NOME E NUMERO DEL PROVIDER: I&C SRL - 5387
ECM N°: 180726
TITOLO: XVII CONGRESSO NAZIONALE GISMAD
SEDE: MILANO, HOTEL NHOW
DATA: 09-10/03/2017

NEL RISPETTO DELLE NUOVE DISPOSIZIONI IN MATERIA DI ECM, A SEGUITO DELL'ATTUAZIONE DELL'ACCORDO STATO-REGIONI DEL 5/11/09 E SUCCESSIVE MODIFICHE, AL FINE DI GARANTIRE LA MASSIMA TRASPARENZA IN MATERIA DI CONFLITTO DI INTERESSI SI INFORMANO I DISCENTI CHE PRESSO IL DESK RELATORI SONO DISPONIBILI I DOCUMENTI ATTESTANTI LE EVENTUALI COLLABORAZIONI CHE I DOCENTI ABBIANO AVUTO NEL CORSO DELL'ULTIMO BIENNIO CON AZIENDE FARMACEUTICHE E/O DIAGNOSTICHE DALLE QUALI SIA DERIVATA L'EROGAZIONE DI COMPENSI O FINANZIAMENTI.

Stato dell'arte sulla terapia dell'IBS-C

Maura Corsetti, MD PhD

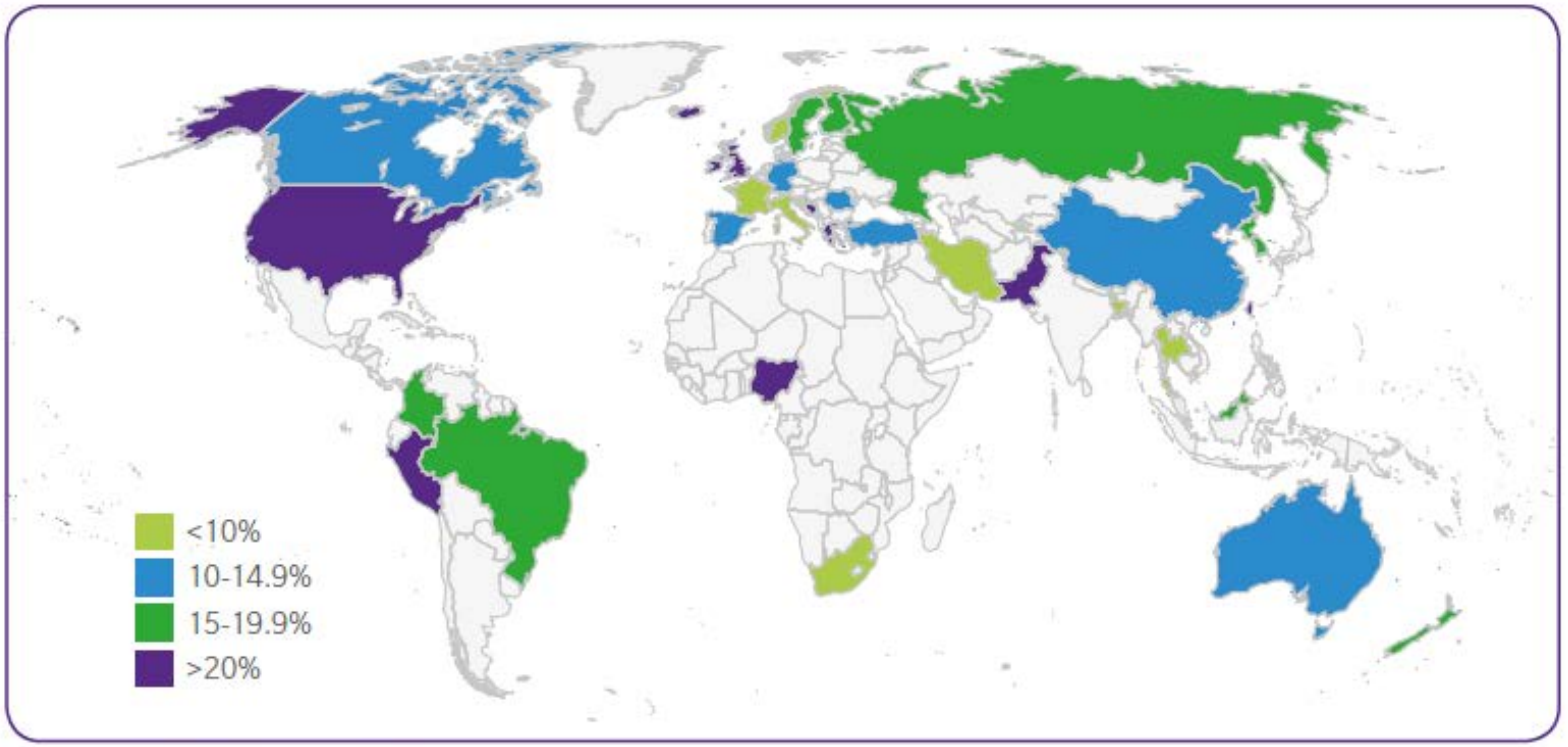
Nottingham Digestive Diseases Centre (NDDC)

University of Nottingham

UK

Why is important for gastroenterologists to study IBS?

Figure 1. Prevalence of IBS – a global picture[16]



Source: *Adapted from Canavan et al 2014*

Globally, IBS is prevalent both in developed and developing countries.[19,20] Early studies suggested a low IBS prevalence in developing countries, with more recent studies indicating an increasing prevalence in newly developed and developing economies (i.e. Asia) as they become 'westernised'.[19] Prevalence estimates for IBS vary considerably between countries, from less

IBS account for up to 50% of consultations of gastroenterologists

Corsetti M, Tack J et al. IBS Global Impact report

Rome IV Diagnostic Criteria for IBS

C1. Diagnostic Criteria[a] for Irritable Bowel Syndrome

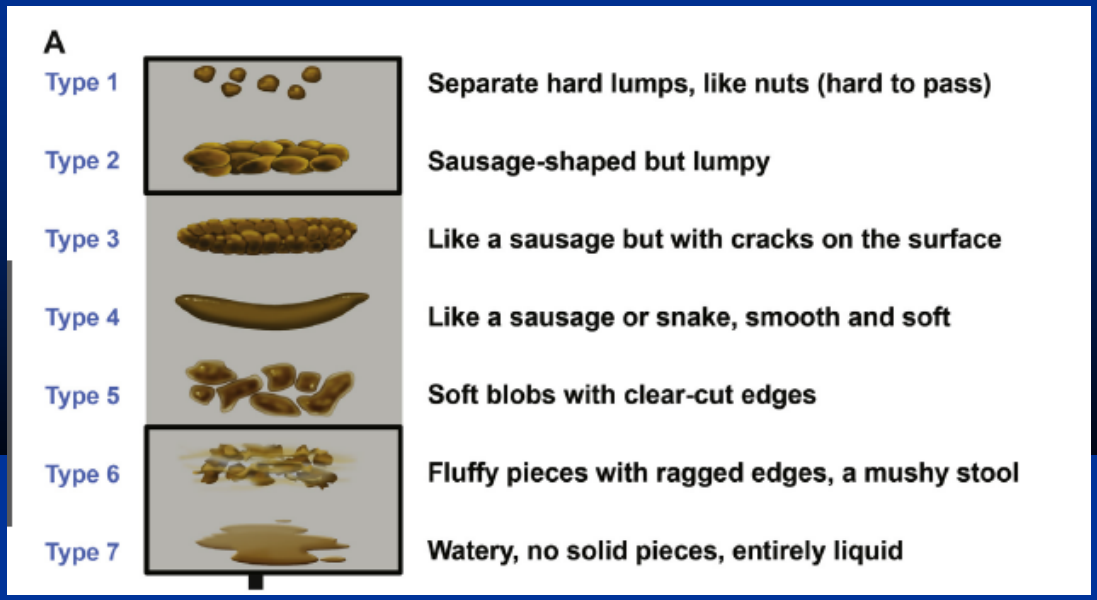
Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months, associated with 2 or more of the following criteria:

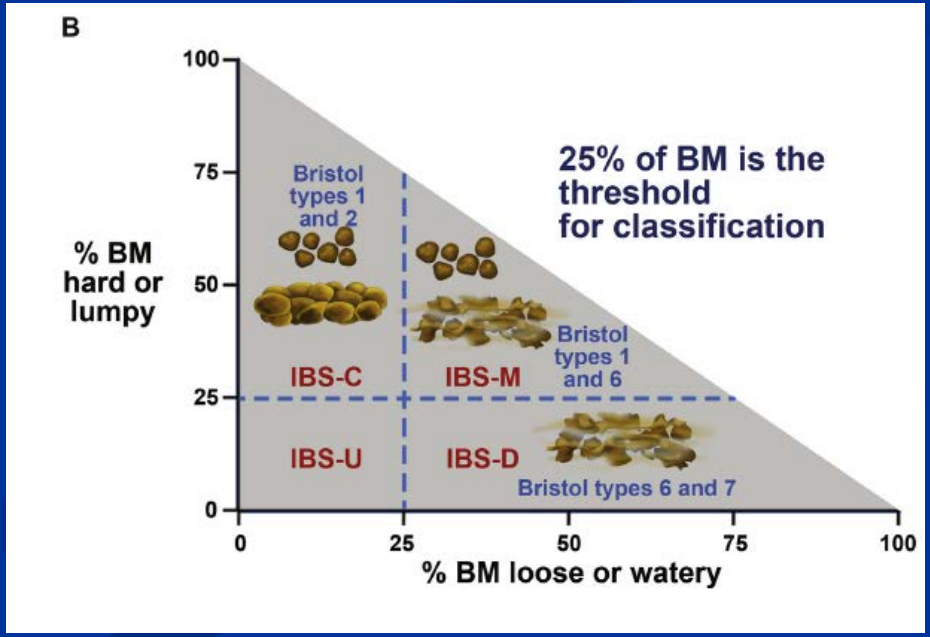
1. Related to defecation
2. Associated with a change in frequency of stool
3. Associated with a change in form (appearance) of stool

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Lacy BE, Gastroenterology 2016

Subtyping of IBS





Lacy BE, Gastroenterology 2016

The biopsychosocial model of IBS

Predisposing factors	Triggering factors	Perpetuating factors
Early trauma Abuse Family history of IBS Anxiety/Depression	Infections Surgical operations Antibiotics Drugs Major loss	Anxiety/Depression

IBS

Altered gut motility
Visceral hypersensitivity

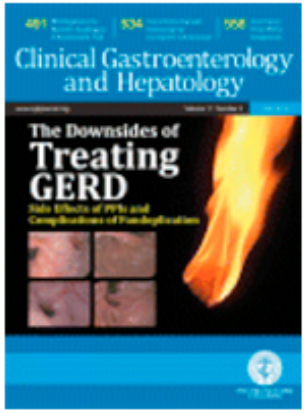
Drossman DA, back in 1994

The psychological disturbances in IBS: cause or consequence?

Accepted Manuscript

Mood and Anxiety Disorders Precede Development of Functional Gastrointestinal Disorders in Patients but not in the Population

Michael P. Jones, Jan Tack, Lukas Van Oudenhove, Marjorie M. Walker, Gerald Holtmann, Natasha A. Koloski, Nicholas J. Talley



The present data are consistent with the findings of Koloski and colleagues[11] who found that the association is bidirectional since individuals free of FGIDs at baseline were more likely to develop an FGID 12 years later if they had higher affective scores and that those free of affective disorder at baseline were more likely to develop one if they had an FGID. Our data

The role of previous infections in IBS

A systematic review has evaluated the results of studies reporting the percentage of infected individuals who develop PI-IBS and has found that between 4% and 36% of these subjects develop the functional disorder.

PI-IBS has been described more frequently as consequence of bacterial infection than of a viral infection.

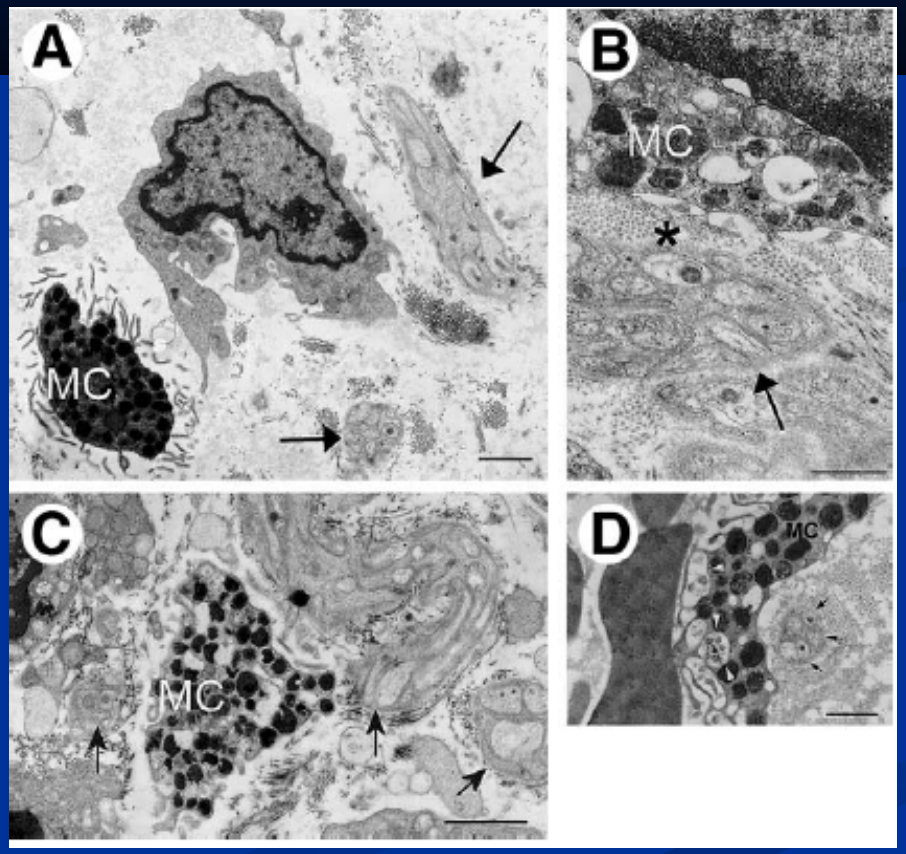
PI-IBS can also occur in subjects with previous Clostridium Difficile infection and after a parasite infection.

After ≥6 months from Clostridium infection, diagnosed by means of both culture and rapid immunoassay toxins detection, 25% of 205 patients without prior Rome III criteria IBS met this diagnosis.

Rome Foundation Working Team on Post-Infectious IBS 2017

Activated Mast Cells in Proximity to Colonic Nerves Correlate With Abdominal Pain in Irritable Bowel Syndrome

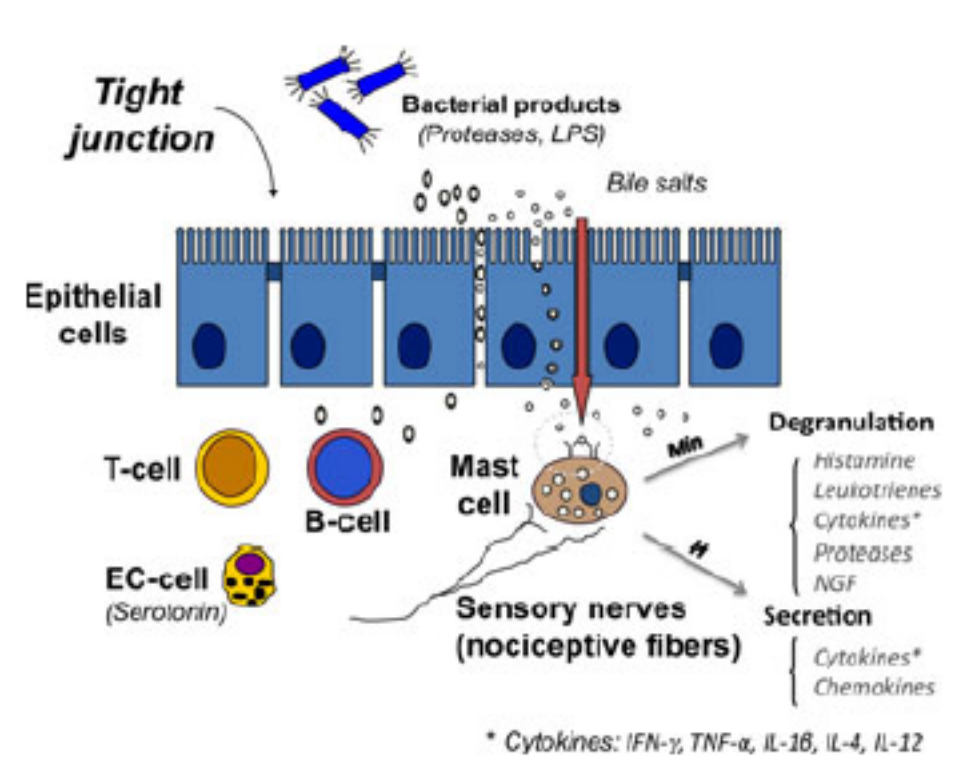
GIOVANNI BARBARA,* VINCENZO STANGHELLINI,* ROBERTO DE GIORGIO,* CESARE CREMON,* GRAEME S. COTTRELL,† DONATELLA SANTINI,§ GIANANDREA PASQUINELLI,§ ANTONIO M. MORSELLI–LABATE,* EILEEN F. GRADY,† NIGEL W. BUNNETT,† STEPHEN M. COLLINS,¶ and ROBERTO CORINALDESI*



