Beyond Glycemic Control: Promoting Weight Loss Using Glucose-Lowering Medications

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Disclosures

- No Financial Disclosures
- I grew up as a child with obesity

Objectives

- Identify preferred medications when there is compelling need to minimize weight gain or promote weight loss
- Discuss options for combination therapy if A1C is above target
- Discuss benefits and side-effect profile for GLP1RA and sglt2i

Obesity: Important Treatment Considerations

Obesity: Important Treatment Considerations

At least 5% weight loss in patients with diabetes and obesity improves hab1c, reduces number and/or doses of glucose lower agents... among other things (AACE Obesity guidelines 2016)

Overweight or Obesity	BMI ≥25 (≥23 in certain ethnicities)	Metabolic syndrome		10%	Prevention of T2DM
		Prediabetes		10%	Prevention of T2DM
		T2DM		5% to ≥15%	• Reduction in A1C • Reduction in number and/or doses of glucose lowering medications
		Dyslipidemia		5% to ≥15%	• Lower triglycerides • Higher HDL-c • Lower non-HDL-c
		Hypertension		5% to ≥15%	• Lower systolic and diastolic BP • Reductions in number and/or doses of antihypertensive medications
		Nonalcoholic fatty liver disease	Steatosis	5% or more	Reduction in intrahepatocellular lipid
			Steatohepatitis	10% to 40%	Reduction in inflammation and fibrosis
		Polycystic ovary syndrome		5% to 15% or more	• Ovulation • Regularization of menses • Reduced hirsuitism • Enhanced insulin sensitivity • Reduced serum androgen levels
		Female infertility		10% or more	• Ovulation • Pregnancy
		Male hypogonadism		5% to 10% or more	Increase in serum testosterone
		Obstructive sleep apnea		7% to 11% or more	• Improved symptomatology • Decreased apnea-hypopnea index
		Asthma/reactive airway disease		7% to 8% or more	• Improvement in forced expiratory volume at 1 second • Improved symptomatology
		Osteoarthritis		• ≥10% • 5% to 10% or more when coupled with exercise	• Improvement in symptomatology • Increased function
		Urinary stress incontinence		5% to 10% or more	Reduced frequency of incontinence episodes
		Gastroesophageal reflux disease		10% or more	Reduced symptom frequency and severity
		Depression		Uncertain	• Reduction in depression symptomatology • Improvement in depression scores

Obesity: Diagnosis

Body Mass Index: Increased Body Fat (Adiposity)

Body mass index (BMI) in kilograms per meters squared (kg/m2)

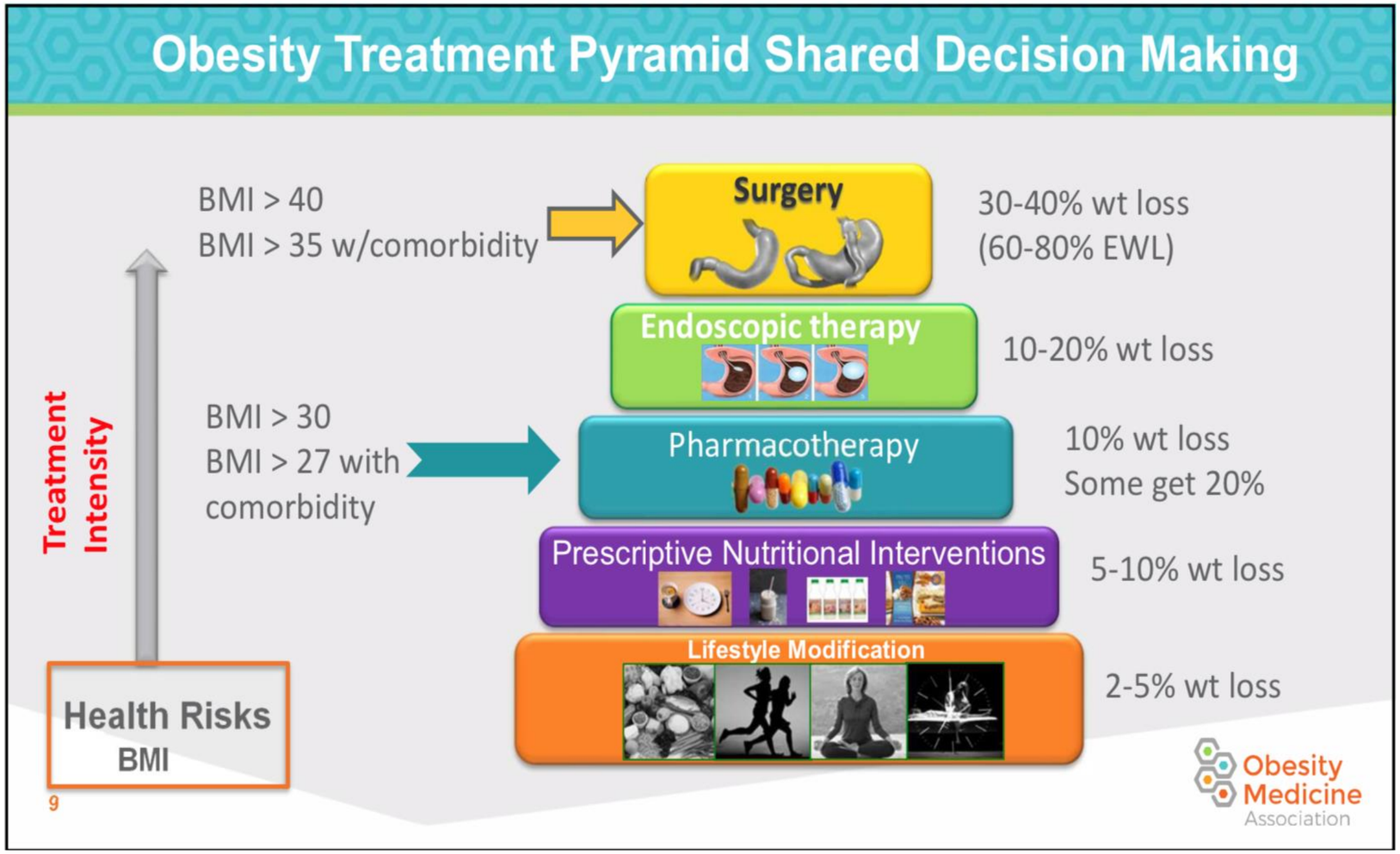
Normal Weight	Overweight	Class I Obesity	Class II Obesity	Class III Obesity
18.5 – 24.9	25 – 29.9	30.0 – 34.9	35.0 – 39.9	≥ 40

*Different BMI cut-off points may be more appropriate based upon gender, race, ethnicity, and menopausal status. For example, among Asians, a BMI ≥ 23 kg/m2 may be more appropriate cut-off point to define overweight and to screen for type-2 diabetes mellitus. Among postmenopausal women, BMI may underestimate percent body fat. (**Obesity Algorithm 2021- Obesity Medicine Association**)

