Liraglutide-Induced AKI and Liver Injury in an Adolescent

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האיגוד הישראלי לנפרולוגית ילדים ISPN The Israeli Society of Pediatric Nephrology

קווים משיקים ברפואת הילדים

7.3.2024, מרכז רפואי שמיר

האגוד הישראלי לאנדוקרינולוגיה פדיאטרית

Current status

- FDA approved and American Academy of Pediatrics recommends:
  - Use Liraglutide (Saxenda) and Semaglutide (Wagovy) among adolescents with significant obesity > 12 years
  - **Who failed conventional intervention**

- Success of Liraglutide at 6-12 years
- Studies of Semaglutide at 6-12 years
- Studies of Terzepetide at 12-18 years

- **Increasing use of GLP-1RAs for adolescent obesity - by everybody – to everybody .**

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Case Reports Pediatrics. 2024 Jul 1;154(1):e2023063719. doi: 10.1542/peds.2023-063719.

Acute Kidney and Liver Injury Associated With Low-Dose Liraglutide in an Obese Adolescent Patient

Rinat Komargodski [# 1 2], Avigail Wittenberg [# 3], Hilla Bahat [4 5], Marianna Rachmiel [3 4]

- **Increasing use of GLP-1RAs for adolescent obesity - by everybody – to everybody .**

Clinical Practice Guideline for the Evaluation and Treatment of Children and Adolescents With Obesity

1. Defining and cuf-offs

American Academy of Pediatrics

PEDIATRICS Volume 151, number 2, February 2023:e2022060640

Children below 2 y of age	
Obesity	Weight for recumbent length ≥97.7th percentile of WHO growth standards
Children and adolescents 2–20 y of age	
Overweight	BMI ≥85th to <95th percentile for age and sex
Obesity	BMI ≥95th percentile for age and sex
Severe Obesity	BMI ≥120% of 95th percentile or BMI ≥35 kg/m^2, whichever is lower

Class I	**BMI ≥95th percentile to <120% of 95th percentile for age and sex**
Class II	BMI ≥120% to <140% of 95th percentile or BMI ≥35 kg/m^2
Class III	BMI ≥140% of 95th percentile or BMI ≥40 kg/m^2

Pediatricians and other PHCPs **SHOULD OFFER** adolescents 12 y and older with obesity (BMI ≥ 95th percentile) **WEIGHT LOSS PHARMACOTHERAPY,**
accourding to medications indication, risks, and benefits, as an **ADUNCT** to health behavior and lifestyle treatment

Aggregate Evidence Quality	Grade B
Benefits	BMI reduction as an adjunct to lifestyle treatment.
Risks, harms, costs	Varies by pharmacotherapeutic agent.
Benefit-harm assessment	Benefit and harm are individualized by patient, must weigh the side effects and potential benefit of the medication and patient-specific factors.
Intentional vagueness	None.
Role of patient preference	Significant; must determine appropriate timing and duration of treatment, monitor for side effects.
Exclusions	Medication-dependent exclusions.
Strengths	Moderate.
Key references	710

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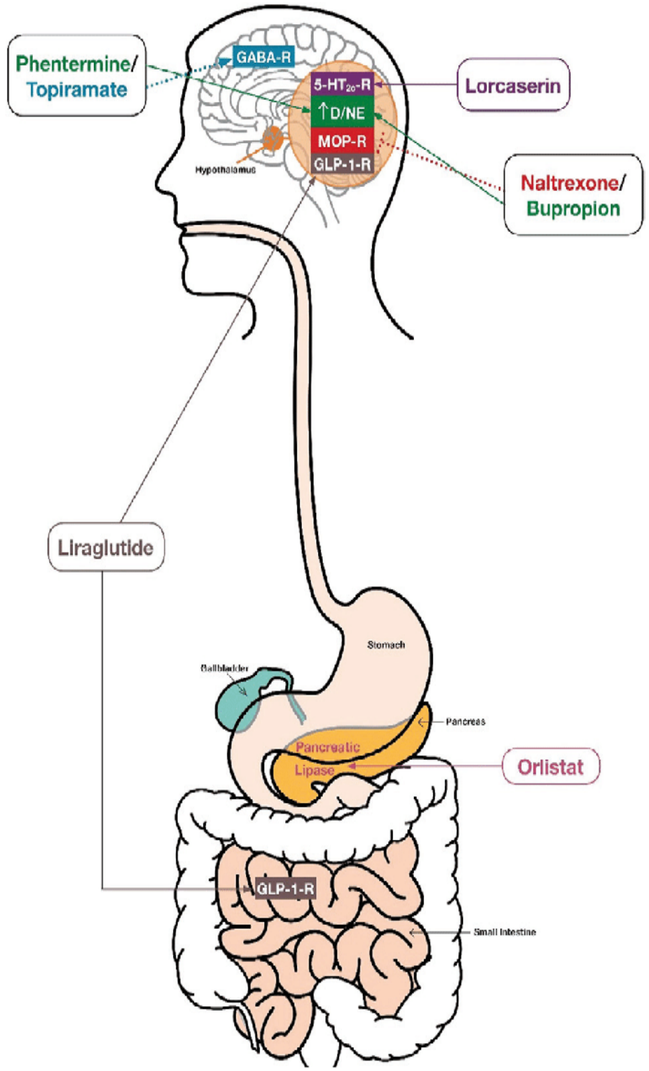
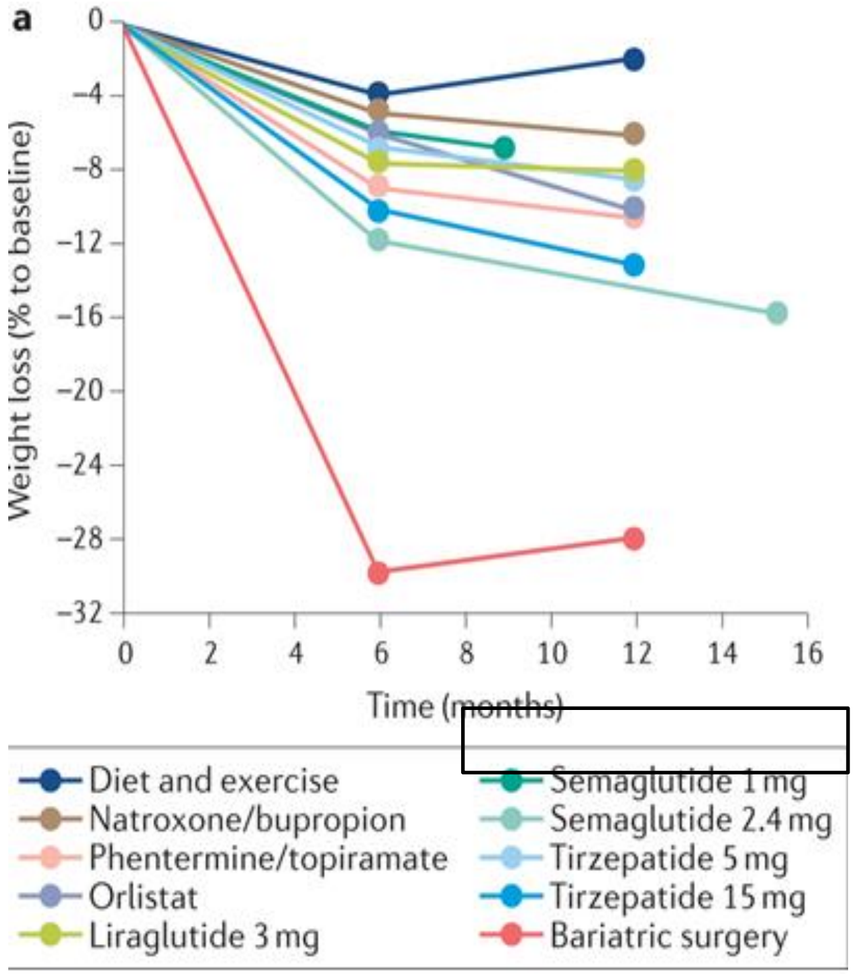
Pharmacotherapeutic options for weight management

