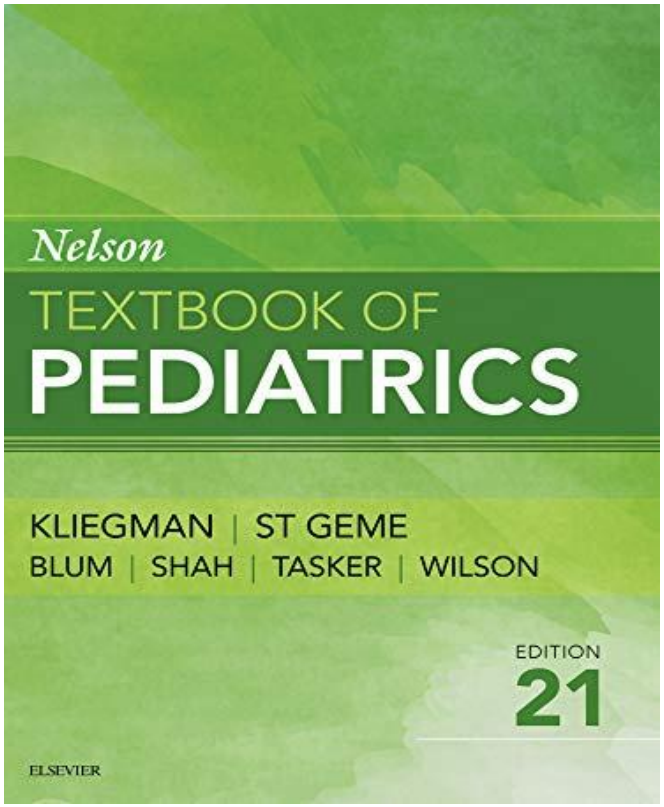
Pediatric Obesity Pharmacotherapy

Dr. M Shahrokhi, Pharmacotherapist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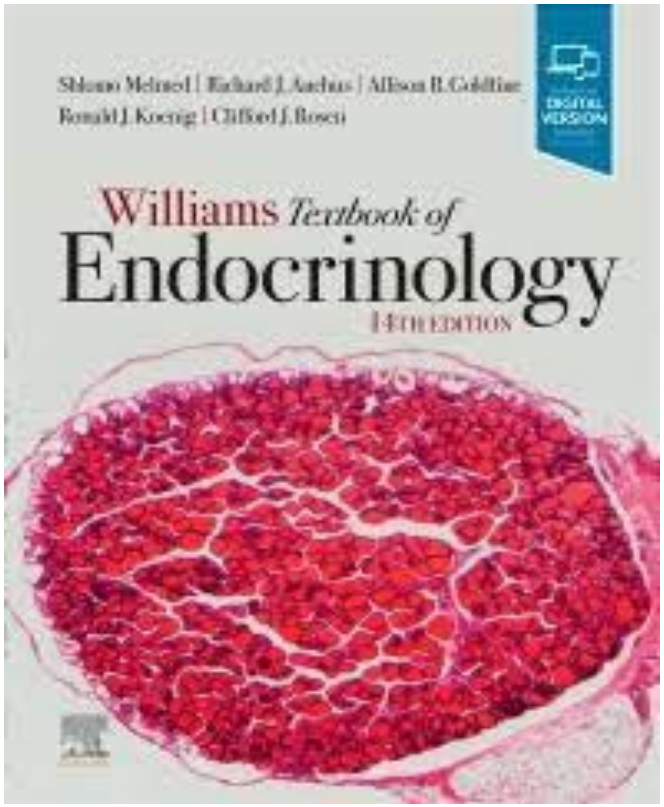
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Pediatric Obesity—Assessment, Treatment, and Prevention: An Endocrine Society Clinical Practice Guideline

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Australian Government
National Health and Medical Research Council
Department of Health

CLINICAL PRACTICE GUIDELINES FOR THE MANAGEMENT OF OVERWEIGHT AND OBESITY IN ADULTS, ADOLESCENTS AND CHILDREN IN AUSTRALIA

Produce weight gain
Antidepressants: monoamine oxidase inhibitors, tricyclic antidepressants (nortriptyline, amitriptyline, doxepin), paroxetine, citalopram, escitalopram, imipramine, mirtazapine
Antipsychotics: thioridazine, olanzapine, risperidone, clozapine, quetiapine
Diabetes medications: eg, insulin, sulfonylureas, thiazolidinediones, meglitinides
Glucocorticoids: eg, prednisone
Hormonal agents: especially progestins, eg, medroxyprogesterone
Anticonvulsants: eg, divalproex
Neurologic and mood-stabilizing agents: eg, lithium, carbamazepine, gabapentin, valproate
Antihistamines: cyproheptadine
Alpha blockers: especially terazosin
Beta blockers: especially propranolol

Produce weight loss
Anticonvulsants: topiramate, zonisamide, lamotrigine
Antidepressants: bupropion, venlafaxine, desvenlafaxine
Antipsychotics: ziprasidone

Physicians should be discouraged from prescribing weight loss medications off-label to those 16 years old because of:

- 1) The lack of FDA approval for use
- 2) The limited number of well-controlled safety and efficacy studies in obese children and adolescents,
- 3) The limited efficacy demonstrated in adults for most agents
- 4) The need to weigh the relative risk of drug-induced adverse events in children and adolescents against a medication's long-term theoretical potential for reducing obesity-related morbidity and mortality.
- Despite these concerns, the negative health impact of pediatric obesity may justify long-term medication.

