Clinical pharmacology of obesity and non-alcoholic fatty liver disease: GRADE evaluation of existing clinical evidence

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Running title: GRADE evaluation of obesity and NAFLD medicines

Abbreviations

ALT, Alanine Aminotransferase; BWL, Behavioral Weight Loss; BED, Binge Eating Disorder; EMA, European Medicines Agency; FDA, Food and Drug Administration; GLP-1, Glucagon-Like Peptide-1; NAFLD, Non-Alcoholic Fatty Liver Disease; NASH, Non-Alcoholic Steatohepatitis; OTC, Over the Counter; PPARγ, Peroxisome Proliferator-Activated Receptors γ; SGLT-2, Sodium Glucose Co-Transporter-2; T2DM, Type 2 Diabetes Mellitus; VAT, Visceral Adipose Tissue; WHO, World Health Organization

Abstract

Obesity and non-alcoholic fatty liver disease (NAFLD) are “lifestyle diseases” related to harmful habits, affecting a large portion of the global population at a steadily increasing prevalence. These disorders are inextricably associated with each other and therapeutic lifestyle changes (TLC) remain the cornerstone of their management. Nevertheless, TLC are difficult to achieve or maintain, and the use of medicines is often suggested. Different categories of medicines have been proposed, many of which are not officially licensed for these conditions. For NAFLD in particular, no drug with official indication exists so far. Thus, it is important that clinicians are aware of the quality of evidence supporting the efficacy of drugs before a decision to treat. To assist rational medical decision, in the present systematic review, we sought to evaluate the quality of evidence from phase III/IV clinical trials of major drugs currently proposed for obesity and NAFLD.

Keywords: Obesity; NAFLD; GRADE evaluation; clinical pharmacology; clinical evidence

Introduction

"Lifestyle diseases" is a contemporary definition used to describe a range of disorders related to harmful habits such as increased food consumption and caloric intake, low physical activity and disturbed circadian clock. They include heart and fatty liver disease, obesity and type 2 diabetes mellitus (T2DM) (Sharma and Majumdar, 2009). These disorders affect a very large part of the global population and despite the fact that current treatment strategies are constantly updated, including the use of novel drugs, there are still numerous unmet medical needs to be addressed and many pharmacological limitations to be tackled.

Obesity is a chronic metabolic disorder, characterized by increased fat depots, either in number or in size (Knittle et al., 1979; Hollstein and Piaggi, 2020). Phenotypically, obesity combines increased body mass mainly due to adipose tissue expansion and lean mass augmentation (Webster et al., 1984). Undoubtedly, a prolonged positive energy balance contributes to the development of the disease (Heymsfield and Wadden, 2017), yet many other parameters such as biological, environmental and social may also be implicated in the etiology of obesity (Yumuk et al., 2015; Heymsfield and Wadden, 2017). In 2016, the World Health Organization (WHO) reported that 39% of adults were overweight and 13% were obese, while the prevalence of overweight and obesity among children and adolescents was 18%. Impressively, it was reported that in 2019, 38 million children younger than 5 years old were overweight and obese (https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight). Obesity, abdominal fat and dysfunctional adipose tissue are associated with the development of cardiovascular diseases, T2DM, several cancers and hepatic or renal impairments

(MacMahon et al., 2009), and are considered as one of the primary causes of disability and death (Frühbeck et al., 2013).

Obesity is also strongly and positively associated with non-alcoholic fatty liver disease (NAFLD), a condition that ranges from simple accumulation of fat in the liver to non-alcoholic steatohepatitis (NASH) characterized by inflammation, hepatocyte injury and fibrosis which if left untreated may progress to cirrhosis and hepatocellular carcinoma (Vilar-Gomez et al., 2018; Brunner et al., 2019). It should be noted however that in some cases NAFLD may also be found in lean individuals, possibly as a result of dysfunctional adipose tissue (Albhaisi et al., 2019). Excessive lipid uptake or impaired lipid catabolism and disposal results in excessive accumulation of triglycerides in the liver, the most benign stage of NAFLD (Musso et al., 2009). Donnelly *et al.* (Donnelly et al., 2005) reported that peripheral adipose tissue lipolysis, hepatic *de novo* lipogenesis, and dietary fats are the three mechanisms leading to increased hepatic lipid accumulation, with a percentage contribution at 59.0%, 26.1%, and 14.9%, respectively. The prevalence of NAFLD worldwide is estimated at over 25% ranging from 13% in Africa to 30% in the Middle East and South America, while it is steadily increasing around the globe in the last twenty years (Mitra et al., 2020). In Europe, disease prevalence varies from 20% to 31% in certain countries and a large percentage of patients with NAFLD are individuals with morbid obesity and T2DM (Blachier et al., 2013).

