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Review article

Semaglutide: effects on eating behavior

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Abstract

Introduction. Drugs from the group of glucagon-like peptide-1 receptor agonists were originally intended to be used to treat patients with type 2 diabetes mellitus. However, with their use, a noticeable weight loss effect was noted, which expanded the list of indications and currently these drugs are prescribed to obese individuals, regardless of the presence of diabetes mellitus. On the Russian market, semavic (semaglutide) has established itself as an effective treatment for obesity.

Aim. To assess the effect of semaglutide on eating behavior in the process of weight loss.

Materials and methods. The literature search was carried out using the PubMed and Google Scholar databases. The selection of publications was carried out according to the principle of open free access, analysis of abstracts and assessment of relevance.

Results. A total of 35 articles were selected for review: 7 Russian-language articles and 28 foreign sources. Data from the vast majority of publications show that semavik for weight loss is prescribed at a dose of 0.5–2.4 mg per week subcutaneously for a course of up to 68 weeks. In alternative cases, the drug is taken orally. The maximum weight loss was 9.6–17.4 % of initial body weight. The most common manifestation of complications was gastrointestinal disorders, but only for a small number of patients did they become a reason to refuse to continue therapy. In trials of the drug, a reduction in the total calorie intake was noted in the absence of external dietary restrictions.

Conclusion. The prescription of semavik is accompanied by increased self-control when eating. Self-control extends not only to food, but also to drinking alcohol. Approximately half of patients indicate an improved quality of life. Activation of metabolism appears to be associated with a decrease in insulin resistance, an increase in insulin concentrations, an effect on the effects of cortisol, and an effect on the hypothalamic-pituitary-adrenal axis.

Keywords: obesity, diabetes, overeating, semaglutide, glucagon-like peptide-1

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INTRODUCTION

Nutritional disorders include a pathology with excessive or inadequate in calories consumption of food, as well as with significant dietary deviations from a balanced diet. One of the most common reasons of overeating is psychogenic (compulsive, hyperphagic) response to stress, known eating disorder that leads to excessive eating, body weight gain and obesity. The situation can be aggravated by existing metabolic disorders. Management of psychogenic overeating is mainly within the competences of two professionals, a psychiatrist (or, in mild cases, a psychologist) and a dietitian. It is necessary to analyse conditions or a mechanism that triggers overeating. People often try to solve the problem by substitution, through increasing number of other enjoyments, action games, active social life, etc. When obesity occurs because of stress, antidepressants and weight loss drugs can be prescribed. Semaglutide has often been prescribed for the treatment of obesity in recent years. It shortens periods of overeating and helps to reduce body weight [1]. Due to the sanctions regime, the imported semaglutide (Ozempic) in the Russian market was replaced by Semavic (active ingredient: semaglutide, GEROPHARM, Russia). A comparative clinical study of Semavic and imported semaglutide showed their bioequivalence and the Russian analogue safety [2].

The study **aim** was to investigate the action of semaglutide on the human body and behavior while undergoing a course of weight loss.

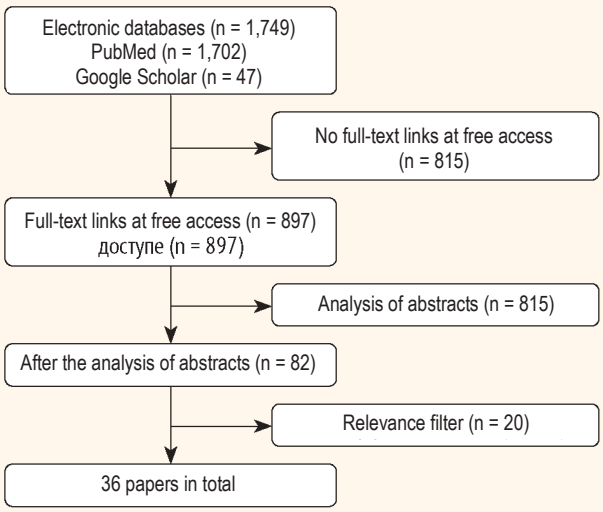
MATERIALS AND METHODS

The literature search for the review was carried out using the PubMed and Google Scholar databases. The search was made with the key phrases: semavic, Ozempic, and ozempic. See the main stages of this search in *Figure 1*.