- Pharmacotherapy should be offered to patients with obesity, when potential **benefits outweigh the risks**, for the chronic treatment of their disease.

- **Short-term treatment** (3 to 6 months) using weight-loss medications has not been demonstrated to produce longer-term health benefits and cannot be generally recommended based on scientific evidence.

- Weight loss should exceed 2kg during the first month of drug therapy (1 pound per week), fall more than 4 to 5 percent below baseline between three to six months, and remain at this level to be considered effective
- A weight loss of 5 to 10% can substantially reduce the development of diabetes in those with prediabetes and reduce blood pressure and risk factors for cardiovascular disease in patients with cardiovascular risk factors
  - W.L, even with pharmacologic assistance, plateaus at around 6 to 9 months.
  - Increasing the duration of treatment does not lead to greater w.l, just weight maintenance

Pharmacotherapy for overweight and obesity

- Pharmacotherapy for overweight and obesity should be used only as an **adjunct** to lifestyle therapy and not alone

- Weight regain may be greater after stopping pharmacotherapy when behavior modification is not included

- Decrease energy intake or act centrally : **Anorexiants**
- Affect the availability of nutrients through intestinal or renal tubular reabsorption
- Affect Metabolism
- The only U.S. Food and Drug Administration (FDA)–approved medication for obesity in children <16 yr old is *orlistat*, *which decreases* absorption of fat, resulting in modest weight loss.

- Liraglutide (daily injection)
- Orlistat
- Combination Phentermine-ER Topiramate
- Combination Naltrexone- Bupropion
- Phentermine

- Metformin does not produce enough weight loss (5 percent) to qualify as a "weight loss drug“ it is a good choice for overweight individuals at high risk for diabetes

Liraglutide

- Liraglutide has beneficial effects on glycemia, in addition to demonstrated efficacy for weight loss.

- It may be used in patients with or without diabetes, but is the preferred drug in patients with type 2 diabetes, and particularly in those with cardiovascular disease owing to its demonstrated reduction of cardiovascular events in this population

- However, gastrointestinal side effects (nausea, vomiting), the need for a daily injection, and insurance coverage/cost may limit the use of this drug

- Liraglutide is GLP-1 receptor agonist

  - T2DM at doses up to 1.8 mg/day
  - Weight loss at a higher dosage of 3.0 mg/day

