In the name of ALLAH

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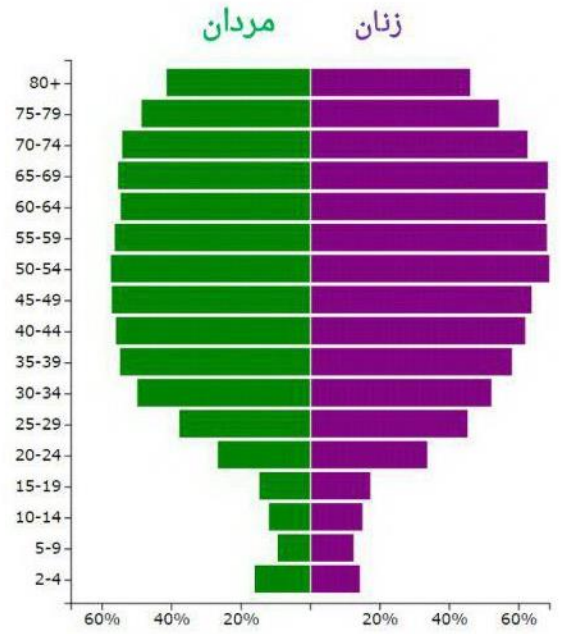
Obesity Pharmacotherapy

Introduction

- **By to 2016,** the prevalence of obesity had increased over twofold and affected 39.8% of the adult population while
- **Severe obesity** affected 7.7% of the adult population **(Speed Up even in children)**
- **In Iran up to 50% of people are overweight or obese!**

- Excessive central adiposity increases risk for development of **type 2 diabetes, hypertension, and dyslipidemia.**



شیوع استاندارد شده سنی مجموع اضافه وزن و چاقی در ایران از سال ۱۹۸۰ تا ۲۰۱۵

Etiology

Causes:

- **1.Genetic:** Genetics plays an important role in determining both obesity and distribution of body fat.
- **2.Environmental:** abundant and easily accessible food supply and the material comforts of modern life in Western civilizations+ inactivity
- **3.Medical causes: less common** iatrogenic and idiopathic Cushing syndrome, growth hormone deficiency, insulinoma, leptin deficiency, and various psychiatric disorders, such as depression ,hypothyroidism ,...
- **4. Medication:** anticonvulsants (eg, carbamazepine, gabapentin, pregabalin, and valproic acid), antidepressants (eg, mirtazapine and tricyclic antidepressants), atypical antipsychotics (eg, clozapine, olanzapine, quetiapine, and risperidone and hormones (eg, corticosteroids, insulin, and medroxyprogesterone).

