Overweight and Obesity

Therapeutic Modalities

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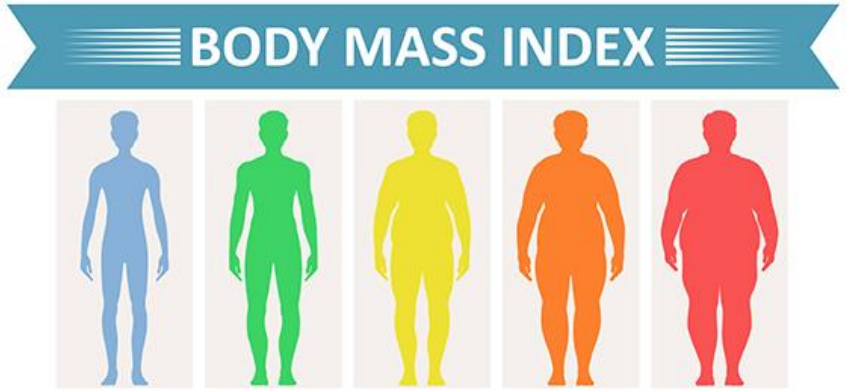
Epidemiology and Definition

Worldwide obesity has more than doubled in the last 4 decades. **Obesity is the second of the leading preventable causes of death worldwide (after smoking).**

BMI is not always an accurate predictor of body fat or fat distribution, particularly in muscular individuals because of the existent differences of fat and muscle proportion and distribution.

Other instruments to describe obesity, fat distribution, cardiovascular risk and mortality are: waist circumference (WC), waist-to-height ratio (WHtR) and waist-to-hip ratio (WHR). The American Heart Association recommended 102 cm for men and 88 cm for women as cutoff levels for waist circumference.



BMI classification	
Underweight	< 18.5
Normal range	18.5 - 24.9
Overweight	⩾ 25.0
Preobese	25.0 - 29.9
Obese	⩾ 30.0
Obese class I	30.0 - 34.9
Obese class II	35.0 - 39.9
Obese class III	⩾ 40.0

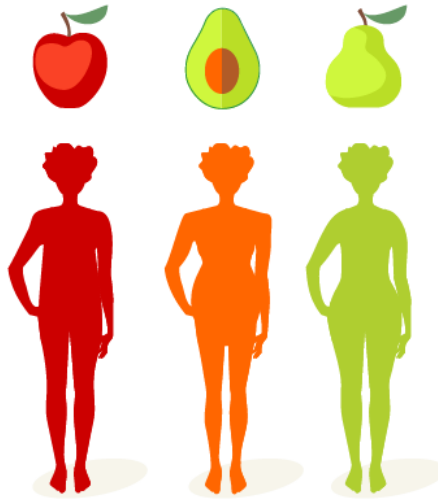
waist-to-height ratio

0.58 and over	0.63 and over	Highly Obese
0.54 - 0.58	0.58 - 0.63	Extremely Overweight
0.49 - 0.54	0.53 - 0.58	Overweight
0.46 - 0.49	0.46 - 0.53	Healthy
0.42 - 0.46	0.43 - 0.46	Slender & Healthy
0.35 - 0.42	0.35 - 0.43	Extremely Slim
0.35 or below	0.35 or below	Abnormally Slim

waist-to-hip ratio

WOMEN	HEALTH RISK	BODY SHAPE
0.80 or below	Low	Pear
0.81 to 0.85	Moderate	Avocado
0.85+	High	Apple

MEN	HEALTH RISK	BODY SHAPE
0.95 or below	Low	Pear
0.96 to 1.0	Moderate	Avocado
1.0+	High	Apple



Health Consequences of Obesity

Cardiovascular diseases	Ischemic heart disease and stroke [24] High blood pressure Venous stasis, phlebitis Deep vein thrombosis, pulmonary embolism [25]
Metabolic diseases: diabetes mellitus, dyslipidemia, gout [5]	
Osteo-arthro-muscular disorders	Osteoarthritis Lower back pain, poor mobility
Increase risk for cancer - endometrial, breast, cervix, colon, prostate, kidney [16]	
Respiratory disorders [24]	Adult-onset asthma Sleep apneea and sleeping disorders [26] Hypoventilation – obesity syndrome
Digestive dis-orders	Hernia Gallstone, hepatic steatosis, severe pancreatitis
Genital abnor-malities [24]	Menstrual irregularities or cessation of menstruation (amenorrhea) Decreased fertility and pregnancy complications Polycystic ovarian syndrome, hypogonadism Erectile dysfunction
Skin disorders	Skin lesions arising from the bacterial breakdown of sweat Intertrigo, cellulites, lymphedema, hirsutism
Catharacta	
Emotional and social problems (stigmatization) [24]	

CLINICAL COMPONENT OF THE MEDICAL DIAGNOSIS OF OBESITY

Evaluation of a checklist of weight-related complications. Candidates for weight-loss therapy can present with either excess adiposity (i.e., the anthropometric component) or weight-related complications (i.e., the clinical component)

Patients Present with Overweight or Obesity (Anthropometric Component)	Candidates for Weight Loss Therapy	Patients Present with Weight-Related Disease or Complication (Clinical Component)
Patients present with BMI ≥25 kg/m^2, or ≥23 kg/m^2 in certain ethnicities, and excess adiposity	Evaluate for weight-related complications →	Prediabetes
		Metabolic Syndrome
		Type 2 Diabetes
		Dyslipidemia
		Hypertension
		Cardiovascular Disease
		Nonalcoholic Fatty Liver Disease
	← Evaluate for overweight or obesity	Polycystic Ovary Syndrome
		Female Infertility
		Male Hypogonadism
		Obstructive Sleep Apnea
		Asthma/Reactive Airway Disease
		Osteoarthritis
		Urinary Stress Incontinence
		Gastroesophageal Reflux Disease
		Depression

LIFESTYLE THERAPY

Evidence-based lifestyle therapy for treatment of obesity should include three components

MEAL PLAN

- Reduced-calorie healthy meal plan
- ~500–750 kcal daily deficit
- Individualize based on personal and cultural preferences
- Meal plans can include: Mediterranean, DASH, low-carb, low-fat, volumetric, high protein, vegetarian
- Meal replacements
- Very low-calorie diet is an option for selected patients and requires medical supervision

Team member or expertise:
dietitian, health educator

PHYSICAL ACTIVITY

- Voluntary aerobic physical activity progressing to >150 minutes/week performed on 3–5 separate days per week
- Resistance exercise: single-set repetitions involving major muscle groups, 2–3 times per week
- Reduce sedentary behavior
- Individualize program based on preferences and take into account physical limitations

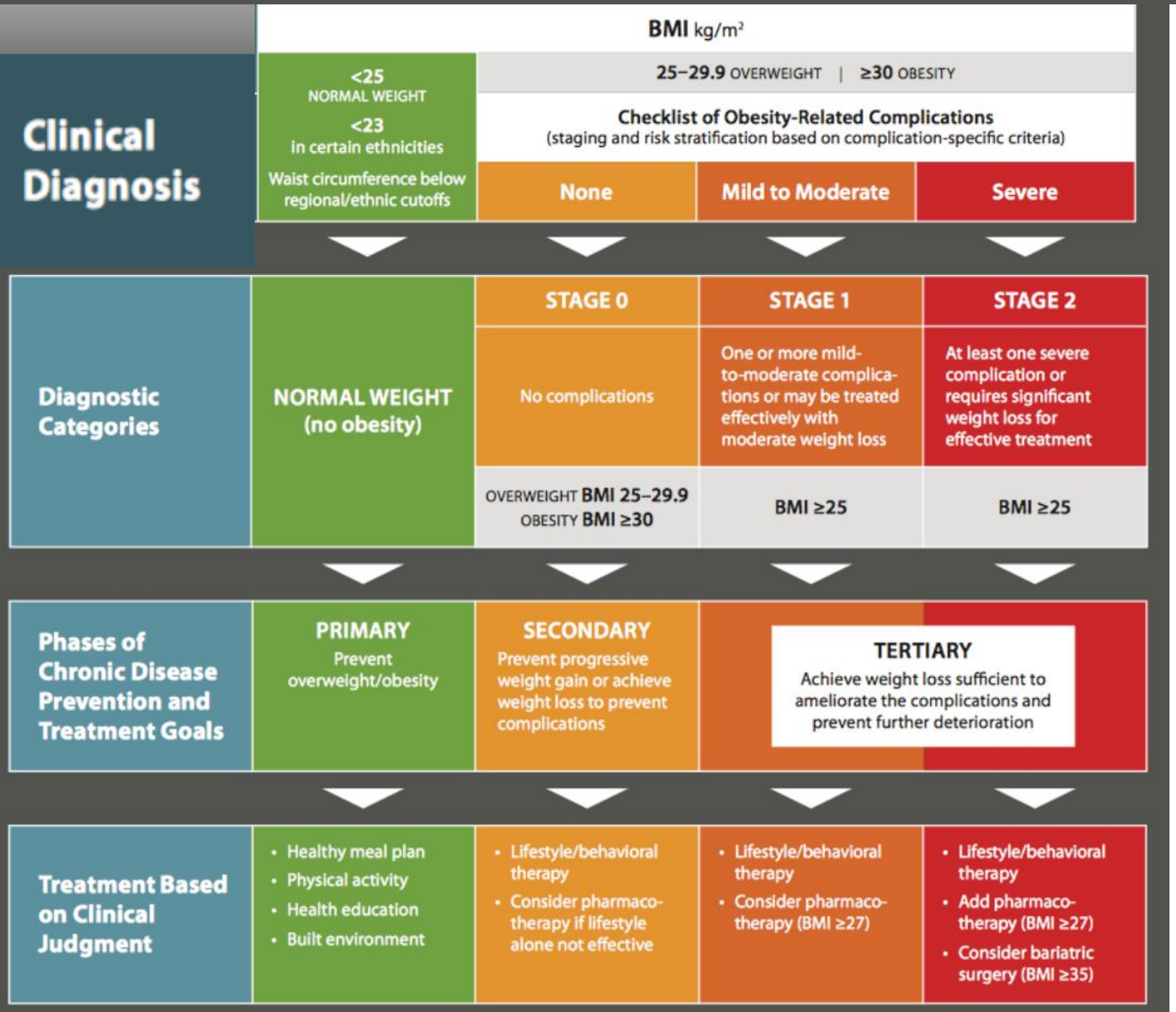
Team member or expertise:
exercise trainer, physical activity coach, physical/occupational therapist

BEHAVIOR

An interventional package that includes any number of the following:

- Self-monitoring (food intake, exercise, weight)
- Goal setting
- Education (face-to-face meetings, group sessions, remote technologies)
- Problem-solving strategies
- Stimulus control
- Behavioral contracting
- Stress reduction
- Psychologic evaluation, counseling, and treatment when needed
- Cognitive restructuring
- Motivational interviewing
- Mobilization of social support structures

Team member or expertise:
health educator, behaviorist, clinical psychologist, psychiatrist