Weight loss and life style changes are considered as the main strategy against obesity and NAFLD (Patel et al., 2015; Hannah and Harrison, 2016). However, drastic lifestyle changes are often difficult to achieve or maintain, therefore many different categories of medicines have been suggested in the literature, many of which are not officially licensed for these conditions (Brunner et al., 2019). Use of these

medicines poses a significant financial burden on health care systems all over the world and oftentimes exposes the patient to side-effects that may put their health at risk. Therefore, the use of such drugs should be mandated only by strong clinical evidence supporting their efficacy. In the absence of quality clinical data, the risk and cost may far exceed benefit, advocating against the use of these drugs. In the present systematic review, we sought to evaluate the quality of clinical evidence for all drugs currently used for obesity and NAFLD, in an effort to assist rational medical decision.

Methodology

In this article, we evaluated the quality of clinical evidence for existing drugs against obesity and NAFLD using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool in order to get clues on their overall usefulness and safety (Guyatt et al., 2008). GRADE provides a methodology for classification of quality of evidence focusing on certain factors. These factors include: Risk of bias (randomization, blindness, etc.), inconsistency (heterogeneity of population or intervention, etc.), indirectness (comparison to placebo, different target population, etc.), imprecision (optimal information size requirement, etc.) and publication bias (small number of trials, all of which are funded by industry, etc.) (Guyatt et al., 2008).

The clinical trials included in the present study have been selected following a Pubmed search using the keywords “non-alcoholic fatty liver disease treatment” and “obesity treatment” and research criteria “free full text”, “clinical trial, phase III”, “clinical trial, phase IV”, “date from 2000/1/1 to 2019/12/31”, “human species” and “English language”. Also, the ClinicalTrials.gov database was used to identify additional studies and collect more relevant information using the following criteria: keywords “non-alcoholic fatty liver disease treatment” and “obesity treatment”, “date

from 2000/1/1 to 2019/12/31", "status completed", "study type: interventional (clinical trials)", "study results: with results", "phase III", "phase IV". EAK, PCG, VK and KA participated in the independent appraisal of the collected manuscripts.

Current Pharmacology of Obesity

Therapeutic strategies for obesity aim not only at weight loss, but also at prevention of weight regain (Toplak et al., 2015; Yumuk et al., 2015), refinement of body composition, treatment of comorbidities, decrease of health risk and improvement of life quality. Both lifestyle interventions and pharmacotherapy contribute significantly to this direction (Bray, 2014; Toplak et al., 2015; Yumuk et al., 2015), however the use of medicines is usually recommended only for individuals with body mass index (BMI)≥ 30 kg/m^2 without comorbidities or BMI≥ 27 kg/m^2 if at least one obesity-related comorbidity, such as dyslipidemia or diabetes is present (Jensen et al., 2014). Currently, both Food and Drug Administration (FDA) and European Medicines Agency (EMA) have given their approval for the indication of obesity to orlistat, liraglutide and the combination of naltrexone/bupropion. Lorcaserin and the combination of phentermine/topiramate are approved only by the FDA. These drugs act through various mechanisms, for example, orlistat diminishes the intestinal digestion of lipids via highly specific inhibition of pancreatic and gastric lipases in the gastrointestinal tract (Ballinger and Peikin, 2002), liraglutide is a long acting agonist for the receptor of glucagon-like peptide-1 (GLP-1) (Crane and McGowan, 2016) while lorcaserin is a selective serotonin agonist, that binds with high affinity to 5-HT_{2C} receptors (Thomsen et al., 2008). Notably, the approved fixed-dose combinations aim at improving effectiveness and safety (Toplak et al., 2015). Particularly, a pooled-data clinical trial showed that phentermine/topiramate combination therapy is more effective in reducing weight compared to either

topiramate or phentermine monotherapies (Thompson et al., 2014). On the other hand, bupropion aims at improving the depression triggered by naltrexone, an opiate antagonist with the highest affinity for μ-type opioid receptors.

Evaluation of Clinical Evidence

Evidence from Phase III and IV clinical trials of drugs with official indication against obesity during the last twenty years, approved either by FDA or EMA, is described and evaluated. In our search we also included clinical trials of drugs approved for other indications which have shown a beneficial effect on weight management.

Drugs with Official Indication against Obesity

Orlistat

Orlistat was the first drug approved by FDA in 1999 for obesity management in patients with an initial BMI≥30 kg/m^2 or BMI≥27 kg/m^2 in the presence of other risk factors such as hypertension, T2DM or dyslipidemia. Almost one decade later, orlistat was the first drug recommended as a non-prescription (over the counter, OTC) product for weight loss by the EMA. As mentioned before, orlistat is a potent, specific and long-acting inhibitor of gastrointestinal lipases (Ballinger and Peikin, 2002).

