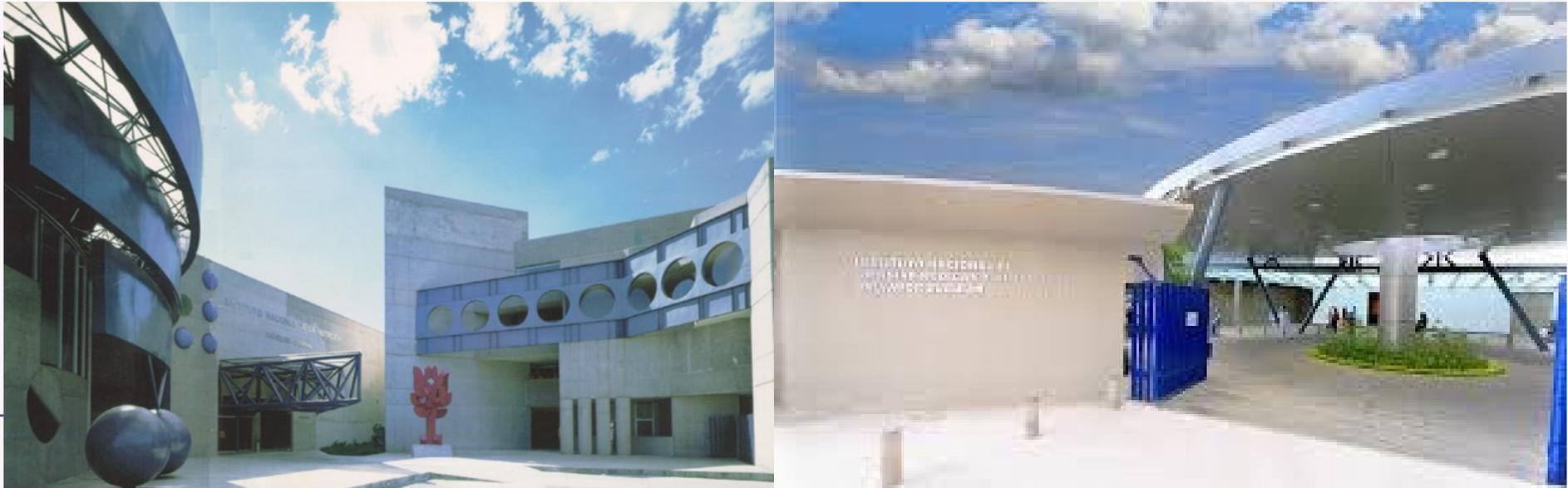


Novedades en el estreñimiento crónico

 **CURSO DE AVANCES
EN GASTROENTEROLOGÍA**
PERSPECTIVAS FUTURAS EN GASTROENTEROLOGÍA
17 - 19 Julio 2024 - Hotel InterContinental, Stgo.  SchGE



Dr. Enrique Coss-Adame

**Neurogastroenterología y motilidad
gastrointestinal**

**Instituto Nacional de Ciencias Médicas y
Nutrición "Salvador Zubirán"**



Definición del estreñimiento

American Gastroenterological Association Medical Position Statement on Constipation

- Defecación insatisfactoria caracterizada por evacuaciones infrecuentes, dificultades con la defecación o ambos por lo menos en los 3 meses previos

Gastroenterology 2013;144:218-238

GUÍAS Y CONSENSOS

Consenso mexicano sobre estreñimiento crónico

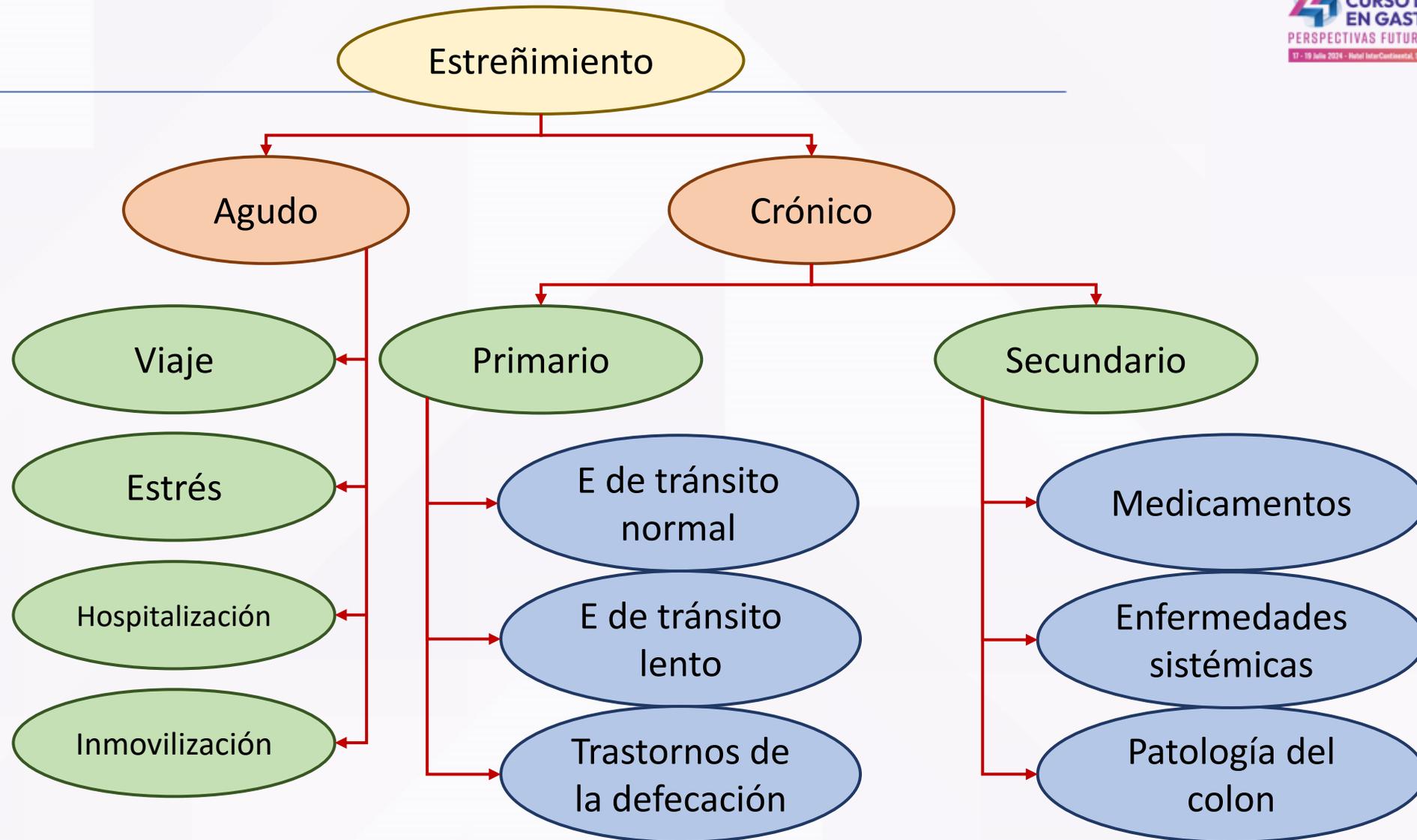
J.M. Remes-Troche^{a,*}, E. Coss-Adame^b, A. López-Colombo^c, M. Amieva-Balmori^a, R. Carmona Sánchez^d, L. Charúa Guindic^e, R. Flores Rendón^f, O. Gómez Escudero^g, M. González Martínez^h, M.E. Icaza Chávezⁱ, M. Morales Arámbula^j, M. Schmulson^k, J.L. Tamayo de la Cuesta^l, M.Á. Valdovinos^b y G. Vázquez Elizondo^m



- La disminución en la frecuencia de las evacuaciones, aumento en la consistencia de las heces, así como la dificultad para expulsarlas de al menos 3 meses de evolución

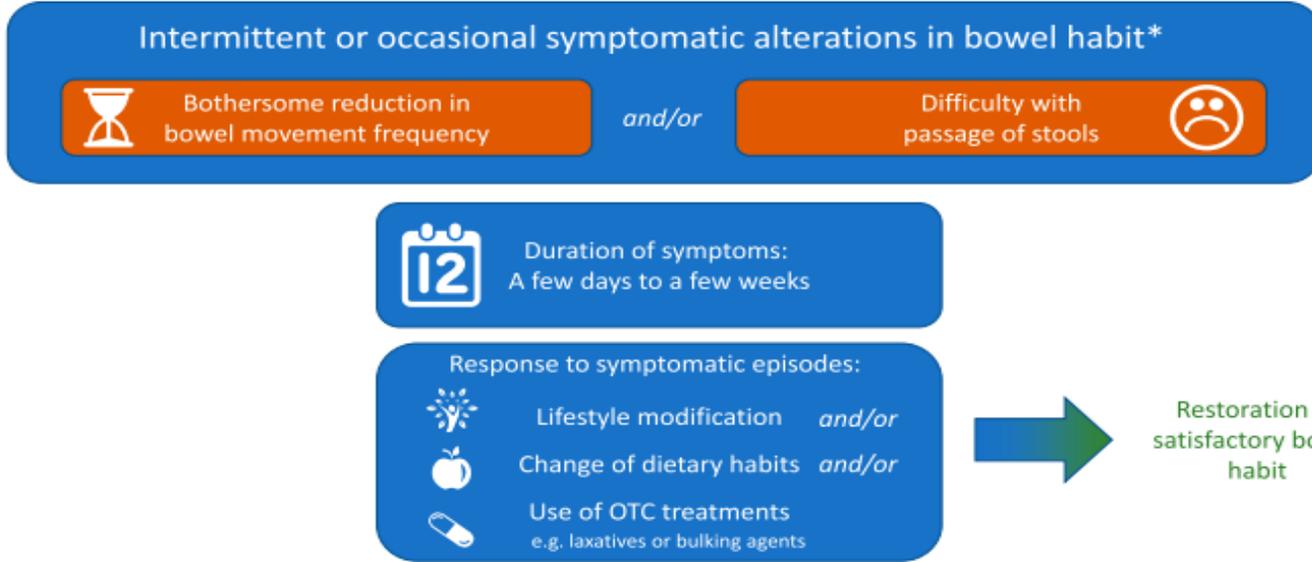


Clasificación del estreñimiento

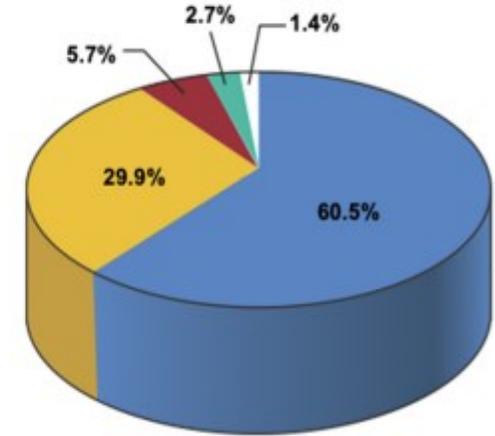


Estreñimiento ocasional

Proposed definition of occasional constipation



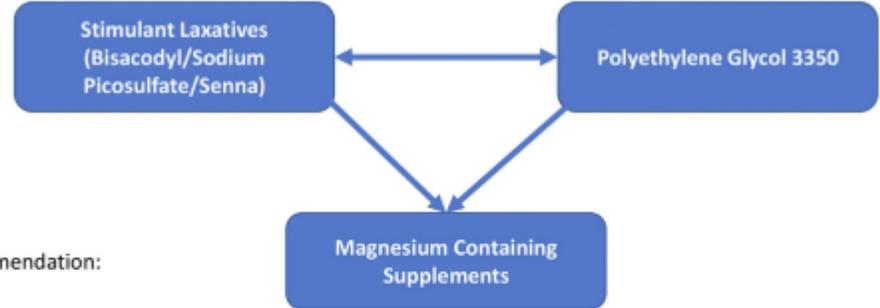
- Reported having between 3 and 7 BMs/week
- Reported having between 8 and 14 BMs/week
- Reported having between 15 and 21 BMs/week
- Reported having < 3 BMs/week
- Reported having > 21 BMs/week



