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Role of Pharmacists in the Management of Patients with Obesity

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Abstract

Obesity, a chronic disease, is increasingly prevalent worldwide, posing a significant public health challenge. It is often accompanied by comorbidities such as hypertension, cardiovascular disease, dyslipidemia, and diabetes, among others.

Pharmacists play a vital role in managing obese patients, being readily accessible members of the healthcare team. Their responsibilities include initiating weight management services, conducting comprehensive patient interviews, devising personalized therapeutic plans, evaluating medications for potential weight gain, monitoring treatment effectiveness and safety, providing patient counseling, and making referrals to other healthcare professionals when necessary.

Obesity induces notable changes in body composition that can impact the pharmacokinetic and pharmacodynamic properties of drugs, necessitating adjustments to dosing regimens. Lipophilic drugs typically experience a significant increase in volume distribution, while hydrophilic drugs may see only a moderate rise. The impact of obesity on drug elimination is relatively minor compared to its effects on distribution and varies depending on the specific metabolic or excretory pathway.

Key words: obesity, pharmaceutical care, patient counselling, pharmacokinetics, drug dosing

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Introduction

Obesity is a growing public health concern worldwide due to the enhanced risk of morbidity and mortality. It is associated with a higher incidence of some cardiovascular and metabolic disorders, but also cancer, and other diseases (1, 2). Obesity represents abnormal body size for a given height. Normal weight individuals have a body mass index (BMI) between 18.5 and 24.9 kg/m^2, while values between 25 and 29.9 kg/m^2 indicate overweight. A BMI of 30 kg/m^2 or more indicates obesity, while the severity is divided into three subgroups: moderate (BMI 30–34.9 kg/m^2), severe (BMI 35–39.9 kg/m^2) and morbid obesity (BMI ≥ 40 kg/m^2) (3).

Pharmacists can play an important role in managing obese patients and common comorbidities, particularly concerning pharmacological therapy and dosing regimen optimization. The aim of this article is therefore to provide an overview of the available therapies for obesity and common comorbidities, as well as the role of pharmacist in managing these conditions. Changes in body composition in obese individuals can affect the pharmacokinetic properties of drugs as well as their pharmacodynamic characteristics (2). A fixed dosing strategy in which all patients receive the same dose is not appropriate, and should be replaced by an individualized dosing approach (3). Hence, the additional aim of this article is to provide a basic understanding of pharmacokinetic properties of drugs in obese adults that may be important for rational dosing.

Pharmaceutical care of patients with obesity

The increasing rates of obesity incidence and prevalence impose a large burden on societies worldwide (4). These rates could be mostly explained by a sedentary lifestyle and an unhealthy diet. Moreover, despite the development of clinical care guidelines for obesity treatment and management, poor outcomes were recorded. A survey of 68 countries has outlined a variety of causes of unsatisfactory results in obesity management, including lack of healthcare services and trained professionals, accompanied by the stigmatization of obese individuals (5). These gaps could be overcome by a more active pharmacist role in support of obese patients, providing therapy counseling, nutrition and physical activity counseling, adherence support and continuing monitoring, since obesity could be defined as a relapsing chronic disease. Pharmacotherapy of obesity is usually intended to be a chronic therapy; therefore, a comprehensive and supportive management plan is needed, as the discontinuation of antiobesity medicines often leads to weight regain (6).

Pharmaceutical care in pharmacologic treatment of obesity

Clinical practice guidelines recommend pharmacotherapy for weight loss for individuals with a BMI ≥ 30 kg/m2 or a BMI ≥ 27 kg/m2 with obesity-related complications, to support nutritional and physical activity and psychological interventions. The antiobesity medications landscape is changing, with new drugs being approved, but also with some being withdrawn (e.g. lorcaserin). The current options include liraglutide, semaglutide, phentermine/topiramate, naltrexone/bupropion

combination and orlistat (7, 8). In Serbia, liraglutide, semaglutide and naltrexone/bupropion are available on the market with obesity-related indications (Table I) (9).

Table I Antiobesity medications: dosing and administration characteristics

Tabela I Lekovi u terapiji gojaznosti: doziranje i način primene

	Liraglutide		Semaglutide		Naltrexone/bupropion	
Pharmaceutical form	6 mg/mL solution for injection in pre-filled pen		0.25 mg/0.5 mg/1 mg/ 1.7 mg/2.4 mg FlexTouch solution for injection in pre-filled pen		8 mg/90 mg prolonged-release tablet	
Method of administration	subcutaneous administration in abdomen, thigh or upper arm, at any time of the day, independent of meals		subcutaneous administration in abdomen, thigh or upper arm, at any time of the day, independent of meals		oral use; the tablets should be swallowed whole with water; not cut, chewed or crushed; preferably taken with food	
Starting dose	0.6 mg once a day		0.25 mg once a week		one tablet (8mg/90 mg) in the morning	
Dose escalation schedule	week 1	0.6 mg once a day	week 1-4	0.25 mg once weekly	week 1	one tablet in the morning
	week 2	1.2 mg once a day	week 5-8	0.5 mg once weekly	week 2	one tablet in the morning and one tablet in the evening
	week 3	1.8 mg once a day	week 9-12	1 mg once weekly	week 3	two tablets in the morning and one tablet in the evening
	week 4	2.4 mg once a day	week 13-16	1.7 mg once weekly	week 4	two tablets in the morning and two tablets in the evening
Maintenance/ maximum dose	3.0 mg once a day; daily doses higher than 3.0 mg are not recommended		2.4 mg once weekly; weekly doses higher than 2.4 mg are not recommended		two tablets taken twice daily for a total dose of 32 mg naltrexone hydrochloride and 360 mg bupropion hydrochloride	
Missed dose	the drug should be taken only if the delay is <12 hours, and then it should be continued with the regular schedule		if the delay is ≤5 days, a dose should be administered as soon as possible; if >5 days, the missed dose should be skipped, and the next dose should be administered on the regularly scheduled day; in each case, patients can then resume their regular once-weekly dosing schedule		if a dose is missed, patients should not take an additional dose, but take the prescribed next dose at the usual time	
Assessment of efficacy	initial body weight loss ≥5% on the 3.0 mg/day dose after 12 weeks		initial body weight loss ≥5% after 6 months		initial body weight loss ≥5% after 16 weeks	

