THE ASSOCIATED RISKS OF ON-LABEL AND OFF-LABEL DRUGS USED IN OBESITY

DENISA-MARIETA PODAR[1], AMELIA TERO-VESCAN[2], ȘTEFANA STĂCESCU[3], GABRIEL HANCU[4]

[1,2,3,4]*University of Medicine, Pharmacy, Sciences and Technology of Târgu-Mureș*

Keywords: *on-label medication, off-label medication, obesity, risk factors, side effects*

Abstract: *The treatment of obesity includes along with lifestyle modification, pharmacological therapy. Until now there are only few drugs approved by FDA for the treatment of obesity, therefore physicians often prescribe off-label drugs. In this article we review tolerability, side effects and contraindication of both on-label and off-label drugs used in obesity treatment. Currently there are 5 approved drugs for long-term use (phentermine/topiramate, bupropion/naltrexone, orlistat, lorcaserin and liraglutide) and 4 approved drugs for short-term use (phentermine, diethylpropion, benzphetamin, phendimetrizine). On-label therapy is generally well tolerated, with specific contraindication for each drug. On the other side, off-label therapy can be considered safe only for drugs that have already long-term safety data (metformin, phentermine). For other drugs (pramlintide, zonisamide, GLP-1 agonists) off-label prescribing should be limited to clinical trials due to their unknown adverse effect profile.*

INTRODUCTION

Obesity is a chronic condition whose prevalence is on the rise worldwide becoming a global public health concern, because it is a significant risk factor for diabetes, high blood pressure and cardiovascular (CV) disease.(1) The World Obesity Federation estimates that by 2025 the prevalence of obesity in men will be over 18% (with a body mass index (BMI)> 40 kg/m² in 6% of cases) and 21% in women (with an estimated BMI> 40 kg/m² in 9% of cases).(2)

With a small number of treatments and medications available for any clinical situation, the overall efficacity of medication and the adverse effects can be determined with a statistical formula known as Number Needed to Treat (NNT) respectively Number Needed to Harm (NNH). Ideally, the NNT value should be low, suggesting a better rate of lower weight in the case of weight loss medications. The NNH should be a high, suggesting that the medication tend to create few side effects (SE). A truly ideal drug would have a high NNT<NNH.(3)

Nevertheless, the prescription of anti-obesity drugs remains remarkably low when compared with pharmacotherapy for other metabolic diseases because there are only a few drugs are with a marketing authorization issued by the Food and Drug Administration (FDA). Hence, after taking into consideration risk–benefit ratio, physicians choose to prescribe sometimes off-label drugs. Just like other drugs, off-label prescriptions may offer benefits to obese patients but may also produce considerable side effects.(4,5)

Since the beginning of the 19th century, a variety of drugs have been evaluated for their ability to decrease body weight, but many of them were withdrawn because of concerns about their safety (sibutramine, rimonabant, dexfenfluramine, methylphenethylamine).(6) There are 5 drugs recommended for long-term treatment of obesity (phentermine/topiramate, bupropion/naltrexone, orlistat, lorcaserin and liraglutide) and 4 for drugs approved for short-term use (phentermine diethylpropion, benzphetamine and phendimetrizine).(4)

The mechanism of action of *orlistat (Xenical®)* involves irreversible inhibition of pancreatic lipase, thus preventing intestinal digestion of food triglycerides into fatty acids and 2 monoglycerides, the form under which they are absorbed.(7) Due to its mechanism of action, orlistat appears to be the safest pharmacological option for treating obesity.(4) Gastrointestinal SE of orlistat were described in the XENDOS clinical trial, in which 91% of the participants experienced at least one adverse effect and 8% of the participants withdrew from the study due to these effects. The most common SE were: fatty diarrhea, fecal incontinence, abdominal pain. Steatorrhea can limit patient tolerability and orlistat long-term use. Reduction in fat consumption led to the reduction of SE and increased adherence of patients to orlistat treatment.(7) Another consequence of orlistat treatment is the decreased absorption of liposoluble vitamins (A, D, E and K) so supplementary intake of vitamins is recommended.(8) The massive elimination of non-digested triglycerides in the stool raised the problem of the increase in colon cancer incidence in patients treated with orlistat, but a retrospective clinical trial showed no differences in orlistat versus placebo-treated patients.(9)