Among individuals with self-reported normal bowel habits 95.9% reported between 3 and 21 BMs/week



1st Line:



Additional Recommendation:

Insufficient Evidence:



Evidence-based consensus recommendation for acute pharmacologic treatment of occasional constipation.

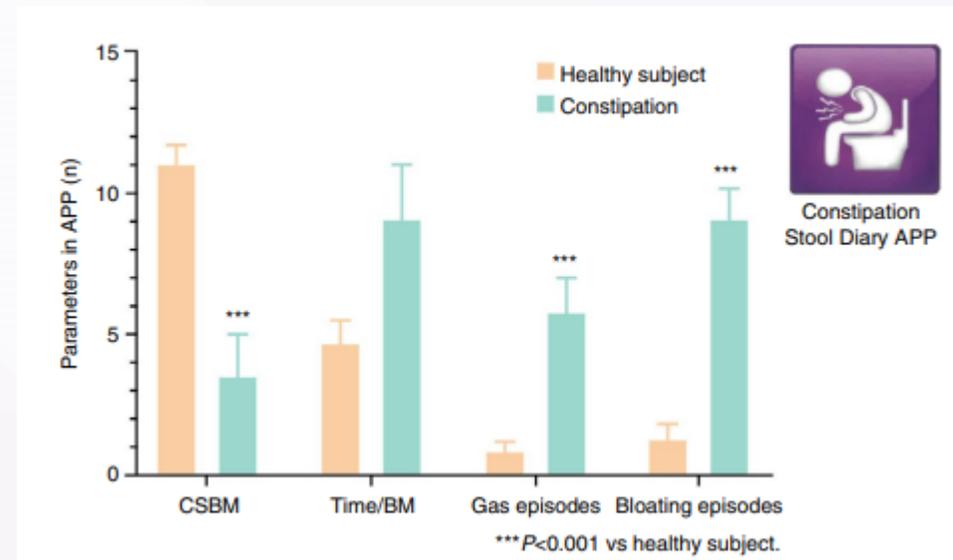


Marco conceptual de los trastornos funcionales intestinales



Registro de síntomas

Type 1		Separate hard lumps, like nuts
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on the surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces.



Tratamiento: Medidas generales

- ✓ Dieta
- ✓ Ejercicio
- ✓ Hábitos (Horarios, omisiones)
- ✓ Agua (No ECA)
- ✓ Fibra natural
- ✓ Patrón de evacuación (entrenar)

Recommendation 1: In adults with CIC, the panel suggests the use of fiber supplementation over management without fiber supplements

Conditional

Low



Tratamiento: Fibras

- ✓ Fibra: Piedra angular del tratamiento
- ✓ Formadores de bolo (15-20 gr/d)
 - Soluble Psyllum, Isphagula
 - Insoluble Derivados del Bran
- ✓ Intolerancia
- ✓ Gusto
- ✓ Mecanismo de acción
 - ✓ Retienen agua, mejoran consistencia

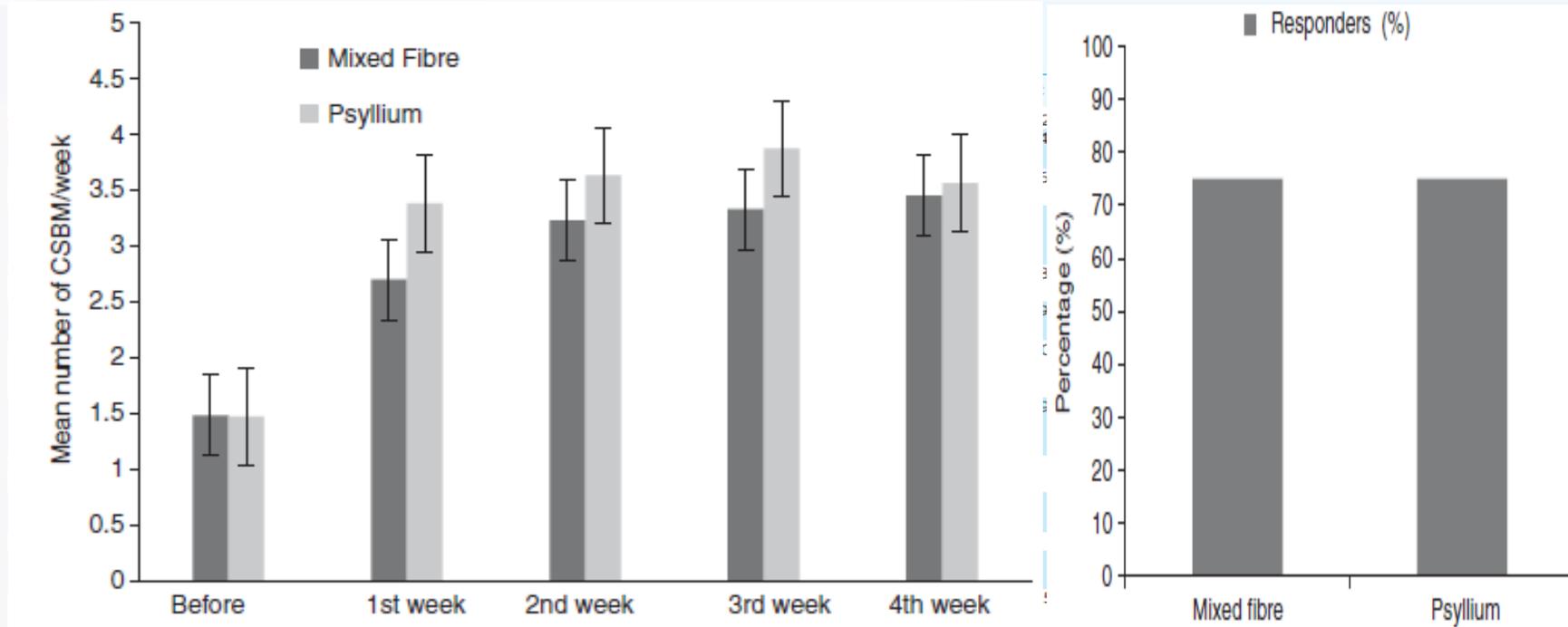


Recommendation 1: In adults with CIC, the panel suggests the use of fiber supplementation over management without fiber supplements

Conditional

Low

Tratamiento: Fibras



Tratamiento: Fibras Agave vs Psyllium plantago

TABLE 1. Demographic Characteristics of the Study Population (Study Inclusion)

Variables	AF 5 g (N = 21)	AF 10 g (N = 18)	AF 5 g+MTDx 10 g (N = 20)	Psyllium platango 5 g+MTDx 10 g (N = 20)	P
Demographics					
Age (y)	35.00 (31.00-46.75)	33.50 (26.00-49.75)	39.50 (27.50-44.00)	30.00 (26.00-41.75)	0.56
Gender (women) [n (%)]	18 (90.00)	14 (77.80)	15 (75)	19 (95.00)	0.41
Antropometric					
Weight (kg)	66.80 (54.10-74.90)	65.85 (60.40-71.10)	62.70 (58.00-67.50)	64.20 (60.10-71.30)	0.72
BMI (kg/m ²)	25.23 (23.22-27.95)	25.77 (23.87-26.28)	24.80 (22.34-28.17)	25.76 (23.93-29.00)	0.28

AF indicates agave fructans; BMI, body mass index; MTDx, maltodextrin.

Coss-Adame et al

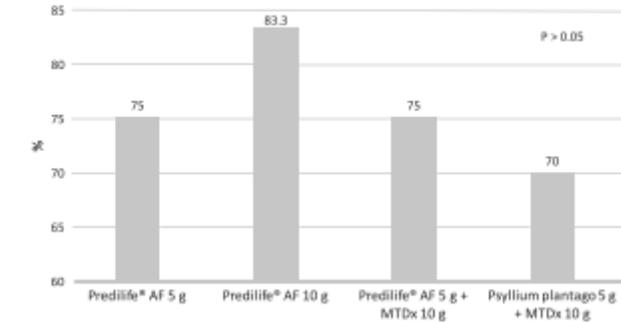


TABLE 3. PAC-QOL Domains Comparison From Baseline to Week 8

Variables	AF 5 g (N = 21)			AF 10 g (N = 18)			AF 5 g+MTDx 10 g (N = 20)			Psyllium platango 5 g+MTDx 10 g (N = 20)			
	Basal	Final	P	Basal	Final	P	Basal	Final	P	Basal	Final	P	P*
Physical discomfort	2.25 (1.30-2.50)	1.00 (0.56-1.50)	0.005	2.00 (1.40-2.50)	0.75 (0.68-1.50)	0.001	1.75 (1.20-2.25)	0.75 (0.50-1.25)	0.002	1.80 (1.50-2.50)	0.75 (0.75-1.00)	< 0.001	0.68
Social discomfort	1.06 (0.56-1.68)	0.43 (0.15-1.06)	0.009	1.00 (0.46-1.90)	0.37 (0.12-0.87)	0.02	0.87 (0.62-1.75)	0.37 (0.12-0.87)	0.002	0.87 (0.56-1.18)	0.37 (0.21-0.50)	0.002	0.49
Worries	1.81 (1.18-2.43)	0.77 (0.45-1.80)	0.001	1.30 (0.88-2.25)	0.45 (0.36-1.09)	0.008	1.63 (1.09-2.18)	0.45 (0.36-1.09)	< 0.001	1.50 (1.06-2.09)	0.45 (0.42-0.54)	< 0.001	0.10
Satisfaction	0.80 (0.60-1.40)	1.60 (1.00-2.30)	0.020	1.00 (0.60-1.40)	1.80 (1.60-2.40)	0.003	1.40 (1.00-2.20)	1.80 (1.60-2.40)	0.160	1.00 (0.60-2.60)	1.60 (1.50-1.90)	0.160	0.46

*Kruskal-Wallis test to assess between-group, Mann-Whitney U test with Bonferroni adjustment, $P=0.0125$.