Asian American:

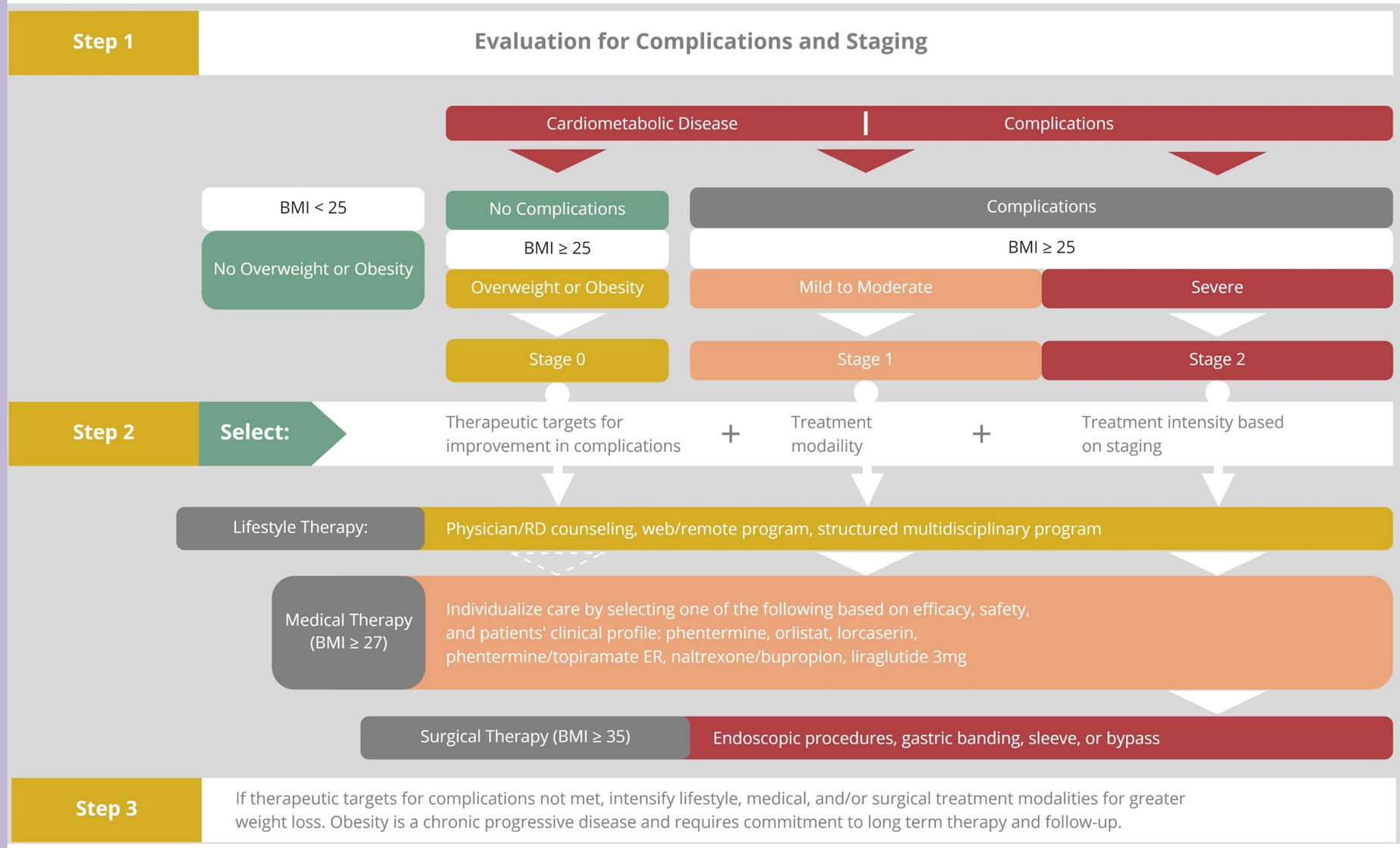
- **BMI 23 and over is overweight**
- **BMI 27 and over is obesity**

Obesity: General Treatment Considerations



Treatment Algorithm for Patients with Overweight/ Obesity and Diabetes

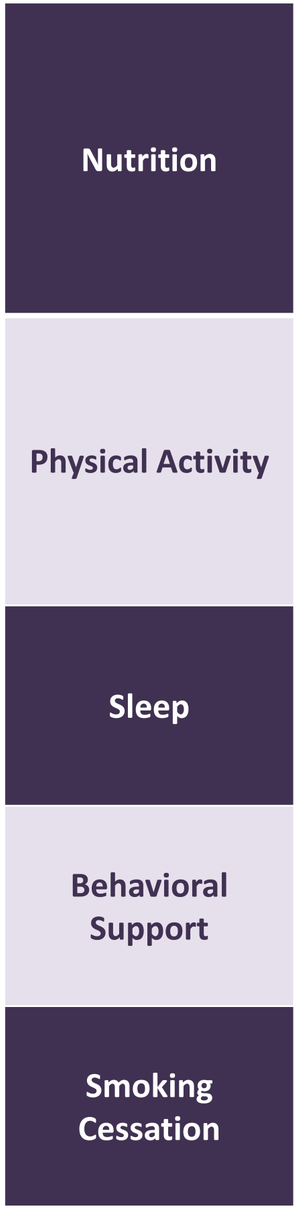
- AACE T2DM management algorithm 2020



Lifestyle Therapy

- AACE T2DM management algorithm 2020

- Essential part of treatment for patients with diabetes and obesity
- Multifaceted
- Multidisciplinary (pcp, RD, PT, psychologist, endocrinologist, sleep medicine, obesity specialist etc.)
- Look AHEAD trial
  - Intensive lifestyle intervention has been shown to help with maintaining long-term weight loss in patients with T2DM



Medical Therapy

- AACE T2DM management algorithm 2020

2 Major Components:

1

8.12 When choosing glucose-lowering medication for patients with type 2 diabetes and overweight or obesity, consider the medications effect on weight. B

8.13 Whenever possible, minimize medications for comorbid conditions that are associated with weight gain E

2

Medical Therapy (BMI ≥ 27):

Individualize care by selecting one of the following based on efficacy, safety, and patients' clinical profile: Phentermine, orlistat, ~~lorcaserin~~, phentermine/topiramate ER, naltrexone,/bupropion, liraglutide 3mg

Medical Therapy

Screen for Obesogenic Medications

CNS Drugs
Atypical Antipsychotics e.g., olanzipine
Anti-epileptics e.g., valproate
Lithium
Anti-depressants
SSRIs e.g., paroxetine
Tricyclic agents e.g., nortriptyline
Others e.g., venlafaxine, mirtazapine

