# A narrative review of anti-obesity medications for obese patients with osteoarthritis

Win Min Oo[1, 2], Ali Mobasheri[3, 4, 5, 6], David J Hunter[1, 7]

[1]Rheumatology Department, Royal North Shore Hospital, and Institute of Bone and Joint Research, Kolling Institute, Faculty of Medicine and Health, The University of Sydney, Sydney, Australia.

[2]Department of Physical Medicine and Rehabilitation, Mandalay General Hospital, University of Medicine, Mandalay, Myanmar.

[3]Research Unit of Medical Imaging, Physics and Technology, Faculty of Medicine, University of Oulu, Oulu, Finland.

[4]Department of Regenerative Medicine, State Research Institute Centre for Innovative Medicine, Vilnius, Lithuania.

[5]Department of Joint Surgery, First Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China.

[6]World Health Organization Collaborating Centre for Public Health Aspects of Musculoskeletal Health and Aging, Liege, Belgium.

[7]Clinical Research Centre, Zhujiang Hospital, Southern Medical University, Guangzhou, Guangdong, China.

**Abstract:**

**Introduction**: The prevalence of both obesity and osteoarthritis (OA) are increasing worldwide (twindemic), and the association between the two chronic diseases is also well-established.

**Areas covered**: In this narrative review, we will briefly describe the double burdens of both diseases, the impact of weight loss or gain on OA incidence and structural progression and discuss the biomechanical and anti-inflammatory mechanisms mediating these effects. FDA-approved anti-obesity drugs are summarized in terms of their clinical efficacy and safety profile, and the completed or ongoing phase 2/3 clinical trials of such drugs in OA patients with obesity are examined.

**Expert opinion**: We will discuss the perspectives related to principles of prescription of anti-obesity drugs, the potential role of phenotype-guided approach, time to drug effects in clinical trials, sustainability of weight loss based on the real-world studies, the importance of concomitant therapies such as dieting and exercises, and the role of weight loss on non-weight bearing OA joints. Although obesity is the major risk factor for OA pathogenesis and progression, and there are a variety of anti-obesity medications on the market, research on the use of these disease-modifying drugs in OA (DMOAD) is still sparse..

**Key words:** osteoarthritis; obesity; anti-obesity drugs; disease-modifying; DMOAD; diet; exercise

## 1. Introduction

### 1.1. The double burden of OA and obesity

Osteoarthritis (OA) represents a major challenge for twenty-first century health care systems due to its high prevalence. In 2020 the global prevalence of OA in persons over 40 years of age was estimated at 22.9% (correspondingly 654.1 million individuals globally)[1]. In the Global Burden of Disease study 2017, age-standardized OA point prevalence showed an increase of 9.3% from 1990 to 2017[2]. It represents the 18$^{th}$ highest cause of years lived with disability (YLDs) worldwide for age groups 50-74 years[3], with a relative increase in YLDs of 36% from 1990 to 2019[4], reflecting the substantial disease burden in terms of functional limitations and quality of life. In addition, direct and indirect costs of OA range from 1 to 2.5% of the gross national product across most developed countries[5]. In the studies using the data from the Johnston County Osteoarthritis Project in the USA (United States of America), the lifetime risk of symptomatic knee, hip and hand OA was 44.7% in 2003[6], 25.3% in 2003[7] and 39.8% in 2010[8] respectively, causing substantial implications for patients, health-care systems, and socioeconomic costs[9]. In 2016 OA was formally proposed as a serious disease to the US Food and Drug Administration (FDA) in a White Paper published by the Osteoarthritis Research Society International (OARSI)[10]. So far, no disease-modifying OA drug (DMOAD) exists[11].

Overweight and obesity are caused by abnormal or excessive accumulation of adipose tissue in the body[12]. In addition to being a primary driver of the global rise in non-communicable diseases, obesity itself has been recognized as a complex, chronic non-communicable disease since 2013 by American Medical Association[13]. For adults, the World Health Organization (WHO) defines overweight as body mass index (BMI) $\geq$ 25 kg/m$^2$ and obesity as BMI $\geq$30 kg/m$^2$[14] for people of European ancestry. Lower cut-off points of 23

kg/m$^2$ and 27.5 kg/m$^2$ may be used in Asian populations as trigger points for public health action[15] as obesity-related comorbidities can develop at lower BMIs in Asians[16]. Globally, obesity has nearly tripled between 1975 and 2016. In 2016, more than 1.9 billion adults (39%) were affected by overweight, and over 650 million (13%) have obesityworldwide[14]. In the US, obesity affected 42.4% of adults in 2017[17] and by 2030 it is projected that almost 1 in 2 adults will have developed obesity (48.9%; 95% confidence interval [CI], 47.7 to 50.1)[18]. In the Global Burden of Disease study 2019, obesity was the seventh leading risk factor and represented a 32.5% increase in age-standardized disability-adjusted life years (DALY) from 2010 to 2019[19].

Although obesity is often labelled as "modifiable" among its risk factors, this terminology may be too simplistic, given that obesity is now considered as a chronic, relapsing, multifactorial disease, which makes sustained long-term weight loss extremely challenging for a large proportion of the population[20]. In a meta-analysis including 29 studies adopting lifestyle modifications (diet and exercise) for at least five years, more than half of the lost weight was regained within 2 years while more than 80% of lost weight was regained by 5 years[21]. Even in the best of cases, diet, exercise, and behavioural counselling only lead to 5% to 10% average weight loss, and few morbidly obese patients are able to maintain an "ideal" body weight[20]. Therefore, comprehensive obesity management, including medical therapies, may be useful as ongoing support to achieve sufficient weight loss or maintain the lost weight[22]. Anti-obesity drugs contribute to as much as 15% weight loss in responders[23,24], and the weight loss is maintained in clinical trials for several years[25].

In this narrative review, we will outline the impact of obesity on the OA disease process and possible pathogenic mechanisms, summarize the clinical efficacy and safety profile of FDA approved anti-obesity drugs, review the completed or ongoing phase 2/3 clinical trials of such drugs evaluated in obese patients with OA and discuss the perspectives related with principles

of drug prescription, time to drug effects and sustainability, role of concomitant therapies, effect of weight loss on non-weight bearing OA joints. In line with the primary objective of this narrative review, one author (WMO) conducted a systematic search of the PubMed database since the database inception to January 31, 2022 for clinical trial reports (excluding the reviews) related to "approved anti-obesity drugs and/or Osteoarthritis" with the following terms in the title: "orlistat," "phentermine/topiramate," "naltrexone/bupropion," "liraglutide," or "Semaglutide," or "Setmelanotide" (orlistat: n=256; phentermine/topiramate; n=9; naltrexone/bupropion: n=11; liraglutide:n=151; Semaglutide: n=24 and Setmelanotide: n=7). For extracting the completed/ongoing phase 2/3 clinical trials conducted in obese patients with OA, www.clinicaltrials.gov was used.

### 1.2. Mechanism of association of obesity with OA

Weight loss may alleviate the symptoms of knee OA due to a reduction in joint compressive forces[26], as each kg of weight loss will contribute to a 4-fold reduction in the load exerted on the knee per step[27]. Weight loss in 157 patients with knee OA over 16 weeks caused significantly lower (7%) knee compressive forces, a 13% lower axial impulse, and internal knee abduction moments (12%)[28]. If an individual with a baseline bodyweight of 90.1 kg lost 12.7 kg, no further progression of the maximum extrusion was observed[29]. Individuals with a BMI between 35 and 41.3 kg/m2 produced excessive peak compressive loads of over 1.2 × 106 N, and excessive peak shear stress of over 206,000 N per mile walking compared to those with a BMI between 27 and 29.9 kg/m2 [30].

Although the mechanism of association between OA and obesity was initially considered purely biomechanical, the evolving and expanding research landscape appears to show a more complex and multifactorial relationship[31]. The inadequate muscle mass and

strength unmatching the loads placed upon the joints in obese individuals in terms of weight bearing index (leg strength (kg)/body weight (kg)[32] lower the capacity of weight bearing joints to absorb the impact forces, altering the loading conditions and thus exacerbating the joint malalignment[33]. Participants who achieved >10% weight-loss had significantly lower resultant knee forces and lower quadriceps, hamstring, and gastrocnemius muscles forces compared with those with less weight-loss. Greater than 10% weight loss at 18-months follow-up had significantly reduced quadriceps, hamstring, and gastrocnemius muscle forces compared to those that lost less weight (n=454)[34].