A 24-week randomized, placebo-controlled, multicenter trial with 131 overweight subjects showed that both orlistat- and placebo-treated patients experienced a significant decreased in their visceral adipose tissue (VAT) which was significantly greater in the orlistat group. Also, orlistat treatment resulted in significantly greater weight and total fat mass loss and trended to a greater loss of intermuscular adipose tissue and liver fat content compared to placebo (Smith et al., 2011). The quality of this evidence is evaluated as very low due to indirectness (comparison to placebo), imprecision (small population size) and publication bias

(publication funded by the marketing authorization holder). Similarly, orlistat was reported to have a beneficial effect in obese patients without binge eating disorder (BED). Specifically, in a randomized placebo-controlled trial, 79 obese Spanish-speaking-only Latins with or without BED were treated for 4 months with orlistat plus behavioral weight loss (BWL) or placebo plus BWL. The results showed that adding orlistat to BWL produced greater weight-loss than adding placebo among obese patients without BED but not among those with (NCT00516919) (Grilo and White, 2013). However, the quality of evidence is classified as low due to bias of indirectness (comparison to placebo) and imprecision (insufficient population number).

Overall, the use of orlistat in the treatment of obesity is based on very low quality clinical evidence which means that any estimate of its benefits is very uncertain (Table 1). Additional and better clinical trials are needed, and they are highly likely to change our confidence on the effectiveness of the drug.

Phentermine/Topiramate

The fixed dose combination of phentermine immediate-release and topiramate extended-release was approved by the FDA in 2012 and it was the first combination drug for obesity (Singh and Kumar, 2015). Phentermine is a sympathomimetic agent that reduces appetite and increases metabolism while topiramate is an antiepileptic drug that has been associated with weight loss as a side effect (Lonneman et al., 2013). Clinical trials provided data suggesting that a fixed dose combination of phentermine with topiramate contributes to weight loss in obese patients or overweight patients with comorbidities (Singh and Kumar, 2015).

In a published randomized, double-blind, placebo controlled study (CONQUER, NCT00553787) (Gadde et al., 2011) consisting of 2487 overweight or

obese adults with a BMI of 27–45 kg/m² and two or more comorbidities (hypertension, dyslipidaemia, diabetes or prediabetes, or abdominal obesity), treatment with phentermine plus topiramate controlled-release combination as an adjunct to diet and lifestyle modifications was related to weight loss after 56 weeks of therapy. According to the GRADE system, the quality of evidence is low due to indirectness bias (comparison to placebo) and publication bias (publication funded by the marketing authorization holder).

Similarly, in another randomized, double-blind, placebo-controlled, 52-week extension of the CONQUER study (SEQUEL, NCT00796367) (676 patients elected to continue in the extension) (Garvey et al., 2012), the same drug combination was associated with significant, sustained weight loss while improved cardiovascular and metabolic variables and decreased rates of incident T2DM compared with placebo. The study concluded that phentermine plus topiramate controlled-release used as an adjunct to lifestyle intervention for the treatment of obesity was well tolerated and produced significant, dose-related weight loss that was maintained during a 108-week period. Using the GRADE instrument, the quality of evidence is classified as very low due to indirectness (comparison to placebo), imprecision (insufficient population number) issues and publication bias (publication funded by the marketing authorization holder).

In addition, a 28−week, randomized, controlled trial in 756 obese adults compared fixed dose combination of phentermine plus topiramate extended−release with each component as monotherapy or with placebo. The study showed that the combination induced greater weight loss in comparison to each monotherapy and improved cardiometabolic parameters at lower doses than each monotherapy (EQUATE, NCT00563368) (Aronne et al., 2013). According to the GRADE system,

the quality of evidence is moderate due to publication bias (publication funded by the marketing authorization holder).

Overall the use of phentermine/topiramate fixed dose combination in the treatment of obesity is based on very low quality of evidence. Future studies are expected to change significantly current recommendations on the use of this combination.

Naltrexone/Bupropion

Almost two years later, in 2014 another drug combination was approved by FDA for the indication of obesity. One of the active components was naltrexone, an opioid μ-receptor antagonist which had been already approved for the treatment of alcohol and opioid dependence. Likewise, bupropion, a dual norepinephrine and dopamine reuptake inhibitor, was approved against depression and seasonal affective disorder and as an aid to smoking cessation treatment (Sherman et al., 2016).

In a multicentre, randomized, double-blind, placebo-controlled, phase III clinical trial (COR-I, NCT00532779) with 1742 participants (Greenway et al., 2010), it was found that use of a sustained-release combination of naltrexone plus bupropion reduced body weight of obese patients with BMI 30-45 kg/m^2 or BMI 27-45 kg/m^2 with dyslipidaemia or hypertension compared to placebo group. According to the GRADE system, the quality of evidence is classified as low due to indirectness bias (comparison to placebo) and publication bias (publication funded by the marketing authorization holder).

Another clinical trial (CONTRAVE Obesity Research-II (COR-II), NCT00567255) (Apovian et al., 2013) showed that 1496 obese (BMI 30-45 kg/m^2) or overweight (27-45 kg/m^2) patients with dyslipidemia and/or hypertension received

naltrexone/bupropion experienced greater weight loss compared to the placebo group while the drug combination produced greater improvements in various cardiometabolic risk markers, participant-reported weight-related quality of life, and control of eating. Using the GRADE instrument, the quality of evidence is classified as low due to indirectness bias (comparison to placebo) and publication bias (publication funded by the marketing authorization holder).

