the people who did the analysis blinded as to groups that people were assigned to? Were the groups similar in every other respect except for the experimental interventions? Were they approximately the same age, same gender, same disease severity? Besides the intervention, did they have equal treatment? As we take a look at some of the studies today, especially when looking at things like cognitive behavioral therapy, we have to take a look at the amount of attention or time that an individual gets when comparing between therapies, because it may be that the amount of time spent with the individual rather than the specifics of the therapy itself was what was beneficial. Then finally, we take a look at the results. And with the results, we want to take a look at the magnitude of the treatment effect. Is it something that's clinically significant? Just because it's statistically significant doesn't mean that something is going to be clinically significant in my practice. The other thing we take a look at is how precise were those results? We typically take a look at confidence intervals, often the 95% confidence interval, but we can also take a look at the standard deviations or the standard errors and say, what's the balance in the study? What would be the least amount of effect that I might get? What would

be the most, compared to what the actual results were? Then, what does it mean? Will these results help me care for my patients? Are my patients similar to the entry criteria that patients are randomized? Sometimes the patients are so clean that they can't be taking certain medications, they can't have certain other diseases and if that's not what's true with your patient population, then it may or may not be as helpful applying it to yours. Were all clinically important outcomes considered? What's most important in a particular disease process? Is it global subject improvement? Is it the constipation and bowel habit? Is it the abdominal pain? What were the positive results? Were those relevant outcomes? If some results were or weren't significant, what does that mean when I take care of my patients? Finally, is the treatment worth the potential harm? No matter what our treatments are, there's always the potential for harm or adverse outcomes. The harm may just be cost or out of pocket expense. But that is a harm for our patients if we're asking them to use certain therapies that may not be as beneficial for them. So, as we take a look at some of these abstracts today, these are some of the criteria that we'll take a look at.

***Abstract 211113: “A randomized controlled trial of therapist-administered vs. minimal-therapist-contact cognitive behavioral treatment for moderate to severe IBS”***

This is by Jeffrey Lackner and colleagues. We know with irritable bowel syndrome that we're incredibly challenged regarding treatment options. We have a few treatments that are available now that appear to be efficacious, but there are still many of our patients who may benefit from this intervention. Cognitive behavioral therapy and hypnotherapy have been shown in good quality studies to benefit patients with irritable bowel syndrome in both the short term and in the long term. However, in the United States, this has not been widely applied or widely accepted. There are a variety of reasons for this. One is that it is costly. Many insurance carriers do not cover this. Secondly, it is time intensive. It is difficult not only to go to your therapy session, but also to do the homework that they ask you to do at the therapy session. This study looked at less intensive cognitive behavioral therapy to see if it is also effective. The authors' aim was to develop and test the feasibility of a behavioral self-management treatment that's less costly, more transportable, but retains the efficacy of the standard cognitive behavioral therapy. They studied 59 patients with irritable bowel syndrome, randomized to one of three groups, each 10-week programs. The first group was a 10 session “manualized” Standard Cognitive Behavioral Therapy. They had manuals and they followed through this manual as they went through each of these sessions. It was consistent from subject to subject. The next group was a four session, “manualized” minimal contact cognitive behavioral therapy. This was a program developed by Dr. Lackner that was taught through a self-study workbook. Then, there was a group that was wait listed. When you're doing behavioral interventions, a wait list is commonly used as a placebo because when you're on the wait list, you're not expecting any improvement. The wait list then gets rolled into the study. They did assessment of their symptoms at the end of the wait list period and then they randomized them one to one into therapy after that. I would like to point out some of the pros and cons of the study design. The primary endpoint was the standard one used in functional bowel disorders which was the adequate relief of pain, adequate relief of GI symptoms, and global rating of IBS symptom improvement. They also looked at a variety of different symptoms. They used an intention to treat analysis, a very robust method of taking a look at the results. Intention to treat analysis means that if you were assigned to a group where you had 10 sessions, but you only attended 2 sessions, you were still analyzed as though you were part of that group. You were not dropped out of the study. This is different from a per-protocol analysis, which meant the patient followed exactly the study design in order to be analyzed at the end. Again, intention to treat analysis makes it a little more “real life.”

Both cognitive behavioral therapy versions were superior to the wait list, with moderate to substantial improvement in irritable bowel symptoms. The standard cognitive behavioral therapy had 74% improvement and the minimal contact had 73% improvement in global symptoms and adequate relief of pain, which is quite impressive. There was 0% improvement on the wait list. There was 68%

improvement in the standard cognitive behavioral group, the minimal contact group had 64% improvement and again, 0% in the wait list for GI symptoms. The minimal contact patients achieved significant improvement in quality of life, IBS symptom severity, distress and coping. They also did a cost-effective analysis and the minimum contact cognitive behavioral therapy was five times more efficient than standard cognitive behavioral therapy. This is potentially a very nice advance. The four session cognitive behavioral therapy was well tolerated, efficient, and clinically effective. The patients were randomized, had complete follow up, balanced and completely analyzed. However, the wait list group did not have equal treatment. The “placebo response” rate that we expect in functional bowel disorders can be as high as 40 and 50% which is a high hurdle if we want efficacy over placebo. So, this particularly study is showing a much greater response because it is compared to a wait list, instead of to another active control. The magnitude of the change therefore may not be quite as great as what we see in this initial study. Will the results help me care for my patients? Were the patients similar to my practice? This was moderate to severe IBS, so in my practice, yes. Were all clinically important outcomes considered? They did a good job of taking a look at clinical outcomes that I feel are important – quality of life, overall improvement, pain. Is the treatment of potential harm? That’s the lovely thing about cognitive behavioral therapy – true risk is very low other than the cost, which is reduced with minimal intervention. Do I have access to this treatment? Again, that remains the challenge. This is a program that was developed by Dr. Lackner so we don’t know yet if this is something widely available or if this is something that my behavioral therapist can give and apply to my patients.

This is clearly something that has been very challenging for us to incorporate into our practices. It is something we do need to consider and see what is available in our communities. If we do have access to a four treatment, minimal contact program, that would be very interesting. One study doesn’t mean that we should change our habits, but we know that standard cognitive behavioral therapy in well-done studies has been shown to work. There are different ways to provide this kind of therapy. I’ve even seen some studies that use web-based support and instant messaging, which is especially helpful in younger patients, so they know someone is out there who cares about them and will connect with them. I think we will have the opportunity in the next few years to see some advances. I can tell you that most of my 40, 50, 60 year old patients may not be quite as amenable to this sort of intervention, but it is exciting.

***Abstract 215072: “Effect of female sex hormone supplementation and withdrawal on gastrointestinal and colonic transit in postmenopausal women”***

This abstract is also on irritable bowel syndrome and constipation. One of the questions that always comes up is what are the effects of hormones on functional bowel disorders and on GI transit. Progesterone has been felt to increase constipation in pregnancy and it has also been shown to prolong gastric emptying, small bowel and colon transit during the luteal phase of the menstrual cycle. These changes have been relatively subtle and they have fallen for the most part within the normal range. This group wanted to evaluate the effects of acute administration 400 mg/day of micronized progesterone, 0.2 mg/day of estradiol (estrogen) alone and with the micronized progesterone, or placebo on GI motility. They used scintigraphic technique to take a look at gastric emptying, small bowel transit, and colon transit. They looked at 48 postmenopausal women (12 per group) and they looked at before and after treatment motility. They found that with the progesterone, there was shorter ascending colon emptying which resulted in accelerated overall transit, but no difference in the other endpoints. There were no changes in the transit endpoints with estradiol or with combination estradiol and progesterone. Progesterone and estradiol were associated with a looser stool consistency. This is different than what we have thought. We thought progesterone would be more likely to cause constipation. In contrast to popular opinion, in this particular study, progesterone actually accelerated colon transit.

This is a well-done physiologic study. The study group that they chose, postmenopausal women, does not address all of the patients that we see in our practice. They looked at objective endpoints and when you're doing studies in motility and functional bowel disorders, if you have a hard, physiologic endpoint, you are much more likely to show a statistical difference, than with symptoms. It's much more difficult to show differences in symptoms because you need large numbers of patients. They didn't report symptoms per se in this study and I wouldn't have expected to see a huge difference between them. When you have small numbers, having a hard physiologic end point is certainly helpful in looking for differences.

***Abstract 218572: "The effect of lipase supplementation on upper gastrointestinal symptoms and gastric myoelectrical activity induced by a high fat meal in healthy volunteers"***

Dyspepsia is common (20-30% of the population) and approximately 55% of these patients do exhibit gastric dysrhythmias. Therapeutic options are limited for this group especially if they do not respond to acid suppression. The authors of this study evaluated the effect of a high fat meal on upper GI symptoms and myoelectrical activity as measured by EGG (electrogastrogram), and they evaluated the effect of lipase supplementation on the same outcomes. They had 16 healthy volunteers, most of them male, which is common in functional dyspepsia. The mean age was 31. This was a double-blind, placebo controlled, crossover study in which the volunteers were given a high fat meal consisting of Pulmocare<sup>®</sup> (which has 55% fat). A capsule containing 280 mg of acid-resistant lipase or placebo were administered immediately before the meal was ingested. The order of the conditions was counterbalanced. They separated the visits by at least one week to try to minimize the carry over effect from one treatment to the next treatment. At each visit, they did a Visual Analog Scale to evaluate the symptoms of nausea, stomach fullness, hunger, bloating and abdominal discomfort. They did this at baseline, immediately after the meal and at 10, 20, 30, 45 and 60 minutes after the meal. The EGG was recorded throughout this time period assessing the gastric electrical activity. They found that nausea, bloating, and stomach fullness were significantly increased 10 minutes after the ingestion of the meal. Hunger was significantly decreased. There was a significant decrease in normal gastric myoelectrical activity and a significant increase in tachygastria at 10 minutes after the meal ingestion. The meal is doing everything they wanted it to do, mimicking some of the changes that we see in dyspepsia. What they found was that stomach fullness was significantly lower with lipase compared to placebo at 20 and 30 minutes after the meal but not at the other time points. Will the results help me care for my patients? Not yet. These were healthy volunteers. This is a hypothesis-generating abstract and we will probably see something in the future regarding this.