Endocrine agents
Glucocorticoids e.g., prednisone
Hormonal Contraceptives e.g., medroxyprogesterone
Diabetes agents
Insulin
Sulfonylureas e.g., glyburide
Thiazolidenediones e.g., pioglitazone

Miscellaneous
Beta blockers e.g., metoprolol
Antihistamines e.g., diphenhydramine
Sleep aides e.g., zolpidem

Leslie, et al. QJM. 2007;100:395-404

Medical Therapy: Consider Using for patients with Diabetes and BMI of 27 and over

- Similar to SSRI, not every tx works for each person
- Need at least 5% weight loss after 3 months of tx to demonstrate efficacy and to justify ongoing use
- long term tx is required for weight loss maintenance---- >when patients stop their anti-obesity tx weight regain occurs (set-point/metabolic adaptation!!)
- Combining agents like blood pressure lowering or hba1c lowering---> more weight loss combine agents for greater weight loss!!!
- pts on pharmaceutical treatments should be evaluated every 3 months to assess efficacy and safety (JCEM)
- Hypoglycemia

Medical Therapy: Choose Diabetes Agents that are weight neutral or cause weight loss

Profiles of Antihyperglycemic Medications

	MET	GLP1-RA	SGLT2i	DPP4i	AGi	TZ2 (moderate dose)	SU/GLN	COLSVL	BCR-QR	INSULIN	PRAML
Weight	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss

AACE 2020

- Weight loss:
  - Metformin
  - SGLT2i
  - GLP1-RA
  - Pramlintide

- Weight Neutral
  - DPP4i
  - Alpha-glucosidase inhibitors
  - Colesvelam
  - Bromocriptine-QR

Anti-diabetes medications that most promote body weight gain include most insulin, sulfonylureas, thiazolidinediones, and meglitinides

OMA 2021

Medical Therapy: Obesity

Table 8.2—Medications approved by the FDA for the treatment of obesity

Medication name	Typical adult maintenance dose	Average wholesale price (30-day supply) (118)	National Average Drug Acquisition Cost (30-day supply) (119)	1-Year (52- or 56-week) mean weight loss (% loss from baseline)		Common side effects (120–124)	Possible safety concerns/ considerations (120–124)
				Treatment arms	Weight loss (% loss from baseline)		
Short-term treatment (≤12 weeks)							
Sympathomimetic amine anorectic							
Phentermine (125)	8–37.5 mg q.d.*	$5–$46 (37.5 mg dose)	$3 (37.5 mg dose)	15 mg q.d.† 7.5 mg q.d.† PBO	6.1 5.5 1.2	Dry mouth, insomnia, dizziness, irritability, increased blood pressure, elevated heart rate	• Contraindicated for use in combination with monoamine oxidase inhibitors
Long-term treatment (>12 weeks)							
Lipase inhibitor							
Orlistat (3)	60 mg t.i.d. (OTC) 120 mg t.i.d. (Rx)	$41−$82 $823	$41 $556	120 mg t.i.d.‡ PBO	9.6 5.6	Abdominal pain, flatulence, fecal urgency	• Potential malabsorption of fat-soluble vitamins (A, D, E, K) and of certain medications (e.g., cyclosporine, thyroid hormone, anticonvulsants, etc.) • Rare cases of severe liver injury reported • Cholelithiasis • Nephrolithiasis
Sympathomimetic amine anorectic/antiepileptic combination							
Phentermine/ topiramate ER (126)	7.5 mg/46 mg q.d.§	$223 (7.5 mg/ 46 mg dose)	$179 (7.5 mg/ 46 mg dose)	15 mg/92 mg q.d.‖ 7.5 mg/46 mg q.d.‖ PBO	9.8 7.8 1.2	Constipation, paresthesia, insomnia, nasopharyngitis, xerostomia, increased blood pressure	• Contraindicated for use in combination with monoamine oxidase inhibitors • Birth defects • Cognitive impairment • Acute angle-closure glaucoma
Opioid antagonist/antidepressant combination							
Naltrexone/ bupropion ER (15)	16 mg/180 mg b.i.d.	$334	$266	16 mg/180 mg b.i.d. PBO	5.0 1.8	Constipation, nausea, headache, xerostomia, insomnia, elevated heart rate and blood pressure	• Contraindicated in patients with uncontrolled hypertension and/or seizure disorders • Contraindicated for use with chronic opioid therapy • Acute angle-closure glaucoma **Black box warning:** • Risk of suicidal behavior/ideation in persons younger than 24 years old who have depression

ADA 2021

Medical Therapy: Obesity

Table 8.2—Continued

Medication name	Typical adult maintenance dose	Average wholesale price (30-day supply) (118)	National Average Drug Acquisition Cost (30-day supply) (119)	1-Year (52- or 56-week) mean weight loss (% loss from baseline)		Common side effects (120–124)	Possible safety concerns/ considerations (120–124)
				Treatment arms	Weight loss (% loss from baseline)		
Glucagon-like peptide 1 receptor agonist							
Liraglutide (16)**	3 mg q.d.	$1,557	$1,243	3.0 mg q.d. 1.8 mg q.d. PBO	6.0 4.7 2.0	Gastrointestinal side effects (nausea, vomiting, diarrhea, esophageal reflux), injection site reactions, elevated heart rate	• Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected. • Use caution in patients with kidney disease when initiating or increasing dose due to potential risk of acute kidney injury **Black box warning:** • Risk of thyroid C-cell tumors in rodents; human relevance not determined

All medications are contraindicated in women who are or may become pregnant. Women of reproductive potential must be counseled regarding the use of reliable methods of contraception. Select safety and side effect information is provided; for a comprehensive discussion of safety considerations, please refer to the prescribing information for each agent. b.i.d., twice daily; ER, extended release; OTC, over the counter; PBO, placebo; q.d., daily; Rx, prescription; t.i.d., three times daily. *Use lowest effective dose; maximum appropriate dose is 37.5 mg. †Duration of treatment was 28 weeks in a general obese adult population. **Agent has demonstrated cardiovascular safety in a dedicated cardiovascular outcome trial (127). ‡Enrolled participants had normal (79%) or impaired (21%) glucose tolerance. §Maximum dose, depending on response, is 15 mg/92 mg q.d. ||Approximately 68% of enrolled participants had type 2 diabetes or impaired glucose tolerance.