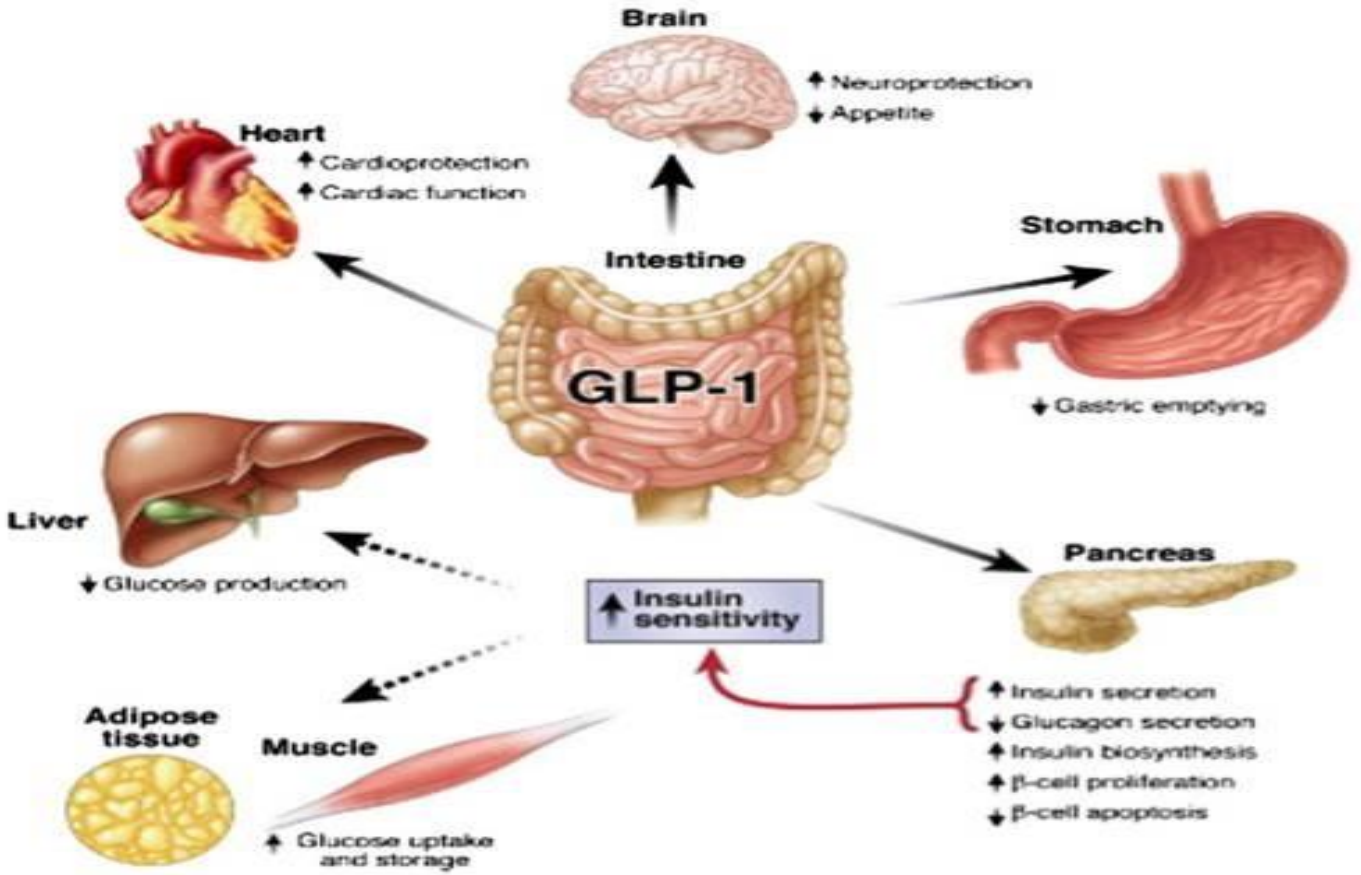
- SubQ: Initial: 0.6 mg once daily for one week; increase by 0.6 mg daily at weekly intervals

- Stimulate glucose-dependent insulin secretion
- Inhibits glucagon release and gastric emptying

- used in combination with metformin (and/or another oral agent) for patients with type 2 diabetes who fail initial therapy with one or two oral agents, particularly when weight loss is a primary consideration

- Reduce major cardiovascular disease events in adults with type 2 diabetes and preexisting cardiovascular disease.


VICTOZA


Brain
Neuroprotection
Appetite
Heart
Cardioprotection
Cardiac function
Intestine
GLP-1
Stomach
Gastric emptying
Liver
Glucose production
Insulin sensitivity
Pancreas
Insulin secretion
Glucagon secretion
Insulin biosynthesis
β-cell proliferation
β-cell apoptosis
Adipose tissue
Muscle
Glucose uptake and storage

Adverse events and contraindication

- **Gastrointestinal side effects**, including nausea and vomiting, diarrhea, low blood sugar, and anorexia

- **Contraindicated** during pregnancy and in patients with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia 2A or 2B.
- Patients taking liraglutide concurrent with insulin or an insulin secretagogue (eg, a sulfonylurea), blood glucose should be monitored, and a dose reduction in the insulin or the sulfonylurea may be necessary to avoid hypoglycemia