***Abstract 220741: "Safety and tolerability of the probiotic organism Bifidobacterium infantis 35624: Clinical experience and molecular basis"***

This is from Eammon Quigley's group. We know that irritable bowel syndrome is a difficult disorder to treat. There is a recurrent interest in the bacterial environment occurring in the gut and our attempts to manipulate it to try to alter symptoms. This group evaluated the tolerability and safety of the probiotic organism Bifidobacterium infantis 35624, so a very specific probiotic. They looked at data from two randomized, placebo controlled, double-blind trials. They included a four week dose ranging study in subjects with irritable bowel. They looked at  $10^6$ , versus  $10^8$ , versus  $10^{10}$  Bifidobacterium in subjects with irritable bowel syndrome. They included for safety reasons review of a one year study where they gave this probiotic to individuals who had altered gut mucosa – patients with inflammatory bowel disease, Crohn's disease, and ulcerative colitis. They also looked at the genome of the organism to see if there were any genetic features that would suggest pathogenicity. In the IBS study, 270 subjects were randomized to one of the three doses of the organism and 92 to placebo. Three hundred and thirty subjects completed the study. Seventeen withdrew for adverse events, however, it was equally distributed between the placebo group and the group receiving the probiotic. Most of them withdrew because their symptoms of IBS seemed to worsen. The overall adverse event rate between the different groups was

similar, though the incidence of severe adverse events was actually highest in the placebo group; treatment groups were 0, 1, and 2% versus 9% in the placebo group. In the IBD group, there were no instances of systemic or major organ system sepsis reported. From the genome analysis, they did not find any evidence that would suggest pathogenicity of these organisms. This study gives us additional information regarding the safety and tolerability of Bifidobacterium infantis 35624 in the short term in IBS patients but also the long term in susceptible patients who would be at risk for developing bacteremia and systemic sepsis. This is, again, an additional piece of information that may help us in choosing probiotics for our patients. Remember, a probiotic is not a probiotic. One of the abstracts in the additional reading section (223192) is a study that took a look at the effects of lactobacillus plantarum 299v and that particular probiotic has not shown any improvement in IBS. While we're all kind of familiar with, and a lot of our patients want to take lactobacillus, it really hasn't fared as well in the treatment of functional bowel disorders. An exception to that might be lactobacillus paracasei but the one that is most readily available, lactobacillus GG (it's in the United States and available in most pharmacies as a product called Culturelle) has not been shown to be beneficial in irritable bowel syndrome. Bifidobacteria appears to be one of the ones that results in symptom improvement. Remember that probiotics in the United States are not FDA regulated. They are considered a supplement. They are like food. They don't undergo a rigorous evaluation process as are other pharmacologic interventions. So we need to be careful about what we use.

Finally, we have a dose finding study. We're starting to identify what the bacteria are that are going to be most helpful to probiotics, what the doses are, and how they should be taken. This is being done by having rigorously well-controlled, double-blind, and randomized controlled trials. Eammon Quigley's group and Fergus Shanahan have really done quite a bit to try to help us in that regard.

The same species of bifidobacter is available in a product that's called Align<sup>®</sup> from Procter & Gamble. That's one that many of the private docs have been using. I've been looking at it prospectively in my patients, but I don't have the data yet. Anecdotally, I can say there are some patients who respond great, there are some patients that don't respond at all, but until you analyze the data at the end, you don't really know if it's really making a difference.

The advantage of lactobacillus GG is that it's not degraded by stomach acid. Lactobacillus GG has actually been proven effective in the pediatric population that take antibiotics because it reduces their post-antibiotic diarrhea. It may have some benefit in other disorders, but it doesn't appear to be beneficial to our patients with irritable bowel.

***Abstract 221015: "Predictors of premature antidepressant discontinuation in functional gastrointestinal disorders (FGIDs): A survival analysis approach"***

This abstract is from Ray Clouse's group at Washington University. One of the biggest difficulties in using tricyclic antidepressants or SSRIs is first of all getting patient buy in, and second of all getting the patients to tolerate the side effects. The tricyclics cause dry mouth, sleepiness, make patients feel a little foggy, and patients that have lots of symptoms tend to be the ones that are more likely to have the side effects. That's actually what Ray shows. He took a look at 173 consecutive patients that were being treated for a functional gastrointestinal disorder. Approximately 29% of these had irritable bowel syndrome. They did a systematic chart review and then did a survival analysis and logistic regression to try and identify which factors predicted premature discontinuation of antidepressants. What they found was not too surprising, but it does confirm that a high degree of somatization was present in 42%. If you have a lot of somatic symptoms, you're also likely to develop side effects when you take an antidepressant and then subsequently discontinue it. Interestingly, and this wasn't what that I would have predicted, male sex (odds ratio 2.8) predicted early discontinuation (CI 1.1-6.8; p=0.02). Although the odds ratio looks pretty good, the precision for that particular one is not great. In the logistic regression model, they

took a look at all these factors together. The only thing that really predicted poorer treatment outcomes was some somatization. Thus, patients who have lots of different symptoms are going to be more likely to discontinue their antidepressants. That may mean we need to spend a little bit more time educating or potentially trying a different therapy that isn't going to have those side effects. Cognitive behavioral therapy or hypnotherapy may be more appropriate for this particular patient group.

Now to progressively less controversial topics.

***Abstract 222021: “A 10-day course of rifaximin, a non-absorbable antibiotic, produces a durable improvement in all symptoms of irritable bowel syndrome: A double-blind randomized controlled study”***

This is from Cedars Sinai LA group including Mark Pimentel. Patients with IBS were randomized to rifaximin 400 mg or placebo TID for ten days. I'm not quite sure why, but they used Rome I criteria to identify IBS. That's not a huge criticism because some people would argue that Rome I is better at identifying IBS than Rome II, which is why we see some changes with Rome III. This was double-blind, randomized, and placebo controlled. They had a one week run in and did a symptom questionnaire that included diarrhea, constipation, bloating and abdominal pain, and they rated on a visual analog score from 0 – 100. The visual analog scale is one of the more standard ones that are used in functional bowel disorders. The reason for that is you have to have enough room for improvement. Patients want whatever the therapy is to work –whether it's placebo or active treatment, there's a tendency to rate up. There also tends to be a group in the middle. You like to have more room for improvement. Subjects were evaluated one week after completion by repeating the questionnaire. Subjects were followed for an additional nine weeks with weekly questionnaires and they took the overall 10-week period. They had two endpoints – the one-week period and overall for the 10-week period. Eighty-seven patients were randomized in the study – half to placebo and half to rifaximin. One week after rifaximin, 49% of the subjects demonstrated a clinical response with diarrhea, with more than 50% improvement compared to 24% on placebo ( $p < .05$ ). That's a very robust difference. Bloating was 35% versus 19% ( $p = 0.07$ ). This is not as great of a difference between the two, with a relatively low placebo response rate, but this may be a type II error due to small sample size. With the first endpoint, there was no difference in constipation or abdominal pain. When they took a look at the 10-week study, with the same marker of greater than 50% improvement, all four symptoms were statistically significantly improved including bloating (49 versus 22), diarrhea (51 versus 35), abdominal pain (40 versus 29), and constipation (35 versus 28). They showed that rifaximin treatment resulted in significant improvement in the four major symptoms of IBS for 10 weeks after completion of treatment.

There's a lot of confusion and controversy related to this area. Do these patients have small bowel bacterial overgrowth or an alteration in bacterial flora? We need more information and confirmatory randomized trials with rigorous methodology before we can embrace the expensive treatment. Until we have these and a better diagnostic test than lactulose breath testing, we should be careful.

***Abstract 222095: “Newer antiepileptic drugs for adults with cyclic vomiting syndrome (CVS): A novel approach to maintenance therapy”***

This is a hypothesis generating abstract. Cyclic vomiting syndrome is discreet episodes of nausea and vomiting with symptom free intervals. Approximately half the group also had abdominal pain, which is not uncommon. There are no randomized controlled trials but in prospective uncontrolled trials, you get some benefit with tricyclic antidepressants, however, there's a group that's refractory to this and gets side effects. Newer antiepileptic drugs (AED's) have been used in migraines. As there is some overlap between cyclic vomiting syndrome and migraine headaches AED's might be beneficial for this group.

The authors studied two of the antiepileptic drugs – Zonegran and Keppra in 18 patients with CVS refractory to tricyclics. Patients were treated for  $\geq$  three months and response to treatment evaluated on a 0-3 Likert scale. In this refractory group of patients who failed tricyclic antidepressant therapy, quite a few (72%) had moderate resolution of symptoms with near complete resolution in 44%. Only one patient was intolerant with side effects, which is pretty impressive. Again, hypothesis generating. I'm not going to start using these on my patients yet, but certainly would be willing to participate in a placebo controlled trial to see whether it is beneficial or not. Again, these are also expensive medications and they do require some degree of monitoring.

***Abstract 222711: “A dose-ranging, double-blind, placebo-controlled study of lubiprostone in subjects with irritable bowel syndrome and constipation (c-IBS)”***

This is by John Johanson and the Rockford private practice group. Lubiprostone has just been FDA approved for use in constipation. It is a type-2 chloride channel activator so it increases secretion into the gut. Approximately one third of patients get nausea and 8% of them discontinue the medication. We talked earlier about the somatic focus that many patients with IBS have and that would be one of the concerns, whether or not at this stage it would be appropriate for use in irritable bowel syndrome. This is a study that's looking not only at constipation, but irritable bowel syndrome with constipation. They did a dose ranging and 12-week study in individuals with IBS looking at placebo 8, 16, and 24 micrograms twice a day. They looked at electronic symptom diaries and found there was a dose-related increase in improvement in abdominal pain compared to placebo at months 1, 2 and 3. What was impressive was that there was a definite dose-related improvement in each dose that appeared to be maintained or actually enhanced at the three-month period. The highest improvements were with the highest dose group – the 48 microgram group (24 micrograms twice a day). It appeared to be safe in this small study of 50. They did notice an increase in adverse events and drop outs with increase in dose. This is a phase II type trial which sets the stage for a larger, randomized, controlled trial to determine whether or not this drug helps patients with irritable bowel syndrome and constipation, because of the tremendous overlap between constipation and constipation predominant irritable bowel syndrome (IBS-C). We'll likely be using it in our practice, although we will need to wait for a randomized controlled trial to be able to determine whether or not it is clearly efficacious in this particular group.

***Abstract 224824: “Efficacy of mesalazine in the treatment of symptomatic diverticular disease”***

Symptomatic diverticular disease has tremendous overlap with irritable bowel syndrome, which makes this abstract worthy of review. This is a large study – 268 patients with symptomatic diverticulosis randomized to rifaximin low dose (200 mg twice a day), 400 mg twice a day or two doses of mesalazine (400 mg or 800 mg BID) for 10 days each month for 12 months. There was no placebo control. They found that mesalazine at the higher dose showed less abdominal pain, bloating, tenesmus, diarrhea, fever, general illness and a variety of different symptoms compared to rifaximin. While this is interesting, we need a more proper randomized controlled trial to determine whether it is really helpful or not. It is a provocative study however!