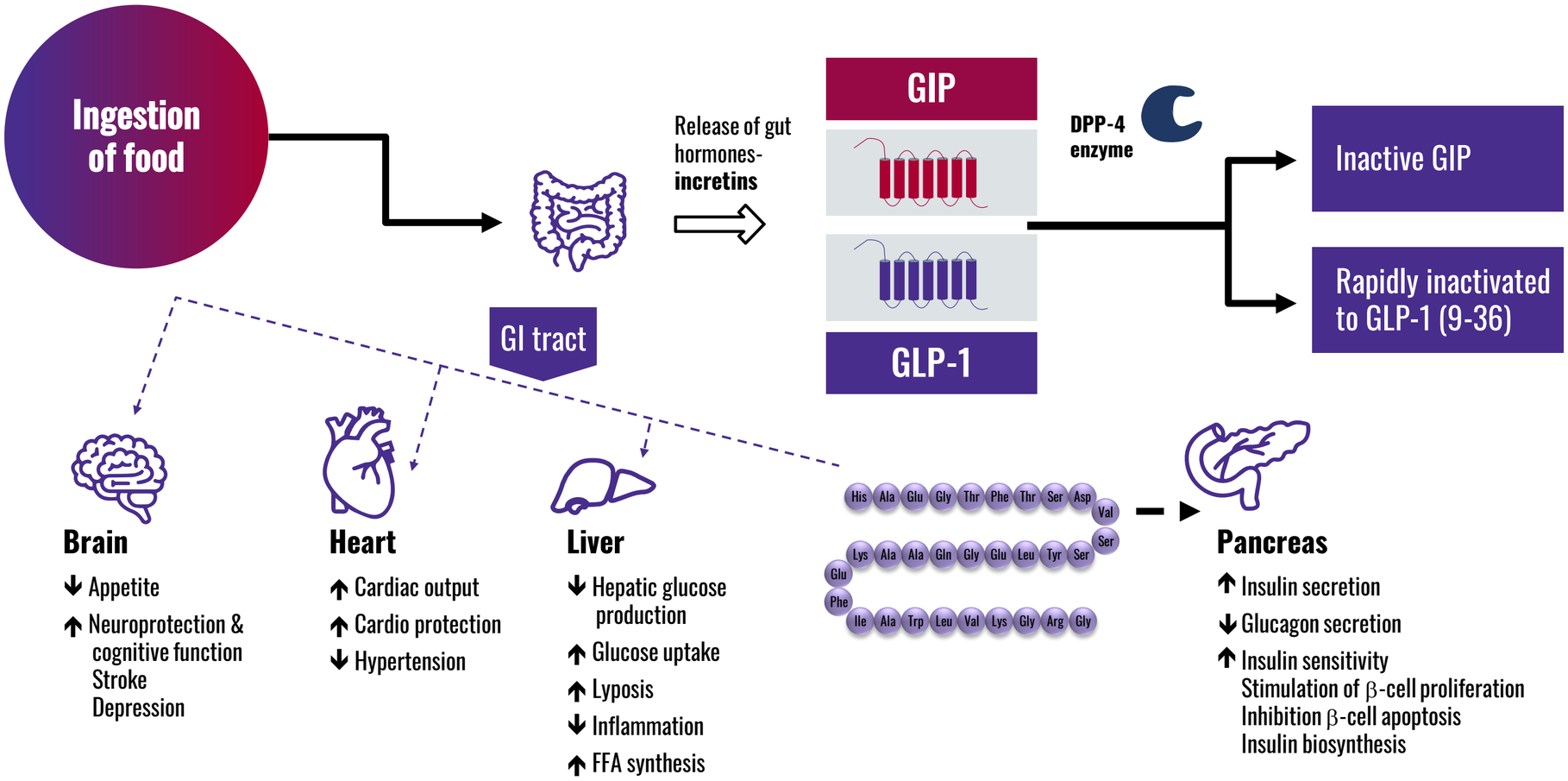


Drug	Currently available
Phentermine*	
Orlistat	
Liraglutide 3.0 mg	
Naltroxone/Bupropion	
Phentermine/Topiramate	
Semaglutide 2.4 mg	
Setmelanotide	



Data presented for adults and\or preclinical

GLP-1 SYNTHESIS, RELEASE, METABOLISM AND EFFECTS OF GLP-1 ON BODY ORGANS



FFA, free fatty acids; GLP-1, Glucagon like peptide-1; GIP, Gastrointestinal peptide; DPP-4, Dipeptidyl peptidase 4
Sharma et al. Biomed Pharmacother. 2018;108:952-962

ORIGINAL ARTICLES

www.jpeds.com • THE JOURNAL OF PEDIATRICS

Liraglutide in an Adolescent Population with Obesity: A Randomized, Double-Blind, Placebo-Controlled 5-Week Trial to Assess Safety, Tolerability, and Pharmacokinetics of Liraglutide in Adolescents Aged 12-17 Years

(N=21)

Thomas Danne, MD[1], Torben Biester, MD[1], Kerstin Kapitzke, MD[1], Sanja H. Jacobsen, MSc[2], Lisbeth V. Jacobsen, MSc[2], Kristin C. Carlsson Petri, PhD[2], Paula M. Hale, MD[3], and Olga Kordonouri, MD[1]

Received: 12 July 2018 | Revised: 28 October 2018 | Accepted: 11 November 2018

DOI: 10.1111/ijpo.12495

(N=24)

ORIGINAL RESEARCH

WILEY pediatricobesity

Liraglutide effects in a paediatric (7-11 y) population with obesity: A randomized, double-blind, placebo-controlled, short-term trial to assess safety, tolerability, pharmacokinetics, and pharmacodynamics

Lucy D. Mastrandrea[1] | Louise Witten[2] | Kristin C. Carlsson Petri[3] | Paula M. Hale[4] | Hanna K. Hedman[5] | Robert A. Riesenberg[6]

(N=251)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

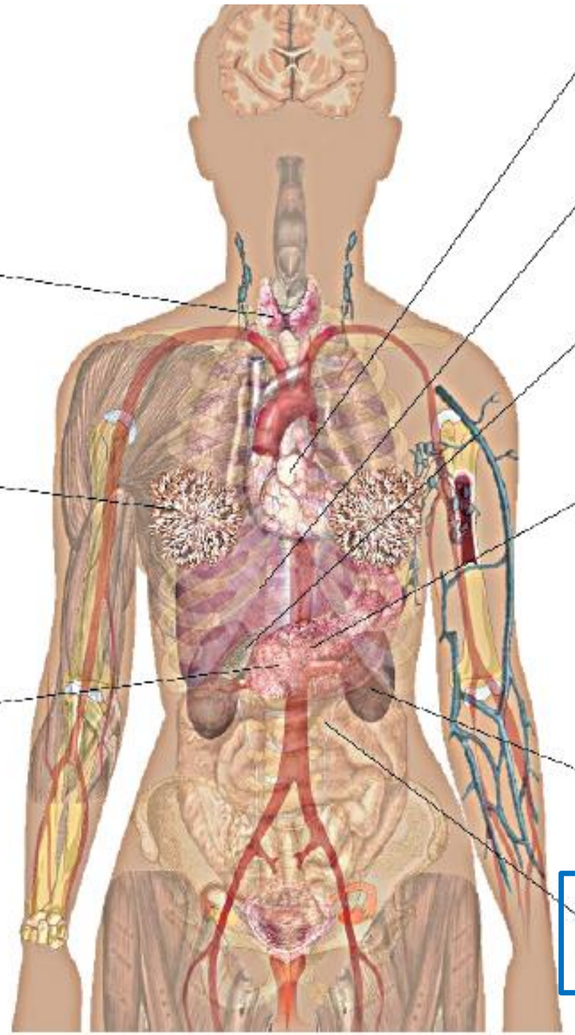