As a result, the final reference list included 35 sources including 7 papers in Russian and

28 papers in English.

Figure 1. Stages in a literature search



RESULTS

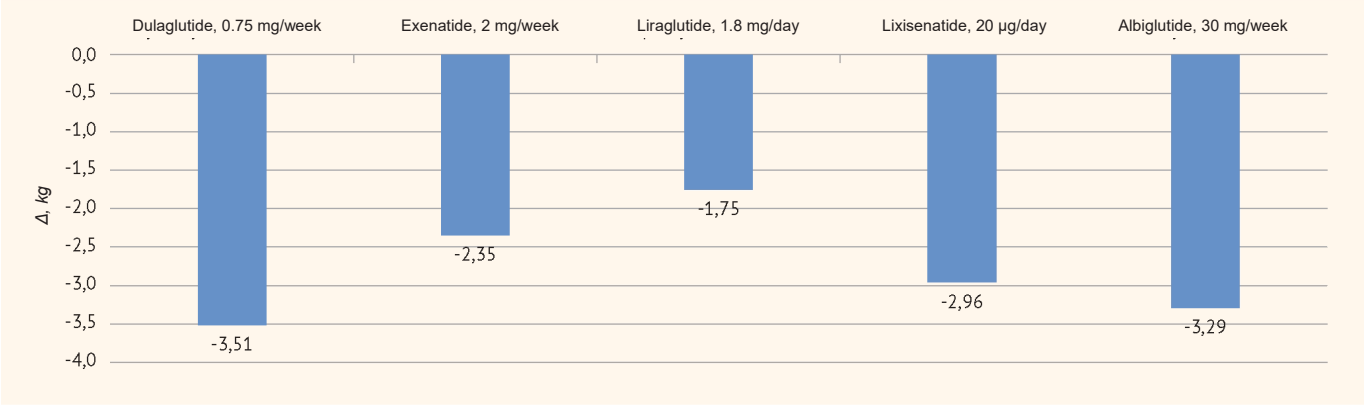
Thirty-six sources from among the selected ones were own clinical trials (including retrospective observational studies) and animal model studies. The remaining sources were reviews summarizing the main common patterns related to the use of semaglutide as a medicinal product for weight loss.

Semaglutide characteristics

Semaglutide is an analogue of natural human glucagon-like peptide-1 (GLP-1) having a prominent (94 %) structural homology. Modification of the product molecule allows using it 1 time per week in injections. Semaglutide is more effective than other GLP-1 analogues as concerns normalizing the body weight in diabetic patients (*Figure 2*) [3].

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are a priority treatment for patients who are overweight secondary to diabetes mellitus. The American Diabetes Association (ADA) updates the position about the role of GLP-1 RAs in treatment of the concerned patient group along with the drug therapy and psychological support.

Figure 2. Difference in weight loss changes (kg) while taking semaglutide (1 mg per week) and other GLP-1 receptor antagonists combined with oral sugar-lowering agents at the end of treatment [3]



Increase of GLP-1 concentration as caused by GLP-1 RAs results in appetite suppression, reduction of the total volume and frequency of food intakes [4]. Semaglutide has a low molecular weight allowing it to penetrate into the brain and take part in appetite and satiety regulation [3].

Effect of semaglutide on weight loss

The basis of obesity treatment is lifestyle changes involving normalizing diet and increasing physical activity. Nevertheless, in the overwhelming majority of cases, it is not sufficient to reach direct results and patients are prescribed to take drug therapy. The following medications for obesity treatment are authorised in the Russian Federation: liraglutide, sibutramine, reduxin (metformin in combination with sibutramine), orlistat [5]. The USA have the vastest market of weight loss medications. By now, the Food and Drug Administration (FDA) has approved a number of weight loss medicinal products, including orlistat, phentermine/topiramate, naltrexone/bupropion and GLP-1 RA liraglutide and semaglutide. The latter was approved by the FDA in 2021. The results of Phase III of STEP clinical trial programme (The Semaglutide Treatment Effect in People with Obesity) showed that semaglutide conduced to the clinically significant weight loss in obese people versus placebo [6].

