
بسم الله الرحمن الرحیم

Drug therapy IN obesity

Dr Tahere Dadpey

Obstetric & Gynecology Department
Tehran University of Medical Sciences

Introduction

A number of medications are approved by the FDA for the treatment of overweight or obesity. It is essential that the medications are used in conjunction with healthy eating, physical activity, and behavior modification, as medication usage without such changes are generally ineffective.

The decision to initiate drug therapy in overweight individuals should be made after consideration of the risks and benefits , and the goals of drug therapy should be clear.

GOALS OF THERAPY

- Reduce and maintain weight loss
- Improve health status
- Minimize adverse effects

Reduce and maintain weight loss

In short-term (6 to 12 months) clinical trials evaluating drug therapy, weight loss of 4 to 8 percent is typical .

Upon **initiation of anti-obesity medication**, we communicate several important messages to patients. **First**, **not every drug works for every patient**; individual responses vary widely. **Second**, when the maximal therapeutic effect is achieved, **a plateau is reached** and weight loss ceases. **Finally**, when drug therapy is discontinued, **weight gain can be expected.**

Achieving and **maintaining** weight loss is made **difficult** by many factors, including weight loss-induced **changes in energy expenditure** and **hormonal mediators of appetite**, which favor weight regain .

Therefore

we favor using anti-obesity medications longer term for weight loss maintenance if they are well-tolerated **and** individuals have achieved a greater than five percent weight loss while on them.

Improve health status

If improvement in one's health is the goal, success may be measured by the **degree of weight loss** and measurable or perceived **improvement in physical function**, **comorbidities**, and/or **sense of well-being**. Weight loss should exceed 2 kg 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 percent 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

Improvement in health status after weight loss is an important criterion in the determination of whether to continue drug therapy

Minimize adverse effects

The potential benefits of weight loss must be considered in light of the potential risks of drug therapy.

In patients wishing to use anti-obesity medication for longer than **four years**, the lack of longer-term **safety** (and efficacy) data should be made known.

General principles

- Initial management – (counsultation)**lifestyle changes** are used alone or in combination with anti-obesity **medication** or bariatric **surgery**.

- Approach to underlying comorbidities_ the assessment of weight-related comorbid conditions such as diabetes mellitus, dyslipidemia, hypertension, heart disease, sleep apnea, and symptomatic osteoarthritis.

If possible, to select the drugs to treat the comorbidity that may produce weight loss, rather than weight gain .

Candidates for drug therapy

- BMI ≥30 kg/m2
- BMI of 27 to 29.9 kg/m2 with weight-related comorbidities
  not met weight-loss goals with a lifestyle intervention alone.

The decision to initiate drug therapy should be individualized weighing the risks and benefits of all treatment options

Some **UpToDate** experts **do not use** drug therapy often

Choice of agent

Our approach takes into account patient comorbidities, patient preferences, insurance coverage and cost, and potential adverse effects.

Single agents are **preferred** over combination medications as **initial** pharmacotherapy.

GLP-1 receptor agonist

Liraglutide(once-daily subcutaneous injection)

Beneficial effects :

Improvement in glycemia

Efficacy for weight loss

Reduction of cardiovascular events

Semaglutide(once- weekly subcutaneous injection)

Beneficial effects :

Weight reduction

Improvement in glycemia and lipids

Cardiovascular benefits(with the exception of individuals with a history of heart failure)

Limitation:

Gastrointestinal side effects (nausea, vomiting), the need for an injection, and insurance coverage/cost

GLP-1 RECEPTOR AGONISTS

with or without diabetes mellitus (first-line pharmacotherapy)

For patients **with diabetes in particular**, the side effects, need for injections, and expense are balanced by improved glycemia and weight loss.

We prefer treatment with semaglutide rather than liraglutide(once weekly rather than once daily, and slightly greater efficacy for weight loss)

Adverse events

Other side effects :
diarrhea, low blood sugar, and anorexia, pancreatitis(more frequently with liraglutide) , gallbladder disease, and renal impairment

In rats studies, **liraglutide** was associated with benign and malignant thyroid C-cell tumors.
In multiple trials, there has been no evidence of these tumors in humans.

Liraglutide

Dosing :
In addition, we will continue a patient on the maximum tolerated dose (if less than the goal of 3 mg) if goal weight loss is achieved on that dose.

Contraindications: pregnancy , personal history of pancreatitis, personal or family history of medullary thyroid cancer or multiple endocrine neoplasia

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

Semaglutide

Semaglutide(oral and injectable)
maximum dose (2.4 mg weekly)

For patients unable to tolerate this dose, lower doses can be used as long as ≥5 percent weight loss is achieved.

In patients who also have type 2 diabetes, glycemic control as well as weight loss should be monitored.

Adverse effects

_ gastrointestinal, including nausea, diarrhea, and vomiting.

_ If dose escalation is **not tolerated** due to side effects the **increase in dose can be delayed by another four weeks**.

_**angioedema** and **anaphylaxis** have been reported with semaglutide.

_ Patients with **diabetic retinopathy** should be monitored for complications

contraindications

- pregnancy, personal history of pancreatitis , personal or family history of medullary thyroid cancer or multiple endocrine neoplasia
- 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.

DRUGS THAT ALTER FAT DIGESTION

Orlistat

- Orlistat alters fat digestion by **inhibiting pancreatic lipases**. Thus, fecal fat excretion is increased.
- inhibiting the absorption of approximately **25 to 30 percent of calories** ingested as fat.

