	Fasting (mean)		Lubiprostone (mean)	
	Noted in Proximal/Mid/Distal Sensors		Noted in Proximal/Mid/Distal Sensors	
	Amplitude (mmHg)	Motility index	Amplitude (mmHg)	Motility index
Patient A	19.9/33.4/48.2	6.2/9.5/10.3	26.2/39.7/41.7	26.2/39.7/41.7
Patient B	46.2/45.1/26.5	10.6/10/9.5	47.3/31.1/26.2	12.1/11.6/10.9
Patient C	24.6/27.6/27.7	9.9/9.7/9.2	26.3/30/24.9	9.2/9.5/9.1
Patient D	76.2/49.3/27.9	11.7/12.3/11.2	89.2/35/30.3	10.5/10.4/9.2
Patient E	25.1/32.2/25.4	6.8/7.6/4.8	24.6/24.7/25.6	8.6/8.9/9.1

MI= LN[(no.of contractions x Sum contraction amplitude)+1]

S1328

Patients Can Self-Manage Their Stimulant Laxative Dose to Achieve Effective Relief of Chronic Constipation, as Demonstrated in Two Randomized Trials

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INTRODUCTION: Many patients with chronic constipation require chronic laxatives, which are often used without medical supervision. There are doubts about the ability of patients to self-manage these medications. We tested this in two trials involving the stimulant laxatives bisacodyl (BIS) and sodium picosulfate (SPS). AIMS & METHODS: Within two randomized, double-blind, multi-center, placebo-controlled trials with BIS and SPS patients were permitted to adjust the dose of oral laxatives or to use BIS suppositories. In these studies, patients with chronic constipation (ROME III diagnostic criteria) were randomized to 4-weeks treatment with BIS tablets and SPS drops, respectively, or placebo. Starting dose was 10 mg oral daily that could be reduced by half in case of diarrhea, with dose restoration or use of a suppository if constipation recurred. Patients recorded data daily in an electronic diary. RESULTS: 735 patients were randomized, 233 to SPS, 247 to BIS, and 255 to placebo. The percentage of patients assigned to placebo taking the full dose of medication throughout the trial varied between 92.1 and 95.4%. In contrast, patients treated with SPS or BIS quickly tapered the dose according to their needs. At the end of treatment 46% of patients taking SPS and 58% of patients taking bisacodyl had reduced the dose to half. During treatment, the weekly proportion of patients using rescue medication was much lower in the SPS group (between 9.2 and 10.5%) than in the placebo group (between 22.6 and 27.8%) (all $p < 0.002$). In the bisacodyl trial these proportions were 0.4 to 2.5 % in the bisacodyl group and 1.7 to 10.3% in the placebo group ($p < 0.01$ for weeks 2 to 4). Despite the dose adjustments patients on the active drug achieved high levels of relief of constipation and associated symptoms compared to placebo (Mean number of complete spontaneous bowel movements per week >=3: 51.1% SPS vs 18.0 % placebo, 67.4% BIS vs 27.4% placebo, both $p<0.0001$) CONCLUSION: In contrast to physicians` concerns, patients can self-regulate the dose of stimulant laxatives, both oral and rectal, while maintaining effective treatment of chronic constipation.

S1329

VSL#3 use in a Double-Blinded, Placebo-Controlled Pilot Trial in Diarrhea-Predominant Irritable Bowel Syndrome