Regarding bupropion as monotherapy a small study among 296 adolescents between the ages of 14 to 17 who smoked at least 6 cigarettes a day showed that bupropion could potentially mitigate the risk of weight gain during smoking cessation (NCT00344695) (Floden et al., 2016). However, the significant reduction in BMI z-score at 6th week post quit was not sustained at the six-month follow up. According to the GRADE system, the quality of evidence is very low due to risk of bias (dropouts/ withdrawals not accounted for), indirectness (comparison to placebo) and imprecision (insufficient information for optimal sample size calculation). Furthermore, in a randomized, double-blind, placebo-controlled trial (NCT00414167) (White and Grilo, 2013) with 61 overweight and obese woman who suffered from binge-eating disorder, woman received bupropion for 8 weeks lost significantly more weight. However, the authors suggested that their findings did not support monotherapy with bupropion as treatment for binge-eating disorder. The quality of evidence is low due to indirectness (comparison to placebo) and imprecision (insufficient population size) issues.

Considering only the clinical trials that evaluated the combined intervention, the use of naltrexone/bupropion fixed dose combination in the treatment of obesity is based on evidence of low quality. Future studies are very likely to change significantly our confidence in the estimate of the effect of naltrexone/bupropion and probably change the estimate.

Liraglutide

Liraglutide is a GLP-1 agonist used for the improvement of glycemic control in patients with T2DM. Different clinical trials indicated a beneficial effect of GLP−1 analogs on obesity, thus, liraglutide was also licensed as a weight loss agent with encouraging results in phase III clinical trials (Astrup et al., 2009; Davies et al., 2015). Liraglutide received approval by EMA for weight management in adults as adjunct to reduced-calorie diet and physical activity (Crane and McGowan, 2016).

A recent post hoc analysis of pooled data from four phase IIIa trials in patients with either a minimum BMI of 27 kg/m^2 and (at least) one comorbidity, or a minimum BMI of 30 kg/m^2 compared the efficacy and safety of liraglutide versus placebo, combined with a low-calorie diet and physical activity (NCT01272219, NCT01272232, NCT01557166, NCT00781937) (O'Neil et al., 2016). The study showed that both Hispanic (n=534) and non-Hispanic (n=4597) subgroups had clinically significant mean weight loss after treatment with liraglutide while more patients in both subgroups lost ≥5%, >10%, and >15% of their initial weight compared to placebo. The quality of this clinical evidence is rated as low due to indirectness bias (comparison to placebo) and publication bias (publication funded by the marketing authorization holder).

Furthermore, another randomized placebo-controlled, 12-week clinical trial in 72 overweight and obese patients with type 1 diabetes (T1D), showed that the addition of either high (1.2 and 1.8 mg) or low (0.6 mg) liraglutide dose to insulin therapy resulted in significant weight reduction but increased gastrointestinal adverse effects (NCT01722266) (Kuhadiya et al., 2016). Again, the quality of evidence is low

due to indirectness (comparison to placebo) and imprecision (insufficient population size) issues.

A 56-week, randomized, double-blind, placebo-controlled, multinational, multicenter trial with 396 participants (SCALE™ Insulin, NCT02963922) (Garvey et al., 2020) showed that overweight or obese and insulin-treated T2DM patients showed increased weight loss when liraglutide was added as an adjunct to intensive behavioral therapy (IBT) compared to placebo. However, the quality of clinical evidence is rated again as low due to indirectness (comparison to placebo) and publication bias (publication funded by the marketing authorization holder). Similar results were reported in another study with obese patients without T2DM. Particularly, a 56-week, randomized, double-blind, placebo-controlled, multicenter trial with 282 participants (SCALE™ IBT, NCT02963935) (Wadden et al., 2020), showed that at week 56, mean weight loss with liraglutide plus IBT was greater compared to placebo combined with IBT. Again, the quality of evidence is low due to indirectness (comparison to placebo) and publication bias (publication funded by the marketing authorization holder).

Overall the use of liraglutide as anti-obesity drug is based on clinical evidence of low quality, which means that further studies are very likely to change our confidence in the estimate of its effect.

Lorcaserin

In 2012, lorcaserin received approval by FDA following evaluation of additional data addressing previous safety concerns of carcinogenesis in animal models (Brashier et al., 2014). Lorcaserin is a selective 5-HT_{2C} receptor agonist with indication of weight

management in combination with lifestyle modification for obese or overweight adults with more than one weight related comorbidity (Thomsen et al., 2008).

Two phase III clinical trials of similar design, the Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM, NCT00395135, n=3182) and the Behavioral Modification and Lorcaserin Second Study for Obesity Management (BLOSSOM, NCT00603902, n=4008) assessed the safety and effectiveness of lorcaserin in adults without T2DM. A pooled analysis of these clinical trials showed that lorcaserin-treated patients in combination with diet and physical activity lost significantly more body weight compared to placebo group while clinically relevant improvements in cardiometabolic parameters were reported (Aronne et al., 2014). Unfortunately, the quality of evidence is very low due to risk of bias (loss of follow up), indirectness (comparison to placebo) and publication bias (publication funded by the marketing authorization holder).