Liraglutide

Liraglutide is glucagon-like-peptide 1 (GLP-1) agonist available in a pre-filled pen aimed for subcutaneous administration once a day. The starting dose is 0.6 mg, with a recommended dose increase of additional 0.6 mg per week to improve gastrointestinal tolerability. If a patient cannot tolerate dose escalation for two consecutive weeks, treatment discontinuation can be considered (10). A patient who has been prescribed liraglutide should receive a pharmacist's counseling on appropriate drug administration, including education on subcutaneous administration technique, managing a missed dose, recognizing the characteristic symptoms of adverse effects, and the importance of avoiding dehydration. Liraglutide should be injected in the abdomen, thigh or upper arm, at any time, independent of meals. The change in injection site or dose timing does not require dose adjustment. However, the drug should be administered around the same time of the day. In case of a missed dose, the drug should be taken only if the delay is less than 12 hours, and then the patient should return to the regular schedule. The liraglutide safety profile lists headache and gastrointestinal problems as very common (nausea, vomiting, diarrhea, constipation) (10). Gastrointestinal disorders are mild to moderate, transient and should subside during the dose titration phase. They usually do not represent a serious issue to a patient nor lead to discontinuation of therapy. Patients should be advised to prevent dehydration, which may occur due to gastrointestinal side effects. However, a patient should be informed and educated on how to recognize the characteristic symptoms of acute pancreatitis, cholelithiasis and cholecystitis, as well as palpitations (10). The signs or symptoms of acute pancreatitis or cholecystitis require immediate stopping of liraglutide use and referral to a doctor (severe abdominal pain, tenderness of the upper abdomen, temperature 38 °C or above, jaundice, nausea, vomiting, activity of the serum lipase or amylase at least three times greater than the upper limit of normal). Furthermore, the resting heart rate should be monitored in patients, with suggested liraglutide discontinuation in case of sustained and symptomatic pulse increase. Additionally, a pharmacist should regularly assess the patient's symptoms or signs related to thyroid, renal or hepatic dysfunction, to ensure the continuation of safe and effective treatment. Regarding liraglutide pharmacokinetic profile, *in vitro* studies have shown low potential of liraglutide to cause clinically significant drug-drug interactions on distribution or elimination level. However, due to the pharmacologic action of GLP-1 agonists on delayed gastric emptying, drug interaction studies have quantified certain changes in the extent or the rate of absorption for some orally administered drugs. Still, the concurrent administration of liraglutide does not imply dose changes of other orally administered drugs, since the observed changes in systemic drug exposure were not clinically significant (10). Pharmacists in community pharmacies are in a unique position to detect adverse drug reactions, performing short interviews with the patients during drug dispensing, which was also confirmed for liraglutide in studies (11). Finally, liraglutide treatment should be discontinued after 12 weeks on the maximum daily dose of 3 mg if patients have not reached at least a 5% loss of their initial body weight. However, a decrease in adherence and persistence has been observed over time, which is when

pharmacists' role in adherence assessment and tailored counseling is more than necessary (12). Furthermore, studies have found lower rates of adherence in obese patients without diabetes, as compared to diabetic obese patients (13, 14). As the main causes of low level of adherence to antiobesity medications, the patients reported a lack of motivation and unsatisfactory results for their efforts (15, 16). Surprisingly, real-world data reported an unexpectedly high rate of primary non-adherence among 1,563 obese patients collected between 2012 and 2019, where only 8.9% of patients filled their newly prescribed antiobesity medication within 60 days (17). Nevertheless, face-to-face consultation with health care professionals is still the most useful intervention, associated with a 3.1-fold increase in the odds of adhering to liraglutide (15).

Semaglutide

Semaglutide is a GLP-1 agonist available in a pre-filled pen aimed for subcutaneous administration once a week, due to its long elimination half-life of 7 days. The dose should be gradually increased, starting from 0.25 mg once a week, up to a maximum weekly dose of 2.4 mg achieved after at least 16 weeks of dose titration (Table I). Like liraglutide, semaglutide should be injected in the abdomen, thigh or upper arm, at any time, independent of meals. Moreover, the injection site can be changed during drug use. If a dose was missed, the drug can be administered only within 5 days of a delay, in which case the regular weekly schedule can be continued. The second option is to reschedule weekly administration for another day if more than 5 days have passed since missing the dose. However, the minimum period between the two doses should not be less than 72 hours (3 days). Semaglutide safety profile was well determined in phase 2 and 3 randomized controlled clinical trials (18, 19). The most frequent adverse events were dose-related gastrointestinal symptoms, primarily nausea. The onset of gastrointestinal adverse events was typically during the initial 12 weeks of semaglutide use (19). Besides nausea, patients on semaglutide could expect diarrhea, vomiting, constipation and abdominal pain. Gallbladder disorders (cholelithiasis or cholecystitis) were also associated with the semaglutide dose. Abdominal pain should therefore be reported to a healthcare professional for further assessment (18, 19). However, other adverse events such as pancreatitis or thyroid dysfunctions were very rare with semaglutide. A recent systematic review emphasized a dose-related increase in the incidence of adverse events associated with semaglutide use, indicating more vigilant patient monitoring, especially during the dose escalation period (20). In comparison to liraglutide, where the dose titration phase usually takes up to 4 weeks, pharmacists should employ prolonged drug safety monitoring, even up to 12-16 weeks after the introduction of semaglutide. Patient education should also encompass instructions on how to avoid or prevent dehydration, which may lead to renal function deterioration. Like liraglutide, semaglutide can increase resting heart rate, which patients should be warned about. Xie et al. reported an increased rate of hypoglycemic events with semaglutide in the 2.4 mg dose. Patients should therefore be counseled on how to recognize and react during hypoglycemic episodes (20). Drug-drug interactions with semaglutide are not of clinical concern; delayed gastric