AF indicates agave fructans; MTDx, maltodextrin; PAC-QOL, Patient Assessment of Constipation Quality of Life.

TABLE 5. Adverse Events After 8 Weeks of Intervention in the Study Groups

Variables	n (%)				P
	AF 5 g (N = 21)	AF 10 g (N = 18)	AF 5 g+MTDx 10 g (N = 20)	Psyllium platango 5 g+MTDx 10 g (N = 20)	
Gas	1 (4.7)	3 (16.6)	1 (5)	3 (16.6)	0.53
Distension	1 (4.7)	2 (11.1)	1 (5)	3 (16.6)	0.62
Diarrhea	0 (0)	1 (5.5)	1 (5)	1 (5)	0.70

AF indicates agave fructans; MTDx, maltodextrin.



Laxantes over-the-counter...

Effect of laxatives and pharmacological therapies in chronic idiopathic constipation: systematic review and meta-analysis

Study or Subgroup	Laxatives			Placebo			Weight	Mean Difference IV, Random, 95% CI	Year	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total				
1.2.1 Osmotic laxatives										
Laxative class	Medications	Mechanism of action			Adverse effects			Level of evidence	Grade of recommendation	
Bulk (fibre) laxatives	Psyllium, calcium polycarbophil, methylcellulose, bran	Retaining water in stool, increasing stool bulk and improving consistency			Flatulence, bloating, abdominal distension; rarely causing mechanical obstruction of oesophagus and colon			Psyllium – II; Others – III	B/C	
Stool softeners or wetting agents	Docusate sodium, docusate calcium	Promoting luminal water binding by detergent-like action, increasing stool bulk			Intestinal cramping; irritation of throat (liquid formulation)			III	C	
Stimulant laxatives	Senna, aloe, bisacodyl, sodium picosulfate	Increasing intestinal peristalsis by acting on myenteric nerve plexus, decreasing large intestinal water absorption			Abdominal discomfort, rarely electrolytes disturbance, melanosis coli			Sodium picosulfate – II; Others – III	B/C	
Osmotic laxatives	PEG, lactulose, sorbitol, milk of magnesia, magnesium citrate	Osmotic water binding			Bloating, flatulence, abdominal cramping; in rare instances, electrolytes disturbances			PEG – I	A	
								Lactulose – I	A	
								Sorbitol/milk of magnesia – III	B/C	
Mixed laxatives	Dried plums	Stool bulking and osmotic action			Flatulence, bloating			II	B	

Stimulant laxatives

Recommendation 5: In adults with CIC, the panel recommends the use of bisacodyl or sodium picosulphate short term or as rescue therapy over management without bisacodyl or sodium picosulphate

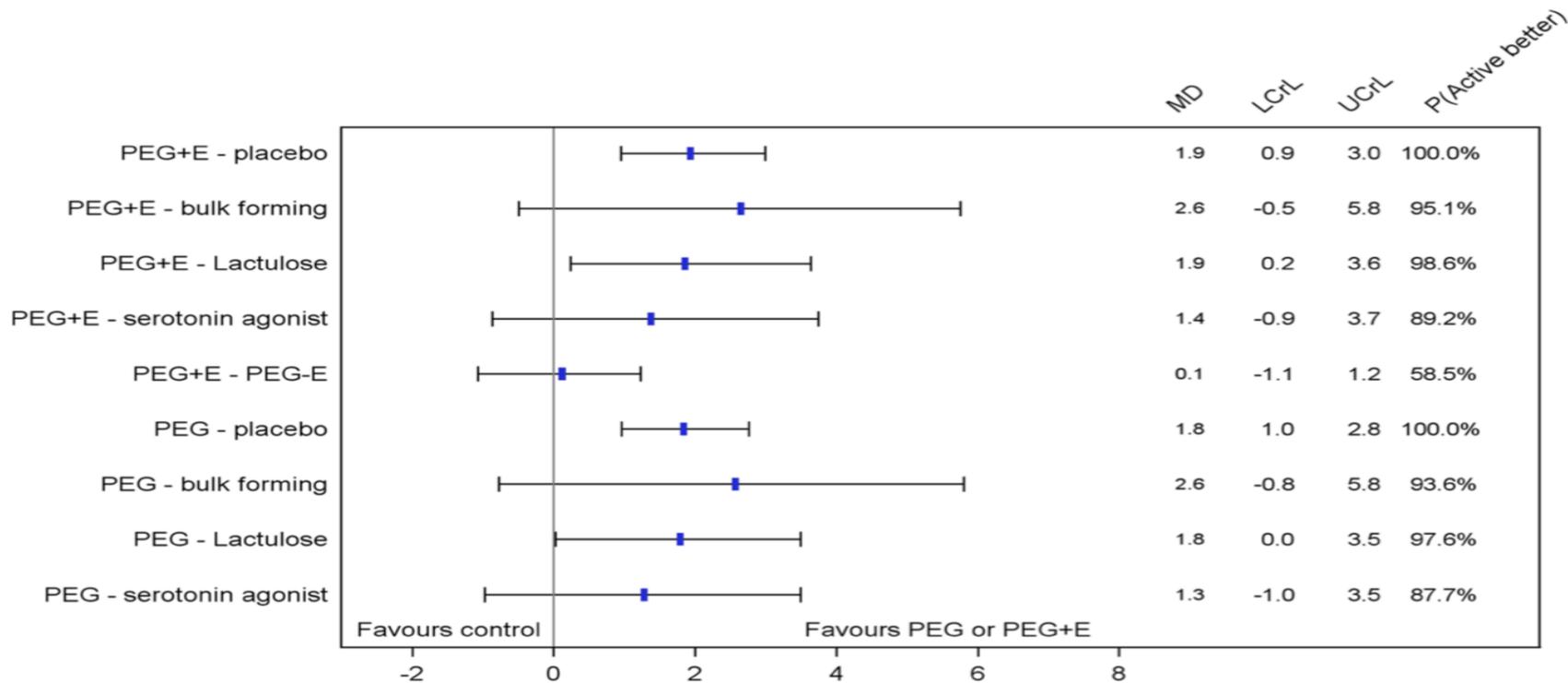
Strong

Moderate



PEG en estreñimiento crónico, Revisión sistemática y metaanálisis

Diferencias promedio en número de evacuaciones por semana



Osmotic laxatives

Recommendation 2: In adults with CIC, the panel recommends the use of PEG compared with management without PEG