Phentermine/Topiramat (Qsymia®) is a fixed-dose combination between an antiepileptic drug (topiramate) and an amphetamine derivative (phentermine) approved by the FDA for weight loss in 2012. Phentermine promotes weight loss by increasing norepinephrine release and decreasing its leading to a decrease appetite, while topiramate decreases caloric intake and promotes taste aversion. Since the commercial product Qsymia® is a combination of two substances, consideration should be given to the SE produced by both substances. The most common SE with phentermine refers to CV events: tachycardia, palpitations, insomnia, anxiety, elevated blood pressure.(10) Topiramate is not recommended as a monotherapy for the treatment of obesity due to dose-dependent neuropsychiatric SE: memory disorder, concentration disorder, speech or cognitive difficulties. Two large phase 3 trials, EQUIP and CONQUER, reported the following SE: constipation, insomnia, dry mouth (caused by phentermine) and attention

[1]Corresponding author: Amelia Tero-Vescan, Str. Gheorghe Marinescu, Nr. 38, Tîrgu-Mureș, Romania, E-mail: amelia.tero.vescan@umftgm.ro, Phone: +40265 215551

Article received on 07.02.2019 and accepted for publication on 29.03.2019
ACTA MEDICA TRANSILVANICA March 2019;24(1):23-26

disorders, metabolic acidosis, cognitive dysfunction (due to topiramate) to which migraines, headache, alopecia, hypokalemia were added.(11) The use of this combination is not recommended for patients with CV or cerebrovascular disease.(10) Also, topiramate is contraindicated in patients with closed-angle glaucoma due to an increased risk of acute blindness due to angle closure. Other ophthalmological SE of topiramate are blurred vision, ocular inflammatory and retinal reactions, visual feed defects and neuroophtalmologic manifestations.(12) Regarding the teratogenity, the use of topiramate during the first trimester of pregnancy is associated with an 88% increase in the risk of oral cleft in infants, so women patient be carefully monitored, including having monthly pregnancy test.(11)

Lorcaserin (Belviq, Belviq XR) is a selective serotonin receptor agonist, which reduces appetite by binding to the 5-HT2C receptors. It has the second highest NNH, making it one of the safer and more tolerable option for many patients.(3) This selectivity should minimize adverse effects that are observed with nonselective serotonergic agonists.(13) CAMELLIA-TIMI trial found that lorcaserin was not associated with a higher rate of CV events as compared to placebo. The study also showed slight, but significant, improvements in CV risk factors in the group treated with lorcaserin as compared to placebo, including a decrease in systolic and diastolic blood pressure, LDL-cholesterol and triglyceride levels. Typical SE for lorcaserin include headaches, dizziness, fatigue, diarrhea and nausea.(14) Concomitant use of lorcaserin in obese patients undergoing selective serotonin reuptake inhibitors may trigger serotonin syndrome.(15)

Naltrexon/Bupropion (Contrave® in USA and Mysimba® in UE).

Bupropion is a norepinephrine and serotonin reuptake inhibitor antidepressant while naltrexone is a pure opioid receptor antagonist that diminishes the auto-inhibitory feedback loop on neurons activated by bupropion, thereby allowing for sustained weight loss.(13) Generally, adverse events associated with this combination are mild to moderate in severity (nausea, constipation, headache and vomiting), and occur early in treatment initiation during dose escalation, and do not result in discontinuation. Also, it is not recommended to use the combination in individuals who already take an opioid medication because it can produce a fulminant opioid withdrawal.(16) Due to its bupropion component, the combination is contraindicated in those with a history of seizure disorder, anorexia or bulimia nervosa. Moreover, the combination should be prescribed with precaution on patient with CV disease because of the noradrenergic action of bupropion.(17) Despite the fact that some antidepressants are associated with suicidal events, COR-II study, shows that this combination was not associated with increased depression, depressed mood, or suicidality in the treatment of obese patients.(18) The mechanism of how bupropion may trigger psoriasis is unknown, but there are several case reports of generalized and erythrodermic psoriasis triggered in patients with history of psoriasis.(19) The combination has a NNH based on adverse effects higher than the rest of the medications, and may have the best effectiveness/tolerability ratio.(3)

