



Of mice and men: Why progress in the pharmacological management of obesity is slower than anticipated and what could be done about it?



1. Introduction

Obesity is one of the major pandemics of the 21st century. In 2013–2014, the prevalence of obesity in the US was >35% among men and >40% among women [1]. The World Health Organization (WHO) reported that 39% of men and 39% of women were overweight, and 11% of men and 15% of women were obese in 2016. Thus, approximately 2 billion adults worldwide were overweight and, among them, more than half a billion were obese [2]. Obesity is a chronic disease adversely affecting the quality of life and is associated with many comorbidities, like hypertension, dyslipidemia, type 2 diabetes (T2DM), cardiovascular disease (CVD), nonalcoholic fatty liver disease (NAFLD), chronic kidney disease, particular types of cancer, arthritis and respiratory diseases [3–6]. Since there is a parallel rise in childhood obesity rates (approximately 15% of children and adolescents are obese), the health consequences of obesity are expected to appear earlier in the near future. Thus, a reversal of the 20th century gains in life expectancy, due to the adverse consequences of obesity in the coming decades has been proposed [7], further underlining that obesity remains an important and largely unmet clinical need.

Timely prevention and appropriate management of obesity are expected to limit the obesity-associated morbidity and mortality [8]. Nevertheless, the prevention of obesity is still not as effective as needed and truly safe and completely effective treatments, let alone a magic bullet for obesity, are not in sight, despite remaining in the epicenter of academic and pharmaceutical research.

Abdominal obesity is closely associated with the insulin resistance (IR) or metabolic syndrome (MetS) and related metabolic aberrations. Obesity-associated IR is linked to increased hepatic glucose output and reduced glucose disposal for a given amount of insulin [9] and is associated with not only the total quantity of adipose tissue, but mainly its distribution and more specifically with the degree of ectopic fat distribution [10]. Ectopically deposited fatty acids (FAs), lead to hepatic steatosis, inhibit insulin uptake by the liver and contribute to the increased glucose release [11]. Importantly, levels of cytokines, such as tumor necrosis factor (TNF)- α , and hormones, such as leptin, are increased, whereas levels of other hormones, including adiponectin, an endogenous insulin sensitizer secreted by the adipose tissue, are decreased, thus being potential mediators of obesity-associated IR.

Peripheral mechanisms, such as gastric emptying, sensory mechanisms, which convey signals of satiation to the brain, and peripherally released peptides and hormones also contribute towards the regulation of metabolism and appetite [12]. It is the brain, however, which integrates signals from the internal milieu as well as cues and stimuli from the environment to alter the balance of energy intake vs. expenditure

and ultimately affect body weight. Consequently, all these loci, but most importantly brain centers integrating peripheral signals as well as reward centers and cortical centers that regulate control and behavior represent predominant targets for potential treatments for obesity.

This issue of *Metabolism, Clinical and Experimental*, publishes a novel article on the effects of phentermine as add-on following a one-year liraglutide treatment [13]. We present below comments on this paper and we try to assess its true position in relation to other similar recent publications in the field as well as the two obesity guidelines released in 2018, from the American Diabetes Association [14] and the Centers for Disease Control and Prevention (CDC) [15] as well as the Endocrine Society guidelines on pharmacological management of obesity [16].

2. What key messages are conveyed by the obesity guidelines?

Recent guidelines [14–16] are in agreement that lifestyle modification remains the cornerstone of obesity treatment, but also that optimizing lifestyle is difficult to achieve and sustain. Behavioral intervention may offer an additional benefit, which however is debatable. The CDC with the U.S. Preventive Services Task Force (USPSTF) [15] conclude that referring adults with obesity to intensive, multicomponent behavioral interventions has a moderate net benefit. Additional options, such as pharmacotherapy or bariatric surgery, should be provided to patients who failed to lose weight with lifestyle modification and who meet certain indications. In general, anti-obesity medications are indicated for individuals with a BMI ≥ 30 kg/m² or ≥ 27 kg/m² and at least one obesity-related comorbidity (e.g., T2DM, hypertension, dyslipidemia) [14,16]. Pharmacotherapy should be considered as an adjunct to a healthy lifestyle, and not as a single alternative of lifestyle modifications, meaning that medication should be viewed as a next-step treatment option for those already on a healthy lifestyle [17]. Several clinical studies have demonstrated that pharmacotherapy combined with lifestyle changes lead to greater and longer-term weight loss as compared to lifestyle modifications alone [18].