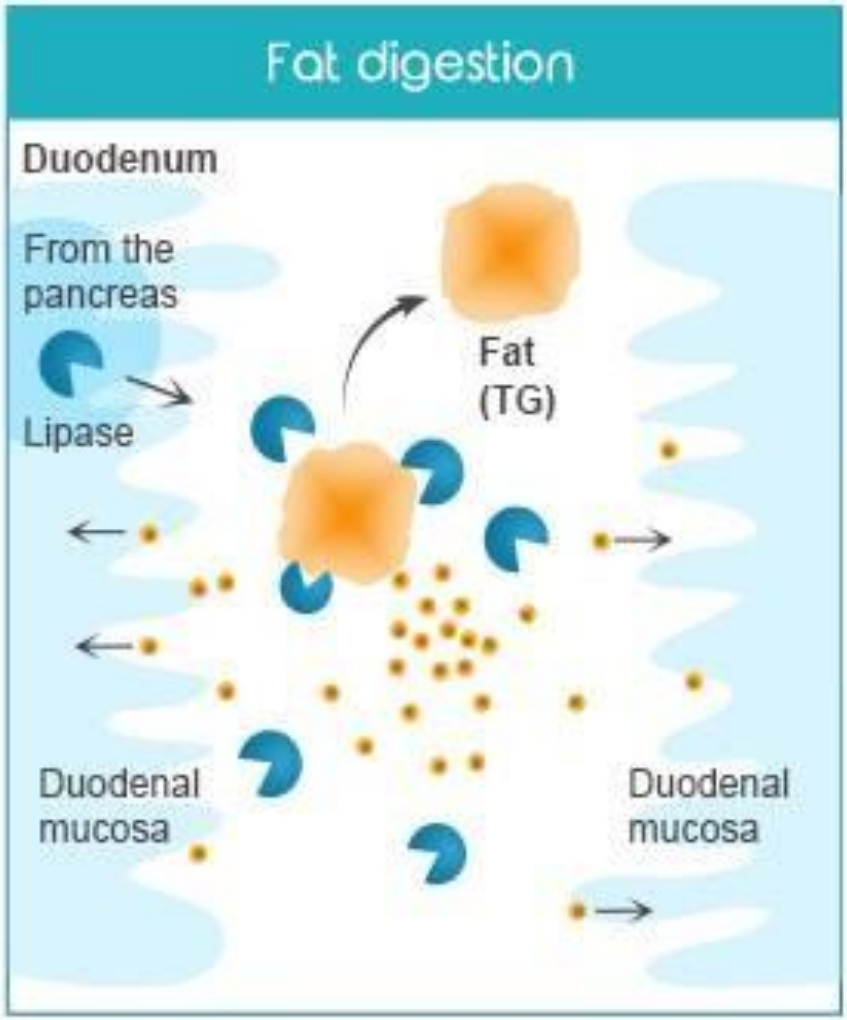
Orlistat

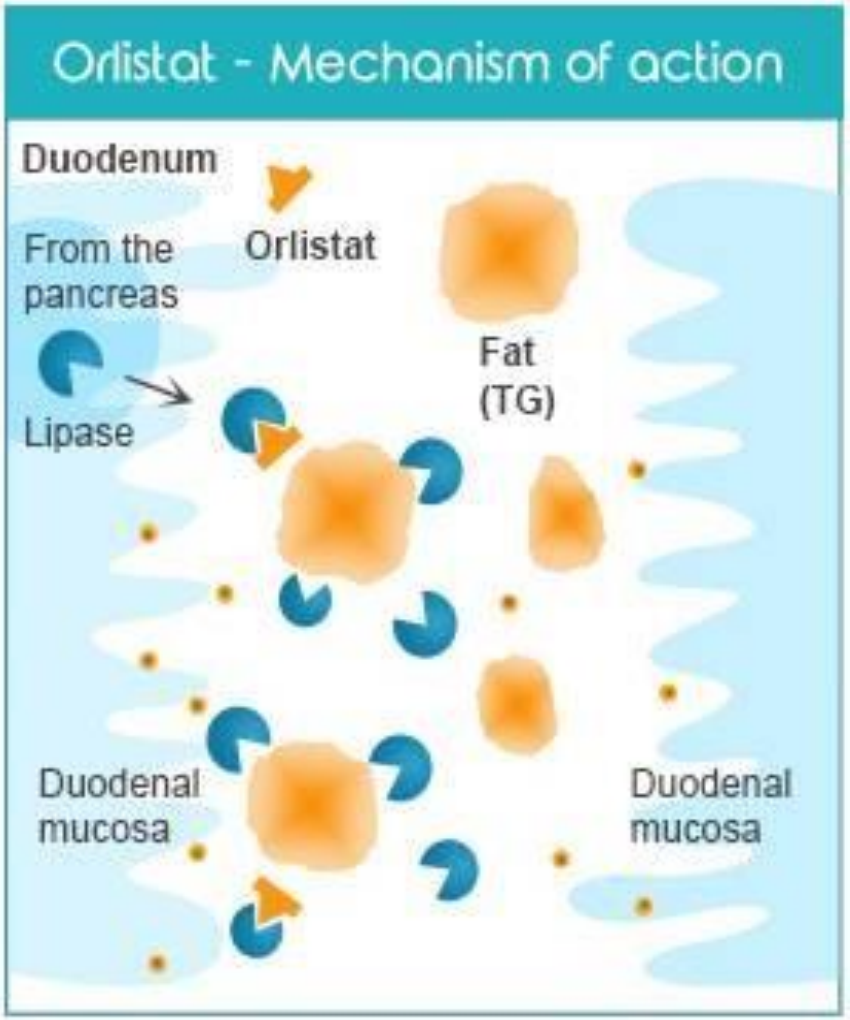
- Orlistat has proven benefits with regard to glycemia, lipids, and blood pressure.
- Unfortunately, it frequently causes gastrointestinal side effects and is often not tolerated by patients.
- The longest clinical trial examining the safety and efficacy of pharmacotherapy for weight loss utilized orlistat for 4 years

Orlistat 1999 FDA & EMA approved

- Orlistat is an intestinal lipase inhibitor: fat malabsorption.
- Significant W.L VS lifestyle alone
- Helps maintain W.L
- Prevent weight regain.

- Orlistat has also been approved in a reduced dosage form (60 mg) for over-the-counter sales.