ADA 2021

Medical Therapy: Obesity

Phentermine

- Sympathomimetic amine that came out in 1959
- Controlled substance
- Anorexiant/ Central nervous system stimulant
- Short-term adjunct (a few weeks) to lifestyle modification- But Obesity is a Chronic disease!!!!
- Individualize tx to get response with lowest effective dose
- Tolerance usually develops within the first month of use (smokers?)
- tablet: 37.5 mg
- Capsule: 15mg, 30mg
- Tablet 8mg BID-TID
- Avoid in patients with any hx of substance abuse

Medical Therapy: Obesity

Phentermine

Dosing Hepatic Impairment: no dose adjustments/ has not been studied *(Willson C et al- Toxicology reports 2019- no hepatotoxicity)*

Dosing Renal Impairment:

- eGFR ≥30 mL/minute/1.73 m2: There are no dosage adjustments provided in the manufacturer's labeling; systemic exposure may be increased; use with caution.
- eGFR 15 to 29 mL/minute/1.73 m2: Maximum dose: 15 mg/day.
- eGFR <15 mL/minute/1.73 m2: Avoid use (has not been studied).
- End-stage renal disease (ESRD) requiring dialysis: Avoid use (has not been studied).

Medical Therapy: Obesity

Phentermine

Contraindications:

- “Hypersensitivity to phentermine, other sympathomimetic amines or any component of the formulation; history of cardiovascular disease (eg, arrhythmias, heart failure, coronary artery disease, stroke, uncontrolled hypertension); hyperthyroidism; glaucoma; agitated states; history of drug abuse; use during or within 14 days following MAO inhibitor therapy; pregnancy; breast-feeding” – UptoDate

Medical Therapy: Obesity

Phentermine

- Long term use/off-label use

Safety and Effectiveness of Longer-Term Phentermine Use: Clinical Outcomes from an Electronic Health Record Cohort

Kristina H. Lewis [1,2], Heidi Fischer[3], Jamy Ard [1], Lee Barton[3], Daniel H. Bessesen[4], Matthew F. Daley[5], Jay Desai[6], Stephanie L. Fitzpatrick[7], Michael Horberg[8], Corinna Koebnick[3], Caryn Oshiro[9], Ayae Yamamoto[3], Deborah R. Young[3], and David E. Arterburn[10]

Medical Therapy: Obesity

Phentermine

- Addiction/Withdrawal?

Published: 17 May 2013

Addiction potential of phentermine prescribed during long-term treatment of obesity

E J Hendricks✉, M Srisurapanont, S L Schmidt, M Haggard, S Souter, C L Mitchell, D G De Marco, M J Hendricks, Y Istratiy & F L Greenway

International Journal of Obesity **38**, 292–298(2014)

A Study of Abrupt Phentermine Cessation in Patients in a Weight Management Program

Hendricks, Ed J MD[1*]; Greenway, Frank L MD[2]

American Journal of Therapeutics: July 2011 - Volume 18 - Issue 4 - p 292-299

Medical Therapy: Obesity

Phentermine and Topiramate

- Prescribing each rx separately is not FDA approved for Obesity but it is very similar to Qsymia – expert opinion
- Topiramate is dopaminergic, metabolic and….
- Topiramate can increase risk of kidney stones
- common topiramate side effects: numbness or tinging, dizziness/drowsiness, brain fog, mood change, vision change*
- Renal dosing
- No special hepatic dosing- use with caution
- Must taper off due to risk of seizures
- Pregnancy implications - 2 forms of birth control
- Dosing: 50-100mg for weight loss

Medical Therapy: Obesity and Diabetes

GLP1RA

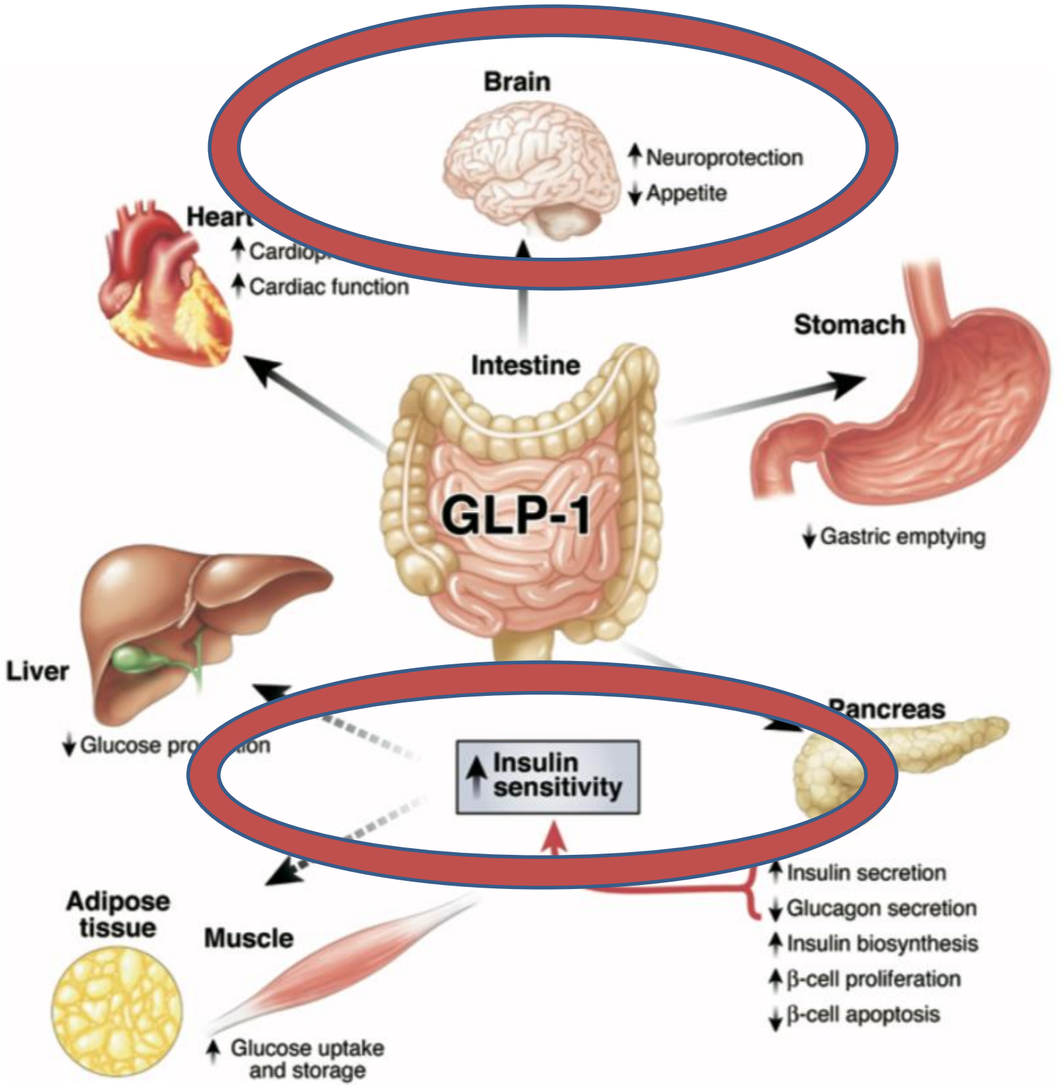


Figure 3. GLP-1 actions in peripheral tissues. The majority of the effects of GLP-1 are mediated by direct interaction with GLP-1Rs on specific tissues. However, the actions of GLP-1 in liver, fat, and muscle most likely occur through indirect mechanisms.