emptying has not been shown to impact therapy efficacy or safety even for drugs with narrow therapeutic index, such as digoxin or warfarin (21). However, caution is advised when semaglutide is coadministered with oral drugs that require rapid gastrointestinal absorption. The other example of potentially clinically relevant interactions is via semaglutide-caused diarrhea, which may impact intestinal absorption of orally administered drugs (21). Although a review or randomized controlled trials with semaglutide vs. liraglutide or placebo showed higher efficacy in weight loss for semaglutide in the maximum dose of 2.4 mg (−12.47 kg), in comparison to a maximum liraglutide dose of 3.0 mg (−5.24 kg), the assessment of drug efficacy should still be routinely performed for all antiobesity medications (20). Pharmacists should provide initial counseling on drug administration methods, including instructions for subcutaneous use, weekly dosing regimen, or handling delayed or missed doses, along with informing the patients about the expected (common) adverse events. However, the patients also require strong support with adherence to drug use. It should be kept in mind that semaglutide efficacy should be evaluated somewhat later than for other GLP-1 agonists, after 6 months, whereas the cut-off value of ≥5% loss in initial body weight for liraglutide was required after 3 months (Table I).

Naltrexone/bupropion

Naltrexone/bupropion is available as an 8 mg/90 mg prolonged-release tablet. Dose escalation should be performed over 4 weeks, starting from one tablet in the morning during week 1, then adding one tablet in the evening during week 2, increasing to two tablets in the morning and one tablet in the evening during week 3, and reaching the usual schedule of two tablets in the morning and two tablets in the evening. The maximum daily dose is 32 mg naltrexone hydrochloride and 360 mg bupropion hydrochloride (22). If a patient misses a dose, the prescribed next dose should be taken at the usual time, and no additional dose is to be taken. Patients have to be advised to take tablets with water and preferably with food. The tablets should be swallowed whole, without cutting, chewing, or crushing. In contrast to liraglutide, naltrexone/bupropion combination has more listed contraindications, such as uncontrolled hypertension, current seizure disorder or a history of seizures, in patients undergoing acute alcohol or benzodiazepine withdrawal, a history of bipolar disorder, or administration of monoamine oxidase inhibitors less than 14 days apart. Patients should be educated to closely monitor blood pressure when starting the therapy. Treatment discontinuation should be considered in case of sustained increases in blood pressure or heart rate. A very significant safety aspect is the risk of seizures, which may be increased in patients taking alcohol or stimulants, which has to be clearly explained to the patients. Therefore, the patients should be advised to avoid alcohol. Moreover, diabetic patients taking this drug combination may be exposed to a higher risk of hypoglycemia if the dose of the current antidiabetic medications is not corrected. Furthermore, hypoglycemia may provoke seizures in diabetic patients taking naltrexone/bupropion. Another clinically significant feature is the potential for harmful drug interactions. Therefore, a pharmacist should review cotherapy in patients on

naltrexone/bupropion therapy, since concomitant administration of antidepressants, tramadol, theophylline, systemic steroids, quinolones or sedating antihistamines may lower the seizure threshold. Patients or caregivers should be warned to recognize and report to healthcare professionals any suicidal thoughts or behavior. Naltrexone-bupropion may influence the ability to drive and operate machines, as it causes somnolence, dizziness, and even loss of consciousness due to seizures. Somnolence or dizziness is more pronounced during the initial titration phase, and the patients should be advised not to drive during the first weeks of therapy (up to 12 weeks). The summary of products characteristics lists the most frequent adverse reactions for naltrexone/bupropion: very common – nausea, constipation and vomiting; common – dizziness and dry mouth. Dry mouth may lead to toothache and dental caries; therefore, proper dental hygiene should be advised to the patients. The safety risks list is not exhaustively presented here, but hepatotoxicity is another aspect that should be discussed with the patient, since cases of drug-induced liver injury have been reported. In case of abdominal pain, jaundice or elevated liver enzymes, the patient should be warned to stop the therapy and seek medical help. Data from clinical studies phase III have reported an increased risk of adverse events, with the number needed to treat to harm of 12 (23). Therefore, vigilant postmarketing surveillance is required. Pharmacists should keep in mind that naltrexone/bupropion is subject to additional pharmacovigilance monitoring and any suspected adverse reactions have to be reported. Real-world data are still missing, but the reasons for drug discontinuation in clinical trials were nausea, vomiting, constipation, headaches and dizziness (23, 24). In terms of optimized benefit/risk ratio, naltrexone/bupropion could be recommended for the treatment of overweight or obesity in patients with depression or in patients starting the smoking cessation (25). A large comparative study (26,522 patients) on persistence with different newly prescribed antiobesity drugs has shown that after 6 months, 41.8% of patients were still on liraglutide 3 mg, compared to 18.1% in the case of naltrexone/bupropion ($p<0.001$). After controlling for other variables, patients on liraglutide had a significantly lower risk of discontinuation in comparison to naltrexone/bupropion (hazard ratio, $HR=0.48$, $p<0.001$) or phentermine/topiramate ($HR=0.64$, $p<0.001$) (26). In regard to monitoring drug effectiveness, treatment should be discontinued after 16 weeks if patients have not reached a loss of at least 5% of their initial body weight. If the initial goals were achieved, the need for potential treatment continuation should be reviewed annually.

The guidelines clearly recommend introducing long-term use of antiobesity medications only along with lifestyle interventions. Pharmacological interventions are combined with non-pharmacological interventions, either as adjunctive therapy, or sequentially, depending on the severity of obesity (25). The benefit/risk ratio should be thoroughly assessed before prescribing long-term therapy. Moreover, antiobesity treatment should be tailored to the specific patient depending on patient's characteristics, comorbidities, preferences, risk of adverse events, cost and access to therapy (25, 27-29).