Certainly, the decision to initiate drug therapy should be individualized and should be made only after a careful evaluation of the risks and benefits of the treatment options and the relative contraindications for each patient [19]. Specifically, phentermine is the most often prescribed drug for weight loss in the US and was approved by the Food and Drug Administration (FDA) for short-term use (12 weeks), but it is often prescribed off-label for longer-term use [18,20]. There are three other drugs, diethylpropion, phendimetrazine and benzphetamine, also approved by the FDA for short-term use [18]. These are all sympathomimetic drugs that may increase heart rate and blood pressure and, consequently, they are contraindicated in patients with CVD and

hypertension [20]. Orlistat reduces absorption of dietary fat, up to 30%, through inhibiting gastrointestinal lipase [21] and provides weight loss benefits for T2DM patients [22]. Lorcaserin is a selective agonist of the serotonin 2C receptor that regulates mechanisms related to satiety, ingestive behavior, glucose tolerance and hepatic insulin sensitivity [23]. The FDA approved lorcaserin in obese or overweight patients with at least one relevant comorbidity, such as T2DM, hypertension, high cholesterol or sleep apnea [24,25]. Also, this agent has beneficial effects on glucose tolerance, lipid profile, blood pressure and heart rate [23,26].

Phentermine/topiramate is the first drug combination approved for weight loss. Topiramate is an antiepileptic drug that has been shown to reduce body weight by causing taste aversion and decreasing caloric intake [27]. However, the exact mechanisms by which this combination promotes weight loss remain largely unknown [28]. Another combination therapy is naltrexone/bupropion. Naltrexone is an opioid receptor antagonist, which is clinically used to treat alcohol use disorder, and bupropion is a dopamine/norepinephrine reuptake inhibitor, which is clinically approved for depression and smoking cessation. Its anorexigenic effect is likely due to combined dopaminergic and noradrenergic effects on proopiomelanocortin signaling [29].

As for liraglutide, it is a long acting glucagon-like peptide-1 receptor agonist (GLP-1RA) that increases satiety by acting mainly on the central nervous system, but also in the periphery [30,31]. By acting peripherally, it increases the release of insulin from the pancreas in the presence of glucose [32]. Its weight-reducing effect has already been observed among patients with T2DM who were receiving the doses of 1.2 and 1.8 mg/d. Liraglutide, usually prescribed at a higher dose (3.0 mg/d), is effective at inducing and sustaining weight loss in obese patients with hypertension, dyslipidemia and obstructive sleep apnea, with or without T2DM [33–37]. Its limitations are the high cost and the need of daily injections. However, its relatively few contraindications in comparison to other weight loss agents make it an attractive option for obese, especially those with T2DM or CVD.

As our knowledge of the physiology of obesity and energy homeostasis improves, we are getting closer to achieving the goal of improving existing medications by developing agents in the same class that have increased effectiveness and reduced toxicity as well as discovering novel selective agents, some of which act through different pathways than the existing drugs. Other GLP-1RA, such as exenatide and semaglutide, approved for the treatment of T2DM, are being currently evaluated as anti-obesity drugs [38–42]. Dulaglutide, another GLP-1RA, was superior to liraglutide in treatment satisfaction in patients with T2DM [43]. The results of a phase 2 randomized controlled trial (RCT) concerning the effects of dulaglutide on the body weight of obese subjects with T2DM are expected (NCT00630825).

Sodium-glucose co-transporter inhibitors (SGLT-2i), such as dapagliflozin and canagliflozin, prevent reabsorption of glucose at the level of nephrons, thus inducing glycosuria [44], which is the main mechanism by which they decrease body weight [45–47]. Although glycosuria leads to weight loss observed with SGLT-2i treatment, weight reduction is often restricted (<4 kg) after 52 weeks of treatment [48], because of compensatory hyperphagia [49,50]. For this reason, the combination of an SGLT-2i and a GLP-1RA could potentially weaken the hyperphagia caused by SGLT-2 inhibition, because of the effect of GLP-1RA on satiety [51]. In the CANVAS study [52] the combination of canagliflozin with a dipeptidyl peptidase-4 inhibitor or GLP-1RA led to a weight loss between 2.3 and 3.2% after 18 weeks.