By now, there have been received a large number of weight loss proofs in patients, even though initially the product was expected to be used as a hypoglycemic agent. Semaglutide demonstrates a far higher hypoglycaemic activity than other analogues (liraglutide, dulaglutide, exenatide, etc.). When semaglutide as 0.5 mg injection was added to basal insulin and oral blood sugar-lowering medications, the discernibly better glycaemia control and HbA level decrease were noted as compared to combinations with other medicinal products from GLP-1 RA group. Semaglutide 1.0 mg excessed all the medications from GLP-1 RA group in glycaemia control level [3].

Treatment of patients with type 2 diabetes (T2D) with semaglutide plus metformin throughout 16 weeks resulted in weight loss on average from 87.3 ± 1.2 kg to 79.8 ± 0.9 kg, waist circumference reduction from 87 ± 2 cm to 82 ± 1.2 cm [7].

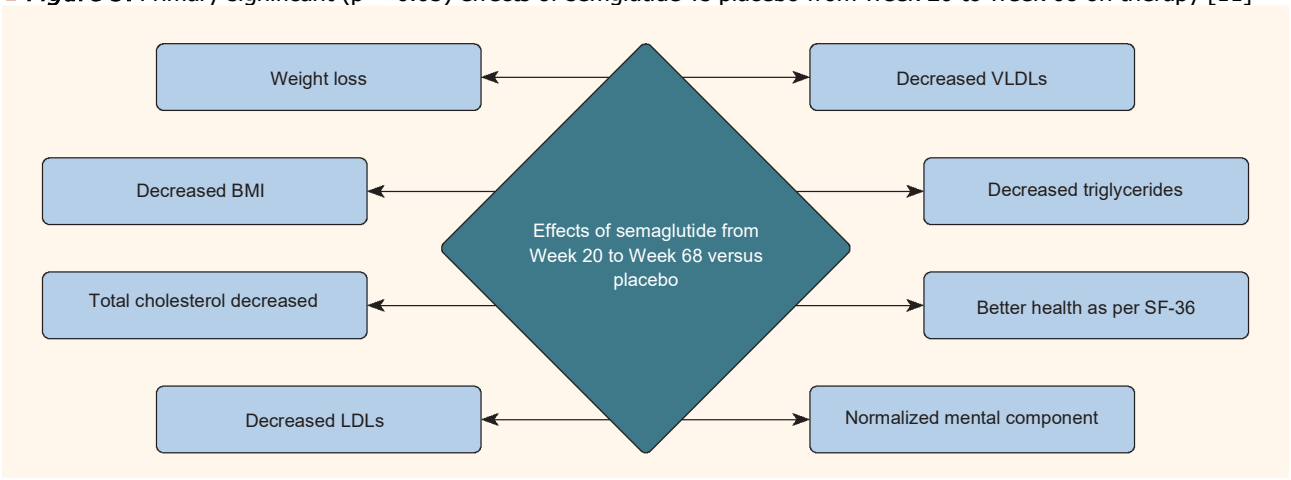
Decrease of the total body weight and fat mass sets off the mechanism for satiety signal activation and hunger effect reduction, as well as better control of eating and reduction of food cravings (especially to fatty food). It is surmised that weight loss increments insulin resistance [8, p. 171–178].

In their study, J. Blundell et al. analyzed effects of 12-week treatment with semaglutide subcutaneously once a week with the dose increase to 1.0 mg in obese persons (n = 30). After a standard breakfast, the semaglutide injection (compared with placebo) led to a lower energy intake during lunch while there were no food restrictions (-1,255 kJ; p < 0.0001), during a dinner (p = 0.0401) and snacks (p = 0,0034). This resulted in a 24 % reduction in total energy intake with ad libitum dietary regimen (-3,036 kJ, or 725 kcal; p < 0.0001). Semaglutide administration was associated with less hunger and food cravings, better control of eating, and a lower preference for high-fat foods [9].