The increased loading forces are sensed by mechanosensitive ion channels of the articular chondrocytes [35], triggering the initiation of intracellular signalling cascades of cytokines, growth factors, and metalloproteinases[36]. Microscopic horizontal fissuring at the osteochondral interface was the major pathological manifestation of obesity-related OA with an increase in the odds of horizontal fissures by 14.7% per an increase in one unit of BMI[37].

Adipose tissue is a highly metabolic endocrine organ[38] capable of secreting active adipocytokines, such as leptin, resistin, and adiponectin[39]. Obesity causes an inflammatory synovial phenotype in the OA joint not only by increased synovial fluid IL-6 production through chondrocyte-synovial fibroblast cross-talk (mediated by pro-inflammatory leptin)[40] but also by imprinting an inflammatory transcriptome on the synovial tissue/synovial fibroblasts, with increased expression of proinflammatory messenger RNAs (mRNAs)[41]. Resistin are elevated in obese patients with hip OA and can drive abnormal type I collagen phenotype in the subchondral bone[42] Macrophage-induced inflammation of white adipose tissue was associated with local joint degradation by inducing pro-inflammatory cytokines and degradative enzymes[43]. Obesity leads to macrophages' phenotypic switch toward the pro-inflammatory subtype and TNF-α-induced insulin resistance and lipolysis of adipocytes[44]. Macrophage-mediated synovitis seems to be crucial in the initiation and progression of obesity-

induced OA[45] as weight gain was associated with increased prevalence of synovial inflammation even before the cartilage degradation compared with stable weight in human[46] and animal[47] studies.

### 1.3. Impact of obesity on OA (risk factor for incident disease, progression, and disease management)

OA is becoming a highly prevalent articular disease with growing epidemics of obesity[48,49] (twindemic), causing massive co-morbidity and health care issues worldwide. The significant association between obesity and knee OA compared with other types of rheumatism was first documented in 1945[50]. Two in three individuals with obesity may develop symptomatic knee OA in their lifetime[6].

In addition, obesity is the dominant risk factor for OA. In a large population-based cohort (n=1,764,061) with a median follow-up of 4.45 years, individuals with overweight (25 to <30 $kg/m^2$), obesity grade 1 (30 to <35 $kg/m^2$) and obesity grade 2 (≥35 $kg/m^2$) demonstrated an increased risk for knee OA by a factor of 2, 3.1 and 4.7 fold respectively, compared with normal control (BMI <25 $kg/m^2$)[51]. In a meta-analysis (n= 872 717), every 5-unit increase in BMI can lead to a 35% increased risk of knee OA (RR: 1.35; 95%CI: 1.21, 1.51) with a stronger risk in women [52]. An estimated 24.6% of new cases of knee pain could be attributed to having overweight and obesity [53]. On the other hand, weight loss of 5.1 kg over the 10 years decreased the odds for developing knee OA by 54%[54].

In adults with mean BMI of 33.6 to 36.4 kg/m2 and mild to moderate knee OA, a 5% to 10% weight loss significantly improved pain [effect size (ES) 0.33, 95% CI 0.17 to 0.48], self-reported disability (ES 0.42, 95% CI 0.25 to 0.59) and quality of life (physical) (ES 0.39, 95%CI 0.24 to 0.54)[55]. A dose-response gradient of weight loss/gain for pain and function seems to

be more obvious for body weight shifts of ≥10% over a 3-year period[56]. There also seems to have a dose-response effect of weight loss of up to 20% of baseline body weight on clinical and mechanistic outcomes[57].

In addition to symptomatic benefits, there are beneficial effects of weight loss on knee joint structures in obese patients. A recent post-hoc analysis of the Intensive Diet and Exercise for Arthritis (IDEA) trial[58] showed less progression of medial meniscus extrusion measured by quantitative MRI after losing weight over 18 months[29], perhaps due to a reduction in knee compressive forces on the pain-sensitive structures (i.e., the meniscus and the joint capsule)[59]. Similarly, a decrease in low-grade inflammation and biomarkers of cartilage catabolism[60], reduced loss of cartilage thickness over time[61-63], less progression of cartilage degeneration as measured with global T2 relaxation time over 8 years[64] were reported. The lowest weight loss cut-off associated with reduced loss of medial femoral cartilage thickness was 7%[61]. In addition, the international consensus on the specific structural pathologies and optimal imaging outcomes a should be prioritized for capturing the structural effects of weight loss on hip or knee OA with high sensitivity[65].

## 2. FDA-approved anti-obesity medications

### 2.1. FDA guidelines for drug approval

After the 2004 FDA Advisory Committee Meeting to discuss updating the first 1996 draft guidance for obesity drug[66], the 2007 Draft Obesity Drug Guidance was published to facilitate the development of anti-obesity drugs for medical weight loss[67], defined as a long-term reduction in fat mass with a goal of reduced morbidity and mortality. According to the guidance, the phase 3 clinical trials should target individuals with a BMI ≥27 kg/$m^2$ with at least 1 obesity-related comorbidity, or a BMI ≥30 kg/m2. To capture adequate efficacy and

safety data, the trial duration was defined as at least 1 year, and the active group should include ≈3000 subjects while the placebo group include at least 1500 subjects. A lifestyle modification program was recommended as the standard of care for all participants. The drug requires to meeting one of these efficacy endpoints (1) mean placebo-subtracted weight loss ≥5% and (2) the proportion in the active group who lose ≥5% of baseline body weight is ≥35% and approximately double the proportion in the placebo group who lose ≥5%. In addition, improvements in blood pressure, lipids, glycemia, and other weight-related comorbidities will be considered in the benefit-risk assessment[68].

Obesity pharmacotherapy has evolved significantly since the approval of the first drug, desoxyephedrine, in 1947 (later withdrawn from the market after Kefauver-Harris amendments in 1962)[69]. Currently, six anti-obesity medications have been approved by US FDA for long-term use: orlistat in 1999[70], phentermine-topiramate in 2012, bupropion-naltrexone in 2014[71], and liraglutide 3.0 mg in 2014[72], Setmelanotide in 2020 (only for rare genetic diseases of obesity)[73] and Semaglutide 2.4 mg in 2021[74]. The mechanisms of action for these drugs[75] are illustrated in **Figure 1**.

Two medications have been recalled: sibutramine in 2010 due to concerns over the elevated risk of nonfatal myocardial infarction [(hazard ratio (HR)= 1.28; 95% CI, 1.04 to 1.57)] and nonfatal stroke (HR=1.36; 95% CI, 1.04 to 1.77) in pre-existing cardiovascular conditions [76], lorcaserin in 2020 for increased cancer risk over a latency period of 2.5 years[77].

These medications are indicated for patients who have failed to achieve ≥ 5% of baseline weight after 6 months of lifestyle interventions which comprise nutritional, physical activity, and behavioural changes. Professional guidelines recommend the following FDA-approved anti-obesity medications for individuals with BMI ≥ 30 kg/m2 or BMI ≥ 27 kg/m2 with

comorbidities[78,79]. The efficacy of currently approved anti-obesity drugs in placebo-subtracted weight loss in kilograms is illustrated in **Figure 2**.

The following section will provide a brief description of mechanisms, efficacy, and safety profile of each of the pharmacologic agents currently approved. Their dosage, common adverse reactions and contraindications are described in **Table 1**.

### 2.1.1. Orlistat

Orlistat (Xenical, Alli) reduces fat absorption from the gastrointestinal tract up to 32% via inhibiting intestinal lipase[80]. The inhibition of fat digestion was much greater with the solid foods than with the liquids (57.4% vs 18.8%)[81]. Either 60 mg (over the counter use) or 120 mg capsules (need a prescription) are orally administered three times a day (TID)[82]. 31% and 38% of patients taking either the orlistat 60 mg or 120 mg achieved more than 10% loss of baseline body weight after 1 year[83]. In a meta-analysis (n=10 631 participants), orlistat reduced weight by 2.9 kg (95%CI 2.5, to 3.2) and 21% and 12% of participants achieved 5% and 10% weight loss thresholds, respectively[84].