Strong

Moderate



Tratamiento farmacológico del EF

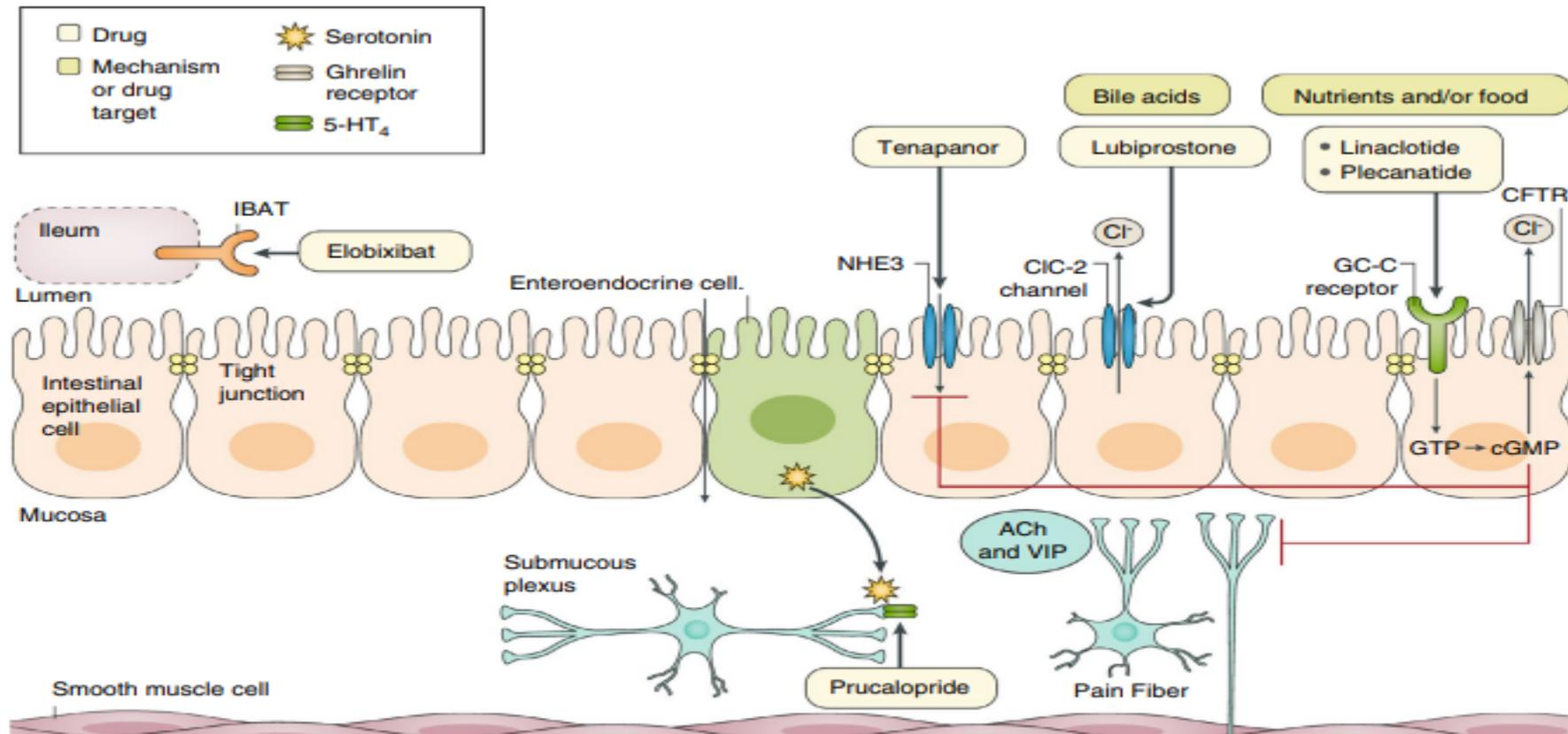
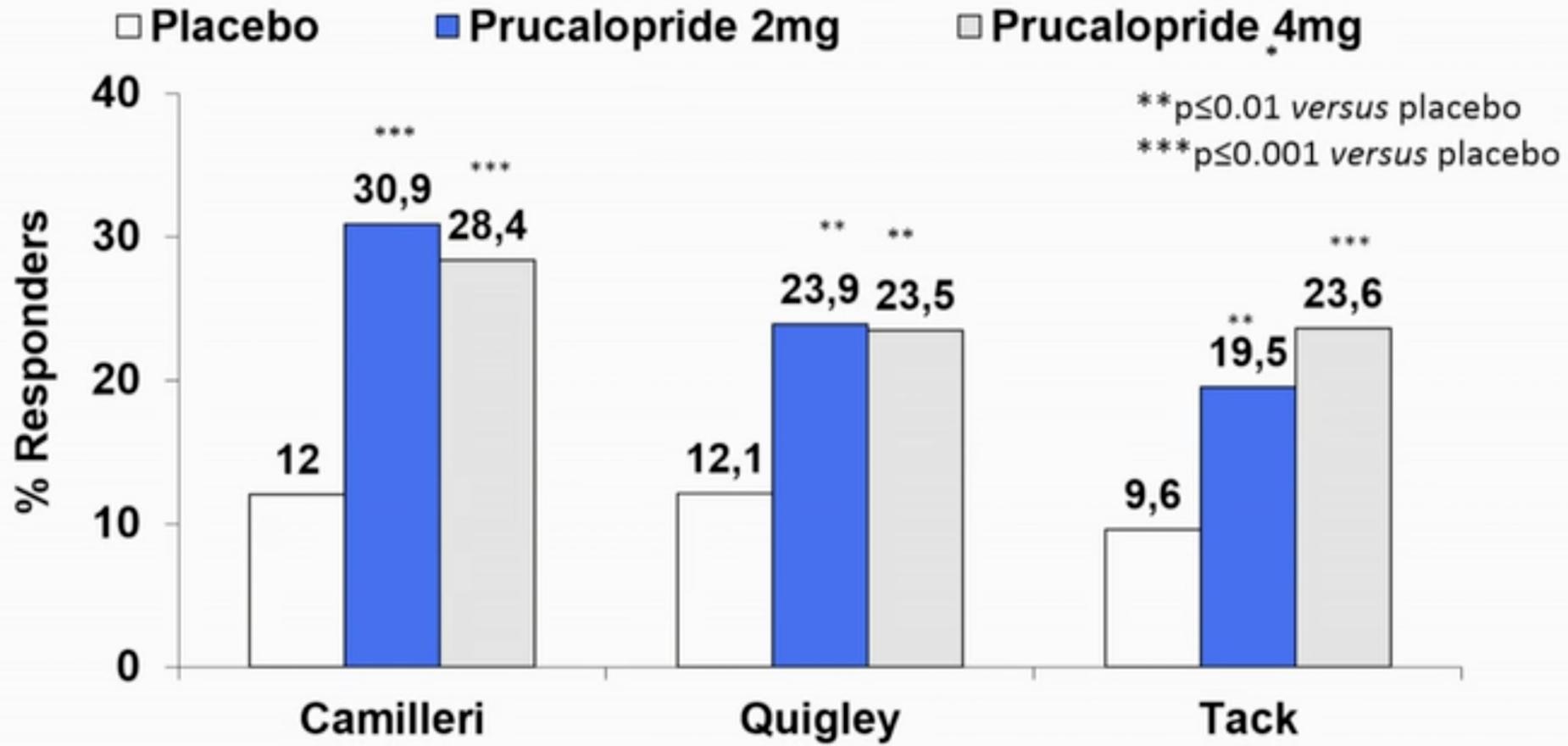


FIGURE 3 Mechanism of action of agents used for the treatment of constipation. This figure has been modified from Simrén et al *Nature Reviews Gastroenterology & Hepatology* 2018 with permission from Springer Nature Customer Service GmbH: Wiley.¹⁷¹ ACh, acetylcholine; CFTR, cystic fibrosis transmembrane conductance regulator; CIC-2, type-2 chloride channel; GC-C, guanylate cyclase-C; IBAT, ileal bile acid transporter; NHE3, sodium/hydrogen exchanger 3; VIP, vasoactive intestinal polypeptide



Prucaloprida en estreñimiento crónico

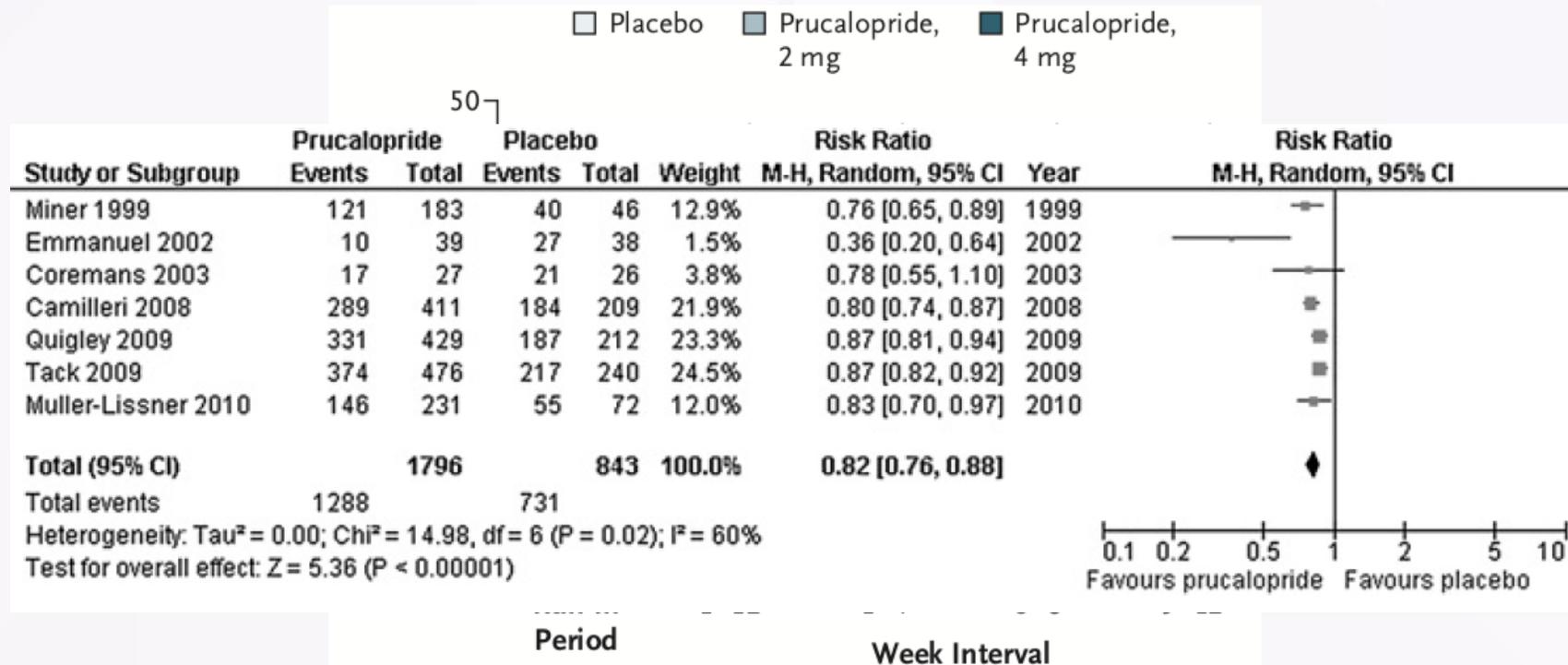


N Engl J Med. 2008;358:2344-54
Aliment Pharmacol Ther. 2009;29:315-28
Gut. 2009;58:357-65.



Agonista serotoninérgico...

A Placebo-Controlled Trial of Prucalopride for Severe Chronic Constipation



Recommendation 10: In adults with CIC who do not respond to OTC agents, the panel recommends the use of prucalopride over management without prucalopride

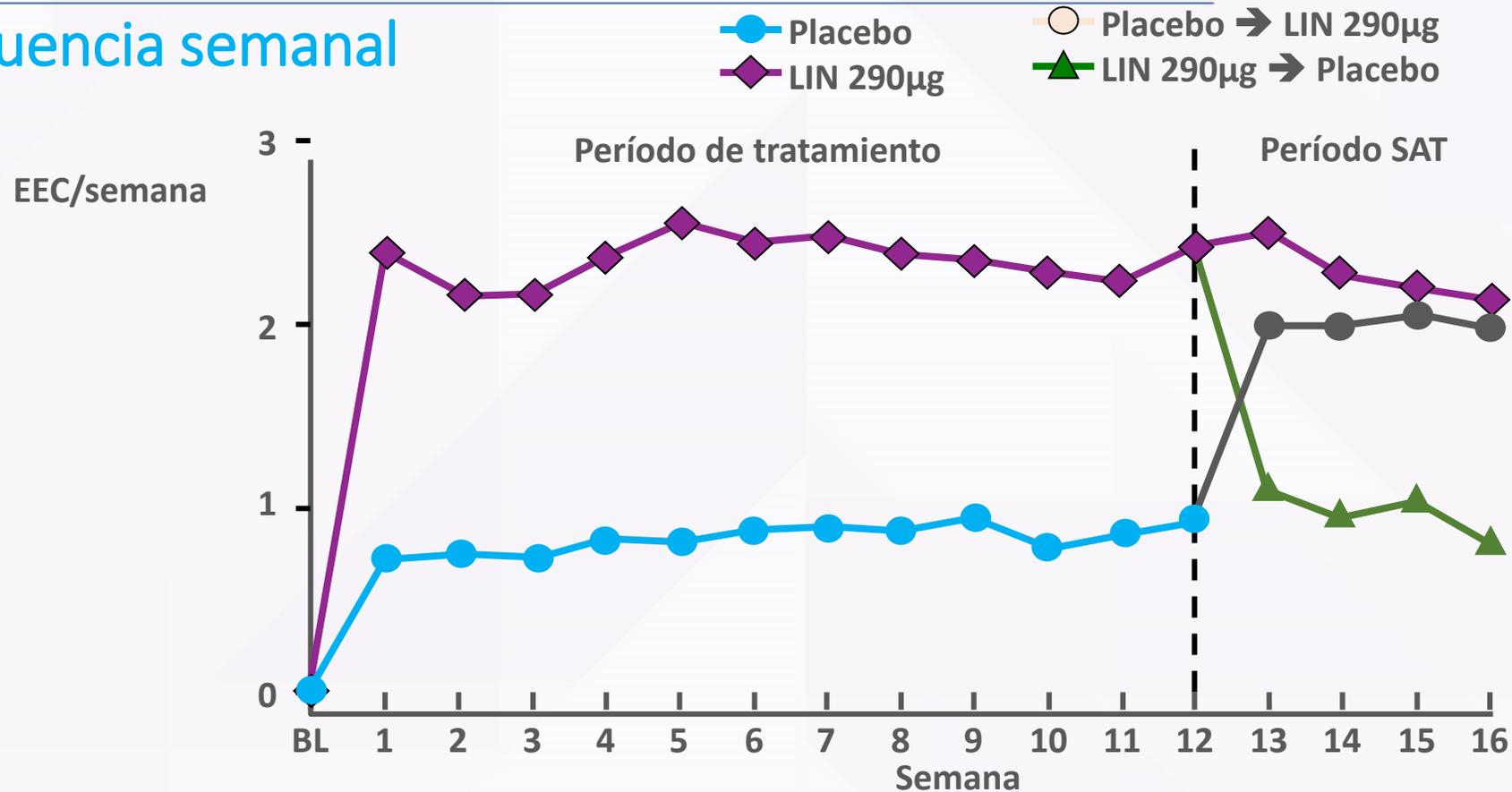
Strong

Moderate



Linaclotida

EEC: frecuencia semanal (Estudio 31)



