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# Review of upcoming and currently available anti-obesity drugs in Europe

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**Abstract:**
Obesity is a chronic metabolic disease currently holding status of an epidemic. Number of patients suffering from this condition has been steadily increasing for over 50 years. Complications and comorbidities related to obesity, such as hypertension, diabetes mellitus type 2, coronary artery disease and dyslipidemia are currently the main causes of death in Europe. Therefore, effective anti-obesity treatment as a pharmacological support for weight loss is highly recommended in overweight and obese patients as a therapeutic and preventive measure. This review focuses on selected therapeutic options available for clinicians in Europe.

**Keywords: obesity; pharmacology; liraglutide; semaglutide; tirzepatide**

**Learning points**
1. Pharmacological treatment of obesity has a long history, but most of the drugs approved in the US were withdrawn from or never approved for the European market. Why?
2. As of now clinicians have many options of treatment which they should consider for their patients suffering from overweight and obesity.

3. Studies are being conducted for new drugs (especially new antidiabetic drugs) with possibly remarkable effects on body mass.

## 1. INTRUDUCTION

In 2016 WHO estimated that over 650 million people suffer from obesity worldwide. Furthermore, only in 2017 over 4 million overweight and obesity-related deaths were reported. Obesity is defined as a body mass index (BMI) exceeding 30 kg/m$^2$ and can be divided into 3 classes. (Table 1.)

| **Class of obesity** | **BMI (**kg/m$^2$) |
|---|---|
| Overweight | 25-29.9 |
| Class I | 30-34.9 |
| Class II | 35-39.9 |
| Class III | ≥ 40.0 |

**Table 1.** Classes of obesity characterized by BMI value.

Obesity increases the risk of various health complications, especially cardiovascular diseases, which accounted for 37% of deaths in Europe in 2017 [1] and are currently the first cause of death in the European Union. Obesity is also proven to increase risk of cancers, which are the second cause of death in the EU - 26% [1]. Table 2. lists selected obesity-related cancers. Most of the studies found a linear correlation between increasing body weight and risk of cancer. Overweight patients had smaller risk of developing cancer than obese and severely obese patients. Same principle applies to hypertension risk [2] and diabetes mellitus type 2 risk [3]. Therefore, even if attaining normal weight in certain patients is impossible (whether it is due to coexisting medical conditions, immobility or poor compliance) every body mass reduction is beneficial, potentially prolongs patients' life [4] and increases its quality.

| **Cancer type** | **Risk increase in overweight and obese patients vs general population** |
|---|---|
| Endometrial | Up to 4 times [5] |
| Gastric | 2 times for gastric cardia cancer [6]<br>No increased risk for non-cardia gastric cancer |
| Esophageal adenocarcinoma | 5 times for esophageal carcinoma<br>3 times for esophagogastric junction adenocarcinoma [7] |
| Liver | 2 times [8] |
| Kidney | Up to 2 times [9] |
| Gallbladder and extrahepatic bile ducts | Up to 1.6 times [10] |

**Table 2.** Risk increase of selected cancer types in overweight and obese patients.

As of now, weight loss is recommended for patients with BMI ≥30 kg/m$^2$ or ≥25 kg/m$^2$ coexisting with obesity-related comorbidity (such as increased waist circumference) [11]. First-step intervention should include behavioral changes, dietary restriction and introduction of physical activity.
Low-energy diet (LED, 800-1800 kcal/day) and very low-energy diet (VLED, <800 kcal/day) were to proven to induce a short-term body mass reduction (-9.7% for LED and -16.1% for VLED in 12.7 weeks average) [12]. Long-term effects on body mass of those diets are similar (at >1 year -5% with LED vs -6.3% with VLED). Diet discontinuation risk was similar in patients prescribed LED and VLED.
Physical activity is another recommended non-pharmacological measure to lose weight [13]. Endurance training, high intensity interval training (HIIT) and resistance training decrease body mass. Endurance training and HIIT are similarly effective, but endurance training was proven to have a superior effect on abdominal fat reduction in comparison with HIIT [13]. Minimal recommended exercise time for weight loss is 150 min/week and for prevention it ranges from 250 to 300 min/week.
Additional pharmacological intervention is advised for patients with BMI ≥30 kg/m$^2$ or with BMI ≥27 kg/m$^2$ and coexisting obesity-related comorbidity such as:

- Depression,
- Increased waist circumference,
- Obstructive sleep apnea,
- Cardiovascular disease,
- Diabetes mellitus type 2,
- Metabolic syndrome,
- Dyslipidemia,
- Hypertension,
- Nonalcoholic fatty liver disease.