Gastroenterology 2004

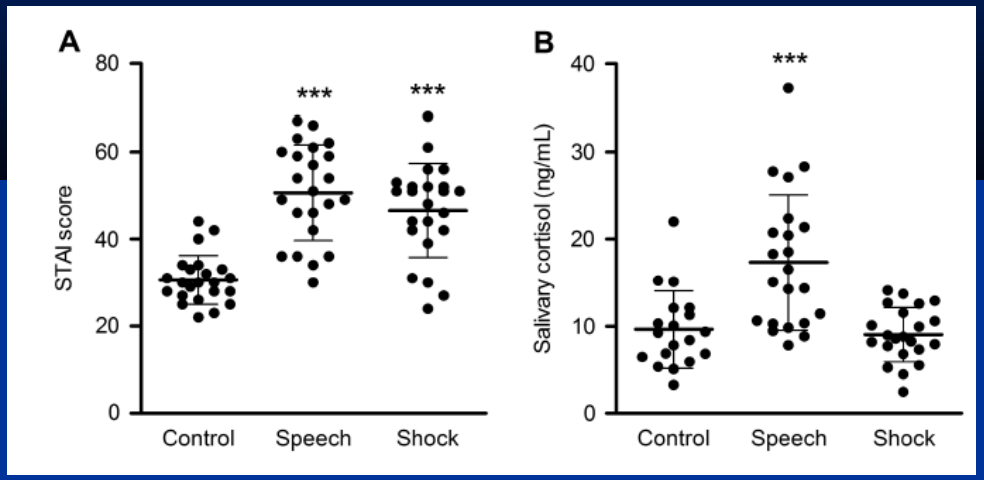
Gut permeability: the key player in IBS

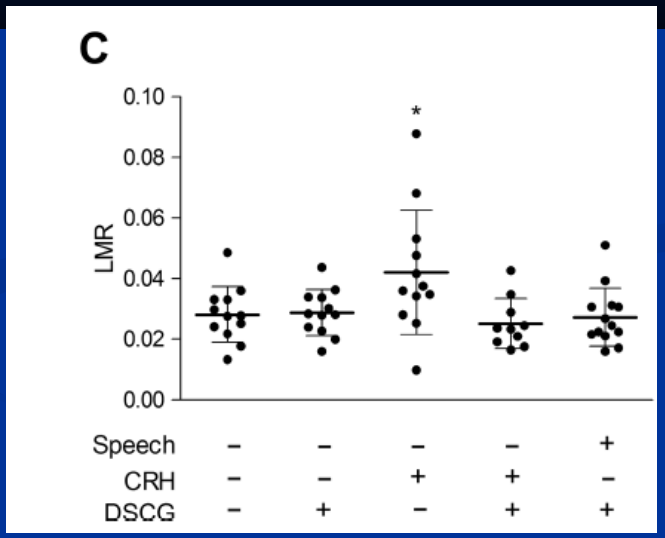
Tight junctions and IBS - the link between epithelial permeability, low-grade inflammation, and symptom generation?

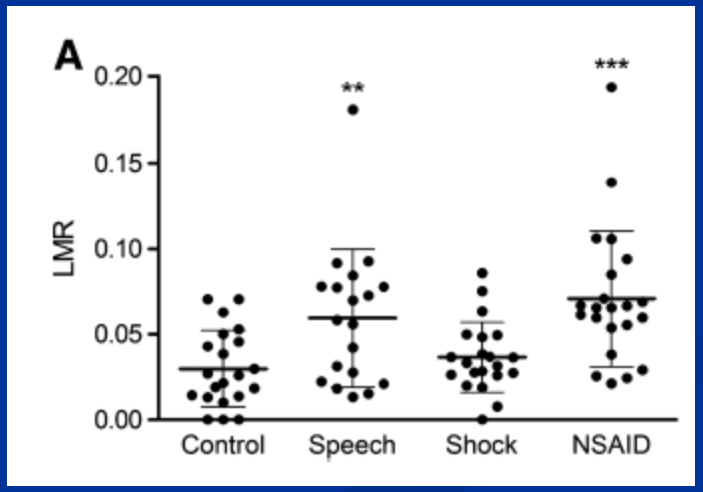


Piche T, Neurogastroenterol Mot 2014

Psychological stress and corticotropin-releasing hormone increase intestinal permeability in humans by a mast cell-dependent mechanism

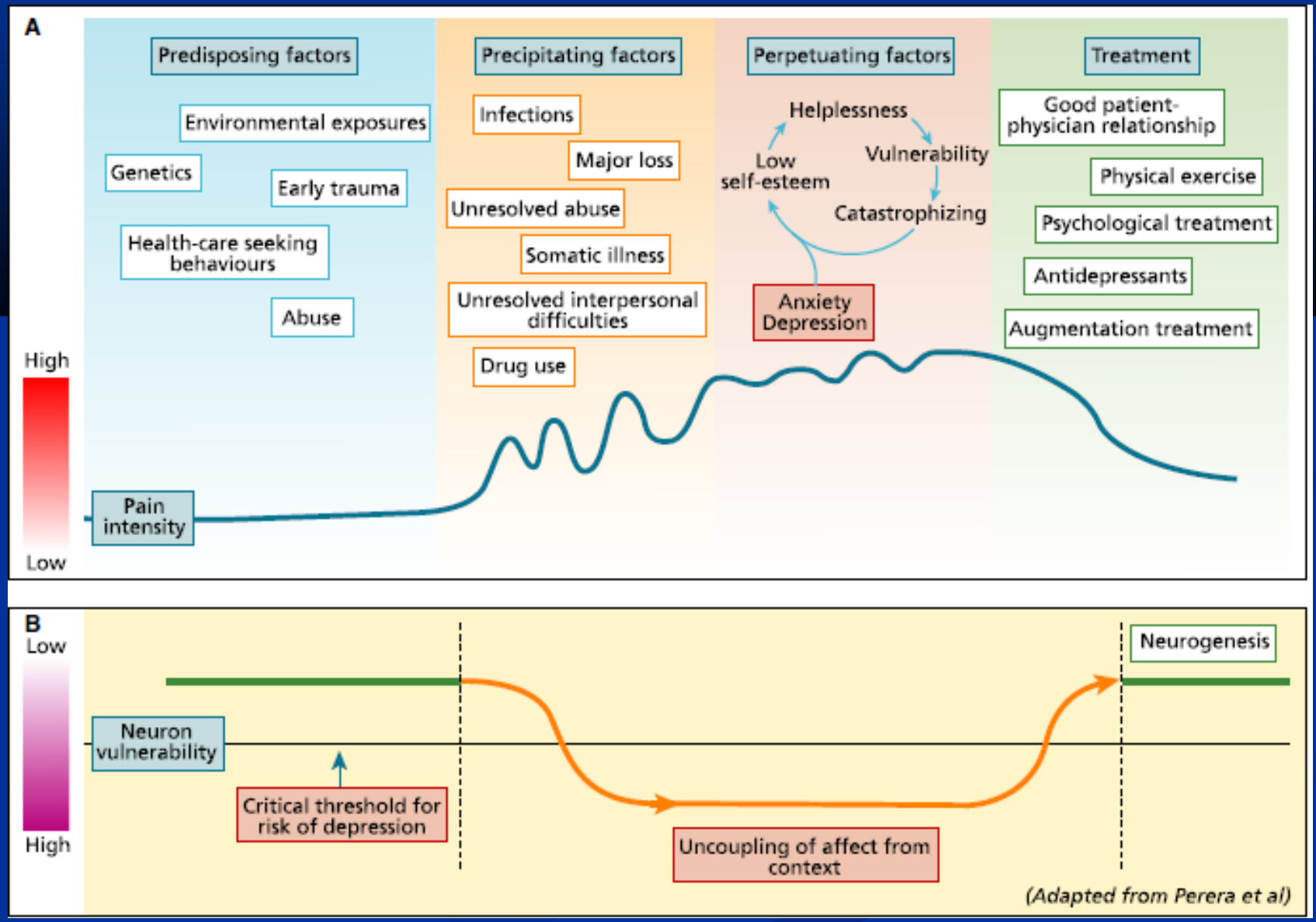






Gut 2014;**63**:1293–1299.