Semaglutide 2.4 mg consistently demonstrated the clinically significant weight loss in all the STEP 3 trials (semaglutide treatment effect in obese patients, n = 611), while its long-term efficacy and safety were confirmed for a period of up to 2 years [10]. Phase IIIa of STEP clinical programme involved checking the semaglutide effect in long-term therapy (2.4 mg per week) for a long-time weight loss in obese subjects. The study was conducted for 68 weeks in 902 subjects with the BMI of more than 30 kg/m^2. Weight loss from Week 20 to Week 68 was -7.9 % vs +6.9 % in the placebo group (p < 0.001). Waist circumference decreased by 9.7 cm (*Figure 3*) on average [11]. The review made by N. Bergman et al. shows that semaglutide 2.4 mg was associated with mean weight losses of 14.9–17.4 % in individuals with overweight or obesity (without diabetes) from baseline to Week 68 [12].

STEP programme (n = 1,961) evaluated the consequences of semaglutide withdrawal (2.4 mg/week, 68 weeks) for the patients' body weight. Right after the therapy completion the weight loss in the semaglutide group and placebo group was -17.6 % and -2.0 %, respectively. By Week 120, the patients regained the previously lost weight by 11.6 % and 1.9 %, respectively, resulting in net body weight losses of -5.6 % and -0.1 % [13]. Phase IIIb of STEP programme (n = 338) compared effects of semaglutide (1.7–2.4 mg/week) and liraglutide (3 mg/day) within a 68-week therapy in 338 overweight or obese patients. The therapy was accompanied by diet and physical activity. The mean weight change from baseline was -15.8 % with semaglutide vs -6.4 % with liraglutide. There gastrointestinal adverse events were reported for 84.1 % in semaglutide group and for 82.7 % in liraglutide group [14].

Figure 3. Primary significant (p < 0.05) effects of semglutide vs placebo from week 20 to week 68 on therapy [11]



STEP 1, 3 and 4 were Phase III of 68-week double-blind, randomised, multicentre, multinational studies of different designs. The subjects in STEP 1 and 3 were randomised (2:1) to receive semaglutide 2.4 mg subcutaneously once a week or placebo, accompanied with a lifestyle change (STEP 1) or intensive behavior therapy (STEP 3) during 68 weeks. STEP 4 subjects changed their lifestyle throughout the entire study and initially received semaglutide subcutaneously within a 20-week run-in period. The subjects who reached the maintenance dose of 2.4 mg by Week 16 and continued receiving it at Week 20 were randomised (2:1) to continue semaglutide or switch to placebo during Weeks 20–68 with a follow-up period of 7 weeks. As per results of Phase III semaglutide trials in STEP programme (STEP 1, 3, and 4, n = 3,375), significantly more subjects with baseline prediabetes had normoglycaemia at Week 68 with semaglutide versus placebo (Step 1: 84.1 % vs 47.8 %; Step 3: 89.5 % vs 55.0 %; Step 4: 89.8 % vs 70.4 %, p < 0.0001). Fewer subjects with baseline normoglycaemia had prediabetes at Week 68 with semaglutide versus placebo (Step 1: 2.9 % vs 10.9 %; Step 3: 3.2 % vs 5.8 %; Step 4: 1.1 % vs 5 %) [15]. Semaglutide (2.4 mg/week) was effective for weight loss in adolescents (n = 201) with BMI ≥ 95 percentile and overweight ≥ 85 percentile. The medicinal product caused the significant weight loss (-16.1 % vs 0.6 % in the placebo group) by the

end of Week 68 [16]. The incidence of gastrointestinal adverse events was greater with semaglutide (62 % vs 42 %). Semaglutide proved to be effective both in injections and oral administration. Subcutaneous injection of semaglutide decreased body weight more than all the tested analogues, while oral semaglutide decreased body weight more than sitagliptin and liraglutide and with the same effect as empagliflozin [17]. The lack of effect (or insufficient effect) of bariatric surgery was an indication for semaglutide prescription (64.7 ± 47.6 months) that resulted in a relative weight loss by 10.3 ± 5.5 % in 6 months after the onset of the therapy [18]. Comparison of long-term effects of bariatric surgery with semaglutide administration showed that in the first instance there was a higher efficacy in weight loss and treatment of obesity-induced complications such as diabetes. Nevertheless, bariatric surgery is an invasive treatment method and bears a high risk of complications [19].

It was shown that 3 months after semaglutide treatment, the mass of body fat, fat weight percentage, and mass of skeletal muscles reduced. At the same time, the percentage of skeletal muscles did not change [20]. Studies in animal models showed that semaglutide considerably reduced body weight and accumulated intramuscular fat, promoted muscle protein synthesis, increased a relative proportion of skeletal muscles, and improved muscle function by improving muscle metabolism [21].