The efficacy and safety of antiobesity medications should be performed at least monthly for the first 3 months upon initiating therapy, followed by at least quarterly

follow-ups (30). Certainly, pharmacists, as the most accessible healthcare professionals, can provide patient education, therapy counseling, monitoring of therapy safety and efficacy, as well as motivation and adherence support, which are the prerequisites for achieving the desired clinical outcomes (31).

Pharmaceutical care in non-pharmacologic treatment of obesity

Lifestyle modifications, including nutrition and physical activity interventions, are necessary in obesity management. The main targets are restricted calorie intake and increased physical activity. Aerobic physical activity of 30–60 minutes of moderate to vigorous intensity should be advised to the patients most days of the week, at minimum 150 minutes per week (7, 25). There is evidence that aerobic physical activity leads to a loss of abdominal visceral fat and ectopic fat, such as in the liver or the heart, even if there is no measured loss in total body weight. Moreover, physical activity increases mobility, improves cardiac and respiratory function, and decreases cardiometabolic risk factors in overweight or obese patients, including hyperglycemia, high blood pressure and dyslipidemia (7, 32). Additionally, better quality of life and mood are achieved in patients following physical activity measures. Resistance training can further improve mobility and weight maintenance and should be recommended to the patients gradually with adopting lifestyle changes (8, 33). In addition, patients should be advised to decrease their sedentary time and increase active leisure (8, 33). However, restrictions in caloric intake are more effective in achieving initial weight loss than only increasing physical activity (34, 35). Still, physical activity is important for maintaining weight loss (36).

Obese patients have to adopt a healthy, well-balanced diet, achieving nutritional needs and treatment goals. The basic principle of weight loss and weight-loss maintenance is a long-term reduction in caloric intake, since no specific diet has been highlighted in the studies (7, 37). Studies have found that different dietary approaches (such as selectively restricting fat or carbohydrates, or selectively increasing protein or fiber) were equally effective in promoting weight loss if the restrictions in total calorie intake were accomplished (36, 38, 39). Restricted calorie intake refers to a reduction of 500-750 kcal/day, and it is usually achieved by diets of 1200–1500 kcal/day for females and 1500–1800 kcal/d for males (40). In line with that, the main recommendations should include home preparation of meals, reduced portion size, avoiding fast, excessive fat or sugar intake, as well as processed foods (41, 42). Increased consumption of vegetables and fruit has many health benefits as well (41).

The preferable model is individualized medical nutrition therapy, provided by a registered dietitian, and engaging the patient in such weight-loss programs for at least a year (7, 42-44). Not only were the weight outcomes improved in such programs (body weight, BMI, waist circumference), but glycemic, lipid and blood pressure targets were also achieved (7). However, those programs are not affordable to all patients (7), and hence a pharmacist is well-placed to provide basic nutritional and physical activity counseling (31, 45, 46). To ensure the patients' long-term compliance with the nutrition plan and the effectiveness of nutritional interventions, it is essential to assess their health

status, preferences, food availability and cultural circumstances (30, 47). Complementary to nutrition and exercise, behavioral (psychological) interventions are needed to foster adherence to physical activity and meal plan prescriptions, and to teach patients how to practice mindful eating to prevent weight regain (7, 40, 44). Self-monitoring has proven to be an effective tool in weight loss and weight maintenance (48). Daily self-monitoring of body weight, physical activity and food intake has been associated with weight loss (39, 49-51). In contrast, interruptions in daily weight monitoring were associated with weight regain (36, 50). Therefore, a pharmacist should provide counseling and education on daily self-monitoring and its benefits in real life. Moreover, motivating obese patients to adhere to and persist with non-pharmacological approaches, such as diet and exercise, is crucial for achieving sustainable weight loss and improving overall health outcomes (52). Motivation support represents an initial, crucial step in any antiobesity intervention, but it also requires constant reinforcement throughout the obesity management process. Consistent engagement in these lifestyle changes can significantly reduce the risk of comorbidities such as diabetes and cardiovascular diseases, enhancing the quality of life and long-term health. Studies have shown that personalized support and behavioral interventions can greatly increase adherence, leading to more successful and lasting results (53, 54).

Pharmaceutical care in management of obesity-related comorbidities

Obesity is a proven major risk factor for diabetes, hypertension, and dyslipidemia in all age groups (≥18 years) and in both genders, contributing significantly to the cardiovascular disease morbidity and mortality (55). Hence, diabetes, hypertension, dyslipidemia and metabolic dysfunction-associated steatotic liver disease (MASLD; formerly known as nonalcoholic fatty liver disease) are considered obesity-related comorbidities, and the primary goal of their treatment is weight loss because it causes the reversion of pathophysiological mechanisms leading to metabolic diseases. The basic health screening of overweight or obese individuals should include measuring blood pressure in both arms, obtaining fasting glucose or glycated hemoglobin values, lipid panel and alanine aminotransferase to screen for MASLD (7).

In patients who are unable to achieve the recommended blood pressure, glycemic or lipid targets with weight loss through lifestyle modifications, adjuvant pharmacotherapy may be required. As a general principle of treating other health conditions, drugs that are not associated with weight gain are the preferred options. Comprehensive medication management is needed, and therefore clinicians should also assess any other medications that could lead to weight gain. Some examples of medications that can increase appetite and promote weight gain are sedating antihistamines, steroids, selective serotonin reuptake inhibitors, beta-blockers, and antipsychotic agents (36, 56). When possible, appropriate alternatives to those medications should be considered.