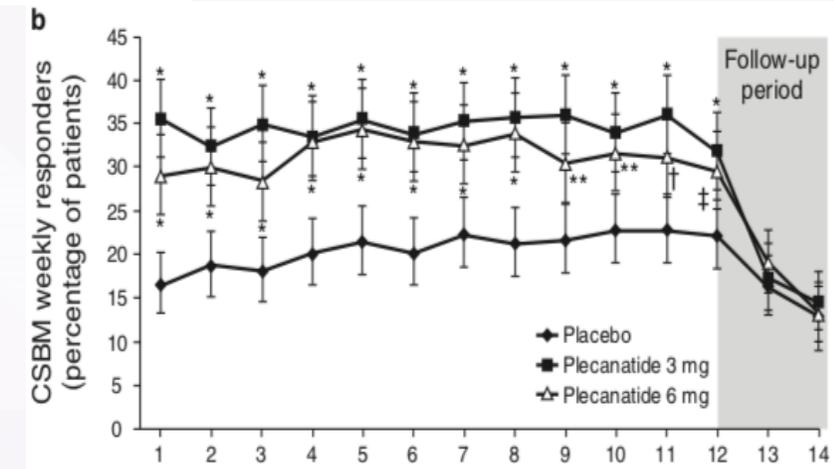
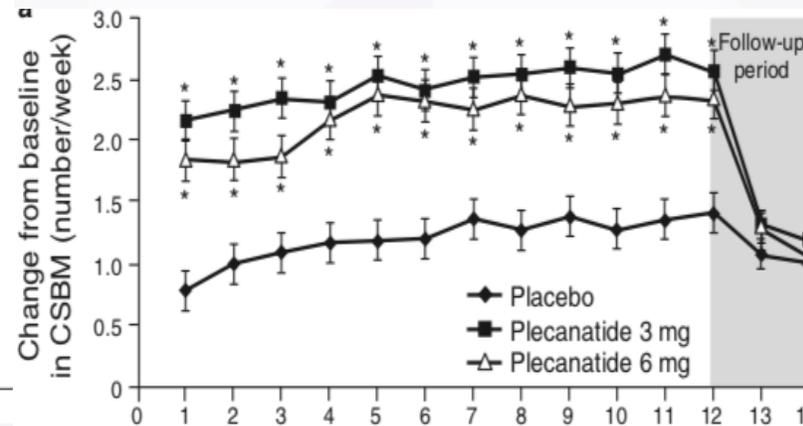
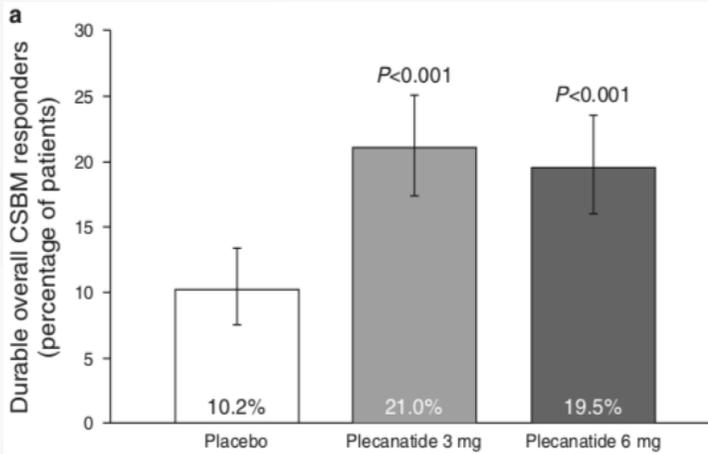
Recommendation 8: In adults with CIC who do not respond to OTC agents, the panel recommends the use of linaclotide over management without linaclotide

Strong Moderate



Agentes prosecretores...

A Randomized Phase III Clinical Trial of Plecanatide, a Uroguanylin Analog, in Patients With Chronic Idiopathic Constipation



Recommendation 9: In adults with CIC who do not respond to OTC agents, the panel recommends the use of plecanatide over management without plecanatide

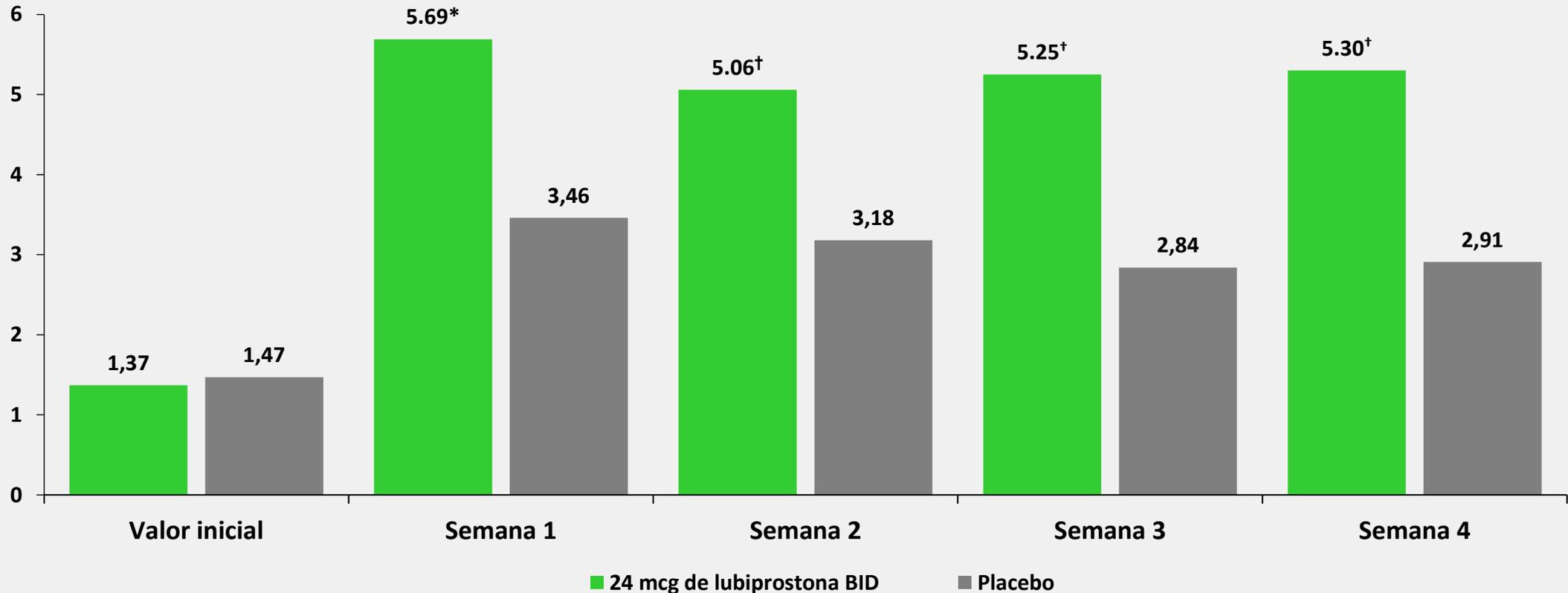
Strong

Moderate



Lubiprostona en el ECF-Estudio SC0131: Frecuencia de evacuaciones espontáneas en las semanas 1 y 4

Evacuaciones
espontáneas por semana
(N)



Recommendation 7: In adults with CIC who do not respond to OTC agents, the panel suggests the use of lubiproston over management without lubiproston

Conditional

Low



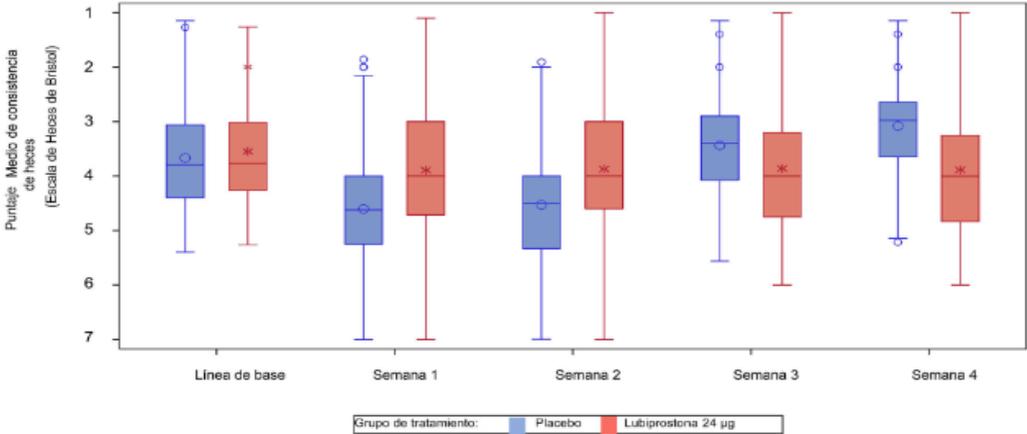
Lubiprostona en México: Frecuencia de evacuaciones espontáneas en las semanas 1 y 4

Tabla 2 Frecuencia de las evacuaciones espontáneas completas (EEC) a la primera semana (prueba de van Elteren)

