JORNADAS 2020

FORMATO WEBINAR

DE ACTUALIZACIÓN EN ATENCIÓN FARMACÉUTICA AL PACIENTE CON PATOLOGÍAS VÍRICAS

Esteatosis Hepática Metabólica (Manejo Multidisciplinar)

Javier Ampuero Herrojo
Hospital Universitario Virgen del Rocío
Instituto de Biomedicina de Sevilla
Universidad de Sevilla

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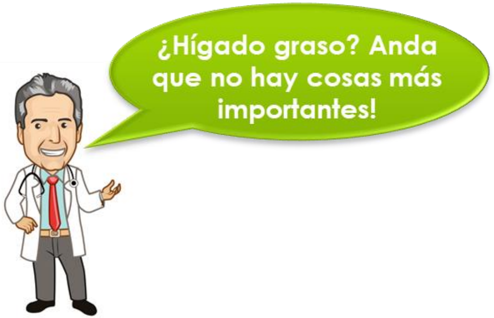
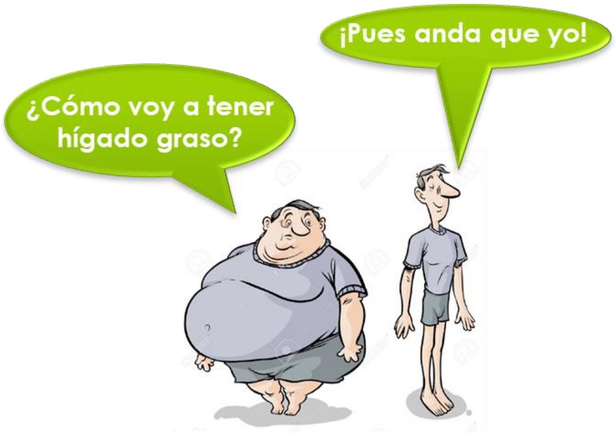
ORGANIZA:

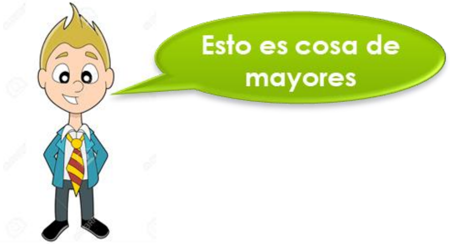
sefh Sociedad Española de Farmacia Hospitalaria
ghevi Grupo de trabajo de Hepatologías Víricas de la sefh
vih Grupo de trabajo de Atención Farmacéutica al Paciente de VIH de la sefh
fefh Fundación Española de Farmacia Hospitalaria

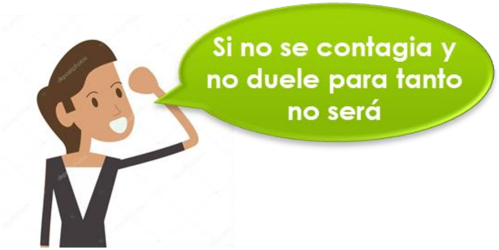
Barreras sociales y científicas de la EHGNA

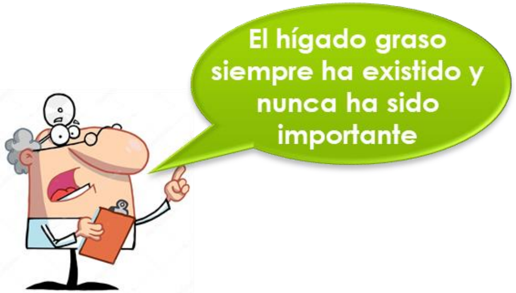
Estoy perfectamente, no tengo síntomas


¿Hígado graso? Anda que no hay cosas más importantes!

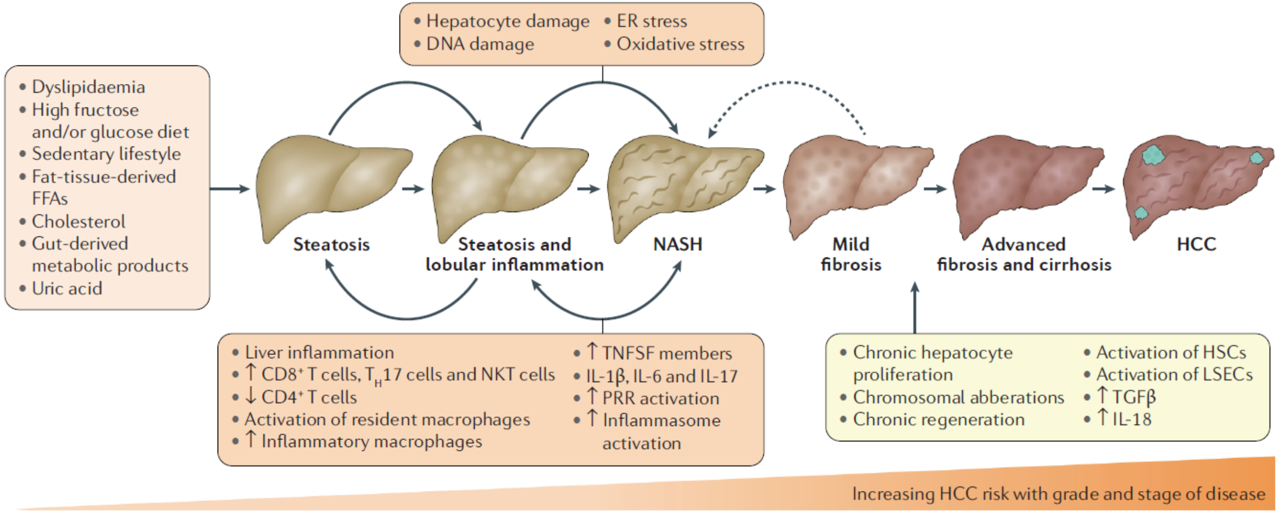

¿Cómo voy a tener hígado graso?
¡Pues anda que yo!


Esto es cosa de mayores


Si no se contagia y no duele para tanto no será


El hígado graso siempre ha existido y nunca ha sido importante

¿Qué es y cuánta gente tiene EHGNA?



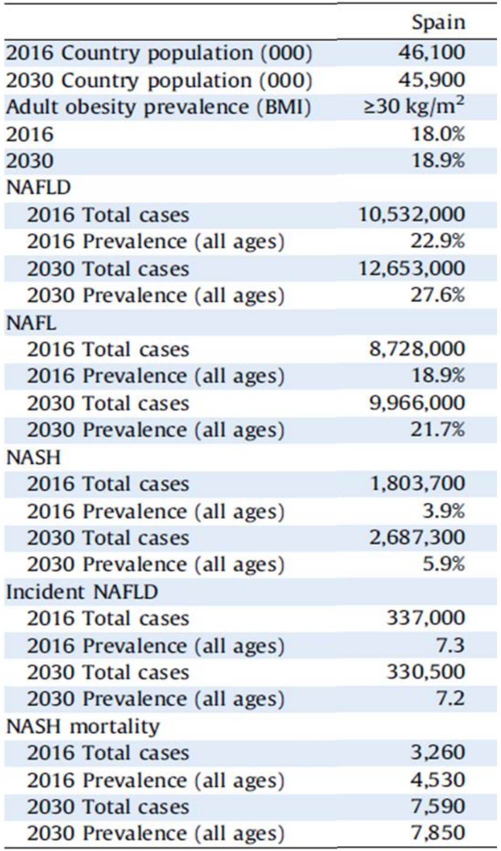
- Dyslipidaemia
- High fructose and/or glucose diet
- Sedentary lifestyle
- Fat-tissue-derived FFAs
- Cholesterol
- Gut-derived metabolic products
- Uric acid

- Hepatocyte damage
- DNA damage
- ER stress
- Oxidative stress

- Liver inflammation
- ↑ CD8$^+$ T cells, T$_H$17 cells and NKT cells
- ↓ CD4$^+$ T cells
- Activation of resident macrophages
- ↑ Inflammatory macrophages
- ↑ TNFSF members
- IL-1β, IL-6 and IL-17
- ↑ PRR activation
- ↑ Inflammasome activation

- Chronic hepatocyte proliferation
- Chromosomal abberations
- Chronic regeneration
- Activation of HSCs
- Activation of LSECs
- ↑ TGFβ
- ↑ IL-18

Steatosis
Steatosis and lobular inflammation
NASH
Mild fibrosis
Advanced fibrosis and cirrhosis
HCC
Increasing HCC risk with grade and stage of disease

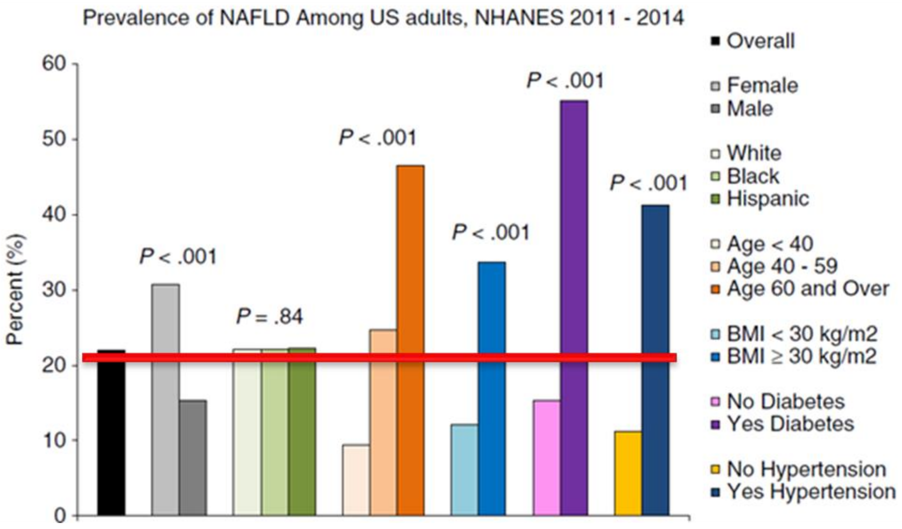


	Spain
2016 Country population (000)	46,100
2030 Country population (000)	45,900
Adult obesity prevalence (BMI)	≥ 30 kg/m^2
2016	18.0%
2030	18.9%
NAFLD	
2016 Total cases	10,532,000
2016 Prevalence (all ages)	22.9%
2030 Total cases	12,653,000
2030 Prevalence (all ages)	27.6%
NAFL	
2016 Total cases	8,728,000
2016 Prevalence (all ages)	18.9%
2030 Total cases	9,966,000
2030 Prevalence (all ages)	21.7%
NASH	
2016 Total cases	1,803,700
2016 Prevalence (all ages)	3.9%
2030 Total cases	2,687,300
2030 Prevalence (all ages)	5.9%
Incident NAFLD	
2016 Total cases	337,000
2016 Prevalence (all ages)	7.3
2030 Total cases	330,500
2030 Prevalence (all ages)	7.2
NASH mortality	
2016 Total cases	3,260
2016 Prevalence (all ages)	4,530
2030 Total cases	7,590
2030 Prevalence (all ages)	7,850