Hypertension

The pathophysiology of hypertension in obesity is complex, including changes in the function of endothelium, sympathetic nervous system or renal system, activation of the renin-angiotensin-aldosterone system (RAAS), insulin resistance, hyperleptinemia, and inflammatory processes (57-59). Therefore, it is not surprising that 78% of newly diagnosed cases of hypertension in men and 65% in women are classified as obesity-related (60). Moreover, there is a linear relation between hypertension and obesity, with a decrease in blood pressure of around 1 mmHg per kg of weight loss (61). Weight loss is the mainstay of treatment for obesity-related hypertension; however, it is usually not a feasible solution in the long-term. Additionally, obesity is a risk factor for treatment-resistant hypertension (defined as blood pressure that remains above 140/90 mm Hg despite the concurrent use of three antihypertensive agents of different classes, or controlled blood pressure with >3 medications) (62). Therefore, comprehensive antihypertensive treatment includes the introduction of antihypertensive medications combined with diet and physical activity, aiming to lower blood pressure but also to prevent complications (63). Guidelines recommend dual- and triple-combination therapies using RAAS blockers, calcium channel blockers, and/or a diuretic (64). Due to the RAAS role in obesity-related hypertension, ACEIs and ARBs are the first-line therapies, with added beneficial nephroprotective effect (65, 66). Calcium channel blockers (dihydropyridine), due to their neutral effect on glucose metabolism and weight gain, are recommended as add-on therapy in combination with ACEIs/ARBs (66, 67). Although metabolic adverse effects of thiazide diuretics are well known, they were proven to exert beneficial effect by decreasing volume overload seen in obesity-related hypertension (68). Due to the overactive sympathetic nervous system in hypertension, beta blockers would be expected to have a marked blood pressure-lowering effect, but many beta blockers are associated with insulin resistance or weight gain. Therefore, their use in hypertensive obese patients should be restricted to specific cardiovascular indications, such as heart failure or post-myocardial infarction (69). In that case, third-generation beta blockers carvedilol and nebivolol should be prescribed, with better safety profiles (less weight gain potential and fewer adverse metabolic effects) than older beta blockers (70). Mineralocorticoid-receptor antagonists were associated with decreased risk of heart failure, heart failure-related hospitalizations and cardiovascular death; however, their role in the initial treatment of hypertension in obese or overweight individuals remains less grounded than for treatment-resistant hypertension (71, 72). New drugs such as sodium-glucose cotransporter 2 inhibitors decrease blood pressure by targeting multiple hypertensive pathophysiological mechanisms. Still, large-scale clinical trials are needed to assess the efficacy of sodium-glucose cotransporter 2 inhibitors for obesity-related hypertension (59, 64).

The main pharmacists' interventions in obesity-related hypertension involve counseling on restrictive diet and physical activity, as the mainstay of weight management, blood pressure control and cardiovascular risk reduction. Additionally, the focus should be placed on restricted sodium intake. Studies have found increased salt

intake in obese patients, which is related to highly processed industrial food and beverage consumption (73). Next, due to renal hyperfiltration and fat compression in obese patients, there is an increase in renal sodium reabsorption and impaired renal-pressure natriuresis, followed by increased sensitivity to salt (74). The Mediterranean or DASH diet could be offered to patients, along with physical activity recommendations (75). Patients should be encouraged to follow the diet and explained that a further reduction in blood pressure could be expected with each loss in weight. Adherence to antihypertensive medications should be assessed by at least indirect measures (refill frequency), accompanied by motivational counseling and information about the possibility of decreasing the dose of antihypertensive therapy due to weight loss (76). Pharmacist-led interventions, including education and counseling, significantly improve medication adherence and blood pressure control, which was reported across the studies in both non-obese and obese hypertensive patients (31, 77, 78). Additionally, patients should be educated on self-monitoring of blood pressure, increasing their engagement in therapy and disease management, and leading to improved outcomes (76). Besides face-to-face counseling provided by a pharmacist, leaflets and educational materials were useful for achieving blood pressure control and better health-related quality of life. Leaflets should include information about lifestyle modifications, the importance of adherence to diet and drug therapy, physical activity, as well as smoking and alcohol cessation (79). Patients on antihypertensive treatment who are starting antiobesity medications have to be informed about the possibility of an additional reduction in their blood pressure due to weight loss; therefore, caution is needed with subsequent introduction of antiobesity medications (25). This intervention should be followed by more frequent patient monitoring to recognize hypotension and appropriately optimize antihypertensive therapy.

Diabetes

The co-occurrence of diabetes and obesity is highly prevalent, to such an extent that more than 90% of patients with diabetes are overweight or obese (36). Therefore, weight loss is particularly important for patients who have both diabetes and obesity (36). Weight loss of 5–10% of baseline body weight is recommended as an initial treatment goal, leading to a 0.6–1.0% reduction in glycated hemoglobin (36, 39). Besides being highly effective in treating type 2 diabetes, a 7% weight loss can even delay the progression from prediabetes to type 2 diabetes (30, 38, 80). In patients with type 2 diabetes and overweight or obese, weight loss improves glycemia, reduces the need for glucose-lowering medications or doses of glucose-lowering medications, improves waist circumference, blood pressure, peripheral neuropathy symptoms, sexual function, condition and well-being (30, 36, 80).

The latest American Diabetes Association guideline highlights the preferred pharmacotherapy with the GLP-1 receptor agonist or dual glucose-dependent insulinotropic polypeptide (GIP) and (GLP-1) receptor agonist with greater weight loss efficacy (i.e., semaglutide or tirzepatide), treating both obesity and diabetes, along with

lifestyle changes (30). If GIP or GLP-1 receptor agonists fail to achieve weight loss goals, or when they are not tolerated or are contraindicated, other obesity treatment options should be considered (30). Other glucose-lowering medications with a beneficial effect on weight (neutral or promoting weight loss) are metformin, pramlintide (amylin analogue), dipeptidyl peptidase 4 (DPP-4) inhibitors, and sodium–glucose cotransporter 2 (SGLT2) inhibitors. Metformin has been associated with a 3-kg weight loss, pramlintide with a 3.7-kg weight loss, SGLT2 inhibitors with a 2.4-kg weight loss, whereas DPP-4 inhibitors are generally weight neutral (36). In contrast, insulin secretagogues (sulfonylureas and meglitinides), thiazolidinediones, and insulin are associated with weight gain (30).