Interaction between biopsychosocial factors and neurodegeneration

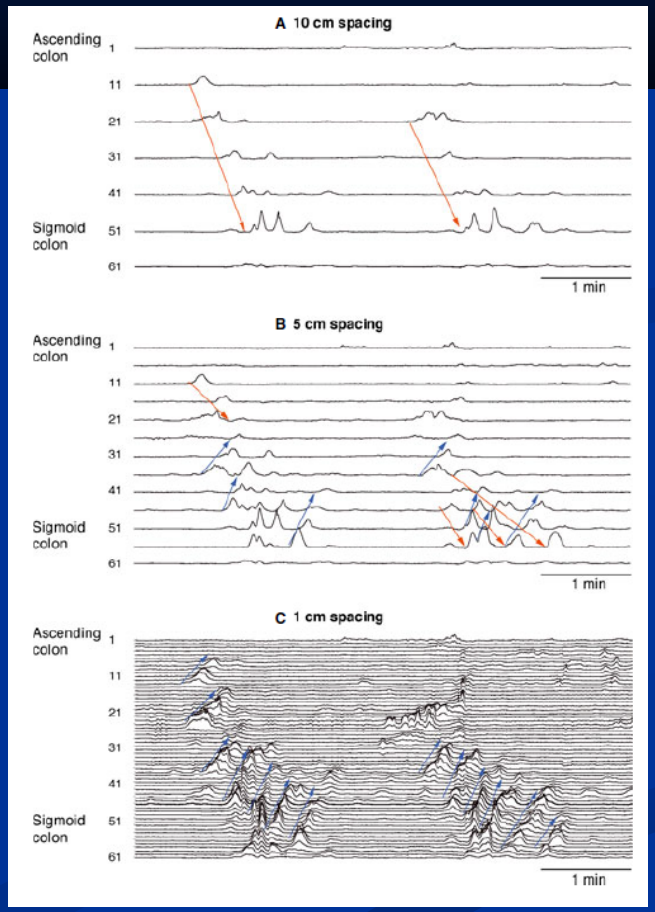


Drossman DA, Neurogastroenterol Mot 2015

The role of visceral hypersensitivity and altered motility in IBS

Low-resolution colonic manometry leads to a gross misinterpretation of the frequency and polarity of propagating sequences: Initial results from fiber-optic high-resolution manometry studies

P. G. DINNING, *,† L. WIKLENDT,‡ I. GIBBINS,§ V. PATTON,†,¶ P. BAMPTON,* D. Z. LUBOWSKI,†,¶,‖ I. J. COOK†,** & J. W. ARKWRIGHT††



Neurogastroenterol Motil (2013) **25**, e640–e649

Pan-Colonic Pressurizations Associated With Relaxation of the Anal Sphincter in Health and Disease: A New Colonic Motor Pattern Identified Using High-Resolution Manometry

Maura Corsetti, MD, PhD[1,2], Giuseppe Pagliaro, MD[1], Ingrid Demedts, MD, PhD[1], Ewaline Deloose, PhD[1], Annemie Gevers, MD[1], Charlotte Schaerens[1], Nathalie Rommel, PhD[1] and Jan Tack, MD, PhD[1]

OBJECTIVES: **Only a few studies have applied high-resolution manometry (HRM) to the study of colonic motility in adults and none of them have concurrently evaluated colonic and anal motor activity. The aim of the study was to evaluate colonic and anal motor activity by means of HRM in healthy subjects. As the present study revealed the presence of a new colonic motor pattern (pan-colonic pressurizations) in healthy subjects, three additional studies were conducted: the first and the second to exclude that this motor event results from an artifact due to abdominal wall contraction and to confirm its modulation by cholinergic stimulation, and the third, as pilot study, to test the hypothesis that this colonic pattern is defective in patients with chronic constipation refractory to current pharmacological treatments.**

METHODS: **In both volunteers and patients the HRM catheter was advanced proximally during colonoscopy.**

RESULTS: **In all subjects, pressure increases of 15±3 mm Hg and 24±4 s simultaneously occurring in all colonic sensors (pan-colonic pressurizations) and associated with anal sphincter relaxation were identified. Subjects had 85±38 pan-colonic pressurizations, which increased significantly during meal (P=0.007) and decreased afterward (P=0.01), and were correlated with feelings of and desire to evacuate gas. The mean number of propagating sequences was 47±39, and only retrograde increased significantly postprandially (P=0.01). Pan-colonic pressurizations differed from strain artifacts and significantly increased after prostigmine. In patients pan-colonic pressurizations were significantly reduced as compared with volunteers.**

CONCLUSIONS: **Pan-colonic pressurizations associated with relaxations of the anal sphincter represent a new colonic motor pattern that seems to be defective in patients with treatment-refractory chronic constipation and may have a role in the transport of colonic gas and in the facilitation of the propagating sequence-induced colonic transport.**

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg

Am J Gastroenterol advance online publication, 6 September 2016; doi:10.1038/ajg.2016.341

[1]Translational Research Center for Gastrointestinal Disorders (TARGID), Department of Clinical and Experimental Medicine, University of Leuven, Leuven, Belgium; [2]National Institute for Health Research, Nottingham Digestive Diseases Biomedical Research Unit, Nottingham University Hospitals NHS Trust, University of Nottingham, Nottingham, UK. **Correspondence:** Jan Tack, MD, PhD, Department of Internal Medicine, Division of Gastroenterology, University Hospital Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium. E-mail: Jan.Tack@med.kuleuven.be

The data of the present manuscript have been presented as oral presentations at the *First Federation of Neurogastroenterology and Motility Meeting in Guangzhou, China September 2014 (Neurogastroenterol Mot 2014; Issue 26: 91*, at *Digestive Disease Week (DDW) Washington, USA, May 2015 (Gastroenterology 2015; 148: S-192)* and at *Neurogastro 2015 Istanbul, Turkey, June 2015 (Neurogastroenterol Mot 2015; 27: S-34).*

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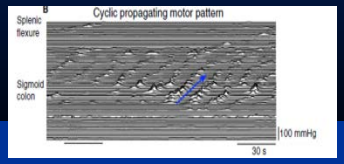
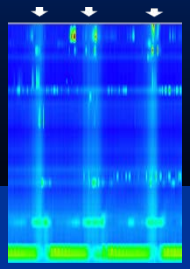
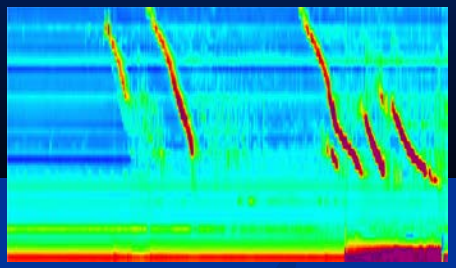
The colonic motility during…