Sonia Michail, Frank W. Abernathy, Harshavadran Kenche, Adrienne Stolfi

Irritable Bowel Syndrome (IBS) is a common condition that negatively impacts the quality of life of many individuals. The exact etiology of this disorder is still largely unknown but a contributing role of the gut microbiome is suspected. Several studies suggest that probiotics can have a favorable effect on IBS. VSL#3 is a poly-microbial probiotic agent that shows some promise in managing IBS. The goal of this study was to investigate the safety and efficacy of VSL#3 in this pilot, double-blinded, randomized, placebo-controlled study in diarrhea-predominant IBS. Culture independent methods were used for fecal recovery and quantification of individual probiotic strains.In addition, the bacterial make up of the fecal microbiome was investigated using high-throughput microarray technology to detect 16s RNA. Ten adult patients were randomized to receive VSL#3 or placebo for 8 weeks. IBS symptoms were monitored using GSRS and quality of life questionnaires. Safety of the probiotic product was closely monitored. All of the eight bacterial strains of VSL#3 were successfully recovered and quantified individually using RT-PCR. The mean baseline pain score for both groups combined was 3.5±1.2, and decreased by 1.6±1.3 points at the end of the treatment period. GSRS-IBS pain, bloating, diarrhea, QOL score and global scores decreased significantly over the treatment period in both groups, but there was no difference between the groups in the degree of change. However, the decrease was significantly greater in the VSL #3 group for the satiety subscale. Spearman rank correlations between the change in GSRS-IBS pain scores and bacterial counts ranged from -0.82 to 0.36 at week 4, and from -0.87 to 0.15 at week 8. Correlations for changes in global scores ranged from -0.82 to 0.30 at week 4 and -0.80 to 0.60 at week 8. Two correlations were statistically significant: the change in global score and *Bifidobacterium infantis* at week 8 (rs = -0.90, p = .04), and the change in pain score and *Lactobacillus delbrueckii* at week 4 (rs = -0.95, p = .01). Aside from a significant increase in individual VSL#3 bacteria, the consumption of the probiotic did not change the gut microbiome. There were no adverse events or any safety concerns encountered during this study. To summarize, the use of VSL#3 in this pilot study in diarrhea-predominant IBS subjects was safe and showed some improvement in some specific GSRS-IBS scores. The improvement in symptoms correlated well with stool recovery of *Bifidobacterium infantis* and *Lactobacillus delbrueckii*. The gut microbiome was not otherwise affected by the consumption of the probiotic product. This work was supported by NIH.

S1330

Comparative Pharmacokinetics of Prucalopride in Healthy Young and Elderly Subjects

Vera J. Van de Velde, Jannie Ausma, Lieve Vandeplassche

INTRODUCTION: Prucalopride (PRU) is a highly selective 5-HT_4 receptor agonist with strong enterokinetic activity, developed for the treatment of chronic constipation. **AIMS & METHODS:** The aim of the study was to compare the single dose and steady state pharmacokinetics of PRU in healthy young and elderly subjects. This was an open, parallel group trial in 12 healthy elderly (8 male/4 female, aged 65-81 years) and 12 healthy young subjects (8 male/4 female, 20-32 years old). All were given a single 1 mg tablet of PRU on day 1, followed by a 1-week treatment of 1 mg o.d. on days 5 to 11. All doses were administered in the morning, 30 min before breakfast. Blood samples were taken up to 96 h after dosing on days 1 and 11, and pre-dose on days 9, 10 and 11. The complete urinary output of a 24-h dosing interval was collected on day 11. Plasma and urine concentrations of PRU were measured using radioimmunoassay, with a lower limit of quantification of 0.10 ng/ml in plasma and 20 ng/ml in urine. *In Vitro* plasma protein binding of PRU was determined in the day 1 pre-dose samples by equilibrium dialysis. Pharmacokinetic parameters were calculated using standard non-compartmental methods. **RESULTS:** After single dosing, maximum plasma concentration (C_{max}) was comparable in elderly (2.17 ± 0.67 ng/ml) and young subjects (2.24 ± 0.79 ng/ml), but area under the curve (AUC) was 19% higher in the elderly (69.6 ± 9.3 *vs.* 58.3 ± 14.7 ng.h/ml). Steady state was attained after 4 days of treatment. Steady state plasma concentrations were higher in the elderly than in the young subjects with the AUC increased by 28% (72.2 ± 12.5 ng.h/ml *vs.* 56.2 ± 16.5 ng.h/ml). The effect was larger on minimum plasma concentration (C_{min}) (+41%) than on C_{max} (+19%). Urinary excretion at steady state accounted for 61% (young) to 66% (elderly) of the dose. Both the apparent oral clearance and renal clearance were lower in the elderly than in the young subjects. The mean creatinine clearance was 132 ml/min in young and 78.6 ml/min in elderly subjects. Plasma protein binding of PRU was similar in elderly (32.8%) and young subjects (33.3%). **CONCLUSION:** Urinary excretion is a major elimination pathway for PRU. As renal function decreases with age, the somewhat lower renal clearance and consequently higher exposure of PRU in elderly subjects is not unexpected. Results of clinical trials indicated that a lower dose is needed in elderly subjects (1 mg o.d.) than in young and middle-aged adult subjects (2 mg o.d.). However, there is no pharmacokinetic basis for this finding, as the increase in exposure by approximately 30% is too low to justify halving the dose.

