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Naltrexone and Bupropion for obesity: an investigational combination pharmacotherapy for weight loss

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❖ Abstract:

Obesity is an emerging disease worldwide. Changing lifestyle habits, particularly increased consumption of high-calorie foods and reduced physical activity, lead to an energy imbalance that leads to weight gain. More than one-third of U.S. adults suffer from obesity, which negatively impacts numerous medical comorbidities, including diabetes mellitus and cardiovascular disease.The severity of the condition necessitates more extreme measures, like as medication, medical devices, and bariatric surgery, even in the face of drastic lifestyle modifications. Cost, accessibility, and perioperative and postoperative problems are the most frequent drawbacks of bariatric surgery. Naltrexone and bupropion are centrally acting drugs that have demonstrated potential efficacy in treating obesity both individually and in combination. Long-term success is unusual in weight loss attempts.Weight gain, recurrent binge eating, conversions and reoperations ranging from 1.6% to 3.5%, and a 7.3% perioperative complication rate are all linked to bariatric surgery.

Keywords: Bupropion, Naltrexone, Contrave, Pharmacotherapy.

❖ Introduction:

Worldwide, obesity defined as a body mass index (BMI) of ≥30 kg/m² is an emerging chronic illness. Recent estimates indicate that 10–30% of adults in European Union countries are fat, and 30–70% of persons are overweight. According to data from the National Health and Nutrition Examination Survey, in the United States, in 2009–2010, about 17% of children and adolescents and more than a third of adults were obese [1]. and linear trend forecasts suggest that 51% of the population will be obese by 2030 [2]. Treating obesity is complex, difficult and often

daunting. Although most people want to lose two to three times more weight than they normally achieve [3]. Lifestyle interventions, consisting of behavioural therapy to reduce food intake and increase physical activity, are strongly recommended as the first line of treatment for obesity [4].

Obesity is associated with diabetes, hypertension, hyperlipidemia, stroke, heart disease, respiratory disease, osteoarthritis and various cancers [5]. The use of medication or pharmacotherapy to promote weight loss or long-term weight maintenance to prevent weight gain has also been shown to be effective and useful, particularly in patients who are unable to lose weight with style treatments alone. It has been argued that behavioral treatments alter the external environment while pharmacotherapy alters the internal environment [6]. Naltrexone/bupropion (Contrave; Orexigen Therapeutics, Inc., La Jolla, CA, USA) is a combination therapy being studied for weight loss and maintenance in obese patients (BMI ≥ 30 kg/m²) or with a BMI ≥ 27 kg/ m² with comorbidities (two or more diseases at the same time) such as diabetes, high blood pressure or hyperlipidemia. Naltrexone is indicated for alcohol and opioid addiction at a usual dose of 50 mg per day [7].

Bupropion is approved to treat major depressive disorder and seasonal affective disorder and to assist in smoking cessation and is generally administered in daily doses of 300 mg [8]. Both active ingredients have been marketed as monotherapy in the USA since 1985. The FDA Advisory Committee voted 13-7 on December 7, 2010 to approve naltrexone/bupropion [9]. However, combined use of bupropion and naltrexone increased activation of proopiomelanocortin (POMC) at approximately 11 Hz [10]. Since the mid-1970s, the prevalence of obesity in adults has doubled, while the prevalence of overweight/obesity in children, adolescents, and young adults has tripled [11,12]. This was despite public health advice on the benefits of exercise and reducing calorie intake [13]. Behavioural interventions such as diet and exercise are the most common weight loss treatments, but many overweight and obese people cannot achieve moderate weight loss with behavioural interventions alone [14]. The FDA's recent approval of two new anti-obesity drugs in 2012 increased the total to three long-term drugs approved by the FDA for the treatment of obesity: Orlistat (orlistat lipase inhibitor for the treatment of obesity), lorcaserin, and the combination of phentermine and Topiramate [15]. Orlistat is a lipase inhibitor that reduces the body's ability to absorb fat from food. Weight loss with orlistat is moderate, between 2 and 4% greater than with placebo [16-19]. With the exception of orlistat, which has a clear peripheral mechanism of action, lorcaserin and phentermine/topiramate are thought to cause weight loss through actions in the brain, although the exact mechanisms are unknown [20]. They should reduce food intake through their eating behavior. However, they can also have other effects that contribute to weight loss. Many physiological processes that reduce appetite also reciprocally regulate energy expenditure, although none of the therapies discussed here have been formally studied in humans [21].