Anstee et al, Nat Gastroenterol Hepatol 2019

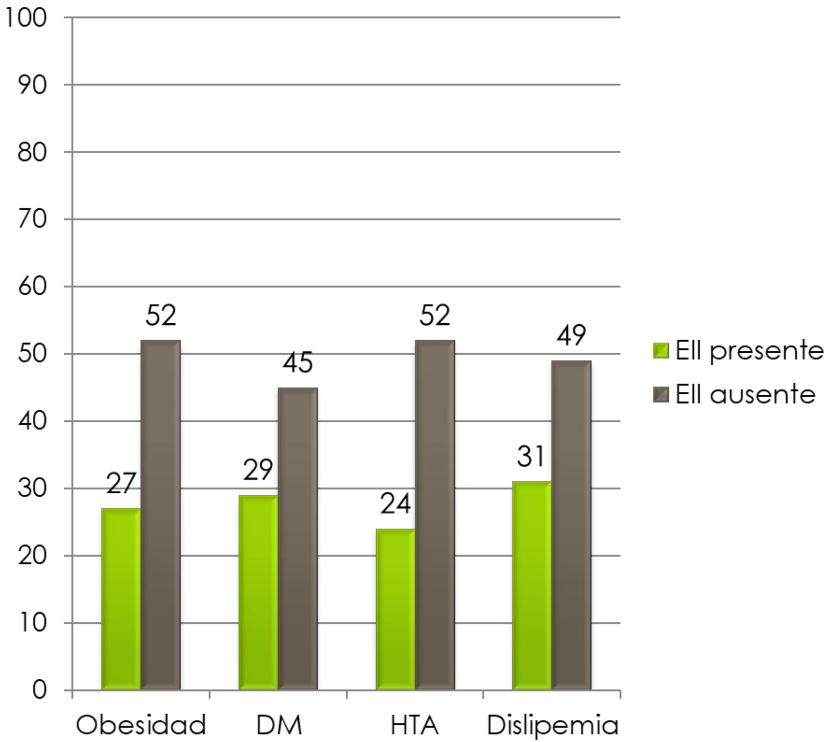
Younossi et al, J Hepatol 2019

Factores de Riesgo → Fenotipos clínicos


Prevalence of NAFLD Among US adults, NHANES 2011 - 2014

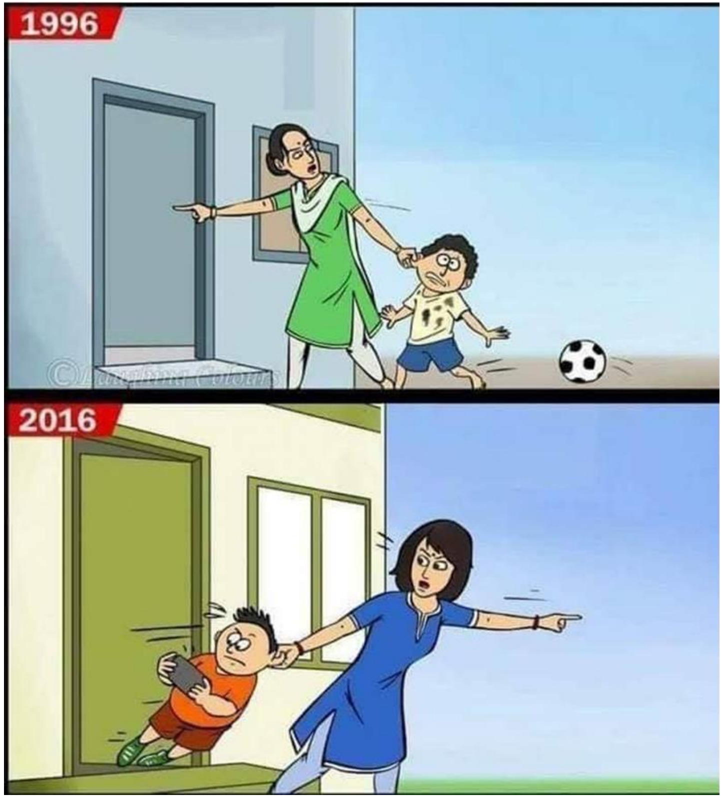
Wong et al, Aliment Pharmacol Ther 2017

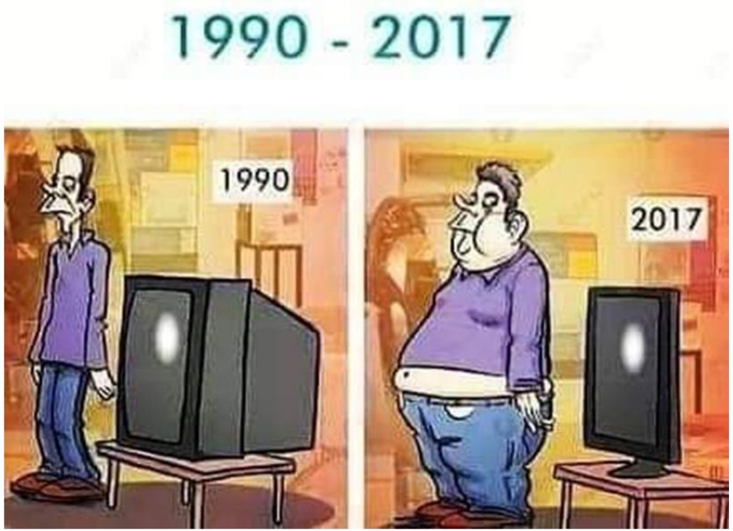
Pacientes con EHGNA (%)



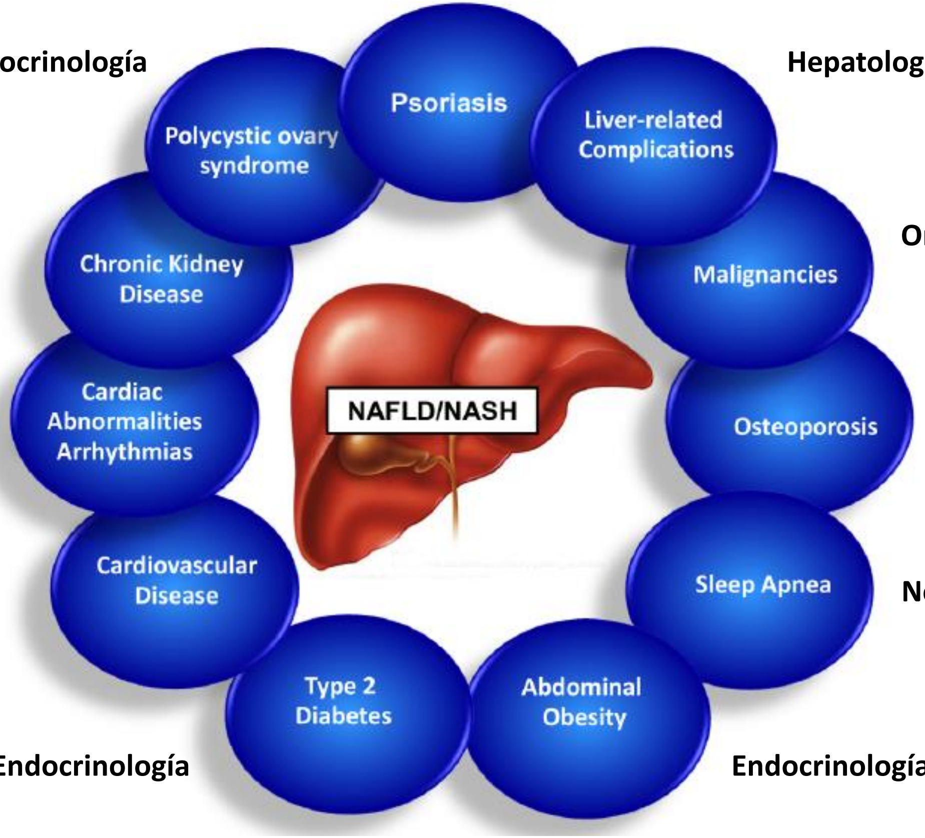
Sartini et al, Cell Death Dis 2018

Fenotipo Metabólico: Cómo hemos cambiado




1990 - 2017
1990
2017

Necesidad de Manejo Multidisciplinar


Psoriasis
Liver-related Complications
Malignancies
Osteoporosis
Sleep Apnea
Abdominal Obesity
Type 2 Diabetes
Cardiovascular Disease
Cardiac Abnormalities Arrhythmias
Chronic Kidney Disease
Polycystic ovary syndrome
NAFLD/NASH