Moreover, a post hoc analysis of the BLOOM-DM trial (NCT00603291) suggested that lorcaserin treatment of overweight and obese patients with T2DM for 52 weeks promoted weight reduction and facilitated glycemic control compared to placebo (Pi-Sunyer et al., 2016). The quality of evidence is rated again as low due to indirectness bias (comparison to placebo) and publication bias (publication funded by the marketing authorization holder).

Overall, the use of lorcaserin in the treatment of obesity is supported by very low quality of evidence indicating that the estimate of its effect is very uncertain and future studies may change this estimate.

Drugs with no official indication for Obesity

Exenatide

As liraglutide, another GLP-1 agonist, exenatide is the first drug of the category derived from a peptide isolated from the salivary secretions of the Gila monster (Parkes et al., 2013). Exenatide is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM, however it, also appears to reduce body weight in clinical trials (Gupta, 2013).

A combination of three placebo-controlled trials and their open-label extensions with 217 type 2 diabetic and obese patients evaluated the effects of at least 3 year exenatide therapy on glycemic control, body weight, cardiometabolic markers and safety (NCT00111540) (Klonoff et al., 2008). Regarding obesity, it was reported that exenatide progressively reduced body weight compared to starting values, at 3 years of treatment while improved lipid profile of patients. Nevertheless, the quality of clinical evidence is very low due to risk of bias (open label study), indirectness (comparison to placebo), imprecision (insufficient information for placebo population) and publication bias (publication funded by the marketing authorization holder).

Similarly, a recent randomized multicenter, double-blind study (DURATION-7, NCT02229383) in 464 patients with persistent hyperglycaemia showed that exenatide once weekly decreased significantly body weight, a secondary clinical outcome of the trial, compared to placebo (Guja et al., 2018). Once again, the quality of evidence is low due to indirectness bias (comparison to placebo) and publication bias (publication funded by the marketing authorization holder).

Interestingly, when exenatide was compared to semaglutide, another GLP-1 agonist, its superiority was not confirmed. Indicatively, a phase IIIa, open-label, parallel-group, randomized controlled trial (SUSTAIN 3, NCT01885208) (Ahmann et

al., 2018) with 813 participants with T2DM indicated that semaglutide was superior to exenatide extended-release in improving glycemic control and reducing body weight at week 56 of treatment. The quality of evidence from the SUSTAIN trial is rated as low due to risk of bias (open label study) and publication bias (publication funded by the marketing authorization holder).

Exenatide, recently, was evaluated in combination with dapagliflozin, another antidiabetic drug that inhibits sodium glucose co-transporter-2 (SGLT-2) in the intestine. Specifically, in a post hoc analysis in 695 patients with T2DM inadequately controlled with metformin monotherapy (subpopulations from the DURATION-8 trial, NCT02229396), it was found that a 28-week treatment with exenatide once weekly plus dapagliflozin resulted in body weight reduction that was no greater than that observed with exenatide once weekly or dapagliflozin alone (Jabbour et al., 2018). For each group, weight loss was numerically greater as baseline BMI increased. According to the GRADE system, the quality of evidence from this trial is rated as low due to imprecision (insufficient information for population) and publication bias (publication funded by the marketing authorization holder).

Taking into account the clinical evidence stemming from trials evaluating the effect of exenatide monotherapy on weight loss, its use as medicine against obesity is classified as of very low quality, suggesting that the estimate of its effect is very uncertain.

Ertugliflozin, Empagliflozin and Luseogliflozin

The benefit of novel SGLT-2 inhibitors ertugliflozin, empagliflozin and luseogliflozin on body weight loss when administered as monotherapies, was assessed in clinical trials which offered only limited proof of efficacy (Lee et al., 2018).

Regarding ertugliflozin, a 52-week double-blind, multicentre, randomized, parallel-group study showed that a 26-week treatment with 5 mg and 15 mg of ertugliflozin reduced significantly body weight of obese patients with T2DM inadequately controlled with diet and exercise alone, compared to placebo treated group while also provided effective glycaemic control (NCT01958671) (Terra et al., 2017). According to the GRADE system, the quality of evidence is very low since there were issues of indirectness bias (comparison to placebo), imprecision bias (insufficient information for population proportion) and publication bias (publication funded by the marketing authorization holder).

Empagliflozin's efficacy and safety were evaluated in a pooled post hoc analysis of three multicenter, phase III, randomized, double-blind, placebo-controlled clinical trials [EMPA-REG PIO (NCT01289990), EMPAREG MET (NCT01159600), EMPA-REG METSU (NCT01159600)] (Romera et al., 2016). This clinical trial studied empagliflozin as monotherapy or combined with metformin, metformin plus sulfonylurea or metformin plus pioglitazone in 439 overweight or obese patients with poorly controlled T2DM baseline. The results indicated that after 24 weeks, the greater reduction in glycosylated hemoglobin, type A1C (HbA1c) experienced by patients treated with empagliflozin was accompanied by significantly decreased body weight, regardless of the background therapy. However, the quality of evidence is classified as very low since there were issues of indirectness bias (comparison to placebo), imprecision bias (insufficient information for optimal sample size calculation) and publication bias (publication funded by the marketing authorization holder).