Fat digestion
Duodenum
From the pancreas
Lipase
Fat (TG)
Duodenal mucosa
Duodenal mucosa


Orlistat - Mechanism of action
Duodenum
From the pancreas
Orlistat
Lipase
Fat (TG)
Duodenal mucosa
Duodenal mucosa

- Inhibiting pancreatic lipases
- Fat is not completely hydrolyzed
- Fecal fat excretion is increased

- In normal individuals eating a diet that contains 30 percent fat, orlistat causes a dose-dependent increase in fecal fat excretion, inhibiting the absorption of approximately 25 to 30 percent of calories ingested as fat.

- In hypertensive patients, orlistat improves blood pressure (likely due to weight loss)

- Improves some serum lipid values more than can be explained by weight reduction alone

Adverse effects

- **Gastrointestinal:** intestinal borborygmi and cramps, fecal incontinence, oily spotting
- **Absorption of fat-soluble vitamins:** levels of fatsoluble vitamins (A, D, E, K) and beta-carotene is lowered by orlistat therapy, with vitamin D the most frequently affected.
- Orlistat does not seem to affect the absorption of other drugs, with the exception of cyclosporine, thyroid hormone, and anti-epileptic drugs
- However, for patients taking warfarin, a decrease in vitamin K may necessitate a reduction in the dose of warfarin
- Oxalate-induced acute kidney injury: Malabsorption syndromes are a risk factor for calcium oxalate stones.

Dosing and contraindications

Phentermine-Topiramate

- Combination phentermine-topiramate (ER)

- The efficacy for weight loss of phentermine-extended release topiramate appears to be greater than for either orlistat, but it may have more side effects (eg, increased heart rate, dose-related increase in the incidence of psychiatric [eg, depression, anxiety] and cognitive

- Phentermine (a NEP releasing agent that suppresses appetite): only for short-term use (i.e., <3 months).

- Phentermine + topiramate ER(a carbonic anhydrase i), : chronic treatment of obesity.

- Phentermine/topiramate ER :
- stop if <%5 weight loss at 12 weeks
- Starting dose: 3.75/23 mg PO QD for 2 weeks
- Recommended dose: 7.5/46 mg PO QD

- Not recommend for patients with cardiovascular disease (hypertension or coronary heart disease)
- **Adverse effects:** dry mouth ,constipation, and paresthesia
- Dose-related increase in the incidence of psychiatric (eg, depression, anxiety) and cognitive (eg, disturbance in attention)
- Contraindicated during pregnancy and in patients with hyperthyroidism or glaucoma and in patients who have taken MAOI within 14 day
- Cautiously in patients with a history of renal stones.

Naltrexone-Bupropion

- Combination naltrexone-bupropion (sustained release) produces similar weight loss as orlistat, but it has more side effects and contraindications .
- Owing to the uncertainty about cardiovascular effects, prefer to use orlistat or liraglutide, rather than naltrexone-bupropion.
- Bupropion (a DA and NEP reuptake inhibitor) + naltrexone (a m-opioid receptor antagonist): combination works synergistically to suppress appetite
- Starting dose: naltrexone 8 mg/bupropion 90 mg once daily

- Do not suggest combination naltrexone-bupropion as first-line pharmacologic therapy
- Obese smoker who desires pharmacologic therapy for smoking cessation and obesity
- Owing to the uncertainty about cardiovascular effects, prefer to use orlistat or liraglutide.

SYMPATHOMIMETIC DRUGS

- Phentermine, benzphetamine, phendimetrazine, and diethylpropion are only approved by the US Food and Drug Administration (FDA) for short-term (ie, 12 weeks) use, have more side effects, and have potential for abuse.
- However, some clinicians and their patients choose to use phentermine for longer periods of time, owing to long-term clinical experience with this drug
- contraindicated in patients with coronary heart disease, uncontrolled hypertension, hyperthyroidism, or in patients with a history of drug abuse

Phentermine

- the most often prescribed drug for weight loss in the United States
- approved in 1959 for short-term use for weight loss

Sympathomimetics ADR

- increase heart rate and blood pressure and cause insomnia, dry mouth, constipation, and nervousness
- Sibutramine: systolic and diastolic blood pressure increased on average by 1 to 3 mmHg and pulse increased by approximately 4 to 5 beats per minute
- Phenylpropanolamine: a small but significant risk of hemorrhagic stroke in women
- Sibutramine can still be found illicitly in dietary supplements marketed for weight loss

- **Combinations** of FDA-approved w.l medications should only be used in a manner approved by the FDA

- Orlistat has also been used off label in combination with other drugs.
- However, orlistat, which acts to inhibit lipase in the intestinal lumen, can interfere with the absorption of many drugs.