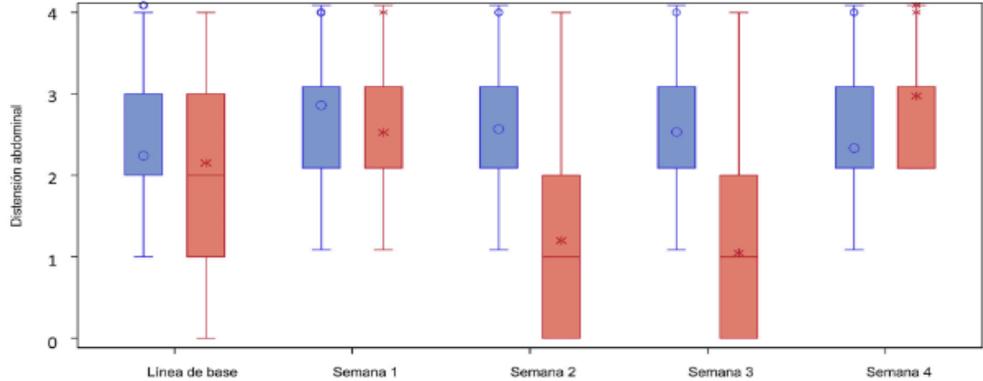
Tiempo	Grupo	n ^a	Media (DE)	Mediana	Min, Max	IC95% para la diferencia media (lubiprostona-placebo)	CI mediana	Valor de p ^b
Línea de base	Lubiprostona	104	1.9 (0.71)	2.0	0, 5	(0.1, 1.9)	1.0	0.020
	Placebo	106	2.1 (2.04)	2.0	1, 22			
Semana 1	Lubiprostona	105	6.7 (4.55)	5.0	1, 25	n/a		
	Placebo	106	5.2 (2.82)	5.0	1, 19			
Cambio a partir del basal	Lubiprostona	104	4.9 (4.45)	3.8	-1, 23	n/a		
	Placebo	106	3.0 (3.14)	2.5	-13, 18			

IC95%: intervalo de confianza al 95%; DE: desviación estándar; n/a: no aplica.
^a N para cada grupo es el número de sujetos que fueron utilizados en el análisis.
^b Prueba de van Elteren estratificada por centro. Significancia estadística si $p \leq 0.05$.

A

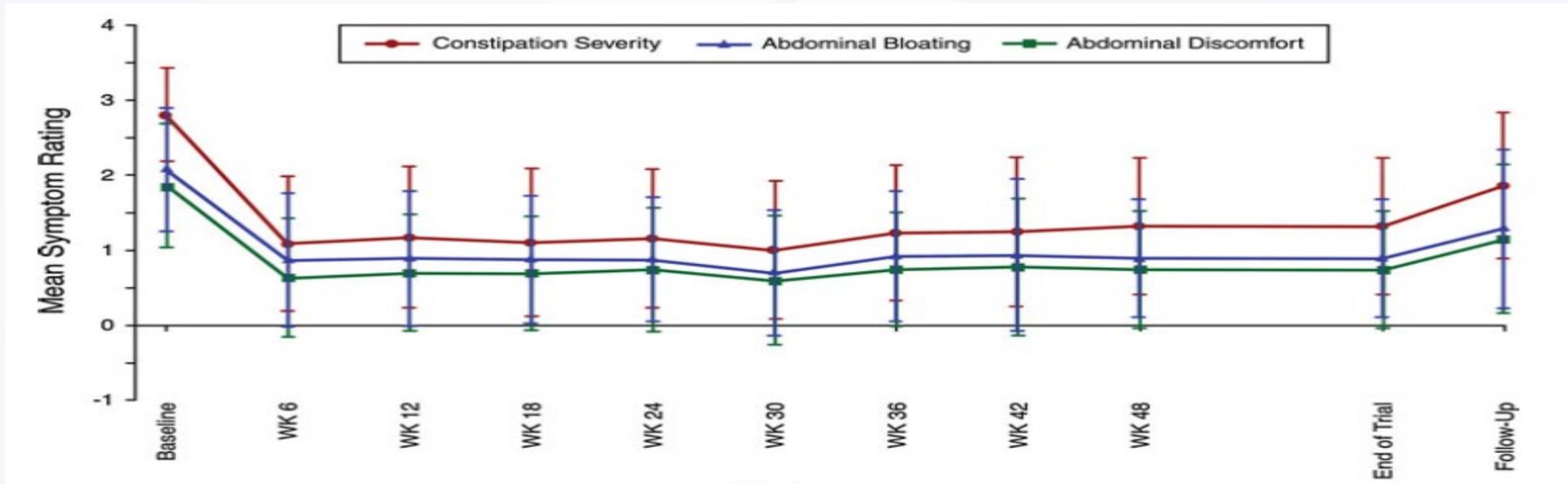


B



Lubiprostona en ECF: Largo plazo

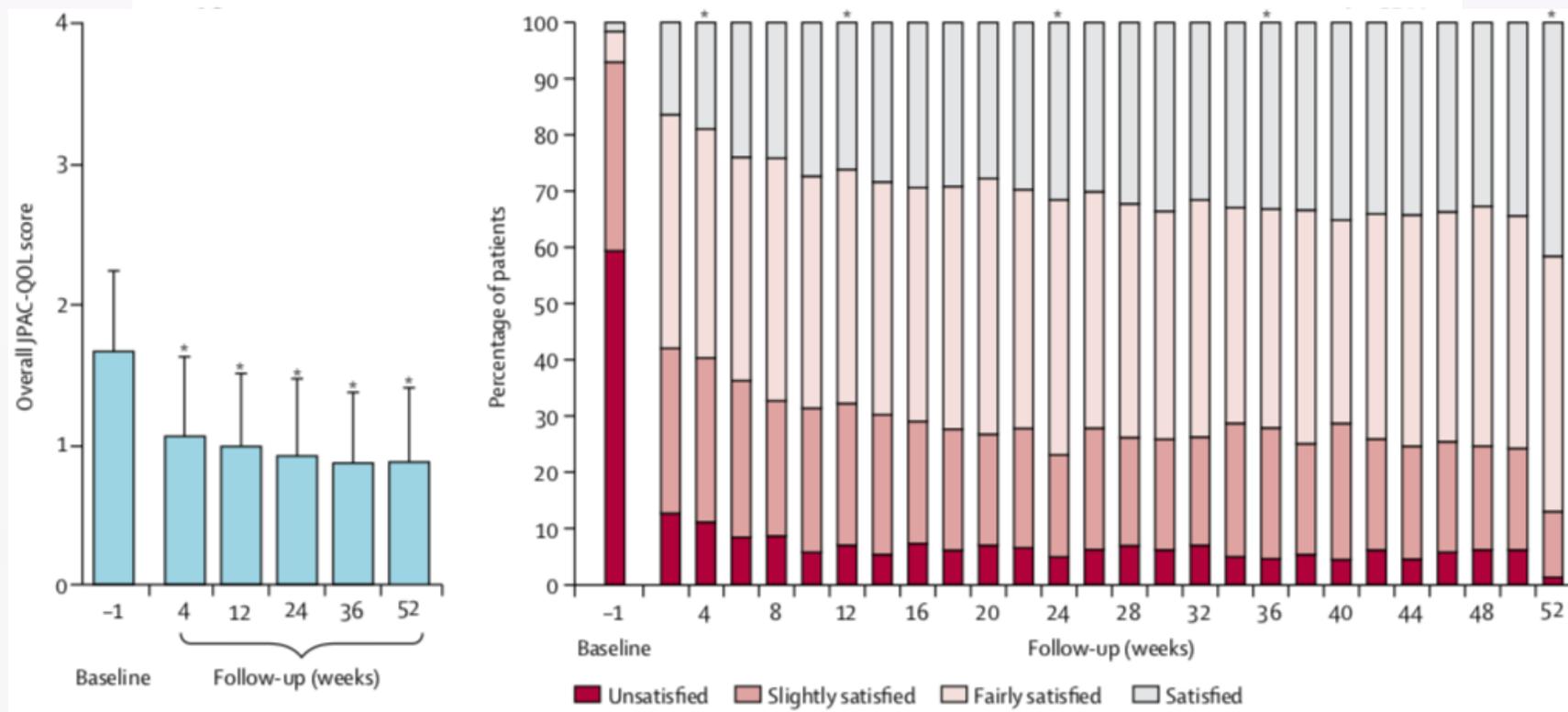
Ensayo abierto 48 semanas



13% suspendieron por EA; 5% por náusea

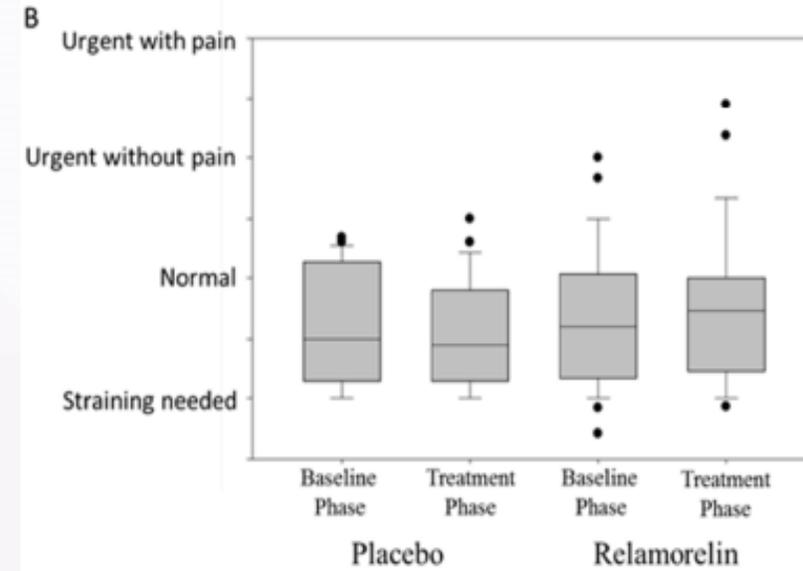
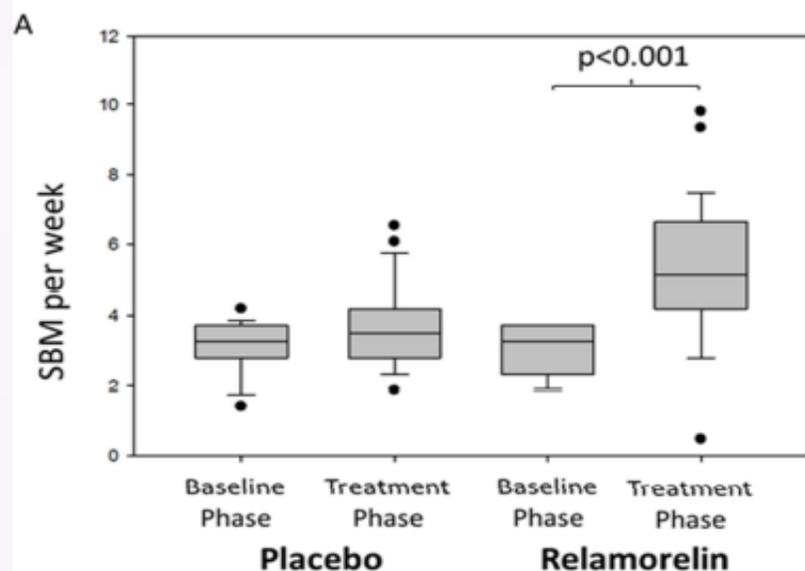
Elobixibat...