❖ Naltrexone:

Naltrexone is an opioid antagonist with a high affinity for the u-opioid receptor. It is approved to treat alcoholism and opioid addiction. For these indications, taking naltrexone in a daily dose of 50 mg is recommended. Naltrexone reduces food intake, possibly by blocking the action of ß-endorphins at the u-opioid receptor, thereby preventing autoinhibition of proopiomelanocortin (POMC) neurons. Naltrexone monotherapy appears to produce long-term weight loss of less than 5% and may be less effective than bupropion monotherapy in terms of the extent of weight loss. Naltrexone undergoes significant first-pass metabolism with an oral bioavailability of 5 to 40%. The activity

of naltrexone is due to both the parent metabolite and 6-B-naltrexol. Naltrexone is primarily eliminated by the kidneys. The mean elimination half-life of naltrexone and 6-B-naltrexol is 4 hours and 13 hours, respectively. Naltrexone should not be used by people with impaired liver function or those who have recently taken opioids. The most important drug interaction is with opioids [22-24].

- **Chemistry and mechanism of action:**

Naltrexone, a pure opioid antagonist, is a derivative of oxymorphone (a semisynthetic derivative of morphine). Its chemical name is 17-(cyclopropylmethyl)-4,5t-epoxy-3. 14-Dihydroxymorphinan-6-one and its chemical formula is $C_2OH_23NO_4$ By competitively binding to opioid receptors in the CNS, naltrexone blocks the effects of opioid medications [25].

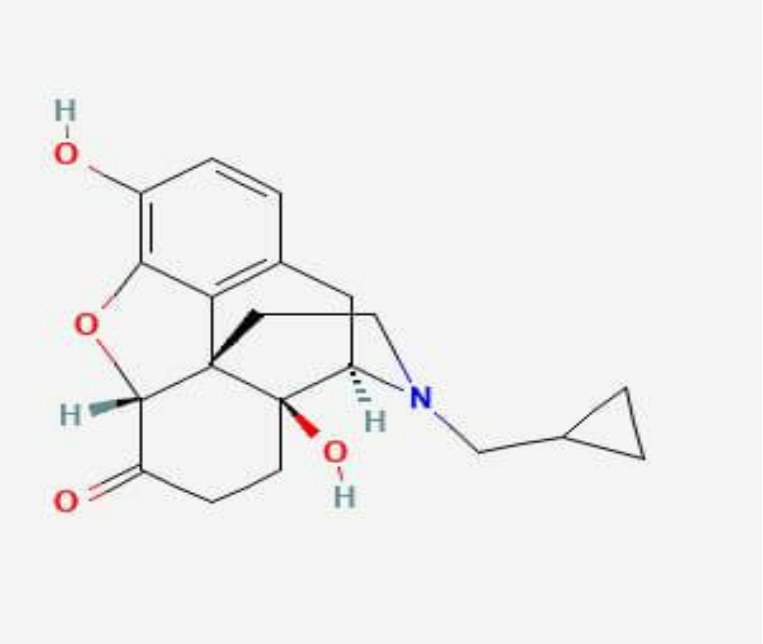

Fig.1 Naltrexone structure ($C_2OH_23NO_4$)

❖ Bupropion:

Bupropion is an atypical antidepressant currently approved as an aid to smoking cessation and for the treatment of depression and seasonal affective disorder [26-28]. Bupropion inhibits the reuptake of the catecholamines dopamine and norepinephrine and is a weak antagonist of the nicotinic acetylcholine receptor [29]. By blocking the synaptic clearance of dopamine and norepinephrine, acute peripheral treatment with bupropion results in transient changes in the extracellular concentrations of dopamine and norepinephrine in the brain and may also alter the activity of neurons that release dopamine and norepinephrine [30-32].

- **Chemistry and mechanism of action:**

Bupropion, an antidepressant, is structurally different from all other labeled antidepressants (i.e., tricyclic, tetracyclic, selective serotonin reuptake inhibitors), but is very similar in structure to diethylpropion, an appetite suppressant with minimal CNS effects. As a racemic mixture, the chemical name is (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone and the chemical formula is $C_{13}H_{18}ClNO$. It is a weak inhibitor of the uptake of dopamine and norepinephrine in the central nervous system (CNS) [33].