Recent meta-analyses displayed beneficial effects on plasma lipids[85], reduction of blood pressure[86] and no signal for hepatic damage[87]. However, the high non-responder rate and frequent lingering gastrointestinal (GI) side effects such as flatulence and steatorrhea have limited its widespread use[88]. Fat-soluble vitamin deficiencies may occur and can be mitigated with the prescription of vitamin supplements[89].

### 2.1.2. Phentermine/topiramate

The exact mechanism of action of phentermine/topiramate ER combination therapy is unknown. Phentermine is a noradrenergic sympathomimetic amine[90]. Although its exact

mechanism of weight loss is not fully elucidated, it is postulated to act on β-adrenergic receptors in the perifornical hypothalamus[91] , leading to decreased food intake and body weight [92]. Proposed mechanisms of weight loss associated with topiramate are blockage of voltage-dependent sodium channels, augmentation of γ-aminobutyric acid activity (GABA-A), and inhibition of carbonic anhydrase isoenzymes II and IV [93,94]. Qsymia is a single-tablet fixed-dose combination capsule containing immediate-release phentermine and controlled-release topiramate and available in four doses: (1) starting dose (3.75 mg/23 mg), (2) recommended dose (7.5 mg/46 mg), (3) transition dose (11.25 mg/69 mg), and (4) top dose (15 mg/92 mg)[95,96]. In the latest phase 3 randomized controlled trial (RCT) (n=676), the top dose resulted in a 10.5% weight loss at 2 years, which was 8.7% higher than with placebo (1.8%). Almost 54% of patients achieved 10% weight loss, and over 15% achieved 20% weight loss[97]. It also decreases LDL by 4.2 mg/dL, systolic blood pressure by 3.7 mm Hg and diastolic blood pressure by 1.4 mm Hg, while the increase in HDL cholesterol was 2.2 mg/dL[98].

Before FDA approval of Semaglutide, several meta-analyses reported that phentermine/topiramate provided the greatest magnitude of weight loss among the anti-obesity medications [99,100]. The weight loss effect and safety profile are dose-dependent, and the commonest adverse effects are dysgeusia (odds ratio [OR] = 8.86, 95% CI: 5.65-13.89), paraesthesia (OR = 8.51, 95% CI: 6.20-11.67), dry mouth (OR = 6.71, 95% CI: 5.03-8.94)[101]. It carries a warning for increased heart rate (>5 to >20 beats/min [102] ),particularly in patients with known cardiac or cerebrovascular diseases [96,103]. In the recent retrospective study (n=13 972) using outpatient information from an electronic health record, longer term phentermine use revealed no increase in risk for incident cardiovascular events or death over 3 years of follow-up in a population without diagnosis and/or procedure codes for any cardiovascular disease[104]. The European Medicines Agency (EMA) refused its marketing

authorisation due to safety concerns such as effects on the cardiovascular system, psychiatric and cognitive effects, teratogenic risk (cleft lip/palate), and off-label use[105]. Patients who do not achieve at least 5% of weight loss after 12 weeks on the full dose should discontinue it after tapering over 1 week[96,103].

### 2.1.3. Naltrexone/bupropion

Bupropion is a reuptake inhibitor of dopamine and norepinephrine that activates anorexigenic pro-opiomelanocortin (POMC) neurons in the hypothalamus, resulting in decreased food intake and increased energy expenditure, while naltrexone is an opioid antagonist that diminishes the auto-inhibitory feedback loop on these POMC neurons via mu-opioid receptor antagonism, facilitating the effect of bupropion on POMC signalling for sustained weight loss[106,107]. Contrave is an oral, sustained-release combination of bupropion and naltrexone, causing dual mechanisms of complementary stimulation of POMC signalling[108]. It is a fixed-dose combination tablet containing naltrexone 8 mg/bupropion 90 mg; the starting dose is 1 tablet daily, increasing by 1 tablet each week until a maximum daily dose of naltrexone 32 mg/bupropion 360 mg (2 tablets twice a day) is achieved at week 4[109].

In a meta-analysis of 4 phase-3 RCTs, placebo-subtracted weight loss was 5.0 kg, with 55% and 30% of participants achieving a ≥5% or ≥10% weight loss, respectively[99]. It increases HDL cholesterol by 2.5 mg/dL[98] and increases blood pressure (BP) and heart rate, especially in the titration stage [109]. There were no significant associations with major cardiovascular adverse events (MACE, defined as cardiovascular death, nonfatal stroke, or nonfatal myocardial infarction) in recent meta-analyses of published trials[100,110]. However, a recent meta-analysis of unpublished clinical study reports suggested an urgent need for a

rigorous process of post marketing surveillance due to the increased risk of serious adverse events and recommended not to prescribe it as a first-line anti-obesity agent[111].

### 2.1.4. Liraglutide

Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor (GLP-1 R) agonist which can delay gastric emptying, and reduce appetite[112] through direct action on GLP-1 receptors in the hypothalamic paraventricular and arcuate nucleus[113]. Unlike GLP-1, with a short half-life of 1.5 min after intravenous dosing and 1.5 h after subcutaneous dosing[114], liraglutide possesses high receptor potency as well as pharmacokinetics that are optimum for once daily dosing[115]. Saxenda contains liraglutide, which is administered once daily by the subcutaneous route, and starts with 0.6 mg per day for one week and is then titrated in 0.6 mg weekly increments up to a maximum of 3.0 mg per day[116].

In a meta-analysis including all phase-3 studies of liraglutide, a mean 5.3 kg placebo-subtracted weight loss was 5.3 kg at 1 year, with 63% and 34% of participants achieving a ≥5% or ≥10% weight loss[99]. It reduced fasting blood glucose by 15.7 mg/dL, haemoglobin A1c by 0.5%, and systolic blood pressure by 2.8 mmHg[98]. Post-hoc analyses of phase-3 SCALE (Satiety and Clinical Adiposity-Liraglutide Evidence in individuals with and without diabetes) studies demonstrated cardiovascular risk reduction (HR=0.42 (95% CI 0.17, 1.08)[117] and no between-treatment imbalances for neuropsychiatric safety[118]. A recent meta-analysis demonstrated a lack of association of GLP-1 receptor agonists (n= 48 267) with breast neoplasms compared with placebo (n= 40 755)[119].

### 2.1.5. Semaglutide

Semaglutide is a long-acting glucagon-like peptide-1 analogue with pharmacokinetics that were optimized for once weekly subcutaneous dosing by modifying the molecular structure[120]. Compared with liraglutide, Semaglutide has an alanine to alpha-aminoisobutyric acid amino acid substitution instead of alanine at position 8 and a C-18 fatty diacid side chain with a Glu-2xOEG linker instead of a C-16 fatty acid chain with a gamma glutamate linker at position 26[121] leading to clinically relevant superiority of Semaglutide in efficacy endpoints such as weight loss (5.8 kg vs 1.9 kg) and proportions of subjects achieving weight loss of = 5% and = 10% at week 30 (56% vs 18% and 19% vs 4%, respectively) [122].

In a recent head to head phase-3 open label study, body weight was reduced by 5.8 kg with once-weekly Semaglutide 1.0 mg and by 1.9 kg with once-daily liraglutide 1.2 mg (-3.83 kg; 95% CI -4.57 to -3.09) at week 30[122]. Furthermore, 56% vs 18% and 19% vs 4% of subjects achieved weight loss of 5% or 10% at week 30 with Semaglutide vs liraglutide, respectively. Their safety profile is similar except for more frequent gastrointestinal disorders with Semaglutide (43.9% vs 38.3%). In addition to sustained, clinically relevant weight loss, significant improvements were demonstrated over placebo in HbA1c, systolic blood pressure, triglycerides, C-reactive protein in four phase-3 RCTs[123-126]. In a recent meta-analysis examining the effects of 21 antidiabetic medications on body weight and blood pressure in patients with type 2 DM (276 336 patients), Semaglutide was the most efficacious in weight reduction as well as improving systolic blood pressure and may be the preferred treatment option in overweight/obese and/or hypertensive patients with type 2 DM[127]. In patients with type 2 DM and high cardiovascular risk (n= 3297), Semaglutide showed 26% reduction in MACE risk over 2.1 years (HR=0.74; 95% CI=0.58, 0.95)[128].