Nonpharmacologic therapy

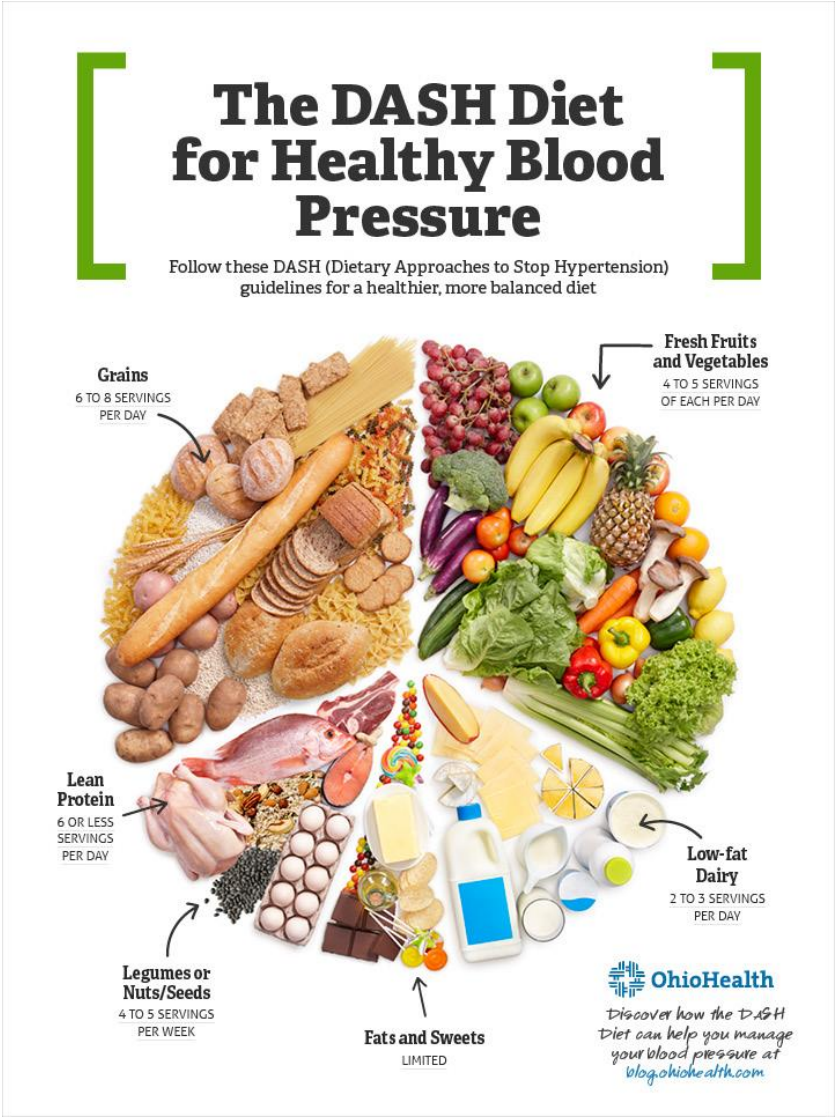
- **Nonpharmacologic** therapy including reduced caloric intake, increased physical activity, and behavioral modification

- Current adult guidelines recommend reduced caloric intake through
- adherence to a **low-calorie diet (LCD).**
- The LCD should provide a daily caloric deficit of 500 to 750 kcal which generally correlates to a total intake of 1,200 to 1,500 kcal/day
- **Short-term weight loss** is significant for almost all diet plans. However, **long term weight loss** and maintenance of weight loss are less promising,

DASH

- DASH diet: The DASH diet is a healthy-eating plan designed to help treat or prevent high blood pressure (hypertension).
- The DASH diet includes foods that are rich in **potassium, calcium and magnesium**. These nutrients help control blood pressure. The diet limits foods that are high in sodium (2,300 mg a day), saturated fat and added sugars.

- **Sodium:** Using sodium-free spices or flavorings instead of salt/Reading food labels and choosing low-sodium or no-salt-added options/Not adding salt when cooking rice, pasta or hot cereal



Comprehensive lifestyle intervention

- **Comprehensive lifestyle intervention** encompasses the combination of reduced-caloric intake, increased physical activity, and behavioral modification.

- **Aerobic physical activity** for at least 150 minutes per week, completed over three to five days is recommended for adults
- **Modest effect as monotherapy** but more effective in addition to diet and behavioral change

Pharmacotherapy

- **Pharmacotherapy helps to lose weight 4-8 % during 3-12 months**

- 1. **An adjunctive treatment** in patients with a BMI more than or equal **to 30 kg/m2**
- 2. **BMI of 27 to 30 kg/m2** with a comorbidity if comprehensive lifestyle modifications (eg, diet, exercise, and behavioral modification) fail to achieve or sustain weight loss.

- **Comorbidities:** DM,HTN.CV Diseases, Dyslipidemia, GERD, NASH, PCOS, Psychiatric issues?