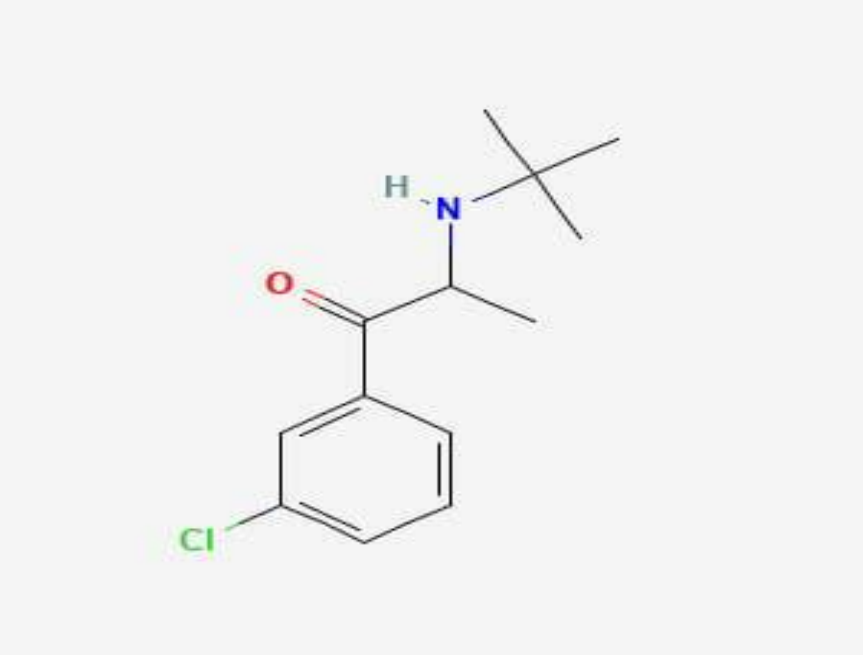

Fig.2 Bupropion structure ($C_{13}H_{18}ClNO$)

❖ Naltrexone / Bupropion:

Naltrexone is a nonselective opioid receptor antagonist used to treat opioid and alcohol addiction. Bupropion is a dopamine and norepinephrine reuptake inhibitor approved in certain countries to treat depression and nicotine addiction. Naltrexone/Bupropion (Contrave 8/90) is an oral, extended-release formulation of naltrexone hydrochloride and bupropion hydrochloride [34]. The naltrexone/bupropion combination is commercially available as a fixed-dose combination of extended-release (PR) naltrexone and PR-bupropion in a single tablet (NB32). Each tablet contains 8 mg naltrexone PR and 90 mg bupropion PR. The FDA approved the naltrexone/bupropion combination, marketed as Contrave, in September 2014 for the treatment of obesity. The EMA has approved naltrexone/bupropion, marketed under the name Mysimba (Mysimba drug used together with diet and exercise to control weight in adults). In March 2015, the launch of a weight loss pill to treat obesity was introduced. Dose titration at the start of naltrexone/bupropion treatment is aimed at reducing the main side effect, namely nausea [23,24][35-38].

- **Mechanism of action:**

Naltrexone and bupropion modulate two brain regions that control eating behavior In the melanocortin system of the hypothalamus, naltrexone and bupropion work synergistically to reduce hunger. There is evidence that both naltrexone and bupropion individually suppress hunger. However, the combination of both active ingredients appears to have a synergistic effect. The reason for this was shown in in vitro studies using the hypothalamus of mice. Bupropion activates proopiomelanocortin (POMC) neurons, increasing the production of proopiomelanocortin (POMC), which can be broken down into MSH and ß-endorphin. As mentioned above, MSH strongly inhibits food absorption. In contrast, it has been hypothesized that B-endorphin, acting through the u-opioid receptor, inhibits the activity of POMC neurons. Therefore, inhibition of the action of B-endorphin with naltrexone leads to an increase in the activity of proopiomelanocortin (POMC). Mechanism for increased

activation of proopiomelanocortin (POMC) neurons observed when bupropion is combined with naltrexone [34,39-41].