Pre-prandial period	Post-prandial period	Response to bisacodyl

Healthy subjects
n= 10

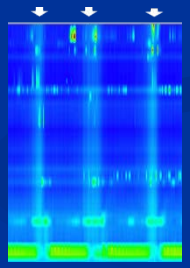


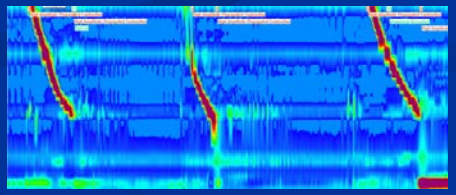




Painful constipation
(treatment refractory)
n= 15

+ Symptoms

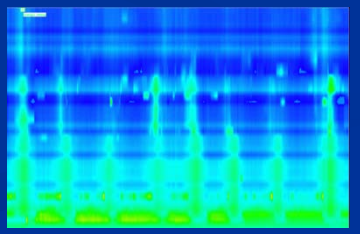




Reduced number

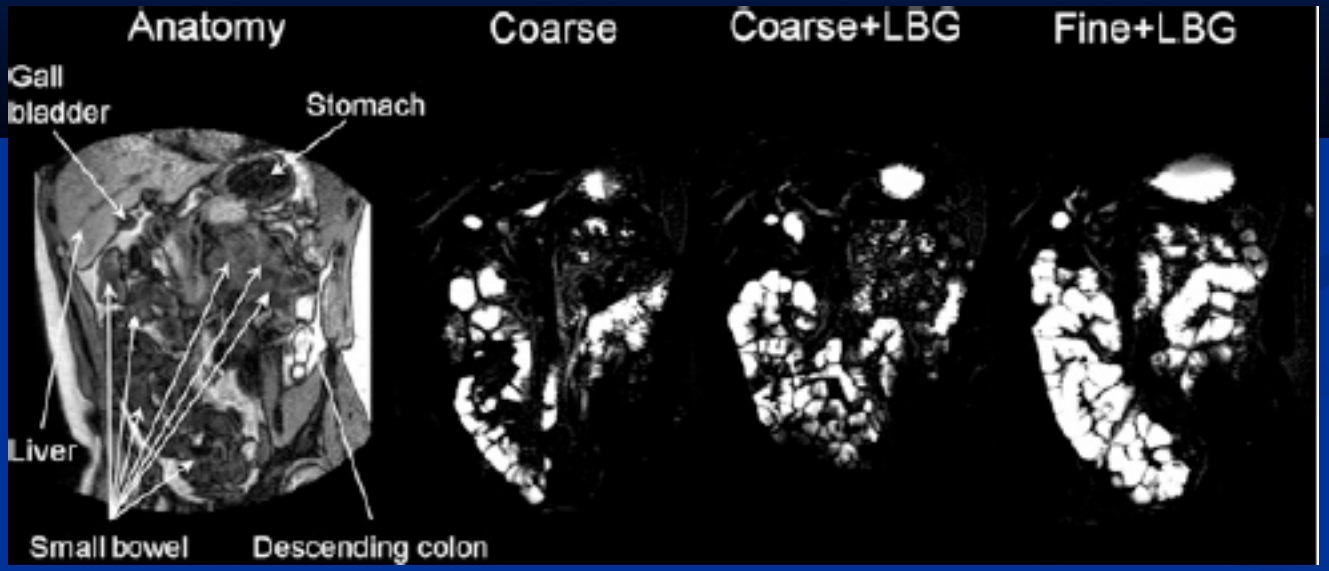
Painless constipation
(treatment refractory)
n= 10

No response n= 4



Corsetti M, FNM 2016

The effect of different foods on the small bowel water content as measured by MRI in health



Hussein M, J Nutr 2015

The management of IBS

Which antispasmodic is effective in IBS-C?

American College of Gastroenterology Monograph on the Management of Irritable Bowel Syndrome and Chronic Idiopathic Constipation

Statement	No. of trials	No. of patients	RR symptoms (95% CI)	NNT (95% CI)	Recommendation	Quality of evidence
Certain antispasmodics provide symptomatic short-term relief in IBS.	23	2,154	0.69 (0.59–0.81)	5 (4–9)	Weak	Low
Peppermint oil is superior to placebo in improving IBS symptoms.	5	482	0.51 (0.33–0.79)	3 (2–4)	Weak	Moderate

With respect to individual agents, otilonium (128,129,131, 132,138), hyoscine bromide (64,67,146), cimetropium bromide (130,134,143), pinaverium bromide (133,139,147), and dicyclomine hydrochloride (142) showed beneficial effects with NNTs of 5, 3, 3, 3, and 4, respectively. However, some of these were evalu-

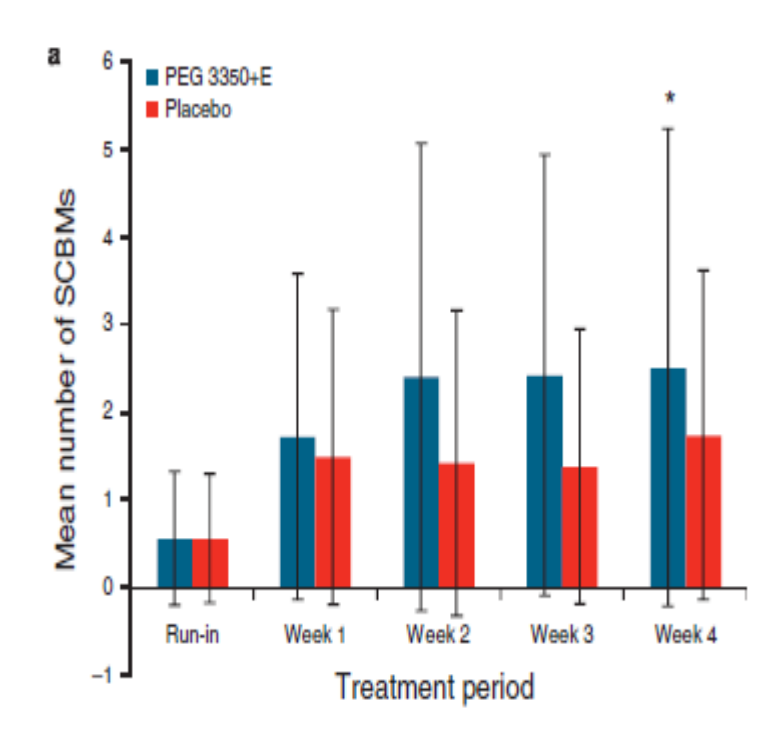
Mebeverine (one trial), trimebutine (three trials), pirenzipine (one trial), alverine (one trial), rociverine (one trial), prifinium (one trial), and propinox (one trial) did not have a statistically significant effect on IBS symptoms, although the numbers of patients studied were small.

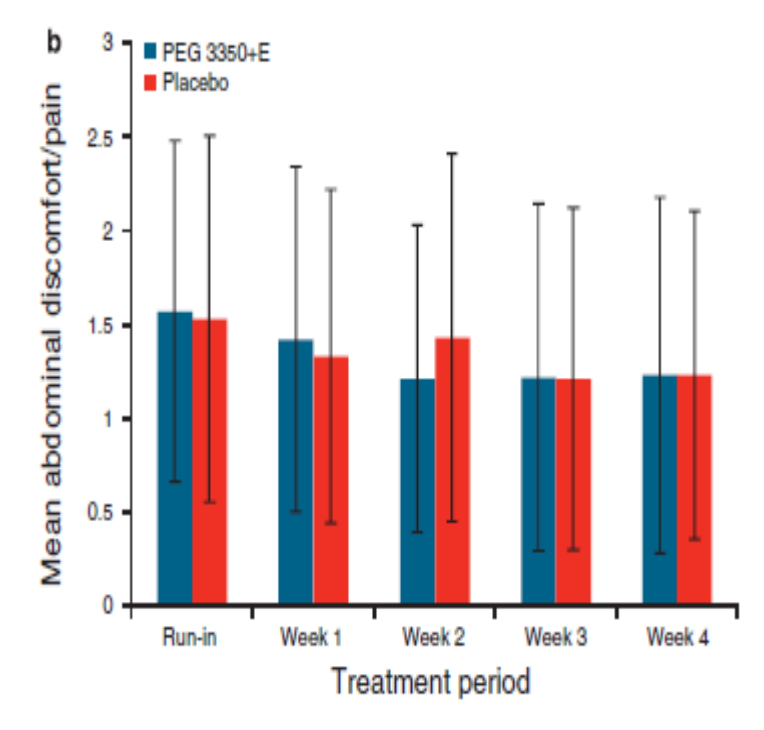
Ford AC, Am J Gastroenterol 2014; Camilleri M, Gut 2017

Laxatives

Randomized Clinical Trial: Macrogol/PEG 3350 Plus Electrolytes for Treatment of Patients With Constipation Associated With Irritable Bowel Syndrome

R.W. Chapman, MD[1], V. Stanghellini, MD[2], M. Geraint, MB ChB[3] and M. Halphen, MD[3]