Mild to moderate adiposity-related complications

- Metabolic syndrome
- Prediabetes
- Type 2 diabetes
- Dyslipidemia
- Hypertension
- Cardiovascular disease
- Nonalcoholic fatty liver disease
- Polycystic ovary syndrome
- Female infertility
- Male hypogonadism
- Obstructive sleep apnea
- Asthma/reactive airway disease
- Osteoarthritis
- Urinary stress incontinence
- Gastroesophageal reflux disease
- Depression

Severe adiposity-related complications

- Myocardial infarction
- Heart failure
- Diabetic complications
- Incapacitating osteoarthritis
- Significant psychopathology
- Significant functional limitations (severe dyspnea on exertion, …)

Obesity guideline	Main recommendations
American Association of Clinical Endocrinologists and American College of Endocrinology[14]	• No complications: lifestyle/behavioural therapy and consider pharmacotherapy if lifestyle alone is not effective • If one or more mild-to-moderate complications: lifestyle/behaviour therapy and consider pharmacotherapy if BMI ≥27 kg/m^2 • If at least one severe complication: lifestyle/behavioural therapy with pharmacotherapy (BMI ≥27 kg/m^2)
National Health and Medical Research Council (Australia)[16]	• Lifestyle change including reduced energy intake, increased physical activity and support for behaviour change • Consider orlistat as an adjunct if BMI ≥30 kg/m^2 (or ≥27 kg/m^2 with comorbidities) • Consider bariatric surgery if BMI ≥40 kg/m^2 (or ≥35 kg/m^2 with comorbidities)

Pharmacotherapy if BMI ≥ 30 **or** ≥ 27 with at least one (mild-to-moderate or severe) complication

Bariatric surgery if BMI ≥ 40 **or** ≥ 35 with at least one severe (mild-to-moderate?) complication **or** ≥ 30 with type 2 diabetes (?)

Obesity Treatment Pyramid

Increasing health risks
Increasing adiposity

Treatment Intensity

BMI > 40
BMI > 35 with comorbidity

Surgery



20-40% goal wt loss

Endoscopic Procedures



10-20% goal wt loss

BMI > 30
BMI > 27 with comorbidity

Pharmacotherapy



5-20% goal wt loss

Prescriptive Nutritional Intervention

(e.g. meal replacements, intermittent fasting, specific diet)



5-10% goal wt loss

Multicomponent/Intensive Behavioral Intervention



2-5% goal wt loss

Pharmacotherapy

Pharmacotherapy for weight loss should be considered to help overweight or obese patients achieve targeted weight loss and health goals as an adjunct to comprehensive lifestyle intervention for individuals who are motivated to lose weight and have:

- a BMI greater than or equal to 30 kg/m2 **or**
- a BMI greater than or equal to 27 kg/m2 with at least 1 obesity-associated comorbidity (eg, T2D, hypertension, hyperlipidemia, …) **or**
- have not met weight-loss goals (≥ 5% of total body weight at 3–6 months) with lifestyle intervention alone

Medications should always be used as an adjunct to lifestyle modifications. A medication should be continued for no longer than 3 months if no significant weight loss is seen, at which point the medication options should be reassessed.



Medication	Mechanism, adverse effects	Contraindications	Dosing	Monitoring/cautions
FDA-approved medications				
Orlistat	Intestinal lipase inhibitor. SEs: GI side effects — diarrhea, fecal urgency, decreased absorption of fat-soluble vitamins	Malabsorption disorder, cholecystitis	60-mg TID or 120-mg TID with meals	Consider checking levels of fat-soluble vitamins, when indicated
Phentermine (FDA-approved duration varies by state)	Norepinephrine reuptake inhibitor SEs: elevated BP, tachycardia, insomnia, dry mouth, serotonin syndrome	Uncontrolled hypertension, cardiovascular disease, congestive heart failure, seizures glaucoma, MAOI use.	Once daily dosing: 8mg; 15mg; 30mg; 37.5mg	Check BP and HR monthly for 3 months, then every 3 months after patient loses 5% of body weight
Phentermine-topiramate	See separate sections for phentermine and topiramate	Phentermine 3.75 mg/topiramate 23 mg, phentermine 7.5 mg/topiramate 46 mg, phentermine 11.25mg/topiramate 69mg, phentermine 15 mg/topiramate 92 mg		
Naltrexone-bupropion	Naltrexone is a μ-opioid receptor antagonist. Bupropion is a dopamine and norepinephrine reuptake inhibitor. SEs: nausea, which usually subsides, headache, vomiting, dizziness, insomnia, and dry mouth, elevated BP, HR	Uncontrolled hypertension, seizures, regular opioid use, opiate withdrawal, recent abrupt discontinuation of alcohol, MAOIs	Week 1: 1 tab in AM Week 2: 1 tab in AM and 1 tab in PM Week 3: 2 tabs in the AM, 1 tab in the PM Week 4: 2 tabs in AM 2 tabs in the PM	Monitor BP, HR, suicidal ideation, neuropsychiatric symptoms, signs of withdrawal. Medication reconciliation (opioids medications) and MAOIs. Careful social history for current and recent opioid and alcohol use
Liraglutide 3.0 mg	GLP-1 receptor agonist. SEs: nausea, diarrhea, and constipation, usually avoidable with slow dose increases Other SEs: cholecystitis and pancreatitis	Personal or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2, or chronic pancreatitis	0.6 mg daily for 1 week; increase by 0.6 mg at 1- to 2-week intervals to 3mg daily. Efficacy has not been established for<3 mg/day but consider using highest tolerated dose.	Patients currently on insulin and being started on a this GLP-1 agonist should be monitored for hypoglycemia and must be given clear and direct guidelines on how to titrate their insulin down accordingly.
Semaglutide 2.4mg	Same as above	Same as above	Initiate at 0.25 mg once weekly for 4 weeks, then increase the dose every 4 weeks (0.5 mg, 1 mg, then 1.7 mg) until maintenance dose of 2.4 mg weekly in reached. If patients do not tolerate the maintenance 2.4 mg dose, the dose can be temporarily decreased to 1.7 mg weekly for a maximum of 4 weeks and then increase to 2.4 mg weekly.	Same as above

Medication	Mechanism, adverse effects	Contraindications	Dosing	Monitoring/cautions
Off-label medications for weight loss (not FDA approved for obesity treatment)				
Metformin	Anti-diabetic agent, biguanide Decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. SEs: nausea, loose stools, abdominal discomfort.	Acute or chronic renal dysfunction (eGFR<30 mL/min).	Start 500mg daily IR (immediate release) or ER (extended release). Increase to max dose tolerated (up to 2500mg daily). IR is taken across divided doses. ER may be taken as once or divided doses.	Basic metabolic panel at initiation to assess GFR. About 10–20% of individuals will experience loose stool, GI upset. It will usually go away and will be decreased by having metformin at the end of a meal or by using the ER form.
Topiramate	Carbonic anhydrase inhibitor. SEs: paresthesias, dysgeusia, cognitive dysfunction (poor concentration, psychomotor slowing), suicidal ideation, kidney stones, and hypokalemia.	Women of child-bearing age (must be on contraception), glaucoma, MAOI use, and hyperthyroidism	25mg BID Can increase AM or PM dose as needed)	Use with caution in women of child-bearing age, as topiramate is teratogenic. Ensure they are on contraception.

Anti-obesity Medication (Trade Name) Year of FDA Approval	Mechanism of Action, Study Name, Study Duration: % TBWL Greater Than Placebo	Dose	Common Side Effects	Contraindications, Cautions, and Safety Concerns ✓ Contraindication • Warning, Safety Concern	Monitoring and Comments

Orlistat
 	
(Xenical™)
(Alli™) – OTC
 	
1999
	Lipase inhibitor
	
	XENDOS
	
	1 yr: 4.0%
	4 yr: 2.6%
		120 mg PO TID (before meals)
		
		OTC: 60 mg PO TID (before meals)
			• Steatorrhea
			• Fecal urgency
			• Incontinence
			• Flatulence
			• Oily spotting
			• Frequent bowel movements
			• Abdominal pain
			• Headache
				✓ Pregnancy and breastfeeding
				✓ Chronic malabsorption syndrome
				✓ Cholestasis
				✓ Oxalate nephrolithiasis
				• Rare severe liver injury
				• Cholelithiasis
				• Malabsorption of fat-soluble vitamins
				• Effects on other medications:
				  • Warfarin (enhance)
				  • Anti-epileptics (decrease)
				  • Levothyroxine (decrease)
				  • Cyclosporine (decrease)
					Monitor for:
					• Cholelithiasis
					• Nephrolithiasis
					
					- Recommend standard multivitamin (to include vitamins A, D, E, and K) at bedtime or 2 hours after orlistat dose
					- Eating >30% kcal from fat results in greater GI side effects
					- FDA-approved for children ≥12 years old
					- Administer levothyroxine and orlistat 4 hours apart

Lorcaserin (Belviq®) 2012	Serotonin (5HT2c) receptor agonist BLOSSOM BLOOM **1 yr: 3.0%-3.6%** **2 yr: 3.1%**	10 mg PO BID	• Headache • Nausea • Dizziness • Fatigue • Xerostomia • Dry eye • Constipation • Diarrhea • Back pain • Nasopharyngitis • Hyperprolactinemia	✓ Pregnancy and breastfeeding ✓ Serotonin syndrome or neuroleptic malignant syndrome • Safety data lacking in patients who have depression • Concomitant use of SSRI, SNRI, MAOI, bupropion, St. John's wort as may increase risk of developing serotonin syndrome • Uncontrolled mood disorder • Cognitive impairment • Avoid in patients with severe liver injury or renal insufficiency • Caution for patients with bradycardia, heart block, or heart failure • Unproven concern for potential cardiac valvulopathy • Leukopenia	**Monitor for:** • Symptoms of cardiac valve disease • Bradycardia • Serotonin syndrome • Neuroleptic malignant syndrome • Depression • Severe mood alteration, euphoria, dissociative state • Confusion/somnolence • Priapism • Leukopenia • Euphoria at high doses could predispose to abuse • Hypoglycemia in patients having T2DM treated with insulin and/or sulfonylureas

