The Young and the Old
Looking into the future - drugs or surgery?

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Acknowledgment of Professor Louise Baur

I have the following potential conflict(s) of interest to report:

- Novo Nordisk – speaker fees 2021

THE GOAL OF TREATMENT OF CLINICAL OBESITY IN CHILDREN AND ADOLESCENTS

- **TO BE AS HEALTHY AS CAN BE**

(NOT JUST WEIGHT LOSS)

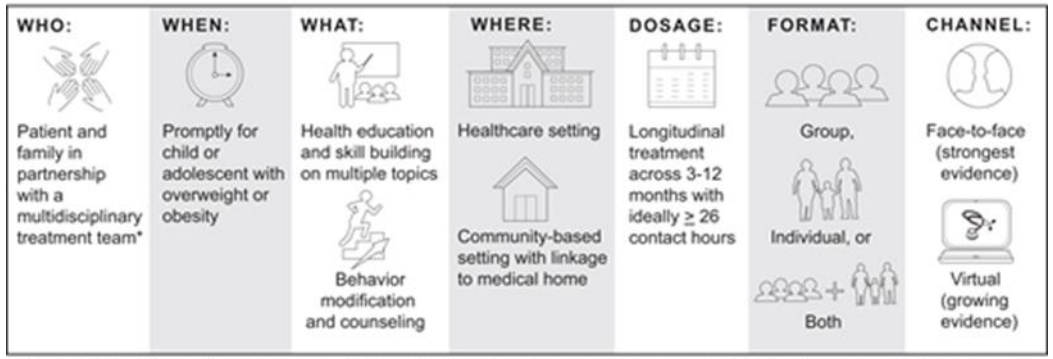
- **FAMILY-CENTRED, AGE-APPROPRIATE LIFESTYLE INTERVENTIONS**
- **CHRONIC DISEASE MODEL of CARE**

(obesity tracks strongly from childhood into adulthood)

FROM THE AMERICAN ACADEMY OF PEDIATRICS | CLINICAL PRACTICE GUIDELINE | JANUARY 09 2023

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

Intensive Health Behavior and Lifestyle Treatment (IHBLT)



* PCPs and/or PHCPs with training in obesity as well as other professionals trained in behavior and lifestyle fields such as dietitians, exercise specialists and behavioral health practitioners

Hampl SE et al. Pediatrics 2023; 151:e2022060640

The AAP algorithm for the treatment of children and adolescents with obesity

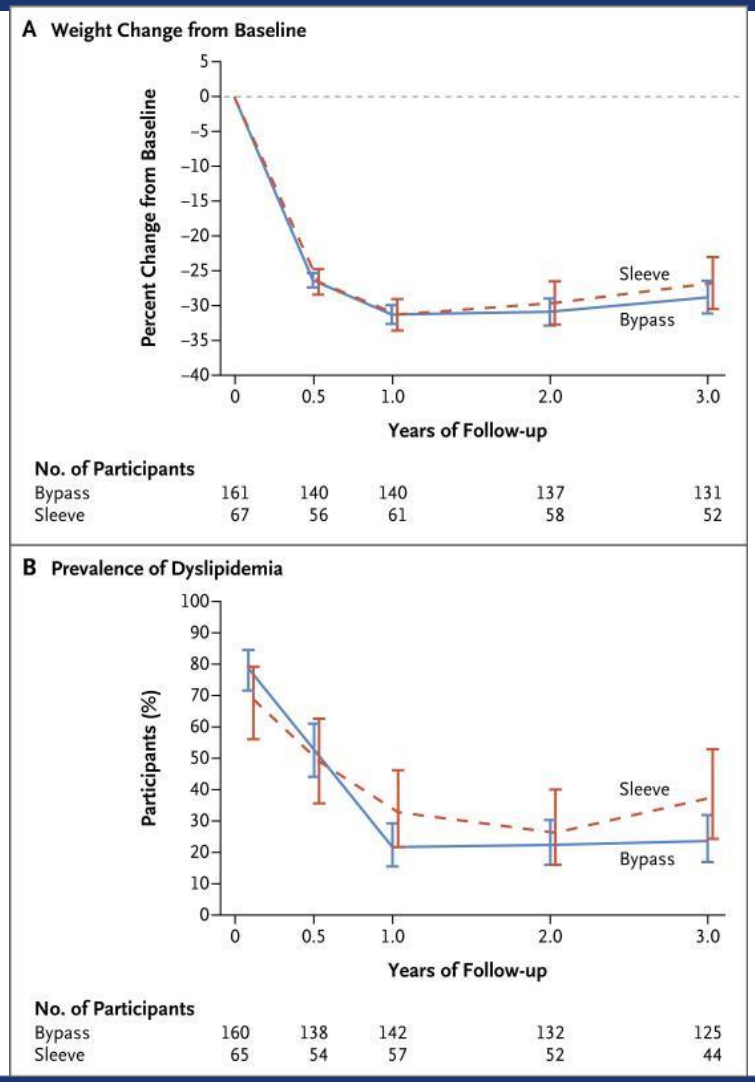
TREATMENT

P&PHCPs *should* treat overweight/obesity & comorbidities concurrently (KAS 4) following the principles of the **medical home** and the **chronic care model,** using a **family-centered** and **non-stigmatizing** approach that acknowledges obesity's **biologic, social, and structural drivers.**(KAS 9)