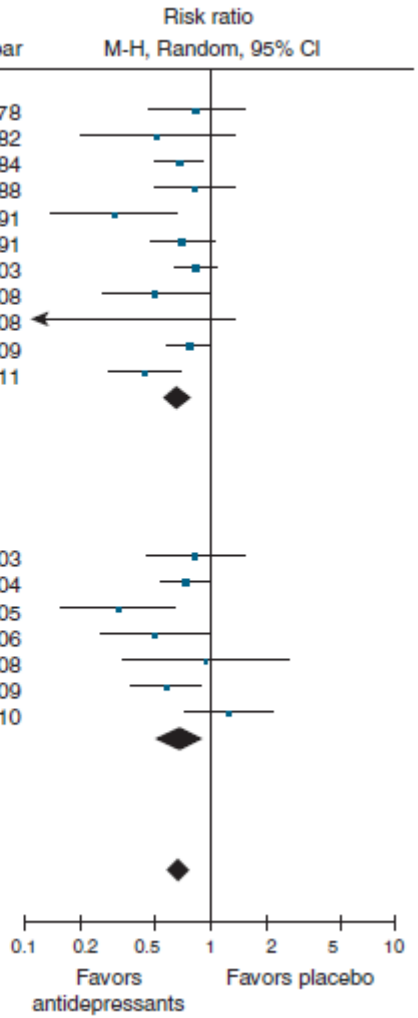


Am J Gastroenterol 2016

Antidepressants

The efficacy of antidepressants in IBS

Study or subgroup	Antidepressants Events	Total	Placebo Events	Total	Weight	Risk ratio M-H, Random, 95% CI	Year
1.1.1 Tricyclic antidepressants							
Heefner, 1978	10	22	12	22	4.5%	0.83 (0.46, 1.51)	1978
Myren, 1982	5	30	10	31	2.1%	0.52 (0.20, 1.33)	1982
Nigam, 1984	14	21	21	21	9.8%	0.67 (0.50, 0.92)	1984
Boerner, 1988	16	42	19	41	5.6%	0.82 (0.50, 1.36)	1988
Bergmann, 1991	5	19	14	16	3.0%	0.30 (0.14, 0.65)	1991
Vij, 1991	14	25	20	25	7.5%	0.70 (0.47, 1.04)	1991
Drossman, 2003	60	115	36	57	11.0%	0.83 (0.63, 1.08)	2003
Vahedi, 2008	8	27	16	27	3.8%	0.50 (0.26, 0.97)	2008
Talley, 2008	0	18	5	16	0.3%	0.08 (0.00, 1.36)	2008
Abdul-Baki, 2009	34	59	36	48	10.7%	0.77 (0.58, 1.01)	2009
Ghadir, 2011	14	38	20	24	6.5%	0.44 (0.28, 0.70)	2011
Subtotal (95% CI)		416		328	64.7%	0.66 (0.56, 0.79)	
Total events	180		209				
Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 15.31$, d.f. = 10 ($P = 0.12$); $I^2 = 35\%$							
Test for overall effect: $Z = 4.61$ ($P < 0.00001$)							
1.1.2 Selective serotonin re-uptake inhibitors							
Kuiken 2003	9	19	12	21	4.4%	0.83 (0.45, 1.51)	2003
Tabas 2004	25	44	36	46	10.0%	0.73 (0.54, 0.98)	2004
Vahedi 2005	6	22	19	22	3.5%	0.32 (0.16, 0.64)	2005
Tack 2006	5	11	11	12	3.7%	0.50 (0.25, 0.97)	2006
Talley 2008	5	17	5	16	1.8%	0.94 (0.33, 2.65)	2008
Masand 2009	15	36	26	36	6.8%	0.58 (0.37, 0.89)	2009
Ladabaum 2010	15	27	12	27	5.1%	1.25 (0.73, 2.15)	2010
Subtotal (95% CI)		176		180	35.3%	0.68 (0.51, 0.91)	
Total events	80		121				
Heterogeneity: $\tau^2 = 0.07$; $\chi^2 = 11.85$, d.f. = 6 ($P = 0.07$); $I^2 = 49\%$							
Test for overall effect: $Z = 2.57$ ($P = 0.01$)							
Total (95% CI)		592		508	100.0%	0.67 [0.58, 0.77]	
Total events	260		330				
Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 27.09$, d.f. = 17 ($P = 0.06$); $I^2 = 37\%$							
Test for overall effect: $Z = 5.39$ ($P = 0.00001$)							
Test for subgroup differences: $\chi^2 = 0.02$, d.f. = 1 ($P = 0.88$), $I^2 = 0\%$							



Overall, in our meta-analysis, there appeared to be a benefit of antidepressants in IBS, but there was significant heterogeneity between studies of SSRIs. However, in one RCT of citalopram, the

Ford AC, Am J Gastroenterol 2014

Which antidepressant is effective on pain in IBS-C?

American College of Gastroenterology Monograph on the Management of Irritable Bowel Syndrome and Chronic Idiopathic Constipation

Summary: Both tricyclic antidepressants and selective serotonin reuptake inhibitors are effective in providing global symptom relief and reducing pain in IBS. Adverse events and patient, as well as physician, acceptability have limited their use and influenced our recommendation. Available data, other than adverse event profile (e.g., constipating effects of tricyclic antidepressants), do not permit guidance on patient selection for antidepressant therapy.

Ford AC, Am J Gastroenterol 2014

The use of antidepressants in IBS

Table 1. Rational for the use of antidepressants in irritable bowel syndrome.

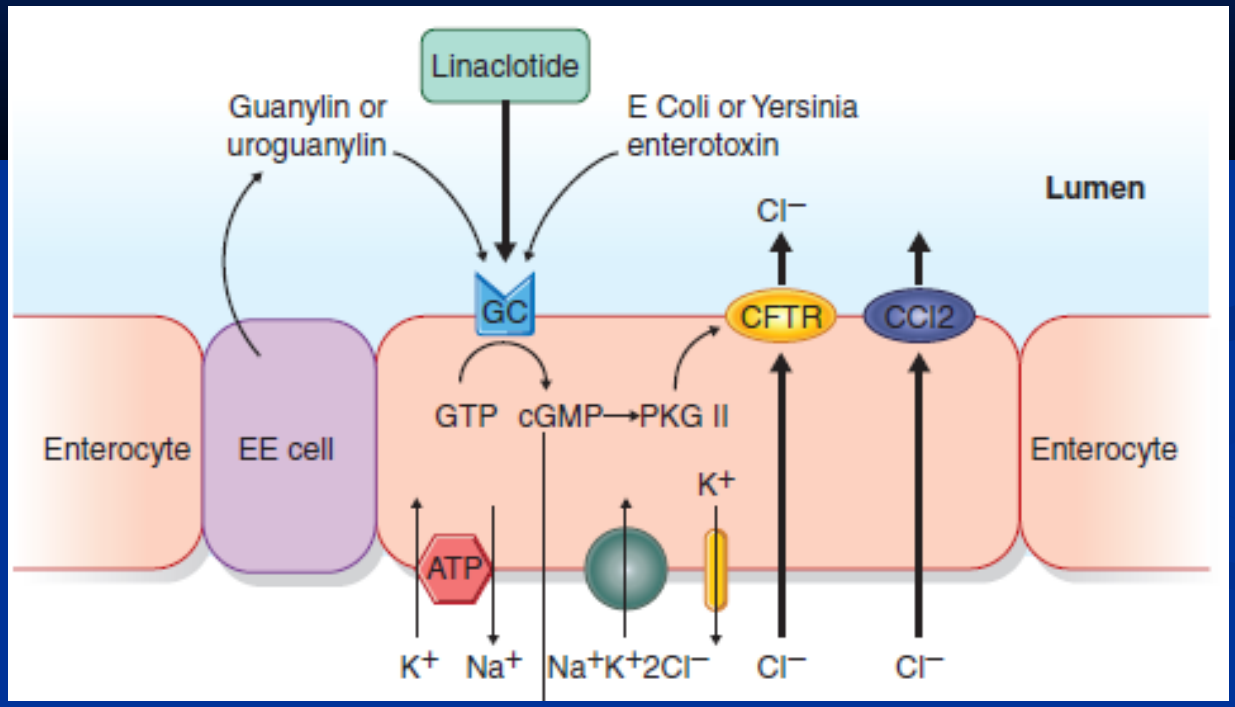
Alterations in the brain-gut axis play a major role in IBS pathophysiology
Comorbid psychopathology is frequently seen in IBS
Antidepressants are helpful in similar mind-body conditions (e.g., fibromyalgia)
Some antidepressants have analgesic properties that are independent of their psychiatric effects
Antidepressants affect gastrointestinal motility
Antidepressants have a synergetic effect with other IBS treatment options (e.g., behavioral treatment, hypnosis)

	TCA	SSRI	SNRI
Potential benefit	Pain reduction Depression	Depression, panic, anxiety (Pain reduction)	Pain reduction Depression
Side effects	Sedation, constipation, hypotension, xerostoma, arrhythmias, weight gain, sexual dysfunction	Agitation, diarrhea, insomnia, night sweats, headache, weight loss, sexual dysfunction	Nausea, agitation, dizziness, sleep disturbance, fatigue, liver dysfunction
Risk for overdose	Moderate	Minimal	Minimal
Dose adjustment	Yes	Not usual	Varies

Dekel R, Expert Opin Investig Drugs 2013; Tornblom H, Neurogastroenterol Mot 2015