Anti-obesity Medication (Trade Name) Year of FDA Approval	Mechanism of Action, Study Name, Study Duration: % TBWL Greater Than Placebo	Dose	Common Side Effects	Contraindications, Cautions, and Safety Concerns ✓ Contraindication • Warning, Safety Concern	Monitoring and Comments
Phentermine/ Topiramate ER (Qsymia®) 2012	NE-releasing agent (phentermine) GABA receptor modulation (topiramate) EQUIP CONQUER SEQUEL **1 yr: 8.6%-9.3% on high dose; 6.6% on treatment dose** **2 yr: 8.7% on high dose; 7.5% on treatment dose**	**Starting dose:** 3.75/23 mg PO QD for 2 weeks **Recommended dose:** 7.5/46 mg PO QD **Escalation dose:** 11.25/69 mg PO QD **Maximum dose:** 15/92 mg PO QD	• Headache • Paresthesia • Insomnia • Decreased bicarbonate • Xerostomia • Constipation • Nasopharyngitis • Anxiety • Depression • Cognitive impairment (concentration and memory) • Dizziness • Nausea • Dysgeusia	✓ Pregnancy and breastfeeding (topiramate teratogenicity) ✓ Hyperthyroidism ✓ Acute angle-closure glaucoma ✓ Concomitant MAOI use (within 14 days) • Tachyarrhythmia • Decreased cognition • Seizure disorder • Anxiety and panic attacks • Nephrolithiasis • Hyperchloremic metabolic acidosis • Dose adjustment with hepatic or renal impairment • Concern for abuse potential • Combined use with alcohol or depressant drugs can worsen cognitive impairment	**Monitor for:** • Increased heart rate • Depressive symptomatology or worsening depression especially on maximum dose • Hypokalemia (especially with HCTZ or furosemide) • Acute myopia and/or ocular pain • Acute kidney stone formation • Hypoglycemia in patients having T2DM treated with insulin and/or sulfonylureas - Potential for lactic acidosis (hyperchloremic non-anion gap) in combination with metformin - MAOI (allow ≥14 days between discontinuation) - 15 mg/92 mg dose should not be discontinued abruptly (increased risk of seizure); taper over at least 1 week - Health care professional should check ßHCG before initiating, followed by monthly self-testing at home - Monitor electrolytes and creatinine before and during treatment - Can cause menstrual spotting in women taking birth control pills due to altered metabolism of estrogen and progestins

Anti-obesity Medication (Trade Name) Year of FDA Approval	Mechanism of Action, Study Name, Study Duration: % TBWL Greater Than Placebo	Dose	Common Side Effects	Contraindications, Cautions, and Safety Concerns ✓ Contraindication • Warning, Safety Concern	Monitoring and Comments
Naltrexone ER/ Bupropion ER (Contrave®) 2014	Opiate antagonist (naltrexone) Reuptake inhibitor of DA and NE (bupropion) COR-I COR-II COR-BMOD **1 yr: 4.2%-5.2%**	**Titrate dose:** **Week 1:** 1 tab (8/90 mg) PO QAM **Week 2:** 1 tab (8/90 mg) PO BID **Week 3:** 2 tabs (total 16/180 mg) PO QAM and 1 tab (8/90 mg) PO QHS **Week 4:** 2 tabs (total 16/180 mg) PO QHS	• Nausea • Headache • Insomnia • Vomiting • Constipation • Diarrhea • Dizziness • Anxiety • Xerostomia	✓ Pregnancy and breastfeeding ✓ Uncontrolled hypertension ✓ Seizure disorder ✓ Anorexia nervosa ✓ Bulimia nervosa ✓ Severe depression ✓ Drug or alcohol withdrawal ✓ Concomitant MAOI (within 14 days) ✓ Chronic opioid use • Cardiac arrhythmia • Dose adjustment for liver or kidney impairment • Narrow-angle glaucoma • Uncontrolled migraine disorder • Generalized anxiety disorder • Bipolar disorder • Safety data lacking in patients who have depression • Seizures (bupropion lowers seizure threshold)	**Monitor for:** • Increased heart rate and blood pressure • Worsening depression or suicidal ideation • Worsening of migraines • Liver injury (naltrexone) • Hypoglycemia in patients having T2DM treated with insulin and/or sulfonylureas • Seizures (bupropion lowers seizure threshold) - MAOI (allow ≥14 days between discontinuation) - Dose adjustment for patients with renal and hepatic impairment - Avoid taking medication with a high-fat meal - Can cause false positive urine test for amphetamine - Bupropion inhibits CYP2D6
Liraglutide 3 mg (Saxenda®) 2014	GLP-1 analog SCALE Obesity & Prediabetes **1 yr: 5.6%**	**Titrate dose weekly by 0.6 mg as tolerated by patient (side effects):** 0.6 mg SC QD→ 1.2 mg SC QD→ 1.8 mg SC QD→ 2.4 mg SC QD→ 3.0 mg SC QD	• Nausea • Vomiting • Diarrhea • Constipation • Headache • Dyspepsia • Increased heart rate	✓ Pregnancy and breastfeeding ✓ Personal or family history of medullary thyroid cancer or MEN2 ✓ Pancreatitis ✓ Acute gallbladder disease • Gastroparesis • Severe renal impairment can result from vomiting and dehydration • Use caution in patients with history of pancreatitis • Use caution in patients with cholelithiasis • Suicidal ideation and behavior • Injection site reactions	**Monitor for:** • Pancreatitis • Cholelithiasis and cholecystitis • Hypoglycemia in patients having T2DM treated with insulin and/or sulfonylureas • Increased heart rate • Dehydration from nausea/vomiting • Injection site reactions - Titrate dose based on tolerability (nausea and GI side effects)

PREFERRED WEIGHT-LOSS MEDICATIONS: INDIVIDUALIZATION OF THERAPY

KEY: PREFERRED DRUG | USE WITH CAUTION | AVOID

CLINICAL CHARACTERISTICS OR CO-EXISTING DISEASES		MEDICATIONS FOR CHRONIC WEIGHT MANAGEMENT				
		Orlistat	Lorcaserin	Phentermine/ topiramate ER	Naltrexone ER/ bupropion ER	Liraglutide 3 mg
Diabetes Prevention (metabolic syndrome, prediabetes)			Insufficient data for T2DM prevention		Insufficient data for T2DM prevention	
Type 2 Diabetes Mellitus						
Hypertension				Monitor heart rate	Monitor BP and heart rate Contraindicated in uncontrolled HTN	Monitor heart rate
Cardiovascular Disease	CAD			Monitor heart rate	Monitor heart rate, BP	Monitor heart rate
	Arrhythmia		Monitor for bradycardia	Monitor heart rate, rhythm	Monitor heart rate, rhythm, BP	Monitor heart rate, rhythm
	CHF	Insufficient data	Insufficient data	Insufficient data	Insufficient data	Insufficient data
Chronic Kidney Disease	Mild (50–79 mL/min)					
	Moderate (30–49 mL/min)			Do not exceed 7.5 mg/46 mg per day	Do not exceed 8 mg/90 mg bid	
	Severe (<30 mL/min)	Watch for oxalate nephropathy	Urinary clearance of drug metabolites	Urinary clearance of drug	Urinary clearance of drug	Avoid vomiting and volume depletion
Nephrolithiasis		Calcium oxalate stones		Calcium phosphate stones		

PREFERRED WEIGHT-LOSS MEDICATIONS: INDIVIDUALIZATION OF THERAPY

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CLINICAL CHARACTERISTICS OR CO-EXISTING DISEASES		MEDICATIONS FOR CHRONIC WEIGHT MANAGEMENT				
		Orlistat	Lorcaserin	Phentermine/ topiramate ER	Naltrexone ER/ bupropion ER	Liraglutide 3 mg
Hepatic Impairment	Mild-Moderate (Child-Pugh 5–9)	Watch for cholelithiasis	Hepatic metabolism of drug	Do not exceed 7.5 mg/46 mg per day	Do not exceed 8 mg/90 mg in AM	Watch for cholelithiasis
	Severe (Child-Pugh >9)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
Depression			Insufficient safety data Avoid combinations of serotonergic drugs	Avoid maximum dose: 15 mg/92 mg per day	Insufficient safety data Avoid in adolescents and young adults	
Anxiety				Avoid max dose: 15 mg/92 mg per day		
Psychoses		Insufficient data	Insufficient data	Insufficient data	Insufficient data	Insufficient data
Women of Reproductive Potential	Pregnancy	Use contraception and discontinue orlistat should pregnancy occur	Use contraception and discontinue lorcaserin should pregnancy occur	Use contraception and discontinue phentermine/topiramate should pregnancy occur (perform monthly pregnacy checks to identify early pregnancy)	Use contraception and discontinue naltrexone ER/bupropion ER should pregnancy occur	Use contraception and discontinue liraglutide 3 mg should pregnancy occur
	Breast-feeding	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
Age ≥65 years *		Limited data available	Insufficient data	Limited data available	Insufficient data	Limited data available

PREFERRED WEIGHT-LOSS MEDICATIONS: INDIVIDUALIZATION OF THERAPY

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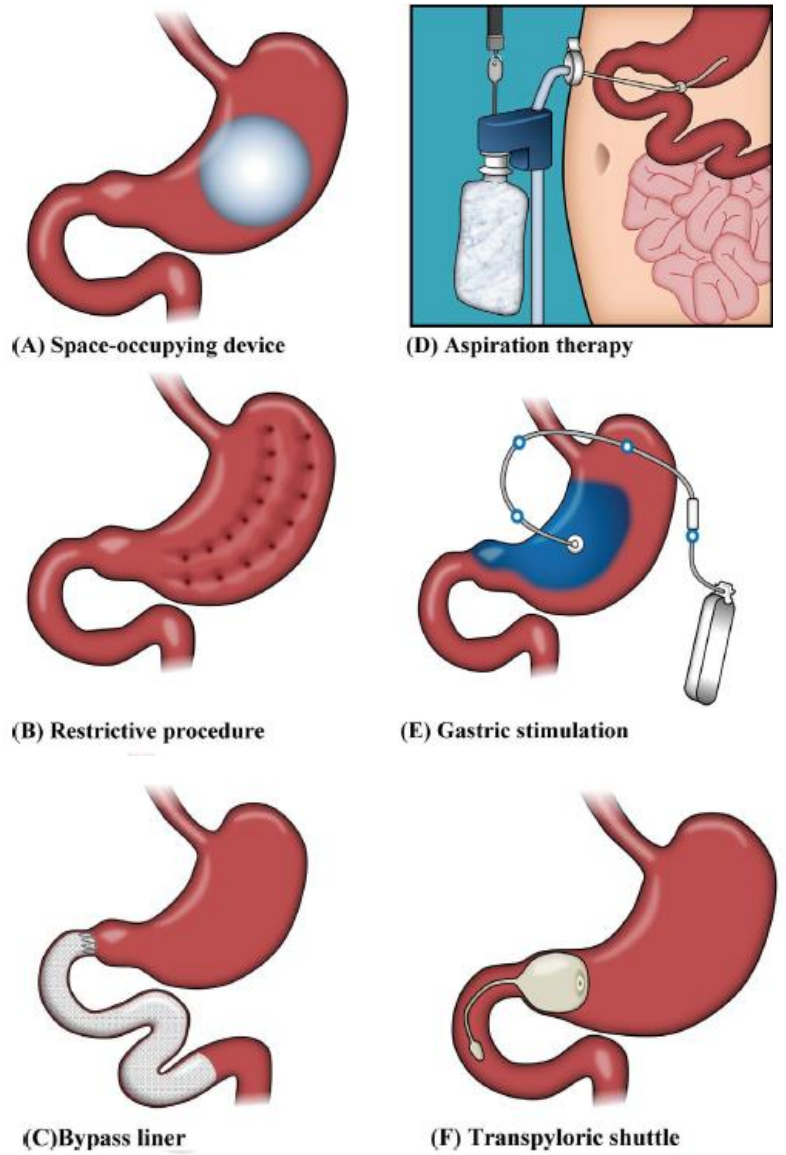
CLINICAL CHARACTERISTICS OR CO-EXISTING DISEASES		MEDICATIONS FOR CHRONIC WEIGHT MANAGEMENT				
		Orlistat	Lorcaserin	Phentermine/ topiramate ER	Naltrexone ER/ bupropion ER	Liraglutide 3 mg
Binge Eating Disorder			Insufficient data; however, possible benefit based on reduction in food cravings	Insufficient data; however, possible benefit based on studies with topiramate	Insufficient data, though possible benefit based on studies with bupropion Avoid in patients with purging or bulimia nervosa	Insufficient data
Glaucoma				Contraindicated, may trigger angle closure	May trigger angle closure	
Seizure Disorder				If discontinuing from max dose, taper slowly	Bupropion lowers seizure threshold	
Pancreatitis		Monitor for symptoms				Monitor for symptoms Avoid if prior or current disease
Opioid Use					Will antagonize opioids and opiates	
Alcoholism/ Addiction			Might have abuse potential due to euphoria at high doses	Insufficient data, though topiramate might exert therapeutic benefits	Avoid due to seizure risk and lower seizure threshold on bupropion	
Post-Bariatric Surgery		Insufficient data	Insufficient data	Limited data available	Insufficient data	Data available at 1.8 – 3.0 mg/day