Bariatric surgery (gastric sleeve surgery being the most common) is recommended for patients with BMI ≥40 kg/m$^2$ or patients with BMI ≥35 kg/m$^2$ with coexisting obesity-related comorbidity.
Selected pharmacological options presented below are available for clinicians in Europe for treatment of obesity. The list also includes few anorectic drugs withdrawn from the European market and new upcoming prospects in pharmacologically-assisted body weight reduction.

## WITHDRAWN MEDICINES

### Sibutramine

Medications containing sibutramine were approved by EMA (European Medicines Agency) in 1999 [14]. This substance was used to treat obesity and facilitate maintaining weight loss in patients with BMI equal to or higher than 30kg/m$^2$. If the patient was in a group with increased cardiovascular risk or other risk factors (such as type 2 diabetes) sibutramine could be prescribed when the BMI was greater or equal to 27 kg/m$^2$. [15]
Sibutramine can be classified as a serotonin-norepinephrine reuptake inhibitor (SNRI). To some extent it also works as a dopamine reuptake inhibitor. By preventing the reuptake of these neurotransmitters in the brain sibutramine increases their levels in synaptic clefts which results in suppression of appetite and enhanced satiety. [16] In turn this mechanism allows the patient to feel fuller after a meal, reduces the amount of food consumed and achieve greater reduction in body weight when combined with a calorie-deficit diet and proper exercise routines.
Adverse effects of using sibutramine overlap with common side effects of popular antidepressants. The most frequent side effects of sibutramine include: dry mouth, nausea, dyspepsia, constipation, sleeplessness, headache, muscle ache and flushing. The most dangerous side effects are related to the cardiovascular system. Sibutramine can substantially increase heart rate and blood pressure. It can also lead to the development of arrhythmias, liver damage and liver failure, paresthesia, seizures, hemiplegia and other critical complications. [17] Sibutramine has also presented several clinically relevant interactions with other commonly used drugs. The most important of these were interactions with monoamine oxidase inhibitors (MAOIs), triptans and some opioids. Concurrent use of these substances can lead to development of serotonin syndrome.
Despite initial popularity and success of medications containing sibutramine it has been noticed that the adverse effects may outweigh potential benefits. By 2003 a number of studies had been published regarding sibutramine safety. In 2002 a large randomized-controlled trial ("SCOUT") began to analyze the impact of sibutramine on both weight loss and related health risks. The study has concluded that sibutramine substantially increased the risk of cardiovascular incidents such as strokes, heart attacks and cardiac arrest [18].
Based on the data from "SCOUT" study and other concerning reports, in 2010 EMA decided to suspend marketing authorizations for all medicines containing sibutramine throughout the European Union. The reason behind this decision was the fact that benefits of treatment with sibutramine do not outweigh its risks. [19]
Currently sibutramine is still used by some groups of patients. It can be found in a number of illicit products imported from countries outside of the European Union. This phenomenon constitutes a significant health

hazard, as many of those products do not disclose their full composition. [20] Therefore, in clinical practice it is important to question the patient about all the weight loss supplements they might be taking and review the necessity of their usage in depth.

**Phentermine and phentermine/topiramate**

Phentermine is a chemical compound derived from amphetamine. It can be classified as TAAR1 agonist. [21] Clinically phentermine causes increased release of norepinephrine, serotonin and dopamine into the synapses. This results in decreased hunger perception by affecting the responsible nuclei in the hypothalamus. Moreover phentermine increases breakdown of fat cells by increasing blood levels of adrenaline and noradrenaline. [22]

Phentermine was introduced to the market in 1959 as an anorectic drug. It has been quickly noticed that usage of phentermine leads to increased tolerance of the drug and can cause development of drug-dependance. It can also lead to impaired mental state and cause adverse reactions with alcohol along with other clinically significant side effects. [23]