Hence, the main pharmacists' interventions should target patient education on weight loss, including a calorie-restricted diet and physical activity. Furthermore, if patients use insulin, they should be warned about potential hypoglycemia when starting a new exercise regimen. To avoid potential adverse events of hypoglycemia during or after exercise, the patient should be informed to increase glucose monitoring (36). Nevertheless, the recommendation of at least 150 minutes of moderate aerobic activity per week and resistance exercise twice per week is valid for all obese patients, regardless of the diabetes status (36, 80). Similarly, the same nutritional counseling should be given as previously described within the non-pharmacologic treatment of obesity subsection. However, patients with diabetes should receive additional counseling on restricted consumption of alcohol or other highly caloric liquids (81).

Pharmaceutical care interventions, including screening, patient education, counseling on medication use, nutrition and physical activity, disease management, as well as promoting adherence, led to improved diabetes control and other cardiovascular risk factors (glycated hemoglobin, glycemia, blood pressure, lipid profile) (82-85). An interesting viewpoint was revealed in studies investigating the perspective of patients with obesity and complications, where they recognized the need for additional support from healthcare professionals to enhance their knowledge and health literacy about obesity and obesity-related comorbidities (86).

Dyslipidemia

Abnormalities in lipoprotein metabolism in obesity could be explained by the metabolic effect of insulin resistance and an excess of abdominal visceral fat, as characteristic features of metabolic syndrome (87, 88). Many studies have reported a positive correlation between BMI and dyslipidemia, which is not surprising since ectopic fat accumulation, especially in the liver, and inflammation promote the development of dyslipidemia (88-91). A combination of multiple mechanisms is involved in dyslipidemia, including increased production of very-low-density (VLDL) lipoprotein, decreased catabolism of apoB-containing particles, and increased catabolism of high-density lipoprotein (HDL) particles (87). Lifestyle modifications (calorie-restricted diet and increased physical activity) are the first-line interventions to improve lipid abnormalities in obese patients (87). Weight loss leads to markedly reduced fasting and

non-fasting triglyceride concentrations, but a smaller reduction in high-density lipoprotein (LDL-C). Hence, lifestyle modifications are often insufficient to achieve the target goal of dyslipidemia (92). Antiobesity medications decrease fasting lipid levels, which correlates with the degree of weight loss, while only orlistat can further decrease LDL-C beyond the weight loss effect. However, the decrease in lipid levels induced by antiobesity medications is modest and varying (88). A meta-analysis on antiobesity medications showed limited improvements in dyslipidemia (92).

Pharmacological treatments, such as statins, fibrates, ezetimibe, and omega-3 fatty acids, could be used alone or in combination with other agents to achieve the desired dyslipidemia outcomes along with lifestyle modifications (87). Before initiation of lipid-lowering drugs in obese or overweight patients, a complete lipid profile should be evaluated to determine potential underlying primary lipid disorders, the total cardiovascular risk and the risk of pancreatitis (triglyceride level exceed 10 mmol/L) (92, 93). A clinician should make up the choice of lipid-lowering drug(s), based on the abovementioned patient characteristics (92-94). Still, the observed effect of lipid-lowering drugs is similar both in obese and in patients with normal weight. In general, statins are the first-line lipid lowering drugs. The exception are patients with very high triglyceride levels, when fibrates or omega-3 fatty acids should be used initially (92). However, the characteristic of dyslipidemia in obesity involves increased triglyceride levels, which cannot be fully corrected with statins, which may contribute to the residual risk after initiating statin therapy (92, 95). Therefore, fibrates, proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors or omega-3 fatty acids can be added to statin therapy to treat residual dyslipidemia (92, 93).

Regarding the safety concerns, muscle symptoms and tolerability of statins did not differ in obese patients in comparison to normal-weight persons. However, patients starting statins should be closely monitored, since they are associated with an increased risk of developing diabetes (93). Elderly obese patients with higher baseline glucose levels are at the greatest risk for developing diabetes during statin therapy (92, 93, 96). In cases where bile acid sequestrants have been prescribed, the patient should be educated on proper use to avoid drug-drug interactions on the absorption level. Bempedoic acid further elevates serum uric acid levels, which are commonly increased in obese persons, and increase the risk of gout (88). Ezetimibe and fibrates did not raise clinically relevant safety concerns in obese patients (88).

Postprandial lipemia is strongly related to total calories, the amount of ingested fat and the type of dietary fat (92, 97). Besides calorie-restricted diet and consumption of unsaturated fat, the intake of dietary fibers such as resistant starch from bread, cereals and vegetables showed beneficial effects on dyslipidemia (92, 98). However, the estimated average consumption of resistant starch in the amount of 5g/day in the Western countries is not sufficient to achieve health benefits (92, 98). Patients with concomitant obesity and dyslipidemia should receive health and dietary education, along with the monitoring of the efficacy and safety of lipid-lowering therapy. Treatment targets in obese patients should also include ApoB and non-HDL-C concentrations, since those parameters reflect

the atherogenic lipid risk more accurately than LDL-C alone (93). Patients should be closely monitored for response to lipid-lowering therapy and timely referred to a doctor for potential intensification of therapy (93). Frequent follow-ups on treatment effectiveness in obese patients are necessary to reduce the risk of cardiovascular events or pancreatitis. Studies have reported a positive impact of community pharmacist interventions and education on lipid parameters and reduction of cardiovascular risk (99-101). Patients should be educated on the benefits and risks of the prescribed lipid-lowering therapy (100). Additionally, none of the OTC or herbal products with lipid-lowering claims should be recommended, due to the potential for causing adverse effects when used either with or instead of lipid-lowering medications (100).