Components of Comprehensive Treatment	Overweight			Obesity		
	<6y	6 to <12y	≥12y	<6y	6 to <12y	≥12y
Motivational Interviewing[f] (KAS 10)	✓	✓	✓	✓	✓	✓
Intensive Health Behavior and Lifestyle Treatment[g] (KAS 11)	⚖	✓	✓	⚖	✓	✓
Weight Loss Pharmacotherapy[h] (KAS 12)						✓
Offer referral to Comprehensive Pediatric Metabolic & Bariatric Surgery programs[i] (KAS 13)						✓[i]

Hampl SE et al. Pediatrics 2023; 151:e2022060640

BARIATRIC SURGERY



Teen-Longitudinal Assessment of Bariatric Surgery

Prospective enrolment of 242 adolescents
5 US centres
Mean baseline age 17 ± 1.6yrs
Mean baseline BMI 53kg/m^2
Ruox-en-Y Gastric Bypass (161) or Sleeve Gastrectomy (67)
20-25% loss to follow up
Significant improvements in:
- Remission of Hypertension, Dyslipidaemia and T2DM
- Quality of Life

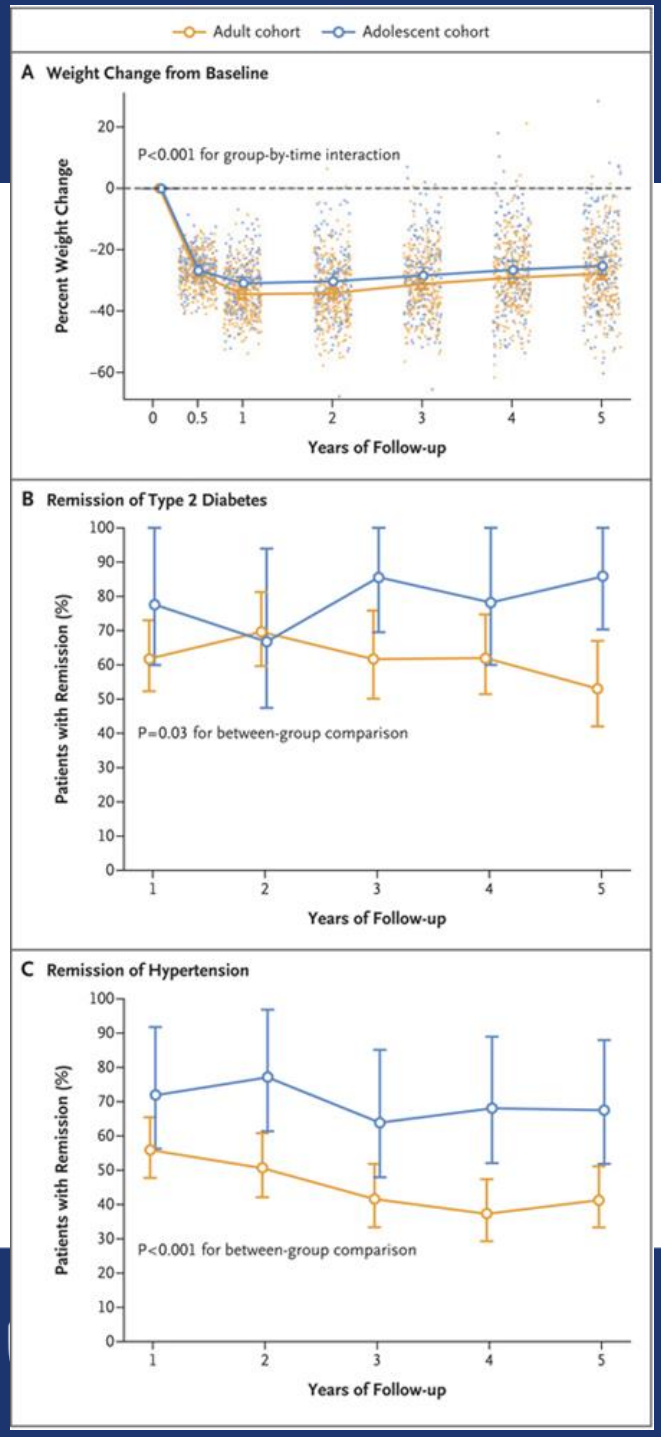
Iron deficiency in 57%
13% required one or more additional intra-abdominal procedures

Inge T et al. N Engl J Med 2016 Jan 14;374(2):113-23.

Teen-Longitudinal Assessment of Bariatric Surgery v LABS

5 year outcomes Gastric Bypass

Adolescent (161) compared with adult (396) outcomes
No significant difference in % weight change
Adolescents more likely to remain in remission for T2DM and hypertension
Abdominal reoperations significantly higher in adolescents
(19 v 10)
Adherence to nutritional supplementation decreased over time
48% adolescents had iron deficiency v 29% adults
5-year all-cause mortality similar in adolescents and adults (1.9% vs 1.8%)
– 2 of 3 deaths in adolescents due to substance use



Inge T et al. N Engl J Med 2019 May 30;380(22):2136-2145

GOALS in WEIGHT MANAGEMENT:

- ✓ Weight Loss
- ✓ Improvement in overall health parameters

Potential downsides:

Complications – nutritional, reoperations,
?Long term outcomes
Cost and equity of access
(not readily available in public health service in Australia)

ANTI-OBESITY MEDICATIONS (AOM)
For treatment in adolescents

Expanding portfolio of AOM's approved for use in adults……..