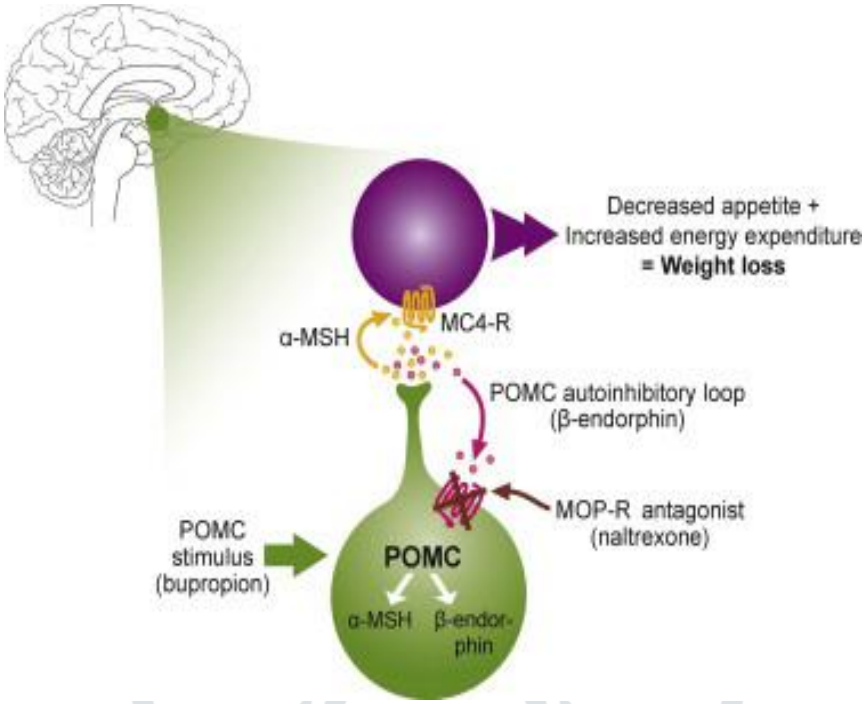

Fig.3 Synergistic mechanism of action of naltrexone/bupropion in the melanocortin system of the hypothalamus, which regulate appetite and energy expenditure.

- **Dosage and administration:**

Naltrexone/bupropion is indicated as an adjunct to a low-calorie diet and increased physical activity for the treatment of obesity in adult patients (≥ 18 years) with an initial BMI of ≥ 30 kg/m² (obese) or ≥ 27 kg/m². M² to <30 kg/m² (overweight) in the presence of one or more weight-related comorbidities (e.g. type 2 diabetes, dyslipidemia or controlled hypertension). Naltrexone/bupropion 8 mg/90 mg modified-release tablets should be administered. Swallow whole with water and preferably with a meal [42].

- **Dosing Schedule for naltrexone and bupropion**

	Morning dose	**Evening dose**
Week 1	1 tablet	None
Week 2	1 tablet	1 tablet
Week 3	2 tablet	1 tablet
Week 4	2 tablet	2 tablet

1. 1 tablet once daily every morning.
2. 1 tablet every morning and evening.

3. 2 tablets every morning and I in the evening.
4. From week 4, 2 tablets every morning and evening [22].

❖ Future application:

The drug has not been studied. Naltrexone/bupropion One-to-One With Other Drugs For weight management, orlistat, a lipase inhibitor, is currently the only FDA-approved drug for long-term weight management. In October 2010, the FDA denied approval of the serotonin 2C agonist lorcaserin (Lorqess, Arena Pharmaceuticals. San Diego, CA, USA) and the combination drug phentermine/topiramate (Onexa, Vivus Pharmaceuticals, Mountain View, CA. USA) for weight management [43,44].

Orlistat is associated with gastrointestinal side effects. and there are rare reports of severe liver damage from its use [45,46]. Lorcaserin is generally well tolerated. Common side effects include nausea, vomiting, headache and dizziness [47].