Metabolic dysfunction-associated steatotic liver disease (MASLD)

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously referred to as nonalcoholic fatty liver disease (NAFLD), encompasses a range of conditions. It refers to simple hepatic steatosis without significant inflammation, and with at least one metabolic risk factor (e.g., obesity, diabetes mellitus, dyslipidemia, hypertension) or fibrosis to metabolic dysfunction-associated steatohepatitis (MASH; previously known as nonalcoholic steatohepatitis (NASH)), which manifests with varying degrees of inflammation and fibrosis. Obesity is common among MASLD patients, although hepatic steatosis may also occur in individuals who are not overweight (102).

A recent comprehensive review and meta-analysis, incorporating 116 relevant studies and a total of 2,667,052 participants from the general population, revealed a staggering global prevalence of MASLD. This prevalence exceeds half (50.7%) of the overweight and obese adults, irrespective of the diagnostic methods employed. Alarmingly, MASLD has reached pandemic proportions regardless of country or regional development and economic status. Consequently, the implications for patient care are significant, demanding attention and concerted action, given the remarkably high prevalence rate of MASLD among overweight and obese individuals (103).

The primary treatment approach for MASLD is weight loss through lifestyle interventions. However, adherence to these interventions is often hindered by low compliance (104). For patients aiming to achieve a reduction of at least five to seven percent in body weight, a gradual pace of 0.5 to 1.0 kg per week through lifestyle changes such as dietary adjustments and regular exercise is typically advised. Additionally, abstaining from alcohol is generally recommended for individuals with MASLD. Alternative approaches to weight loss include targeted dietary interventions, pharmacotherapy, and bariatric surgery. Up until now, there hasn't been any official pharmacological treatment for MASH. The FDA approved the first drug to treat MASH in March 2024. Named Rezdiffra (resmetirom), it is anticipated to be accessible in the US starting April 2024. Clinicians' recommendations for drug therapy to facilitate weight loss exhibit considerable variation. In instances where patients diagnosed with biopsy-proven MASH and fibrosis stage ≥F2 do not attain weight reduction through lifestyle interventions, some clinicians may opt for the use of a GLP-1 receptor agonist (e.g.,

semaglutide, liraglutide; off-label) (105, 106). For patients diagnosed with MASH but without diabetes mellitus, the recommendation is to consider vitamin E supplementation (at a dosage of 800 international units per day). However, there is limited evidence supporting the efficacy of vitamin E in such patients (107). While metformin is typically the initial therapy for type 2 diabetes mellitus, other insulin-sensitizing agents such as pioglitazone and GLP-1 receptor agonists could be reasonable alternatives, considering their potential beneficial impact on liver histology. Various other therapies have been investigated for the management of metabolic MASLD, although none have undergone sufficient scrutiny to warrant recommendation for their use in treating MASLD or MASH. These include atorvastatin (108), omega-3 fatty acids (109), and promising trials suggesting the hepatoprotective effects of aspirin (110).

Given the anticipated insufficiency of specialized healthcare providers, notably hepatologists and gastroenterologists, pharmacists play a crucial role in MASLD management. A new study highlights that the role of pharmacists within community pharmacy settings extends beyond diagnostic functions to encompass facilitation in identifying and screening individuals at elevated risk of MASLD through the utilization of validated non-invasive tools, such as portable devices and calculators. By emphasizing patient education, facilitating referrals, and providing ongoing monitoring, pharmacists can enhance the management of MASLD, thereby improving patient outcomes. Augmenting the influence of pharmacists in the early detection and management of MASLD can be accomplished through collaborative partnerships with healthcare institutions and the incorporation of patient self-assessment tools (111).

Pharmacokinetic consideration in drug dosing to obese patients

The pharmacokinetics of drugs and consequently the required dosage regimen can be influenced by certain pathophysiological alterations in obese individuals. Significant changes in body composition, but also increased blood flow and accelerated gastrointestinal transit, are associated with obesity. Even hepatic dysfunction or enlargement or renal dysfunction have been observed in some patients (1, 112). These changes mostly lead to variations in the distribution and elimination of drugs. Data on absorption characteristics in obese patients are limited and most results indicate no clinically significant alterations compared to non-obese patients (1, 113). However, some reports suggest accelerated gastrointestinal transit and gastric emptying, which could theoretically alter the gastric absorption of some drugs (112).

Changes in body composition have the greatest influence on the distribution of medicines (112). Obesity is primarily associated with an increase in adipose weight, while the increase in lean mass accounts for 20 to 40% of the total excess weight (3). In addition, changes in blood volume and tissue perfusion can influence the distribution of drugs, while protein binding alteration has only limited impact (1).

The volume of distribution does not increase proportionately with total weight. It depends on the properties of the drug, but also on changes in body composition (112). Hydrophilic drugs are generally distributed in the extracellular fluid and the increase in

fat mass is unlikely to significantly affect their volume of distribution (3, 112). Interestingly, volume of distribution of aminoglycosides is increased in obese patients due to the additional extracellular fluid contained in fat tissue (114). On the other hand, lipophilic drugs are extensively distributed into adipose tissue, so their volume of distribution is likely to be greater than that of less lipophilic drugs. Depending on the lipophilicity, the distribution of drugs in the lean and fat mass occurs in the variable fraction (112). Since the increased body weight in obese people is not only related to the increase in adipose tissue, the volume of distribution is variable as well (114).

Given the importance of this pharmacokinetic parameter for determining the initial dose of drugs, a change in distribution in obesity may require an adjustment of the dosing regimen. Changes in body composition primarily lead to a significant increase in the volume of distribution for lipophilic medicines, and only a slight or moderate increase for hydrophilic medicines (112). However, the direction and extent of the change are not always predictable (1). It is indicated that changes in this parameter cannot be predicted only based on physiochemical properties, but also on others factors, such as tissue and plasma protein binding (115). In addition, many drugs are not purely hydrophilic or lipophilic (114). If the drug distributes into fat mass tissue, total body weight should generally be taken into account when calculating the initial dose. In the case of limited distribution in extra fat, ideal or lean body weight should be more appropriate (114). Alternatively, to compensate for the increased volume of distribution of aminoglycosides in obese patients, the adjusted body weight should be considered for dose calculation (112, 116).