There is evidence that IR and hyperinsulinemia, in addition to being caused by obesity, can contribute to the development of obesity [9]. Based on this concept, improving insulin sensitivity and intermediary metabolism may target the root causes of obesity. Thus, targeting ketohexokinase (KHK), which catalyzes the first step of fructose metabolism, with a novel antisense oligonucleotide (ASO) decreases *de novo* lipogenesis and improves insulin-mediated glucose metabolism [53]. Acetyl-CoA carboxylase enzymes (ACC1 and ACC2) convert acetyl-CoA

to malonyl-CoA, which is a committed step in *de novo* lipogenesis. Inhibition of ACC may inhibit lipogenesis and several inhibitors of ACC are in various stages of clinical development for obesity and related diseases, including NAFLD [54]. Steroyl-CoA desaturase (SCD)1 catalyzes the conversion of long-chain saturated fatty acids to monounsaturated fatty acids and promotes obesity and related diseases. Mice lacking SCD1 are largely protected against diet-induced obesity and IR [55–58]. Accumulating data suggest that SCD1 may play a role in limiting lipid accumulation, thus in weight loss [57,59]. Diacylglycerol acyltransferase (DGAT) catalyzes the addition of a FA to diacylglycerol to produce triglycerides. DGAT1, one of the two isoforms of DGAT, increases plasma very low-density lipoprotein cholesterol concentrations and may promote obesity. Therefore, DGAT1 is considered a potential therapeutic target for obesity [60]. Another proposed target is mitochondrial pyruvate carrier (MPC) inhibitors. The MPC transports pyruvate from the cytosol into the mitochondrial matrix, thereby gating pyruvate-driven gluconeogenesis. Inhibition of the hepatocyte MPC attenuates hyperglycemia [61,62]. This mechanism needs to be fully proven and it has been suggested that certain peroxisome proliferator activated receptor γ (PPAR γ) modulators, including thiazolidinediones, may act by inhibiting MPC. Furthermore, the thyroid hormone mediates its effects by engaging the thyroid hormone receptor (TR) α and TR β to increase metabolic rate, enhance FA oxidation and, consequently, reduce adiposity. Therefore, TR β selective agents may be useful for treating obesity [63]. Moreover, farnesoid X receptor agonists (FXR) have recently emerged as an attractive target to combat obesity. They suppress the expression of several enzymes involved in cholesterol and bile acid synthesis, improve insulin sensitivity, and decrease systemic inflammation and body weight [64]. Finally, since PPARs regulate energy homeostasis, enhance glucose and FA metabolism, they may offer a valuable therapeutic option against obesity, mainly by redistributing fat from visceral to subcutaneous adipose tissue, a metabolically beneficial effect [65–67].

Novel agents, such as GLP-1RA and SGLT-2i, besides glucose lowering and weight loss effects, provide also protection against obesity related comorbidities. Improved adipose tissue function and reduced inflammation may be responsible for the favorable cardiovascular (CV) outcomes with these agents [68]. Specifically, liraglutide has anti-thrombotic and antiatherogenic effects, decreases CV mortality and seems to reduce non-fatal myocardial infarction and/or stroke [69]. Moreover, SGLT-2i appears to positively affect heart failure [70–72]. Of note, these agents may benefit also non-diabetic subjects and patients without established CVD. Dulaglutide significantly reduces the risk of major adverse CV events in a study population in which the majority of the participants did not have a prior CVD [73]. Furthermore, although both SGLT-2i and GLP-1RA reduce albuminuria, SGLT-2i may also prevent the onset of end-stage renal disease, reducing the estimated glomerular filtrate rate (eGFR) decline [70–72], but this has recently failed to be documented in a real world trial [74].

3. What is new in metabolism, clinical and experimental?

Tronieri et al. [13] publish herein an RCT, as an extension of a previously completed RCT, on the effects of the combination of liraglutide and phentermine in participants with obesity who had previously received liraglutide alone for one year and their BMI remained >27 kg/m². The participants were re-randomized to liraglutide plus phentermine or liraglutide plus placebo for 12 weeks in an attempt to examine whether adding another treatment, in this case phentermine, would alter the expected plateauing weight loss in response to long-term liraglutide and lead to further weight loss. At week 12, the addition of phentermine reduced body weight by an additional 1.6% vs. 0.1% in liraglutide/placebo group. However, these small reductions of body weight were not significantly different, and, thus, the examined combination did not lead to any additional clinically meaningful weight loss compared with a one-year liraglutide monotherapy, although the

addition of phentermine to liraglutide, which appeared to be well tolerated, led to short-term improvements in appetite. More specifically, participants on liraglutide/phentermine reported larger reductions in hunger than the ones on liraglutide/placebo during the first 4 to 8 weeks of the extension trial.