METFORMIN

- Patients with overweight or obesity and PCOS should be considered for treatment with orlistat, metformin, or liraglutide, alone or in combination, because these medications can be effective in **decreasing weight or improving PCOS manifestations**
  - Insulin resistance
  - Glucose tolerance
  - Dyslipidemia
  - Hyperandrogenemia
  - Oligomenorrhea
  - Anovulation **(Grade A; BEL 1).**

- Diabetes medications, including **Metformin, Acarbose, and Thiazolidinediones**, can be considered in selected **high-risk** patients with **prediabetes** who are **not successfully** treated with lifestyle and weight-loss medications and who remain **glucose intolerant (Grade A; BEL 1).**

- FDA laboratory tests have revealed the presence of sibutramine, fenproporex, bumetanide, furosemide, phenytoin, rimonabant, cetilistat, and phenolphthalein in weight loss products being sold over the counter

- Green tea, Garcinia cambogia (hydroxycitric acid), conjugated linoleic acid, and chitosan were ineffective for weight loss, and their use should be discouraged.
- Efficacy and safety data were unclear for chromium, Gambisan, Hoodia gordonii, and Cynanchum auriculatum

- *Selective Inhibitors of Serotonin Reuptake. Fluoxetine*

Drugs Commonly Prescribed for Weight Loss [146]

Year Approved	Generic Name	Trade Name	Placebo-Corrected Anticipated Weight Loss (kg)
1959	Phentermine	Ionamin, Adipex-P, Fastin, Oby-Trim (approved only for short-term weight loss)	Approved for short-term use only
1999	Orlistat	Xenical, Ally (over the counter)	2.63
2010	Liraglutide	Victoza (approved for type 2 diabetes mellitus)	0 to 3.7[a]
2012	Phentermine-topiramate extended release	Qsymia	8.80
2013	Lorcaserin	Belviq	3.25
2014	Liraglutide	Saxenda (approved for obesity)	5.24
2014	Bupropion-naltrexone	Contrave	4.95

Note: Intensity of lifestyle interventions and maximum weight loss differs in studies. Represented values mean weight loss in excess of placebo.

[a] Ã, Depending on comparator.

MEDICATION	MECHANISM OF ACTION	AVAILABLE FOR CHRONIC USE		MEAN PERCENTAG
		USA	European Union	Placebo
Phentermine, 15-30 mg PO	Sympathomimetic	For short-term use	No	Not stated in label
Orlistat, 120 mg PO tid before meals	Pancreatic lipase inhibitor	Yes	Yes	−2.6% ‡ (svbfile:///var/mobile/Cc 0EDC-4F5A-AE02-CE8 C20161017121/base/hl
Lorcaserin, 10 mg PO bid	5-HT $_{2c}$ serotonin agonist with little affinity for other serotonergic receptors	Yes	No	−2.5%
Phentermine/topiramate ER, 7.5 mg/46 mg or 15 mg/92 mg PO indicated as rescue (requires titration)	Sympathomimetic anticonvulsant (GABA receptor modulation, carbonic	Yes	No	−1.2%

	anhydrase inhibition, glutamate antagonism)			
Naltrexone SR/bupropion SR, 32 mg/360 mg PO (requires titration)	Opioid receptor antagonist; dopamine and noradrenaline reuptake inhibitor	Yes	Yes	−1.3%
Liraglutide, 3.0 mg injection (requires titration)	GLP-1 receptor agonist	Yes	Yes	−3%