The influence of obesity on the elimination of drugs differs depending on specific metabolic or excretory pathway (1, 117). Obese patients often have liver abnormalities, including fatty infiltration and its progression, which can affect the drug metabolism. In addition, increased liver volume and hepatic blood flow have been observed in obese people (112). As far as phase I metabolism is concerned, the changes may vary depending on the enzyme involved. The clearance of drugs metabolized by cytochrome P450 (CYP) 3A4 is lower in obese patients than in normal-weight individuals. It has been reported that the activity of CYP3A4 was reduced by 10% to 35% (112). On the other hand, clearance of CYP2E1 substrates may be higher in obese patients. Although some reports indicate a trend towards an increased value of this parameter for drugs metabolized by CYP2D6, CYP2C9 and CYP1A2, other result are conflicting, so further studies are needed (1, 112, 117). The clearance of uridine diphosphate glucuronosyltransferase (UGT) substrates has been reported to increase in obesity. Regarding other phase II metabolic pathways, the number of studies is limited and further research is needed (112). These effects on the metabolism are especially important for drugs with low or moderate extraction rates, while the changes in drugs with high extraction rates are usually masked by the increased hepatic blood flow and hepatomegaly (112). Drugs that are mainly eliminated by glomerular filtration and/or tubular-mediated mechanisms can be expected to have increased clearance in obesity (1, 117). However, it should be noted that drug clearance generally does not increase proportionally with weight. Hence, values of

weight-corrected clearance were either comparable or decreased in obese patients (112, 117). Furthermore, the effects of obesity on drug excretion may be more difficult to assess due to possible comorbidities and glomerular hyperfiltration leading to impaired kidney function (112, 113). To calculate creatinine clearance in obese adults, which correlates with renal clearance of drugs that are primarily eliminated via the kidneys, it is recommended to use the Salazar-Corcoran equation based on total body weight, or the Cockroft-Gault equation based on lean or ideal body weight (112, 114).

In general, the capacity for hepatic and renal elimination of drugs is usually similar or lower than in normal weight patients, as their progress is not proportional to a significant weight gain (112). For drugs that are dosed chronically, the clearance of drugs is important for the maintenance dose calculation. As this parameter does not increase proportionally with total weight, there is no uniform agreement on which body size measure provides the best prediction of clearance, but some authors recommend lean body weight (3, 114, 118). Moreover, accompanying therapeutic drug monitoring is a useful tool for optimal dosing, particularly for drugs with a narrow therapeutic index (3).

Healthcare professionals must take into account the need to adapt the dosage regimen based on recommendations, if available. However, there is currently a lack of knowledge and universal dosing strategies for obese patients (2, 115). Instead, it should be developed on the basis of a separate assessment of the effects of obesity on the disposition of a particular drug. In addition, pharmacodynamic changes in obese individuals should be taken into account (114). Drugs whose dosage often needs to be adjusted for obesity include low-molecular-weight heparins, some antibiotics and anesthetics, monoclonal antibodies and chemotherapeutic agents (3, 115, 119). In a large community hospital, a pharmacist-driven protocol was developed for the dosing regimen modification in obese individuals. The protocol included recommendations for several antimicrobial and anticoagulant drugs, based on the available literature. The pharmacists corrected the dosage regimen in 40% of the evaluated cases, most frequently for heparin and cefazolin (2).

Conclusion

In conclusion, our paper provides a comprehensive overview of the current knowledge and recommendations for the holistic management of patients with obesity and related comorbidities, highlighting the indispensable role of pharmacists. We also address the significant impact of obesity-induced changes in body composition on drug pharmacokinetics and pharmacodynamics, underscoring the need for tailored dosing regimens in clinical practice.

Our discussion delves into pharmaceutical care interventions, encompassing both pharmacologic and non-pharmacologic treatments. Effective management of antiobesity medications necessitates structured patient counseling, diligent monitoring of efficacy and safety, and ongoing support for adherence to prescribed therapy and lifestyle modifications.

Pharmacists, as accessible members of the healthcare team, play a pivotal role in the management of obese patients. Their interventions, including education, screening, and disease management, have been associated with positive outcomes such as weight loss, improved blood pressure control, and reduced cardiovascular risk.

In summary, pharmacists' contributions are essential in optimizing the care of obese patients and improving overall health outcomes.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

Conceptualization: MJ, MK, MĆ. Writing – original draft: MJ, MK, MĆ. Writing - review & editing: MJ, MK, MĆ.

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Uloga farmaceuta u zbrinjavanju gojaznih pacijenta

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Kratak sadržaj

Gojaznost je hronična bolest koja postaje sve češća i predstavlja globalni javno-zdravstveni problem. Povezana je sa većom stopom komorbiditeta kao što su hipertenzija, kardiovaskularne bolesti, dislipidemija, dijabetes i druge.

Farmaceut ima ključnu ulogu u zbrinjavanju pacijenata sa gojaznošću, kao najpristupačniji član zdravstvenog tima. Ova uloga uključuje uvođenje usluga upravljanja gojaznošću kroz detaljne intervjue sa pacijentima, kreiranje personalizovanih terapijskih planova, procenu lekova sa potencijalom za povećanje telesne mase kroz uslugu pregleda terapije, praćenje efikasnosti i bezbednosti lečenja, pružanje relevantnog savetovanja pacijentima i upućivanje pacijenata drugim zdravstvenim profesionalcima kada je neophodno. Gojaznost dovodi do značajnog povećanja volumena distribucije za lipofilne lekove i samo do malog ili umerenog povećanja za hidrofilne lekove. Uticaj gojaznosti na eliminaciju uticaja lekova je relativno mali u poređenju sa uticajem na distribuciju i varira u zavisnosti od specifičnog metaboličkog ili ekskretornog puta.

Ključne reči: gojaznost, farmaceutska zdravstvena zaštita, savetovanje pacijenata, farmakokinetika, doziranje lekova