A Randomized, Controlled Trial of Liraglutide for Adolescents with Obesity

Aaron S. Kelly, Ph.D., Pernille Auerbach, M.D., Ph.D., Margarita Barrientos-Perez, M.D., Inge Gies, M.D., Ph.D., Paula M. Hale, M.D., Claude Marcus, M.D., Ph.D., Lucy D. Mastrandrea, M.D., Ph.D., Nandana Prabhu, M.Sc., and Silva Arslanian, M.D., for the NN8022-4180 Trial Investigators*

ABSTRACT

Change in BMI standard-deviation score at 56 wk	−0.23±0.05	−0.00±0.05

Complications



Cancer

Thyroid
Cases of medullary thyroid carcinoma have been reported during postapproval use

Breast
Significant increase in breast cancer risk was identified in patients using glucagon-like peptide-1 receptor agonists for 2 to 3 years

Pancreas
Pancreatic cancer was more commonly reported among patients with type 2 diabetes mellitus who took glucagon-like peptide-1 receptor agonists

Heart
Increase heart rate

Liver
Elevation of liver enzymes and development of cholestasis and hepatitis have been reported during post-approval use

Gallbladder
Increase gallbladder or biliary disease

Pancreas
Increase serum lipase and amylase levels
The absolute risk of acute pancreatitis is numerically higher
Not increase the risk of hypoglycemia
However, it is recommended that co-administered antidiabetic drugs such as sulfonylurea or insulin be adjusted according to glucose monitoring results and hypoglycemic risk

Kidney
Dehydration due to nausea, vomiting, and diarrhea, increased serum creatinine, and acute renal failure have been reported during post-approval use

Gastrointestinal tract
Increase gastrointestinal symptoms

Mood, depression ??