### 2.1.6. Setmelanotide

Setmelanotide is an agonist of melanocortin 4 receptor (MC4R), a component of the leptin-melanocortin pathway, which regulates energy balance and body weight[129]. Mutations in the MC4R gene result in hyperphagia and severe childhood-onset obesity (0.5% to 5.8% of childhood-onset obesity)[130]. It is approved for treating childhood obesity arising from pro-opiomelanocortin (POMC) [80% (n=10) achieved ≥ 10% weight loss at 1 year[131]], proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency [45% (n=11) achieved ≥ 10% weight loss at one year[131]] in a personalized medicine approach. In a phase-3 trial, 34.5% (n=31) achieved a ≥ 10% weight loss in patients with Bardet–Biedl or Alström syndrome[132]. It is administered once daily by the subcutaneous route, using a titration schedule up to a maximum of 3 mg daily[133].

## 2.2. Phase 2 and 3 clinical trials in OA patients with obesity

Weight reduction in overweight/obese patients with knee OA is a critical core component of a plethora of international guidelines[134,135], based on evidence from diet and exercise studies, not from pharmacologic or bariatric surgery studies. Ideally, the optimal target for weight loss should be to lose 10% of baseline weight[57,136], consistent with the NIH recommendation[137], although the benefits in clinical and mechanistic outcomes start with a loss of ≥5% of body weight in OA patients[135,138]. However, only 14% of OA patients were provided with weight-loss counselling during clinical consultations (n=199)[139], perhaps due to the obesity bias and stigma associated with the topic[140]. This can lead to missed opportunities for introducing anti-obesity medications to the patients who may need them most[141].

The active and completed clinical trials were searched on the PubMed database and www.clinicaltrials.gov using the disease conditions and the approved pharmaceutical agent of interest as described in the review objective. We identified one published clinical trial for liraglutide on PubMed but none for other anti-obesity drugs. One completed phase 4 RCT for liraglutide (NCT02905864), and an ongoing phase 3 RCT for Semaglutide (NCT05064735) were identified on www.clinicaltrials.gov.

### 2.2.1. Liraglutide in OA patients

OA is a chronic articular disease involving multiple tissues in the pathogenic process, such as cartilage damage, inflammation of synovium, etc. In an OA model of knee joints in vivo, activation of GLP-1R on chondrocytes with liraglutide is anti-inflammatory via regulation of NF-κB signalling and anti-apoptotic via the PI3K/Akt signalling, leading to reduced rat cartilage damage[142]. These mechanisms were confirmed in another study with a monoiodoacetate-induced knee OA rat model[143], suggesting this as a potential therapeutic option for OA.

In a phase 3 RCT, patients with knee OA and a BMI ≥27 kg/m$^2$ were provided with diet intervention as a pre–random assignment (week –8 to 0), those with >5% of weight loss at week 0 were administered with liraglutide 3 mg once daily (n=80) or placebo (n=76) for 52 weeks[144]. The placebo-subtracted weight loss was 3.9 kg (95% CI −6.9, −1.0) and those who lost ≥5% and ≥10% body weight was twice as high in the liraglutide group (35% vs 17% and 21% vs 10% respectively). However, no significant effects on the Knee injury and Osteoarthritis Outcome Score (KOOS) pain subscale were revealed (0.9 points; 95% CI −3.9, 5.7). Other secondary pain and function outcomes showed no between-group difference. More frequent gastrointestinal adverse events and higher withdrawal rates were reported in the liraglutide

group compared with the placebo group (50% vs 39% and 13% vs 5%, respectively). As a note, the pre–random assignment dietary intervention caused a weight loss of ∼12.5 kg prior to random assignment, which might lead to amelioration of knee pain at random assignment and limit the potential for further symptomatic benefits during the study.

### 2.2.2. Semaglutide in OA patients

As discussed in an earlier section, Semaglutide has a longer duration of action and results in larger weight loss, compared with liraglutide. Currently, a phase 3 RCT is ongoing in knee OA patients with obesity using 2.4 mg Semaglutide subcutaneously once weekly and is expected to be complete in June 2023 (NCT05064735).

## 3. Expert opinion

As obesity is the major modifiable risk factor for OA pathogenesis and disease progression, successful weight loss leads to symptomatic and structural improvements in the long term[29,56,57,63], the implementation of weight loss in clinical practice are core aspects of OA guidelines[134,135]. A multifaceted approach is required to achieve successful obesity management. This should be started with empathy, realizing that obesity is a pathological disease, not a stigma or series of bad choices[141].

The clinical approach to obesity management is similar in principle to that of hypertension, which is based on adding appropriate medications where necessary to a foundation of lifestyle modifications such as reduced-salt intake, caloric restriction, physical exercises, etc[145]. If the 25–30% of the daily caloric intake is reduced by the energy deficit of 500–1000 kcal per day, there should be a weight loss of 0.5 and 1 kg/week (the so-called 3,500

kcals rule), leading to ≥ 5% weight loss in an average period of 6 months[146]. However, most individuals with obesity achieve only modest weight loss [1.80 kg, 95% CI (-2.40 to -1.19)] with non-pharmacological interventions alone due to a low rate of long-term adherence to lifestyle modifications (see section 3.6) [147]. For those who cannot achieve adequate weight loss from lifestyle interventions, anti-obesity medications are indicated if BMI is 30 or higher, or if it is at least 27 with one obesity-related comorbidity[148].

### 3.1. Principles of prescribing

As obesity is a chronic disease, anti-obesity treatment should be considered a lifelong intervention as in the management of hypertension. Discontinuation of the drug administration usually leads to recurrent weight gain and comorbidity exacerbation[149]. There is an enormous inter-individual and inter-drug variability in the drug response, with the most effective drugs being phentermine and topiramate in a recent network meta-analysis including the clinical studies in anti-obesity medications until 2020 before FDA approval of Semaglutide [SMD= − 9.1 (95% CI − 7.8, − 10.4)][150]. Validated tools to predict the extent of drug response are still lacking. The usual recommendation is to assess the initial response at 3–4 months and to stop the medication if weight loss is less than 5% (<4% weight loss at 16 weeks for liraglutide)[89] to enhance the risk–benefit ratio and avoid unnecessary drug exposure[151]. Pharmacotherapy should be used as an adjunct to lifestyle modifications and not as a substitute.

### 3.2. How to choose an anti-obesity medication

Given the enormous burden and prevalence of obesity, fewer therapeutic options exist for anti-obesity medications compared with other chronic diseases such as hypertension, dyslipidaemia, and DM. The current standard of care is individualized depending on the

presence of comorbidities, risk of potential adverse events, patient preference, or insurance coverage, according to the white paper published by the American Gastroenterological Association[152].

In a recent pragmatic, real-world clinical trial in a Mayo Clinic Weight Management Program, obesity phenotype classification was conducted in 450 obese participants according to the underlying pathophysiology and behaviour of energy balance, resulting in hungry brain (abnormal satiation) (n=143), emotional hunger (hedonic eating) (n=96), hungry gut (abnormal satiety) (n=144) and slow burn (decreased metabolic rate) (n=82)[153]. As a note, 15% (n=68) did not meet the criteria for any single phenotype with 27% eligible for two or more phenotypes in the study, highlighting the complexity of obesity. Then, in the second part of clinical trial, the outcomes of 84 obesity phenotype-guided treated patients [hungry brain with phentermine-topiramate at a dose of 7.5/46 mg daily (n=26) or lorcaserin at 20 mg daily (n=10), emotional hunger with naltrexone/bupropion at a dose of 16/180 mg twice daily (n=24), hungry gut with 3 mg liraglutide daily (n=13), and slow burn with phentermine 15 mg daily plus increased resistance training (n=11) were compared to 228 non-phenotype treated patients (standard of care) over 12 months. The phenotype-guided prescription resulted in a 1.75-fold greater weight loss compared with the non-phenotype-guided group (15% vs 9%), and 79% vs 34% achieved >10% weight loss in the phenotype-guided vs non-phenotype-guided (standard care) groups, suggesting the potential for phenotype-specific targeted trials.. However, further replication and validation in larger, more racially and metabolically diverse cohorts are required before application of the outcomes in clinical practice.