- **Does the patient need pharmacotherapy???**
- **Processes: first search for secondary causes+ calculate BMI+ assess risk factors+ encourage lifestyle modification**
- Pharmacotherapy should be **discontinued** if weight loss of at least 5% is not achieved **after 12** weeks

Agents Approved for Long-Term Use

- **Lipase inhibitor orlistat (Xenical)**
- **Combination product phentermine–topiramate extended-release**
- **Combination product naltrexone–bupropion extended-release tablets**
- **GLP-1 receptor agonist liraglutide (liraglutide,Semaglutide)**
- **Dual MOA: GIP/GLP1 agonist: Tirzepatide**

Medications for the Treatment of Obesity

Generic Name	Trade Name	Dosing
Orlistat	Xenical	120 mg PO TID
	Alli	60 mg PO TID
Phentermine/topiramate	Qsymia	3.75/23 mg PO QAM × 14 days; then 7.5/46 mg QAM for 12 weeks then evaluate weight loss, if less than 3%, dose may be titrated to 11.25/69 mg QAM × 14 days then 15/92 mg QAM
Lorcaserin	Belviq	10 mg PO BID
Naltrexone/bupropion	Contrave	8/90 mg PO QAM × 1 week then 8/90 mg BID ×1 week then 16/180 mg QAM and 8/90 mg QPM then 16/180 mg BID
Liraglutide	Saxenda	0.6 mg SC daily × 1 week increase dose by 0.6 mg weekly until therapeutic dose of 3 mg daily
Phentermine hydrochloride[a]	Adipex-P	TID; 30–37.5 mg QAM

Other 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.

Lipase Inhibitor: Orlistat

- lipases are essential in the **absorption of the long-chain triglycerides.**
- Reduce calorie intake **(1gr fat= 10kcal)**
- **Take with fatty meals** (within 1 hrs) , Up to **30% reduction in fat absorption** occurred with daily doses of 120 mg three times daily with meals.
- **Modest weight loss, Beneficial for DM, Dyslipidemia ,...**
- **Dose: 60 (OTC)-120mg TDS**

- **ADRS:**
- **GI complaint** (soft stools, abdominal pain or colic, flatulence, fecal urgency, or incontinence) : usually improve after 1 months.
- **Supplementation:** with a multivitamin (including ADEK) should be considered during therapy (4 hrs separation)
- **Drug- Interaction: lipophilic drugs** (lamotrigine, valproic acid, gabapentin, cyclosporine and amiodarone), OCP, Warfarin (vit k reduction and rise in INR), separation between two drugs.
- **Orlistat is contraindicated in pregnancy and in patients with chronic malabsorption syndrome, or cholestasis.**

Phentermine–Topiramate Extended-Release

- **Phentermine** is structurally **similar to amphetamine**, but it has less severe CNS stimulation and a lower abuse potential.
- **Topiramate** is an antiepileptic drug. (MOA: unknown)
- **Both decrease appetite and increase satiety.**
- **Effective: weight loss of 10.9% after 1 year of treatment in one trial (dose dependent)**
- **Dose:** lower than therapeutic doses:
- **Staring with 3.75 mg of phentermine and 23 mg of topiramate once daily** for 14 days and then increasing the dose to 7.5 mg of phentermine and 46 mg of topiramate once daily.

ADRs: Constipation, dry mouth, paranesthesia, dysgeusia, and insomnia, tachycardia ,...
Topiramate is a known teratogen, this drug is contraindicated in pregnancy+ anhydrase carbonic inhibitor. (metabolic acidosis)

It is contraindicated in Glaucoma
BUN,Scr ,K and Mg heart rate should be monitored in all patients, particularly those with preexisting CVD at baseline and during therapy.

Naltrexone–Bupropion Extended-Release

- **Bupropion** is a dopamine and norepinephrine reuptake inhibitor, and **naltrexone is an opioid antagonist.**
- MOA: decrease appetite
- **Efficacy:** The average total weight loss reported among the four studies was 7.3 kg

- **Dose:** starting with one tablet (**8-mg naltrexone/90-mg bupropion) per day** and slowly increasing the dose over a period of 4 weeks to a maintenance dose of two tablets twice daily.
- **ADRs**: nausea, constipation, headache, vomiting, **dizziness**, insomnia, dry mouth, and diarrhea , increases in heart rate (2.1 beats/min) and SBP 2mmhg.
- **Monitoring:** blood pressure and pulse should be monitored at baseline and at regular intervals
- **CI: Uncontrolled HTN, Seizure(caution), Opioid addicts or on opioids drugs.**