Dermatología

Endocrinología

Hepatología

Nefrología

Oncología

Cardiología

Reumatología

Cardiología

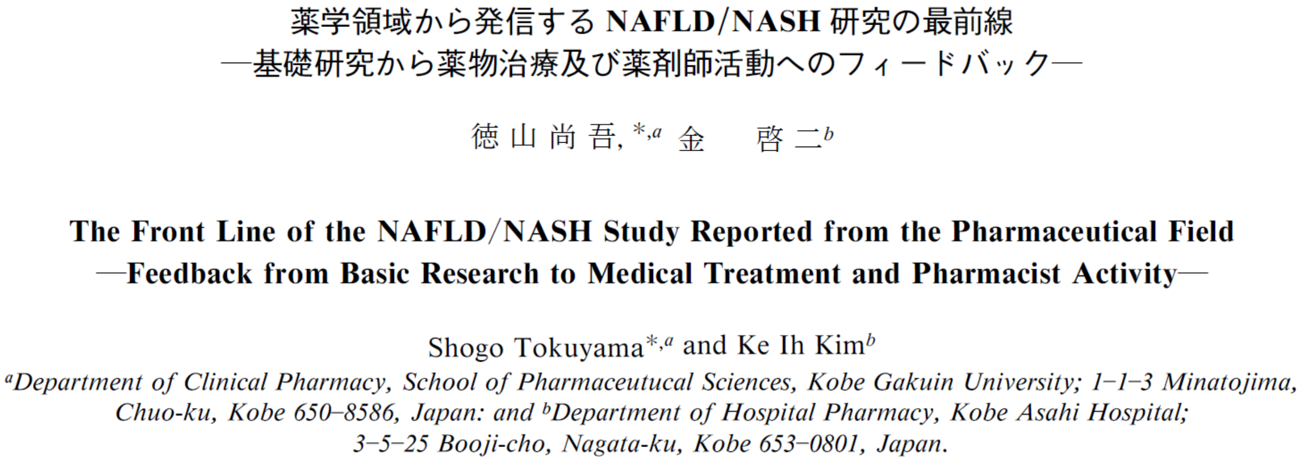
Neumología

Endocrinología

Endocrinología

Adams et al, Gut 2017

¿Qué hay sobre EHGNA y Farmacia Hospitalaria?



薬学領域から発信する NAFLD/NASH 研究の最前線
—基礎研究から薬物治療及び薬剤師活動へのフィードバック—

徳山尚吾,*[,a] 金 啓二[b]

The Front Line of the NAFLD/NASH Study Reported from the Pharmaceutical Field
—Feedback from Basic Research to Medical Treatment and Pharmacist Activity—

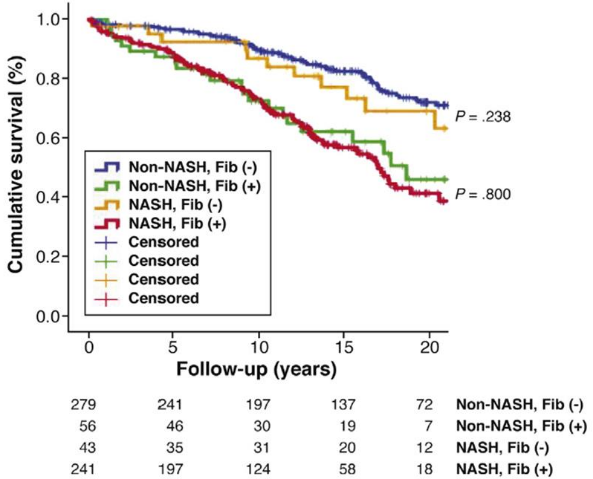
Shogo Tokuyama*[,a] and Ke Ih Kim[b]
[a]Department of Clinical Pharmacy, School of Pharmaceutucal Sciences, Kobe Gakuin University; 1–1–3 Minatojima,
Chuo-ku, Kobe 650–8586, Japan: and [b]Department of Hospital Pharmacy, Kobe Asahi Hospital;
3–5–25 Booji-cho, Nagata-ku, Kobe 653–0801, Japan.

Tokuyama et al, Yakugaku Zasshi 2019

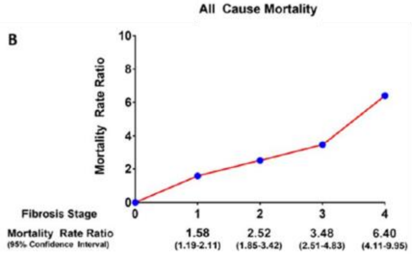
Métodos Diagnósticos

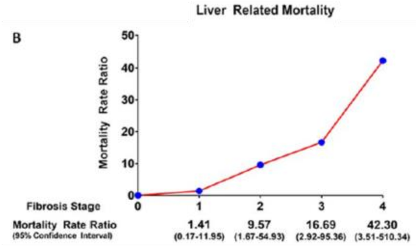
Evaluación no invasiva

Aproximación diagnóstica de EHGNA



	Hepamet Score	NAFLD Fibrosis Score	FIB-4
Edad	✓	✓	✓
Sexo	✓		
IMC		✓	
AST	✓	✓	✓
ALT		✓	✓
Plaquetas	✓	✓	✓
DM	✓	✓	
HOMA	✓		
Albúmina	✓	✓	





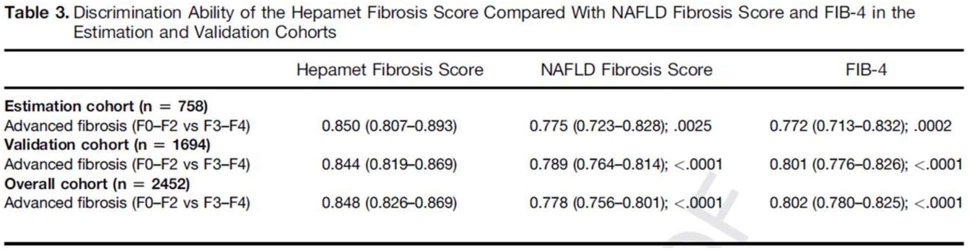


Table 3. Discrimination Ability of the Hepamet Fibrosis Score Compared With NAFLD Fibrosis Score and FIB-4 in the Estimation and Validation Cohorts

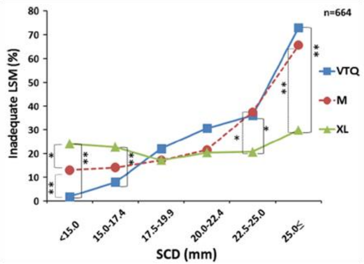
	Hepamet Fibrosis Score	NAFLD Fibrosis Score	FIB-4
Estimation cohort (n = 758)			
Advanced fibrosis (F0–F2 vs F3–F4)	0.850 (0.807–0.893)	0.775 (0.723–0.828); .0025	0.772 (0.713–0.832); .0002
Validation cohort (n = 1694)			
Advanced fibrosis (F0–F2 vs F3–F4)	0.844 (0.819–0.869)	0.789 (0.764–0.814); <.0001	0.801 (0.776–0.826); <.0001
Overall cohort (n = 2452)			
Advanced fibrosis (F0–F2 vs F3–F4)	0.848 (0.826–0.869)	0.778 (0.756–0.801); <.0001	0.802 (0.780–0.825); <.0001

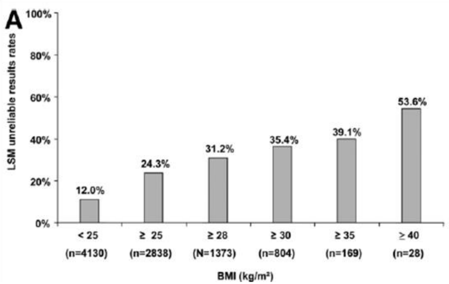
Ampuero et al, Clin Gastroenterol Hepatol 2020

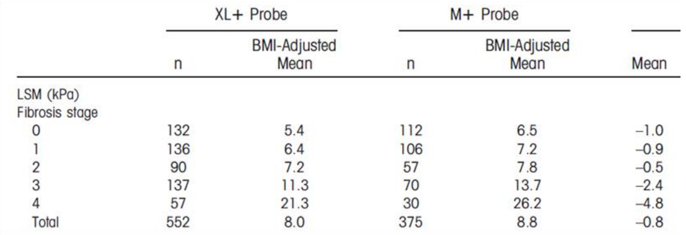
Angulo et al, Gastroenterology 2017

Aproximación diagnóstica de EHGNA

Transient Elastography

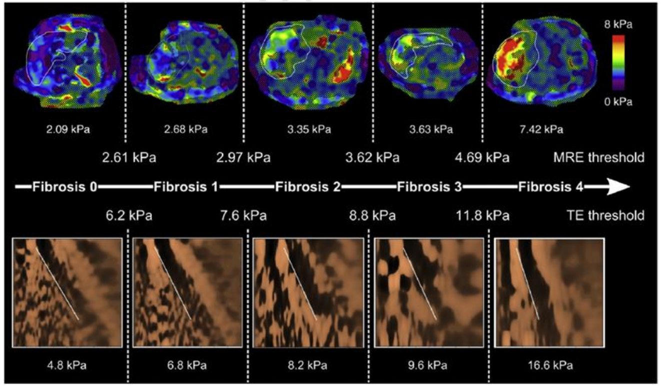


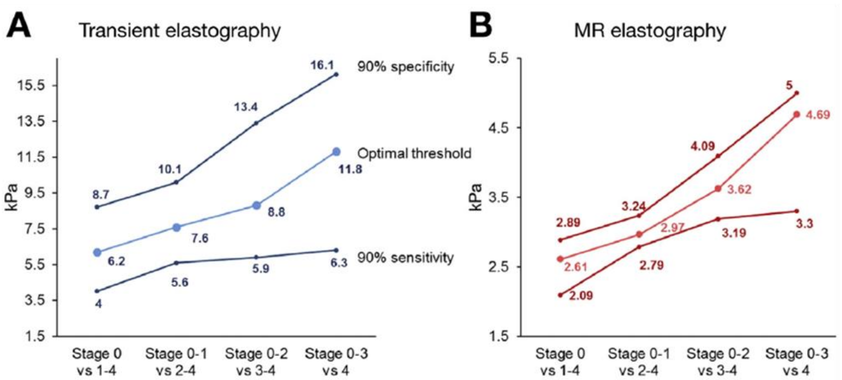




	XL+ Probe		M+ Probe		
	n	BMI-Adjusted Mean	n	BMI-Adjusted Mean	Mean
LSM (kPa)					
Fibrosis stage					
0	132	5.4	112	6.5	–1.0
1	136	6.4	106	7.2	–0.9
2	90	7.2	57	7.8	–0.5
3	137	11.3	70	13.7	–2.4
4	57	21.3	30	26.2	–4.8
Total	552	8.0	375	8.8	–0.8