Endoscopic Treatments

Procedure	Device
Space-Occupying Devices	
Intragastric balloons	ORBERA; Heliosphere; Semistationary Antral Balloon; Silimed Gastric Balloon; Endball; Easy Life; Adjustable Totally Implantable Intragastric Prosthesis; Ullorex; ReShape Duo; Obalon; Elipse; Ullorex
Other space-occupying therapies	TransPyloric Shuttle; Full Sense Device; SatiSphere
Restrictive Procedures	
Endoscopic sleeve gastroplasty	Apollo OverStitch
Primary obesity surgery endoluminal (POSE)	Incisionless Operating Platform
Endoscopic gastroplasty	EndoCinch; RESTORe
Transoral gastroplasty	TOGA System
Articulating circular endoscopic stapling procedure	ACE stapler
BYPASS LINERS	
Duodenal-jejunal bypass liner	EndoBarrier
Gastroduodenojejunal bypass liner	Gastroduodenojejunal bypass sleeve
Electrical Stimulation (RGES)	Transvenous cardiac pacing lead system
Aspiration Therapy	Aspire Assist
Other Therapies	Self-assembling magnets for endoscopy; Duodenal mucosal resurfacing; Botulinum toxin A

RGES, retrograde gastric electrical stimulation; ACE, articulating circular endoscopic.



Visual representations of select endoscopic treatments of obesity.

Space-occupying Devices; *Intragastric Balloons*

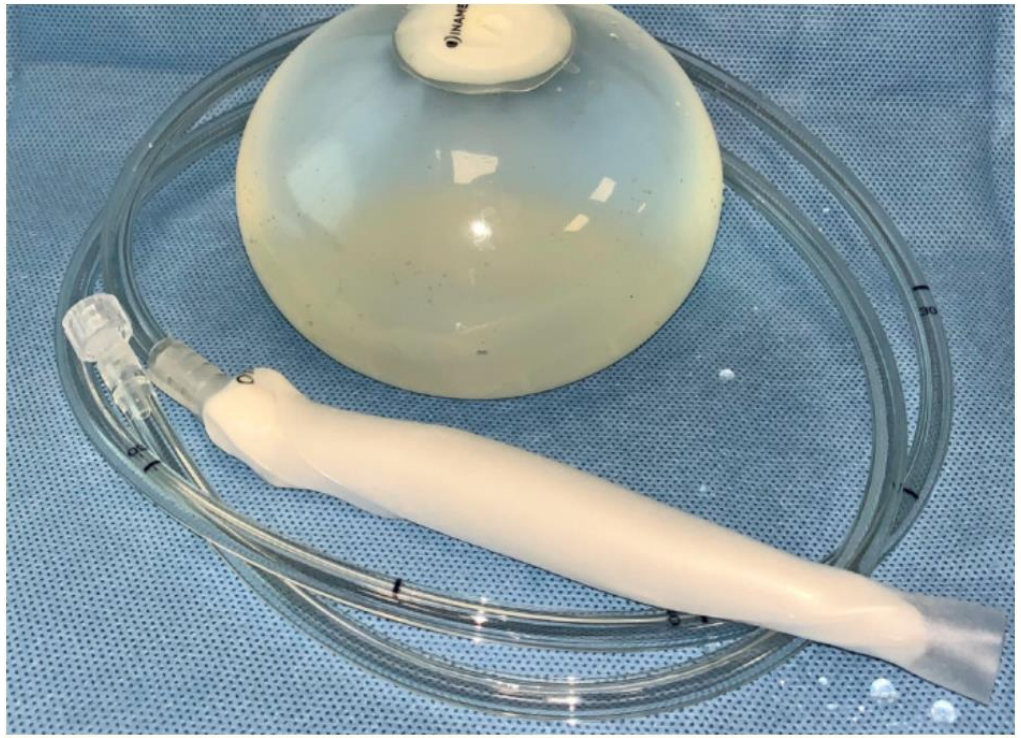
Broad spectrum of indications
• the overweight to the obese individual who does not fulfill the criteria for bariatric surgery, • the morbidly obese, who qualifies for bariatric surgery but has uncontrolled co-morbidities causing her/him to be of high-risk for anesthesia and surgery or denied anesthesia and/or surgery, or • its use as a bridge to bariatric surgery, and, finally, to • anyone who just needs to achieve limited weight reduction, either prior to surgery and for whatever reason or merely for aesthetic purposes.

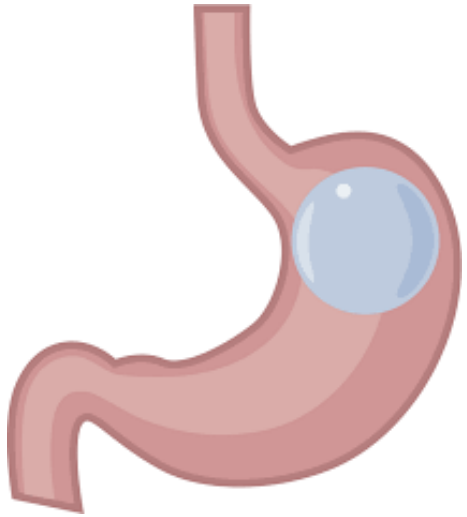
Orbera IGB (Apollo Endosurgery, Austin, TX, United States), formerly BioEnterics IGB (BIB, Inamed Corporation, Santa Barbara, CA, United States) was the first of the new generation of balloons.

The FDA-approved Orbera (2005) is a single spherical silicone-made balloon of about 13 cm in diameter, arriving commercially compressed and impacted at the end of a filling tube attached to a radiopaque self-sealing valve.

After an initial diagnostic endoscopy, the balloon placement assembly is inserted orally into the gastric fundus and a volume of 500 to 700 mL saline solution is used for balloon inflation.

According to manufacturer, the Orbera balloon could safety remain implanted for up to a maximum of 6 mo (a balloon which can remain in situ for 12 mo has also been available), because of the increasing risk of perforation and sudden emptying thereafter, which might allow the balloon to migrate towards the gut and possibly obstruct the bowel.





Over the years, it has become obvious that the excess weight of a liquid-filled balloon is the cause of an increased rate of nausea, vomiting and epigastric pain in the days immediately following balloon placement; thus, the air-filled Heliosphere balloon, known as the **Heliosphere bag** (Helioscopie Medical implants, Vienne, France) was developed to circumvent this disadvantage, and was introduced into clinical practice in 2004.

It is a single spherical high-volume-capacity, air-filled, polyurethane balloon weighing less than 30 g and is enclosed in a silicone envelope. It requires endoscopy for positioning and is loaded with a simple inflation system, allowing 900-1000 mL of air, within a median time of 12 min. The balloon is generally well-tolerated during the 6 mo implantation period.

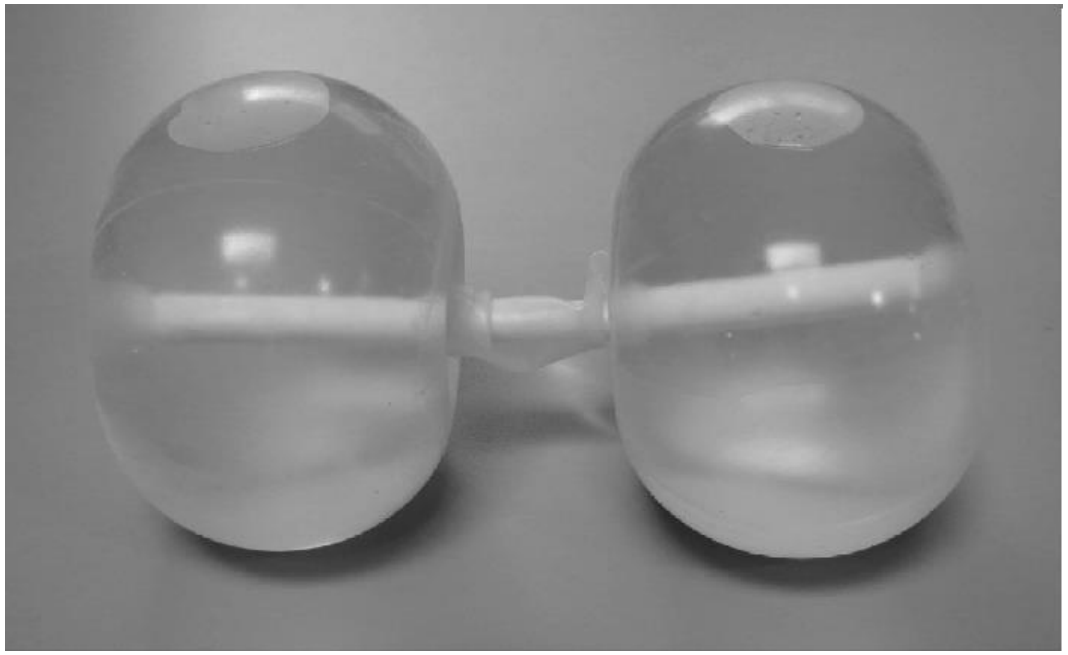
However, its use has raised several concerns about procedure-related complications due to technical difficulties in balloon passage through the cardia and the upper esophageal sphincter–large size, low pliability, high failure rates for positioning and spontaneous deflation. A severe warning for those candidates for gas-filled-Helioshere balloons is to totally refrain from scuba diving and travelling in unpressurized airplane cabins.



The **ReShape Duo** (ReShape Medical, San Clemente, CA), FDA-approved system consists of two closely attached, independently fluid filled balloons approved for 6-month implantation.