S1331

I.V. Kinetics and Absolute Oral Bioavailability of Prucalopride

Vera J. Van de Velde, Jannie Ausma, Lieve Vandeplassche

INTRODUCTION: Prucalopride is a highly selective 5-HT_4 receptor agonist with strong enterokinetic activity, developed for the treatment of chronic constipation. **AIMS & METHODS:** Five male and 8 female subjects completed this open study. They were administered single doses of 2 mg prucalopride, first as a 2 mg tablet (fasting), and 2 to 4 weeks later, as a 10-min i.v. infusion. Plasma concentrations of prucalopride were determined at multiple time points up to 96 h after each dose by a validated radioimmunoassay, with a lower limit of quantification of 0.10 ng/ml. Pharmacokinetic parameters were calculated using standard non-compartmental methods. A compartmental analysis was also applied on the i.v. data, using WinNonlin (Pharsight Corporation). **RESULTS:** Peak plasma concentrations at the end of the infusion averaged 9.21 ± 5.96 ng/ml (mean ± SD), about twice the peak plasma levels after the oral dose, which were obtained in about 2 h. The data were best fitted using a two- (n=7) or three- (n=6) compartment model. Individual and average $AUC_{infinity}$ and Clearance (Cl) obtained by non-compartmental (108 ± 21 ng.h/ml, 19.1 ± 3.1 L/h) and compartmental analysis (109 ± 21 ng.h/ml, 19.0 ± 3.1 L/h) were very close. Volume of distribution at steady state (Vd_{ss}) averaged 567 ± 107 L and the non-compartmental volume of distribution (Vd_{area}) was 611 ± 100 L. The terminal half-life of prucalopride averaged 22.5 h after the i.v. treatment and 21.2 h after the oral dose. The absolute oral bioavailability was 93.2 ± 11.6%. **CONCLUSION:** After i.v. dosing prucalopride was rapidly and extensively distributed. It has a large volume of distribution and a low plasma clearance. The high absolute oral bioavailability of prucalopride demonstrates that its absorption after oral dosing is almost complete and that no appreciable first-pass metabolism occurs. The latter is in line with results from *In Vitro* and *In Vivo* metabolism studies in man, showing slow metabolism, and only minor amounts of relatively few metabolites. Also the involvement of an efflux pump (such as P-glycoprotein) in the oral absorption of prucalopride is unlikely in view of the high absolute bioavailability.

S1332

Expected Frequency of Stool Patterns According to the Bristol Scale After 4 Weeks of Treatment With Pinaverium Bromide + Simethicone for IBS ROME III Patients. A Report From the Mexican IBS Working Group

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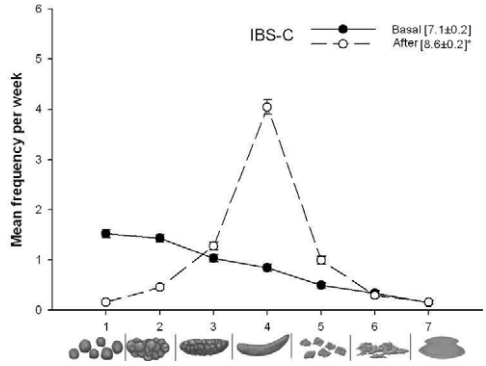
We have previously shown the usefulness of the stool consistency-frequency relationship transformed into polar vectors to evaluate the clinical response to a pharmacological treatment in IBS. Aim:To explore the mathematical expectation of the frequency of each stool pattern according to the Bristol scale (Basal) and the change after 4 week of treatment with pinaverium bromide 100mg + simethicone 300mg (PB + S) (After). Methods:In a nationwide study in Mexico, 1369 IBS-Rome III patients recorded during one week the daily frequency of each bowel movement(BM) in a table with the figures of the 7 Bristol stool patterns. The expected distribution probability was calculated by the area under the curve of the observed frequency of each stool pattern. Patients (F:76%, Age:37±9 yrs, BMI 26.5±6 were classified as IBS-C:577 (42%), IBS-D:206 (15%), IBS-M:88 (6%), IBS-U:498 (37%). Results:The table shows the Basal and After-treatment probability(P) of having Bristol pattern >2 and <6 according

to the IBS subtypes. After treatment all IBS subgroups had a trend towards a Bristol pattern of 4.The IBS-M showed the highest likelihood ratio for changing while the IBS-U showed the lowest ratio. Conclusions:Patients with IBS have less than a 38% probability of having a Bristol between 3 and 5 except for the IBS-U that has a 78% probability. A 4-week treatment with PB+S has a notable impact on the expected frequency of stool patterns, especially in the IBS-M followed by the IBS-C. Figure show the basal and after treatment expected frequencies of stool patterns in IBS-C.

