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

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

• Novo Nordisk – speaker fees 2021

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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 dietilians, exercise specialists and behavioral health practitioners

Hampl SE et al. Pediatrics 2023; 151:e2022060640

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FSO MELEOURNE 2024

			Components of		Overweight			Obesity		
TREATMENT	P&PHCPs <u>should</u> 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)		Comprehensive Treatment	<6y	6 to <12y	≥12y	<6y	6 to <12y	≥12y	
			Motivational Interviewing ^f (KAS 10)	✓	✓	~	~	✓	1	
			Intensive Health Behavior and Lifestyle Treatment ^g (KAS 11)	₽	~	~	亚	~	~	
			Weight Loss Pharmacotherapy ^h (KAS 12)					~		
			Offer referral to Comprehensive Pediatric Metabolic & Bariatric Surgery programs ⁱ (KAS 13)						~ 1	
		L								

Hampl SE et al. Pediatrics 2023; 151:e2022060640

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BARIATRIC SURGERY



Teen-Longitudinal Assessment of Bariatric Surgery

Prospective enrolment of 242 adolescents

5 US centres

Mean baseline age 17 \pm 1.6yrs

Mean baseline BMI 53kg/m²

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.

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BARIATRIC SURGERY

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

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BARIATRIC SURGERY

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)

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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		\checkmark	X	 Image: A second s	~	\checkmark	X
EMA European Medicines Agency		~	X	X	~	\checkmark	X
TGA Therapeutic Goods Administration		~	x	X	~	~	X

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"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/m²
- 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

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- 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.

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

- Indications:
 - Adults BMI ≥30kg/m² 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

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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)

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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

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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