…….and adolescents (aged 12 years and above)

Though many still used off-label

AGENCY	DRUG	Orlistat (Xenical)	Metformin (Diabex)	Phentermine / Topiramate (Qsymia)	Liraglutide (Saxenda)	Semaglutide (Wegovy)	Tirzepatide (Mounjaro)
FDA Food and Drug Aministration		✓	X	✓	✓	✓	X
EMA European Medicines Agency		✓	X	X	✓	✓	X
TGA Therapeutic Goods Administration		✓	X	X	✓	✓	X

“OLD” V “NEW” AOM’s
“The Oldies”

Orlistat (early 2000’s)
- Gastric and pancreatic lipase inhibitor
- reduces 30% absorption of dietary fat
- BMI reduced by 0.5kg/m^2
- SE - faecal spotting, faecal incontinence and urgency, abdominal pain

Metformin (1950’s for DM)
- Biguanide, suppresses hepatic glucose production
- Used in insulin resistance, metabolic syndrome, T2DM,
- Associated with some weight loss - BMI z-score -0.1; BMI -0.86kg/m^2
- SE (reduced using extended release) – nausea, abdominal pain

Phentermine / Topiramate (early-mid 2010)
- Central action - norepinephrine and gamma-aminbutyric acid agonist leading to appetite suppression
- Graded escalation therapy
- Shorter term use (12 weeks) – gradually reduced if wgt loss not ≥ 5%
- SE – dry mouth, constipation, insomnia, depression, parasthesia (1-7%) – need to monitor for suicidal ideation
- Phentermine – generic, cheap

"OLD" V "NEW" AOM's
"The new generation drugs"

- Nutrient-stimulated hormone-based medications
- Mimic enteral-pancreatic hormones – GLP1, GIP, Glucagon, Amylin
  - GLP1 RA - Liraglutide, Semaglutide,
  - Dual agonist - Tirzepatide (GLP1 and GIP)

(GLP1 - Glucagon-like peptide1, GIP – Glucose-dependent insulinotropic polypeptide)

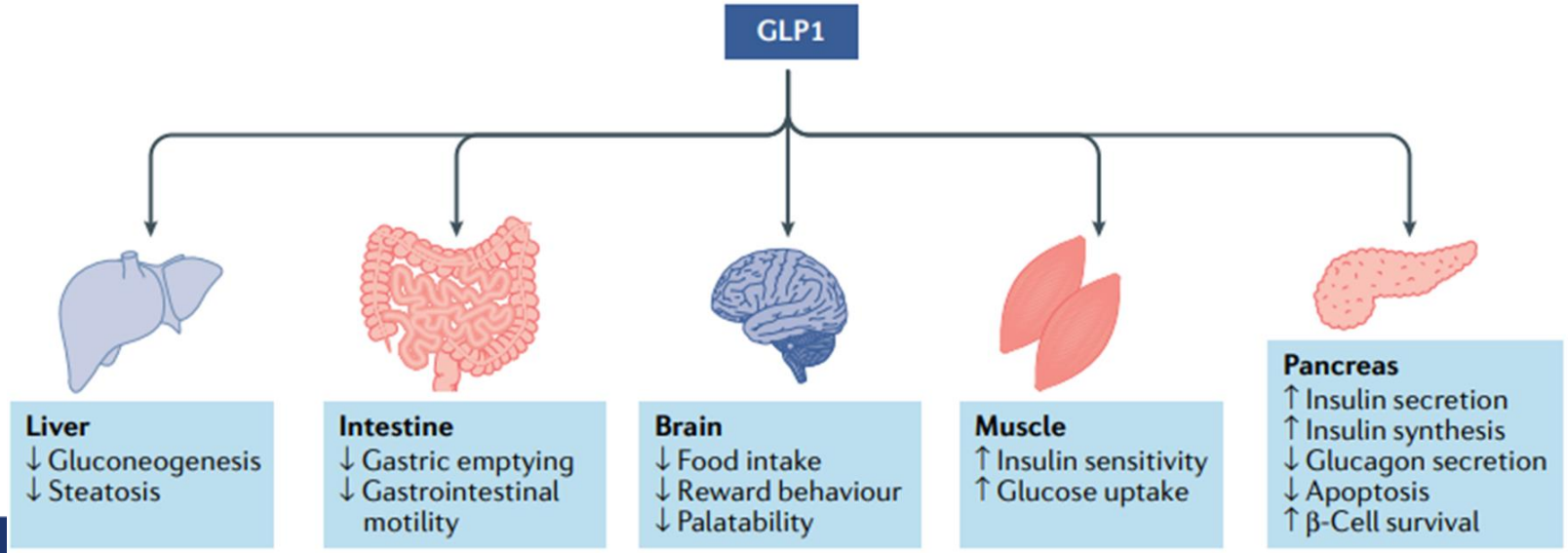


Fig. 4 | **Regulation of body weight and glucose metabolism by GLP1R agonism.** Glucagon-like peptide 1 receptor (GLP1R) agonism exerts both direct and indirect effects on energy and glucose metabolism in key peripheral organs as well as the brain.