❖ Adverse events:

1. Adverse events from NB32 can result from the individual actions of naltrexone and bupropion. The common effects of this combination were nausea (29-42%), constipation (16-24%), headache (14). -24%) vomiting (9-18%), dizziness (7-15%), drowsiness (8-11%), dry mouth (6-9%) and diarrhoea (5-15%).
2. Side effects are mild to moderate. It occurs at the beginning of treatment during dose titration. and usually does not lead to treatment discontinuation [35].
3. The most common adverse event is nausea. Most of these are caused by naltrexone. NB32 is associated with very few side effects. especially There is an increased risk of suicidal thoughts due to bupropion.NB32 can cause seizures due to bupropion. and should not be used in patients with seizure disorders.
4. NB32 should be discontinued and not restarted in patients who experience a seizure while being treated with this drug combination.
5. The clinical significance of the small increases in blood pressure and HR observed with NB32 treatment is unclear. This is especially true for patients dealing with heart disease and stroke. This is because patients with a history of heart attack or stroke in the past six months with life-threatening arrhythmia or heart failure were excluded from clinical trials. Blood pressure and pulse should be measured before starting treatment and should be monitored periodically [48].

❖ Pharmacotherapy:

- **Aerobic exercise interventions without calorie restriction:**

Aerobic exercise (AE) is a popular intervention for the management of obesity and overweight. In a recent systematic review and meta-analysis [49]. evaluated the efficacy of Aerobic exercise (AE) in obese individuals. They pooled the results of the 6 months and 12 months programs. Six-month exercise interventions effected a modest weight reduction of 1.6 kg (95% CI, 1.56 to 1.64) Aerobic exercise (AE) for 12 months resulted in a weight loss of 1.7 kg (95% CI 1.11 to 2.29) and a reduction in waist circumference by 1.95 cm (95% CI, 0.29 to 3.62). In addition, a single moderate AE intervention slightly improved blood pressure and lipid levels. However, the results of this meta-analysis showed that 6-12 months of exercise independent of moderate intensity aerobic exercise (AE) causes less weight loss in overweight and obese people. Another randomized controlled trial conducted in Japan involved

obese participants with two or more risk factors for cardiovascular disease [50]. The intervention group used it 2-4 times a week for 6 months. Exercise for 6 months improved the cardiovascular disease risk profile of the participants. Some of our studies have shown that 6-12 months of aerobic exercise (AE) without calorie restriction will cause the initial body weight to decrease by 2-3% Results this finding has been confirmed by several trials. In fact, even a small weight loss of less than 3% can be achieved with a lifestyle that includes weight gain. It has the same health benefits as losing weight without exercise [51]. The relationship between the amount of anaerobic exercise and the rate of weight loss is important. 6 months of moderate aerobic exercise (AE) without calorie restriction In general, weight loss is 2-3% [50,52].

❖ **Bariatric Surgery:**

Weight loss surgery is also called bariatric and metabolic surgery. These terms are used to describe the effect this surgery has on the patient's weight and metabolic health. (breaking down food into energy) more than being able to treat obesity. This surgery is also very effective in treating diabetes. high blood pressure sleep apnea and high cholesterol It includes many other diseases. This surgery can also prevent future health problems. Those benefits help obese patients who choose treatment have a better quality of life and live longer [53]. Bariatric surgery is a well-established and accepted procedure for weight loss and treatment of various conditions. As for obesity, however, not everyone qualifies for bariatric surgery. There are certain requirements that people must meet in order to be a candidate for bariatric surgery. In addition to weight loss surgery, there are also FDA approved weight loss devices for obesity treatment [54].

- **An historical perspective of Bariatric surgery:**

Despite the weight loss that comes with surgery This is especially true if the stomach or small intestine is involved. It has been respected for as long as such programs have existed. But the direct use of surgery for the specific purpose of bariatric surgery to reduce weight began in 1954 with the small intestine bypass procedure. It appears that three phases have passed. The small bowel bypass phase was replaced by the gastric suture phase in the late 1960s and then in the early 1990s laparoscopic surgery and gastric banding were introduced. Causing the third stage [55].

- **Types of Bariatric Surgery :**

1. Sleeve Gastrectomy
2. Roux-en Y Gastric Bypass (RYGB)
3. Biliopancreatic Diversion with Duodenal Switch (BPD/DS)
4. Adjustable Gastric Banding (LAP-BAND®)
5. Laparoscopic surgery
6. Robotic Surgery [54].

1. Sleeve Gastrectomy:

Gastric sleeve, also called sleeve gastrectomy, is bariatric surgery performed to reduce weight. It works by reducing the size of your stomach. The term "gastrectomy" means to remove part or all of your stomach. Gastric bypass surgery removes about 80% of the stomach, leaving behind the "wrapper," a tube the size and shape of a banana. It will reduce the amount of hunger hormones your stomach can produce. This reduces your appetite and cravings. And it can help prevent cravings that make people regain the weight they've lost [56].