One would have expected a more robust weight loss and a more significant reversal of the plateauing weight loss effect of liraglutide, if the two medications were working in different brain centers controlling energy balance in the brain. Although the brain areas where liraglutide acts to alter appetite in humans have recently been identified [19,75,76], no studies have been performed in humans to identify brain centers activated or deactivated by phentermine. Tronieri et al. [13] highlighted the concept of the combination and/or sequential treatment of obesity, similar to what has been proposed for other closely related multifactorial diseases, including NAFLD [77] and their non-significant results imply that the two medications used may act in the same or similar brain centers. This has to be fully proven by specific neurocognitive and neuroimaging studies in the future.

Despite their originality, these results should be interpreted cautiously, since they carry some of the limitations of RCTs extensions, including the potentiality for selection bias. However, the marginally non-significant differences shown between groups warrant further studies with *a priori* sufficiently powered study sizes in the context of a much needed organized effort to discover underlying mechanisms and ideally, over the long-term, a mechanism-based solution for the plateauing phenomenon in weight loss, which is routinely observed in response to any and all known anti-obesity medications [19]. Moreover, the combination of liraglutide and phentermine from the very beginning of treatment vs. monotherapy with liraglutide or phentermine combined with the other medication later on and possibly at the point of initiation of the plateauing phenomenon deserves further research. Moreover, the addition of phentermine for a given period of time and/or alternating periods of phentermine with no treatment for periods of one week or possibly longer to avoid habituation of brain centers to its effects needs further investigation.

Combination therapies, one of them examined by Tronieri et al. herein [13], seem to offer an attractive synergistic approach for the management of obesity, since different mechanisms are targeted by different medications and, therefore, they could potentially enhance the efficacy of monotherapies. In this context, the combined pharmacotherapy of pramlintide and phentermine was proven to be superior to pramlintide alone [78]. Another example is the combination of amylin and bupropion/naltrexone, which was effective in rodent models [79]. Amylin analogues inhibit postprandial glucose secretion, slow gastric emptying, increase satiety, and thus decrease caloric intake [80]. A combination of a long acting amylin analogue, AM833, with semaglutide is on a phase 1 RCT (NCT03600480). Moreover, exenatide once weekly plus daily dapagliflozin turned out to be an efficient treatment [81]. Moreover, a glucagon and GLP-1 co-agonist (GG-co-agonist 1177) intended to reduce appetite and provoke energy expenditure (NCT0330874). The gut hormone peptide YY₃₋₃₆ (PYY₃₋₃₆) exerts appetite suppressive action and reduces caloric intake in rodents [82], monkeys [83] and humans [84]. Despite its potential for the treatment of obesity, PYY₃₋₃₆-based therapies have not yet made it to clinic due to the adverse effects observed in humans, such as nausea, vomiting and abdominal discomfort [85]. However, since adverse effects of PYY seem to be dose-dependent and linked to activation of Y2 receptors, reduced PYY doses in combination with other medications involved in energy balance regulation, such as GLP-1RA, might be of interest, as it has been shown in a human study [86]. Another agent, the Y5 receptor antagonist velneperit, prevents the binding of neuropeptide Y (NPY) to the Y5 receptors, thus reducing hunger and modulating energy balance. Nevertheless, velneperit induced a mean placebo-adjusted weight loss of just 5.0% over 54 weeks of therapy [87]. Possibly, the combined Y1/Y5 receptor antagonism may be proved more effective, although we are not aware of any Y1/Y5 receptor antagonist in development

date. In addition, a triple agonist, combining glucagon, gastric inhibitory polypeptide (GIP) and GLP-1RA actions resulted in remarkable weight loss when administered in mice and is on a phase 1 RCT (NCT03374241) [88].

The Endocrine Society guidelines [16] refer also to the role of medications provoking weight gain, including some prescribed for T2DM, hypertension, and depression. Approaching obese patients, clinicians should pay attention to these drugs and consider weight-beneficial alternative medications for these diseases, if any [16].

Future guidelines should also incorporate the recommendation of bariatric surgery as a treatment approach for patients with severe obesity [89], as the ADA guidelines do [14] (for patients with T2DM, bariatric surgery should be recommended for those with BMI ≥ 40 kg/m² or ≥ 35.0 kg/m² in the presence of poor glycemic control). A focus on obesity devices approved by FDA is also needed. Currently, there are four types (electrical stimulation systems, gastric balloon systems, gastric bands and gastric aspiration devices), but, given some concerns in the scientific community, these have not yet been widely adopted [90].