ReShape Duo integrated dual balloon system consists of two independently filled silicone spheres joined by a central, short, non-communicating flexible silicone shaft, approved for 6-month implantation.

The main idea behind this system design is to decrease the chance of balloon intestinal migration should one of the balloons accidentally deflate. Additionally, this flexible configuration, according to the manufacturers, allows the balloons to conform to the natural contours of the stomach.



The Spatz3 Adjustable Balloon (SpatzMedical, Great Neck, NY) has an attached catheter to prevent migration and an extractable injection tube for volume adjustment.

The adjustable nature theoretically enables the balloon volume to be titrated to tolerability and efficacy. its volume can be adjusted - increased or reduced - throughout the treatment period and not only initially at the time of inflation.

Additionally, it is the first balloon that can safely remain in the stomach for 360 d, thus facilitating sustained weight loss for one full year, as well as leaving more time for the patient to undergo feeding re-education and lifestyle modification.





The **Elipse balloon** (Elipse; Allurion Technologies, Wellesley, MA, United States) is a non-FDA-approved IGB, is the first intragastric device not requiring anaesthesia, or an invasive endoscopic procedure, either for placement or removal.

It thus represents an innovative option for weight loss, minimizing the costs and the complication risks of the endoscopic procedure for insertion or removal and hence offers an option to obese individuals feeling uncomfortable with endoscopy and/or at risk for anesthesia.

However, by omitting the pre-implantation endoscopic surveillance of the stomach, the possibility of recognizing mucosal lesions (erosions or ulcers) or anatomical abnormalities (hiatus hernia), which could, theoretically, lead to unexpected complications at the time of balloon remaining in the stomach, is lost.



allurion

Elipse™: The world's first procedureless gastric balloon for weight loss

The balloon, made from a thin polymer film without rigid parts, is enclosed, well compressed, inside a small, swallowable vegetarian capsule attached to a thin catheter 75 cm long and 1.3 mm in diameter, *via* a self-sealing valve, and is designed to deploy spontaneously in the stomach.

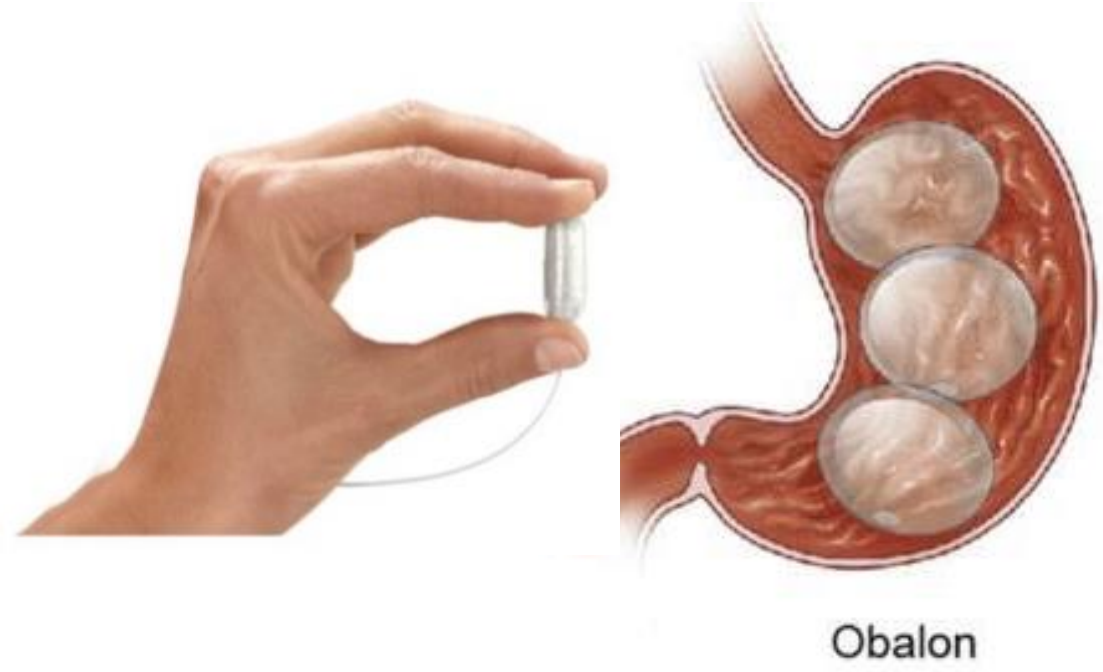
Once swallowed, its proper position in the stomach is confirmed through X-ray visualization of the balloon's radiopaque ring-shape marker; after which, the balloon is filled with 550 mL of fluid, consisting of distilled water with potassium sorbate preservative, through the catheter which is then removed by simply pulling it back. Placement is performed in a 20 min outpatient visit.

After a 4 mo period, the device is designed to spontaneously empty; the reabsorbable material, remaining closed inside the sealing balloon valve, completely degrades, leaving the device to self - deflate and then naturally pass - thanks to its construction from a thin film without rigid parts-through the gastrointestinal tract and be excreted.

The **Obalon®** (Obalon Therapeutics Inc, Carlsbad, CA, United States) is a new thin-walled, 250 mL gas-filled, swallowable IGB, designed to allow easy gastric volume titration, by using additional balloons.

It is an FDA-approved device, consisting of a series of three individual balloons, equating to a total volume of 750 mL that can be consequently swallowed one month apart, and is relatively well-tolerated by most patients.

Each balloon is compressed, folded, and fitted into a 6 g dissolvable gelatin capsule, which is swallowed under fluoroscopic visualization to verify that the entire capsule has entered the stomach. A thin, 2 Fr catheter is attached to the balloon and once the capsule reaches the stomach the other end of the catheter, which extends outside the mouth, is used for remote, automated balloon inflation to a maximal volume of 250 mL, using a canister filled with a proprietary air mixture that is mostly nitrogen based.





Intragastric Balloons Characteristics

		FDA/CE approved			CE approved	
Balloon type	**Orbera**	**ReShape Duo**	**Obalon**	**Heliosphere**	**Spatz**	**Elipse**
Manufacturer	Apollo Endosurgery	ReShape Medical	Obalon Therapeutics	Helioscopie Medical Implants	Spatz FGIA	Allurion Technologies
Filled with	Saline	Saline	Nitrogen gas	Air	Saline	Liquid
Capacity (mL)	400-700	450 × 2	250 × 3	900-1000	300-900	550
Number of balloons	1	2	Up to 3	1	1	1
Insertion	Endoscopy	Endoscopy	Swallowed	Endoscopy	Endoscopy	Swallowed
Removal	Endoscopy	Endoscopy	Endoscopy	Endoscopy	Endoscopy	Natural pass
Duration	6	6	6	6	12	4
Adjustable	No	No	No	No	Yes	No

Types of Intragastric Balloons and Their Respective Individual Outcomes.

Balloon type	Weight loss (%)	Implantation	Placement method	Composition	FDA approval
Orbera®	Pooled meta-analysis TWL: 13.6[37]	6 months	Endoscopic	Silicone Sphere (saline)	Yes; BMI 30–40 kg/m^2; Age 22–60
ReShape™	EWL: 31.8 ± 21.3[38]	6 months	Endoscopic	Silicone Sphere (saline)	Yes; BMI 30–40 kg/m^2; Age 22+
Spatz®	EWL: 26.4[39]	12 months	Endoscopic	Silicone Sphere	No
Heliosphere® Bag	EWL: 33.2[40]	6 months	Endoscopic	Polyurethane and silicone (Air)	No
MedSil®	EWL: 19.3 ± 12.7[41]	6 months	Endoscopic	Silicone (Saline)	No
LexBal	EWL: 26.8 ± 12.3[42]	6 months	Endoscopic	Silicone (Saline)	No
End-Ball®	EWL: 31.1[43]	6 months	Endoscopic	Polyurethane (Air/Saline)	No
Silimed	EWL: 46.5 ± 36.7[44]	6 months	Endoscopic	Silicone(Saline)	No
Medicone®	TWL: 18.4 ± 2.9[45]	6 months	Endoscopic	Silicone (Saline)	No
Semisationary and balloon	EWL: 8.35 ± 6.4[46]	6 months	Endoscopic	Silicone (Saline)	No

BMI, body mass index; EWL, excess weight loss; TWL, total weight loss.

Space-occupying Devices; *Transpyloric Shuttle*

The device is designed to self-position across the pylorus during peristalsis, resulting in intermittent obstruction and resulting in delayed gastric emptying, which induces early and prolonged satiety.

The TPS is composed of silicone and consists of a large spherical bulb connected to a smaller cylindrical bulb by a flexible catheter.

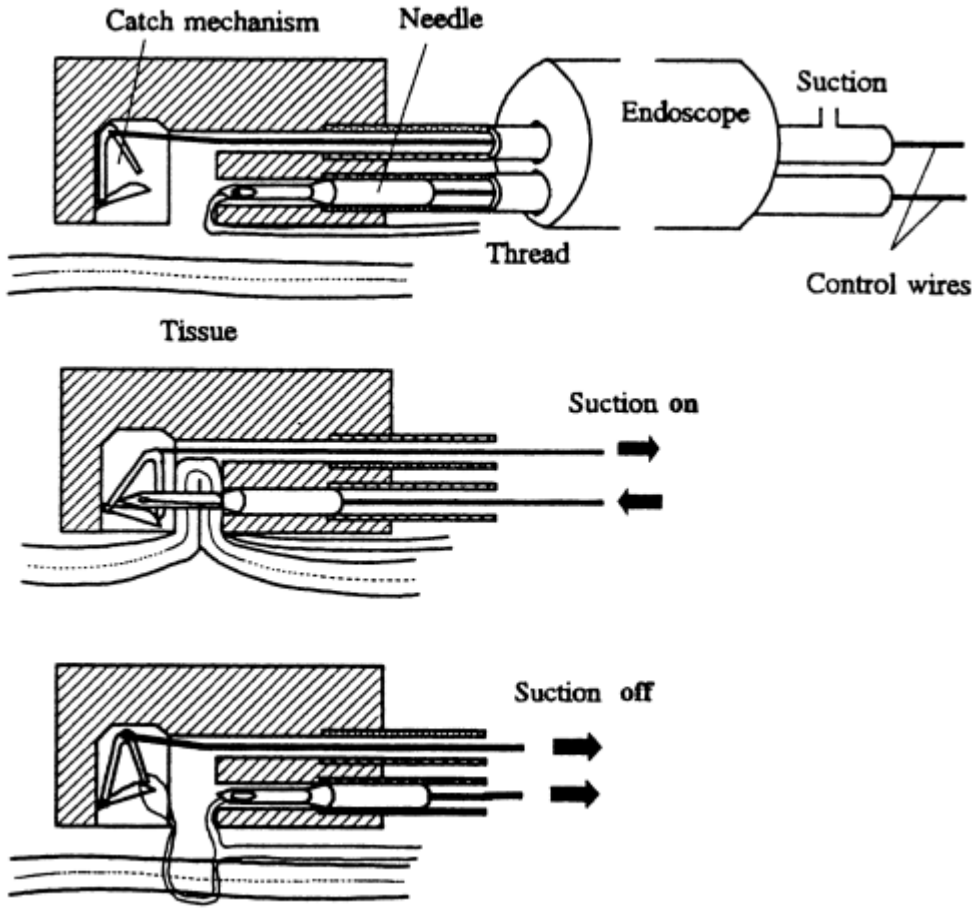
After deployment into the stomach, the TPS moves freely without any physical attachment or invasive anchoring to the tissues.