Semaglutide improves postprandial metabolism of glucose and lipids, as well as delays stomach emptying. The latter may postpone the next food intake and/or make it less rich in calories. Postprandial glucose concentration curve (0–5 hours) was significantly lower in the semaglutide group versus placebo (estimated coefficient = 0.71, $p < 0.0001$). Similar results were reported for postprandial glucagon concentration, lipid profile improved [22]. Glucose level normalization, in its turn, may reduce concentration of blood insulin that is conducive to lipid synthesis. Thus, it has indirect normalizing effect on body weight.

Another randomised, double-blind, placebo-controlled study had similar conclusions. Administration of semaglutide resulted in decrease of postprandial glucose (-1.34 mmol/L), insulin (-921 pmol h/L), C-peptide (-1.42 nmol h/L) [23]. The incidence of adverse gastrointestinal events was higher with semaglutide (2.4 mg) than with placebo, the most frequent ones were nausea (43.9 % vs 16.1 %), diarrhea (29.7 % vs 15.9 %), vomiting (24.5 % vs 6.3 %), and constipation (24.2 % vs 11.1 %). Severe adverse events were reported only in 1.9 % of cases. 4.3 % of patients rejected to take semaglutide [24].

Eating behavior management capabilities using semaglutide

Every person has his/her own response to stress (coping strategy). Eating can be one of ways to reduce a problem by regulating the emotional sphere. Eating behavior is defined as a value-based attitude to food, its intake, as well as eating habits in ordinary life and when experiencing stress. For people with eating disorders, the structure of coping strategies is dominated by escape and distancing, i. e. denying the problem through distraction by eating [25]. In this connection, the use of medications for changing eating behavior seems to be an attractive prospect.

In animal models, semaglutide was shown to be able to change eating behavior by reducing the need for food and causing the weight loss without decreasing energy expenditures. Semaglutide directly accessed the brainstem, septal nucleus, and hypothalamus but did not cross the blood-brain barrier. The drug interacted with the brain through the circumventricular organs and several sites adjacent to the ventricles. Semaglutide induced central c-Fos activation in 10 brain areas (including hindbrain areas directly targeted by semaglutide), and secondary areas without direct interaction with GLP-1 receptor (lateral parabrachial nucleus). Activation of c-Fos leads to meal termination controlled by neurons in the lateral parabrachial nucleus. Moreover, there was upregulation of prolactin-releasing hormone and tyrosine hydroxylase (that participates in the synthesis of catecholamines) in the postrema area. Semaglutide probably lowers body weight by direct interaction with diverse GLP-1 receptor populations and by directly and indirectly affecting the activity of neural pathways involved in food intake, reward, and energy expenditure. It is supposed that semaglutide can affect the food intake both hedonistically and homeostatically [26].

The effect of GLP-1 RAs is not fully understood. Significant role is played by L-population of enteroendocrine cells (EECs) that is capable to produce GLP-1. All the hormones produced by EECs transmit a signal from gut to brain and stimulate receptors located in periventricular nuclei of the brain (not blocked by the blood-brain barrier). Intact vagus nerve is required for GLP-1 to affect the food intake. Knockdown and knockout of GLP-1 receptors show that GLP-1 effects which control glucose levels depend on the expression of GLP-1 receptors in peripheral neurons. People who underwent stem vagotomy do not respond to GLP-1 RAs with reduced food intake, stomach emptying, glucagon secretion or pancreatic insulin hypersecretion [27].

M. Friedrichsen et al. studied the effect of semaglutide (2.4 mg once weekly, for 20 weeks) on eating behavior in 72 adult obese patients. The subjects' appetite was assessed using the Control of Eating Questionnaires (CoEQ), and energy intake was measured during a meal ad libitum without any external food restrictions. The study results showed that the energy intake ad libitum was 35 % lower in the semaglutide group versus placebo (1736 kJ vs 2676 kJ, $p < 0.0001$). Semaglutide decreased a feeling of hunger and food requirement, increased a

sense of fullness as compared to placebo, improved eating control ($p < 0.02$) [28]. Oral formulation of semaglutide also effectively influenced the eating behavior. In a double-blind, placebo-controlled study, 15 patients with T2D received semaglutide 3–14 mg orally (gradually increased dose) once a day for 12 weeks. After a standard breakfast, energy intake was 38.9 % lower with semaglutide administered orally as compared to the placebo group (-5,096 kJ, $p = 0.0001$). Following a high-fat breakfast, the semaglutide group showed fewer craving for food and better control over food intake. Weight loss in the patients who received semaglutide was on average 2.7 kg (vs 0.1 kg in the placebo group). Administration of semaglutide led to a general increase in satiety, and better control over food intake [29].