As to luseogliflozin, a pooled analysis of four 52-week phase III trials in 1031 Japanese patients with T2DM showed that the treatment significantly reduced body

weight mainly in patients with higher BMI and especially in those with BMI ≥30 kg/ m^2 (Sakai et al., 2016). Furthermore, luseogliflozin was especially beneficial in patients with higher BMI in terms of metabolic abnormalities, including insulin secretion and hypertension. Again, the quality of evidence was very low due to risk of bias (not randomized, not double-blind), indirectness bias (no placebo, no other intervention), imprecision bias (no percentage of population with reduced body weight) and publication bias (publication funded by the marketing authorization holder).

Overall, the beneficial effect of ertugliflozin, empagliflozin and luseogliflozin on weight loss is based on rather very low quality of evidence implying that the estimate of their effect is very uncertain and future studies may change significantly this estimate.

Sibutramine

Sibutramine was approved by FDA in 1997 for weight loss and maintenance of weight loss in patients with a BMI ≥30 kg/m^2 or for patients with a BMI ≥27 kg/m^2 who have other cardiovascular risk factors. Sibutramine inhibits the neuronal reuptake of norepinephrine, serotonin, and, to a lesser extent, dopamine enhancing the appetite suppressing actions of these neurotransmitters (R. Araujo and Martel, 2012). Nevertheless, in 2010 EMA and FDA decided that sibutramine should be withdrawn from the market due to safety concerns (Williams, 2010).

The Sibutramine Cardiovascular OUTcomes (SCOUT, NCT00234832) (Weeke et al., 2010) trial with 10742 obese and overweight patients at increased risk of cardiovascular events treated with 10 mg sibutramine in combination with diet instructions and exercise for 6 weeks showed that decrease in BMI resulted in plasma

lipid changes that were affected by diabetes status. The authors suggested that short term weight management with sibutramine therapy induced significant mean reductions for all plasma lipids and patients without T2DM benefited most. The quality of evidence from the SCOUT trial is classified as very low due to risk of bias (single-blind), inconsistency bias (intervention heterogeneity), indirectness bias (no comparison to placebo or other intervention), imprecision bias (no proportion of population) and publication bias (publication funded by the marketing authorization holder).

A randomized trial (NCT00537810) compared the effectiveness compared the effectiveness of self-help cognitive behavioral therapy (shCBT) and sibutramine, alone and in combination, in 104 obese patients with BED for 16 weeks. Percent weight loss over time favored subjects receiving sibutramine compared to placebo. However, weight regain was observed following treatment termination and study arms no longer differed significantly at 6- and 12-month follow-ups. The findings suggested that initial weight loss observed is not sustained and sibutramine needs to be continued for weight loss maintenance (Grilo et al., 2014). According to GRADE, the quality of evidence is classified as low due to indirectness bias (comparison to placebo) and imprecision bias (insufficient information for population proportion).

Overall, the efficacy of sibutramine as anti-obesity drug is based on very low quality of evidence indicating that the estimate of its effect is very uncertain.

NAFLD and current pharmacology

Currently, there is no officially approved drug with formal indication for NAFLD and NASH, either by EMA, or FDA (Leoni et al., 2018) and any pharmacological treatment should solely aim at controlling comorbidities such as T2DM, dyslipidemia,

and obesity (Stahl et al., 2019). Thus, antidiabetic drugs (GLP-1 analogues), insulin sensitizers (thiazolidinediones), lipid-lowering agents (statins, ezetimibe, fibrates) and vitamin E, commonly reported in the literature as possible therapies for NAFLD are used as off-label treatments and they should be carefully prescribed (Leoni et al., 2018). Also, silymarin, an antioxidant derivative from *Silybum marianum*, is recommended for NASH patients only by the Asia-Pacific guidelines (Leoni et al., 2018), although more clinical evidence for its efficacy is still needed (Chitturi et al., 2018).

NAFLD: Evaluation of Clinical Trials of Drugs for NAFLD Comorbidities

Phase III and IV clinical trials of drugs that have taken place for the treatment of NAFLD in the last two decades are described and evaluated below. In our search we included clinical trials of drugs that have been approved for other disease and have been suggested to have a positive effect on hepatic lipid accumulation.

Empagliflozin

As mentioned before, empagliflozin is an SGLT-2 inhibitor approved for reducing the risk of cardiovascular death in adult patients with T2DM and cardiovascular disease (https://www.fda.gov/news-events/press-announcements/fda-approves-jardiance-reduce-cardiovascular-death-adults-type-2-diabetes). Regarding its role in the treatment of NAFLD, Kuchay et *al.* (Kuchay et al., 2018), presented findings suggesting that empagliflozin reduces liver fat and improves plasma alanine aminotransferase (ALT) levels in patients with T2DM and NAFLD.