Gastric Restrictive Methods: *Transoral Gastroplasty*

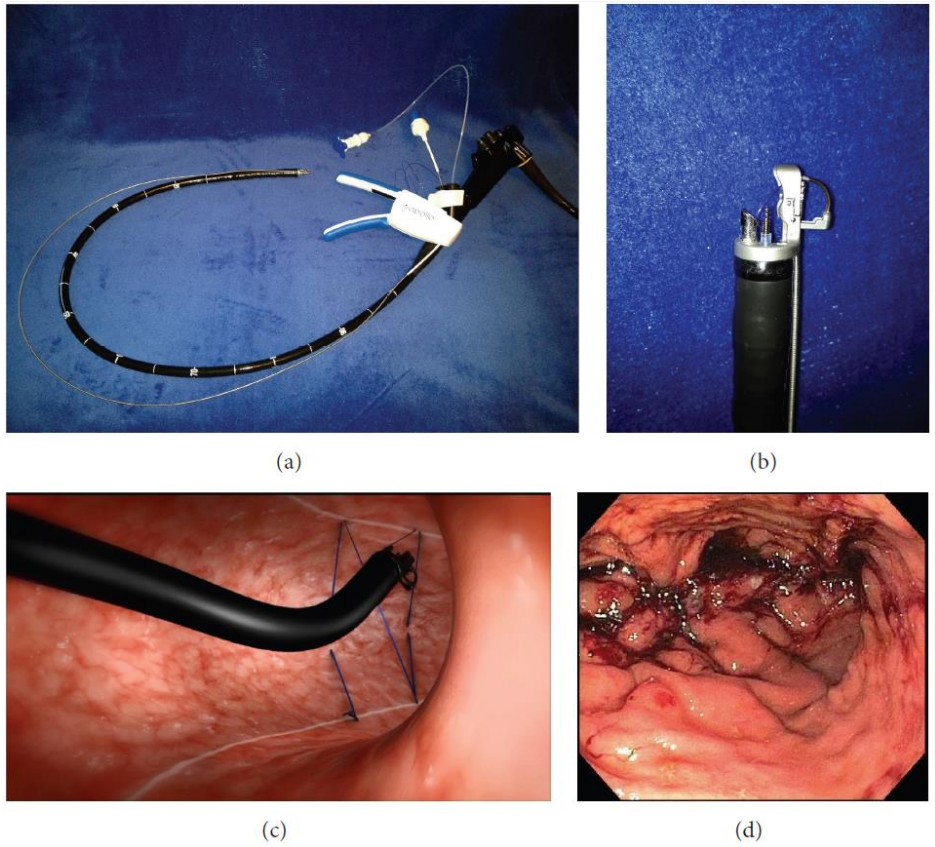
The Endocinch (C.R. Bard, Inc., Murray Hill, NJ) device has been used for endoluminal vertical gastroplasty. This technique involves the use of a suturing device contained within a capsule that is attached to the end of a diagnostic gastroscope.

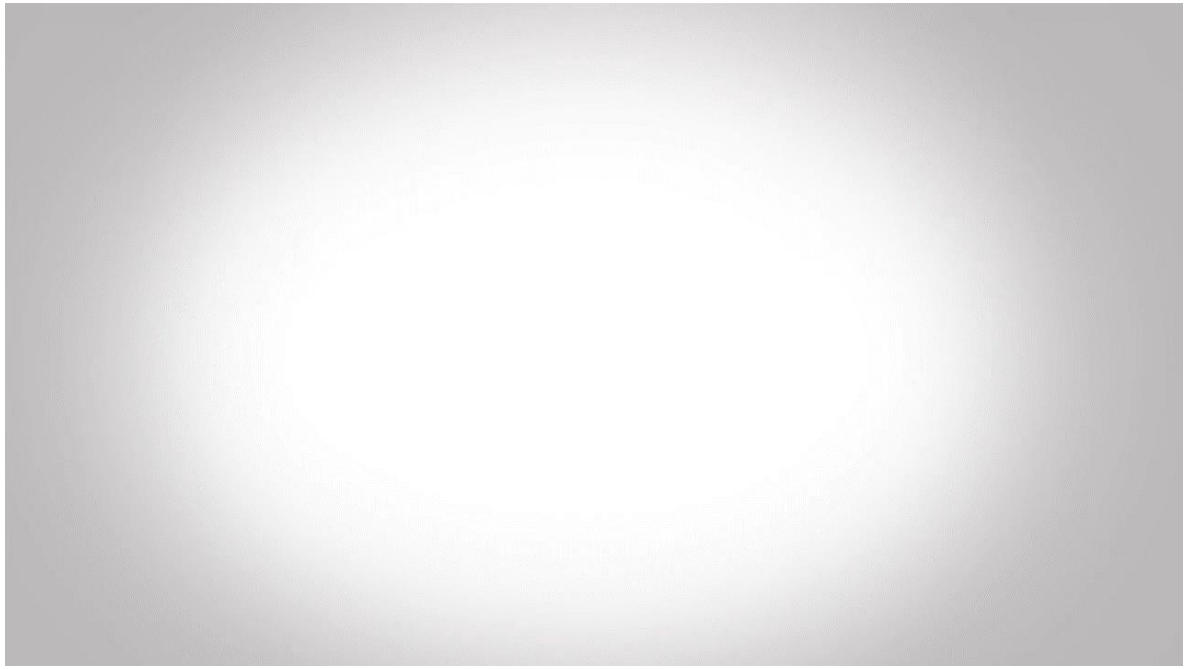
After suctioning tissue into the capsule, a preloaded suture is advanced through the captured tissue. Sutures are deployed in a continuous and cross-linked fashion from the proximal fundus to the distal body of the stomach to create a narrow tube-like passage.



Gastric Restrictive Methods: *Transoral Gastroplasty*

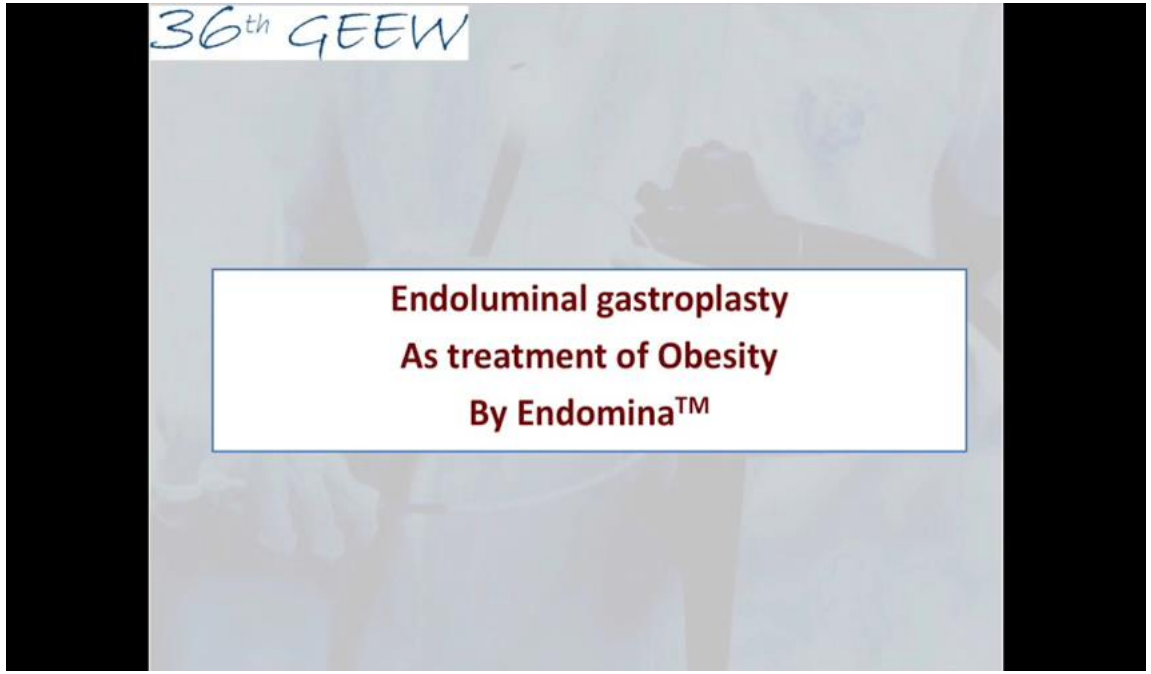
Overstitch; Apollo Endosurgery, Austin, TX





Gastric Restrictive Methods: *Endomina Suturing System*

The Endomina triangulation platform (Endo Tools Therapeutics SA – ETT, Gosselies, Belgium) is a novel single-use suturing device that is assembled in the stomach using an endoscope and allows physicians to perform large plications with transmural sutures and serosa to serosa apposition.



Malabsorptive Endoscopic Procedures: *Duodenal-Jejunal Bypass Liner (DJBL)*

Duodenal-jejunal bypass liner (DJBL) was designed as a nonsurgical approach that enabled components of the Roux-en-Y procedure, namely, exclusion of the duodenum and proximal jejunum and exposure of the distal jejunum to undigested nutrients, reducing absorption and preventing the action of biliary and pancreatic secretions.

The **EndoBarrier** gastrointestinal liner (GI Dynamics Inc., Lexington, MA, USA) is a flexible, nutrient-impermeable 60 cm sleeve that is anchored in the duodenal bulb and extended into the proximal jejunum deployed using dynamic fluoroscopy.

The anchor is a self-expanding stent that enables fixation within the duodenal bulb. The sleeve is maintained from 3 months to 12 months after fixation.



Malabsorptive Endoscopic Procedures: *Duodenal Mucosal Resurfacing*

Duodenal mucosal resurfacing (DMR) is a novel, minimally invasive endoscopic procedure that involves circumferential hydrothermal ablation of the duodenal mucosa using the Revita DMR system (Fractyl Laboratories, Inc., Lexington, KY, USA). DMR involves catheter-based circumferential mucosal lifting followed by hydrothermal ablation of duodenal mucosa.

DMR is not associated with significant weight loss, but it has been shown to improve glycemic control in people with type 2 diabetes mellitus irrespective of BMI changes.

It is hypothesized that DMR results in the destruction of diseased duodenal mucosa and subsequent regeneration after ablation.



Other techniques: *Aspiration Therapy*

Aspiration therapy is a relatively new technique that involves endoscopic placement of a gastrostomy tube (A-tube) and the Aspire Assist siphon assembly (Aspire Bariatrics, King of Prussia, PA) to aspirate gastric contents 20 minutes after meal consumption.