***Abstract 225051: “Peppermint oil (Mintoil®) in the treatment of irritable bowel syndrome. A prospective double blind placebo controlled randomized trial”***

Peppermint oil relaxes smooth muscle and has been useful in patients with irritable bowel. There are two randomized controlled trials that show improved symptoms, but are very short duration. One is a pediatric study and a four-week study in a predominantly male population which showed improvement. The authors randomized 48 patients with IBS to mint oil – two enteric coated capsules twice per day or placebo for four weeks. They excluded patients with lactose intolerance or a positive lactulose breath test.

They found significant improvement in all symptoms (diarrhea, bloating, constipation, abdominal pain, feeling of incomplete evacuation, and pain on defecation) after four weeks with mint oil, although they did see some symptom improvement with placebo in diarrhea and abdominal bloating. Again, we've got another relatively short study, only four weeks, which given the natural variation fluctuations in IBS, wouldn't be considered the optimum duration. Looking at does this apply to my patients? Well, four weeks is obviously not an adequate interval for our patients. Patients tend to come and see you at their worst, so no matter what you do in an early period, they tend to get some improvement. Peppermint oil is an interesting option but we need longer, more focused trials.

***Abstract 225841: "Protein and ginger for the treatment of chemotherapy-induced delayed nausea and gastric dysrhythmia"***

The authors studied 28 cancer patients on chemotherapy to determine if high protein meals and ginger can reduce drug induced nausea, as they do in nausea of motion sickness and pregnancy, by measuring gastric dysrhythmia by EGG. They randomized patients to a moderate protein supplement, and a higher protein supplement, both with ginger 1 gm twice a day. A control group received their usual diet. They found that reports of nausea were experienced less frequently in the high protein group with the ginger than in the control group, and that high protein meals generally reduced the delayed nausea and the use of antiemetic medicine. They also changed the gastric myoelectrical activity favorably. It's interesting, because we don't usually give protein to these patients. It's a paradigm shift that makes us think is this something that would be useful with these patients. It's not necessarily directly referable to our functional patients, but I consider it to be hypothesis generating.

I think this is an exciting time to be involved in functional bowel disorders. I think it's exciting for us and for our patients. We're going to have some new, better, and more precise treatments. We still have a lot to learn.

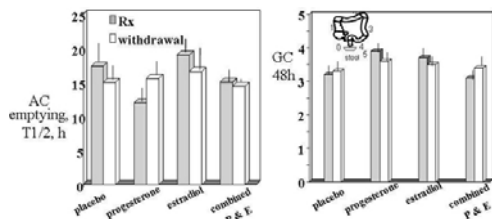
**Abstracts Discussed**

**211113: A Randomized Controlled Trial of Therapist-Administered vs Minimal-Therapist-Contact Cognitive Behavioral Treatment for Moderate to Severe IBS.** Jeffrey M Lackner, Kenneth A Holroyd, Gregory D Gudleski, Susan S Krasner, Leonard A Katz, Catherine D Powell, Praveen K Sampath, Rebecca S Firth, Brian T Yates

**BACKGROUND.** While cognitive behavioral therapy (CBT) is regarded as an efficacious treatment for IBS (Gastroenterology, 2003;125(1):19-31), it has not shown a commensurate level of clinical utility because of its cost, limited availability, and labor-intensive demands. Given the prevalence of IBS, the absence of a consistently satisfactory medical option, and a chronic course whose trajectory is subject to strong psychosocial influences, there is an unmet need for a behavioral self management treatment that is less costly to deliver and more transportable yet retains the efficacy of standard, therapist administered CBT. **AIMS.** To develop and test the feasibility of a largely self administered version of CBT. **METHOD.** 59 Rome II diagnosed IBS patients (80% female) were stratified by symptom severity and, after a 4 week baseline, randomized (1:1:1) to 1 of 3, 10-week conditions: (a) 10 session manualized Standard-CBT (S-CBT; n = 20); (b) 4 session manualized Minimal Contact CBT (MC-CBT, n = 22); or (c) wait list (WL, n = 17). MC-CBT covered the same range of procedures featured in S-CBT but they were taught through a self-study workbook (Breaking Free of IBS: A Step by Step Guide, Lackner & Holroyd, 2005) developed expressly for the trial. WL patients' data were obtained before they crossed over (1:1) to an active condition. Primary endpoints were adequate relief from pain and GI symptoms (2 Yes/No items) and global ratings of IBS symptom improvement. Secondary endpoints were distress (BSI), quality of life (IBS-QOL), coping (CSQ, IBS-SEQ), IBS symptom severity (IBS-SS), and cost-efficiency. **RESULTS.** In intent-to-treat analyses, both CBT versions were significantly ( $p < .0001$ ) superior to WL at post-treatment in the percentage of participants reporting moderate-to-substantial improvement in IBS symptoms (MC-CBT = 72.8%, S-CBT = 73.7%, WL = 0.0%). A similar pattern was found for the percentage of patients reporting adequate relief of pain (MC-CBT = 72.7%, S-CBT = 73.7%, WL = 11.8%) and GI symptoms (MC-CBT = 63.6%, S-CBT = 68.4%, WL = 0.0%). MC-CBT patients achieved significant improvements in QOL, IBS symptom severity, distress, and coping (e.g., catastrophizing, self-efficacy to control IBS symptoms), with all pre-post therapy difference p values  $< .01$ . Cost effectiveness analyses indicated that MC-CBT achieved symptom relief about 5 times as efficiently as S-CBT. 16% of MC-CBT (vs 15% of S-CBT) patients dropped out. **CONCLUSIONS.** Data suggest that a 4-session CBT regimen is a well tolerated, efficient, and clinically effective treatment that provides significant relief from the range of problems of more severe IBS. Supported by NIDDK grant 67878.

**215072: Effect of Female Sex Hormone Supplementation and Withdrawal on Gastrointestinal and Colonic Transit in Postmenopausal Women.** Jonathan Gonenne, Tuba Esfandyari, Michael Camilleri, Lorraine Fitzpatrick, Duane D Burton, DebraStephens, Kari Baxter, Alan R Zinsmeister

Females are disproportionately affected by constipation, which is often aggravated during pregnancy and the luteal phase of the menstrual cycle. **Aims:** To evaluate effects of acute administration of 400 mg/day micronized progesterone, 0.2 mg/day estradiol, combination of the same doses of progesterone and estradiol, or placebo on gastric emptying (GE), small bowel transit, and colonic transit (CT) in healthy postmenopausal subjects; and to determine whether withdrawal of the hormones was associated with a change in transit. **Methods:** 48 postmenopausal females were randomized (12 per group) and underwent scintigraphy using a  $^{99m}\text{Tc}$ -egg meal and  $^{111}\text{In}$ -charcoal. All kept daily stool diaries. After withdrawal of medications, transit measurement was repeated. Treatment assignment was double-blinded; treatment groups were balanced on age. Primary endpoints were ascending colon emptying t1/2 (hr) and colonic geometric center (GC) at 24 hours. Secondary variables were colon GC at 4 and 48 hours, GE at 4 hours, colonic filling at 6 hours, and stool frequency, consistency (Bristol stool form scale) and ease of passage. **Results:** A statistically significant effect of progesterone on colonic transit was evident by shorter ascending colon emptying t1/2 (Fig.) and significantly accelerated overall transit shown by colonic geometric center at 48 hours. Other transit endpoints were not significantly altered by progesterone. No transit endpoints were altered by estradiol or combined hormonal treatment relative to placebo. Withdrawal of the hormone supplement was not associated with any significant alteration in transit. Progesterone ( $p=0.024$ ) and estradiol ( $p=0.04$ ) were associated with looser stool consistency. **Conclusion:** Micronized progesterone accelerates colonic transit in postmenopausal females. This has implications for the pathophysiology and management of slow transit constipation in postmenopausal females.



**218572: The Effect of Lipase Supplementation on Upper Gastrointestinal Symptoms and Gastric Myoelectrical Activity Induced by a High Fat Meal in Healthy Volunteers.** Max E Levine, Vikram D Gopal, Sara Yanchis, Kenneth L Koch

**Background/Aims:** Dyspepsia symptoms of abdominal discomfort, fullness, early satiety, and nausea occur after ingestion of meals in 20-30% of the population. Gastric dysrhythmias are exhibited by approximately 55% of dyspepsia patients. Currently there are limited therapies to reduce these symptoms. Gastric and pancreatic lipases are key enzymes in fat digestion, and hydrolyze fat into fatty acids and monoglycerides. The aims of this study were to characterize the effects of a high fat meal on upper gastrointestinal symptoms and gastric myoelectrical activity, and to evaluate the effect of acid-resistant lipase supplementation on the same outcomes. **Method:** Sixteen healthy volunteers (12 males; mean age= 31 yrs) were enrolled in a double-blind, placebo controlled, cross-over trial. Volunteers were given a high fat meal (Pulmocare®) that was 55% fat, 28% carbohydrates, and 17% protein (237 ml; 355 Kcal). A capsule containing 280 mg of acid-resistant lipase (Amano Enzyme USA) or placebo was administered immediately before ingestion of the meal. The order of conditions was counterbalanced, and visits were separated by at least one week. At each visit, individuals completed a Visual Analog Scale (VAS) concerning symptoms of nausea, stomach fullness, hunger, bloating, and abdominal discomfort. The VAS was completed at baseline, immediately after the meal, and at 10, 20, 30, 45, and 60 minutes after the meal. Electrogastrograms (EGGs) were recorded throughout each visit to assess gastric myoelectrical activity. **Results:** Nausea, bloating, and stomach fullness were significantly increased 10 min after ingestion of the meal ( $p < .05$ ), and hunger was significantly decreased ( $p < .001$ ); there was also a significant decrease in normal gastric myoelectrical activity (3 cycles/min), and a significant increase in tachygastria (3.7-10 cycles/min) at 10 min after the meal ( $p < .05$ ). By 45 min after the meal, dyspepsia symptoms and tachygastria had decreased significantly from immediately after the meal, and normal gastric myoelectrical activity had increased significantly ( $p < .05$ ). Stomach fullness was significantly lower with lipase supplementation than with placebo condition at 20 and 30 min after the meal ( $p < .05$ ); no effect of lipase supplementation on gastric myoelectrical activity was detected. **Conclusions:** 1) The high fat meal induced dyspepsia symptoms and gastric dysrhythmias, suggesting the meal may be a useful test for assessing gastric neuromuscular disorders; and 2) Acid-resistant lipase supplementation decreased stomach fullness after ingestion of the meal, and warrants further study in individuals with functional dyspepsia.