Gastrointestinal side effects	64.8%	P<0.001	36.5%

Case presentation

- 17-year-old male with class III obesity
  - 156 kg, BMI 50.9 kg/m^2.

- No pre-existing co-morbidities
- Failure to comply with physical activity and food

- Parents - registered nurses

Case presentation

Liraglutide 0.6 mg/day (lowest dose) prescribed for weight management, along with diet and exercise guidance.

Presentation to ED – after 3 months :

- Vomiting, epigastric pain, and low urine output after 3 months of treatment.

- Weight 120 Kg, BMI 42 kg/m2.

Case presentation

- Still Liraglutide 0.6 mg/day (lowest dose)
- Abdominal pain
- Complete appetite loss.
- Melancholy

- No follow-up….

Case presentation

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- Abdominal pain
- Complete appetite loss.
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- No follow-up….

No current evidence supports weight loss medication use as a monotherapy; thus, pediatricians and other PHCPs who prescribe weight loss medication to children should provide or refer to intensive behavioral interventions for patients and families as an adjunct to medication therapy.

PEDIATRICS Volume 151, number 2, February 2023:

During Hospitalization

- Scleral jaundice,
- Eepigastric tenderness.
- Abdominal ultrasound:
  - Hepatic steatosis,
  - Distended gallbladder with sludge,
  - Normal kidneys.

Table 1: Laboratory values before Saxenda treatment, and at presentation			
	Normal range	Before treatment	At admission
Blood			
PH	7.35-7.45		7.35
HCO3	23 – 27		23
BE	-2.0 – 2.0		-3.5
HgBA1C %	<5.7	4.7	4.7
Glucose mg/dL	70 - 100	89	86
Potassium mmol/L	3.6 – 5.2	4.5	3.3
Sodium mmol/L	136 - 145	140.4	141
Calcium mg/dL	8.6 – 10.3		8.7
Creatinine mg/dL	0.7 – 1.2	0.69	**1.92**
Urea mg/dL	20 – 45	28.7	**25**
Uric Acid mg/dL	2 – 5.5		11
AST U/L	5 – 38	30	**187**
ALT U/L	4 – 41	41	**230**
GGT U/L	10 – 55	29.5	**176**
Bilirubin mg/dL	0.2 – 1.2		2.15
LDH U/L	240 – 480		650
Albumin g/L	32 - 45		41
PT sec	9.7-117		13.1
INR	0.8-1.2		1.13
Amylase U/L	28 - 100		52
Lipase U/L	13 - 60		16.9
C-reactive protein mg/L			5.5

Table 1: Laboratory values before Saxenda treatment, and at presentation				
	Normal range	Before treatment	At admission	After 4 days
Urine				
Creatinine mg/dL	20 - 320		157.9	154.9
Osmolality mOsm/Kg H_2O	50 - 1200		270	
Potassium mmol/L			15.6	
Sodium mmol/L			21	
Fractional excretion of sodium			0.2%	
Calcium mg/dL			<0.48	
Chloride mmol/L			29	
Protein Total /Cre (mg/mg)				0.13

AKI & HEPATIC DYSFUNCTION

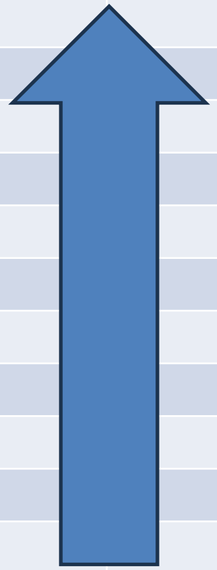
Treatment :

- Intravenous fluids,
- Low-salt/potassium diet,
- Proton pump inhibitors, Antiemetics.

- Crucially, Liraglutide was discontinued.
- Rapid improvement

Weight/Liver/Renal before Liraglutide 0.6 mg, at presentation and during follow up

	Normal range	Before treatment	At admission	After 4 days	After 1 month	After 6 months	After 1 year
Weight (kg)		156	120	.	115	110	88
Glucose mg/dL	70 - 100	89	86		79		
Potassium mmol/L	3.6 – 5.2	4.5	3.3		4.3		
Sodium mmol/L	136 - 145	140.4	141		143.3		
Calcium mg/dL	8.6 – 10.3		8.7		9.8		
Creatinine mg/dL	0.7 – 1.2	0.69	1.92	0.77	0.71		
Urea mg/dL	20 – 45	28.7	25	14	19.4		
Uric Acid mg/dL	2 – 5.5		11	6.5	8.67		
AST U/L	5 – 38	30	187	70	49		
ALT U/L	4 – 41	41	230	160	46		
GGT U/L	10 – 55	29.5	176	135	45		
Bilirubin mg/dL	0.2 – 1.2		2.15	0.76	0.73		
LDH U/L	240 – 480		650	458			
Albumin g/L	32 - 45		41	39	40		
C-reactive protein mg/L			5.5	1.66	1.5		
				0.13			