Safety and efficacy of elobixibat for chronic constipation: results from a randomised, double-blind, placebo-controlled, phase 3 trial and an open-label, single-arm, phase 3 trial



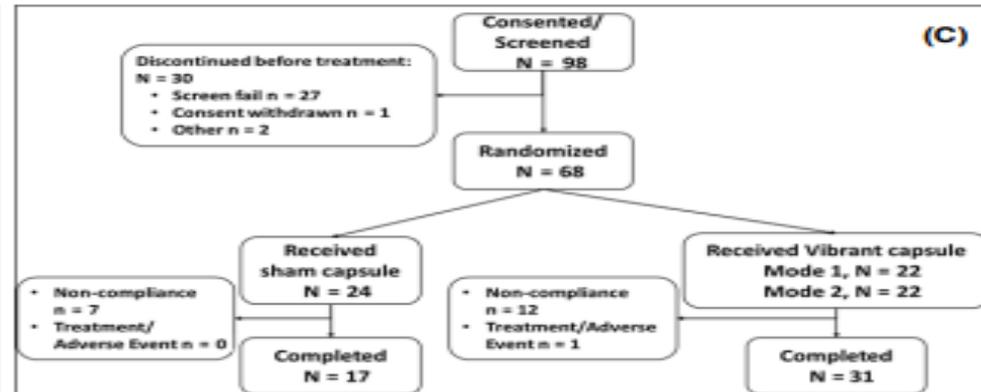
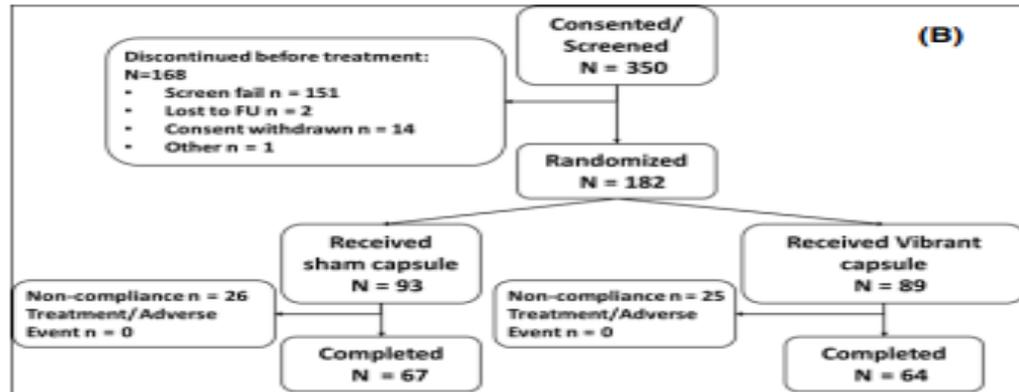
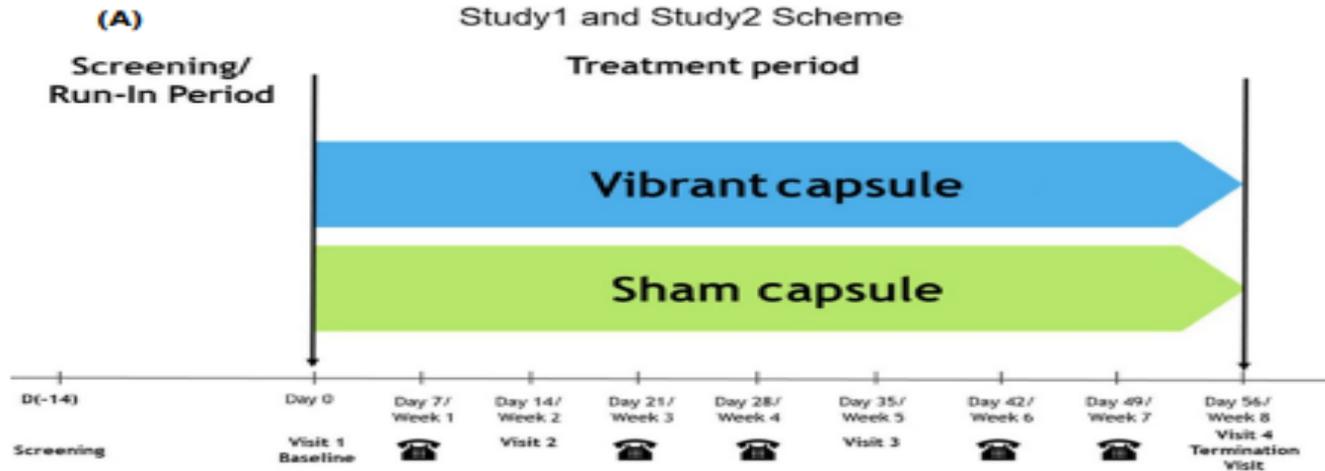
Agonistas de Ghrelina

- ✓ Agonistas de Ghrelina: Péptido 28 aminoácidos
- ✓ Relamorelin (RM-131): Receptor GHS-1a