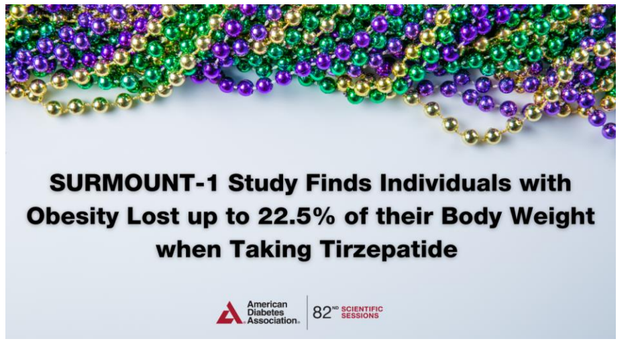
Gastroenterology 2007; 132:2131-2157

Medical Therapy: Obesity and Diabetes

GLP1RA

- 2 approved for tx of obesity:
  - Liraglutide and Semaglutide
- Contraindications: personal or family hx of medullary thyroid carcinoma or MEN 2, pregnancy

Coming soon:

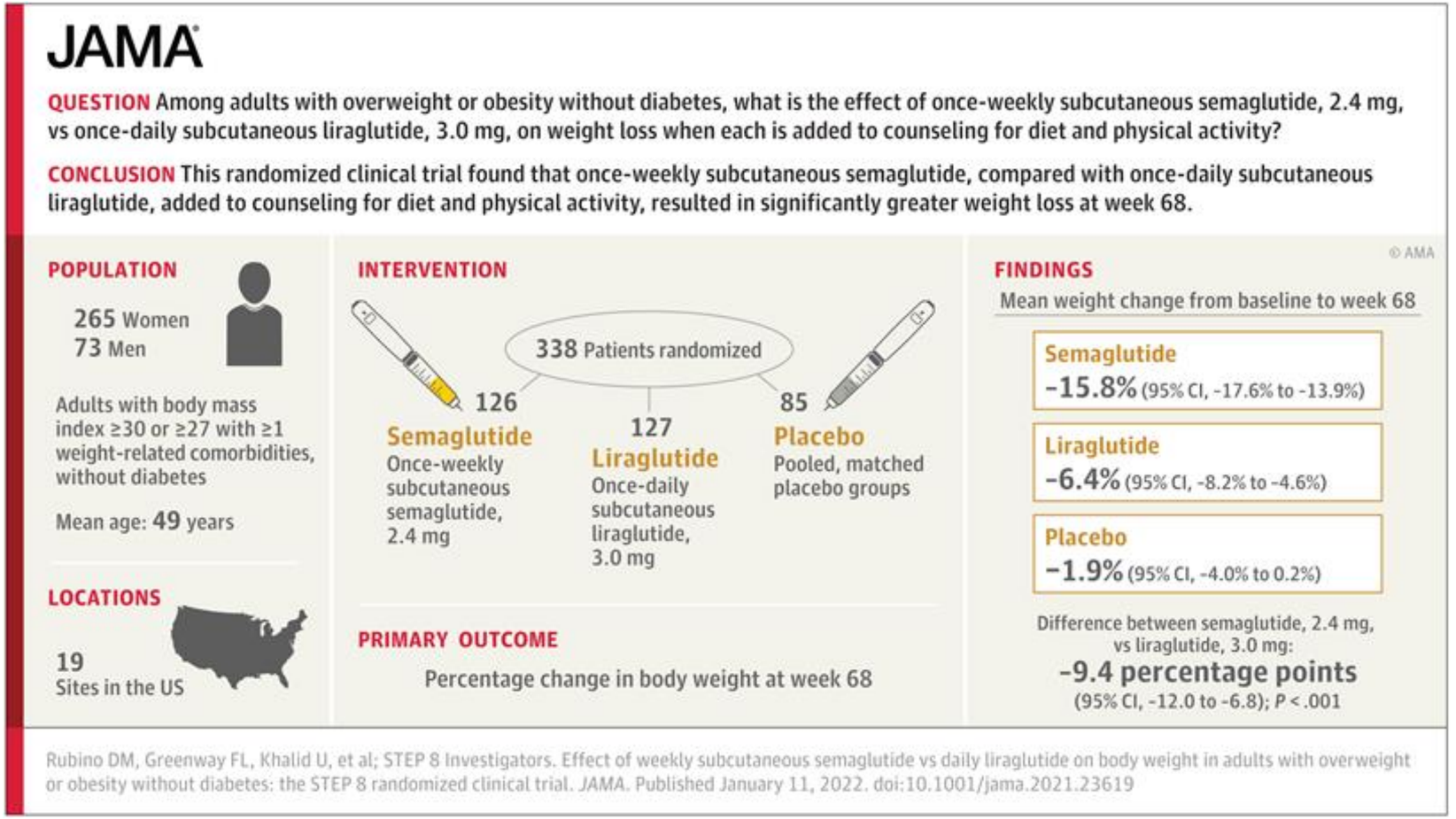


Medical Therapy: Obesity

GLP1RA

STEP 8 trial:
Liraglutide vs. Semaglutide

Published 1/11/22



Medical Therapy: Diabetes

GLP1RA

- Several approved for diabetes

GLP-1 RA	First approved (date)	Molecular weight (Da)[c]	Reference amino acid sequence	Other important components	Elimination half-life	Administration schedule	Pharmaceutical company	Reference
For subcutaneous injection								
Short-acting compounds								
Exenatide b.i.d.	2005 (USA); 2006 (Europe); Byetta	4186.6	Exendin-4	None	3.3—4.0 h	Twice daily	AstraZeneca[i]	[21]
Lixisenatide	2013 (Europe); Lyxumia; 2016 (USA); Adlyxin	4858.5	Exendin-4	Poly-lysine tail	2.6 h	Once daily	Sanofi	[22]
Long-acting compounds/preparations								
Liraglutide	2009 (Europe); 2010 (USA); Victoza	3751.2	Mammalian GLP-1	Free fatty acid[e]	12.6—14.3 h	Once daily	Novo Nordisk	[23]
Once-weekly exenatide	2012; BYDUREON[a]	4186.6	Exendin-4	Active ingredient encapsulated in microspheres of poly-(D,L-lactide-co-glycolide)	3.3—4.0 h[f]	Once weekly	AstraZeneca[i]	[21]
Dulaglutide	2014; Trulicity	59670.6	Mammalian GLP-1	Immunoglobulin Fc fragment	4.7—5.5 d	Once weekly	Eli Lilly and Company	[24]
Albiglutide	2014 (Europe); Eperzan Tanzeum (USA)[b]	72971.3	Mammalian GLP-1	Albumin	5.7—6.8 d	Once weekly	GlaxoSmithKline	[25]
Semaglutide	2017 (USA); 2019 (Europe); Ozempic	4113.6	Mammalian GLP-1	Free fatty acid[e]	5.7—6.7 d	Once weekly	Novo Nordisk	[26]
For oral administration								
Semaglutide (long-acting)	2020; Rybelsus	4113.6	Mammalian GLP-1	Free fatty acid[e]	5.7—6.7 d	Once daily	Novo Nordisk	[27]
Fixed-dose combinations								
With basal insulin (for subcutaneous injection)								
Liraglutide/insulin degludec (iDegLira)	2014 (Europe); 2016 (USA); Xultophy	3751.2[d]	Mammalian GLP-1	Basal insulin	12.6—14.3 h	Once daily (anytime[g])	Novo Nordisk	[28]
Lixisenatide/insulin glargine (iGlarLixi)	2016 (USA); Soliqua 100/33; 2017 (Europe); Suliqua	4858.5[d]	Exendin-4	Basal Insulin	2.6 h	Once daily[h]	Sanofi	[29]