Liraglutide: solution pen-injector, SC : Saxenda® 6 mg/ml, Victoza® 18 mg/3ml

0.6-1.8 mg SC	Once daily	Limited experience in severe renal impairment	• Multidose pen (6 mg/mL, 3 mL; each pen delivers doses of 0.6, 1.2, or 1.8 mg) • Pen needles not supplied with pen • Keep refrigerated • After first use, store at room temperature; discard 30 days after first use

Pros:
- High efficacy
- Low hypoglycemia risk (monotherapy or combination with metformin)
- Cardiovascular (liraglutide, semaglutide, dulaglutide) benefits & renal (liraglutide, semaglutide) benefits
- Weight loss

Potential Cons:
- Cost
- Need for renal dose adjustment
- Injectable (with the exception of oral semaglutide)
- GI intolerance
- Rare/Serious Safety Concerns: Thyroid C-cell tumors (long-acting agents), Acute pancreatitis

Liraglutide

It mimics the action of endogenous GLP-1, stimulate insulin secretion from pancreatic beta-cells reduce inappropriately elevated levels of glucagon ,direct effect on the stomach through the autonomic nervous system to slow gastric emptying

Efficacy: 8.4 kg during 1 yr.

Dose : 0.6- 1.8 mg daily (SC)

Dose (obesity): start with lower doses, upto 3mg/day

- **One of The Best option in obese patients with cardiovascular diseases or DM**

Semaglutide

- Semaglutide, another GLP-1 agonist approved for the treatment of **obesity**,
- is administered as a **once weekly subcutaneous** injection.
- It has demonstrated efficacy in weight reduction, as well improvement in glycemia and lipids

- **Dose:** 0.25-0.5 mg/ week up to 2.4 mg/week

Tirzepatide

- **In a double-blind placebo-controlled (Obesity without diabetes)** randomized trial including over 2500 adults with obesity (but without diabetes), tirzepatide once weekly was compared with placebo.
- **At 72 weeks,** reduction in body weight at all tirzepatide doses (5, 10, and **15 mg**) was greater compared with placebo (-**16.1, -22.2, and -23.6 kg,** respectively, versus -2.4 kg).

RESEARCH SUMMARY

Tirzepatide Once Weekly for the Treatment of Obesity

Jastreboff AM et al. DOI: 10.1056/NEJMoa2206038

CLINICAL PROBLEM

Several clinical guidelines recommend pharmacotherapy for obesity. Tirzepatide — a dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist recently approved in the United States to treat type 2 diabetes — induced clinically relevant weight reduction in phase 2 studies of people with diabetes. However, its efficacy for weight reduction in those without diabetes is unknown.

CLINICAL TRIAL

Design: An international, phase 3, double-blind, randomized, placebo-controlled trial examined the efficacy and safety of tirzepatide in adults with obesity or overweight who did not have diabetes.

Intervention: 2539 adults with a body-mass index of 30 or higher, or 27 or higher with at least one weight-related complication, were assigned to once-weekly subcutaneous tirzepatide at one of three doses (5 mg, 10 mg, or 15 mg) or placebo, in addition to lifestyle intervention. Treatment included a dose-escalation phase and lasted for 72 weeks. The coprimary end points were the percentage change in weight from baseline to week 72 and weight reduction of at least 5% by week 72.

RESULTS

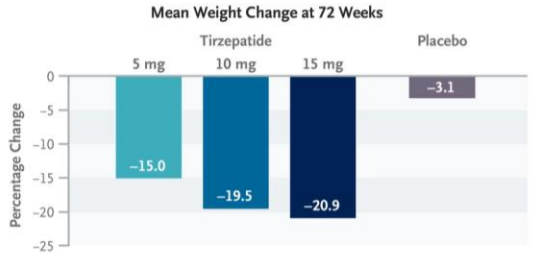
Efficacy: Both the percentage change in weight and the percentage of participants with at least 5% weight reduction were significantly greater with all three doses of tirzepatide than with placebo.