Liraglutide (Saxenda) is the most recent anti-obesity medication approved both by FDA (2014) and EMA (2015).(20) In SCALE trial, the patients reported gastrointestinal events (nausea, vomiting, diarrhea). The most common SE was nausea (the liraglutide group experienced a rate of 39.3%, while the placebo group experienced the nausea at a rate of 13.8%) that occurred mostly during dose escalation. Liraglutide appears somewhat favourable based on NNT, but the lower NNH that resulted from reported nausea may decrease patient's adherence to medication. SCALE studies have shown an increased risk of pancreatitis in liraglutide-treated patients compared to placebo groups.(3) However, LEADER studies did not show statistically significant differences in the risk of pancreatitis in patients treated with liraglutide compared to placebo. Weight loss is directly associated with gallbladder disease and the incidence of biliary lithiasis after 56 weeks of liraglutide treatment was increased (5% of the participants) compared to the placebo group (2% of the study participants).(20) Long-term exposure to liraglutide in rodents was found to be associated with thyroid C-cell hyperplasia, although this finding has not been confirmed in human studies (LEADER, SCALE) in which no significant differences were observed in the incidence of benign and malignant neoplasms in liraglutide group compared with placebo.(21) Post-marketing reports indicated cases of medullary thyroid carcinoma in obese patients treated with liraglutide, so it is contraindicated in case of family history of medullary thyroid carcinoma.(13)

However, the wide use of some off-label drugs that are supposed to be effective in the treatment of obesity is not recommended especially if their safety is not fully studied.(15)

Phentermine is frequently prescribed in treating obese patients with BMI lower than conventional limits, in short-term use (up to 3 months), although long-time clinical trials also demonstrated its safety.(15) The maximum dose of phentermine is 15 mg/day, but it is frequently prescribed in higher doses or in combination with topiramate.(5) Based on the mechanism of action, phentermine and sympathomimetic agents (diethylpropion, benzphetamine and phendimetrizine) have the potential to increase heart rate and blood pressure, and for safety reasons are contraindicated in patients with CV diseases, hyperthyroidism, narrow-angle glaucoma.(22) Phentermine use in not associated with abuse or addiction. Amphetamine-like withdrawal does not occur upon abrupt treatment cessation even at doses much higher than commonly recommended (37.5 mg/day).(23) Combination therapy can promote additional weight loss, so physicians combine phentermine with lorcaserin, fluoxetine or bupropion. After administrating phentermine/bupropion, the most serious SE than can occur is lowered seizure threshold and potential worsening of suicidal ideation. The incidence of seizure is dose dependent so, the drug has been used in a lower dose, to reduce the probability of severe SE.(24) Phentermine may increase serotonergic effects although a pilot study suggests that co-administration of phentermine 15 mg in combination with lorcaserin 10 mg did not increase the incidence of serotonergic SE but did significantly increase weight loss compared to lorcaserin monotherapy.(25) Despite the weight loss efficacy of fluoxetine, nowadays combination with phentermine, is not very frequently used, due to the risk for suicidality.(24)

Metformine is a first-line antidiabetic drug which acts by decreasing production of glucose by the liver and possibly increasing peripheral insulin sensitivity and has a good safety profile and a long-term clinical experience, so there is frequently used as off-label indication for obesity. Metformine also prevents weight gain of antipsychotic drugs patients. Until now, no severe adverse events have been reported. Adherence to treatment is influenced by the well-known gastrointestinal SE of metformin.(26)

Pramlintide is an injectable amylin analogue antidiabetic drug used off-label for weight loss in non-diabetic patients, but most trials have been short-term, offering minimal information about long-term safety. Most common SE that occur in randomized studies, were mild to moderate nausea which decreased over time. When pramlintide is gradually titrated to

the recommended dosage, the incidence and severity of nausea are reduced.(27) Particularly, in patients with type I diabetes, co-administration of pramlintide with insulin may increase the risk of insulin-induced hypoglycemia.(28) Prescription of pramlintide in combination with phentermine(29) or with metraleptine(30) was stopped due to CV SE, respectively antibody formation.