The associated comorbidity of each patient should also be considered to maximize the benefits and reduce the risks and drug interactions. i.e., liraglutide may be preferred for an obese knee OA patient with type 2 DM due to dual action on both obesity and DM. In addition, the risk-benefit profile should be assessed focusing on the presence of the precautions/warnings

and contraindications; i.e. regular BP monitoring is mandatory when prescribing the sympathomimetics like phentermine/topiramate ER and naltrexone/bupropion to patients with hypertension[154]. Patient preferences based on tolerability should also be central in the prescription process due to overwhelming effects on poor adherence or discontinuation, thereby negating the treatment effects. Other factors to be considered in drug prescription are the paucity of RCTs in the context of OA, the need for long-term safety data[155], and adherence to stopping rules[151].

### 3.3. Time to effect/benefit

Depending on the first timing of outcome assessment reported, the onset of weight loss varies between the antiobesity drugs, ranging from 1 week for liraglutide 3.0 mg in SCALE Maintenance trial[156] to 3 months for orlistat in XENDOS trial[157]. The minimum time taken to achieve ≥5% weight loss is observed between 8-12 weeks in the majority of trials. Weight loss of more than 10% was found only in the trials of the Semaglutide 2.4 (up to 18%)[126] and phentermine 15 mg plus topiramate 92 mg (up to 13%)[158]. In available clinical trials of at least 2-years' duration, regain (reversal) of lost weight seems to occur gradually with orlistat[157], liraglutide 3.0[159] and phentermine/topiramate[158] after 1 year time-point.

### 3.4. Persistence/ sustainability of effect

Maintenance of weight loss is as critical as weight loss to reduce obesity-related comorbidity. As obesity is a remarkably heterogeneous disease[160] with highly varying responses among different individuals to obesity interventions, sustained weight loss therefore remains a huge challenge in real world clinical practice[149]. Recent longitudinal data from a large electronic medical records database (n=177,743) showed that weight cycling, defined as

fluctuations in weight of 5% or greater, is a common phenomenon up to over 70% among individuals with modest (≥5% to <10%), moderate (≥10% to <15%) weight loss, irrespective of the interventions[161]. In a recent meta-analysis, each kilogram of weight loss was associated with faster weight regain at a rate of 0.13-0.19 kg/year[162].

Another barrier to utilization of these medications is adherence, due to the need for long-term prescription; this results in poor adherence in some patients, especially if the desired weight-loss goal is not achieved[141]. In a real-world setting, patients on liraglutide 3.0 mg had 42% persistence rate at 6 months compared to 27 % for phentermine/topiramate and 18% for naltrexone/bupropion (n=26,522) with older age, male gender, presence of hyperlipidaemia and no prior phentermine use being predictors for higher persistence[145]. A recent systemic review of real world studies (n=41) reported a general pattern of poor compliance with all approved anti-obesity drugs and discontinuation of treatment up to > 50% of participants within 6–12 months due to adverse effects or perceived ineffectiveness[163].

Anti-obesity medications are still underused, perhaps due to concerns over the adverse effects profile[69] and scepticism about the pharmacotherapy due to the disappointing history of withdrawing several anti-obesity drugs from the market since 1997[149,164]. In a recent population-level study (n=11,195,020) in US, only 2.4% were prescribed with anti-obesity pharmacotherapy in 2019 with an increase from 1.1% in 2010[165]. Only 3.5% of those with morbid obesity started these drugs within 5 years of post-bariatric surgery. Therefore, further studies exploring the barriers to anti-obesity medications are required to facilitate their utilization.

### 3.5. Role for weight loss in other types of OA e.g., hand, hip and spinal

Compared with incident knee OA[51], obesity has a positive but lesser effect on susceptibility to hand[166] and hip[167] OA despite conflicting evidence on the progression of hand OA[168,169]. The biomechanical link between obesity and knee or hip OA is well-established, the mechanisms by which metabolic abnormalities lead to non-weight-bearing hand OA are not clear[170]. In a recent systemic review of weight-loss interventions in people with common musculoskeletal disorders which included 19 papers, 17 are conducted in patients only with knee OA while knee or hip OA were included in the 2 papers and spinal pain only in 3 papers [171], suggesting a paucity of research evaluating the efficacy of weight-loss interventions in hip and spinal OA types especially in hand OA. This was reflected in the 2019 American College of Rheumatology's OA management guideline, which recommended weight loss only in knee and hip OA[135].

### 3.6. Concomitant therapies- can weight loss by dieting be enhanced with the addition of exercise?

Although dieting causes loss of bodyweight, an increased appetite (an increase in∼100 kcal/day per kg of lost weight)[172], endocrine changes, reductions in energy expenditure accompanied by dieting can lead to a plateau of weight loss or even weight regain[173]. Without dietary restriction, physical activities (PA) > 150 min per week leads to a weight loss of ∼2-3 kg, and PA between 225 and 420 min per week elicit a weight reduction of 5- to 7.5-kg[174]. On the other hand, total energy expenditure eventually plateaus above moderate (>230 activity counts per minute per day) activity levels (constrained total energy expenditure model rather than additive model)[175], perhaps due to compensatory mechanisms such as increases in muscle efficiency and decreases in resting energy expenditure[173]. A combination of a low-calorie diet (1200–2000 kcal/day, <30% fat) and moderate-intensity exercise (5 days/week,

225 min/week) resulted in a larger weight loss (10.8%) compared to the diet only, (8.5%) or the exercise-only groups (2.4%)[176]. Therefore, a combination weight-loss program is recommended and provides a greater effect size for pain and function compared with dieting alone (SMD= −0.48; 95% CI: −0.94, −0.03, and SMD= −0.38; 95% CI: −0.76, 0.00)[171]. Similar results were reported in another recent meta-analysis[177]. It seems to suggest that there will be a greater weight loss with the higher intensity of lifestyle interventions at a rate of 0.13 kg lost per lifestyle intervention session at 1 year[178].

### 3.7. How does the magnitude of weight loss from pharmacologic therapy compare to diet and exercise, bariatric surgery?

Compared with DM support and education (n=2575), intense lifestyle intervention (n=2570) can produce averages of 4.7% vs 2.1% loss of initial weight over 8 years with a higher proportion achieving 5% and 10% weight loss (50.3% vs 35.7%, and 26.9% vs 17.2%, respectively) in a long-term study[179]. In a network meta-analysis, anti-obesity drugs can result in between 20% to 54% of individuals achieving 10% weight loss, compared with placebo (9%), with a greater amount of weight loss (2.6 to 8.8 kg) at 1 year with medical therapy compared with placebo[99].

Metabolic or bariatric surgery can be considered for severely obese individuals with a body mass index >40 or >35 with serious obesity-related comorbidities, according to an NIH consensus panel published in 1991[180,181]. A lower BMI (BMI <32) cut-off may be appropriate in younger patients with the severe categories of comorbidities[182]. Metabolic surgery is the most effective intervention for maintaining clinically significant long-term weight loss[183,184]. Based on the latest available meta-analysis, the amount of placebo-subtracted weight loss of pharmacological treatments in comparison with life-style modifications and

bariatric surgery at 1-year follow-up are illustrated in **Figure 3**. Generally, among the non-pharmacological interventions, diet plus exercises cause the largest weight loss of 7.9 kg at 1 year, while exercises or diet lose weight by 1 kg and 4.6 kg respectively, compared with education and support[185]. Among the pharmacological treatments, orlistat produces the lowest weight loss while Semaglutide results in greatest weight loss, compared with the placebo, which includes diet and exercise[186,187]. The metabolic surgery leads to the greatest weight loss with 25.9 kg, compared with all non-surgical interventions[188].

The most commonly used surgical techniques are Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy, and laparoscopic adjustable gastric banding (LAGB)[188]. RYGB participants (n=1738) and LAGB participants (n=610) achieved a weight loss of 32% and 16% at 3-year follow-ups, respectively[189]. The perioperative mortality rates range from 0.03% to 0.2% and an estimated 15% underwent surgical revisions [190]. Compared with medical obesity treatment (n-956), metabolic surgery (n=932) increased the risk of additional gastrointestinal surgeries (31% vs 16%) and complications such as abdominal pain, gastroduodenal ulcers, and iron deficiency anaemia, despite lower risks of obesity-related comorbidities[188,191,192]. A systematic review and economic evaluation (n=131 RCTs) published in 2018 reported the greatest weight loss at 60 months [-20.23 kg, 95% CI -23.75, -16.71] by RYGB and suggested it as the most cost-effective intervention with usual care or a 'do nothing' approach in high-income countries[193,194].