[a] Improved once-weekly auto-injector BYDUREON BCise was approved in 2018.
[b] Marketing was discontinued in 2018.
[c] Mammalian GLP-1: 3297.7.
[d] For the GLP-1 RA component only.
[e] Promoting binding to albumin.
[f] Identical to the short-acting preparation.
[g] Approximately the same time every day.
[h] Before meals with the highest expected glycemic excursion.
[i] Previously Amylin Pharmaceuticals, Eli Lilly and Company, and Bristol Myers Squibb.

Michael A. Nauck, Daniel R. Quast, Jakob Wefers, Juris J. Meier. GLP-1 receptor agonists in the treatment of type 2 diabetes – state-of-the-art. Molecular Metabolism,Volume 46,2021,101102; ISSN 2212-8778,

Medical Therapy: Diabetes

GLP1RA

FDA NEWS RELEASE

FDA Approves Novel, Dual-Targeted Treatment for Type 2 Diabetes

In Clinical Trials, Treatment Proved More Effective Than Other Therapies Evaluated

For Immediate Release:

May 13, 2022

Today, the U.S. Food and Drug Administration ap roved Mounjaro (tirzepatide) in ction to improve blood sugar control in adults with type 2 diabe addi et and exercise. Mounjaro was effective at improving blood sugar and was more effective than the other diabetes therapies with which it was compared in clinical studies.

Medical Therapy: Diabetes

GLP1RA

RESEARCH SUMMARY

Tirzepatide vs. Semaglutide Once Weekly in Patients with Type 2 Diabetes

Frías JP et al. DOI: 10.1056/NEJMoa2107519

CLINICAL PROBLEM

Not all patients with type 2 diabetes have adequate glucose control with metformin monotherapy. Tirzepatide is a dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1) receptor agonist under development for treatment of diabetes; how it compares with the selective GLP-1 receptor agonist semaglutide is unknown.

CLINICAL TRIAL

Design: An international, randomized, open-label, phase 3, noninferiority trial was conducted to compare tirzepatide with semaglutide in adults with type 2 diabetes.

Intervention: 1879 adults with inadequately controlled diabetes despite metformin treatment were assigned to a once-weekly subcutaneous injection of tirzepatide (5, 10, or 15 mg) or semaglutide (1 mg) for 40 weeks. The primary efficacy end point was the change in glycated hemoglobin level from baseline to 40 weeks.

RESULTS

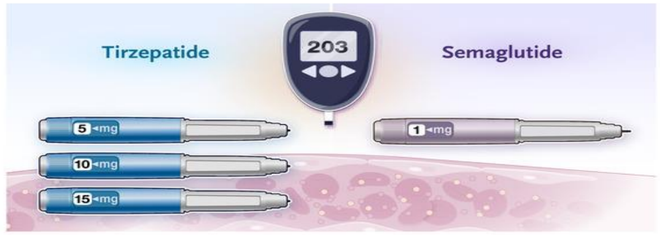
Efficacy: All three tirzepatide doses were noninferior to and also superior to semaglutide with respect to the mean reduction in glycated hemoglobin level. Patients in the tirzepatide groups also lost more weight than those in the semaglutide group.

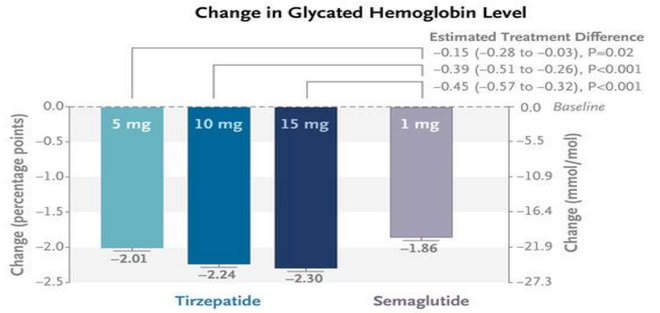
Safety: The percentage of patients reporting any adverse event was similar across the groups, with gastrointestinal events most common. However, serious adverse events were reported by 5.3 to 7.0% of patients in the tirzepatide groups and 2.8% of those in the semaglutide group.

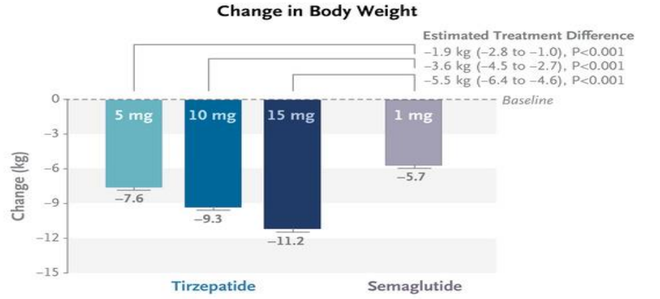
LIMITATIONS AND REMAINING QUESTIONS

- Treatments were not blinded because of differences in devices and dose-escalation schemes (although individual tirzepatide doses were blinded).
- Higher doses of semaglutide were not compared with tirzepatide.
- Black patients accounted for only 4% of the trial population, so generalizability of the findings is limited.
- How tirzepatide performs in patients with increased cardiovascular risk requires further study.

Links: Full Article | NEJM Quick Take | Editorial







CONCLUSIONS

Tirzepatide was noninferior and also superior to semaglutide in reducing glycated hemoglobin levels in adults with type 2 diabetes.