**220741: Safety and Tolerability of the Probiotic Organism *Bifidobacterium infantis* 35624: Clinical Experience and Molecular Basis.** Eamonn M Quigley, Peter J Whorwell, Fergus Shanahan, Douwe VanSinderen, Jun Xu, Linda Altringer, Liam O'Mahony, Francisco Guarner, Progid Investigators

**Background:** Evidence for probiotic efficacy in a variety of gastrointestinal disorders accumulates. While probiotics are generally regarded as safe, there have been few large-scale investigations of short-term tolerance or long-term safety and theoretical concerns have been raised regarding short-term tolerability in functional disorders and risk of systemic infections among those with impaired barrier function. **Aim:** To evaluate the tolerability and safety of the probiotic organism *Bifidobacterium infantis* 35624. **Methods:** Data from two randomised, placebo-controlled, double-blind trials were used in this analysis. A four-week dose-ranging study, (*Bifidobacterium*  $10^6$  vs.  $10^8$  vs.  $10^{10}$ ) in subjects with irritable bowel syndrome (IBS) and a one-year study among subjects with active Crohn's disease and ulcerative colitis, were reviewed for evidence of short-term tolerability and long-term safety, respectively. The genome of the organism was also evaluated for evidence of genetic features of pathogenicity. **Results:** In the IBS study, 270 subjects were randomised to one of the three doses of the organism and 92 to placebo; 330 completed the study, including 243 on active treatment. A total of 17 subjects withdrew due to adverse events (AE's), 9 from the placebo group and 8 from the three treatment groups combined. The majority were occasioned by worsening of IBS symptoms. The overall incidence of all AE's was similar in the four groups at 48%, 37%, 52% and 43% for placebo,  $10^6$ ,  $10^8$ , and  $10^{10}$ , respectively with the majority (29%, 37%, 28% and 24%) being IBS-type gastrointestinal symptoms. The incidence of severe AE's adjudged as treatment related was highest in the placebo group at 9%; rates for the three treatment groups were 0%, 1% and 2%, respectively. In the inflammatory bowel disease (IBD) study, 32 patients with Crohn's disease and 50 with ulcerative colitis completed the study. No instances of systemic or major organ sepsis were recorded. From genome analysis it was apparent that *Bifidobacterium infantis* 35624 did not contain DNA that was homologous to known pathogenicity islands or transferable antibiotic resistance markers. **Conclusions:** *Bifidobacterium infantis* 35624 is well tolerated in the short term by patients with IBS and is not associated, in long-term therapy, in a susceptible population (IBD), with any evidence of risk for systemic sepsis. These clinical findings are supported by genome analysis.

**221015: Predictors of Premature Antidepressant Discontinuation in Functional Gastrointestinal Disorders (FGIDs): A Survival Analysis Approach.** Gregory S Sayuk, Jill E Elwing, Patrick J Lustman, Ray E Clouse

Antidepressants (AD) are a mainstay in the management of moderate to severe FGID, but patient adherence to AD regimens can be poor. Preliminary data from a placebo-controlled trial of a tricyclic antidepressant (TCA) in women with functional bowel disorders suggest that high degrees of somatic complaints (somatization, SOM) predict subsequent side effects. Other potential risk factors for premature discontinuation have not been determined nor have the preliminary findings been confirmed

in open-label treatment of broader subject groups. Methods: 173 consecutive patients (45.9±1.2 yr; 70% female) with FGID (29.6% IBS) treated with AD specifically for management of the FGID and followed by an academic gastroenterology practice were studied. Clinical features, AD type, duration of Rx, side effect type and severity, global AD treatment response (GTR), presence of psychiatric disorder (PSY: anxiety disorder or depression), and degree of SOM were based on systematic chart review. High degree of SOM was present if subjects endorsed >7 recent symptoms from the PHQ-15 or scored >median on # of historical functional GI and non-GI disorders. Survival analysis methods with Cox proportional hazards models were used to determine independent predictors of Rx discontinuation with 12 mo of AD initiation. Logistic regression models were used to determine predictors of maximal GTR as well as side effect severity. Results: Subjects were followed for 12.4±1.4 mo after AD initiation. At time of discontinuation or censoring, 94.2% were receiving TCAs with the remainder receiving other agents. High degree of SOM was present in 41.9% by PHQ-15 threshold; 34.1% had history of PSY. In Cox models that included age, sex, FGID dx, PSY, and SOM, both high degree of SOM (by PHQ-15: OR 2.9, 95%CI 1.4-6.3; by medical history: OR 2.5, 95%CI 1.3-4.8; p<0.01 for each) and male sex (OR 2.8, 95%CI 1.1-6.8; p=0.02) predicted early discontinuation. The logistic regression models showed that only high degree of SOM predicted poor GTR (OR 3.0, 95%CI 1.3-6.9; p=0.005), whereas both high degree of SOM and male sex predicted high side effect severity (OR 3.4, 95%CI 1.4-8.7; and OR 2.7, 95%CI 1.03-7.3, respectively; p<0.05 for each). Conclusions: A high degree of SOM, manifested either by recent symptoms or a medical hx of functional disorders, is a strong predictor of poor treatment outcome, side effect severity, and premature Rx discontinuation when AD are used for FGIDs in clinical practice. Male subjects without high degrees of SOM also tolerate AD poorly. Designs for clinical trials and treatment algorithms should consider these observations to optimize adherence to AD maintenance regimens.

**222021: A 10-Day Course of Rifaximin, A Non-Absorbable Antibiotic, Produces A Durable Improvement In All Symptoms of Irritable Bowel Syndrome: A Double-Blind Randomized Controlled Study.** *Mark Pimentel, Sandy Park, Yuthana Kong, Kimberly Low, Soumya Chatterjee, Hyo-rang Lee*

Recent data suggest a relationship between gut bacteria and IBS symptoms such that improvement in IBS is observed after antibiotic treatment. We have recently reported the beneficial effects of rifaximin, a non-absorbed antibiotic, on global improvement in IBS. In this sub-analysis, the component symptoms of IBS and their response to rifaximin are determined. Methods: Rome I criteria positive IBS patients were enrolled in a double-blind randomized placebo-controlled study. After a 1-week run in, subjects were asked to complete a symptom questionnaire with diarrhea, constipation, bloating and abdominal pain rated on a VAS score from 0-100mm after which a lactulose breath test was conducted. Subjects were then randomized to rifaximin 400mg or placebo tid for 10-days. One week after completion of treatment, subjects repeated their questions. Thereafter, for an additional 9 weeks, subjects completed a weekly symptom questionnaire. The number of subjects with > 50% improvement in each of the symptom categories was determined over the 10-week follow-up time period. Two endpoints were examined. The first endpoint was one week after completing treatment. The second was the overall 10-week period. Results: 87 subjects were randomized in the study (44 placebo, 43 rifaximin). One week after rifaximin, 48.6% of subjects demonstrated a clinical response with diarrhea (>50% improved) compared to 23.5% for placebo (p<0.05). For bloating, 34.9% of subjects demonstrated relief compared to 18.6% for placebo (p=0.07). At this first endpoint, constipation and abdominal pain were not improved. When the proportion of patients with clinical improvement (>50% improvement) was determined for the entire 10-week follow-up period for each symptom, all four symptoms were statistically improved including bloating (49.2±6.8 vs. 22.6±3.5%, p<0.000001), diarrhea (50.6±5.7 vs 35.3±6.3%, p<0.00001), abdominal pain (39.7±7.4 vs 28.9±7.2%, p<0.01) and constipation (35.1±7.0 vs 28.1±5.0%, p<0.05). Conclusions: Rifaximin treatment results in a significant improvement in the four major symptoms of IBS for 10 weeks after completion of treatment.

**222095: Newer Antiepileptic Drugs for Adults with Cyclic Vomiting Syndrome (CVS): A Novel Approach to Maintenance Therapy.** *Ray E Clouse, Gregory S Sayuk, Rajesh Shah, Patrick J Lustman, Chandra Prakash*

Management of CVS in adult patients is limited by the small number of effective agents either for abortive treatment of episodes or maintenance of the episode-free interval. Tricyclic antidepressants (TCAs) have been the most commonly used maintenance medications in adults, but their use often is limited by high side effect profiles. Newer antiepileptic drugs (AEDs), including zonisamide (Zonegran®, ZN) and levetiracetam (Keppra®, KP), are well tolerated, are being used for off-label prophylaxis against migraine headache, but have not been tested in CVS. Methods: 18 adult patients with CVS (mean age 38.6 ±3.3 yr; range 19-71; 7 female/11 male) were treated with maintenance open-label AEDs after TCA failure (13 pts) or intolerance (5 pts). Each patient had typical Rome II features of CVS; 9 (50%) also had a dominant abdominal pain component; and 5 subjects (28%) had a CVS picture in face of diabetes mellitus without other satisfactory explanation for the stereotypical vomiting episodes. 2 (22%) had personal or family history of migraine headache and 3 (9%) had prodromal features. 4 subjects had used marijuana regularly but had no improvement on withdrawal. Duration of CVS averaged 5.4 ±1.4 yr (range 0.2-21 yr), and episode rate over the 1 year pre-AED averaged 1.1 ±0.3/month. Each subject was followed for ≥3 months on AEDs; response to treatment was evaluated on a 0-3 Likert scale (worse/no improvement to near complete or complete response) with comparison to pre-treatment course. Results: 15 subjects (83%) were treated with ZN and 3 (17%) with KP; median final daily dose (range) was 300 mg (100-600 mg) for ZN and 1000 mg (500-2000 mg) for KP. TCAs were discontinued in 10 subjects

(75%). Duration of follow-up on AEDs averaged  $9.7 \pm 2.0$  mo. Response  $\geq 2$  on the Likert scale (at least moderate response) occurred in 13 (72%) of subjects, while complete or near complete resolution of episodes was reported by 8 of these (44% of total). Episode rate reduced to  $0.5 \pm 0.2/\text{mo}$  ( $p < 0.05$  compared with pre-AED value) for responders. Only 1 subject was intolerant (CNS side effects from ZN). Conclusions: Newer AEDs, specifically ZN and KP, are beneficial in open-label, maintenance use for reducing vomiting episodes in adults with CVS. Nearly three-fourths of subjects who were unsatisfactorily managed with TCAs benefited over this short follow-up period. Further investigation of these AEDs in CVS is indicated to better define efficacy, dosing and drug superiority. Considering their high tolerance and lower side effect profiles, they may prove superior to TCAs in primary maintenance strategies.