MR Elastography


8 kPa
0 kPa
2.09 kPa
2.68 kPa
3.35 kPa
3.63 kPa
7.42 kPa
2.61 kPa
2.97 kPa
3.62 kPa
4.69 kPa
MRE threshold
Fibrosis 0
Fibrosis 1
Fibrosis 2
Fibrosis 3
Fibrosis 4
6.2 kPa
7.6 kPa
8.8 kPa
11.8 kPa
TE threshold
4.8 kPa
6.8 kPa
8.2 kPa
9.6 kPa
16.6 kPa



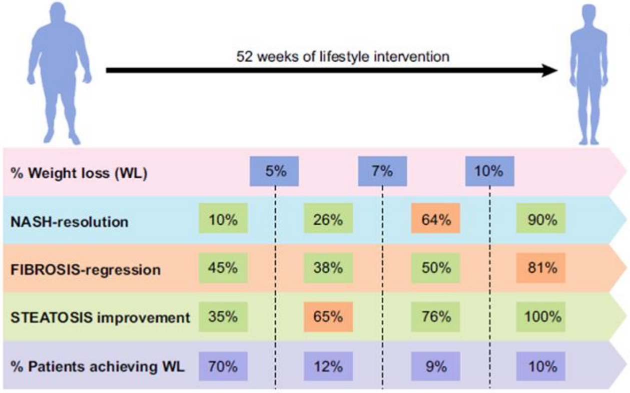
Vuppalanchi et al, Hepatology 2018

Hsu et al, Clin Gastroenterol Hepatol 2018

¿Cuál es el tratamiento?

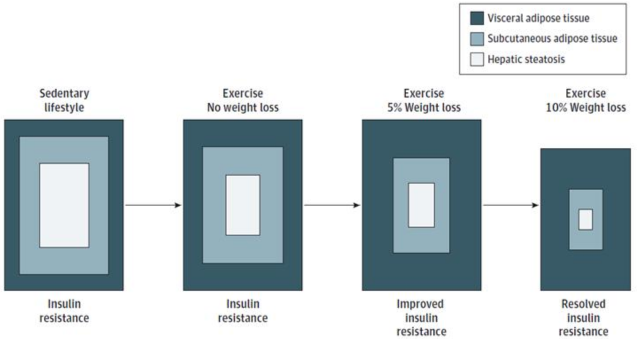
¿Existen terapias eficaces?

Cambios en el estilo de vida

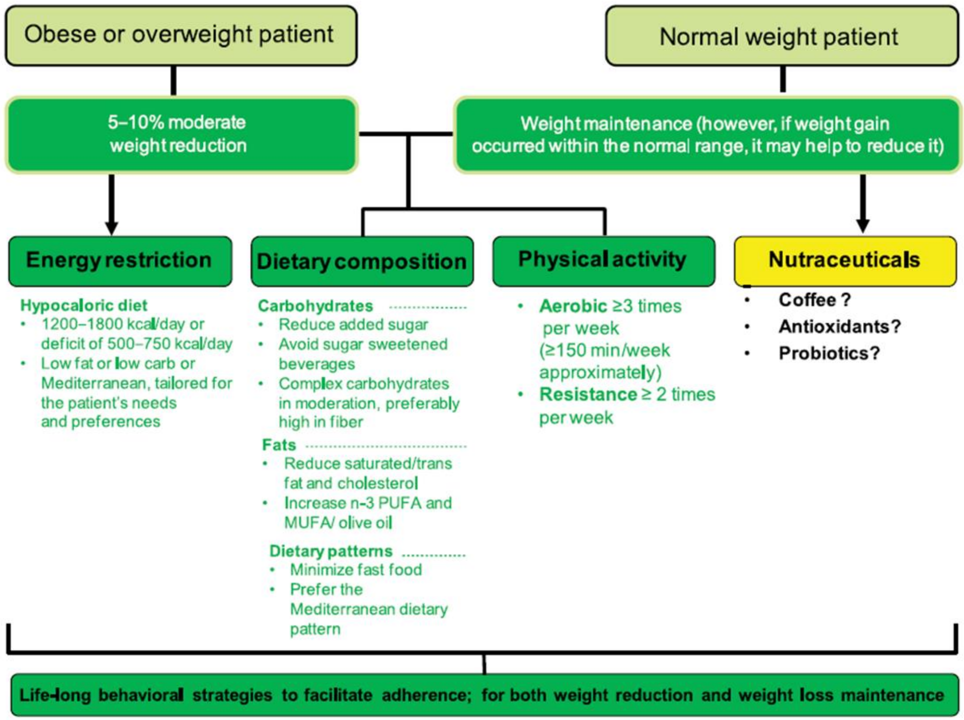


% Weight loss (WL)		5%		7%		10%	
NASH-resolution	10%		26%		64%		90%
FIBROSIS-regression	45%		38%		50%		81%
STEATOSIS improvement	35%		65%		76%		100%
% Patients achieving WL	70%		12%		9%		10%

Figure. Benefits of Exercise and Weight Loss on Adipose Tissue Compartments and Insulin Resistance



Visceral adipose tissue
Subcutaneous adipose tissue
Hepatic steatosis
Sedentary lifestyle
Exercise No weight loss
Exercise 5% Weight loss
Exercise 10% Weight loss
Insulin resistance
Insulin resistance
Improved insulin resistance
Resolved insulin resistance



Obese or overweight patient

5–10% moderate weight reduction

Normal weight patient

Weight maintenance (however, if weight gain occurred within the normal range, it may help to reduce it)

Energy restriction

Hypocaloric diet
- 1200–1800 kcal/day or deficit of 500–750 kcal/day
- Low fat or low carb or Mediterranean, tailored for the patient's needs and preferences

Dietary composition

Carbohydrates
- Reduce added sugar
- Avoid sugar sweetened beverages
- Complex carbohydrates in moderation, preferably high in fiber

Fats
- Reduce saturated/trans fat and cholesterol
- Increase n-3 PUFA and MUFA/ olive oil

Dietary patterns
- Minimize fast food
- Prefer the Mediterranean dietary pattern

Physical activity
- **Aerobic** ≥3 times per week (≥150 min/week approximately)
- **Resistance** ≥ 2 times per week

Nutraceuticals
- **Coffee ?**
- **Antioxidants?**
- **Probiotics?**

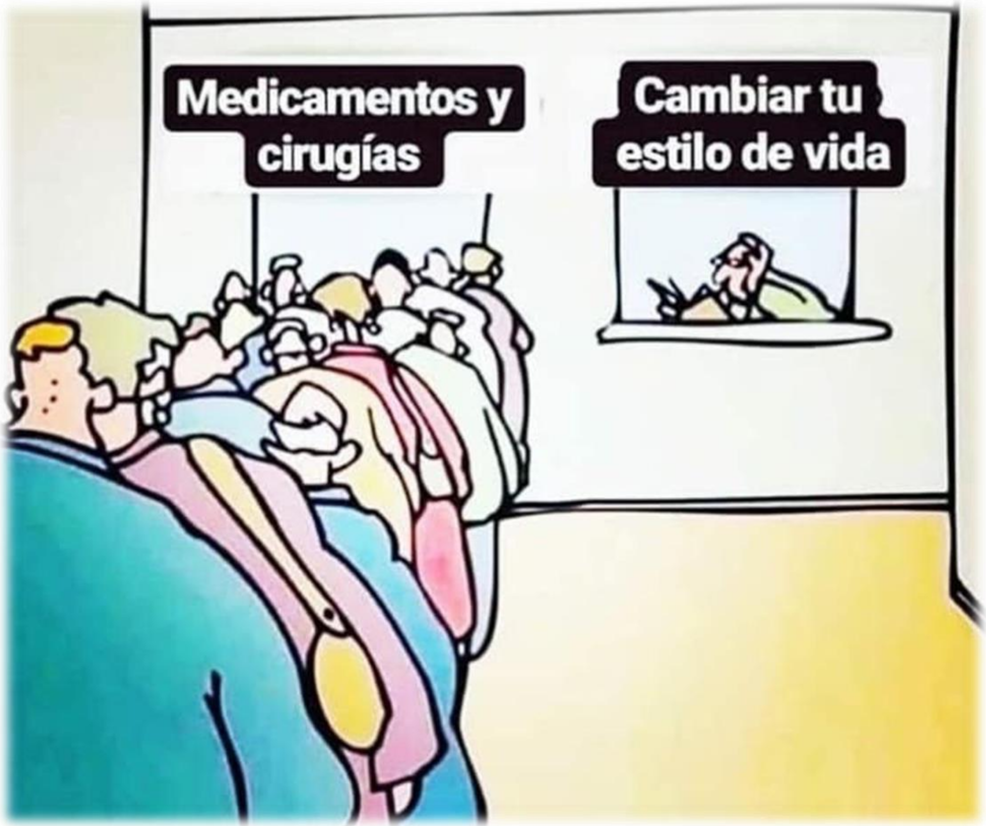
Life-long behavioral strategies to facilitate adherence; for both weight reduction and weight loss maintenance