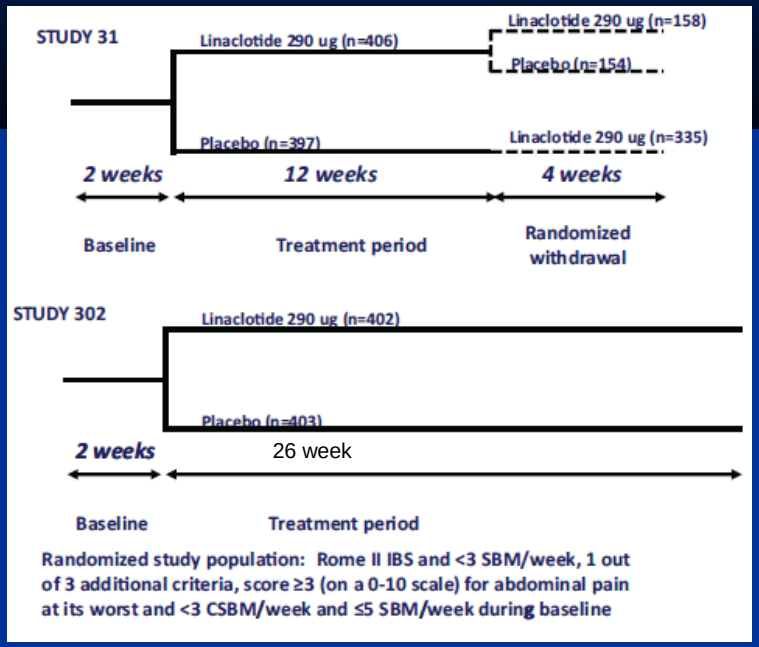
Linaclotide

Mechanism of action of linaclotide

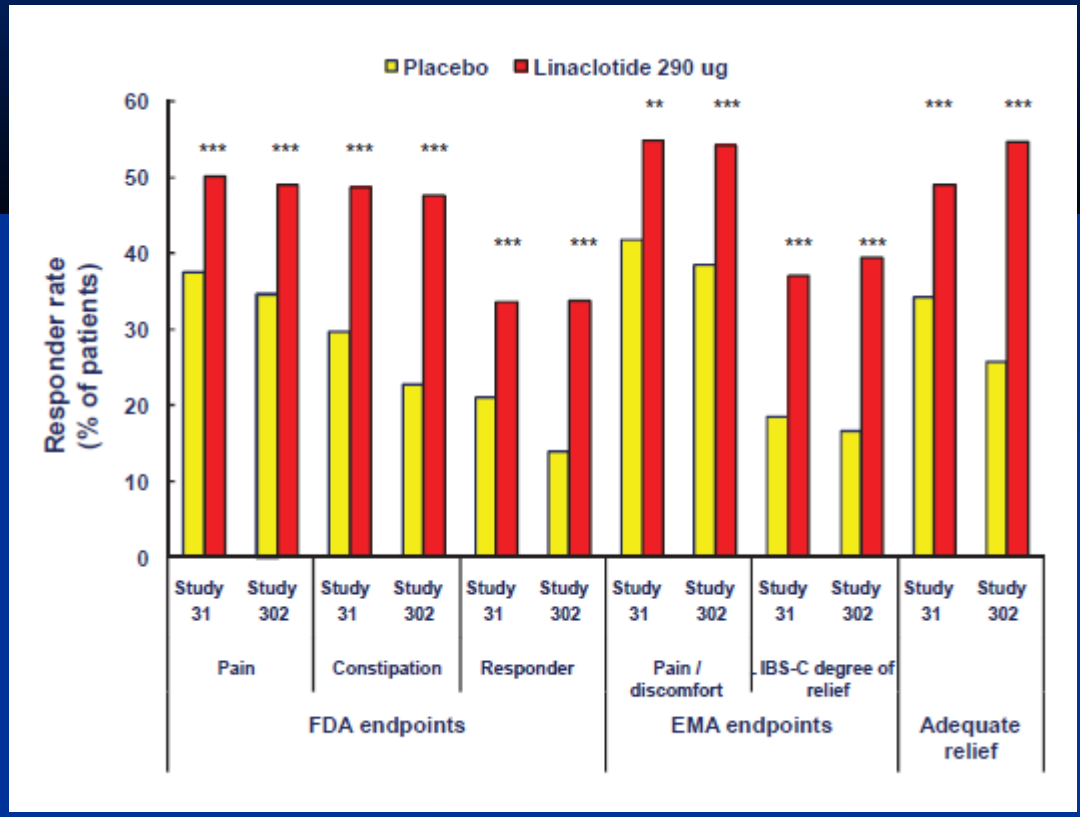


Corsetti M, United European Gastroenterol J 2013

Results of the phase III studies with linaclotide in IBS-C



Randomized study population: Rome II IBS and <3 SBM/week, 1 out of 3 additional criteria, score ≥3 (on a 0-10 scale) for abdominal pain at its worst and <3 CSBM/week and ≤5 SBM/week during baseline



Corsetti M, United European Gastroenterol J 2013

Down-regulation of GC-C in patients with IBS-C

Guanylate Cyclase-C Expression Is Down-Regulated in Colonic Biopsies From Female Irritable Bowel Syndrome Patients With Constipation

Sonia Garcia-Carraballo, Andrea Harrington, Joel Castro, Gerhard Hannig, Caroline B. Kurtz, Ada Silos-Santiago, Lin Chang, Stuart Brierley

pathway components tested ($P>0.05$). **Conclusions:** In this cohort of female IBS-C patients, GC-C, but not other evaluated components of the GC-C cGMP pathway, was significantly reduced. A decrease of GC-C in these patients may result in a reduction of cGMP production, which may impair intestinal secretion and the anti-nociceptive actions of cGMP compared with healthy controls. Given that they were apparent in IBS-C but not CIC, IBS-D or IBS-M patients, these changes may help to explain some aspects of the pathophysiology associated with IBS-C.

But how can we use these evidences?

1° Step: a good patient-doctor relationship!

- Explain IBS as hyper-reactive and hyper-sensitive gut and clarify it does not put the patient at risk of cancer
- Suggest simple and practical dietary and lifestyle advice of NICE guidelines

Then…

- Linaclotide (290 µg 1 daily)
- Bloating: Low FODMAP diet
- Still abdominal pain: TCA
- Still abdominal pain but anxiety and depression: TCA and SSRI
- Still constipation: ballon expulsion test and if positive biofeedback
  if negative colonic transit time
- Rectal irrigation

Conclusions

The state of the art treatment of IBS-C :

- **Remember the factors demonstrated to trigger the symptoms**
- **Good patient-doctor relationship.**
- **Some antispasmodics have been found to be effective in the short term but availability of the compounds across countries may limit their clinical application.**
- **Peppermint oil has been found to be effective in the short-term.**
- **Linaclotide has been recently approved by both FDA and EMA and demonstrated to be effective in the short- and in the long-term.**
- **TCA and SSRI have been found to be effective but their clinical application is limited by adherence to treatment (doctors mistake!).**

The University of Nottingham & Queen Mary College London seek to appoint 2 Clinical Research Fellows. This post is suitable for doctors with an interest in research, particularly those planning to pursue a career in gastroenterology or colorectal surgery. The successful applicant will be expected to register for a higher degree (MD/PhD) with the relevant University. Honorary contracts with the relevant NHS Trusts will be arranged so an applicant's success will be contingent on the post holder having a licence to practise from the General Medical Council. This post will be offered on a fixed-term contract for a period of 3 years starting on 1st October 2017 or after a notice period up to 3 months, whichever is later.

The post is fully funded for three years by the National Institute of Health Research administered by the Medical Research Council through their prestigious Efficacy and Mechanism Evaluation programme. The project is titled: "A randomised, placebo controlled trial to determine the efficacy and mode of action of ondansetron in the treatment of irritable bowel syndrome with diarrhoea" (IBS-D). The aim of the project is to evaluate the efficacy of ondansetron in treating the symptoms of IBS-D and its mode of action on the abnormal motility and sensitivity which are key features of this condition. The area of functional GI diseases is a rapidly expanding area with many new treatments and improved understanding within the last decade.