Long list of adverse effects, risks associated with prescribing phentermine and availability of better alternatives caused the European Commission to withdraw phentermine from the European Union's market in the year 2000. [24]

In 2001 a new drug containing phentermine was developed. This two-component medication is made of phentermine and topiramate which is an anti-epileptic drug used in treating migraines and alcohol dependance. Phentermine/topiramate was never given a marketing authorization in the European Union. Despite proving effective in terms of weight loss the potential risks stemming from treatment with phentermine/topiramate were unacceptable. Most common side effects include unfavorable influence on cardiovascular health, development of psychiatric disorders (such as depression and anxiety) and impairing cognitive functions. [25]

Along with phentermine other anorectic drugs have also been withdrawn from the European Union. The decision was based on an unfavorable risk to benefits profile of these medicines. The affected products were amfepramone, fenproporex, clobenzorex, mefenorex, norpseudoephedrine and phendimetrazine. Some of these substances are still in use outside of the EU and therefore it is crucial to carefully question the patient about any medical product they may be using. [26]

## APPROVED MEDICATIONS

**Bupropion/naltrexone**

Bupropion/naltrexone combination (90 mg of bupropion hydrochloride/8 mg of naltrexone hydrochloride) was approved in Europe in 2015 for treatment of obesity in adults. It is recommended for patients with BMI $\geq$30kg/m$^2$ or for patients with BMI $\geq$27 kg/m$^2$ with obesity related comorbidities. [27]

Bupropion is a norepinephrine and dopamine reuptake inhibitor used as a smoking cessation drug and in treatment of depression. Naltrexone is an opioid receptor antagonist. Combined, those drugs (by influencing satiety and reward centers in the central nervous system) inhibit appetite and lead to decreased caloric intake. It is administered orally (Table 3. for dosing pattern). Treatment should be discontinued after 12 weeks if body mass was not reduced by at least 5%.

Patients who were administered bupropion/naltrexone showed significant body mass reduction (mean -2.53 kg vs placebo), waist circumference reduction (mean -3.14 cm vs placebo) and fasting plasma glucose level (mean -1.19 mg% vs placebo). The patients also showed increased blood pressure (mean 1.47 mmHg systolic blood pressure vs placebo and mean 0.98 mmHg diastolic blood pressure vs placebo). [28]

This drug is contraindicated in patients with uncontrolled hypertension, history of seizures, alcohol or benzodiazepines withdrawal, eating disorders, hypersensitivity to any of the ingredients of the drug and/or currently treated with MAO inhibitors or other drugs with a mechanism of action similar to bupropion or naltrexone.

Selected adverse effect of bupropion/naltrexone may include nausea (common), vomiting (common), headache (common), constipation (common), dizziness (less common), dry mouth (less common), insomnia (less common), diarrhea (less common).

Discontinuation of treatment with bupropion/naltrexone occurred in 23.8% vs 11.9% in placebo. [28] In summary the drug is tolerated moderately due to high prevalence of adverse effects, difficulties in dosing (especially during the first four weeks) and high price.

| Week | Dose |
|---|---|
| 1. | 1-0-0 |
| 2. | 1-0-1 |
| 3. | 2-0-1 |
| 4.+ | 2-0-2 |

**Table 3.** Dosage of bupropion/naltrexone.

**Orlistat**

Orlistat (tetrahydrolipstatin) is an EMA approved anti-obesity medication. Indications for treatment with this drug include patients with BMI ≥30 kg/m$^2$ and patients with BMI ≥28 kg/m$^2$ and risk factors for cardiovascular disease. If after 12 weeks from the start of treatment the patient has not lost 5% of the body weight compared to the weight before the study it is advisable to discontinue therapy. [29]

Orlistat works by blocking gastric and pancreatic lipases. These enzymes are responsible for breaking down triglycerides into free fatty acids and glycerol in the gastrointestinal tract. This results in a smaller amount of free fatty acids in the digestive tract being absorbed into the bloodstream. A decreased absorption of fatty acids directly reduces the risk of developing hypertension, dyslipidemia and promotes weight loss. [30] At the recommended dosage, orlistat decreases the dietary fat absorption by approximately 30%.