Zonisamide is a drug approved for the treatment of epilepsy, which induces weight loss and has been used in off-label treatments alone or in combination with bupropion or phentermine.(31) The side effects of zonisamide administration such as depression and sedation may be overcome by its combination treatment with bupropion. Conversely, the seizure-inducing property of bupropion could be offset by zonisamide.(32) A phase II study clinical trial showed that adverse effects were limited to relatively mild events, including headache, insomnia and nausea.(31)

Agonists of GLP-1 receptor are drugs used in type-2 diabetes. Semaglutide has been found to be more effective than liraglutide for weight loss and it has an attractive benefit–risk profile. In a phase II randomized, double bind, dose-ranging trial, gastrointestinal events were dose-dependent; the most frequent side-effect was nausea and, in several cases, were reported gallbladder disorders (cholelithiasis or cholecystitis). No risks for pancreatitis, hepatic, thyroid or renal adverse events, were observed after semaglutide administration.(33) The other approved GLP-1 agonists (exenatide, albiglutide, taspoglutide, lixisenatide, dulaglutide) are used just in clinical trials and further long-term prospective randomized trials will establish their safety regarding the risk of pancreatitis and cancer.(34)

CONCLUSIONS

A growing number of drugs and natural products that arrogate their ability to lead to weight loss are available on the market. Although the majority have not at all the effect affirmed and expected by the patient there are also some that are based on scientific principles of action and whose effectiveness has been demonstrated. Pharmacological management of obesity is very important if we consider the demonstrated health risks. Even if on-label drugs are much safer they still have SE that can lead to some patients' lack of compliance to treatment. If we consider these aspects, treatment should be individualized to each patient according to their tolerability.

Taking into consideration that in the last seven years, FDA approved four new anti-obesity drugs, evaluation of their long-term safety, requires post-authorization clinical studies. Some of the off-label drugs (metformine, phentermine) have already long-term safety data and can be a better option for patients taking into consideration their clinical situation. For other new drugs (pramlintide, zonisamide, GLP-1 agonists) off-label prescription is controversial due to exiguous clinical data regarding long-term administration and their use should be limited only to clinical trials in order to develop novel weight-loss therapies.

REFERENCES

1. Violeta F. Obesity and its implications on quality of life. A major challenge of the XXI century. Acta Medica Transilvanica. 2016;21(2):8-10.
2. Bray GA, Kim KK, Wilding JPH. Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation. Obes Rev. 2017;18:715-723.
3. Jeffrey SM, Thomas LS. Effectiveness, tolerability and practical application of the newer generation anti-obesity medications. Drugs Context. 2016;5:212-291.
4. Matyjaszek-Matuszek B, Szafraniec A, Porada D. Pharmacotherapy of obesity state of the art. Endokrynol Pol. 2018;69(4):448-466.
5. Hendricks EJ. Off-label drugs for weight management. Diabetes Metab Syndr Obes. 2017;10:223-234.
6. Igho JO, Carl JH, Jeffrey KA. Post-marketing withdrawal of anti-obesity medicinal products because of adverse drug reactions: a systematic review. BMC Medicine. 2016;14:191.
7. Tongerson JS, Hauptman J, Boldrin MN, Sjostrom L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. Diabetes Care. 2004;27:155-161.
8. Hodkinson A, Gamble C, Smith CT. Reporting of harms outcomes: a comparison of journal publications with unpublished clinical study reports of orlistat trials. Trials. 2016;17(1):207.
9. Hong JL, Meier CR, Sandler RS, et al. Risk of colorectal cancer after initiation of orlistat: matched cohort study. BMJ. 2013;347:f5039.
10. Alfaris N, Minnick AM, Hopkins CM, et al. Combination phentermine and topiramate extended release in the management of obesity. Expert Opin Pharmacother. 2015;16(8):1263-1274.
11. Manning S, Pucci A, Finer N. Pharmacotherapy for obesity: novel agents and paradigms. The Adv Chronic Dis. 2014;5(3):135–148.
12. Abtahi MA, Abtahi SH, Fazel SH, et al. Topiramate and the vision: a systematic review. Clin Ophthalmol. 2012;6:117-131.
13. Patel DK, Stanford FC. Safety and tolerability of new-generation anti-obesity medications: a narrative review. Postgrad Med. 2018;130(2):173-182.
14. Bohula E, Wiviott S, McGuire D, et al. Cardiovascular safety of lorcaserin in overweight or obese patients. N Engl J Med. 2018;379(12):1107-1117.
15. Yanovski SZ, Yanovski JA. Long-term Drug Treatment for Obesity. JAMA. 2014;311(1):74–86.
16. Greig SL, Keating GM. Naltrexone ER/Bupropion ER: a review in obesity management. Drugs. 2015;75(11):1269-1280.
17. Halpern B, Mancini MC. Safety assessment of combination therapies in the treatment of obesity: focus on naltrexone/bupropion extended release and phentermine/topiramate extended release. Expert Opin Drug Saf. 2017;16:27-39.
18. Caroline MA, Louis A, Domenica R, Christopher S, Holly W, Colleen B, et al. A Randomized, Phase 3 Trial of Naltrexone SR/Bupropion SR on Weight and Obesity-related Risk Factors (COR-II), Obesity (Silver Spring). 2013;21(5):935-943.
19. Singh PA, Cassel KP, Moscati RM, Eckersley D. Acute Generalized Erythrodermic Pustular Psoriasis Associated with Bupropion/Naltrexone (Contrave®). J Emerg Med. 2017; 52(4):e111-e113.
20. Vilsboll T, Christensen M, Junker AE, Knop FK, Gluud LL. Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. BMJ. 2012;344:d7771.
21. Bjerre KL, Madsen LW, Andersen S, et al. Glucagon-like Peptide-1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation. Endocrinology. 2010;151(4):1473-1486.
22. Wharton S, Serodio KJ. Next generation of weight