Psychologica, Dietary and Medical close follow up

Table 2: Assessment of patient symptoms according to the Naranjo score.*,			
Question	Yes	No	Do Not Know
1. Are there previous conclusive reports on this reaction?	+1	0	0
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
4. Did the adverse event reappear when the drug was readministered?	+2	-1	0
5. Are there alternative causes that could on their own have caused the reaction?	-1	+2	0
6. Did the reaction reappear when a placebo was given?	-1	+1	0
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0
Total		7 points	

Naranjo score indicates the level of association between symptoms and a drug|:

+9: Definite;
5-8: Probable;
1-4: Possible;
0: Doubtful

”Probable" adverse drug reaction

Possible Mechanisms

- *AKI:* Dehydration (due to vomiting), possible interstitial nephritis.
  - Liraglutide is the most common GLP-1RA implicated in AKI.

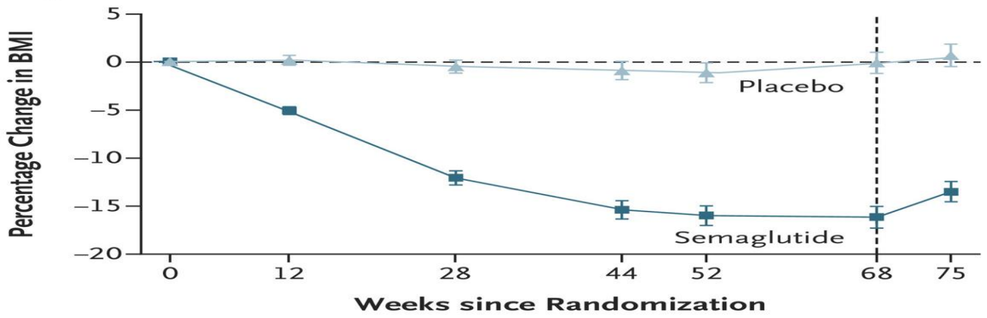
- *Hepatic/Biliary:* Direct GLP-1 effect on biliary secretion and gallbladder motility; Rapid weight loss.

- Conflicting data in the literature regarding GLP-1RA and depression.

Conclusion : NOT ALL GOLD IS SHINING

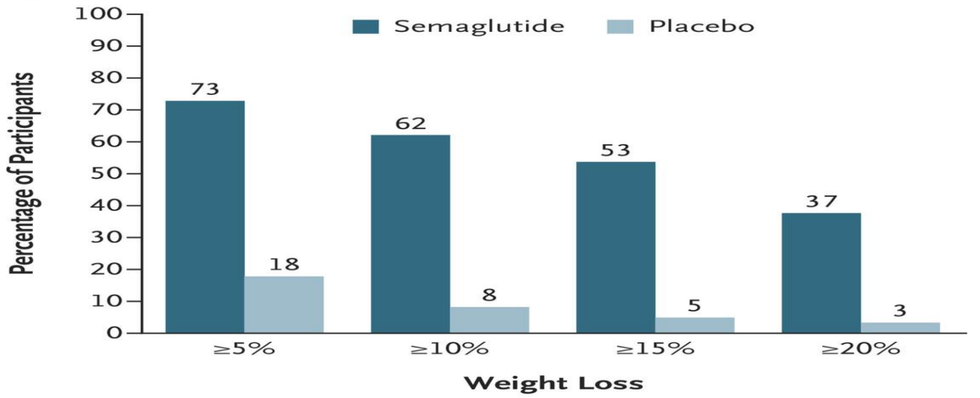
- Vigilance is crucial when prescribing Liraglutide to adolescents, **EVEN AT LOW DOSES**.
- Monitoring renal, liver function, **MOOD** and activity, especially with significant weight loss
- Prospective REAL LIFE studies on GLP-1RA use in adolescents is MANDATORY .
- Careful from TOO disturbed eating

A Change in BMI from Baseline

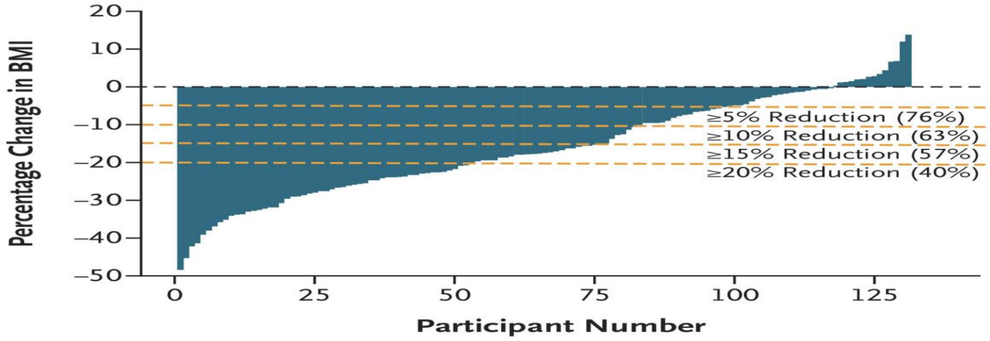


No. of Participants							
Placebo	67	56	63	61	62	62	61
Semaglutide	134	119	131	130	131	131	128