### 3.8. Benefits of weight loss on other body systems e.g., diabetes mellitus, lipid profile, hypertension, and cardiovascular disease

In obese patients, 41% and 5% of BMI-related deaths were caused by CVD and DM, respectively[195]. Beneficial effects on fasting blood glucose, glycated haemoglobin (HbA1c),

lipids, and blood pressure are observed in those with weight loss of >5%[196]. In the most recent meta-analysis of 12 RCTs, anti-obesity drugs result in a significant reduction of fasting plasma glucose by 0.33 mmol/L, HbA1c by 0.3% low-density lipoprotein cholesterol by 1.6%, triglyceride by 6.7%, systolic blood pressure by 0.71 mmHg, high-sensitivity C-reactive protein by 18.3% and a significant increase in high-density lipoprotein cholesterol by 3.3%. Each kg of weight loss leads to a risk reduction of type 2 DM by 16%[197] as well as a 0.1-point reduction of HbA1c in patients with DM[198].

In a recent UK study of primary care database (n= 902,341), 13% weight loss lead to risk reductions for type 2 DM (41%), sleep apnoea (40%), hypertension (22%), dyslipidaemia (19%) and asthma (18%)[199]. Weight loss interventions improve cardiovascular risk factors for at least for 2 years[200]. In patients with type 2 DM, weight loss/stability revealed a positive association with savings in annual medical costs of $2200 while weight gain results in an increased cost of $3400 per year[201], suggesting beneficial effects on healthcare spending[202].

### 3.9. Polypharmacy and drug reactions

There is a high prevalence of using cardiovascular, musculoskeletal and antidiabetic drugs among obese patients[203,204]. Some of the commonly used glucose-lowering drugs, such as insulin and the sulfonylurea drugs, can contribute to weight gain/regain, which further complicates weight loss management[205]. Polypharmacy (taking ≥5 medications a day) with complex treatment regimens can lead to drug–drug interactions, medication nonadherence and undesirable health outcomes[206]. Naltrexone/bupropion should be avoided in patients who are taking antidepressants or anticonvulsants[207].

## 4. Conclusion

Despite the accumulating evidence for the connection between the twindemic (obesity and OA) in the adult population worldwide, imposing a massive health care burden, clinical trials investigating the effects of weight-loss medications on OA are still sparse. The majority of clinical trials focus on the outcomes of interventions that target populations with CVD and DM. In addition, the mechanism(s) by which weight loss can render symptomatic or structural benefits in OA should be explored to identify relevant metabolic and obesity related OA phenotypes. Since obese OA patients may have larger barriers to overzealous physical activities due to pain in the weight-bearing joints compared with normal obese populations, it would be insightful to examine the presence of any differential effects and the role of weight cycling in these populations.

Highlights box

1) Labelling obesity as “modifiable” risk factor for OA is too simplistic as obesity itself is a chronic, relapsing disease with sustained long-term weight loss being extremely challenging.

2) Every 5-unit increase in BMI can lead to a 35% increased risk of knee OA while weight loss of 5.1 kg over the 10 years decreased the odds for developing knee OA by 54%.

3) Anti-obesity medications are indicated if BMI is 30 or higher, or if it is at least 27 with one obesity-related comorbidity if lifestyle interventions fail

4) Among the pharmacological treatment, orlistat produces the lowest weight loss while Semaglutide results in the greatest weight loss

5) Anti-obesity medications are still underused with only 2.4% being prescribed with anti-obesity pharmacotherapy in 2019

6) Despite the enormous disease burden and established pathogenic link, clinical trials of weight-loss medications in OA are still sparse.


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## References


1. Cui A, Li H, Wang D, Zhong J, Chen Y, Lu H: Global, regional prevalence, incidence and risk factors of knee osteoarthritis in population-based studies. *EClinicalMedicine* 2020, 29-30:100587-100587.
2. Safiri S, Kolahi AA, Smith E, Hill C, Bettampadi D, Mansournia MA, Hoy D, Ashrafi-Asgarabad A, Sepidarkish M, Almasi-Hashiani A, et al.: Global, regional and national burden of osteoarthritis 1990-2017: a systematic analysis of the Global Burden of Disease Study 2017. *Ann Rheum Dis* 2020, 79:819-828.
3. Vos T, Lim SS, Abbafati C, Abbas KM, Abbasi M, Abbasifard M, Abbasi-Kangevari M, Abbastabar H, Abd-Allah F, Abdelalim A, et al.: Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet* 2020, 396:1204-1222.
4. The unrecognised burden of osteoarthritis: unmet needs in Europe. In *The Economist*. Edited by: The Economist Newspaper Limited 2022.
5. Leifer VP, Katz JN, Losina E: The burden of OA-health services and economics. *Osteoarthritis and Cartilage*.
6. Murphy L, Schwartz TA, Helmick CG, Renner JB, Tudor G, Koch G, Dragomir A, Kalsbeek WD, Luta G, Jordan JM: Lifetime risk of symptomatic knee osteoarthritis. *Arthritis Rheum* 2008, 59:1207-1213.
7. Murphy LB, Helmick CG, Schwartz TA, Renner JB, Tudor G, Koch GG, Dragomir AD, Kalsbeek WD, Luta G, Jordan JM: One in four people may develop symptomatic hip osteoarthritis in his or her lifetime. *Osteoarthritis Cartilage* 2010, 18:1372-1379.
8. Qin J, Barbour KE, Murphy LB, Nelson AE, Schwartz TA, Helmick CG, Allen KD, Renner JB, Baker NA, Jordan JM: Lifetime Risk of Symptomatic Hand Osteoarthritis: The Johnston County Osteoarthritis Project. *Arthritis & Rheumatology* 2017, 69:1204-1212.
9. Hunter DJ, Bierma-Zeinstra S: Osteoarthritis. *The Lancet* 2019, 393:1745-1759.
10. International ORS: OARSI White Paper- OA as a Serious Disease. Edited by; 2016.
*11. Oo WM, Hunter DJ: Repurposed and investigational disease-modifying drugs in osteoarthritis (DMOADs). *Therapeutic Advances in Musculoskeletal Disease* 2022, 14:1759720X221090297.
(The latest review on the disease-modifying osteoarthritis drugs including the anti-obesity drugs such as liraglutide)
12. Waxman A: WHO global strategy on diet, physical activity and health. *Food Nutr Bull* 2004, 25:292-302.
13. Kyle TK, Dhurandhar EJ, Allison DB: Regarding Obesity as a Disease: Evolving Policies and Their Implications. *Endocrinology and metabolism clinics of North America* 2016, 45:511-520.
14. WHO: Obesity and overweight. Edited by; 2021.