management medications: implications for diabetes and CVD risk. Curr Cardiol Rep. 2015;17(5):35.
23. Hendricks EJ, Srisurapanont M, Schmidt SL, Haggard M, Souter S, Mitchell CL. et al. Addiction potential of phentermine prescribed during long-term treatment of obesity. Int J Obes (Lond). 2013;38(2):292-298.
24. Moyers SB. Medications as Adjunct Therapy for Weight Loss: Approved and Off-Label Agents in Use. J Am Diet Assoc. 2005;105(6):948-959.
25. Smith SR, Garvey WT, Greenway FL, Zhou S, Fain R, Pilson, R, et al. Coadministration of lorcaserin and phentermine for weight management: A 12-week, randomized, pilot safety study. Obesity .2017;25(5):857-865.
26. EL-Arabey AA. Update on off label use of metformin for obesity. Prim Care Diabetes. 2018;12(3):284-285.
27. Hendricks EJ, Rothman RB, Greenway FL. How physician obesity specialists use drugs to treat obesity. Obesity (Silver Spring). 2009;17(9):1730-1735.
28. Tam CS, Lecoultre V, Ravussin E. (2011). Novel strategy for the use of leptin for obesity therapy. Expert Opin Biol Ther. 2011;11(12):1677-1685.
29. Aronne LJ, Halseth AE, Burns CM, Miller S, Shen LZ. Enhanced weight loss following coadministration of pramlintide with sibutramine or phentermine in a multicenter trial. Obesity (Silver Spring). 2010;18(9):1739-1746.
30. DePaoli AM. 20 years of Leptin: Leptin in common obesity and associated disorders of metabolism. J Endocrinol. 2014;223(1):T71-T81.
31. Jackson VM, Price DA, Carpino PA. (2014). Investigational drugs in Phase II clinical trials for the treatment of obesity: implications for future development of novel therapies. Expert Opin Investig Drugs. 2014;23(8):1055-1066.
32. Gadde KM, Yonish GM, Foust MS, Wagner HR. Combination therapy of zonisamide and bupropion for weight reduction in obese women: a preliminary, randomized, open-label study. J Clin Psychiatry. 2007;68(8):1226-1229.
33. O'Neil PM, Birkenfeld AL, McGowan B, et al. Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial. Lancet. 2018;392(10148):637-649.
34. Tomlinson B, Hu M, Zhang Y, Chan P, Liu ZM. Investigational glucagon-like peptide-1 agonists for the treatment of obesity. Expert Opin Investig Drugs, 2016;25(10):1167-1179.