Medical Therapy: Diabetes

GLP1RA

Side effects:

- Nausea
- HYPOGLYEMIA WITH INSULIN or SU
- Constipation
- Pancreatitis

DOI: 10.1002/edm2.100

ORIGINAL RESEARCH ARTICLE

Endocrinology, Diabetes & Metabolism Open Access WILEY

Risk of any hypoglycaemia with newer antihyperglycaemic agents in patients with type 2 diabetes: A systematic review and meta-analysis

Sanaz Kamalinia[1] | Robert G. Josse[2,3] | Patrick J. Donio[4] | Lindsay Leduc[4] | Baiju R. Shah[3,5] | Sheldon W. Tobe[1,3,4,5]

[1]Institute of Medical Sciences, University of Toronto, Toronto, ON, Canada
[2]St. Michael's Hospital, Toronto, ON, Canada
[3]Department of Medicine, University of Toronto, Toronto, ON, Canada
[4]Northern Ontario School of Medicine, Sudbury, ON, Canada
[5]Sunnybrook Research Institute, Toronto, ON, Canada

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Email: sanaz.kamalinia@mail.utoronto.ca

Abstract

Objectives: For patients with type 2 diabetes, newer antihyperglycaemic agents (AHA), including the dipeptidyl peptidase IV inhibitors (DPP4i), glucagon-like peptide-1 receptor agonists (GLP1RA) and sodium glucose co-transporter 2 inhibitors (SGLT2i) offer a lower risk of hypoglycaemia relative to sulfonylurea or insulin. However, it is not clear how AHA compare to placebo on risk of any hypoglycaemia. This study evaluates the risk of any and severe hypoglycaemia with AHA and metformin relative to placebo.

Design: A systematic review and meta-analysis was conducted of randomized, placebo-controlled trials ≥12 weeks in duration. MEDLINE, Embase and the Cochrane Library were searched up to April 16, 2019. Studies allowing use of other diabetes medications were excluded. Mantel-Haenszel risk ratio with 95% confidence intervals were used to pool estimates based on class of AHA and number of concomitant therapies used.

Patients: Eligible studies enrolled patients with type 2 diabetes ≥18 years of age.

Results: 144 studies met our inclusion criteria. Any hypoglycaemia was not increased with AHA when used as monotherapy (DPP4i (RR 1.12; 95% CI 0.81-1.56), GLP1RA (1.77; 0.91-3.46), SGLT2i (1.34; 0.83-2.15)), or as add-on to metformin (DPP4i (0.95; 0.67-1.35), GLP1RA (1.24; 0.80-1.91), SGLT2i (1.29; 0.91-1.83)) or as triple therapy (1.13; 0.67-1.91). However, metformin monotherapy (1.73; 1.02-2.94) and dual therapy initiation (3.56; 1.79-7.10) was associated with an increased risk of any hypoglycaemia. Severe hypoglycaemia was rare not increased for any comparisons.

Conclusions: Metformin and the simultaneous initiation of dual therapy, but not AHA used alone or as single add-on combination therapy, was associated with an increased risk of any hypoglycaemia relative to placebo.

KEYWORDS
diabetes mellitus, type 2, dipeptidyl peptidase IV inhibitor, glucagon-like peptide-1 receptor agonist, hypoglycaemia, sodium glucose co-transporter 2 inhibitor

Medical Therapy: Diabetes

SGLT2i

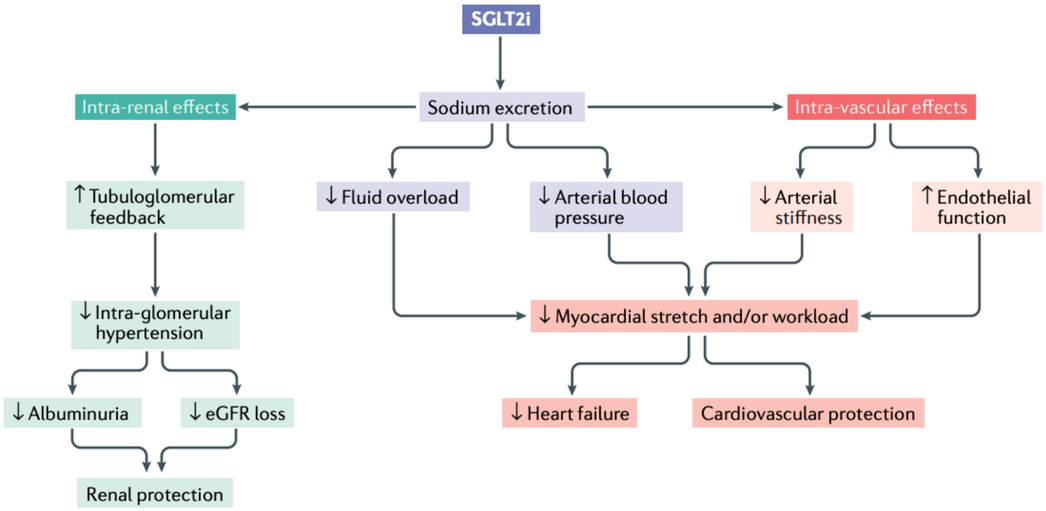

Fig. 1 | **Multiple beneficial effects related to enhanced sodium excretion by SGLT2is.** Aside from glucosuria and osmotic diuresis, sodium–glucose cotransporter type 2 inhibitors (SGLT2is) also induce some natriuresis, which is accompanied by intra-renal and intra-vascular effects. In the kidney, SGLT2is augment distal delivery of sodium to the macula densa, an effect that restores tubuloglomerular feedback mechanisms, leading to vasoconstriction of the afferent artery and thereby to a reduction in glomerular hypertension. This mechanism could explain both the reduction in albuminuria and the slowing of estimated glomerular filtration rate (eGFR) decline reported with SGLT2is, and ultimately renoprotection. In the vascular wall, reduced arterial stiffness and improved endothelial function have been reported, which, along with a reduction in fluid overload, could contribute to lower arterial blood pressure. These combined effects result in a reduction in myocardial stretch and/or workload, thus explaining the reduction in the risk of heart failure and contributing to the overall cardiovascular protection.