**222711: A Dose-Ranging, Double-Blind, Placebo-Controlled Study of Lubiprostone in Subjects with Irritable Bowel Syndrome and Constipation (c-IBS).** *John F Johanson, Raymond Panas, P. Christopher Holland, Ryuji Ueno*

IBS is a condition that affects nearly 30 million individuals in North America and accounts for 25-50% of the referrals to gastroenterologists. Lubiprostone is a novel type-2 chloride channel (ClC-2) activator that has been shown to be efficacious and well tolerated in a number of well-controlled clinical trials in subjects with chronic constipation. We present the results from a 12-week dose-ranging study where lubiprostone was tested, for the first time, exclusively in subjects with IBS with constipation (c-IBS), as defined by the Rome II Criteria. Methods: Approximately 50 subjects were randomized in a double-blind fashion to each of the four treatment groups: placebo (0  $\mu\text{g}$ ) or 16, 32, or 48  $\mu\text{g}$  lubiprostone daily (8, 16, or 24  $\mu\text{g}$  BID). In an electronic diary, subjects recorded data relating to dosing, abdominal symptoms (bloating and discomfort/pain), bowel movements (BMs; frequency and straining and consistency ratings), and rescue medication use. Weekly diary questions queried subjects on their assessment of the treatment effectiveness. Trend-tests were used to detect dose-dependent efficacy relationships and a step-down testing procedure was used to make pairwise comparisons between the active lubiprostone and placebo groups in the case of a dose-dependent trend. Safety was assessed by adverse event (AE) incidence rates. Results: Significant dose-dependent trends were observed during at least 2 of the 3 months for abdominal discomfort/pain, abdominal bloating, spontaneous BM frequency (SBM), stool consistency, bowel straining, and assessments of constipation severity. Pairwise comparisons revealed many significant differences between the active groups and placebo. During months 1 and 2, improvements in abdominal discomfort/pain and SBM frequency rates were more than doubled in all lubiprostone groups as compared to placebo. Specifically, at Month 1, decreases from baseline in abdominal discomfort (based on a 5-point scale) were 0.19, 0.45, 0.40, and 0.46 points in the placebo, 16, 32, and 48  $\mu\text{g}$  groups, respectively; at Month 2, decreases from baseline were 0.23, 0.52, 0.53, and 0.54 points, respectively; and, at Month 3, decreases from baseline were 0.34, 0.56, 0.59, and 0.53 points, respectively. Overall, improvements were typically highest in the 48  $\mu\text{g}$  group. With respect to safety, dose-dependent trends were also observed. AE incidence and drop-out rates typically increased with increasing dose. Conclusion: Lubiprostone is an efficacious and well-tolerated treatment for c-IBS. Dose-dependent trends were observed with respect to safety and efficacy.

**224824: Efficacy of Mesalazine In the Treatment of Symptomatic Diverticular Disease.** *Giuseppe Comparato, Libera Fanigliulo, Lucas G Cavallaro, Giovanni Aragona, Giulia Martina Cavestro, Stefania Liatopoulou Angelo Franze', Cecilia Carloni, Veronica Iori, Marta Maino, Giorgio Nervi, Francesco Di Mari.*

Background and aim. In uncomplicated diverticular disease, treatment is aimed to relieve the symptoms in symptomatic patients. Our aim was to evaluate efficacy of mesalazine in relieving symptoms in patients with symptomatic and uncomplicated diverticular disease of the colon. Materials and methods. Two hundred and sixty-eight consecutive eligible outpatients (122 male, 146 female; age 66.1 years, range 31-81 years) were enrolled in four different schedules according to a randomisation list: Group R1 (66 patients) rifaximin 200 mg bid; Group R2 (69 patients) rifaximin 400 mg bid; Group M1 (67 patients) mesalazine 400 mg bid; Group M2 (66 patients) mesalazine 800 mg bid. Each treatment was administered for 10 days every month for 12 months. Clinical evaluation was performed at admission and at 3-months intervals for 12 months considering 11 clinical variables (upper and lower abdominal pain/discomfort, tenesmus, diarrhoea, abdominal tenderness, fever, general illness, nausea, emesis, dysuria) scored as 0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe. The Global Symptomatic Score (GSS) was calculated by the sum of each symptom score. Results. After 12 months follow-up, Group M2 showed fewer frequency rate of lower abdominal pain ( $p < 0.0001$ ), bloating ( $p < 0.001$ ), tenesmus ( $p < 0.0001$ ), diarrhoea ( $p < 0.01$ ), fever ( $p < 0.0001$ ), general illness ( $p < 0.02$ ), nausea ( $p = 0.002$ ), dysuria ( $p = 0.04$ ), bleeding ( $p = 0.01$ ). Mean GSS was lower in Group M2 after 6 months ( $p < 0.001$ ) and 12 months ( $p < 0.0001$ ) respectively. Patients treated with mesalazine (Groups M1 and M2 together considered) showed a lower GSS if compared to subjects treated with rifaximin (Groups R1 and R2 together considered) after 6 ( $p < 0.001$ ) and 12 months ( $p < 0.0001$ ), respectively. Conclusion. Cyclic administration of mesalazine is effective in obtaining symptom relief in uncomplicated diverticular disease of the colon. Some symptoms improved more with mesalazine 800 mg bid than with the other schedules.

**225051: Peppermint Oil (MINTOIL®) In the Treatment of Irritable Bowel Syndrome. A Prospective Double Blind Placebo Controlled Randomized Trial.** *Giorgio Cappello, Mariangela Spezzaferro, Daniela Coraggio, Laurino Grossi, Leonardo Marzio*

**Introduction:** Peppermint oil has been shown to relax gastrointestinal smooth muscle in vitro and to be useful in patients with irritable bowel syndrome (IBS) and bacterial overgrowth (BO). **Aim:** Aim of the study has been to test the efficacy of peppermint oil (Mintoil®, Cadigroup, Rome, Italy) in patients with IBS without BO and lactose intolerance. **Methods:** Forty eight patients with IBS according to Rome II criteria with normal lactose and lactulose breath test were randomly treated with Mintoil® (2 enteric-coated capsules twice per day or placebo) for four weeks. Symptoms score was assessed before the beginning of therapy at the end of therapy (4 weeks). The symptoms evaluated were: diarrhea (Di), abdominal bloating (AB), constipation (Co), pain lower abdomen (PLA), pain on defecation (PoD), feeling of incomplete evacuation (FIE), difficulty on evacuation (DoE). For each symptom intensity and frequency graded 0 to 4 were scored. Intensity 0: absent, 1: mild, 2 moderate, 3:severe, 4: intolerable, Frequency : 0 absent, 1 once a month, 2: once a week, 3 three times per week, 4 everyday. The mean value between intensity by frequency was calculated for comparison. **Results:** The results show statistical significant improvement in all symptoms evaluated after 4 week of Mintoil® (24 patients) (Table 1), while only diarrhea and abdominal bloating improved after placebo (26 patients) (Table 2). The improvement in symptoms score for AB is greater with peppermint oil than with placebo. **Conclusion:** Peppermint oil and placebo both improve abdominal symptoms in patients with irritable bowel syndrome. Peppermint oil however, improves more symptoms than placebo with a better score of improvement.

Table I

	Di	Bl	Co	PLA	PoD	FIE	DoE
Mintoil®	1.960.23	2.920.12	0.960.11	2.920.81	2.330.87	1.580.21	1.130.21
Mintoil® 4 weeks	1.410.11	1.580.21	0.250.04	1.500.14	1.420.12	0.960.03	0.580.11
P	0.03	0.001	0.05	0.001	0.04	0.05	0.05

Table II

	Di	Bl	Co	PLA	PoD	FIE	DoE
placebo	1.88±0.28	3.12±0.45	1.42±0.23	3.00±0.45	2.08±0.45	2.12±0.15	1.00±0.12
placebo 4 weeks	1.12±0.15	2.31±0.67	0.96±0.24	2.81±0.05	2.42±0.89	1.65±0.54	0.88±0.34
P	0.03	0.03	0.17	0.3	0.025	0.09	0.36

**225841: Protein and Ginger for the Treatment of Chemotherapy-Induced Delayed Nausea and Gastric Dysrhythmia.** *Max E Levine, Marcum Gillis, Sara Yanchis, Anne C Voss, Robert M Stern, Kenneth L Koch.*

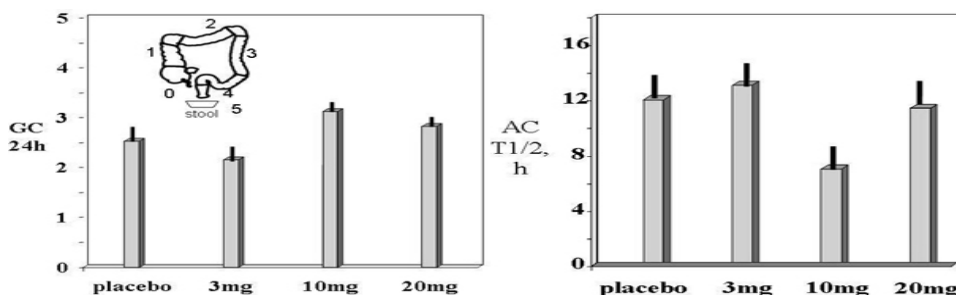
**Background:** Delayed nausea occurs in many cancer patients during the three days following administration of a cytotoxic agent. Meals high in protein content decrease the nausea of motion sickness and pregnancy, possibly by enhancing normal gastric myoelectrical activity and/or by reducing gastric dysrhythmias. Ginger may also have anti-nausea properties. The aim of this study was to explore the use of a nutritional intervention consisting of high protein meals and ginger for the management of delayed nausea experienced by chemotherapy-naïve cancer patients. **Method:** Twenty-eight cancer patients receiving emetogenic cytotoxic agents were assigned to one of three groups. During the three day study period following their first chemotherapy session, Control Group patients (n=9) continued with their normal diet, Protein Group patients (n=9) were provided with a protein drink (ProSure®; 15g whey protein) and 1 g of dried ginger root to consume twice daily, and High Protein Group patients (n=10) were provided with a protein drink with additional protein powder (ProSure® and ProMod®; 31 g whey protein) and 1 g of dried ginger root to consume twice daily. All patients were asked to complete a symptom diary over the three days to assess the severity, frequency, and bothersomeness of the nausea they experienced, as well as their use of antiemetic medication. Gastric myoelectrical activity was assessed by electrogastrigraphy as five patients ingested a protein meal with ginger on the first morning of the study. **Results:** Reports of nausea, of nausea being experienced often, and of nausea being bothersome were significantly less frequent in the High Protein Group than in the Control and Protein Groups ( $p < .05$ ); the Control and Protein Groups were not significantly different from each other. Furthermore, significantly fewer patients in the High Protein Group elected to use antiemetic medication than patients in the other two groups ( $p < .05$ ). A significant increase in normal gastric myoelectrical activity (3 cycles/min), and a significant decrease in gastric tachyarrhythmia (3.7-10 cycles/min), the gastric dysrhythmia that frequently accompanies nausea, occurred with ingestion of the protein meals and ginger ( $p < .05$ ). **Conclusions:** (1) High protein meals with ginger reduced the delayed nausea of chemotherapy, and reduced the use of antiemetic medications. (2) Anti-nausea effects of high protein meals with ginger were associated with

enhancement of normal gastric myoelectrical activity and decreased gastric dysrhythmias. High protein meals with ginger represent a novel, nutritionally-based treatment for the delayed nausea of chemotherapy.