- side effects of the medication may be lessened with a **low-fat diet combination** (less than 30 percent fat)

Orlistat

benefits:

Improvement in glycemia, lipids, and blood pressure.

side effects :

Gastrointestinal(frequently _ often not tolerated)

Due to its limited tolerability, and the safety and benefits of other available agents including liraglutide, we **no consider orlistat to be first-line** pharmacotherapy.

Adverse effects

- There was no evidence of an increased risk of **gallstones, renal stones, or cardiovascular or CNS events.**

- Severe liver injury has been reported rarely patients should **contact** their health care provider if **itching, jaundice, pale color stools, or anorexia develop**.

Adverse effects

- Absorption of **fat-soluble vitamins** (A, D, E, K) and beta-carotene
- not affect the **absorption of other drugs**, with the exception of **cyclosporine**. However, for patients taking **warfarin**, a decrease in vitamin K may necessitate a reduction in the dose of warfarin .
- Renal – **Oxalate-induced acute kidney injury**

Malabsorption syndromes are a risk factor for calcium oxalate stones

Similarly, fat malabsorption induced by orlistat may result in the binding of enteric calcium. When less calcium is available in the intestinal lumen to bind oxalate, intestinal oxalate absorption and urinary oxalate excretion increase. Free oxalate can be deposited in the renal parenchyma, resulting in acute kidney injury.

Dosing and contraindications

- Dosing:

120 mg three times daily

- Contraindications:

pregnancy, chronic malabsorption, cholestasis, history of calcium oxalate stones.

COMBINATION DRUGS

- Hypothesis:

Combination drugs with different mechanisms of action could improve efficacy (and tolerability if used in lower doses) compared with single-drug therapy.

phentermine-topiramate

An option for **males or postmenopausal females** with obesity without uncontrolled hypertension or coronary heart disease, **particularly** those who do not tolerate orlistat or liraglutide.

It may be an **acceptable option** for a patient with an obesity-related **comorbidity**, such as sleep apnea, who does not have any cardiovascular disease.

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phentermine-topiramate

- The presence of **topiramate** in this combination may increase risk of fetal malformations, and should thus be used with caution in females of childbearing potential. Such patients should be **advised about the teratogenic potential** of the medication, counseled to use **reliable contraception**, and should have a **pregnancy test** before initiation of therapy and monthly thereafter.

Adverse effects

dry mouth , constipation and paresthesia .

psychiatric (eg, depression, anxiety) and cognitive (eg, disturbance in attention) adverse events.

Although BP improves slightly but HR increases.

Dosing and contraindications

- The initial dose is 3.75/23 mg .
- the dose can be increased to 15/92 mg daily .
- If an individual does not lose 5 percent of body weight after 12 weeks on the highest dose, phentermine-topiramate should be discontinued gradually as abrupt withdrawal of topiramate can cause seizures .

- **Contraindications:**

pregnancy (increased risk of orofacial clefts in infants) .
hyperthyroidism
glaucoma
patients who have taken **MAO inhibitors** within 14 days.
history of **renal stones**(topiramate can produce renal stones),.

Bupropion-naltrexone

- Bupropion is a drug available for the **treatment of depression** and for use in **prevention of weight gain during smoking cessation**. Naltrexone is an opioid-receptor antagonist used to **treat alcohol and opioid dependence**

Adverse effects

- nausea , headache , constipation ,insomnia, vomiting, dizziness, dry mouth
- bupropion-naltrexone can **raise blood pressure and heart rate**
- Because it contains **bupropion**, the FDA recommends warning **young adults** (18 to 24 years) of the risk of becoming **suicidal** during initial treatment of psychiatric disorders with any antidepressant.
- the **cardiovascular safety** remains **unknown**.

Dosing and contraindications

one tablet (8 mg of naltrexone and 90 mg of bupropion) **daily**. After one week, one tablet **BD**. by week four, to **two tablets BD**.

Dose **adjustment or avoidance** is recommended in patients with **renal or hepatic impairment**, depending upon the severity .

Contraindications :
pregnancy, uncontrolled **hypertension**, **seizure** disorder, **eating** disorder, use of other **bupropion-containing** products, chronic **opioid use**, severe **hepatic dysfunction**, and use within 14 days of taking **MAO inhibitors**.

SYMPATHOMIMETIC DRUGS

- phentermine, diethylpropion, benzphetamine, and phendimetrazine(**only short-term** _up to 12 week) **because** of their potential **side effects**, potential for **abuse**, **limited duration of use**, and **regulatory surveillance**.
- Contraindication:

coronary heart disease, uncontrolled hypertension, hyperthyroidism, history of drug abuse .

phentermine (as a single agent) remains **the most widely** prescribed **weight loss drug**, and the **observed** rate of **abuse** with this drug is **low.**

Monitoring

- Weight, vital signs- **every six weeks**. If patients do not lose 4 to 5 percent of body weight after 12 weeks of therapy (at the maximum tolerated dose), the drug should be tapered and discontinued.

- Blood sugar in patients with diabetes – self-monitoring of blood glucose (SMBG) should be performed more frequently for safty(at least daily)
  In patients with **well-controlled diabetes,** it may also be advisable to **reduce** the doses of sulfonylureas or meglitinides during the **first four weeks of treatment** with an anti-obesity drug and adjust as needed based on blood glucose values.

- Adverse effects – We ask about adverse effects during **every visit**.

Dietary supplements

- Dietary supplements not recommended – We recommend not using dietary supplements marketed for weight loss , owing to **low-quality evidence of efficacy** and **concern for potential adverse effects.**