	Likelihood ratio	Basal	After 4 weeks
Subgroups	P(2		P(4Post)/P(Basal)
IBS-C	0.32	0.85	2.7
IBS-D	0.38	0.77	2.0
IBS-M	0.20	0.79	4.1
IBS-U	0.78	0.85	1.1



S1333

A Comparison of Two Radio-Opaque Marker Methodologies in the Assessment of Colonic Transit of Adults With Constipation

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Background: Two common radio-opaque marker (ROM) protocols used to assess colon transit in constipation include the 5-day ROM study (Hinton protocol requiring 1 x-ray on day 5) and the 7-day ROM study (Metcalf protocol requiring 2 x-rays on days 4 & 7). Although more simplistic, the accuracy of the 5-day ROM study in comparison to the 7-day ROM study remains undefined. Aim: To compare the accuracy of the 5-day ROM study with the 7-day ROM study in the determination of delayed versus normal colon transit in adults with chronic constipation Methods: This is a post hoc analysis of adults with chronic constipation from 11 U.S. sites and 1 U.K. site receiving simultaneous assessment of colon transit utilizing the 5-day ROM protocol and the 7-day ROM protocol. For the 5-day protocol, each participant ingested a capsule containing 24 radio-opaque markers. An abdominal x-ray was obtained 5 days later to determine the number of retained markers. A subject was defined as having a delayed colon transit if 6 more or markers were found on this x-ray. For the 7-day protocol, each participant ingested a single capsule containing 24 radio-opaque markers on three consecutive days (for a total of 72 markers over the 3 days). An abdominal x-ray was obtained 4 & 7 days after the initial day of marker ingestion. The number of retained markers for each x-ray was counted and the two separate marker counts were combined yielding a total marker count for both x-rays. A subject was defined as having delayed colon transit if more than 67markers were identified on the two x-rays. Results: 109 adults (93 female, 16 male) were included with a mean age of 42 years (age range of 19 to 76). 84% were Caucasian. 19 subjects were defined as having delayed colon transit by the 5-day ROM protocol. 24 subjects were defined as having delayed transit by the 7-day ROM protocol. The overall agreement between the 5-day ROM protocol and 7-day protocol was 92% (95% CI: 85-96%). The positive agreement between the two protocols was 71% (95% CI: 49-87%) and the negative agreement was 98% (95% CI: 92-100%). In other words, the sensitivity and specificity of the 5-day protocol using the 7-day protocol as a gold standard were 71% and 98%, respectively. Conclusions: The overall agreement in results between the 5-day and 7-day ROM protocols is reasonably good. However, 30% of constipated adults with delayed colon transit by the 7-day ROM protocol will be missed by the 5-day ROM protocol.

S1334

Patterns of Lubiprostone Utilization in a Large Managed Care Population

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Background: Chronic idiopathic constipation (CIC) and irritable bowel syndrome (IBS) pose a considerable burden of illness and account for increased direct costs and healthcare utilization. The objective of this study was to assess patterns of twice daily lubiprostone (24 mcg) utilization in patients with CIC or IBS in a large managed care population. Methods: We conducted a retrospective cohort study of medical and pharmacy claims from the Humana Inc. administrative database of patients identified as having at least one 30-day prescription for lubiprostone (24 mcg.) between April 1, 2006 and June 30, 2008. The index date was first lubiprostone prescription filled during this identification period. Results: 4593 patients met the inclusion criteria of lubiprostone use with 90 days pre-index and at least 30 days post-index continuous enrollment. Seventy-seven percent were female. The mean age of all patients was 59.6 (SD±16.97). The most common conditions associated with lubiprostone use within 90 days pre-index date were constipation (38%) and IBS (12%). Abdominal pain (22%), spondylosis/other back disorders (18%), hypertension (17%), and other gastrointestinal disorders (36%) were the most common coexisting disease categories identified. The 5 most frequently prescribed drug classes within 90 days prior to the index date were opiates, proton pump inhibitors, statins, thyroid hormones, and selective serotonin reuptake inhibitors. Thirty percent of patients had at least one prescription for a constipation associated drug (defined as prescription laxatives and/or tegaserod) within 90 days prior to index date, 19% had at least two prescriptions, and 9% had at least three such prescriptions. The mean Deyo-Charlson comorbidity score was 0.48 (SD‡1.12). One year of follow up data post-index date were available for 1602 patients. Of those with one year follow-up, the mean number of lubiprostone prescriptions per patient was 3.1 and the median was 2 (1.4). Fifty percent of these patients filled one lubiprostone prescription (30-day supply of 60 capsules), 14% filled two prescriptions, 7% filled 3 prescriptions and 29% filled greater than or equal to 4 prescriptions. Conclusions: Female gender, concomitant medication use, abdominal pain, back disorders, hypertension and other gastrointestinal disorders were prevalent among this population prescribed lubiprostone. Among those with one year of follow-up the average number of prescriptions filled per patient was 3.1 and 50 percent filled two or more lubiprostone prescriptions.