Gut-brain regulation of food intake: Impact on appetite suppression

Müller TD et al. Nature Review Drug Discovery 2022

"OLD" V "NEW" AOM's
"The new generation drugs"

- Indications:
  - Adults BMI ≥30kg/m^2 or 27 with medical complications
  - Adolescents ≥ 12yr with obesity and a body weight >60kg

- Most once weekly subcut injection
- Highly affective for wgt loss and other benefits beyond wgt loss alone (reduces CVD risks in particular)
  - Liraglutide – shorter acting – daily injection - ~6% wgt loss
  - Semaglutide and tirzepatide – 15% wgt loss and 20% wgt loss v's placebo (adults)
  - Semaglutide - Re-evaluate if not lost >5% wgt by 12 weeks of treatment (adolescents)
  - Tirzepatide – current Phase 3 trial in adolescents – recruitment finishing Oct 2026

"OLD" V "NEW" AOM's
"The new generation drugs"

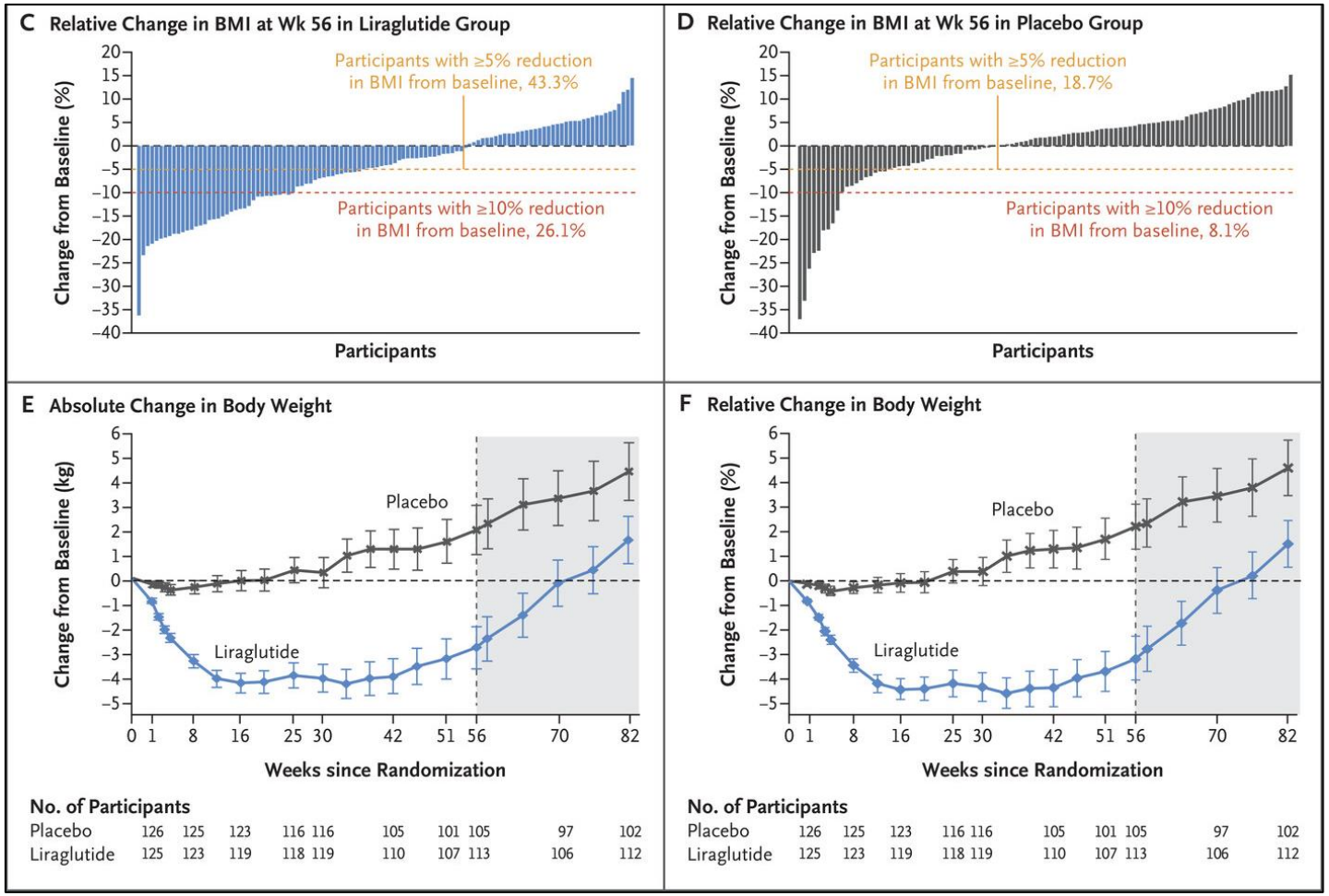
Side Effects:

- mainly GI – nausea, diarrhoea, abdominal pain, vomiting, constipation, pancreatitis, cholelithiasis
  - thyroid tumour (rats) – do not prescribe with Hx of Multiple Endocrine Neoplasia (MEN)
  - Mitigate effects by slowly increasing dose every 4 weeks – can slow escalation if SE

Continue lifestyle interventions

Stopping medication suddenly results in 50-66% wgt regain within 6-12 months (in adults)

RCT of liraglutide 3mg (daily, subcutaneous) vs placebo in adolescents with BMI >30



N=125 Liraglutide: N=126 placebo

56 weeks treatment with 26 weeks follow-up

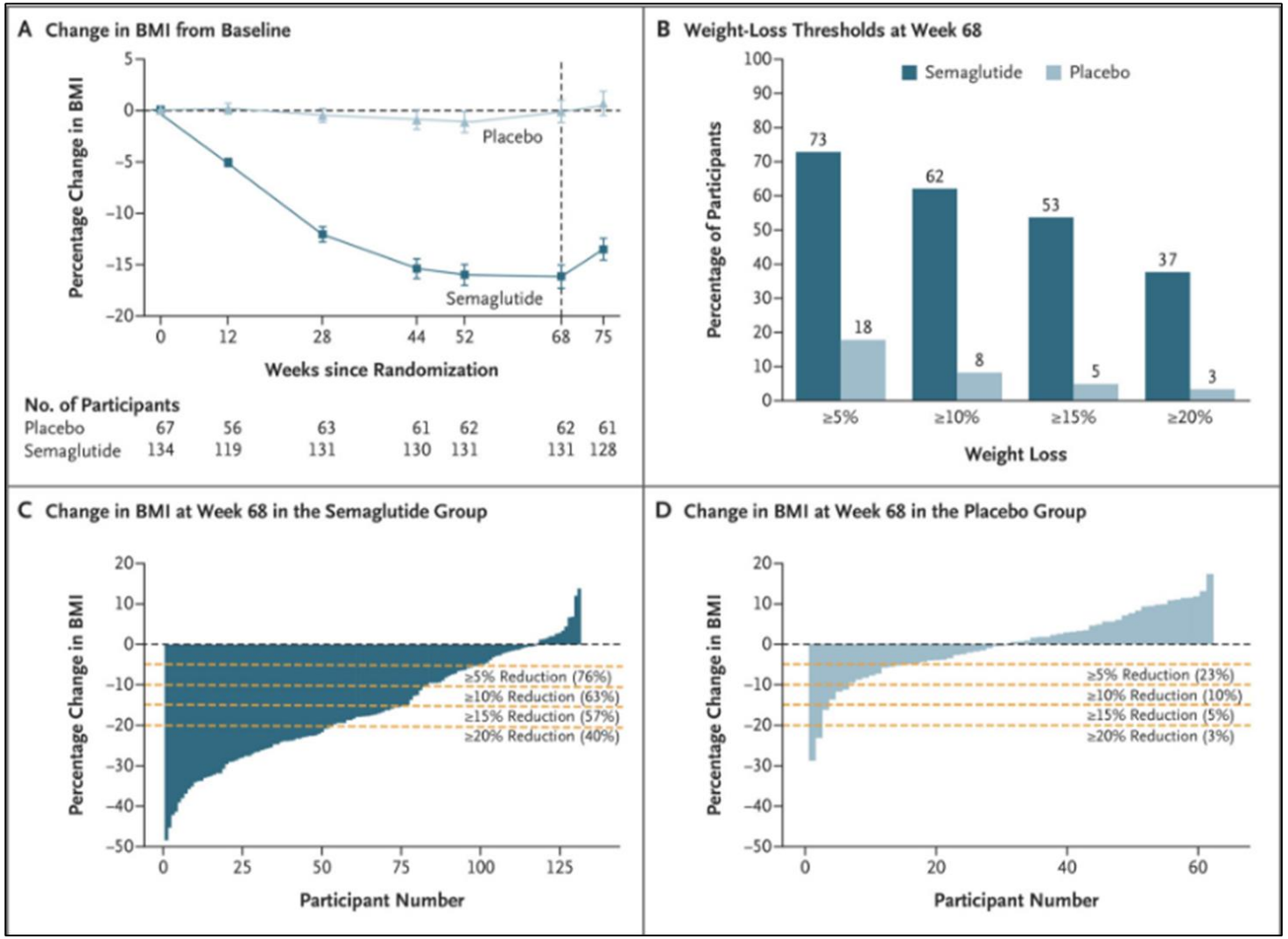
All received lifestyle therapy

Outcomes (drug vs placebo):

- Reduction in BMI of at least 5%: 43.3% vs 18.7%
- Greater increase in BMI z-score on discontinuation: diff. of 0.15
- More GIT adverse events in drug group
  - 64.8% v's 36.5%
  - 10.4% adverse events in drug group leading to discontinuation of trial treatment

Kelly A et al, NEJM 2020; 382:2117-2128

STEP TEENS Trial
Once-Weekly Semaglutide in Adolescents with Obesity:

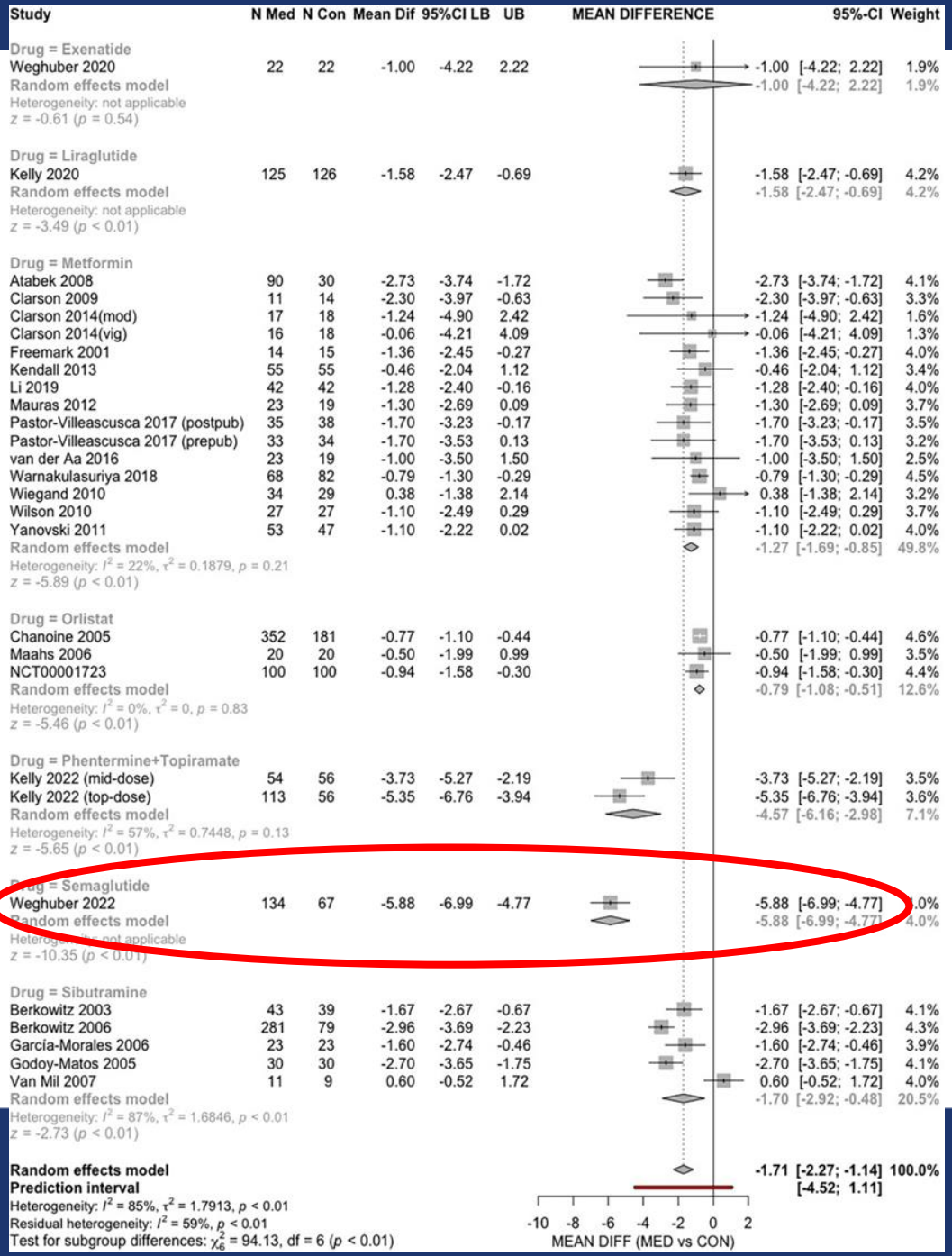


N=134 Semaglutide: N= 67 placebo
Mean age 15.4yr (±1.6)
Mean BMI 37 (±6.4)
68 weeks treatment (up to 2.4mg)
All received lifestyle therapy
Double-blind RCT

Outcomes (drug vs placebo):

- Mean BMI change: -16.1% vs 0.6%
- Wgt loss >5%: 73% vs 18%
- GIT adverse events: 62% vs 42%
  - Cholelithiasis only in drug arm: 4%
- Serious adverse events: 11% vs 9%
- Improvements in cardiometabolic risk factors (WC, HbA1c, Lipids, ALT) greater in drug group

Weghuber D et al. NEJM 2022; 387:2245-2257



Pharmacological interventions for the management of children and adolescents living with obesity—An update of a Cochrane systematic review with meta-analyses

35 Trials, N=4331
Follow-up 6 - 24 months
Age 8.8 - 16.3yrs
BMI 26.2 – 41.7

BMI reduction range -0.8 to -5.9 (largest in Semaglutide trial -5.88)

Adverse events didn't differ between medications and comparators though medication dose adjustments higher

Trend towards improved quality of life

Evidence gaps:
children, psychosocial outcomes, co-morbidities, weight loss maintenance

Torbahn G et al. Pediatr Obes 2024:19:e13113

IFSO MELBOURNE 2024

Melbourne 2024

AOM's

GOALS in WEIGHT MANAGEMENT:

- ✓ Weight Loss
- ✓ Improvement in overall health parameters

Potential downsides:

Complications – drug side effects

?Long term outcomes and safety

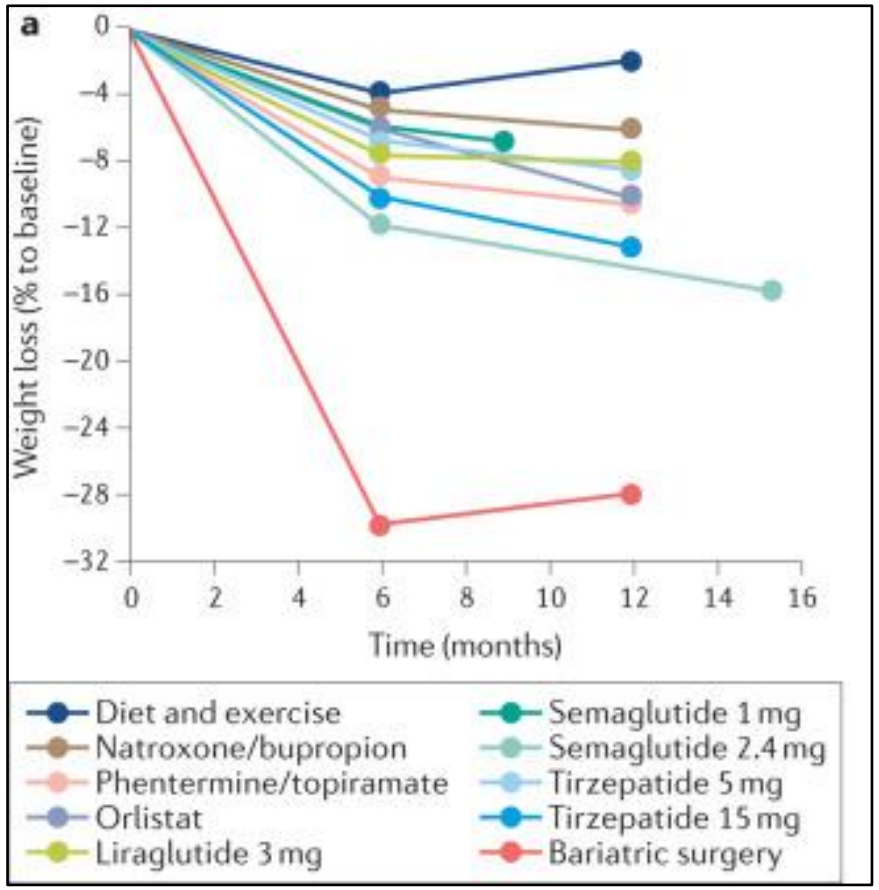
(worldwide use since 2017 (adults), nil concerns to date)

Cost and equity of access

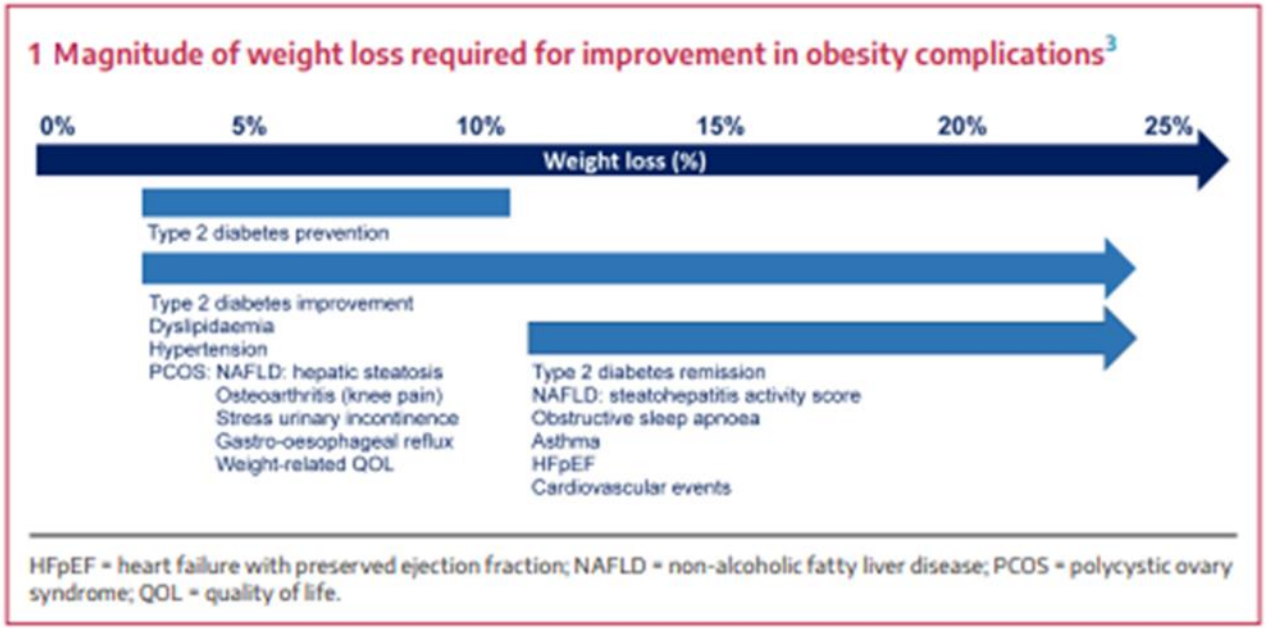
(not on PBS list in public health service in Australia)