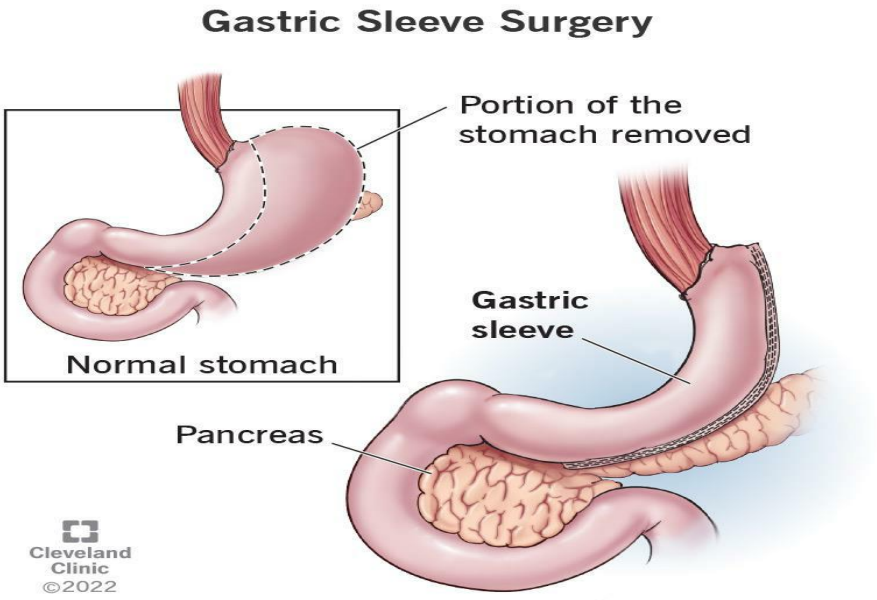

Fig.4 A sleeve gastrectomy divides your stomach to create a narrow gastric sleeve.

- **Advantages**

1. Technically simple and shorter surgery time
2. Can be performed in some high-risk patients
3. Can be performed as a first step in morbidly obese patients
4. **Disadvantages**

1. The procedure cannot be reversed.
2. May worsen or cause acid reflux and heartburn.

2. Roux-en-Y Gastric Bypass:

Roux-en-Y Gastric Bypass, known as "Gastric Bypass" has been performed for more than 50 years and the laparoscopic method has been improved since 1993. It is one of the most common activities and is very effective in its treatment. Obesity and obesity-related diseases The name is a French word meaning "Y-shaped".

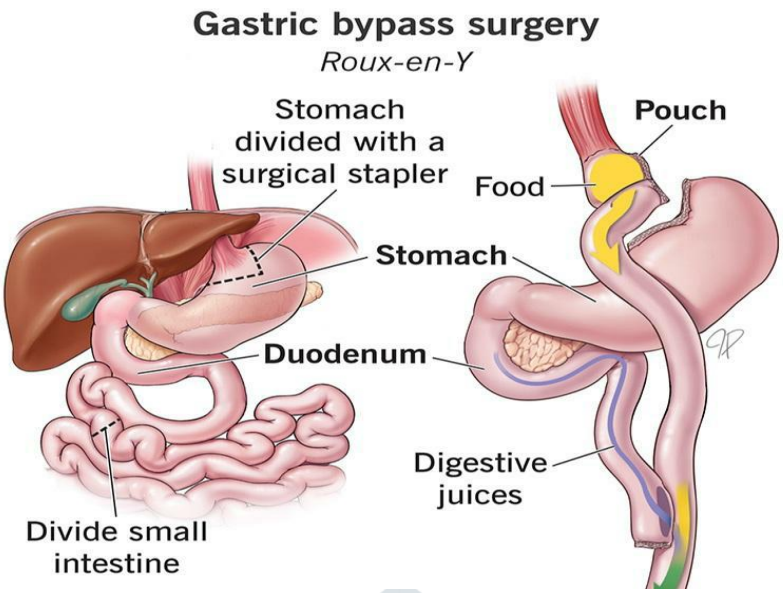

Fig.5 Gastric bypass surgery divide your stomach and your small intestine. The new "branch" of intestine connects to the new stomach "pouch".