Weight loss at 12 months for FDA-approved drugs

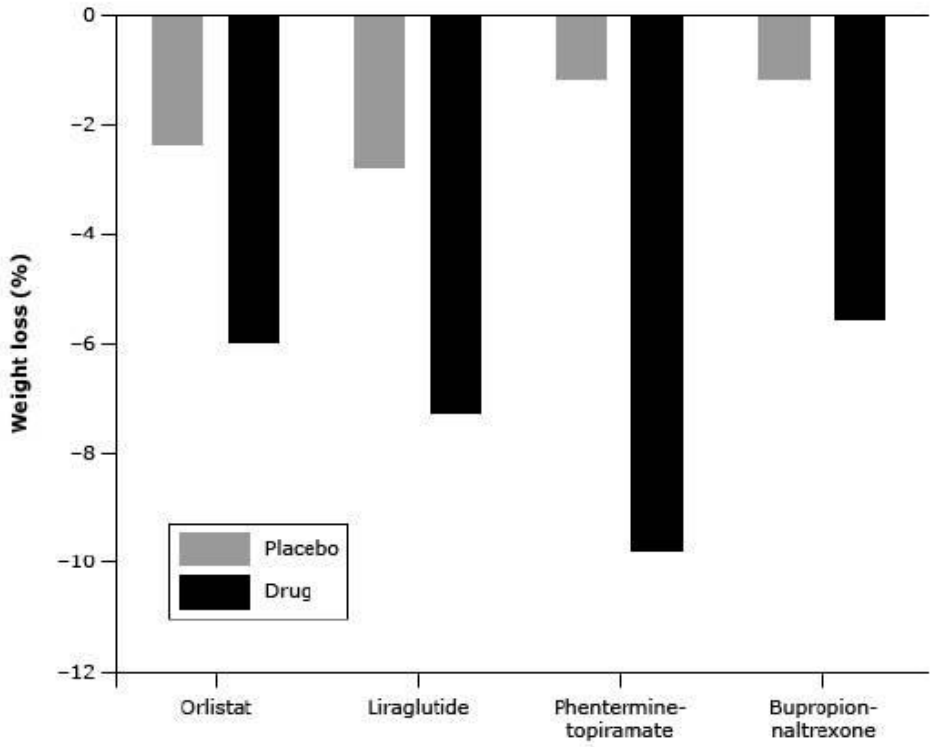


TABLE 3. *Body size descriptors and body mass*

Body mass and body size descriptors	Population	Formula	Application
Term		**Definition**	
TBW		Patient's current weight in kilograms	Used to establish dosage in the pediatric population.
BMI	Older than 2 years old	TBW (kg) divided by height^2 (m)	Used to categorize the degree of obesity. Rarely used to establish drug dosage.
IBW in adults		Man: 49.9 kg + 0.89 x (height in cm – 152.4) Woman: 45.4 kg + 0.89 x (height in cm – 152.4)	Considers sex difference.
IBW in children*	Older than 2 years old	Desirable weight for a specific height and age. It corresponds to the P50 of BMI for age x height^2 (cm).	Suggested for hydrophilic drugs and to establish the maintenance dose.
BSA (m2)**	Children and adults	√ height (cm) x weight (kg)/3600	Frequently used for chemotherapy and fluid therapy.
ABW	Mainly adults	IBW + drug factor x (TBW - IBW) Usual factor 0.3-0.4	Suggested for aminoglycoside dosage.
LBW		TBW - fat weight Child: IBW + 0.29 (TBW - IBW) Man: 1.10 x TBW – 0.0128 x BMI x TBW Woman: 1.07 x TBW – 0.0148 x BMI x TBW	Considers sex difference.

TABLE 4. *Recommended drug dose as per the body descriptor used for obese children*[11,12,22,34,36]

Drug	Body descriptor	Remarks
Antiviral agents		
Acyclovir	IBW	Maximum dose in adults 10 mg/kg/dose every 8 hours
Antifungal agents		
Voriconazole		Maximum dose in adults 300 mg/dose
Antibiotics		
Amikacin	ABW (factor 0.4)	Plasma levels should be determined. Maximum dose in adults 1.5 g/day
Gentamicin	ABW (factor 0.4)	Plasma levels should be determined. Maximum dose in adults 5-7 mg/kg/day, max. 480 mg/day
Clindamycin	TBW	Maximum dose in adults 2.7 g/day
Cephalosporins	TBW	Maximum dose in adults Ceftriaxone: 4 g/day Cefotaxime: 12 g/day Ceftazidime: 9 g/day Cefazoline: 8-12* g/day * Life-threatening infections
Linezolid		Standard dose 600 mg/12 hours Maximum dose in adults 1.2 g/day
Meropenem	TBW	Increased distribution in obese patients. Maximum dose in adults 6 g/day (9 g/day in the case of meningitis)
Metronidazole	TBW	Maximum dose in adults 2.0 g/day
Piperacillin/tazobactam	TBW	Maximum dose in adults 16 g/day
Quinolones	TBW	Some authors recommend using TBW
(ciprofloxacin)	ABW (factor 0.4)	in case a sufficient dose is not achieved. Maximum dose in adults 1.2 g/day
Vancomycin	TBW (loading and maintenance doses)	The recommendation assumes a normal kidney function. Plasma levels should be determined. Maximum dose in adults 4 g/day

Anticonvulsant agents		
Valproic acid	TBW	Wide therapeutic range and drug level monitoring. Maximum dose in adults. Loading dose: 800 mg Maintenance dose: 30 mg/kg/day
Carbamazepine	IBW (loading and maintenance doses)	Drug levels should be monitored.
Phenytoin	ABW (loading dose) IBW (maintenance dose) or fixed dose at 300 mg/day	Plasma levels should be determined. Maximum dose in adults 2 g
Phenobarbital	TBW	Drug levels should be monitored.
Levetiracetam	ABW	Volume of distribution similar to total body water. Maximum dose in adults. Loading dose: 2.5 g
Benzodiazepines (diazepam, lorazepam, midazolam)	TBW (loading dose) IBW (maintenance dose)	Clinical monitoring is necessary.
Inotropes and vasoactive agents		
Adrenaline	TBW	Small volume of distribution Maximum dose in adults 1 mg/dose
Catecholamines (dopamine, dobutamine)	IBW	Titrate to achieve the effect. Rapid initiation and short half-life. Hydrophilic drug with a small therapeutic window. Wide titration range.
Milrinone	TBW	Pharmacokinetics suggest using lean body mass to estimate the dose; however, there is a risk for insufficient dose.
Sodium nitroprusside	TBW	Obesity may be inversely related to drug response. May require higher doses.
Anesthetic agents		
Dexmedetomidine	IBW	High risk for bradycardia and other adverse events in critically ill patients.
Phentanile	IBW	Adjusted to 0.25[21]; clinical monitoring is necessary.
Ketamine	IBW	The use of IBW may reduce adverse events. Maximum dose in adults (intravenous): 5 mg/kg
Methadone	IBW	Maintenance dose: 80-120 mg/day
Morphine	IBW	Intermittent doses may be preferred over continuous infusion. Clinical monitoring is necessary.
Propofol	IBW (loading dose) TBW (maintenance dose)	The dose should start at 2 mg/kg and then titration is required.
Rocuronium	ABW	Clinical response should be assessed and dose titration is required.