Semaglutide can reduce cognitive dysfunction and have a neuroprotective effect [30]. Cognitive enhancement under the influence of semaglutide is able to explain the increased control of eating.

Analysis of 12,136 comments to medicinal products from GLP-1 RA group (including semaglutide) on 3 websites showed that the majority of matches concerned problems related to sleep (including insomnia), anxiety, depression, and mental health problems in general. After starting the medication, the weight loss was associated with marked improvement or worsening of mood, increase/decrease in anxiety/insomnia, and better control of some addictions [31].

There is an opinion that GLP-1 RAs are antidepressants. Perhaps a significant decrease in body weight has an antidepressant action in itself [32]. Moreover, GLP-1 RAs can neutralize the effect of the stress hormone cortisol that reduces the secretion of GLP-1 in intestinal L-cells [33]. This can lead to additional antidepressant effect. GLP-1 RAs are likely to affect the dopamine reward system and reduce cravings for food and alcohol [34]. In addition to weight loss by 9.6–17.4 % throughout the 68-week course of therapy, semaglutide caused improvements in cardiometabolic and psychosocial parameters. Semaglutide in combination with behavior therapy resulted in greater weight loss (-16 %) as compared to the placebo group (-5.7 %) where only behavior therapy was conducted [35]. This result may be due to better modulation of eating behavior in response to injections of the medicinal product. It was also noted that semaglutide improved the quality of life in 40–50 % of patients [36].

DISCUSSION

For people with eating disorders, the structure of coping strategies is dominated by escape and distancing, i. e. denying the problem, distraction by eating [25]. Therefore, one of treatment approaches can be shifting attention from food to other pleasures. However, in difficult cases drug therapy of obesity is used.

Analysis of data from literature sources shows that semaglutide is a relevant medication for the treatment of obesity. In addition to weight loss by 9.6–17.4 % from baseline after 68-week therapy, semaglutide has a positive effect on cardiometabolic and psychosocial parameters [35]. Obese patients receiving semaglutide showed decreased effect of hunger [8], reduced volume and frequency of meals [4]. When taking semaglutide, the patients report an increase in self-control not only with regard to food but also to bad habits [34]. So there is enhanced self-control in general, not only that related to food. Energy restriction is probably affected by the dopamine reward system that is activated by semaglutide. Besides, semaglutide can neutralise some effects of cortisol that often triggers the pathogenesis of obesity [33]. The important result of taking semaglutide is improved quality of life in most patients, which may be due to the weight loss.

Semaglutide proved to be effective both in subcutaneous injections and oral administration. The advantage of semaglutide was that it caused a decrease in body weight primarily due to fat tissues, while the muscles were not affected. At the same time, improvement in muscle functions due to activation of muscle protein synthesis and local metabolism was observed [21].

CONCLUSIONS

Finally, we have come to the following conclusions:

1) 68-week course of semaglutide injections (0.5–2.4 mg/week) leads to a decrease in body weight by 9.6–17.4 % from baseline;

2) Semaglutide acts similar to the natural human glucagon-like peptide-1 (GLP-1) and promotes the activation of c-Fos gene in 10 brain areas that leads to meal termination controlled by neurons in the lateral parabrachial nucleus;

3) The action of semaglutide is based not only on metabolic effects, but also on changes in eating behavior manifested in faster satiation, reduced frequency of food intake, decreased total caloric intake without any external restrictions.

Thus, semaglutide (Semavic) is a promising drug for weight loss, its efficacy studies are still ongoing. This drug caused significant metabolic changes, including normalized fat and carbohydrate metabolism, improved body structure, reduced relative fat weight.

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