One analysis combining data from three different sources [EMPA-REG OUTCOME® trial (NCT01131676, n = 7020), pooled data from four 24-week

placebo-controlled trials (NCT01177813, NCT01159600, NCT01159600 and NCT01210001, n = 2477) and EMPA-REG H2H-SU trial (NCT01167881, n = 1545)] showed that treatment with empagliflozin in individuals with T2DM reduced liver aminotransferases, largely independent of changes in weight and glycemic control, and did so in a pattern that is potentially consistent with reductions in liver fat (Sattar et al., 2018). Unfortunately, the quality of evidence is very low due to strong indirectness bias (comparison to placebo, study population differs from target population since treated subjects were not officially diagnosed with NAFLD, study outcomes differ from outcomes of interest since liver biopsy was not included) and publication bias (publication funded by the marketing authorization holder). Thus, the clinical evidence supporting empagliflozin's benefit on NAFLD is of very low quality and the estimate of its effect on the disease is very uncertain.

Obeticholic acid

Obeticholic acid, a potent specific agonist of farnesoid X receptor (FXR), is currently indicated for the treatment of primary biliary cholangitis as monotherapy or in combination with ursodeoxycholic acid. The effects of obeticholic acid include regulation of bile acids, lipids, cholesterol, and glucose homeostasis (Zhang et al., 2019).

In a multicenter, randomized, double-blind, placebo-controlled study, adult patients with definite NASH, NAFLD activity score of at least 4, and fibrosis stages F2-F3, or F1 with at least one comorbidity, obeticholic acid was evaluated compared to placebo (REGENERATE, NCT02548351) (Younossi et al., 2019). The results showed that obeticholic acid significantly improved fibrosis and key components of NASH such as lobular inflammation and hepatocellular ballooning while clinically

significant histological improvement was shown. Despite these positive effects, induction of treatment resistant dyslidemia may discourage its use in NAFLD. Based on GRADE, the quality of evidence is classified as low due to indirectness (comparison to placebo) and publication bias (publication funded by the marketing authorization holder). The low quality of evidence means that new studies is very likely to impact importantly our confidence in the estimate of obeticholic acid effect.

Pioglitazone

Pioglitazone, a thiazolidinedione is a synthetic ligand for peroxisome proliferator-activated receptors γ (PPARγ) used as an adjunct to diet, exercise, and other antidiabetic medications to manage T2DM was assessed for its role in NAFLD in several clinical trials (Liu et al., 2020).

A randomized, double-blinded, placebo-controlled trial (NCT00994682) in 101 patients with prediabetes or T2DM and biopsy-proven NASH showed that 18-month treatment with pioglitazone improved individual histology scores, including fibrosis score, and reduced hepatic triglyceride content from 19% to 7% compared to placebo. All 18-month metabolic and histologic improvements persisted over 36 months of therapy (Cusi et al., 2016). The quality of evidence is low due to indirectness bias (comparison to placebo) and imprecision bias (insufficient number of population).

Another randomized, multicenter, double-blinded, placebo-controlled trial (PIVENS, NCT00063622) with 247 non-diabetic adults with NASH, treatment with pioglitazone for 96 weeks showed no benefit over placebo while vitamin E was superior to placebo for the treatment of NASH (Sanyal et al., 2010). Again, the

quality of evidence from the PIVENS trial is low due to indirectness bias (comparison to placebo) and imprecision bias (insufficient number of population).

Interestingly, the combination of pioglitazone with vitamin E seemed to have a beneficial effect. Particularly, a randomized, double-blind, placebo-controlled trial (NCT01002547) in patients with T2DM and biopsy-proven NASH showed that the combination therapy of pioglitazone with vitamin E was better than placebo in improving liver histology in patients with NASH and T2DM (Bril et al., 2019). The quality of evidence is moderate due to indirectness bias (comparison to placebo).

Taking into consideration only the clinical trials that evaluated pioglitazone as monotherapy, its use in the treatment of NAFLD is based evidence of low quality. Future studies are very likely to affect our confidence in the estimate of pioglitazone's effect and probably change the estimate.

Purified Docosahexaenoic and Eicosapentaenoic Acids

In 2018, a meta-analysis of randomized controlled trials suggested that omega-3 polyunsaturated fatty acids may have a beneficial role in fatty liver and hepatic enzymes however, the authors emphasized that further studies are needed to confirm this effect (Yan et al., 2018).

During our search, we found one clinical trial which studied the combination of docosahexaenoic acid (DHA) plus eicosapentaenoic acid (EPA) in the treatment of NAFLD. Specifically, in a randomized, double-blind, placebo-controlled trial (WELCOME, NCT00760513) (Scorletti et al., 2014), the combination of DHA plus EPA was administered for 15-18 months and its efficacy was evaluated in 103 patients with NAFLD. The results showed that there was a trend toward improvement in liver fat content with the DHA/EPA combination while no improvement in fibrosis

scores was noted. The quality of evidence from the WELCOME trial is low due to indirectness bias (comparison to placebo) and imprecision bias (insufficient number of population) indicating that further research is very likely to change the estimate of the effect that DHA/EPA combination may have on NAFLD.