As the obesity epidemic continues to grow, and in addition to non-pharmacological approaches to the management of obesity, the need of novel, better tolerated and more efficacious pharmacological interventions becomes crucial. Currently, there are several anti-obesity drugs in clinical trials (see above), but long-term data on their efficacy and safety are needed. More importantly, obesity, as other related diseases (e.g., T2DM, dyslipidemia and hypertension) should be considered chronic diseases requiring long-term treatment. In this regard, future trials should focus on the long-term efficacy and safety of anti-obesity medications, alone, in combination or in sequential administration. Similarly, real world data from large registries [73] elucidating the long-term safety and efficacy of anti-obesity medications in various populations are also very important.

Another, really fundamental, question that needs to be answered is why we are not making major strides, although we are making small steps towards the discovery and development of novel anti-obesity medications. Is it because biological mechanisms play a relatively small role in comparison to environmental and other factors contributing to the obesity epidemic, as some have proposed? Or is it because scientists in the field cannot fully elucidate the underlying biological mechanisms using the scientific tools available to them over the past few decades since the discovery of leptin that revived interest in the obesity and metabolism field by highlighting that obesity is also due to specific underlying mechanisms? Is availability of suboptimal tools and/or the possibly inherent differences in brain function and metabolism between preclinical models (mainly rodents to date) and the species of interest, i.e. humans, the reason the field cannot leverage novel scientific basic research discoveries and translate them into novel compounds as has been shown time and again by so many compounds in development failing in human clinical trials and so many companies abandoning their obesity pharmacotherapy programs and/or not realizing any significant gains for their investments? In this regard, the next obvious question that really needs to be addressed is whether rodent studies, the currently used model for preclinical development, are the most appropriate model to be used to discover compounds to be tested in humans? Discoveries of compounds based on these models have repeatedly failed to result in successful translation of molecules that work in mice into novel medications that work in humans, often with significant resources, i.e. capital investments and jobs, wasted in the process. This would not be unexpected though, if one considers the important differences between rodent and human brains where environmental, exogenous and hormonal, endogenous inputs are integrated to regulate food intake and energy expenditure. Focus on rodent hypothalamic and important neuropeptides acting in the hypothalamus (see NPY, PYY etc. above) for example may be a good starting point to understand what regulates food intake in rodents, but humans do not overeat and/or decrease their exercise mainly due to homeostatic mechanism(s) controlled by the hypothalamus. In contrast, the reward

system and other brain centers responsible for emotions, as well as the cortical areas responsible for executive function, are apparently so different between rodents and humans. This fact needs not be ignored, since these brain areas play much more important roles in regulating behavior and energy homeostasis in humans. Thus, we believe that to move forward faster and more efficiently we, as a scientific community, need to develop better scientific tools and preclinical models that reflect better human biology. In our opinion, we need to start restricting the use of rodent studies to only hypotheses generation, which is its true position in science anyway. In addition, focusing on animals models closer to humans such as primates needs to be tried and carefully assessed in terms of tangible benefits to be provided. Further, developing better tools to study neurocognitive aspects of the energy homeostasis regulation in humans, developing better neuroimaging techniques to be used more often in human studies, and carefully monitoring and assessing all parameters playing a role in alterations of energy homeostasis in humans is of paramount importance. Human physiology studies and small interventional studies in humans as well as multiomic studies using human samples to define the changes in multiome in response to food deprivation or excess at baseline and in response to targeted perturbations of the system are needed to define the pathways regulating energy homeostasis in humans. The availability of big data (really large number of variables per subject in relation to the number of subjects in the study) to be collected and/or currently available in biobanks and population databases, which can now be analyzed through the use of novel artificial intelligence and generalized adversarial network analytical tools offer additional opportunities to be leveraged [91]. Integrating the analysis of as many data as reasonably possible is apparently absolutely essential, in our minds, for novel pathways important in humans to emerge and subsequently for the field to move significantly forward. Scientists need to adopt novel approaches abandoning what appears to be a perfect example of the “streetlight effect” and funding agencies and pharmaceutical companies need to start funding projects along the lines proposed above for novel frontiers to be explored. At this point in time, this seems to be by far the best way forward that provides the possibility for us to accelerate the pace of discovery and eventually provide tangible benefits to our fellow human beings suffering from obesity and its many and significant metabolic complications.

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