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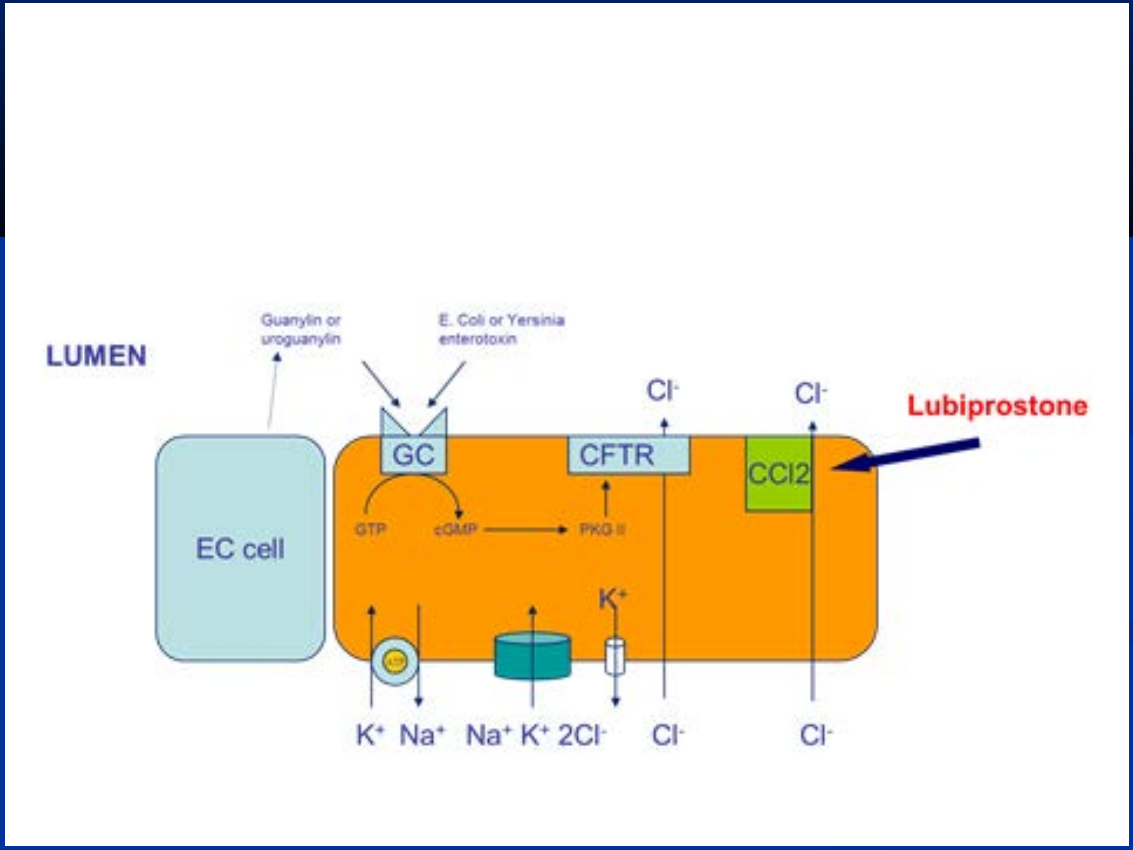
Lubiprostone

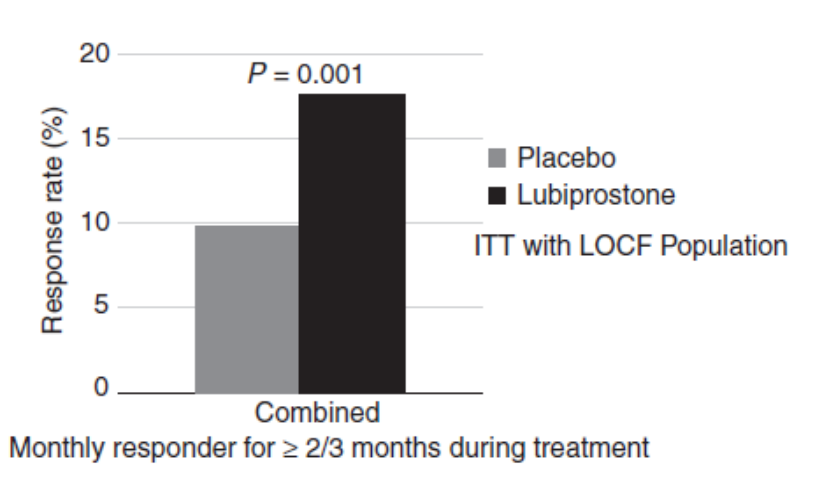
Mechanism of action of lubiprostone



Results of the phase III studies with lubiprostone in IBS-C

Two phase-3 randomized trials of lubiprostone 8 mcg vs. placebo twice daily for 12 weeks in 1171 patients with a Rome II IBS-C

Primary efficacy endpoint: % of overall responders (weekly assessments of symptom relief gathered from the responses to the question "How would you rate your relief of IBS symptoms over the past week compared to how you felt before you entered the study?")



Drossman DA, Aliment Pharmacol Ther 2008

The effect of Lubiprostone on pain in IBS-C

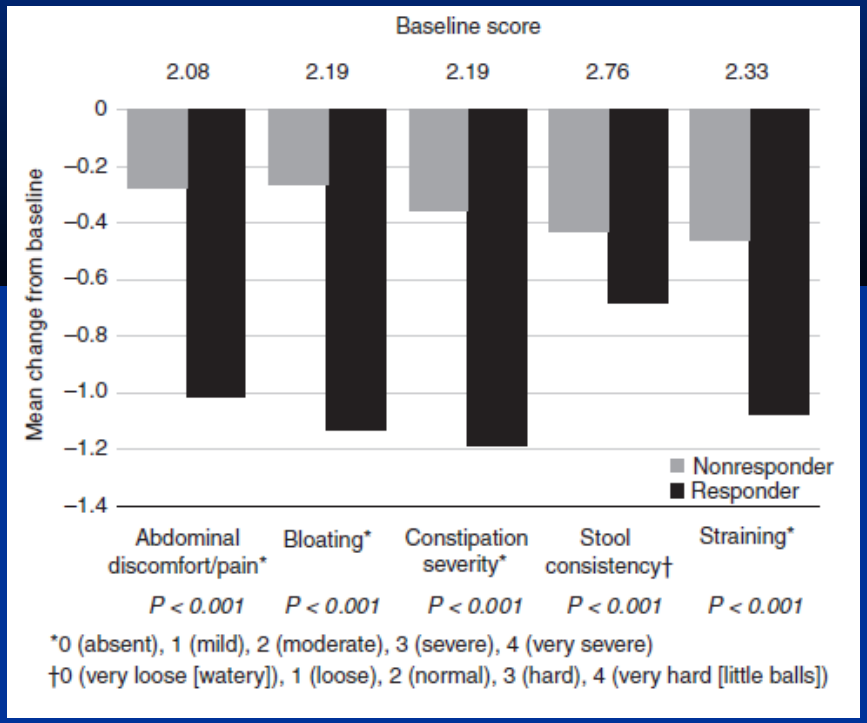


Table 3. Combined secondary efficacy endpoint summary (intent-to-treat, last observation carried forward population)

Symptom measure	Month 1	Month 2	Month 3
Abdominal discomfort/pain		*	*
Abdominal bloating		*	
Bowel movement Frequency	*		
Straining	*	*	*
Constipation severity	*	*	*
Stool consistency	*	*	*

* Statistically significant ($P \leq 0.05$).

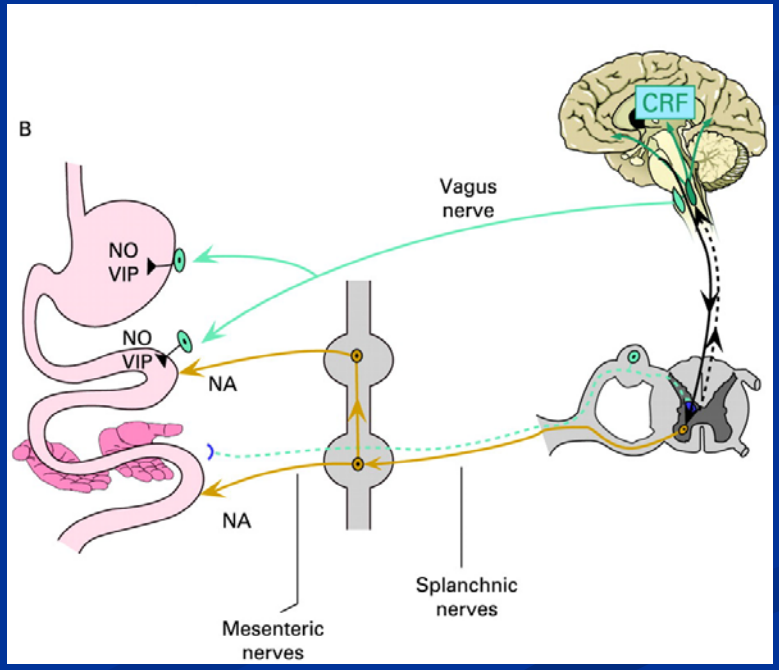
Drossman DA, Aliment Pharmacol Ther 2008

The role of previous surgical operations in IBS

IBS receive twice as many appendectomies or hysterectomies, and two to three times as many cholecystectomies

Longstreth GF, Yao JF. Irritable bowel syndrome and surgery: a multivariable analysis. Gastroenterology. 2004;126:1665–73

Recent advances in insight into the underlying pathophysiology have identified intestinal inflammation triggered by handling of the intestine as the main mechanism for postoperative ileus.



Boeckxstaens G, Gut 2009

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