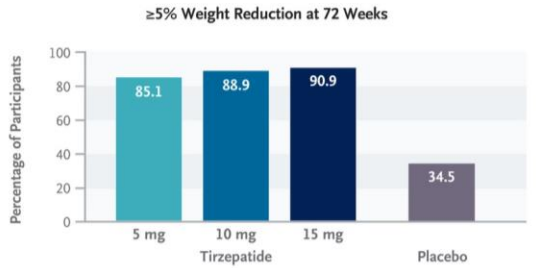
Safety: Gastrointestinal events, including nausea, diarrhea, and constipation, were the most common adverse events seen with tirzepatide; the majority of events were transient and mild to moderate in severity.

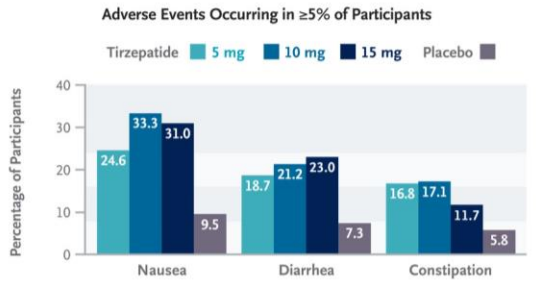
LIMITATIONS AND REMAINING QUESTIONS

- Enrolled participants may have been more committed to weight management than many people with obesity.
- Cardiometabolic variables (e.g., blood pressure and lipid levels) were relatively normal at baseline, so the ability to show a potential improvement within the time frame of this study was limited.
- The number of participants with overweight plus at least one weight-related complication was small (140 of the 2539 participants; 5.5%), which prevented definitive conclusions in this subgroup.

Links: Full Article | NEJM Quick Take | Editorial







CONCLUSIONS

All three doses of once-weekly subcutaneous tirzepatide led to clinically meaningful and sustained weight reduction in obese adults who did not have diabetes.

Lorcaserin (Belviq)

- It is a **selective serotonin (5-HT2C) receptor agonist**, approved for chronic weight management.
- Activation of central 5-HT 2C receptors results in appetite suppression, leading to reduced energy intake and enhanced satiety. **(Mean weight loss at 1 year was 5.8 kg)**

- **Lorcaserin** is also effective in patients with **type 2 diabetes**, with an average weight loss of 4.5% and significant improvements in **HbA1c** and fasting glucose after 1 year of treatment.
- **Adverse Effects** :headache, dizziness, constipation, fatigue, and dry mouth

- **Risk of CV is very low but caution is recommended.**

❖ In February 2020, the FDA requested that the manufacturer of lorcaserin withdraw the drug due **to increase risk of cancer.**

Agents Approved for Short-Term Use

- ***1.Phentermine*** :A single dose of 30 mg once daily in the morning provides effective appetite suppression throughout the day.
- **Caution:** CVD patients or HTN, hyperthyroidism or agitated states, MAOIs **(not recommended),** DM

- ***2.Diethylpropion (Tenuate)*** stimulates NE release from presynaptic storage granules

➢ **Dose:** generally 25 mg three times daily <u>before meals</u> <u>or SR: 75 mg/d in morning</u>

Bulimia Nervosa

- **Pathophysiology:**
- The neurobiology of bulimia nervosa and the mechanism of action for pharmacotherapy are not known .One hypothesis is that central nervous system serotonin pathways are disturbed in at least some patients

➢ **Patients lack control** over their eating and participate in recurrent compensatory behavior to prevent weight gain

- **Behaviors: purging** (by use of vomiting/ laxative/ diuretic) or **non-purging type (uses other fasting or excessive exercise)**

- **Bulimia Vs Bing Eating:** purging is an issue in bulimia but not in binge eating

Binge-Eating Disorder

- Patients with BED present with recurrent episodes of bingeing **without** the compensatory behaviors associated with AN or BN
- **Depression and low self-esteem are common**