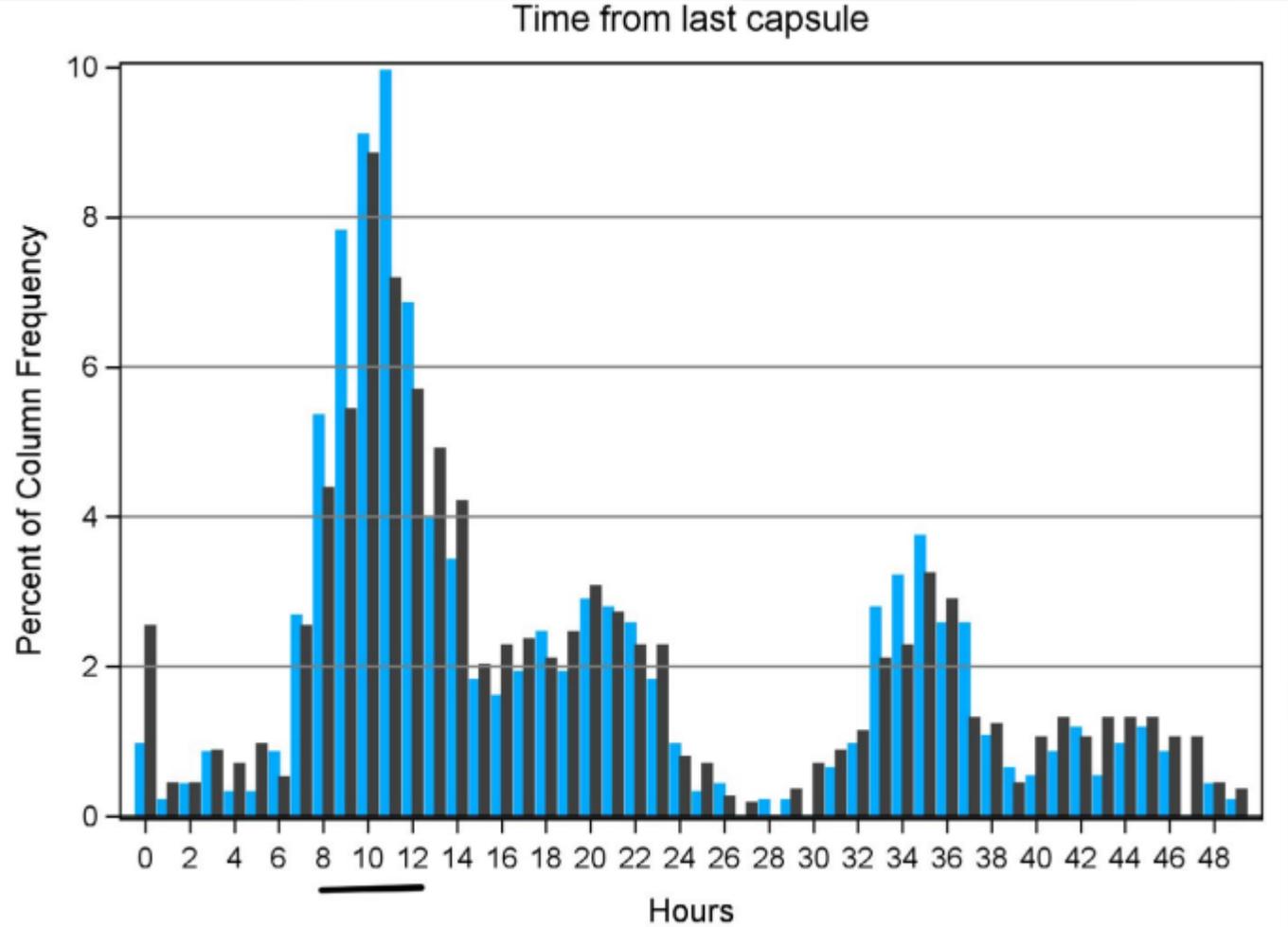


- ✓ Efectos adversos: Cefalea, incremento de apetito

Cápsula vibradora



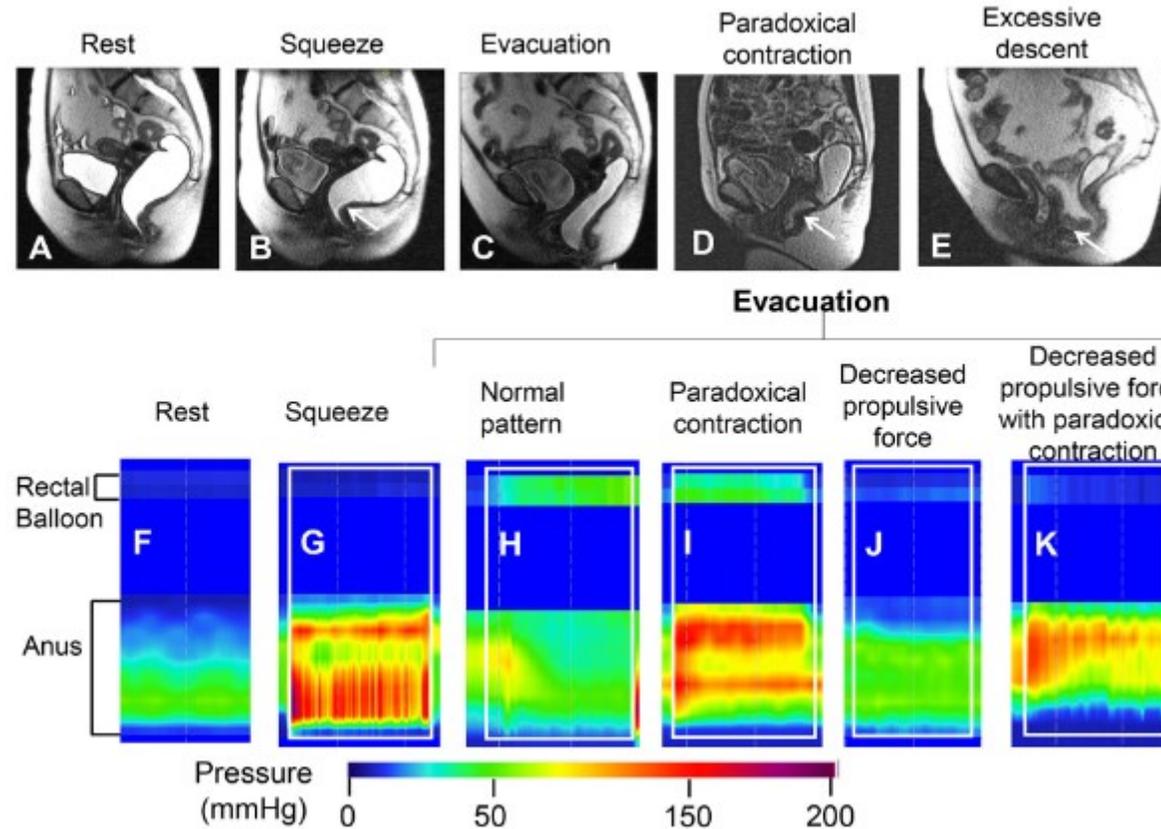
Cápsula vibradora



Estreñimiento asociado a desordenes de la evacuación

Bharucha and Coss-Adame

Page 18



Ensayos clínicos en disinergia: Eficacia

	Chiarioni y cols	Rao y cols	Rao y cols	Heymen y cols	Chiarioni y cols	Rao y cols	Go y cols
Diseño	BRA vs PEG 14.6-29.2 g/día	BRA vs Tx estándar vs BRA disimulado	BRA vs Tx estándar	BRA vs 5 mg de diazepam vs placebo	BRA para tránsito lento vs disinergia	BRA en casa vs consultorio	Calidad de vida y costo-efectividad de BRA en casa vs consultorio
Desenlaces	Mejoría global de síntomas Peor=0 Sin mejoría=1 Leve=2 Débil=3 Importante=4	Presencia de disinergia Tiempo de expulsión de balón No. de evacuaciones espontáneas completas (EEC) Satisfacción global	No de EEC Presencia de disinergia Tiempo de expulsión de balón Satisfacción global	Alivio global de síntomas	Mejoría de síntomas No=0 Leve=1 Débil=2 Importante=3	Cambio en el No de EEC/semana Patrón de disinergia Tiempo de expulsión de balón Puntaje de satisfacción	Efecto del BRA en calidad de vida Cambios en calidad de vida en patrón disinérgico Equivalencia de calidad de vida
Corrección de disinergia o mejoría de síntomas	76.9% mejoría importante a 6 y 12 meses y 81.5% a 24 meses	Corrección de la disinergia a 3 meses en 79% con BRA vs 6% estándar vs 4% BRA disimulado EEC= BRA vs BRA disimulado o Tx estándar (p<0.05)	Aumento significativo de No de EEC/semana (p<0.001); normalización del patrón de disinergia (p<0.0010); mejoría de la expulsión del balón (p<0.001); normalización del tránsito colónico (p<0.0010)	Mejoría de 70% con BRA vs 38% placebo vs 30% diazepam	Mejoría débil en 71% de disinergia vs 8% tránsito lento	No de EEC/semana (p<0.0001); Satisfacción similar en ambos grupos (p<0.0012); mejoría de la expulsión del balón (p<0.001); sin mejoría del patrón de disinergia	Mejoría en: Condicionamiento físico (p=0.0003); papel físico (p=0.0004); dolor (p=0.0090); condición general (p=0.0002); vitalidad (p=0.0108); funcionamiento social (p=0.0383); papel emocional (p=0.0001); salud mental (p=0.0100)
Conclusiones	BRA es superior a los laxantes	BRA superior a BRA disimulado o Tx estándar	BRA es superior al Tx estándar	BRA es superior a placebo y diazepam	BRA mejor para disinergia que para tránsito lento	BRA en casa es segura y efectiva para disinergia	BRA en casa o consultorio mejora calidad de vida

Extraído de Villar-Chavez S, Coss-Adame E. Neurogastrointest Reviews



PAMORA...

Naloxegol for Opioid-Induced Constipation in Patients with Noncancer Pain

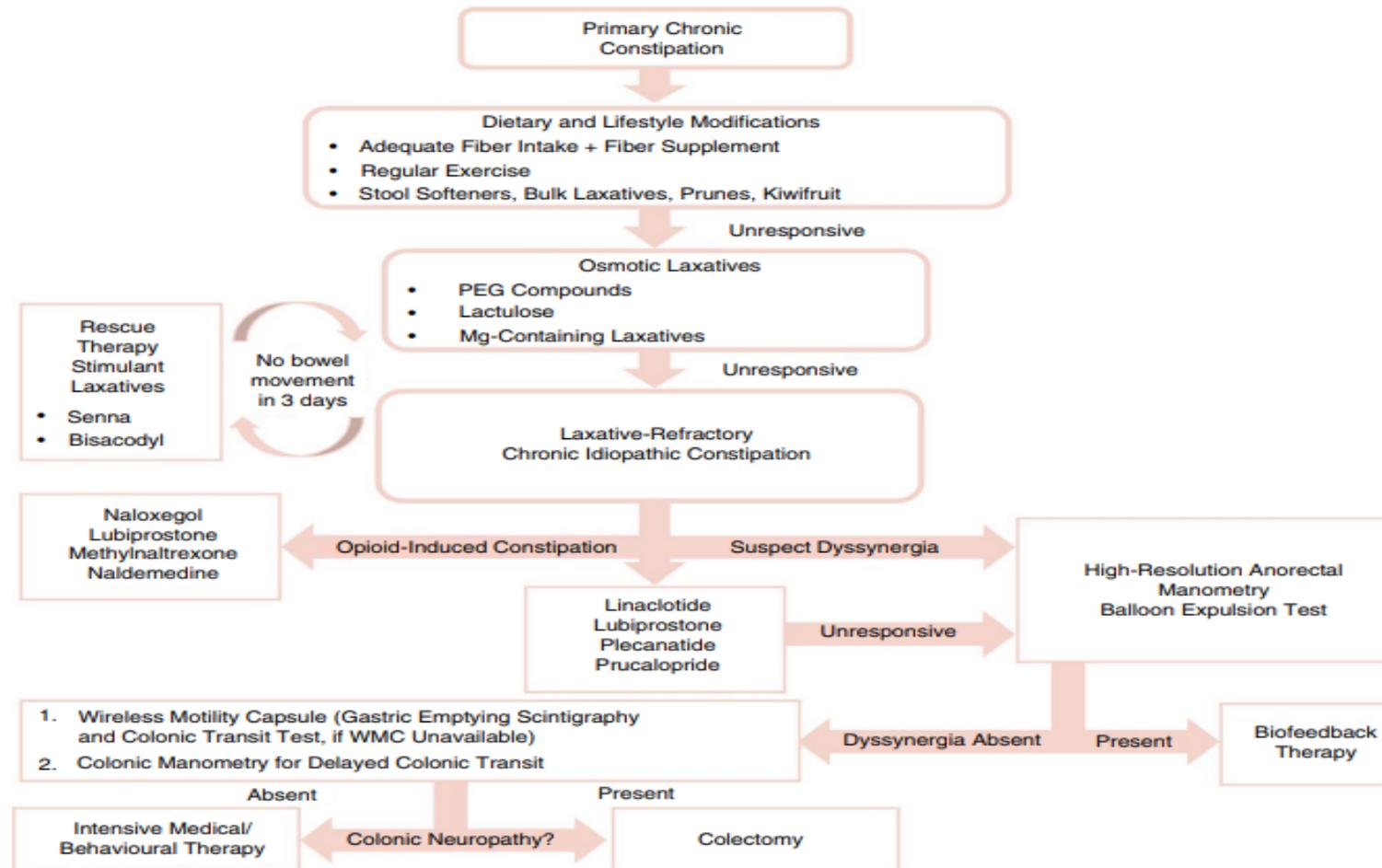
A Randomized, Placebo-Controlled Phase 3 Trial (Study SB-767905/013) of Alvimopan for Opioid-Induced Bowel Dysfunction in Patients With Non-Cancer Pain

Efficacy and Tolerability of Subcutaneous Methylnaltrexone in Patients with Advanced Illness and Opioid-Induced Constipation: A Responder Analysis of 2 Randomized, Placebo-Controlled Trials

<i>Opioid receptor antagonists</i>						
Methylnaltrexone	Enteric opioid receptor antagonism, with minimal absorption and not crossing blood–brain barrier	Opiate-induced constipation; postoperative ileus; chronic methadone users	8–12 mg (0.15–0.3 mg/kg) every other day as needed; subcutaneously	Half dose in severe renal and hepatic impairment	Abdominal cramping, flatulence, nausea	Class B; use with caution during breast feeding
Alvimopan	Enteric opioid receptor antagonism, with minimal absorption and not crossing blood–brain barrier	Postoperative ileus; opiate-induced constipation	6–12 mg twice daily, 30–300 mins prior to surgery, then twice daily for 7 days	Avoid in ESRD and severe hepatic dysfunction	Nausea, vomiting	Class B; avoid during breast feeding
Naloxegol	Enteric opioid receptor antagonism, with minimal absorption and not crossing blood–brain barrier	Opiate-induced constipation	12.5–25 mg; orally	N/A	Abdominal pain, diarrhoea, nausea, vomiting, headache, flatulence	Class C; avoid during breast feeding



Algoritmo de toma de decisiones



Para llevar al consultorio.....

El tratamiento del estreñimiento crónico es variado, múltiples mecanismos de acción

Individualizar el tratamiento de acuerdo a respuesta

Evidencia de monoterapias, puede haber combinaciones

Mejorar la calidad de vida de los pacientes