**Additional Reading: Treatment of Functional Bowel Disorders**

**213331: Effects of a Novel 5-HT4 Agonist, ATI-7505, on Gastrointestinal and Colonic Transit in Humans.** *Michael Camilleri, Duane Burton, Maria I Vazquez-Roque, Thomas Ford, Sanna McKinzie, Alan R Zinsmeister*

Background: ATI-7505 is a prokinetic 5-HT4 agonist shown to be devoid of QT prolongation effects and not metabolized by CYP 450. This study assessed the effect of ATI-7505 on gastrointestinal and colonic transit in healthy humans. Methods: This randomized, parallel-group, double-blind, placebo-controlled study evaluated effects of ATI-7505, 3, 10 or 20 mg t.i.d., in healthy volunteers (12 per group). Validated scintigraphic methods were used to measure gastrointestinal and colonic transit with <sup>99m</sup>Tc-egg meal and <sup>111</sup>In-charcoal. Primary endpoints were gastric emptying (GE) t1/2, colonic geometric center (GC) at 24 hours and ascending colon (AC) emptying t1/2. Stool diaries were kept during the 9-day treatment period. An ANCOVA was used to assess overall treatment group differences, and post-hoc unadjusted pairwise comparisons were also examined. Results: There were borderline overall treatment effects (decrease) on GE t1/2 (p=0.154), with 20 mg t.i.d. ATI-7505 accelerating GE vs. placebo (p=0.038). ATI-7505 increased colonic transit (GC24, p=0.031, Fig.) with fastest transit at 10 mg t.i.d. vs. placebo (p=0.065). ATI-7505 accelerated AC emptying t1/2 (overall p=0.075, Fig.) with 10 mg dose vs. placebo (p=0.042). There were no changes in stool frequency or ease of passage, but there was somewhat looser stool consistency (Bristol stool form scale, overall p=0.056) with the 10 and 20 mg t.i.d. doses. No safety issues were identified. Conclusions: The 5-HT4 agonist, ATI-7505, accelerates overall colonic transit, tends to accelerate GE and AC emptying and loosen stool consistency. The optimal doses in health appear to be 20 mg and 10 mg t.i.d. to accelerate GE and colonic transit, respectively.



**214102: Effects of Hypnotherapy on IBS in Different Clinical Settings - Results from Two Randomized, Controlled Trials.** *Per Johan Lindfors, Peter Unge, Einar S Bjornsson, Annika Stenman, Patrik Arvidsson, Hasse Abrahamsson, Magnus Simren*

Hypnotherapy is considered to be effective in patients with irritable bowel syndrome (IBS). Few randomized, controlled trials exist, and most of the data originate from centers highly specialized in this kind of treatment (Whorwell et al 1984). To be more widely spread the effects of this costly treatment alternative need to be further evaluated in clinical practice. Here we report the results from two randomized, controlled trials on hypnotherapy in IBS in different clinical settings. METHODS: We included 135 patients with IBS refractory to standard management (107 females; mean age 41 (21-68) years). Study 1 was performed in a university hospital specialized in functional GI disorders (n=87) and study 2 in a county hospital (n=48). In both studies patients were randomized to receive gut-directed hypnotherapy 1 h/week for 12 weeks performed by specially trained psychologists, or to serve as control group. At baseline, immediately after the treatment period and after 6 and/or 12 months the treatment effect was evaluated with questionnaires assessing quality of life (IBSQOL / SF-36), anxiety and depression (Hospital Anxiety and Depression (HAD) scale) and GI symptoms (Gastrointestinal Symptom Rating Scale (GSRS)-IBS / GI symptom questionnaire). RESULTS: GI symptoms severity improved after the treatment period in the hypnotherapy group in both study 1 (Cumulative GI symptom score 29±6.9 vs. 26±7.3 (mean±SD); p=0.002) and study 2 (GSRS Total score 4.0±0.9 vs. 3.4±0.9; p=0.03), but not in the control groups, respectively. The improvement was more pronounced for abdominal pain, distension and bloating than for the bowel habits. At the one year assessment the improvement was sustained or even enhanced. Anxiety and depression was improved at one year in study 2 compared with baseline (HAD anxiety 8.5±4.7 vs. 6.3±4.5; p=0.009; HAD depression 6.0±3.1 vs. 4.2±2.8; p=0.005), but no such effect was noted in the hypnotherapy group in study 1 or in the control groups. In both studies we observed clear tendencies towards a better quality of life in the hypnotherapy groups, but not in the control subjects. The total responder rate, in terms of significant improvement of GI symptoms, was higher in the hypnotherapy groups vs. the control groups (52% vs. 32%; p=0.03) CONCLUSION: In these two randomized controlled trials we have demonstrated that hypnotherapy is a useful treatment alternative with long-term effect in IBS patients refractory to standard management. Hypnotherapy can successfully be conducted in different clinical settings, also outside the highly specialized gastroenterology centers focused on functional GI disorders.

**218776: Tegaserod Improves Multiple Symptoms In Women With Mixed/Alternating Bowel Habits As Well As Those With IBS-C.** *William D Chey, Pierre Pare, Andrea Viegas, Gregory Ligozio, Michael A Shetzline*

**BACKGROUND:** Tegaserod, a promotility agent, is safe and effective in the treatment of irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation. IBS patients with a mixed or alternating bowel pattern (IBS-M), although clinically distinct, share clinical characteristics with the IBS-C group. At present, no medical therapy has been demonstrated to be effective in IBS-M patients. **METHODS:** A randomized, double-blind, placebo-controlled, multicenter study was performed in women with IBS-C (Rome II criteria) and IBS-M (not IBS-C or IBS-D by Rome II). The primary efficacy variable was patients' assessment of satisfactory relief over 4 weeks' treatment with tegaserod (T) 6 mg b.i.d. or placebo (P). The proportion of patients reporting satisfactory relief for  $\geq 3$  out of 4 treatment weeks (75% rule) and improvement during each of the 4 weeks in individual IBS symptoms were also assessed. Treatments were compared using a generalized linear model with logit link. **RESULTS:** 661 women were randomized (IBS-C 337; IBS-M 324). Baseline symptom assessment clearly distinguished between the IBS-C and the IBS-M cohorts. Statistically significant differences were found between the two cohorts in bowel movement (BM) frequency, stool consistency and straining. Overall, T provided statistically significant improvement in satisfactory relief of IBS symptoms over a 4-week treatment (OR=1.75; 95% CI: 1.35-2.25;  $p < 0.001$ ) for the IBS-C and IBS-M cohorts. In the two cohorts, the percentage of patients experiencing satisfactory relief of IBS symptoms (75% rule) was significantly higher for T when compared to P (IBS-C: 43.3% vs 28.9%,  $p = 0.008$  and IBS-M: 52.3% vs 36.3%,  $p = 0.010$ ). T was significantly superior ( $p < 0.05$ ) to P at improving weekly BM frequency (IBS-C: T 6.88, P 6.06 and IBS-M: T 9.78, P 8.34), stool consistency score using a 7-point scale (IBS-C: T 3.53, P 2.89 and IBS-M: T 3.95, P 3.49) and days/week with straining (IBS-C: T 3.08, P 3.55 and IBS-M: T 2.42, P 2.87). Adverse event discontinuations were low (IBS-C: T 1.2% vs P 2.4% and IBS-M: T 2.5% vs P 3.6%). The most frequent adverse events with discontinuation of study medication were diarrhea (1.1%) and headache (0.6%). No cases of ischemic colitis were reported. **CONCLUSION:** This study demonstrates that T is effective and safe in treating the overall symptoms of IBS in patients with a mixed/alternating bowel habit. Efficacy in this subgroup was similar to that demonstrated in IBS-C patients. This is the first study to identify an efficacious medical therapy for patients with IBS and a mixed bowel pattern.

**219225: The Gut Response to Stress can be Pharmacologically Modulated - Amitriptyline Modifies Visceral Hypersensitivity in Irritable Bowel Syndrome (IBS).** *Charles Murray, Wendy J Winchester, Eric Tripoli, Maxton C Pitcher, Michael A Kamm, Anton V Emmanuel*

**Introduction:** Acute physical stress causes a measurable acute alteration of gut autonomic function and visceral hypersensitivity in patients with IBS (Murray et al Gastroenterology 2004). Low doses of amitriptyline are effective in over 50% of IBS patients, through mechanisms that are unclear. We present the first report of the effects of amitriptyline on the gut neural response to acute stress. **Methods:** 19 patients with constipation-predominant IBS (16 female, mean age 32, range 19-58) were given amitriptyline 25-50mg at night. Patients underwent stress assessment at baseline and after three months of treatment. Stress assessment comprised a physical (cold-pressor) and psychological (dichotomous listening) stress given in random order at least one day (median 1, range 1-4 days) apart. Physiological parameters measured included: perception of stress (visual analogue scale); systemic autonomic tone (heart rate and blood pressure); gut-specific autonomic innervation (laser Doppler flowmetry of rectal mucosal blood flow (RMBF)); and visceral sensitivity (rectal electrosensitivity). 13 patients underwent barostat assessment of rectal sensitivity. **Results:** 14 of 19 (74%) patients were symptomatically improved after 3 months of amitriptyline (median dose 25mg). Acute stress resulted in increased perception of stress and systemic autonomic tone, and reduced RMBF, which was similar in responders and non-responders ( $p > 0.05$  for all). In contrast, all non-responders and only three out of 14 of responders, continued to exhibit stress-induced reduced pain threshold at 3 months (change from baseline - 31% vs +2%,  $p < 0.03$  respectively). Responders increased thresholds for pain from 21 (pre-) to 31 mmHg (post-treatment) above distending pressure ( $p < 0.03$ ). No such change was seen in non-responders (from 23 to 24 mmHg, respectively). **Discussion:** Amitriptyline is effective in constipation-predominant IBS patients. This effect is primarily on stress-induced visceral hypersensitivity, independent of autonomic tone. The gut response to acute stress is a viable target to study drug efficacy in IBS.