- **Diagnostic criteria:**
- **Similar to BN without compensatory behaviors**
- **with at least three of the following:** eating more rapidly than normal/ eating until feeling uncomfortably full eating large amounts of food
- **When not physically hungry; eating alone because of embarrassment of how much is being eaten; and feeling disgusted with oneself, depressed, or guilty after the episode**

Anorexia Nervosa

- **Anorexia nervosa impacts an estimated 0.9% to 2% of women in the United States, occurring predominantly in girls and young women (90%)**
- **Prevalence:** The estimated lifetime prevalence of anorexia nervosa in **women is 0.9 and in men 0.3 percent**

- **The current preferred treatment approach** for anorexia nervosa (AN) includes a minimum of 6 months of psychotherapy, preferably cognitive behavioral therapy (CBT) in adults and family-based therapy in children

CLINICAL PRESENTATION

Anorexia Nervosa

General

- Restriction of energy intake that leads to low body weight and self-evaluation that is influenced by perceptions of weight and body shape.

Symptoms

- Patients have obsessions and fears about eating and gaining weight.
- They complain about feeling full even when they have eaten very little food.
- Denial of symptoms, failure to recognize low body weight, and low self-esteem.
- Patients often feel ineffective and have a lack of self-control.

Signs

- Weakness, lethargy, cachexia, amenorrhea, vomiting, restricted food intake, inappropriate exercise, delayed sexual development, edema, delayed gastric emptying, constipation, abdominal pain, bradycardia, hypotension, osteoporosis, dry cracking skin, lanugo, callus on dorsum of hand, cold intolerance, perioral dermatitis, and erosion of dental enamel.

Laboratory Abnormalities

- Hypokalemia, hypochloremia, hypothyroidism, hypophosphatemia, hypokalemic alkalosis, hypomagnesemia, metabolic acidosis, blood urea nitrogen, hepatic enzymes, leukopenia, thrombocytopenia, anemia, QT interval prolongation, bradycardia, hypercholesterolemia, and bone mineral density.

Other Diagnostic Tests

- Nonspecific electroencephalogram (EEG) changes.

Treatment

- **The goals for patients** : reduce distorted body image
- **Restore and maintain healthy body weight**

- Establish normal eating patterns
- **Improve psychological, psychosocial,** and physical problems; resolve **contributory family problems**
- **Enhance compliance (follow up)**; and prevent relapse

Anorexia nervosa

- The treatment of anorexia nervosa generally involves **nutritional rehabilitation and psychotherapy**
- **Provision of enough calorie, pr/ vitamins and miner is important by food or supplement**
- **Caution about refeeding syndrome**

- **CBT encourages patients to:** change the dysfunctional cognitions (thoughts and beliefs about **body weight and shape**) and behavioral disturbances (eg, excessive food restriction) that perpetuate anorexia nervosa, and places less emphasis upon the factors that caused the disorder

Goal is a healthy weight, which typically requires a BMI ≥20 kg/m2

Pharmacotherapy

- **Pharmacotherapy** is not an initial or primary treatment for anorexia nervosa

- **1.Antidepressants** currently have no role in the acute treatment of AN, unless there is another clinical indication present
- **Fluoxetine continues to be the most widely studied SSRI in AN.**
- **Mild to moderate comorbid depressive or anxiety** disorders often resolve with standard treatment