S1335

Placebo Response Rates in Trials of Pharmacological Therapies for Irritable Bowel Syndrome: Systematic Review and Meta-Analysis

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Background and aims: Irritable bowel syndrome (IBS) is a chronic, fluctuating functional disorder of the gastrointestinal tract. The magnitude of the placebo response rate in the condition, and what factors may influence this, is important. We conducted a systematic review and meta-analysis of randomized placebo-controlled trials of pharmacological therapies in IBS to examine this issue. Methods: MEDLINE, EMBASE, and the Cochrane Controlled Trials Register were searched (up to July 2009) to identify randomized controlled trials (RCTs) comparing pharmacological therapies with placebo in adult IBS patients, diagnosed using clinical or symptom-based criteria. Follow-up was for at least 1 week, and studies had to report either a global assessment of IBS symptom cure or improvement, or abdominal pain cure or improvement, at trial completion. Data were extracted as intention-to-treat analyses with drop-outs assumed to be treatment failures. Symptom data were pooled using a random effects model, and the proportion of placebo patients experiencing symptom improvement or resolution was reported, with a 95% confidence interval (CI). Effect of study location, number of centers, setting, predominant stool pattern, diagnostic criteria used, dosing schedule, duration of therapy, generation of randomization schedule, concealment of allocation, and study quality (according to the Jadad score) were examined (Table). Results: 71 RCTs were eligible for inclusion, including 21489 patients with IBS, 8289 (38.6%) of whom received placebo. The pooled placebo response rate across all 71 RCTs was 37.5% (95% CI 34%-41%). Conclusions: Pooled placebo response rate across all RCTs of pharmacological therapies in IBS was highest in European studies, studies that defined IBS using clinical criteria, studies with higher dosing schedules, of shorter duration of therapy, and of lower quality.

	Number of trials	Placebo response rate (%)	95% CI
Study location Asia Europe Middle-East North America	6 33 3 15	25 43 22 33	16 - 36 37 - 49 8 - 40 29 - 37
Number of centers Single Multi	36 32	41 37	38.5 - 44 34 - 41
Setting Secondary care Tertiary care	21 20	39 37	31 - 48 26 - 48
Predominant stool pattern Constipation Diarrhea	16 8	36 33	31 - 42 28 - 39
Diagnosis of IBS Clinical Rome I Rome II	28 19 21	42 36 34	33 - 51 31 - 41 29 - 39
Dosing schedule Once daily Twice daily Thrice daily	19 21 25	31 36 43	24 - 39 32 - 40 37 - 50
Duration of therapy 1 - 4 weeks 5 - 8 weeks > 8 weeks	19 10 41	46 38 34	39 - 54 26.5 - 51 30 - 37
Generation of randomization schedule Stated Not stated	25 46	35 39	31 - 40 34.5 - 43
Concealment of allocation Stated Not stated	5 66	36 37.5	28 - 45 34 - 41
Jadad score 3 4 5	14 31 22	40 38 35	30 - 50 34 - 43 31 - 39

S1336

A Qualitative Examination of Irritable Bowel Syndrome (IBS) Symptom Episode Experience via Online Survey

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Background and Aims: Few studies have examined the symptoms of IBS from the patient's perspective nor is it well understood what a patient with IBS means by an "episode". Furthermore recent evaluations of moment to moment reports of GI symptoms using ecological momentary assessment indicate that they may occur variably: in an episodic fashion. Our study aim was to evaluate in a qualitative fashion the symptoms reported by patients with IBS and the factors contributing to an episode. Methods: 303 participants responded to an online survey asking both quantitative and open ended qualitative questions about IBS symptom experience. Participants who met Rome III criteria for IBS, reported a physician