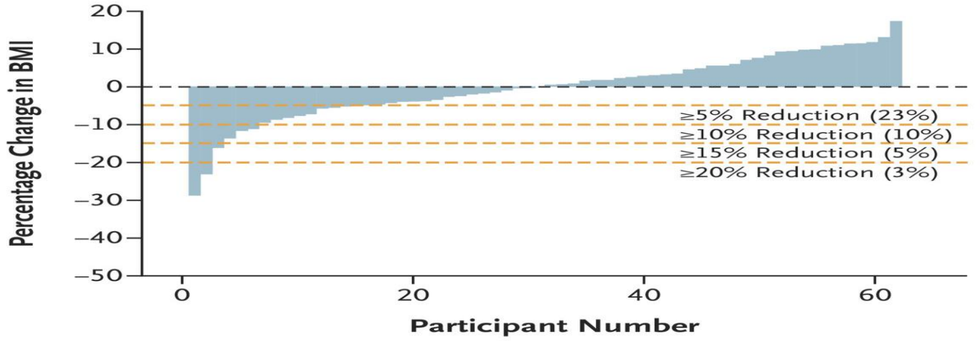
B Weight-Loss Thresholds at Week 68



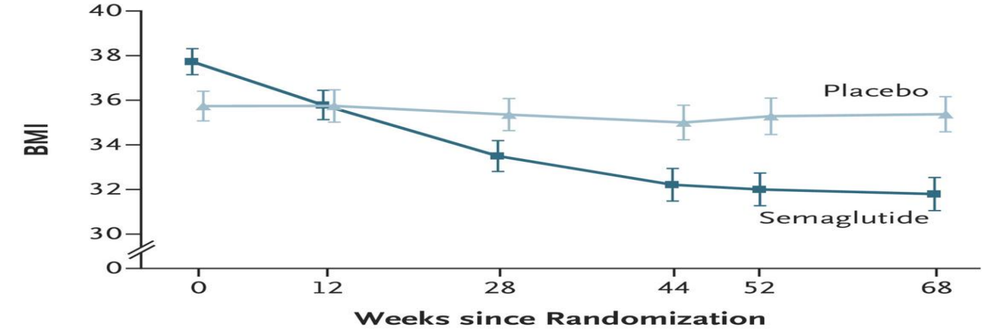
C Change in BMI at Week 68 in the Semaglutide Group