Vilar et al, Gastroenterology 2015

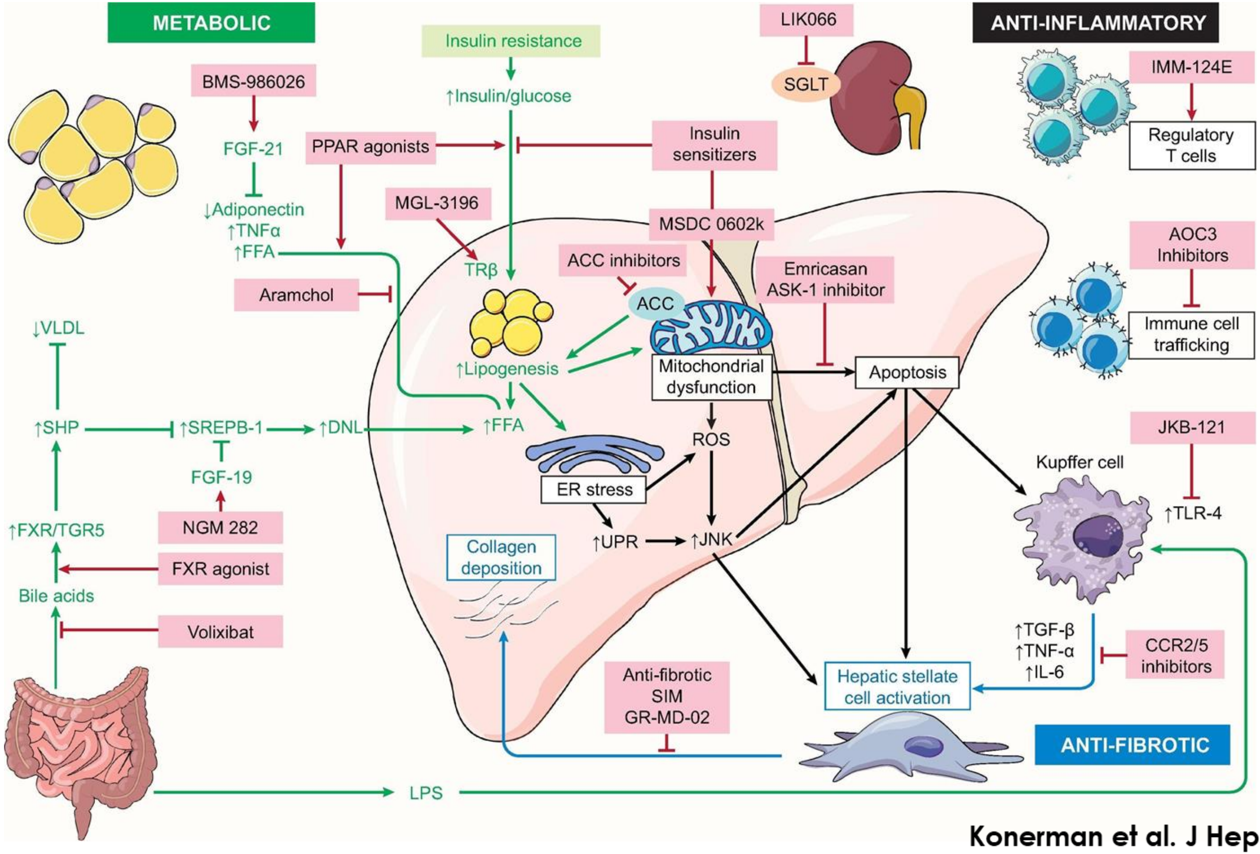
Prenner et al, JAMA 2016

Zelber-Sagi et al, Ther Adv Gastroenterol 2017

Pero somos como somos…


Medicamentos y cirugías
Cambiar tu estilo de vida

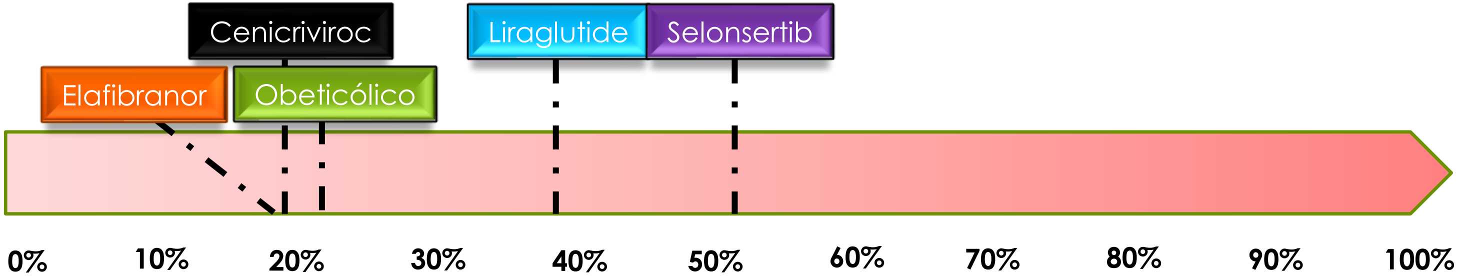
Múltiples opciones farmacológicas


METABOLIC
Insulin resistance
↑Insulin/glucose
LIK066
SGLT
ANTI-INFLAMMATORY
IMM-124E
Regulatory T cells
BMS-986026
FGF-21
PPAR agonists
Insulin sensitizers
↓Adiponectin
↑TNFα
↑FFA
MGL-3196
MSDC 0602k
TRβ
ACC inhibitors
Emricasan ASK-1 inhibitor
AOC3 Inhibitors
Aramchol
ACC
Immune cell trafficking
↓VLDL
↑Lipogenesis
Mitochondrial dysfunction
Apoptosis
↑SHP
↑SREPB-1
↑DNL
↑FFA
ROS
JKB-121
FGF-19
ER stress
Kupffer cell
↑TLR-4
↑FXR/TGR5
NGM 282
↑UPR
↑JNK
FXR agonist
Collagen deposition
Bile acids
Volixibat
↑TGF-β
↑TNF-α
↑IL-6
CCR2/5 inhibitors
Anti-fibrotic
SIM
GR-MD-02
Hepatic stellate cell activation
ANTI-FIBROTIC
LPS

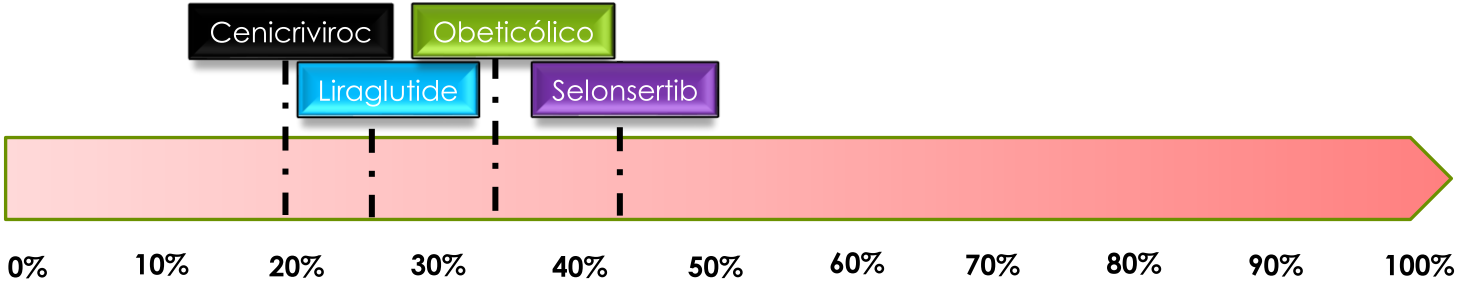
Konerman et al. J Hepatol 2018

Resultados ECA Fase II

NASH improvement

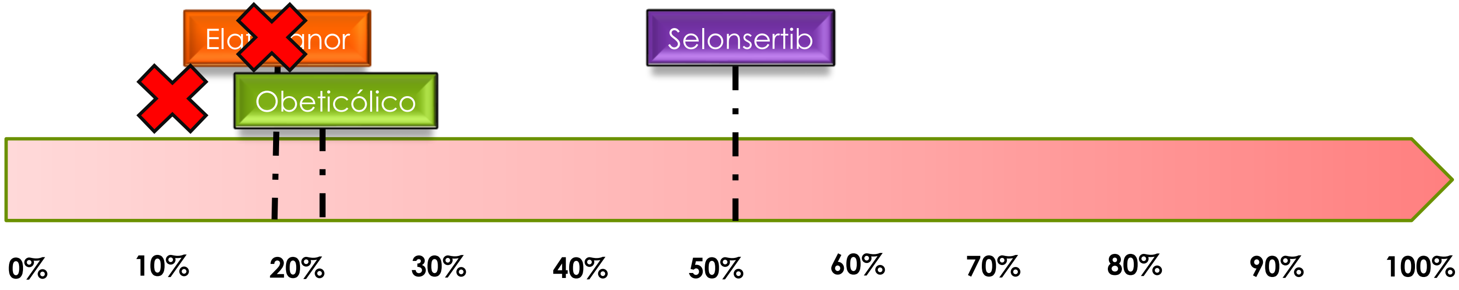


Fibrosis improvement

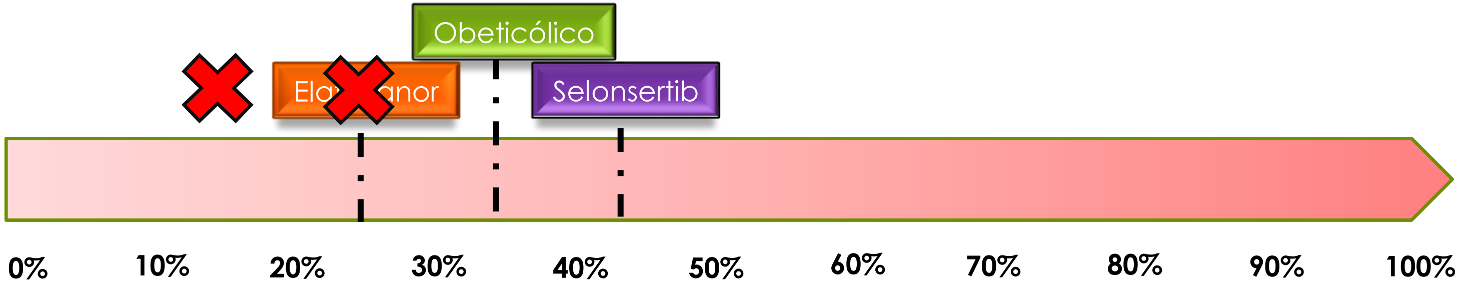


Resultados ECA Fase III (preliminares)