Orlistat 60 mg is available as an over-the-counter drug and as a prescription drug in 120 mg dose. The 60 mg dose is better tolerated by patients than the 120 mg dose, and the gastrointestinal side effects are minimal if in the person's diet less than 30% of energy comes from fat. [31] The recommended dosage of the prescription drug is one 120 mg capsule taken with each of three main meals. It should be taken immediately before a meal, during or within an hour after.

Absorption of some vitamins may be impaired during treatment with orlistat. [32, 33, 34] Patients are particularly at risk of developing fat-soluble vitamins deficiencies (A,D,E,K). For this reason, multivitamin supplementation is recommended. There should be an interval of at least 2 hours between orlistat and intake of the multivitamin.

Compared to the placebo group, patients taking orlistat showed decrease in body weight, BMI, waist circumference and the blood cholesterol levels. [35, 36]

Randomized study conducted in 2011 showed statistically significant reduction of body weight, BMI and waist circumference after 24 weeks in study group vs placebo (Table 4.) [37]

| Marker | Effects in study group vs placebo |
|---|---|
| Body weight | -2.1 kg |
| BMI | -1.27 kg/m$^2$ |
| Waist circumference | -2.84 cm |

**Table 4.** Selected mean effects of orlistat 120 mg three times a day vs placebo after 24 weeks.

It is proven that orlistat has a beneficial effect on glucose and insulin levels compared to placebo. This is a very desirable anti-diabetogenic effect in overweight patients who have an increased likelihood of developing diabetes. [35]

Loose stools (28.5%) are by far the most common side effect. They are the result of reduced digestion and absorption of triglycerides from the digestive tract. Abdominal pain was also reported by patients but less frequently. In most cases side effects subside with the duration of treatment and disappear after discontinuation of treatment. Few cases of liver dysfunction have been reported. The scale of liver damage ranged from mildly elevated liver enzymes to liver failure requiring transplantation. [38]

Cases of acute kidney injury (AKI) have been reported. Patients with pre-existing renal impairment were more at risk. [37, 39]

**Liraglutide**

Liraglutide is indicated for the treatment of obesity in adults with a BMI ≥30 kg/m$^2$ and BMI ≥27 kg/m$^2$ with at least one overweight-related comorbidity. [40]

Liraglutide is administered by subcutaneous injection. Its half-life averages 13 hours, therefore it can be administered once a day, preferably at relatively constant intervals during treatment. [41]

Treatment starts with a dose of 0.6 mg/d. The dose is increased weekly by 0.6 mg to reach the therapeutic dose of 3.0 mg/d, which should be maintained until the end of treatment. The treatment should be discontinued if there is less than 5% weight loss for 12 weeks of liraglutide 3 mg/d.

Liraglutide is a GLP-1 analogue. GLP-1 is an endogenous incretin produced by the cells of the small intestine. [42] GLP1 receptors are located in various tissues, such as the central and peripheral nervous system, digestive tract, pancreas, heart and blood vessels. Due to the multitude of tissues and organs affected by GLP-1 analogues, they show a very wide spectrum of positive health effects. GLP-1 analogues cause a delay in gastric emptying, which translates into a prolonged feeling of postprandial satiety. [43] Through a central inhibitory effect on the subjective sense of satiety, GLP-1 analogues may present a positive effect on the induction of weight loss. [44, 45 46, 47] These drugs reduce cardiovascular risk due to reduction of the postprandial rise in circulating lipids. [48]

Based on the randomized study on participants with BMI ≥ 27 kg/m$^2$ and type 2 diabetes the efficacy of liraglutide 3.0 mg/d in the treatment of overweight and obesity was demonstrated. [49]

After 56 weeks, 51.8% (vs 24% placebo) of the subjects lost ≥5% of their body weight and 33.1% (vs 10.6% placebo) lost ≥10% of their body weight. The liraglutide study group also had a greater reduction in HbA1c compared to the placebo group.