Regulating Gastric Emptying: *Intragastric Botulinum Toxin Injections*

Botulinum toxin A (BTA) acts to inhibit acetylcholine release at the neuromuscular junction, hypothetically delaying gastric emptying and inhibiting ghrelin secretion, a potent hormone released from the gastric fundus that stimulates hunger .



Gastrointestinal Endoscopy
Volume 81, Issue 5, May 2015, Pages 1141-1149.e7



Systematic review and meta-analysis

Effect of intragastric injection of botulinum toxin A for the treatment of obesity: a meta-analysis and meta-regression

Metanalysis: 8 studies and 115 patients

Multiple injections (>10) in fundus,
body and antrum
No need to dose > 500 unit

Conclusion: weight reduction was achieved with wide areas of injections (fundus or body rather than antrum alone) and with multiple injections (10 injections) rather than higher doses (>500 IU) of BTA

Conclusion

In this analysis, intragastric injection of botulinum toxin A is effective for the treatment of obesity.

Is Intragastric Botulinum Toxin A Injection Effective in Obesity Treatment?

Hindawi

October 2020 · Surgery Research and Practice 2020(1393):1-4

56 patients
Mean weight: 82 ± 14 ⇨ 76 ± 12
BMI decreased 3units

Aims: The objective of this prospective study was to evaluate the efficacy of intragastric botulinum toxin A (BTX-A) injection for the treatment of obesity. Materials and methods: The study was performed between January and August 2019. This is a prospective study. After 6-12 hours of fasting, the patients were submitted to upper GI endoscopy under sedation for the injection of BTX-A. A total of 250 U of BTA-X was diluted with 10 ml of 0.9% saline. Injections were administered into the gastric antrum, each containing 1 ml of prepared solution (25 U BX-A + 1 ml saline). Continuous data were compared using a two-sample t-test. Statistical significance was determined as P ≤ 0.05. All statistical analysis was performed using SPSS for Windows 22.1 software (SPSS, Chicago, IL, USA). Results: A total of 56 patients were studied. Mean weight before gastric Botox was 85.25 ± 14.02, and mean weight after gastric Botox was 76.98 ± 12.68. Mean weight loss was approximately 9 kg in studied patients. BMI decreased about 3 units. The mean time for maximum weight loss was 60.39 ± 37.43 days. A total of 49 patients (87.5%) had reported decrease in appetite and early satiety. About 53.6% of patients were satisfied. No complications resulting from the endoscopic procedure were observed in this series. Conclusions: Intragastric BTX-A injection can be beneficial in weight loss. It is a minimally invasive, cost-effective

Weight loss after intragastric botulinum toxin injection in different weight individuals

Fatih Can Karaca

J Health Sci Med 2020; 3(3): 295-300

102 patients ; A total dose of 400 U

a mean total weight loss ratio ranging between 4.76-19.47%

Mean total body weight loss percentages were significantly higher in Class II and III obese subjects compared to the normal- and over-weight and Class I obese individuals.

Conclusion: Intragastric injection of botulinum toxin A administration with a dose of 400 U is a convenient method for weight loss for the individuals of different body mass indices.

	Group 1 (n=44)	Group 2 (n=36)	Group 3 (n=16)	Group 4 (n=6)
BMI	Normal weight <30 kg/m^2	Class I obesity 30-34.9 kg/m^2	Class II obesity 35-39.9 kg/m^2	Class III obesity ≥40 kg/m^2
Total weight loss (%)				
1st month	5.20±0.40 (1.88-7.74)	6.23±0.34 (3.83-10.16)	6.83±0.84 (3.33-9.11)	6.66±0.89 (4.87-7.67)
2nd month$^{\Phi}$	8.25±0.85 (4.83-12.07)	7.89±0.95 (4.76-11.34)	10.76±1.25 (8.37-12.60)	12.74±1.21 (10.16-14.33)
3rd month$^{\Delta}$	10.24±0.85 (7.56-16.51)	9.81±2.02 (4.76-13.71)	14.27±5.19 (9.07-19.47)	17.48±0.59 (12.88-19.07)

Endoscopic Intragastric Injection of Botulinum Toxin A in Obese Patients Accelerates Weight Loss after Bariatric Surgery: Follow-Up of a Randomised Controlled Trial (IntraTox Study)

Francisco José Sánchez-Torralvo [1,2,3,*], Luis Vázquez-Pedreño [4], Montserrat Gonzalo-Marín [1,3,5], María José Tapia [1,3,5], Fuensanta Lima [1,3], Eduardo García-Fuentes [3,6,7], Pilar García [4], Javier Moreno-Ruiz [8], Alberto Rodríguez-Cañete [8], Sergio Valdés [1,2,3,5,†] and Gabriel Olveira [1,2,3,5,†]

J. Clin. Med. **2022**, *11*, 2126.

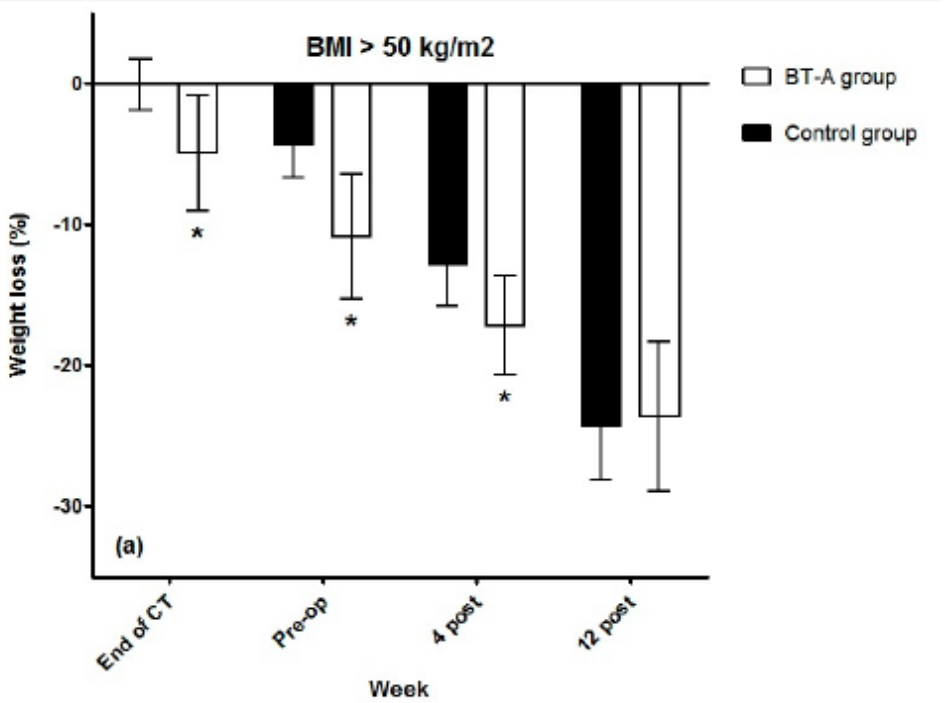
46 patients on bariatric surgery waiting lists

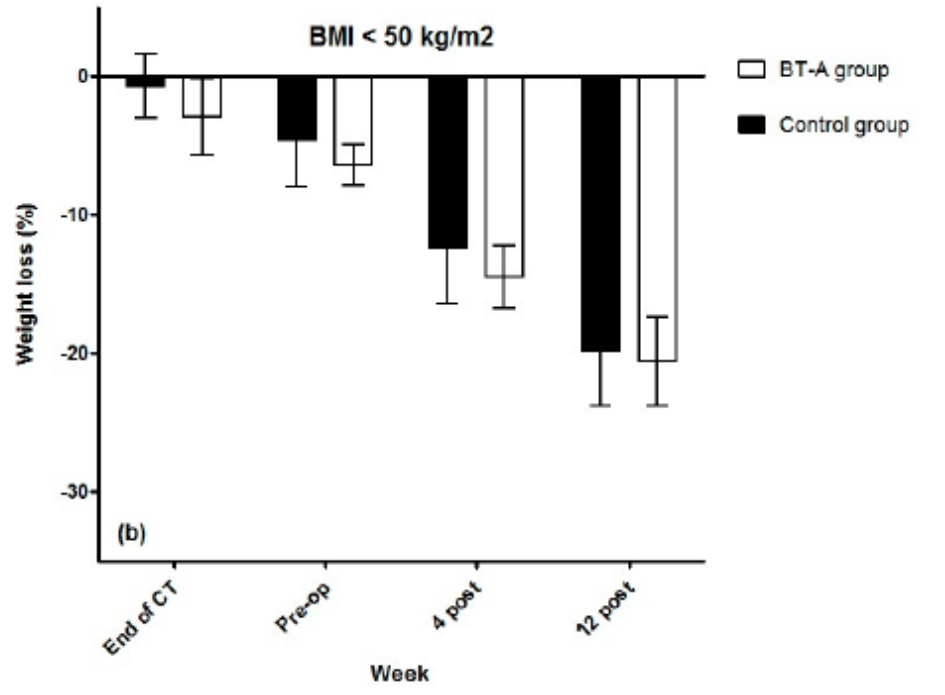
The effect of BT-A on weight loss in the pre- and postoperative period

weight loss percentage on the day of surgery: - 4.5 ± 3.9, in control group vs -7.6 ± 4.2, for the treatment group

weight loss percentage one month after surgery: - 12.7± 4.7, in control group vs -15.2 ± 4.6, for the treatment group

Conclusions: intragastric injection of BT-A is effective to achieve significant weight loss, especially in extreme obesity (BMI >50) . Its use before bariatric surgery enhances perioperative weight loss and maybe lower intraoperative complications.