D Change in BMI at Week 68 in the Placebo Group

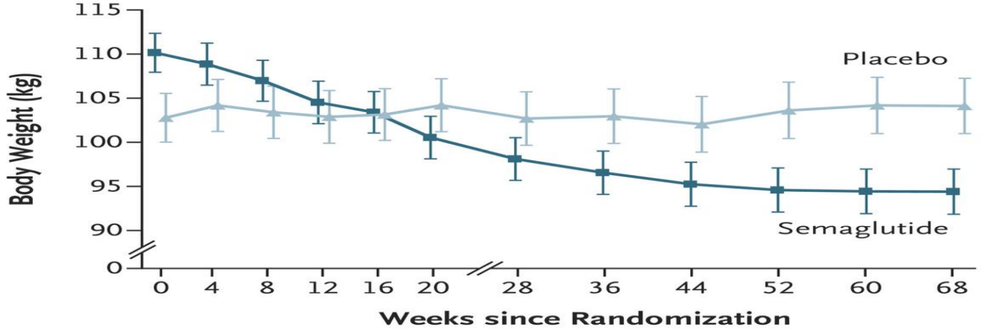


E BMI According to Weeks since Randomization

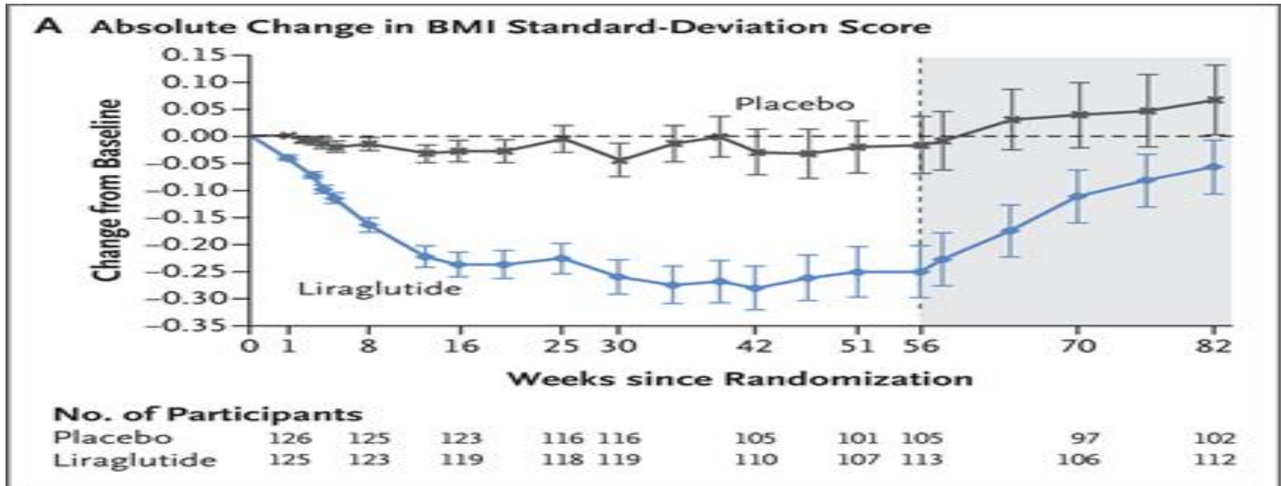


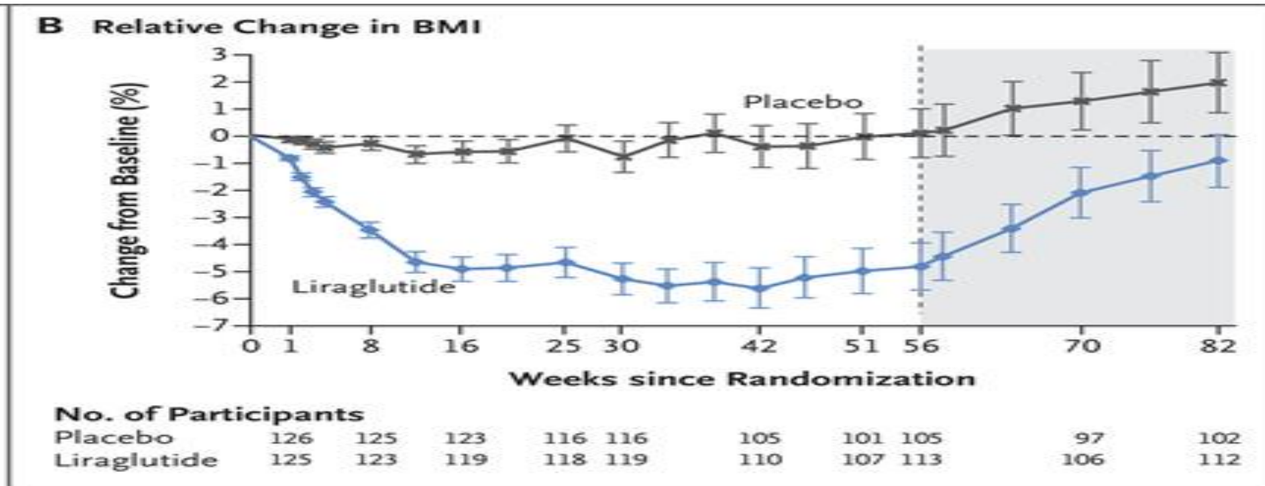
No. of Participants						
Placebo	67	56	63	61	62	62
Semaglutide	134	119	131	130	131	131

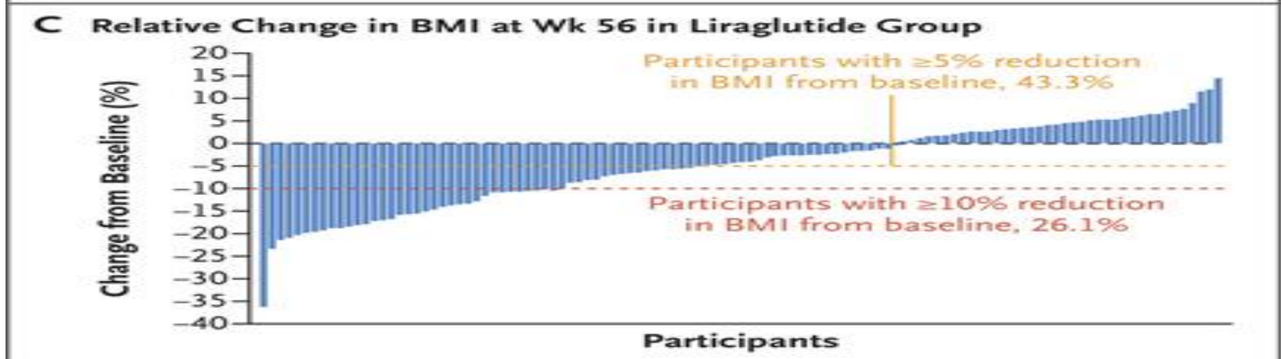
F Body Weight According to Weeks since Randomization