- **Procedure :**
  1. First, the stomach is divided into a small upper area (sac) about the size of an egg. Most of the stomach will pass. and no longer collects or digests food.
  2. The small intestine is then separated and reattached to the stomach cavity to allow food to pass through. The small intestine exits the empty stomach or the large intestine and joins the small intestine about 3-4 meters downstream, creating a Y-shaped intestinal junction.
  3. Finally, stomach acid and digestive enzymes from the stomach and the first part of the small intestine mix with the food you eat.
- **Advantages**
  1. Reliable and Long-Term Weight Loss
  2. Effective in Reducing Obesity-Related Symptoms
- **Disadvantages**
  1. Technically more complicated compared to sleeve gastrectomy or gastric band operation.

3. Biliopancreatic Diversion with Duodenal Switch (BPD/DS):

The biliopncreatic diversion and duodenal switch, or BPD-DS for short, begins by creating a tubular gastric pouch similar to a sleeve gastrectomy. It is similar to gastric bypass. no longer using the small intestine.

- **Procedure**
  1. After creating a sleeve-like stomach The first part of the small intestine is separated from the stomach
  2. A part of the small intestine is pulled and connected to the outlet of the newly created stomach. so that when the patient eats food, the food passes through the sleeve pocket and enters the back of the small intestine.
- **Advantages**
  1. Among the best results in improving obesity 2.m

2. It affects gut hormones, makes you not hungry and full after eating
3. It is the most effective treatment for 2 diabetes.

- **Disadvantages**
  1. It has a slightly higher complication rate than other procedures
  2. Acid reflux and heartburn may occur or worsen [53].

4. Adjustable Gastric Banding:

An example of an adjustable gastric band is the LAP-BAND®, which involves placing a silicone rubber "band" over the stomach. How is it conducted? Basically, the "band" divides the stomach into two parts: a small upper pouch and a large lower pouch. The tourniquet is connected by tubing to a port (filler) under the skin of the abdominal wall. It is usually located in the navel area. (The location of the hole varies by surgeon.) The port cannot be seen from outside. And often they don't feel it. Inside the "belt" is a balloon that can be filled with liquid through a hole. When the balloon is full Food moves slowly from the top bag to the bottom. Patients will feel full when eating small portions. You will work with your surgeon to determine the right amount of padding or brace adjustment for you [54].

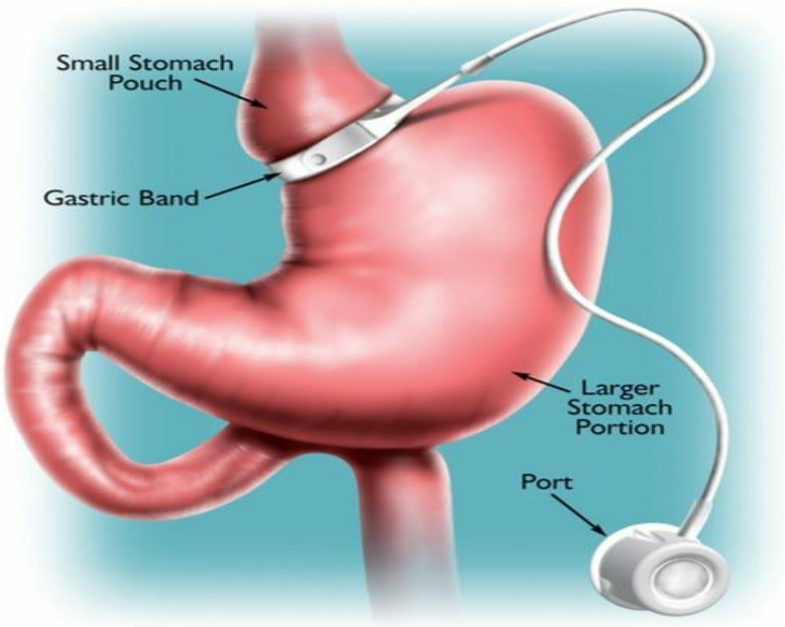

Fig.6 Adjustable Gastric Banding

- **Advantages**
  1. The complication rate after surgery is reduced
  2. No stomach or intestines are separated
  3. Patients can go home on the day of surgery
  4. The band can be removed if needed
- **Disadvantages**
  1. The band may require several adjustments and visits to the doctor every month during the first year
  2. Weight loss is slower and less than other surgical procedures [53].