15. Consultation WE: Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004, 363:157-163.
16. Jayawardana R, Ranasinghe P, Sheriff MH, Matthews DR, Katulanda P: Waist to height ratio: a better anthropometric marker of diabetes and cardio-metabolic risks in South Asian adults. *Diabetes Res Clin Pract* 2013, 99:292-299.
17. CDC: Adult Obesity Facts. Edited by; 2021.
18. Ward ZJ, Bleich SN, Cradock AL, Barrett JL, Giles CM, Flax C, Long MW, Gortmaker SL: Projected U.S. State-Level Prevalence of Adult Obesity and Severe Obesity. *N Engl J Med* 2019, 381:2440-2450.
19. Evaluation IfHMa: High body-mass index — Level 2 risk. Edited by; 2019.
*20. Hall KD, Kahan S: Maintenance of Lost Weight and Long-Term Management of Obesity. *Medical Clinics of North America* 2018, 102:183-197.
(A narrative review focusing on the weight plateau, role of diet and recommendations for weight maintenance-specific strategies)
21. Anderson JW, Konz EC, Frederich RC, Wood CL: Long-term weight-loss maintenance: a meta-analysis of US studies. *Am J Clin Nutr* 2001, 74:579-584.
22. Godziuk K, Prado CM, Beaupre L, Jones CA, Werle JR, Forhan M: A critical review of weight loss recommendations before total knee arthroplasty. *Joint Bone Spine* 2021, 88:105114.
23. Yanovski SZ, Yanovski JA: Progress in Pharmacotherapy for Obesity. *JAMA* 2021, 326:129-130.
*24. Müller TD, Blüher M, Tschöp MH, DiMarchi RD: Anti-obesity drug discovery: advances and challenges. *Nature Reviews Drug Discovery* 2022, 21:201-223.
(A narrative review highlighting the overview of the history of developing the antiobesity medications, the lessons learned and ongoing obstacles)
25. Son JW, Kim S: Comprehensive Review of Current and Upcoming Anti-Obesity Drugs. *Diabetes Metab J* 2020, 44:802-818.
26. Messier SP, Pater M, Beavers DP, Legault C, Loeser RF, Hunter DJ, DeVita P: Influences of alignment and obesity on knee joint loading in osteoarthritic gait. *Osteoarthritis Cartilage* 2014, 22:912-917.
27. Messier SP, Gutekunst DJ, Davis C, DeVita P: Weight loss reduces knee-joint loads in overweight and obese older adults with knee osteoarthritis. *Arthritis Rheum* 2005, 52:2026-2032.
28. Aaboe J, Bliddal H, Messier SP, Alkjær T, Henriksen M: Effects of an intensive weight loss program on knee joint loading in obese adults with knee osteoarthritis. *Osteoarthritis Cartilage* 2011, 19:822-828.
29. Munugoda IP, Beavers DP, Wirth W, Aitken DA, Loeser RF, Miller GD, Lyles M, Carr JJ, Guermazi A, Hunter DJ, et al.: The effect of weight loss on the progression of meniscal extrusion and size in knee osteoarthritis: a post-hoc analysis of the Intensive Diet and Exercise for Arthritis (IDEA) trial. *Osteoarthritis Cartilage* 2020, 28:410-417.
30. Messier SP, Pater M, Beavers DP, Legault C, Loeser RF, Hunter DJ, DeVita P: Influences of alignment and obesity on knee joint loading in osteoarthritic gait. *Osteoarthritis and cartilage* 2014, 22:912-917.
31. Vincent HK, Heywood K, Connelly J, Hurley RW: Obesity and weight loss in the treatment and prevention of osteoarthritis. *Pm r* 2012, 4:S59-67.
32. Miyatake N, Fujii M, Nishikawa H, Wada J, Shikata K, Makino H, Kimura I: Clinical evaluation of muscle strength in 20-79-years-old obese Japanese. *Diabetes Res Clin Pract* 2000, 48:15-21.
33. Bennell KL, Hunt MA, Wrigley TV, Lim BW, Hinman RS: Role of muscle in the genesis and management of knee osteoarthritis. *Rheum Dis Clin North Am* 2008, 34:731-754.
*34. Messier SP, Beavers DP, Mihalko SL, Miller GD, Lyles MF, Hunter DJ, Carr JJ, Eckstein F, Guermazi A, Loeser RF, et al.: The effects of intensive dietary weight loss and exercise on gait in overweight and obese adults with knee osteoarthritis. The Intensive Diet and Exercise for Arthritis (IDEA) trial. *Journal of biomechanics* 2020, 98:109477-109477.

(a paper revealing a significant dose-response to weight loss with participants that lost >10% of baseline body weight having lower resultant knee forces and lower muscle forces than participants that had less weight loss)
35. Zhang K, Wang L, Liu Z, Geng B, Teng Y, Liu X, Yi Q, Yu D, Chen X, Zhao D, et al.: Mechanosensory and mechanotransductive processes mediated by ion channels in articular chondrocytes: Potential therapeutic targets for osteoarthritis. *Channels (Austin)* 2021, 15:339-359.
36. Ramage L, Nuki G, Salter DM: Signalling cascades in mechanotransduction: cell-matrix interactions and mechanical loading. *Scand J Med Sci Sports* 2009, 19:457-469.
37. Chen L, Yao F, Wang T, Li G, Chen P, Bulsara M, Zheng JJY, Landao-Bassonga E, Firth M, Vasantharao P, et al.: Horizontal fissuring at the osteochondral interface: a novel and unique pathological feature in patients with obesity-related osteoarthritis. *Annals of the rheumatic diseases* 2020, 79:811-818.
38. Ouchi N, Parker JL, Lugus JJ, Walsh K: Adipokines in inflammation and metabolic disease. *Nature reviews. Immunology* 2011, 11:85-97.
39. Sowers MR, Karvonen-Gutierrez CA: The evolving role of obesity in knee osteoarthritis. *Current opinion in rheumatology* 2010, 22:533-537.
40. Pearson MJ, Herndler-Brandstetter D, Tariq MA, Nicholson TA, Philp AM, Smith HL, Davis ET, Jones SW, Lord JM: IL-6 secretion in osteoarthritis patients is mediated by chondrocyte-synovial fibroblast cross-talk and is enhanced by obesity. *Sci Rep* 2017, 7:3451.
41. Nanus DE, Wijesinghe SN, Pearson MJ, Hadjicharalambous MR, Rosser A, Davis ET, Lindsay MA, Jones SW: Regulation of the Inflammatory Synovial Fibroblast Phenotype by Metastasis-Associated Lung Adenocarcinoma Transcript 1 Long Noncoding RNA in Obese Patients With Osteoarthritis. *Arthritis Rheumatol* 2020, 72:609-619.
42. Philp AM, Collier RL, Grover LM, Davis ET, Jones SW: Resistin promotes the abnormal Type I collagen phenotype of subchondral bone in obese patients with end stage hip osteoarthritis. *Sci Rep* 2017, 7:4042.
43. Wang X, Hunter D, Xu J, Ding C: Metabolic triggered inflammation in osteoarthritis. *Osteoarthritis Cartilage* 2015, 23:22-30.
44. Loukov D, Karampatos S, Maly MR, Bowdish DME: Monocyte activation is elevated in women with knee-osteoarthritis and associated with inflammation, BMI and pain. *Osteoarthritis Cartilage* 2018, 26:255-263.
45. Sun AR, Udduttula A, Li J, Liu Y, Ren P-G, Zhang P: Cartilage tissue engineering for obesity-induced osteoarthritis: Physiology, challenges, and future prospects. *Journal of orthopaedic translation* 2020, 26:3-15.
46. Landsmeer MLA, de Vos BC, van der Plas P, van Middelkoop M, Vroegindeweij D, Bindels PJE, Oei EHG, Bierma-Zeinstra SMA, Runhaar J: Effect of weight change on progression of knee OA structural features assessed by MRI in overweight and obese women. *Osteoarthritis Cartilage* 2018, 26:1666-1674.
47. Sun AR, Panchal SK, Friis T, Sekar S, Crawford R, Brown L, Xiao Y, Prasadam I: Obesity-associated metabolic syndrome spontaneously induces infiltration of pro-inflammatory macrophage in synovium and promotes osteoarthritis. *PLoS One* 2017, 12:e0183693.
48. Mitchell NS, Catenacci VA, Wyatt HR, Hill JO: Obesity: overview of an epidemic. *The Psychiatric clinics of North America* 2011, 34:717-732.
49. Finch CF, Kemp JL, Clapperton AJ: The incidence and burden of hospital-treated sports-related injury in people aged 15+ years in Victoria, Australia, 2004-2010: a future epidemic of osteoarthritis? *Osteoarthritis Cartilage* 2015, 23:1138-1143.
50. Lewis-Faning E, Fletcher E: A Statistical Study of 1,000 Cases of Chronic Rheumatism-Part III. *Postgrad Med J* 1945, 21:137-146.
51. Reyes C, Leyland KM, Peat G, Cooper C, Arden NK, Prieto-Alhambra D: Association Between Overweight and Obesity and Risk of Clinically Diagnosed Knee, Hip, and Hand Osteoarthritis: A Population-Based Cohort Study. *Arthritis & rheumatology (Hoboken, N.J.)* 2016, 68:1869-1875.