NASH improvement



Fibrosis improvement



Necesidad de abordaje multidisciplinar

Papel de Farmacia Hospitalaria

Usar fármacos eficaces

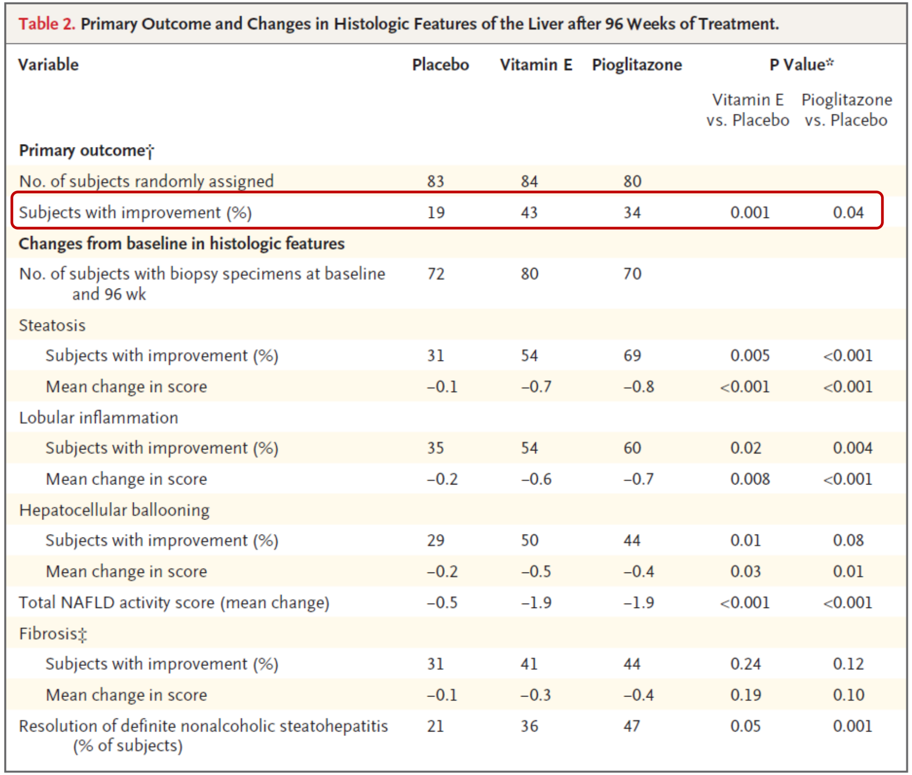


Table 2. Primary Outcome and Changes in Histologic Features of the Liver after 96 Weeks of Treatment.

Variable	Placebo	Vitamin E	Pioglitazone	P Value* Vitamin E vs. Placebo	P Value* Pioglitazone vs. Placebo
Primary outcome†					
No. of subjects randomly assigned	83	84	80		
Subjects with improvement (%)	19	43	34	0.001	0.04
Changes from baseline in histologic features					
No. of subjects with biopsy specimens at baseline and 96 wk	72	80	70		
Steatosis					
Subjects with improvement (%)	31	54	69	0.005	<0.001
Mean change in score	−0.1	−0.7	−0.8	<0.001	<0.001
Lobular inflammation					
Subjects with improvement (%)	35	54	60	0.02	0.004
Mean change in score	−0.2	−0.6	−0.7	0.008	<0.001
Hepatocellular ballooning					
Subjects with improvement (%)	29	50	44	0.01	0.08
Mean change in score	−0.2	−0.5	−0.4	0.03	0.01
Total NAFLD activity score (mean change)	−0.5	−1.9	−1.9	<0.001	<0.001
Fibrosis‡					
Subjects with improvement (%)	31	41	44	0.24	0.12
Mean change in score	−0.1	−0.3	−0.4	0.19	0.10
Resolution of definite nonalcoholic steatohepatitis (% of subjects)	21	36	47	0.05	0.001

Sanyal et al, NEJM 2010

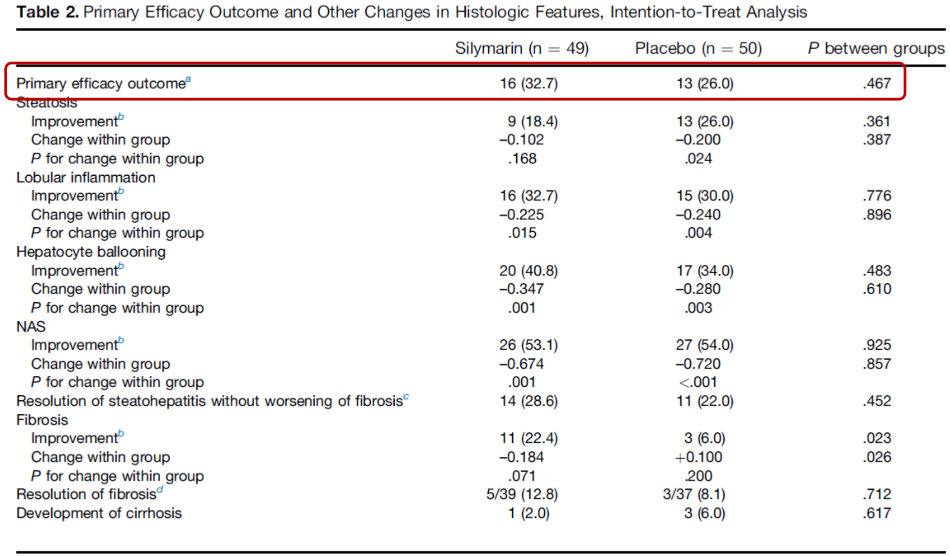
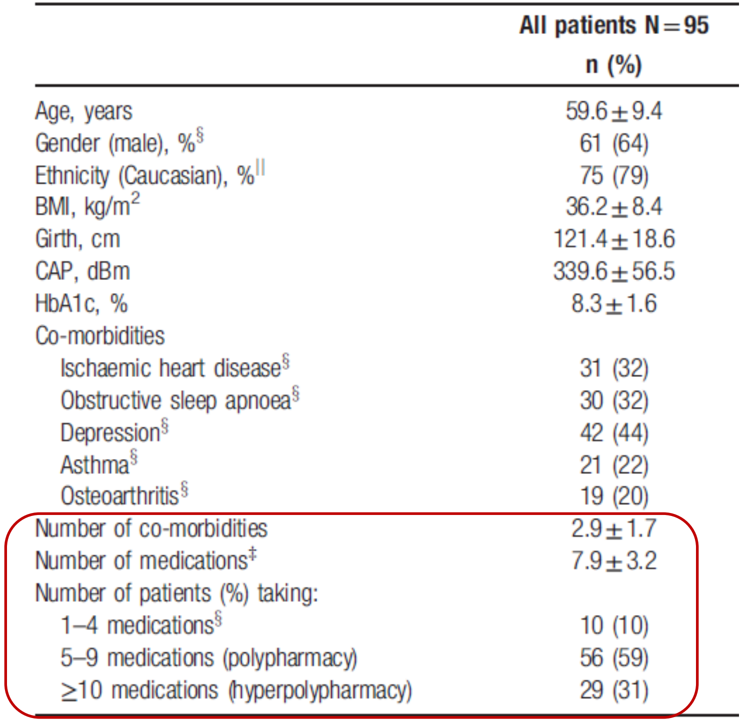


Table 2. Primary Efficacy Outcome and Other Changes in Histologic Features, Intention-to-Treat Analysis

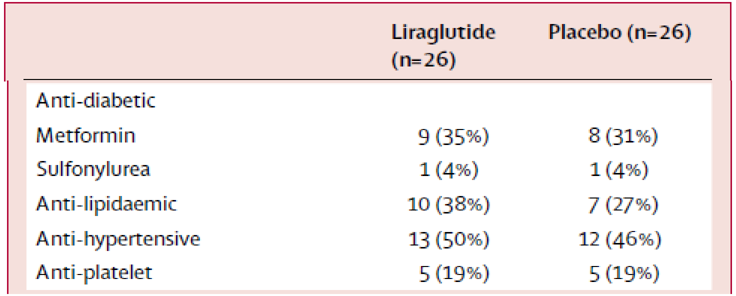
	Silymarin (n = 49)	Placebo (n = 50)	*P* between groups
Primary efficacy outcome[a]	16 (32.7)	13 (26.0)	.467
Steatosis			
Improvement[b]	9 (18.4)	13 (26.0)	.361
Change within group	−0.102	−0.200	.387
P for change within group	.168	.024	
Lobular inflammation			
Improvement[b]	16 (32.7)	15 (30.0)	.776
Change within group	−0.225	−0.240	.896
P for change within group	.015	.004	
Hepatocyte ballooning			
Improvement[b]	20 (40.8)	17 (34.0)	.483
Change within group	−0.347	−0.280	.610
P for change within group	.001	.003	
NAS			
Improvement[b]	26 (53.1)	27 (54.0)	.925
Change within group	−0.674	−0.720	.857
P for change within group	.001	<.001	
Resolution of steatohepatitis without worsening of fibrosis[c]	14 (28.6)	11 (22.0)	.452
Fibrosis			
Improvement[b]	11 (22.4)	3 (6.0)	.023
Change within group	−0.184	+0.100	.026
P for change within group	.071	.200	
Resolution of fibrosis[d]	5/39 (12.8)	3/37 (8.1)	.712
Development of cirrhosis	1 (2.0)	3 (6.0)	.617