5. Laparoscopic procedure:

In laparoscopic surgery, a small video camera is inserted into the abdomen through a small incision. It allows the surgeon to perform and view the procedure on a video screen. Both the camera and the surgical instrument will be inserted through a small incision. made on the abdominal wall The number of incisions will vary depending on the surgical procedure and the surgeon's experience. Some surgical procedures can be performed using a single incision. while other steps may involve 6 or more small wounds [54]. The laparoscope camera projects an image of the inside of your belly or pelvis onto a monitor in real time. Using these images, surgeons can watch their hand motions during the procedure. Your healthcare provider might recommend a laparoscopy if other diagnostic tests can't identify the cause of your condition. Healthcare providers also use laparoscopy to collect tissue samples (biopsies) for testing [56].

6. Robotics:

In the surgical robot A small 3D camera will be inserted into the abdomen. The robotic arm holds a variety of tools, including scissors, boring machines and staplers. These are inserted into the abdomen through a small incision. The surgeon places a computer keyboard next to the patient and uses special equipment to "drive" the robotic arm to perform the operation [54].

- **Surgical complications:**
  1. Bleeding.
  2. Infection.
  3. Blood clots.
  4. Hernias.
  5. Small bowel obstruction.
  6. Anastomotic leaks.
- **Bariatric surgery side effects:**

1. **Dumping syndrome –**

This is a syndrome that can occur when the stomach expels food from the intestines too quickly. Up to 50% of people who have weight loss surgery may later develop symptoms of dumping syndrome. Symptoms include nausea, diarrhea, abdominal pain and hypoglycemia.

2. **Malabsorption and malnutrition** -

Most bariatric surgery procedures are designed to promote malabsorption in your small intestine to reduce the calories you absorb. But improper suction can cause loose stools.

3. **Bile reflux** -

Surgery that affects the pyloric valve, which opens between the stomach and the small intestine. It can cause abnormal surgery. If the pyloric valve does not close completely Another possible result is acid reflux. This means that the bile that the gallbladder sends to the small intestine to help with digestion is not distributed to the back of the stomach. Bile reflux can destroy the lining of the stomach. It can cause gastritis and stomach ulcers.

4. **Gallstones –**

Rapid weight loss sends large amounts of cholesterol to the liver for processing. When the liver sends bile to the gallbladder, it also contains more cholesterol. This excess cholesterol can accumulate in the gallbladder. causes cholesterol stones. Stones do not always cause problems. But it can be dangerous if it travels and gets stuck in the bile duct. Your healthcare provider may prescribe medications to prevent gallstones after surgery.

- **Advantages of Bariatric Surgery:**

1. Significant and sustained weight loss. Surgery is the only treatment proven to be effective long term for class III obesity.
2. Hunger hormones are decreased and metabolism is enhanced through surgery. This is the sole treatment for obesity that alters the metabolic programming of the body post-obesity in order to avoid weight regain.
3. Cholesterol and blood sugar management. Weight loss surgery often result in relief of diabetes symptoms and allows people with various metabolic syndromes to stop taking medications [56].

❖ Conclusion:

Naltrexone/Bupropion is an effective agent for weight management. The mechanism of action of both drugs in combination is synergistic or at least fully additive and more effective than in monotherapy. The limited success of obesity medications to date can most likely be attributed to the complexity of brain pathways that regulate hunger, food craving and eating behavior. We are only beginning to understand the powerful influence of factors such as mood and emotion on eating behavior and body weight. In today's environment where foods that are high in fat and sugar are readily available, neural pathways regulating hedonic drives are sure to play a role in weight regain and to limit weight loss attempts. Preclinical studies show that the naltrexone/bupropion combination acts in hypothalamic brain regions that regulate appetite and energy expenditure, while also influencing eating behavior that is mediated by the reward system. The weight loss produced by NB in humans is likely attributed to these dual actions. In clinical studies, a consistently substantial proportion of overweight and obese subjects responded to NB32 treatment with at least 5% or 10% weight loss. These treatment responders are likely those who would benefit most from NB treatment in clinical practice.

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