**220332: Dexloxiglumide, a CCK1-antagonist, improves gas-related symptoms in healthy subjects.** *Beatriz Lobo, Jordi Serra, Fernando Azpiroz, Massimo D'Amato, Juan R Malagelada*

Patients with irritable bowel syndrome and functional dyspepsia, often complain of gas-related symptoms, particularly after meals. Duodenal lipids impair intestinal gas transit and tolerance in healthy subjects, and this effect is exacerbated in patients with irritable bowel syndrome. Our aim was to test whether dexloxiglumide, a CCK1-antagonist, blocks the effect of lipids on intestinal gas transit and tolerance. **METHODS.** In 12 healthy subjects (6 female, 6 men) we used a validated model inducing gas retention in man (GE 2002; 123:700). Briefly, a mixture of gases mimicking physiological venous gas was infused into the jejunum at 12 ml/min for 3 h (total volume 2160 ml). Simultaneously, lipids were administered into the duodenum (Intralipid, 1 kcal/min), and we quantified anal gas evacuation (via a barostat) and abdominal symptoms (by a 0-6 scale). Paired double-blind

studies with iv infusion of either dexloxiglumide (2.5 mg/Kg bolus followed by 5 mg/Kg.h continuous infusion) or saline (control) were performed on separate days in random order. RESULTS. As expected, subjects developed significant abdominal symptoms (2.6±0.6 score) and intestinal gas retention (665±180 ml) in response to the gas plus lipids challenge test during i.v. saline. In contrast, i.v. infusion of dexloxiglumide reduced abdominal symptoms (1.2±0.4 score; p<0.05 vs saline) and evidenced a trend towards improving intestinal gas clearance (589±197 ml gas retention; NS vs saline). Interestingly, the effects of dexloxiglumide were much more pronounced in the women subgroup (symptoms improved by 56±16% and gas retention by 28±19%; p<0.05 vs saline for both). CONCLUSION. CCK1-antagonist dexloxiglumide reduces gas-related symptoms and improves gas clearance, particularly in women.

**221957: The Gastrointestinal Activity And Peripheral Selectivity of Alvimopan, ADL 08-0011, and Naloxone In Mice.**  
*Scott Armstrong, Christina C Sandlund, Carrie Richardson, Tina Pham, Adrienne Winans, David T Beattie*

Alvimopan, a peripherally restricted  $\mu$ -opioid receptor antagonist, is in development for the treatment of opioid-induced bowel dysfunction and post-operative ileus. Based on the similar  $\mu$ -opioid antagonist potencies of alvimopan and its metabolite, ADL 08-0011, and the higher systemic exposure of the latter after oral dosing of the parent (Foss *et al.*, 2005), it is likely that ADL 08-0011 is responsible for much of the efficacy attributed to alvimopan. In this study, the gastrointestinal (GI) and CNS activities of alvimopan, ADL 08-0011, and the centrally penetrant  $\mu$ -opioid receptor antagonist, naloxone, were determined in mice. In a GI model of acute morphine exposure, morphine (3 mg/kg s.c.) or vehicle was dosed 15 minutes after test agent or vehicle. A charcoal meal was dosed orally and GI transit measured 60 minutes later. To assess CNS activity, test compounds were dosed prior to morphine treatment and subsequent analgesia testing (paw lick latency on a hot-plate). In additional studies, mice were treated for 7 days with morphine (45 mg/kg/day s.c.) or vehicle via an osmotic minipump. Test agent or vehicle was then administered (s.c.) prior to assessment of GI and CNS-mediated responses (i.e. stool output, incidence of soft stools, number of jumps and ambulatory activity). Alvimopan, ADL 08-0011 and naloxone inhibited morphine-mediated reductions in GI transit (ID<sub>50</sub> values of 0.03, 0.02 and 0.5 mg/kg, respectively) and morphine-mediated increases in paw lick latency (ID<sub>50</sub> values of 6, 0.7, and 0.02 mg/kg, respectively). The peripheral selectivities (i.e. the ratios of ID<sub>50</sub> values for reversal of analgesia and delayed GI transit) for alvimopan, ADL 08-0011, and naloxone were 200, 35 and 0.02, respectively. Following chronic morphine exposure, alvimopan, ADL 08-0011 and naloxone increased defecation and had a similar incidence of soft stools. Naloxone and ADL 08-0011 (both 10 mg/kg), but not alvimopan (0.01 - 10 mg/kg) produced a statistically significant (p<0.05, ANOVA and Dunnett's post-hoc test) increase in jumping behavior and ambulatory activity. It is concluded that the rank order of peripheral selectivity in mice is alvimopan > ADL 08-0011 > naloxone. The clinical significance of these data, particularly the lower peripheral selectivity of ADL 08-0011 versus alvimopan, remains to be determined. Foss, J.F.(2005). Clin. Pharm. Therap. 77, 74.

**223192: Effects of Lactobacillus Plantarum 299v On Symptoms and Rectal Sensitivity In Patients With Irritable Bowel Syndrome (IBS) - A Randomized, Double-Blind Controlled Trial**  
*Magnus Simren, Alma Syrous, Anette Lindh, Hasse Abrahamsson*

The effects of probiotic bacteria on symptoms in IBS patients remain controversial. The majority of studies published so far are small and the effects of the different bacteria tested have varied. Lactobacillus Plantarum 299v (LP) has improved gastrointestinal (GI) symptoms in IBS patients in some (Nobaek et al 2000; Niedzielin et al 2001) but not all studies (Sen et al 2002). The mechanism of action is unclear, but recent animal studies have proposed a positive effect of probiotics on visceral sensitivity. The effects of probiotics on visceral sensitivity in humans are unknown. METHODS: We included 76 IBS patients fulfilling the Rome II criteria (48 females; mean age 40 years). After a screening period of two weeks eligible patients were randomized to receive six weeks of treatment with either 400 ml per day of a rose-hip drink containing 5 x 10<sup>7</sup> cfu/ml of LP or a plain rose-hip drink (control), comparable in colour, texture, and taste. Symptoms were assessed before and after the treatment period using the IBS severity scoring system (IBS-SSS) and the Gastrointestinal Symptom Rating Scale-IBS (GSRS-IBS). Rectal sensitivity testing was performed before and after the treatment period, both in the fasting state and after an 800kcal liquid meal. RESULTS: Twenty-nine patients in each group completed the trial, 10 patients were screening failures and 8 dropped out prematurely during the treatment phase, due to lack of effect of the treatment or to factors unrelated to the study. The overall GI symptom severity improved in both groups but the improvement did not differ statistically between the groups (p=0.17). The improvement in the control group was statistically significant (IBS-SSS total score: 305±73 vs. 245± 118 (mean± SD); p=0.0001) and a trend in the same direction was seen in the LP group (295±95 vs. 279± 129; p=0.08). The majority of individual GI symptoms assessed by the GSRS-IBS improved significantly in the control group, whereas only trends in the same direction was seen for the LP group. The change in the severity of the individual GI symptoms did not differ between the treatment groups. The rectal sensory thresholds were not affected in any significant way by the treatments, except for trends towards reduced pain thresholds after the treatment period in both groups, but with no difference between the groups. CONCLUSION: We could not detect a positive effect of Lactobacillus Plantarum 299v on GI symptoms and rectal sensitivity in IBS patients. The effectiveness of probiotics in IBS remains uncertain. This study was supported by an unrestricted grant from Probi AB.

**223275: Pain And Depression Predict Improved Health-Related Quality of Life In Severe IBS Treated With Psychotherapy of Antidepressant.** Francis Creed, Elspeth Guthrie, Joy Ratcliffe, Lakshmi Fernandes, Barbara Tomenson, Nicholas Read, David Thompson

Objective We have reported previously long-term improved health-related quality of life in patients with severe irritable bowel syndrome (IBS) following treatment with an antidepressant or psychotherapy (1). In this study we assessed the relative importance of improved pain or depression in this finding. Method We assessed 257 patients with severe IBS before treatment and 239 one year after the end of treatment (75 psychotherapy, 85 Paroxetine and 79 treatment as usual) using a visual analogue scale (VAS) of abdominal pain and the Hamilton Depression Rating Scale (HDRS). Linear regression was used to predict change in SF36 physical component score. Structural equations modelling using AMOS tested whether baseline depression (HRSD) score predicted follow-up VAS pain score and vice versa. Results. Preliminary analyses confirmed that VAS pain and HDRS depression scores represented well the dimensions of pain and depression experienced by participants in our sample. Linear regression analysis to predict 1 year follow-up SF36 physical component score (health-related quality of life) indicated that pre-treatment VAS pain ( $p<0.001$ ) and HDRS depression scores ( $p=0.005$ ) and change (follow-up minus baseline) of VAS pain ( $p<0.001$ ) and HDRS depression scores ( $p=0.006$ ) were all significant independent predictors. Structural equation modelling including baseline and follow-up scores of VAS pain and HDRS depression showed that the overall fit of the model was excellent,  $\chi^2=2.06$ ,  $df=3$ ,  $p=0.56$ ,  $\chi^2/df=0.69$ ,  $RMSEA<0.0005$  and  $CFI=1.000$ . The standardised regression coefficients for baseline to follow up depression score and VAS pain were 0.36 ( $p<0.005$ ) and 0.38 ( $p<0.005$ ), respectively, demonstrating that each follow up variable is predicted by its own baseline value. The standardised regression coefficient for baseline VAS pain predicting follow-up HRSD was also significant ( $\chi^2=0.15$ ,  $p=0.02$ ), but that for baseline HRSD predicting follow-up VAS pain today was not ( $\chi^2=0.09$ ,  $p=0.16$ ). Addition to the model of psychotherapy and SSRI antidepressant treatments as additional variables did not change the model and the same model fits the data in each of the 3 treatment groups, when these were analysed separately. The model held when only patients who also had a psychiatric disorder were included. Conclusion: In patients with severe IBS receiving psychological treatments, both improved pain and depression influences later health-related quality of life but change in depression is not primarily responsible for this result. Other aspects (eg coping with pain and its attribution) are likely to be involved. (1) *Gastroenterology* 2003; 124 :303-17.