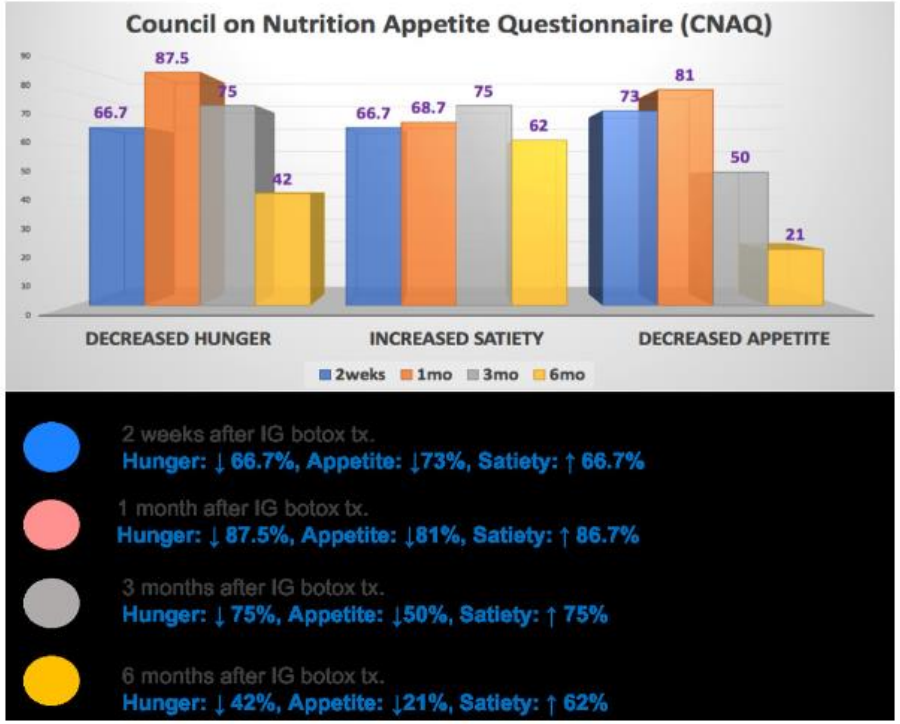
INTRAGASTRIC BOTULINUM TOXIN INJECTION ESPECIALLY ON FUNDUS IS THE POSSIBLE KEY TO INDUCE EARLY SATIETY AND SUCCESSFUL WEIGHT LOSS BY CHANGE OF GHRELIN AND INCRETINS

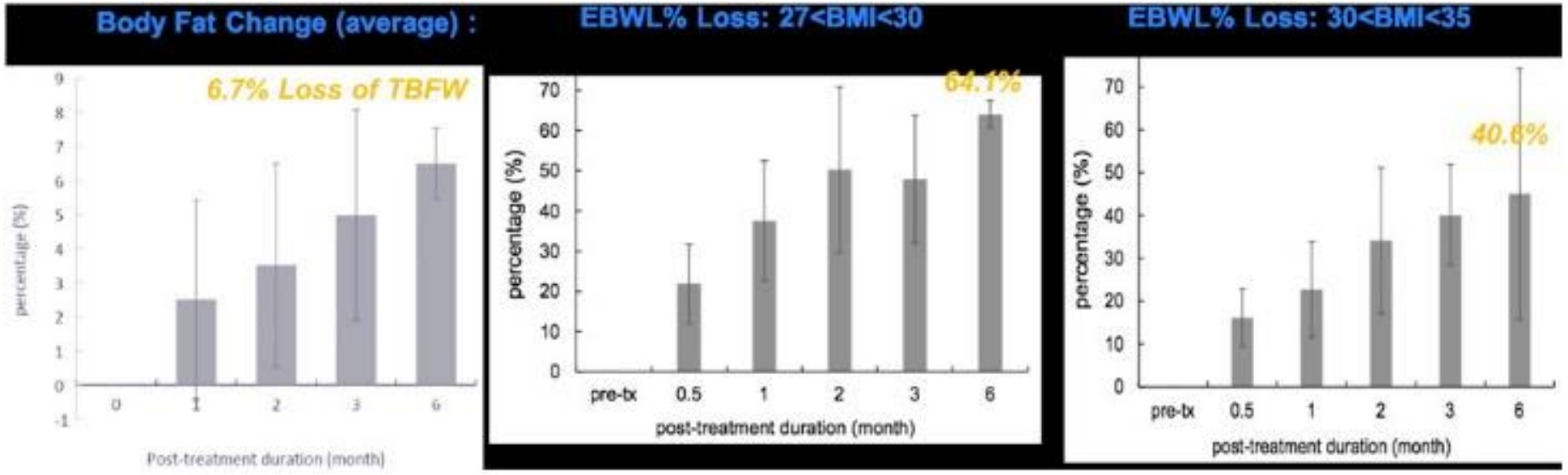
Chia-Chia Liu*

126 patients whose BMI were between 27-35

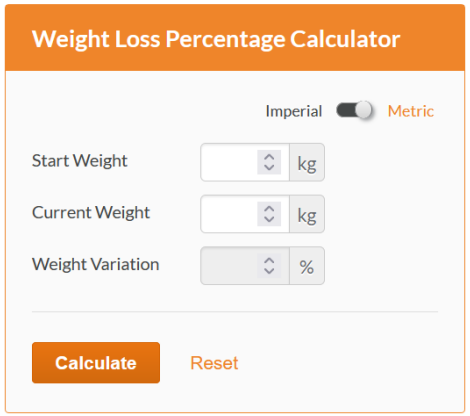
300U-400U IG botox over whole stomach (half of the total injection units, 150-200U, on gastric fundus; the rest of the doses on the gastric body, anterior wall, posterior wall and antrum).

Conclusion: IG botox injection especially on fundus is pivotal. Induced change of ghrelin and other incretins and delayed gastric emptying time were keys to decrease eating amount and reach early satiety. Patients had more controllable wills to cooperate with correct diet. IG Botox is a safe and a successful complementary tool of bariatric endoscopy.





Excess body weight loss (EBWL)



Evaluation of endoscopic ultrasound-guided gastric botulinum toxin injections in the treatment of obesity

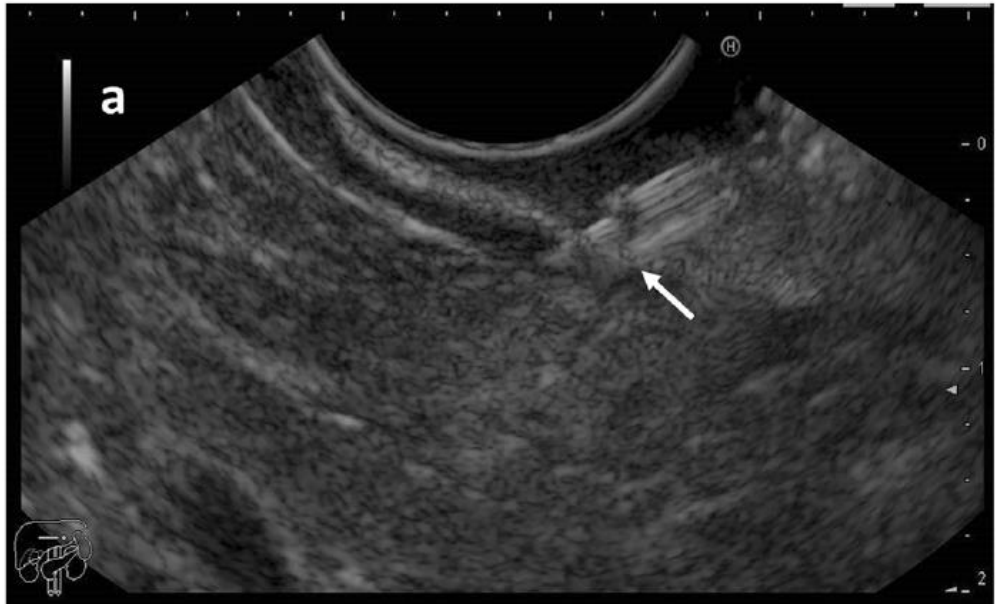
Asmaa Gameel[1], Monir Bahgat[1], Seham Seif[1], Maha Habeeb[1], Mohammed Abd El-Ghany[2] and Ahmed Youssef Altonbary[1*]

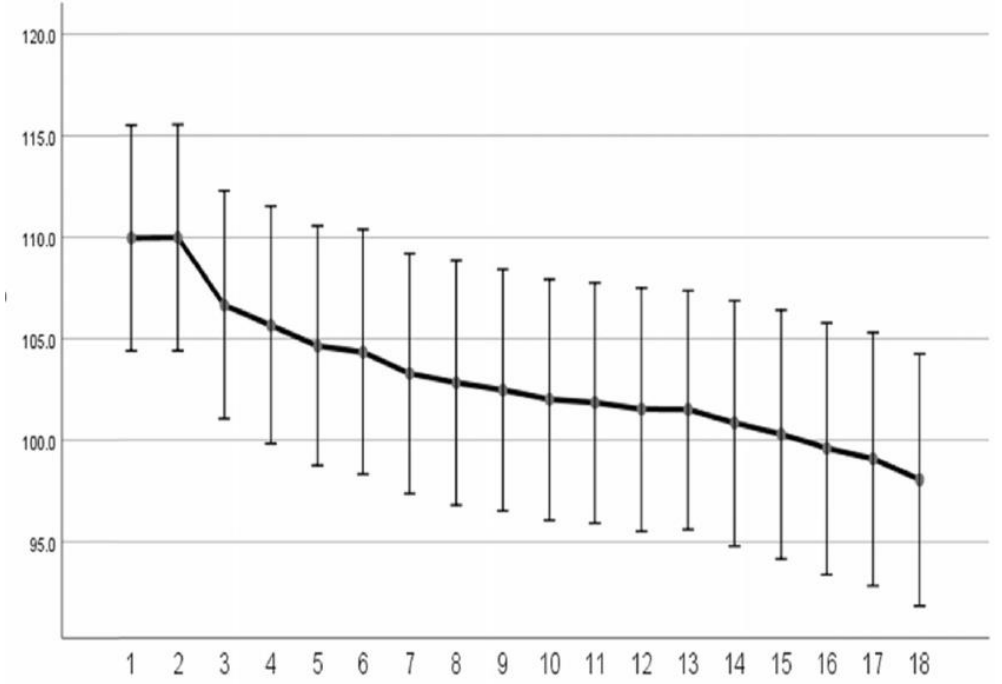
EUS guidance BTA injection into the **antral subserosal layer and muscularis propria**

25 patients (2 males and 23 females)

Mean body weight continued to decrease during the study period from a baseline value of 110 to 98 kg with significant reduction of mean BMI from baseline value of 41.2 to 36.7 at 16 weeks after BTA injection ($p < 0.001$).

Conclusion: EUS-guided BTA injection into the antral subserosa and muscularis propria could be an effective technique for weight reduction, or as a bridge for surgery, which can be done safely with minimal complications.





Device	Weight loss (%)	FDA approval	Complications[14,47,48,49]
TransPyloric Shuttle®	TWL: N/A EWL: 31.3–50%	Yes; BMI 30–40 kg/m^2	Stomach pain, nausea, vomiting, and dyspepsia
Incisionless Anastomosis System	TWL: % EWL: 49.4%	No	N/A
AspireAssist®	TWL: N/A EWL: 49.0%	Yes; BMI 30–40 kg/m^2	Indigestion, nausea, vomiting, constipation, and diarrhea
Botulinum Toxin A	TWL: N/A EWL: N/A	No	Nausea and vomiting
Endoscopic Sleeve Gastroplasty (ESG)	TWL: 20.9 % EWL: 60.4 %	No	Nausea, bleeding, abdominal infection, and stomach leak
Longitudinal Compression Sutures with ESG	TWL: N/A EWL: N/A	No	N/A
EndoBarrier	TWL: N/A EWL: 12.6%	Yes; BMI 30-40 kg/m^2	Bleeding, device migration, cholestasis, and pancreatitis
Endoluminal Bypass	TWL: N/A EWL: 54%	No	Bleeding, stomal and marginal ulcers, stomal stenosis, leaks, and fistulas or pancreatobiliary disorder
Duodenal Mucosal Resurfacing	TWL: N/A EWL: N/A	No	Abdominal pain


THANK
YOU