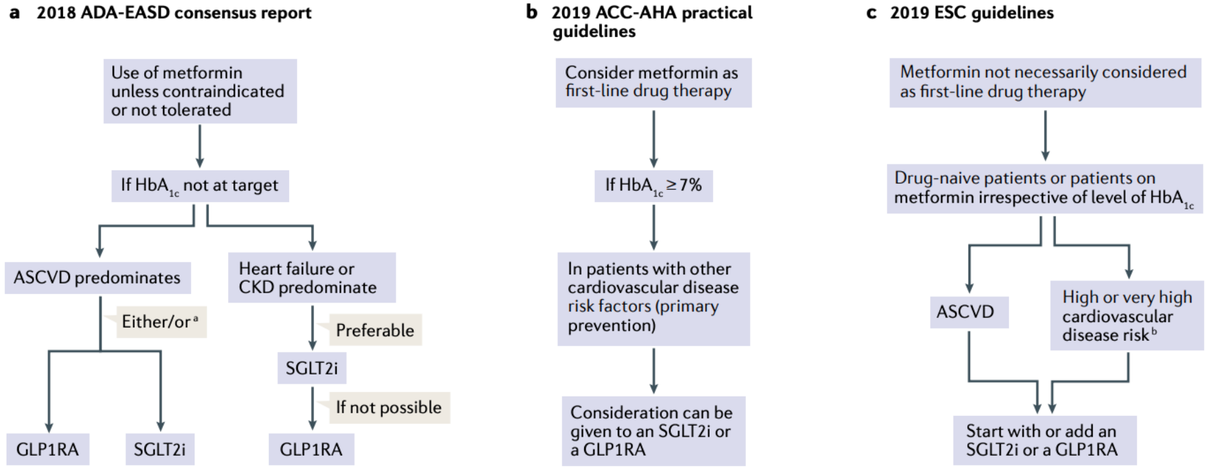

Fig. 3 | **Position of SGLT2is in international guidelines. a** | The 2018 American Diabetes Association and European Association for the Study of Diabetes (ADA-EASD) consensus report[232] introduced a new paradigm in the management of type 2 diabetes mellitus stating that glucose-lowering agents should be selected according to the cardiovascular and renal risk profile of the patient. Since that date, sodium–glucose cotransporter type 2 inhibitors (SGLT2is) occupy a preferable position, after metformin, in patients with heart failure and chronic kidney disease (CKD) and represent an alternative to glucagon-like peptide 1 receptor agonists (GLP1RAs) in patients with atherosclerotic cardiovascular disease. Please note that, in the updated 2019 ADA-EASD version[233], some amendments have been proposed: SGLT2is should be prescribed regardless of HbA_{1c} levels in high-risk patients; some patients without established cardiovascular disease but with specific risk factors might benefit from iSGLT2 or GLP1RAs; GLP1RAs, if well tolerated, are now preferred to SGLT2is in patients with atherosclerotic cardiovascular disease (ASCVD)[233]. **b** | In the 2019 American College of Cardiology–American Heart Association (ACC-AHA) practical guidelines, the indications of SGLT2is are not restricted to patients with established cardiovascular disease (secondary prevention) but are extended to patients with multiple risk factors (primary prevention) as add-on therapy to metformin if $HbA_{1c} \geq 7\%$[235]. **c** | In the 2019 European Society of Cardiology (ESC) guidelines[125], SGLT2is are recommended in patients with cardiovascular risk factors (with an extended definition), independently of HbA_{1c} levels. Of note, in patients at high or very high risk of cardiovascular disease, SGLT2is are preferred to metformin according to 2019 ESC guidelines, a position, however, not endorsed in the 2019 ADA-EASD consensus report. Of note, in all of the most up-to-date recommendations, SGLT2is can be used in patients with type 2 diabetes mellitus and an estimated glomerular filtration rate as low as 30 ml/min/1.73m². [a]In the 2019 updated version, GLP1RAs now preferable if ASCVD predominates. [b]Target organ damaged or multiple risk factors.

Scheen. (2020). Sodium-glucose cotransporter type 2 inhibitors for the treatment of type 2 diabetes mellitus. Nature Reviews. Endocrinology, 16(10), 556–577. https://doi.org/10.1038/s41574-020-0392-2

Medical Therapy: Diabetes

SGLTi2

Adverse Side Effects

- Genitourinary tract
- Hypotension
- Acute Kidney Injury
- Bone fracture
- Diabetic Ketoacidosis
- Amputations

Other Considerations with Combination treatment for diabetes and weight loss

- Need for insulin adjustments when adding weight loss promoting medications
- You may need to adjust anti-hypertensives since hypotension can develop since blood pressure will improve with weight loss
- Protein malnutrition and dehydration can be a risk with reduced appetite and intake
- Rule out Helicobacter pylori for pts intolerant to GLP1RA?
- “Microdosing” with semaglutide can be helpful for intolerant patients
- Gallstones with rapid weight loss

Summary: Take home

- Treatment of obesity and diabetes is multifaceted since both are chronic diseases
- Combine lifestyle treatment (including diet/exercise/sleep/behavioral health) with medication treatment (future session on this in detail)
- Consider the implications of weight gain with any medications you prescribe for patients with diabetes and obesity. PLEASE AVOID GABAPENTIN!
- Use weight-loss or weight neutral diabetes medications when possible
- Don’t hesitate to also use your ”toolbox” of anti-obesity agents for patients with diabetes and BMI of 27
- You can combine treatments to maximize weight loss and lower hba1c
- Consider joining the Obesity Medicine Association and the Obesity Action Coalition to learn more or to get more resources on Obesity

Thank you!

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Questions?

Cardiometabolic teleECHO™ Clinic

Patient Recommendation Form

Presentation Date: July 20, 2022 **Presenter name:** Jessica Karp, MD

Presenter Facility: Healthpoint CHC

Case Recap: 59 y/o female from El Salvador with T2DM w/ hyperglycemia, severe DR w/o ME, microalbuminuria, polyneuropathy, HLD, HTN. She has limited activity due to a knee OA & Hx of back surgeries.

Case Recommendations:

1. Further explore small change goals, specifically encouraging the patient to be mindful of label reading and observing sugar content in packaged foods and fruit
2. Consider professional CGM or sample CGM to assess therapy effect. Alternatively, ask patient to check glucose in AM and alternate prior to dinner or bedtime to see some patterns. Consider asking patient to check 2 hours post one meal to assess how food is affecting their body once some improvement in pre-prandial blood sugars have been made.
3. First goal for a1c is 9.0, then slowly over 2 months to 8.0, then at 6 months goal is 7.0
4. Access baseline exercise steps and consider step count goal to increase by 100 step average per week
5. Consider a nutrition referral
6. Agree with slow titration every 2-4 weeks of liraglutide to goal 1.8. Also consider transition to Semaglutide 0.5mg weekly x 1 month and then 1mg weekly
7. Convert to 70/30 mixed insulin. Start at 20 units twice a day. Do not increase until at max dose of liraglutide for one month. Then if AM sugars > 150, increase by 2-4 units every week. Goal AM sugars should be <150 in attempt to slower normalization of glucose
8. Consider holding empagliflozin for now and consider adding back for microalbuminuria in future (3-6 months) if cost and pill burden not an issue once AAc is 8 or less.
9. If AM sugars are less than 100 for two days or any sugars <70mg/dl, reduce by 4 units twice a day
10. Consider phentermine in long term if needed for weight loss
11. Consider increase to 40mg daily of atorvastatin due to current LDL 101, but LDL may improve with weight loss. If Triglycerides >200 in 6 months, repeat fasting lipid panel. The goal is <150 and may improve with insulin and weight loss.
12. If possible, consider increase in Lisinopril given patients hx of microalbuminuria. This will not increase pill burden.

Nicole Ehrhardt, MD

Physician Signature: *Nicole Ehrhasrdt*
Please Re-present case: sept 2022