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Study	N Med	N Con	Mean Dif	95%CI LB	UB	MEAN DIFFERENCE	95%-CI	Weight
Drug = Exenatide						3.1		
Weghuber 2020	22	22	-1.00	-4.22	2.22		-1.00 [-4.22; 2.22]	1,9%
Random effects model		-				:	-1 00 [-4 22: 2.22]	1.9%
Heterogeneity: not applicable							They formed month	
$z = -0.61 \ (p = 0.54)$								
Develop 1 to a lotted								
Drug = Liraglutide	125	126	1 59	2 47	0.60		1 59 1 2 47: 0 601	4 20/
Relly 2020	125	120	-1.50	-2.47	-0.09		-1.50 [-2.47, -0.09]	4.270
Haterogeneity: not applicable						<u> </u>	-1.50 [-2.47, -0.05]	M.L. 10
z = -3.49 (p < 0.01)								
Drug = Metformin	00	20	0.70	0.74	4 70	100	0 70 / 0 74. 4 701	4 40/
Atabek 2008	90	30	-2.73	-3./4	-1.72	100	-2./3 [-3./4; -1./2]	4.1%
Clarson 2009	17	19	-2.30	-3.97	-0.03		-2.30 [-3.97, -0.03]	1.6%
Clarson 2014(mod)	16	18	-1.24	-4.90	2.42		-1.24 [-4.90, 2.42]	1.0%
Ereemark 2001	14	15	-0.00	-4.21	-0.27		-1.36 [-2.45: -0.27]	4.0%
Kendall 2013	55	55	-0.46	-2.45	1 12		-1.30 [-2.43, -0.27]	3.4%
Li 2019	42	42	-1.28	-2.40	-0.16		-1 28 [-2 40: -0 16]	4.0%
Mauras 2012	23	19	-1 30	-2.69	0.09		-1 30 [-2 69: 0 09]	3.7%
Pastor-Villeascusca 2017 (postpub)	35	38	-1.70	-3.23	-0.17		-1.70 [-3.23: -0.17]	3.5%
Pastor-Villeascusca 2017 (prepub)	33	34	-1 70	-3.53	0.13		-1 70 [-3 53: 0 13]	3.2%
van der Aa 2016	23	19	-1.00	-3.50	1.50		-1.00 [-3.50; 1.50]	2.5%
Warnakulasuriya 2018	68	82	-0.79	-1.30	-0.29	-	-0.79 [-1.30: -0.29]	4.5%
Wiegand 2010	34	29	0.38	-1.38	2.14	— <u> </u>	0.38 [-1.38; 2.14]	3.2%
Wilson 2010	27	27	-1.10	-2.49	0.29		-1.10 [-2.49; 0.29]	3.7%
Yanovski 2011	53	47	-1.10	-2.22	0.02		-1.10 [-2.22; 0.02]	4.0%
Random effects model						\$	-1.27 [-1.69; -0.85]	49.8%
Heterogeneity: $I^2 = 22\%$, $\tau^2 = 0.1879$, p z = -5.89 (p < 0.01)	= 0.21							
Drug = Orlistat								
Chanoine 2005	352	181	-0.77	-1.10	-0 44	55	-0 77 [-1 10: -0 44]	4.6%
Maahs 2006	20	20	-0.50	-1.99	0.99		-0.50 [-1.99: 0.99]	3.5%
NCT00001723	100	100	-0.94	-1.58	-0.30		-0.94 [-1.58; -0.30]	4.4%
Random effects model						\$	-0.79 [-1.08; -0.51]	12.6%
Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.83$ z = -5.46 (p < 0.01)	3							
Drug = Phontormine+Teniremate								
Kelly 2022 (mid-dose)	54	56	.3 73	-5 27	-2 10		-3 73 [-5 27· -2 10]	3 5%
Kelly 2022 (Ind-dose)	113	56	-5.75	-6.76	-3.94		-5.35 [-6.76: -3.94]	3.6%
Random effects model	115	50	-0.00	-0.70	-0.04		-4.57 [-6.16: -2.98]	7.1%
Heterogeneity: $l^2 = 57\%$, $\tau^2 = 0.7448$, p	= 0.13						net fortet meet	
$z = -5.65 \ (p < 0.01)$								
P ou = Semaglutide								
Weghuber 2022	134	67	-5.88	-6.99	-4 77		-5.88 [-6.99 -4.77]	1.0%
Pandom effects model	104	07	0.00	0.00	4.11		-5.88 [-6.99: -4.77]	4.0%
Heterogen its not applicable							eres Lerest m	110.70
z = -10.35 (p < 0.01)								
Drug = Sibutramine								
Berkowitz 2003	43	30	-1 67	-2 67	-0.67		-1 67 [-2 67: -0 67]	4 1%
Berkowitz 2006	281	79	-2.96	-3 69	-2 23		-2.96 [-3.69 -2.23]	4 3%
Garcia-Morales 2006	23	23	-1.60	-2 74	-0.46		-1.60 [-2.74 -0.46]	3.9%
Godov-Matos 2005	30	30	-2 70	-3.65	-1.75		-2 70 [-3 65: -1 75]	4.1%
Van Mil 2007	11	9	0.60	-0.52	1.72		0.60 [-0.52: 1.72]	4.0%
Random effects model			0.00	0.01			-1.70 [-2.92: -0.48]	20.5%
Heterogeneity: $I^2 = 87\%$, $\tau^2 = 1.6846$, p	< 0.01						The Ferneri stant	2010/0
z = -2.73 (p < 0.01)								
Random effects model						\$	-1.71 [-2.27; -1.14]	100.0%
Prediction interval							[-4.52; 1.11]	
Heterogeneity: $I^2 = 85\%$, $\tau^2 = 1.7913$, p	< 0.01							
Residual heterogeneity: $l^2 = 59\%$, $p < 0$	0.01				-1	10 -8 -6 -4 -2 0 2	2	
Test for subgroup differences: $\chi_6^2 = 9$	94.13, d	f = 6 (p)	< 0.01)			MEAN DIFF (MED vs CON)		

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

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)

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Comparative weight loss Lifestyle vs AOM vs Bariatric Surgery





HFpEF = heart failure with preserved ejection fraction; NAFLD = non-alcoholic fatty liver disease; PCOS = polycystic ovary syndrome; QOL = quality of life.

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

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

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What does the future hold for AOM's?

Treatment Experience of Obesity as a Chronic Disease



Hampl SE et al. Pediatrics 2023; 151:e2022060640

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Considerations:

- Weight maintenance dose
- "Drug holidays"
- Drug combinations ideally having different modes of action
- Usage pre/post bariatric surgery
- New formulations dual/triagonists, 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!

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