**224112: The Phytopharmakon STW5 (Iberogast®) has Pro-Secretory Effects in the Human Small and Large Intestine.** Dagmar Kruger, Florian Zeller, Olaf Kelber, D Weiser, Thomas Frieling, Michael Schemann

Phytotherapy is a promising alternative approach to treat functional gut disorders. The hydroethanolic drug STW5 consisting of nine herbal extracts (bitter candy tuft, chamomile flower, peppermint leaves, caraway fruit, liquorice root, lemon balm leaves, angelica root, greater celandine herbs, and milk thistle fruit) is successfully used to treat functional dyspepsia. Clinical data would suggest that it may be of therapeutic value for treating patients with irritable bowel syndrome (IBS). We therefore investigated the effect of STW5 on secretory activity of mucosa/submucosa preparations from human ileum and colon using the Ussing chamber technique. Experiments were performed on normal tissue from surgical specimen (59 preparations from 29 patients, age:  $69.8\pm 11.1$ ). Serosal application of STW5 (256 $\mu$ g/ml-1024 $\mu$ g/ml) concentration dependently increased the short circuit current. Mucosal application had no effect. The response was similar in small and large intestine and the data were therefore pooled. The increase was  $9.7\pm 2.9\mu$ A/cm<sup>2</sup> for 256 $\mu$ g/ml,  $22\pm 7.9\mu$ A/cm<sup>2</sup> for 512 $\mu$ g/ml and  $29\pm 8.1\mu$ A/cm<sup>2</sup> for 1024 $\mu$ g/ml ( $p<0.05$  at all concentrations). The concentrations used are well below the dose used to treat patients with functional dyspepsia which is 3x 51mg/ml daily. The STW5 evoked secretory effect was bumetanide (100 $\mu$ M) sensitive and therefore due to increased chloride secretion. Nerve blockade by tetrodotoxin (1 $\mu$ M) had no effect indicating a direct epithelial action of the drug. In addition the secretory response after electrical field stimulation of nerves remained unchanged in the presence of STW5. Our results indicate that STW5 has a powerful pro-secretory effect in the human intestine *in vitro*. It does not interfere with neurally mediated secretion but appears to stimulate chloride secretion at the level of the epithelial cell. Generally, patients with reduced secretion may profit from this drug. STW5 (Iberogast®) may represent a novel treatment option for IBS patients, in particular those with constipation predominant IBS.

**224696: Effects of Multidose Administration of MD-1100 on Safety, Tolerability, Exposure, and Pharmacodynamics in Healthy Subjects.** Caroline Kurtz, Don Fitch, Robert W Busby, Angelika Fretzen, G. Steven Geis, Mark G Currie

MD-1100 acetate (MD-1100), a guanylate cyclase-C (GC-C) agonist, is a novel agent that acts in animal models to promote intestinal secretion and transit and to reduce visceral pain. These pharmacological actions are ideal attributes for the treatment of constipation-predominant irritable bowel syndrome (IBS-C) and chronic idiopathic constipation (CIC). Aim: In an effort to better understand the potential utility of MD-1100 for treating gastrointestinal (GI) disorders, we have begun to characterize its safety, tolerability, exposure, and pharmacodynamics in healthy male and female subjects. Methods: A placebo-controlled, double-blind, randomized, multiple dose level study was performed with 48 healthy subjects. Oral doses of 30, 100, 300 or 1000  $\mu$ g of MD-1100 or placebo were administered once daily for 7 days. Subjects were assessed for safety, tolerability, MD-1100 systemic exposure, and GI pharmacodynamics using the Bristol Stool Form Scale (BSFS). Subjects recorded stool

characteristics including stool frequency, consistency, and ease of passage in diaries for 7 days preceding dosing and for the duration of the 7 day treatment period. Additionally, stool weight was measured during the 7 day treatment period. Results: MD-1100 was well tolerated at all dose levels. There was no detectable systemic exposure to MD-1100 or any evidence of metabolites at any dose level. All subjects completed the study and there were no serious adverse events. Subjects who received MD-1100 reported a loosening of stools during treatment as measured by a statistically significant increase from the baseline in the mean BSFS stool consistency scores at the 30 µg (p=0.050), 300 µg (p=0.001) and 1000 µg dose levels (p<0.001). Mean ease of stool passage scores showed a statistically significant increase from baseline at the 1000 µg dose level (p<0.001). Other dose-related indications of GI pharmacodynamic activity in subjects receiving MD-1100 included increases in stool frequency and stool weight. Conclusion: In this multiple-dose Phase 1 study, MD-1100 was well tolerated across the dose range studied (30-1000 µg). There was no detectable systemic exposure to MD-1100. MD-1100 demonstrated dose-related effects on GI pharmacodynamics including stool consistency, ease of passage, stool frequency and stool weight. To date, the preclinical and clinical data in healthy subjects support the potential of MD-1100 for the treatment of GI disorders, including IBS-C and CIC.

**225470: Antegrade Continent Enema for Chronic Constipation In Adults: Long Term Results.** *Sushil K Maslekar, Jill Marshall, Graeme S Duthie*

Introduction: Slow transit chronic constipation in adults can be very difficult to treat and defaecation can be often painful. Total colectomy with ileorectal anastomosis is offered conventionally but is associated with persisting constipation in 10-30% patients. Ileostomy brings relief but is not universally acceptable. Antegrade continent enema (ACE) procedure has previously been shown to be effective in approximately half of these patients in the short term, but longer-term results are unknown. The aim of this study was to evaluate the long-term results of the ACE procedure in chronic constipation and faecal leakage, including its impact on quality of life. Methods: All patients undergoing ACE procedure from 1996 to 2000 were included in the study. Telephonic interview was conducted following which questionnaires were sent to all the patients. These questionnaires included SF-36 type questions, faecal incontinence quality of life, Wexner score type and general questions about the procedure. Retrospective review of the case notes was done to obtain clinical, demographic and anorectal physiology data. Results: 24 patients (22 females) with a mean age of 37.9 years underwent the ACE procedure, out of which 17 were done laparoscopically. 18 patients had chronic refractory constipation, 3 patients had faecal leakage and 3 patients had mixed symptoms preoperatively. At a median follow up of 72 months (minimum 5 years follow up), 14 patients (60%) were still successfully irrigating. 8 of the 24 patients needed revision of their conduits. After ACE reversal in the remaining 10 patients, 5 patients (50%) underwent ileostomy. No serious complications occurred in any patient. 75% patients had demonstrated initial improvement in symptoms and 52% showed satisfactory improvement in bowel function at 72 months follow up. Quality of life showed significant improvement in the mean mental score on the SF-36 form from 34.6 preoperatively to 51 (p=0.04; Mann-Whitney U test) and an improvement in mean physical component score from 38.3 to 44.3 (p=0.08). The type of symptoms or type of conduit did not influence the outcomes. Conclusion This is the longest follow up of adults undergoing ACE procedures. The procedure is technically simple and effective, and affords an improvement in the quality of life in patients with chronic constipation and faecal leakage.

**226524: The New CRF<sub>1</sub> Selective Agonist Cortagine Injected Peripherally and Centrally Stimulates Colonic Motor Function and Induces Diarrhea In Rats: A Relevant Tool for Stress-Related Gastrointestinal Disease Studies.** *Muriel H Larauche, Karina Pambukchian, Armen Karapetyan, Mulugeta Million, Jean Rivier, Yvette Tache*

**Background:** Corticotropin releasing factor (CRF) binds to two subtypes of receptors: CRF receptor type 1 (CRF<sub>1</sub>) and type 2 (CRF<sub>2</sub>). Stress via the release of CRF and the activation of peripheral and central CRF<sub>1</sub> induces alterations of colonic motility and secretion and may be relevant for Irritable Bowel Syndrome (IBS) (Br J Pharmacol 2004, 141:1321-30). Whereas highly selective agonists for CRF<sub>2</sub> exist, no agonist with a similar selectivity for CRF<sub>1</sub> was available until the recent development of the new CRF<sub>1</sub> agonist: cortagine (binding affinities: 2.6 nM for rCRF<sub>1</sub> vs 540 nM for mCRF<sub>2</sub>) (PNAS 2004;101:9468-73). **Aim:** To characterize the properties of cortagine on colonic and gastric motor functions in rats and establish its relevance in the study of stress-related gastrointestinal diseases. **Methods:** Studies were performed in conscious male Sprague-Dawley rats (250-300g). The fecal pellet output (FPO) and diarrhea incidence were monitored for 2 h after intraperitoneal (IP) injection of cortagine (3 and 10 µg/kg). The central effect of cortagine (3 and 5 µg/rat, 10 µl) was evaluated on FPO and diarrhea incidence after its intracerebroventricular (ICV) injection. The selectivity of IP cortagine (10 µg/kg) for CRF<sub>1</sub> was tested on the FPO by injecting the specific CRF<sub>1</sub> antagonist, CP154,526 (20 mg/kg) subcutaneously (SC) 30 min before cortagine, and by evaluating its effects on gastric emptying of solid food. **Results:** Cortagine at the dose of 10 µg/kg, but not 3 µg/kg, IP, significantly increased the FPO in rats (6.9±1.9 vs 0.3±0.3 pellet/hour in vehicle IP) and induced diarrhea in 43% of rats within 30-45 min post-injection. Cortagine IP had no effect on gastric emptying of a chow meal compared to vehicle-treated rats. The increase in FPO induced by cortagine (10 µg/kg IP) was significantly reduced by CP154,526 pretreatment (3.1±1.0 vs 6.9±1.9 in cortagine IP). Central cortagine (3 and 5 µg/rat ICV) significantly increased the FPO for both doses and induced diarrhea after 60 min in 14% and 40% of responders respectively. **Conclusions:** The data using the new selective CRF<sub>1</sub> agonist cortagine, confirm the involvement of CRF<sub>1</sub> at both peripheral and central levels in the stimulation of colonic secretory motor functions leading to diarrhea in rats. They also support the selectivity of cortagine for CRF<sub>1</sub> since the solid food gastric emptying known to be CRF<sub>2</sub>

mediated (AJP 2002;282:G34-40) is not modified and the increased FPO is abolished by a selective CRF<sub>1</sub> antagonist. All together, those data highlight the potential of cortagine as a useful tool in the study of stress-related gastrointestinal disorders, such as IBS. Supported by R01 DK33061.