Metformin and Vitamin E

Metformin, a guanidine derivative, was discovered and used to treat diabetes as early as in the 1920s (Bailey, 2017). It was officially introduced to clinical practice in the UK in 1950's (Marita and Patade, 2014). Despite its well-established role in the management of T2DM as a first line medication, its role in NAFLD is still under investigation. Recent data indicate that the protective effects of metformin on the onset of NAFLD are associated with changes in intestinal microbiota composition and lower translocation of bacterial endotoxins (Brandt et al., 2019). On the other hand, vitamin E, is a potent antioxidant that has been shown to reduce oxidative stress in NAFLD (El Hadi et al., 2018).

A randomized, double-blind, placebo-controlled trial in 173 patients (aged 8-17 years) with biopsy-confirmed NAFLD (TONIC, NCT00063635) (Lavine et al., 2011) evaluated the efficacy of metformin or vitamin E monotherapies. Neither vitamin E nor metformin were superior to placebo in attaining the primary outcome of sustained reduction in ALT levels. Also, neither therapy demonstrated significant improvements in histological features compared to placebo. The quality of evidence from the TONIC trial is low due to indirectness bias (comparison to placebo) and imprecision bias (insufficient number of population) indicating that further research may affect the estimate of these inteventions in NAFLD.

Cysteamine Bitartrate Delayed-Release

Cysteamine bitartrate is a cystine-depleting agent indicated for the treatment of nephropathic cystinosis in adult and pediatric patients 2 years of age and older (Medic et al., 2017).

Delayed-release cysteamine bitartrate was evaluated in a randomized, double-blind, placebo-controlled trial with 169 children with NAFLD activity scores of 4 or higher (CyNCh, NCT01529268) (Schwimmer et al., 2016). The results showed that treatment with delayed-release cysteamine bitartrate for one year did not reduce overall histologic markers of NAFLD compared to placebo. However, children received the intervention had significant reductions in serum aminotransferase levels and lobular inflammation. The quality of evidence is classified as moderate due to indirectness bias (comparison to placebo) indicating that further research is likely to have an important impact on our confidence in the estimate of its effect and may change the estimate.

Pentoxifylline

A meta-analysis have shown that pentoxifylline, a methylxanthine derivative with potent hemorrheologic properties, results in weight loss, improved liver function and histological changes in patients with NAFLD and NASH (Du et al., 2014).

In a randomized, double-blind, placebo-controlled trial, 26 participants with biopsy proven NASH received pentoxifylline for 12 months (NCT00267670) (van Wagner et al., 2011). Regarding steatosis and ballooning, the reduction observed with pentoxifylline was not superior compared to placebo. Also, no significant reduction was seen for lobular inflammation in both groups. The quality of evidence for this intervention is low due to indirectness bias (comparison to placebo) and imprecision bias (insufficient number of population). Thus, future studies are very likely to have

an important impact on our confidence in the estimate of its effect and is likely to change the estimate.

Conclusions

Many phase III and IV clinical trials of drugs with different mechanisms of action have shown promising results against obesity and NAFLD. Nevertheless, despite the encouraging data, crucial questions arise for the quality of evidence that supports the use of these drugs in everyday clinical practice.

Based on our assessment, the quality of evidence for the existing obesity and NAFLD pharmacological treatments limits our confidence on their effectiveness.

The quality of clinical evidence from the vast majority of anti-obesity and anti-NAFLD trials ranges from very low to low (Table 1). Most trials suffer from indirectness due to comparison to placebo and imprecision, usually due to a small population sample which does not allow safe, statistically sound outcomes. Another frequent issue is the publication bias where the marketing authorization holder is also the sponsor of the clinical trial. Less frequently trials suffered from risk of bias mainly due to lack of blindness in the treatment. As a result, any estimate of effect based on these clinical trials is very uncertain and further research is likely to impact significantly our confidence in the estimate of their effects. Physicians should be aware that current pharmacotherapies may be inadequate, they may expose patients to serious side-effects and burden public health care systems, offering disproportionally very low or no benefit against obesity and/or NAFLD,

Our systematic analysis strongly suggest that additional high quality, randomized, double blinded, head-to-head clinical trials using appropriate cohorts that meet the optimal information sample size requirement are needed to draw safe

conclusions on the clinical usefulness, safety and efficacy of currently used weight loss and NAFLD medicines. Additionally, our work highlights the need for novel agents that will replace less efficient and potentially unsafe existing medications.

Author contributions

All authors collected literature, analyzed data, contributed in the manuscript preparation and gave their consent for its final submitted form. KEK and OA led the project, contributed to the manuscript design, drafted the final form of the manuscript, and gave their consent for its final submitted form.

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