Morphine	IBW	Intermittent doses may be preferred over continuous infusion. Clinical monitoring is necessary.
Propofol	IBW (loading dose) TBW (maintenance dose)	The dose should start at 2 mg/kg and then titration is required.
Rocuronium	ABW	Clinical response should be assessed and dose titration is required.
Vecuronium	IBW	Kinetic values are similar in obese and normal weight patients.
Anticoagulants		
Enoxaparin	TBW	If total body weight is used, doses above 30 % of the standard dose may be required. A single dose should be avoided if BMI > 27 kg/m^2.
Heparin	Prophylaxis with standard dose 5000-7500 U 3 times/day Treatment of deep vein thrombosis and TBW	For treatment, the bolus could be reduced or dosing may be started as per schedule. Adjust as per activated partial thromboplastin time.
Antidotes		
Flumazenil	IBW	Maximum dose in adults 0.2 mg/dose (accumulated max.: 1 mg)
Naloxone	TBW	Maximum dose in adults: 10 mg
Neostigmine	ABW (cofactor 0.4)	Less adverse events and faster action.
Protamine sulfate	ABW (cofactor 0.4)	The dose should be based on the heparin dose using ABW.
Fluids and electrolyte solutions		
Fluids for baseline requirement	IBW or BSA	
Sodium bicarbonate	IBW	Small therapeutic window when used chronically.
10% sodium chloride Vial: 1 mL = 1.7 mEq	IBW	Dose based on the patient's individual requirements, either age, weight or sodium plasma levels.
10% potassium chloride Vial: 1 mL = 1.3 mEq	IBW	Small therapeutic window. Orally: 20 mEq/dose. Intravenously: 200-400 mEq/day (if K < 2)
Calcium gluconate	IBW	Electrolytes are charged ions, hydrophilic with low volumes of distribution.
Magnesium sulphate	IBW	Small therapeutic window.

Steroids		
Dexamethasone	TBW	Pharmacokinetic profile similar to prednisone.
Hydrocortisone	TBW	Maximum dose in adults 200-300 mg. 6 g for shock
Methylprednisolone	IBW	Maximum dose in adults, pulse therapy 1 g.
Antiarrhythmics		
Adenosine	IBW	Hydrophilic drug with a small volume of distribution Maximum dose in adults, first 6 mg/second 12 mg
Atropine	TBW	Large volume of distribution into the extravascular space.
Amiodarone	TBW	Recommended with caution due to the potential reduced clearance in the long term. Maximum dose in adults. Loading dose: 150 mg 1.2 g/day
Lidocaine	TBW (loading dose), IBW (maintenance dose)	High volume of distribution in obese patients; however, clearance is the same in obese and normal weight patients.
Diuretics		
Furosemide	IBW	Risk for ototoxicity. Maximum dose in adults 40 mg
Immunosupressors		
Ciclosporin	IBW	Monitoring is required because it has a small therapeutic window. Obese children require lower maintenance doses.
Insulin therapy		
Crystalline insulin	TBW IBW (infusion)	Conservative initial dose to prevent hypoglycemia.
Bronchodilators		
Ipratropium	TBW	
Salbutamol	TBW	Supported by current practice. Maximum dose in adults: Nebulization: 10 mg/day Spray: 1.6 mg/day
Theophylline	TBW (loading dose), IBW (maintenance dose)	Plasma levels should be determined. Minimum distribution into adipose tissue. Volume of distribution decreases as adiposity increases.
Blood components		
Blood products		
Red blood cells	IBW	Maximum dose 1 U (200-300 mL)
Platelets	IBW	Maximum dose in adults 5-7 platelet concentrates

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Platelets	IBW	Maximum dose in adults 5-7 platelet concentrates
Plasma	IBW	Maximum dose in adults 10-20 mL/kg
Non-specific immunoglobulin	IBW	IBW should be used when TBW is > 20 % of the IBW.
Analgesics		
Acetaminophen	IBW	Maximum dose in adults 1 g/dose - 4 g/day