A double-blind study published in The New England Journal of Medicine also demonstrated weight loss in people who were administered liraglutide 3 mg/d for 56 weeks. [50]

After 56 weeks patients taking liraglutide lost 5.6% more body weight than patients in the placebo group. There was also a decrease in BMI by 2 kg/m$^2$ more in the control group than in the placebo group. The decrease in waist circumference -4.3 cm vs placebo was documented. [50]

The most common side effects that occurred in both the research group and the control group were gastrointestinal symptoms. In the study group, nausea and diarrhea occurred in 40.2% and 20.4% (vs 14.7% and 9.3% in placebo). Less common side effects included constipation, vomiting and dyspepsia which occurred more often in the study group - 11.6 percentage points (pp), 11.7 pp, and 12.2 pp respectively. [50]

**Semaglutide**

Semaglutide is another GLP-1 analogue which was authorized in the EU as a treatment for obesity in patients with BMI of 30 kg/m$^2$ or greater and in patients with BMI of at least 27 kg/m$^2$ with coexisting weight-related comorbidities. The decision was made in early 2022 based on the positive risk-to-benefit ratio of the drug. [51]

Similarly to liraglutide, semaglutide is an effective and relatively safe substance which significantly facilitates weight-loss process. Numerous studies have been conducted to measure semaglutide's efficacy. They have proven that semaglutide demonstrates a beneficial effect on the reduction of body mass. [52]

In a STEP 5 trial published in 2022 in Nature magazine semaglutide's efficacy was compared to placebo treatment over the course of 104 weeks. Semaglutide was administered in the form of subcutaneous injection once weekly in escalating doses to reach the dose of 2,4 mg or highest tolerated at week 16. Both groups were subjected to behavioral interventions - calorie deficit diet and physical activity regimen.

At the end of the trial semaglutide has proven to be effective in reduction of body weight and other weight-related risk factors, compared to the placebo-receiving group. The mean body weight change in the semaglutide-receiving group of participants was -15,2% while the weight change from the baseline in the placebo group was -2,6% which results in estimated treatment difference (ETD) of -12,6 percentage points. Semaglutide has also demonstrated greater reduction in waist circumference (-14.4cm) vs placebo (-5.2cm, EDT 9.2cm) (Table 5.). Semaglutide, compared to placebo, also had a beneficial influence on systolic blood pressure, diastolic blood pressure, fasting plasma glucose, C-reactive protein, HbA1c, lipid blood profile and fasting serum insulin. Adverse effects of semaglutide use are consistent with other GLP-1 analogues. They present in the form of mild-to-moderate and transient gastrointestinal symptoms. [53]

| Marker | Mean effect vs placebo |
|---|---|
| Body mass reduction | -12.6 pp |
| Waist circumference | -9.2 cm |

**Table 5.** Selected changes in 2.4 mg liraglutide vs placebo after 104 weeks. (Percentage points - pp)

## POTENTIALLY USEFUL AND UPCOMING MEDICATIONS

### SGLT2 inhibitor/GLP1 analogue combination

SGLT2 inhibitors (SGLT2i - flozins, gliflozins) promote urinary secretion of glucose by inhibition of reuptake of glucose in the proximal tubule of nephron leading to net loss of calories with urine. They received approval for treatment of type 2 diabetes (dapagliflozin, empagliflozin, ertugliflozin, canagliflozin). Additionally, empagliflozin was approved for treatment of symptomatic chronic heart failure.

Although in monotherapy flozins to some extent promote weight loss, the effect is hard to maintain due to compensatory mechanisms, such as secondary increase of caloric intake promoted by renal loss of glucose. [54] Mentioned before GLP-1 analogues increase satiety and lessen high-calorie food craving therefore, to some extent, they potentialize SGLT2i-promoted weight loss while having their own beneficial effect. [55]

Randomized placebo controlled studies in overweight and obese patients with no coexisting diabetes (oral dapagliflozin 10 mg daily and subcutaneous exenatide 2 mg weekly) conducted in 2016 with follow-up study in 2017 showed sustained mean weight loss (-4.5kg at 24 weeks vs placebo, -5.7kg at 52 weeks vs placebo) with predominantly adipose tissue loss without changes in lean body mass (Table 6.). [56] Participants attrition rates after 52 weeks were similar in both groups (36% study vs 32% placebo), therefore the combination is well tolerated. Most frequently reported side effects included nausea and injection site irritation.

| Marker | Mean change vs placebo after 52 weeks |
|---|---|
| Body weight | -5.7 kg |
| Adipose tissue volume | -5.3 l |
| Systolic blood pressure | -12 mmHg |