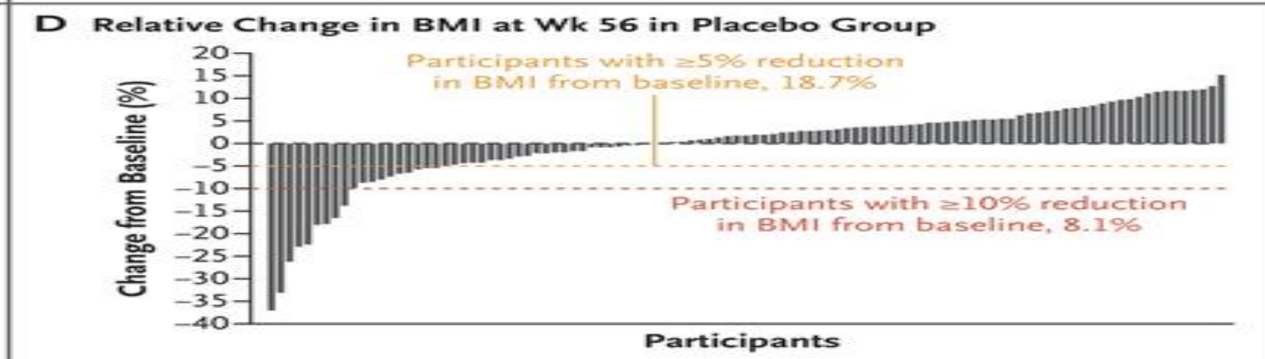


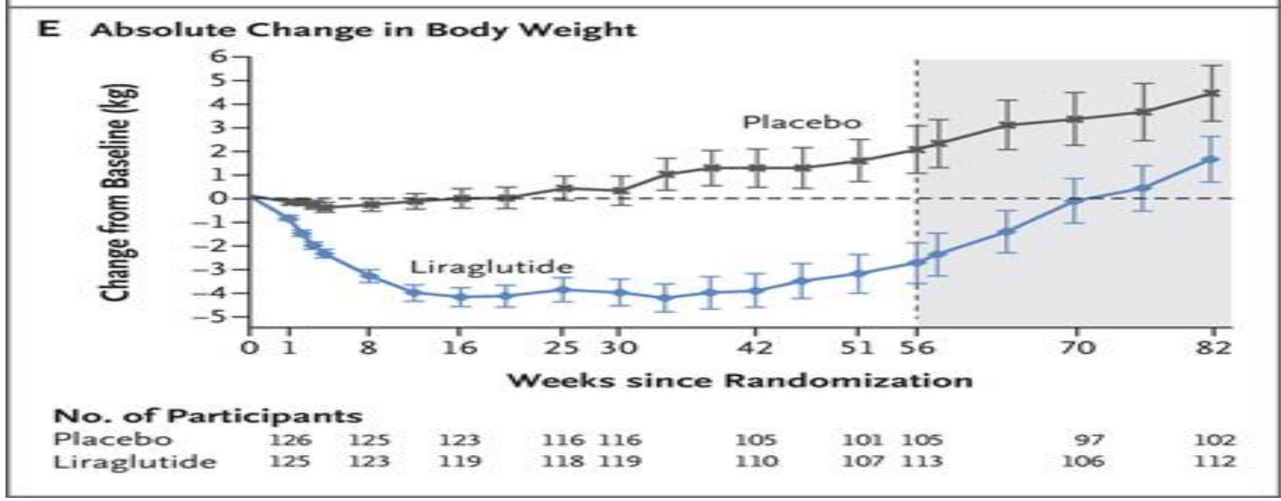
No. of Participants												
Placebo	67	62	63	59	66	64	64	63	61	64	63	62
Semaglutide	134	122	127	121	132	128	133	131	131	131	131	131

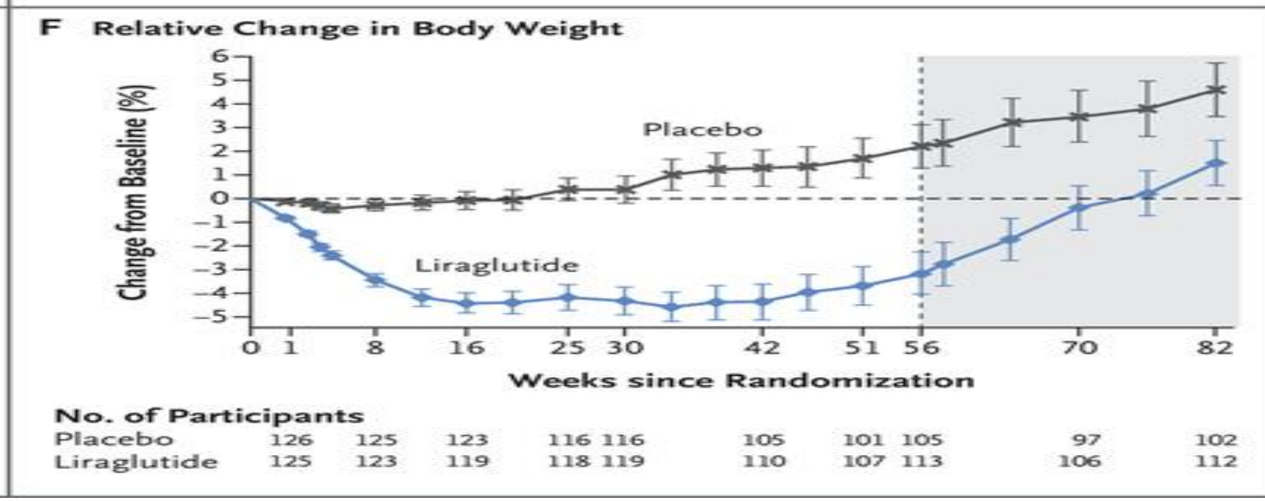

A Absolute Change in BMI Standard-Deviation Score
Change from Baseline
0.15
0.10
0.05
0.00
−0.05
−0.10
−0.15
−0.20
−0.25
−0.30
−0.35
Placebo
Liraglutide
0 1 8 16 25 30 42 51 56 70 82
Weeks since Randomization
No. of Participants
Placebo 126 125 123 116 116 105 101 105 97 102
Liraglutide 125 123 119 118 119 110 107 113 106 112


B Relative Change in BMI
Change from Baseline (%)
3
2
1
0
−1
−2
−3
−4
−5
−6
−7
Placebo
Liraglutide
0 1 8 16 25 30 42 51 56 70 82
Weeks since Randomization
No. of Participants
Placebo 126 125 123 116 116 105 101 105 97 102
Liraglutide 125 123 119 118 119 110 107 113 106 112


C Relative Change in BMI at Wk 56 in Liraglutide Group
Change from Baseline (%)
20
15
10
5
0
−5
−10
−15
−20
−25
−30
−35
−40
Participants with ≥5% reduction in BMI from baseline, 43.3%
Participants with ≥10% reduction in BMI from baseline, 26.1%
Participants


D Relative Change in BMI at Wk 56 in Placebo Group
Change from Baseline (%)
20
15
10
5
0
−5
−10
−15
−20
−25
−30
−35
−40
Participants with ≥5% reduction in BMI from baseline, 18.7%
Participants with ≥10% reduction in BMI from baseline, 8.1%
Participants


E Absolute Change in Body Weight
Change from Baseline (kg)
6
5
4
3
2
1
0
−1
−2
−3
−4
−5
Placebo
Liraglutide
0 1 8 16 25 30 42 51 56 70 82
Weeks since Randomization
No. of Participants
Placebo 126 125 123 116 116 105 101 105 97 102
Liraglutide 125 123 119 118 119 110 107 113 106 112


F Relative Change in Body Weight
Change from Baseline (%)
6
5
4
3
2
1
0
−1
−2
−3
−4
−5
Placebo
Liraglutide
0 1 8 16 25 30 42 51 56 70 82
Weeks since Randomization
No. of Participants
Placebo 126 125 123 116 116 105 101 105 97 102
Liraglutide 125 123 119 118 119 110 107 113 106 112