(Wegovy (wgt loss) double the price vs Ozempic (T2DM)

Comparative weight loss Lifestyle vs AOM vs Bariatric Surgery

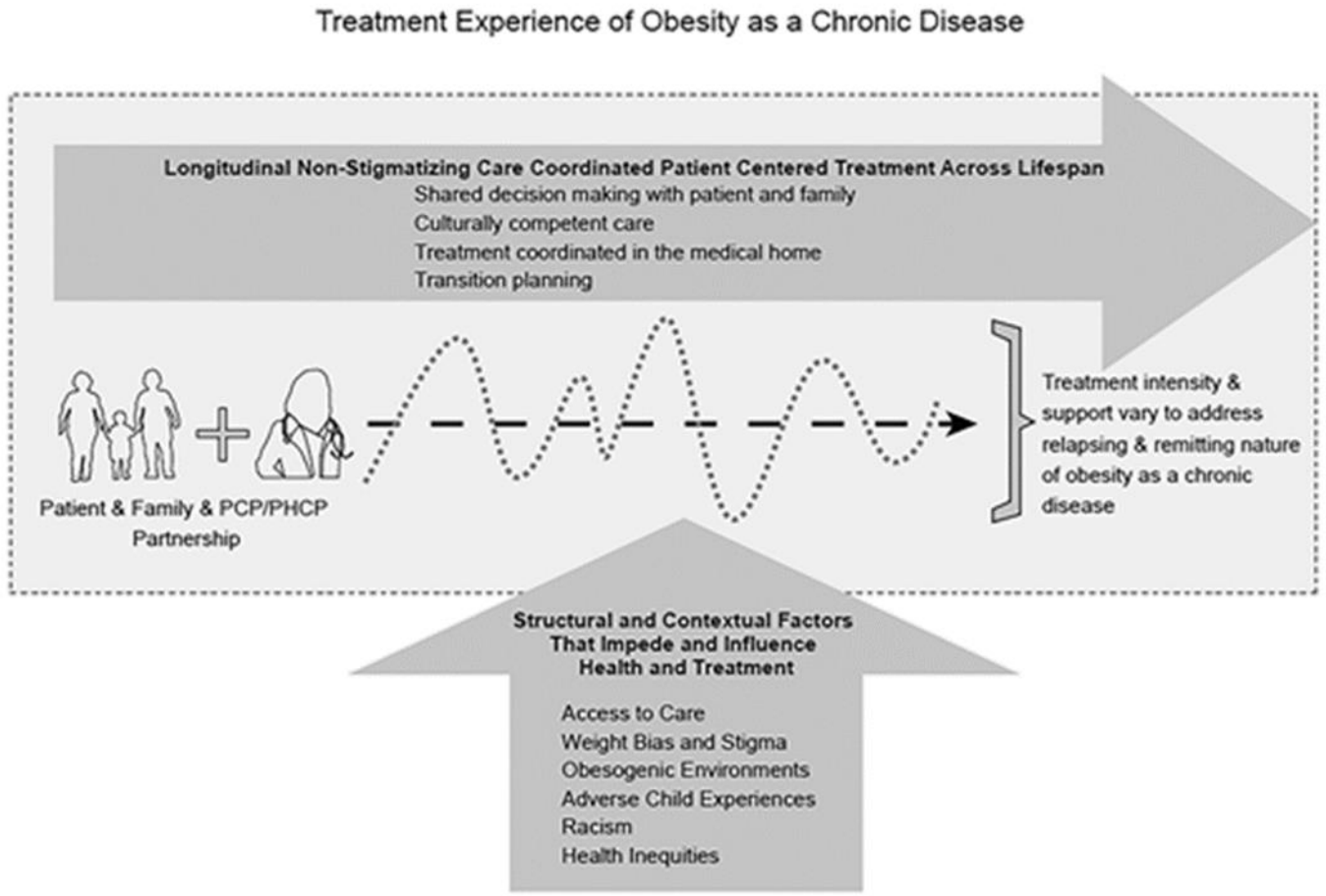


Muller TD Nat Rev Drug Discov 2022 21 (3) 201-223



Walmsley R, Sumithran P. MJA 2023; 218(6) 276-283

What does the future hold for AOM's?



Hampl SE et al. Pediatrics 2023; 151:e2022060640

Considerations:

- Weight maintenance dose
- "Drug holidays"
- Drug combinations – ideally having different modes of action
- Usage pre/post bariatric surgery
- New formulations – dual/tri-agonists, oral delivery

Further research required

SUMMARY

The goal in obesity management in children and adolescents is to aim for overall improvements in health not just weight loss

Management includes an escalation pathway with adjunct therapies such as anti-obesity medications and bariatric surgery in addition to lifestyle changes

Recent explosion of new effective anti-obesity medications now available for treatment in adolescents

Bariatric surgery currently still the most effective intervention for weight loss

More to come in this exciting space!