**Table 6.** Selected mean effects of dapagliflozin/exenatide after 52 weeks vs placebo.

### Tirzepatide

Tirzepatide is authorized for use in the EU from September 2022. It can be used in patients with type 2 diabetes mellitus with unsatisfactory serum glucose level control as a supplemental intervention along with dietary modifications and physical activity. Treatment with tirzepatide can be both a monotherapy and a combination treatment with other anti-diabetic drugs. It is administered in a form of once-weekly subcutaneous injections. [57]

Biochemically tirzepatide is a synthetic peptide which exhibits affinity to both glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors. Therefore tirzepatide can be described as a GIP and GLP-1 analogue. By binding to those receptors tirzepatide causes an increase in both GIP and GLP-1 blood levels after a meal, which stimulates production and release of insulin from pancreatic islet beta-cells and decreases release of glucagon. This mechanism leads to an effective reduction of hyperglycemia in DM2 patients. Tirzepatide has also been proven to increase levels of adiponectin which has a beneficial effect on both lipid and glucose metabolism. [58]

A large phase 3 international clinical trial was conducted to examine tirzepatide's safety and efficacy in treatment of adults with obesity and overweight adults who do not have diabetes. The results were published in the New England Journal of Medicine (NEJM) in 2022. [59]

The study lasted for 72 weeks during which participants were administered placebo or different doses of tirzepatide (5mg, 10mg and 15mg) once weekly in a form of subcutaneous injections. Additionally the

participants were attending regular lifestyle counseling sessions which provided them with information necessary to keep a balanced, healthy calorie-deficit diet as well as a 150 minutes a week training program. [59]
At the end of the study for the treatment-regimen estimand mean body mass change was -15% for 5mg tirzepatide group, -19,5% for 10mg dose group and -20,9% in the group which received the highest dose of 15mg tirzepatide. In the control group which was receiving a placebo mean body mass change was only -3,1% (Table 7.). The mean reduction of body fat mass was also greater in the tirzepatide-receiving group – 33,9% vs 8,2% in the placebo group. [59]

| | **5 mg tirzepatide** | **10 mg tirzepadie** | **15 mg tirzepatide** |
|---|---|---|---|
| Mean body mass reduction vs placebo | -11.9 pp | -16.4 pp | -17.8 pp |
| Mean waist circumference reduction vs placebo | -10.1 cm | -13.8 cm | -14.5 cm |

**Table 7.** Selected effects of tirzepatide vs placebo after 72 weeks. (Percentage points - pp)

Benefits of tirzepatide treatment were noticed also in respect to blood pressure (both systolic and diastolic), lipid levels, fasting insulin levels and waist circumference. Moreover, at the end of the study 95,3% of participants receiving tirzepatide who were diagnosed with prediabetes have achieved normoglycemia while in the placebo group this effect was noted in 61,9% participants. Therefore tirzepatide not only has presented benefits associated with weight reduction but also has beneficially influenced cardiometabolic risk factors. [59]
Adverse effects were reported in the tirzepatide-receiving group and in the control group of participants. The most common side effects were nausea, diarrhea and constipation. They were mild to moderate and transient in nature. Serious adverse effects were occurring in a similar percentage of participants in both groups. Based on these findings, the safety profile of tirzepatide is consistent with other incretin-based treatment methods. The side effects are usually the most prominent in the dose-escalation period and mostly appear in the form of mild-to-moderate gastrointestinal events. [59]
Tirzepatide demonstrated superior efficacy in terms of weight loss compared to other anorectic medicines. Given its positive influence on numerous health risk factors and good safety profile it might be a promising method of treating obesity in the near future.

**Discussion**

Effective treatment of overweight and obesity allows to avoid or at least diminish the risk and severity of secondary complications of excess body weight. Modern pharmacology offers a wide variety of medicines facilitating a cost-effective management of body weight. Non-pharmaceutical interventions (such as behavioral changes, diet and physical activity) still remain a first choice for weight loss. In case of failure of non-pharmacological methods clinicians are equipped with efficacious tools to aid patients in their weight loss process. Currently numerous substances are approved in the European Union for treatment of obesity. More and more existing drugs are receiving recommendations for that use. Many new substances are being developed and tested as possible treatments. As the obesity rates are alarmingly on the rise, research for even more effective pharmacological and systemic methods of addressing that issue is needed.

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