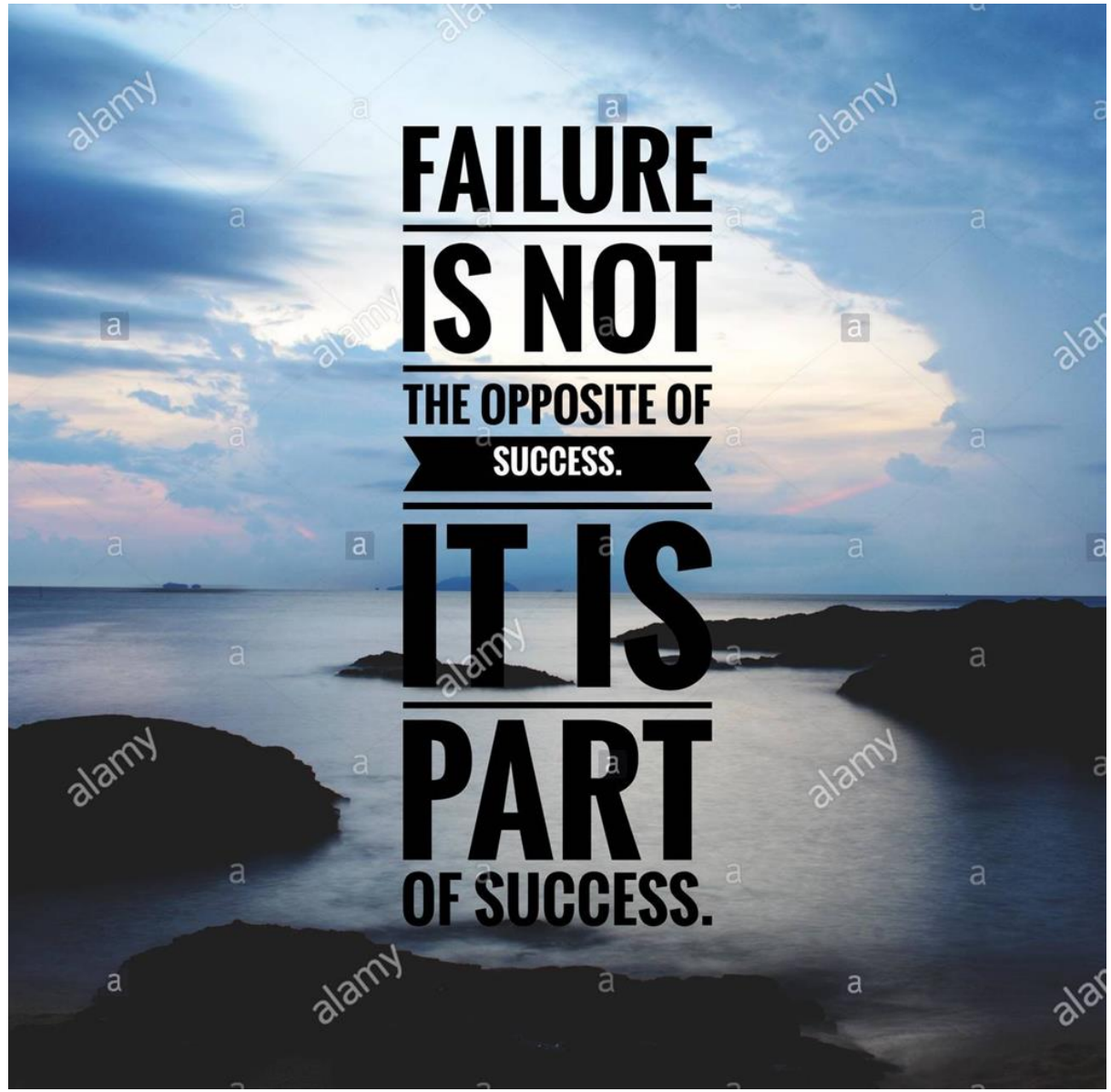
- **2.Antipsychotic medicine: olanzapine** 2.5 -10 mg (t may cause weight gain)
- After restoration of weight. Psychotherapy and SSRI (Fluoxetine ,sertraline) may be helpful
- **3. Other**: Metoclopramide (for bloating, early satiety, and abdominal pain) / Benzodiazepine (for anxiety before meal)
- **Zinc** is also being studied to assist with weight restoration

Bupropion is not recommended

Treatment of Binge-Eating Disorder

- **Psychotherapy**
- **Treat other psychiatric disorders such as bipolar, depression ,...**
- **Antidepressant:** SSRIs (fluoxetine then sertraline) are first choice for 9-12 months in bulimia and Bing disorder

- **Stimulant** : lisdexamfetamine, methylphenidate in Bing on
- **Anticonvulsants, antipsychotic,...**


FAILURE
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