Kheong et al, Clin Gastroenterol Hepatol 2017

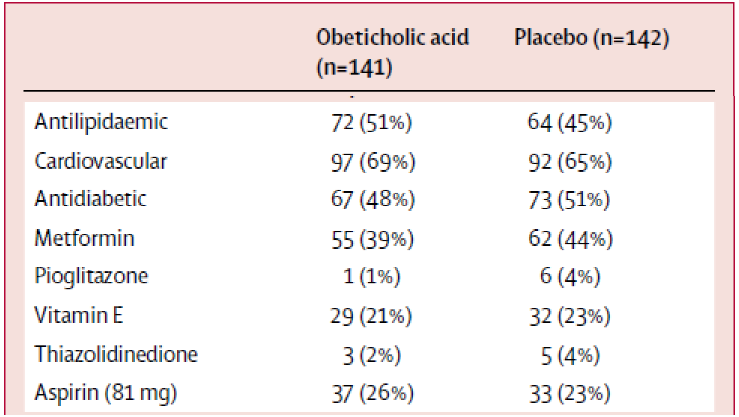
Interacciones farmacológicas



	All patients N = 95 n (%)
Age, years	59.6 ± 9.4
Gender (male), %[§]	61 (64)
Ethnicity (Caucasian), %[‖]	75 (79)
BMI, kg/m^2	36.2 ± 8.4
Girth, cm	121.4 ± 18.6
CAP, dBm	339.6 ± 56.5
HbA1c, %	8.3 ± 1.6
Co-morbidities	
Ischaemic heart disease[§]	31 (32)
Obstructive sleep apnoea[§]	30 (32)
Depression[§]	42 (44)
Asthma[§]	21 (22)
Osteoarthritis[§]	19 (20)
Number of co-morbidities	2.9 ± 1.7
Number of medications[‡]	7.9 ± 3.2
Number of patients (%) taking:	
1–4 medications[§]	10 (10)
5–9 medications (polypharmacy)	56 (59)
≥10 medications (hyperpolypharmacy)	29 (31)



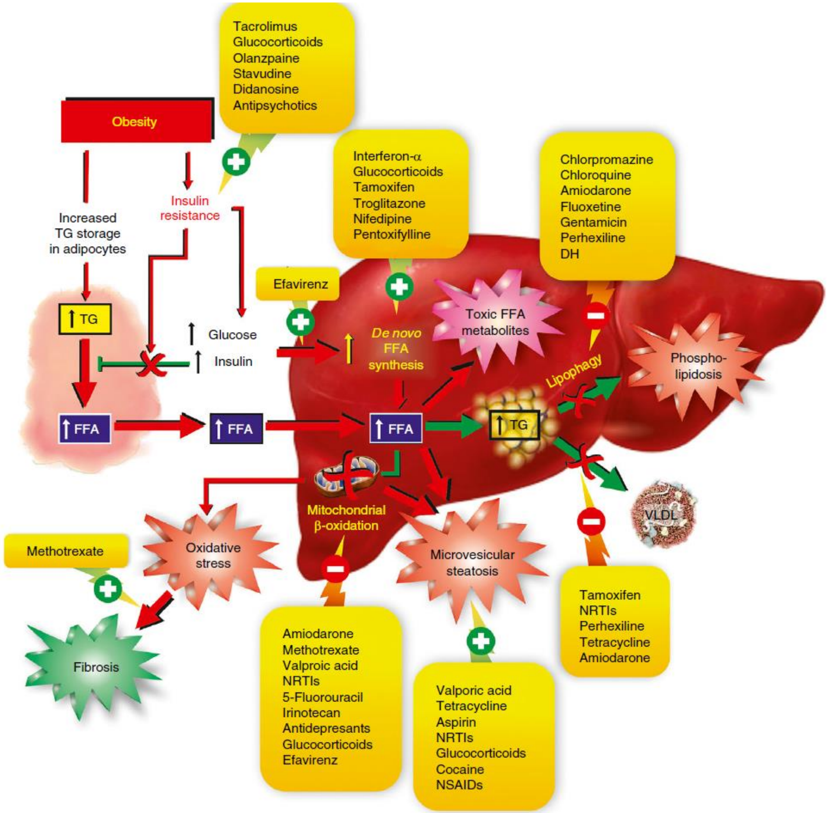
	Liraglutide (n=26)	Placebo (n=26)
Anti-diabetic		
Metformin	9 (35%)	8 (31%)
Sulfonylurea	1 (4%)	1 (4%)
Anti-lipidaemic	10 (38%)	7 (27%)
Anti-hypertensive	13 (50%)	12 (46%)
Anti-platelet	5 (19%)	5 (19%)



	Obeticholic acid (n=141)	Placebo (n=142)
Antilipidaemic	72 (51%)	64 (45%)
Cardiovascular	97 (69%)	92 (65%)
Antidiabetic	67 (48%)	73 (51%)
Metformin	55 (39%)	62 (44%)
Pioglitazone	1 (1%)	6 (4%)
Vitamin E	29 (21%)	32 (23%)
Thiazolidinedione	3 (2%)	5 (4%)
Aspirin (81 mg)	37 (26%)	33 (23%)

Neuschwander-Tetri et al, Lancet 2014 **Patel et al, Medicine 2017** **Armstrong et al, Lancet 2016**

Evitar fármacos esteatogénicos


Tacrolimus
Glucocorticoids
Olanzpaine
Stavudine
Didanosine
Antipsychotics
Obesity
Insulin resistance
Increased TG storage in adipocytes
Interferon-α
Glucocorticoids
Tamoxifen
Troglitazone
Nifedipine
Pentoxifylline
Chlorpromazine
Chloroquine
Amiodarone
Fluoxetine
Gentamicin
Perhexiline
DH
Efavirenz
↑ TG
↑ Glucose
↑ Insulin
De novo FFA synthesis
Toxic FFA metabolites
Lipophagy
Phospho-lipidosis
↑ FFA
↑ FFA
↑ FFA
↑ TG
VLDL
Mitochondrial β-oxidation
Methotrexate
Oxidative stress
Microvesicular steatosis
Fibrosis
Tamoxifen
NRTIs
Perhexiline
Tetracycline
Amiodarone
Amiodarone
Methotrexate
Valproic acid
NRTIs
5-Fluorouracil
Irinotecan
Antidepresants
Glucocorticoids
Efavirenz
Valporic acid
Tetracycline
Aspirin
NRTIs
Glucocorticoids
Cocaine
NSAIDs

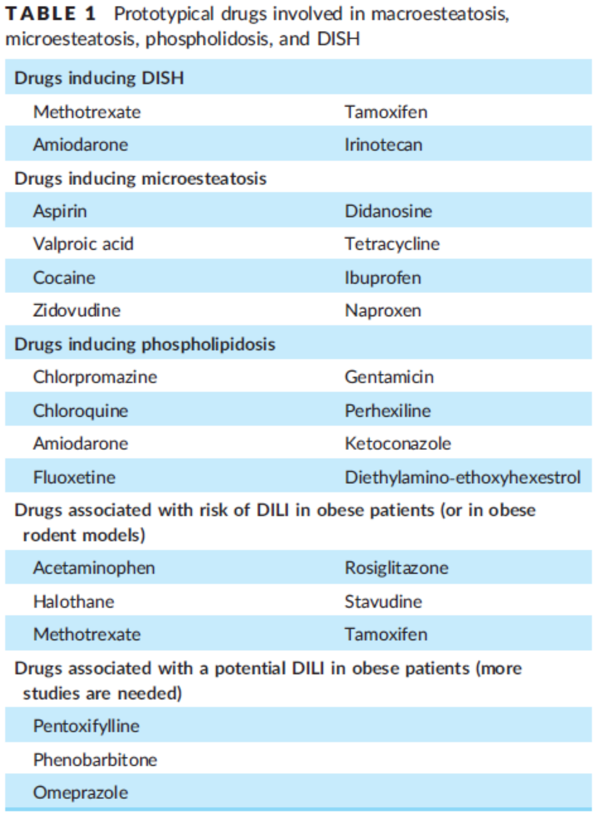
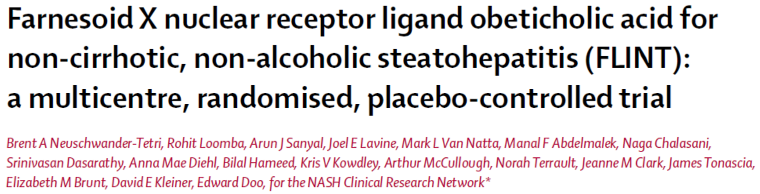


TABLE 1 Prototypical drugs involved in macroesteatosis, microesteatosis, phospholidosis, and DISH

Drugs inducing DISH	
Methotrexate	Tamoxifen
Amiodarone	Irinotecan
Drugs inducing microesteatosis	
Aspirin	Didanosine
Valproic acid	Tetracycline
Cocaine	Ibuprofen
Zidovudine	Naproxen
Drugs inducing phospholipidosis	
Chlorpromazine	Gentamicin
Chloroquine	Perhexiline
Amiodarone	Ketoconazole
Fluoxetine	Diethylamino-ethoxyhexestrol
Drugs associated with risk of DILI in obese patients (or in obese rodent models)	
Acetaminophen	Rosiglitazone
Halothane	Stavudine
Methotrexate	Tamoxifen
Drugs associated with a potential DILI in obese patients (more studies are needed)	
Pentoxifylline	
Phenobarbitone	
Omeprazole	

Bessone et al, Aliment, Pharmacol, Ther 2018

Reposicionamiento de fármacos

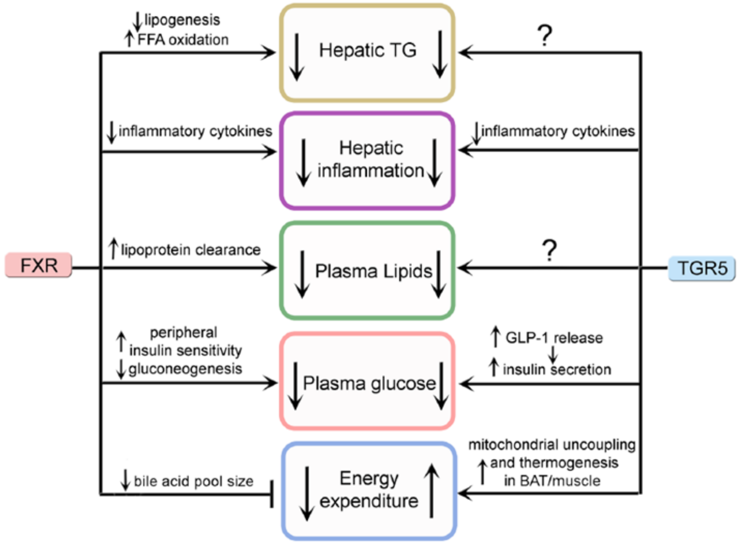


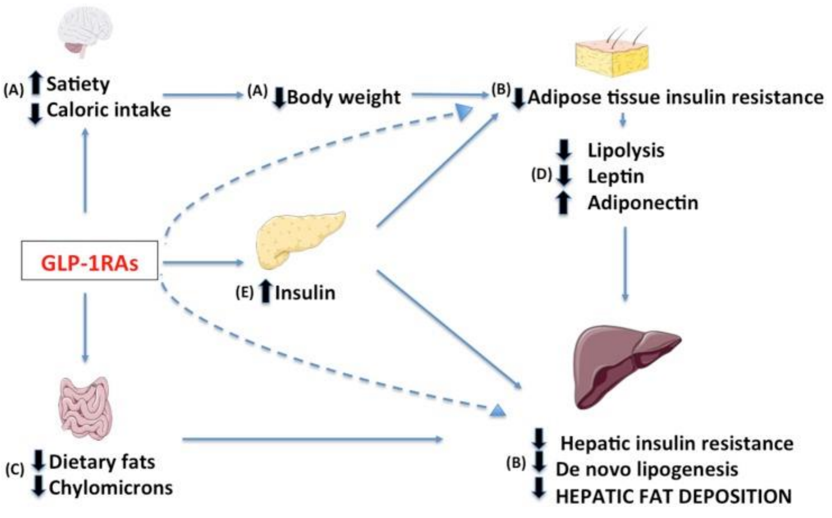
Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial

*Brent A Neuschwander-Tetri, Rohit Loomba, Arun J Sanyal, Joel E Lavine, Mark L Van Natta, Manal F Abdelmalek, Naga Chalasani, Srinivasan Dasarathy, Anna Mae Diehl, Bilal Hameed, Kris V Kowdley, Arthur McCullough, Norah Terrault, Jeanne M Clark, James Tonascia, Elizabeth M Brunt, David E Kleiner, Edward Doo, for the NASH Clinical Research Network**

Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study

Matthew James Armstrong, Piers Gaunt, Guruprasad P Aithal, Darren Barton, Diana Hull, Richard Parker, Jonathan M Hazlehurst, Kathy Guo, LEAN trial team, George Abouda, Mark A Aldersley, Deborah Stocken, Stephen C Gough, Jeremy W Tomlinson, Rachel M Brown, Stefan G Hübscher, Philip N Newsome*


↓lipogenesis
↑FFA oxidation
Hepatic TG ↓ ↓
?
↓inflammatory cytokines
Hepatic inflammation ↓ ↓
↓inflammatory cytokines
FXR
↑lipoprotein clearance
Plasma Lipids ↓ ↓
?
TGR5
↑ peripheral insulin sensitivity
↓gluconeogenesis
Plasma glucose ↓ ↓
↑ GLP-1 release
↓
↑ insulin secretion
↓bile acid pool size
Energy expenditure ↓ ↑
mitochondrial uncoupling
↑ and thermogenesis
in BAT/muscle


(A) ↑Satiety
↓Caloric intake
(A) ↓Body weight
(B) ↓Adipose tissue insulin resistance
↓ Lipolysis
(D) ↓ Leptin
↑ Adiponectin
GLP-1RAs
(E) ↑Insulin
(C) ↓Dietary fats
↓Chylomicrons
↓ Hepatic insulin resistance
(B) ↓ De novo lipogenesis
↓ HEPATIC FAT DEPOSITION

Neuschwander-Tetri et al, Lancet 2014 **Li et al, Biochem Pharmacol 2013** **Armstrong et al, Lancet 2016** **Seghieri et al, Front Endocrinol 2018**

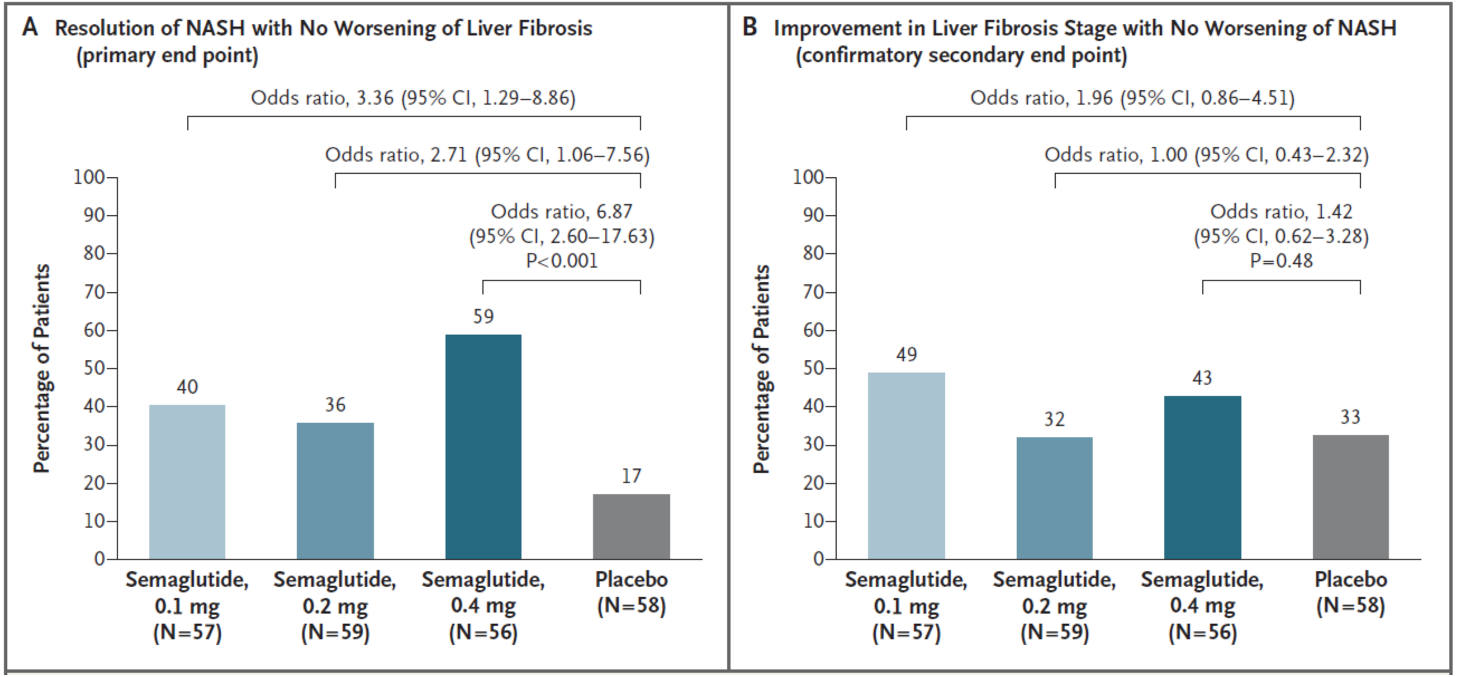
Reposicionamiento de fármacos

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis

P.N. Newsome, K. Buchholtz, K. Cusi, M. Linder, T. Okanoue, V. Ratziu, A.J. Sanyal, A.-S. Sejling, and S.A. Harrison, for the NN9931-4296 Investigators*

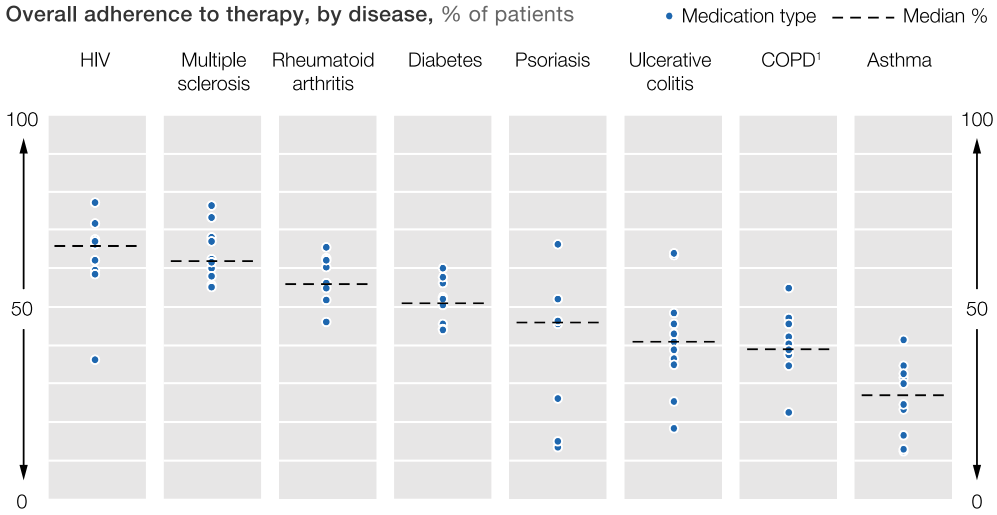


Newsome et al, NEJM 2020

Adherencia en enfermedades crónicas

Table 1. Prevalence of non-adherence behaviors in chronic diseases.

	All patients ($n = 1,530$)	Rheumatic disease ($n = 336$)	IBD ($n = 322$)	HIV infection ($n = 442$)	DM ($n = 430$)
At least one non-adherence behavior, *n* (%)	812 (53.1)	188 (56.0)	179 (55.6)	189 (42.8)	257 (59.8)
Forgetfulness in taking medication (skipping doses), *n* (%)	496 (32.4)	96 (28.6)	117 (36.2)	140 (31.6)	143 (33.3)
Taking medication at unscheduled hours, *n* (%)	89 (5.8)	19 (5.6)	18 (5.5)	22 (5.0)	31 (7.1)
Stopping medication when feeling well, *n* (%)	90 (5.9)	34 (10.1)	21 (6.5)	11 (2.5)	25 (5.7)
Stopping medication if it makes the patient feel unwell, *n* (%)	418 (27.3)	111 (33.0)	91 (28.3)	55 (12.5)	160 (37.2)
Stopping medication after reading the patients' information leaflet, *n* (%)	179 (11.7)	39 (11.5)	27 (8.4)	30 (6.8)	83 (19.4)



Overall adherence to therapy, by disease, % of patients

Cea-Calvo et al, Curr Med Res Opin 2019

Y a vosotros, ¿qué más se os ocurre?

to be continued...

@Dr_Ampuero