52. Jiang L, Tian W, Wang Y, Rong J, Bao C, Liu Y, Zhao Y, Wang C: Body mass index and susceptibility to knee osteoarthritis: a systematic review and meta-analysis. *Joint Bone Spine* 2012, 79:291-297.
53. Silverwood V, Blagojevic-Bucknall M, Jinks C, Jordan JL, Protheroe J, Jordan KP: Current evidence on risk factors for knee osteoarthritis in older adults: a systematic review and meta-analysis. *Osteoarthritis Cartilage* 2015, 23:507-515.
54. Felson DT, Zhang Y, Anthony JM, Naimark A, Anderson JJ: Weight loss reduces the risk for symptomatic knee osteoarthritis in women. The Framingham Study. *Ann Intern Med* 1992, 116:535-539.
55. Chu IJH, Lim AYT, Ng CLW: Effects of meaningful weight loss beyond symptomatic relief in adults with knee osteoarthritis and obesity: a systematic review and meta-analysis. *Obes Rev* 2018, 19:1597-1607.
56. Riddle DL, Stratford PW: Body weight changes and corresponding changes in pain and function in persons with symptomatic knee osteoarthritis: a cohort study. *Arthritis Care Res (Hoboken)* 2013, 65:15-22.
57. Messier SP, Resnik AE, Beavers DP, Mihalko SL, Miller GD, Nicklas BJ, deVita P, Hunter DJ, Lyles MF, Eckstein F, et al.: Intentional Weight Loss in Overweight and Obese Patients With Knee Osteoarthritis: Is More Better? *Arthritis Care Res (Hoboken)* 2018, 70:1569-1575.
58. Hunter DJ, Beavers DP, Eckstein F, Guermazi A, Loeser RF, Nicklas BJ, Mihalko SL, Miller GD, Lyles M, DeVita P, et al.: The Intensive Diet and Exercise for Arthritis (IDEA) trial: 18-month radiographic and MRI outcomes. *Osteoarthritis Cartilage* 2015, 23:1090-1098.
59. Wenger A, Englund M, Wirth W, Hudelmaier M, Kwoh K, Eckstein F: Relationship of 3D meniscal morphology and position with knee pain in subjects with knee osteoarthritis: a pilot study. *Eur Radiol* 2012, 22:211-220.
60. Richette P, Poitou C, Garnero P, Vicaut E, Bouillot JL, Lacorte JM, Basdevant A, Clément K, Bardin T, Chevalier X: Benefits of massive weight loss on symptoms, systemic inflammation and cartilage turnover in obese patients with knee osteoarthritis. *Ann Rheum Dis* 2011, 70:139-144.
61. Anandacoomarasamy A, Leibman S, Smith G, Caterson I, Giuffre B, Fransen M, Sambrook PN, March L: Weight loss in obese people has structure-modifying effects on medial but not on lateral knee articular cartilage. *Ann Rheum Dis* 2012, 71:26-32.
62. Teichtahl AJ, Wluka AE, Tanamas SK, Wang Y, Strauss BJ, Proietto J, Dixon JB, Jones G, Forbes A, Cicuttini FM: Weight change and change in tibial cartilage volume and symptoms in obese adults. *Ann Rheum Dis* 2015, 74:1024-1029.
63. Gersing AS, Schwaiger BJ, Nevitt MC, Joseph GB, Chanchek N, Guimaraes JB, Mbapte Wamba J, Facchetti L, McCulloch CE, Link TM: Is Weight Loss Associated with Less Progression of Changes in Knee Articular Cartilage among Obese and Overweight Patients as Assessed with MR Imaging over 48 Months? Data from the Osteoarthritis Initiative. *Radiology* 2017, 284:508-520.
64. Gersing AS, Schwaiger BJ, Nevitt MC, Zarnowski J, Joseph GB, Feuerriegel G, Jungmann PM, Guimaraes JB, Facchetti L, McCulloch CE, et al.: Weight loss regimen in obese and overweight individuals is associated with reduced cartilage degeneration: 96-month data from the Osteoarthritis Initiative. *Osteoarthritis Cartilage* 2019, 27:863-870.
*65. Daugaard CL, Hangaard S, Bartels EM, Gudbergsen H, Christensen R, Bliddal H, Englund M, Conaghan PG, Boesen M: The effects of weight loss on imaging outcomes in osteoarthritis of the hip or knee in people who are overweight or obese: a systematic review. *Osteoarthritis Cartilage* 2020, 28:10-21.
(no consistent evidence of the effects of weight loss on OA structural pathology in people with obesity)
66. Administration FaD: Guidance for the Clinical Evaluation of Weight-Control Drugs. 1996.
67. Administration FaD: Draft Guidance for Industry on Developing Products for Weight Management. Edited by; 2007.

68. Colman E: Food and Drug Administration's Obesity Drug Guidance Document. *Circulation* 2012, 125:2156-2164.
69. Colman E: Anorectics on Trial: A Half Century of Federal Regulation of Prescription Appetite Suppressants. *Annals of Internal Medicine* 2005, 143:380-385.
70. Hauptman J, Lucas C, Boldrin MN, Collins H, Segal KR: Orlistat in the long-term treatment of obesity in primary care settings. *Arch Fam Med* 2000, 9:160-167.
71. Greenway FL, Fujioka K, Plodkowski RA, Mudaliar S, Guttadauria M, Erickson J, Kim DD, Dunayevich E: Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2010, 376:595-605.
72. Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, Lau DC, le Roux CW, Violante Ortiz R, Jensen CB, et al.: A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. *N Engl J Med* 2015, 373:11-22.
73. Administration FaD: FDA approves first treatment for weight management for people with certain rare genetic conditions. 2020.
74. Administration FaD: FDA Approves New Drug Treatment for Chronic Weight Management, First Since 2014. 2021.
75. Tak YJ, Lee SY: Long-Term Efficacy and Safety of Anti-Obesity Treatment: Where Do We Stand? *Curr Obes Rep* 2021, 10:14-30.
76. James WP, Caterson ID, Coutinho W, Finer N, Van Gaal LF, Maggioni AP, Torp-Pedersen C, Sharma AM, Shepherd GM, Rode RA, et al.: Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. *N Engl J Med* 2010, 363:905-917.
77. Sharretts J, Galescu O, Gomatam S, Andraca-Carrera E, Hampp C, Yanoff L: Cancer Risk Associated with Lorcaserin - The FDA's Review of the CAMELLIA-TIMI 61 Trial. *N Engl J Med* 2020, 383:1000-1002.
78. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, Hu FB, Hubbard VS, Jakicic JM, Kushner RF, et al.: 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Circulation* 2014, 129:S102-138.
79. Garvey WT, Mechanick JI, Brett EM, Garber AJ, Hurley DL, Jastreboff AM, Nadolsky K, Pessah-Pollack R, Plodkowski R: American Association of Clinical Endocrinologists and American College of Endocrinology Comprehensive Clinical Practice Guidelines For medical Care of Patients with Obesity. *Endocr Pract* 2016, 22 Suppl 3:1-203.
80. Zhi J, Melia AT, Guerciolini R, Chung J, Kinberg J, Hauptman JB, Patel IH: Retrospective population-based analysis of the dose-response (fecal fat excretion) relationship of orlistat in normal and obese volunteers. *Clin Pharmacol Ther* 1994, 56:82-85.
81. Carrière F, Renou C, Ransac S, Lopez V, De Caro J, Ferrato F, De Caro A, Fleury A, Sanwald-Ducray P, Lengsfeld H, et al.: Inhibition of gastrointestinal lipolysis by Orlistat during digestion of test meals in healthy volunteers. *Am J Physiol Gastrointest Liver Physiol* 2001, 281:G16-28.
82. Williams G: Orlistat over the counter. *BMJ (Clinical research ed.)* 2007, 335:1163-1164.
83. Rössner S, Sjöström L, Noack R, Meinders AE, Noseda G: Weight loss, weight maintenance, and improved cardiovascular risk factors after 2 years treatment with orlistat for obesity. European Orlistat Obesity Study Group. *Obes Res* 2000, 8:49-61.
84. Rucker D, Padwal R, Li SK, Curioni C, Lau DCW: Long term pharmacotherapy for obesity and overweight: updated meta-analysis. *BMJ (Clinical research ed.)* 2007, 335:1194-1199.
85. Sahebkar A, Simental-Mendía LE, Reiner Ž, Kovanen PT, Simental-Mendía M, Bianconi V, Pirro M: Effect of orlistat on plasma lipids and body weight: A systematic review and meta-analysis of 33 randomized controlled trials. *Pharmacological Research* 2017, 122:53-65.
86. Sahebkar A, Simental-Mendía LE, Kovanen PT, Pedone C, Simental-Mendía M, Cicero AFG: Effects of orlistat on blood pressure: a systematic review and meta-analysis of 27 randomized controlled clinical trials. *J Am Soc Hypertens* 2018, 12:80-96.

87. Morris M, Lane P, Lee K, Parks D: An integrated analysis of liver safety data from orlistat clinical trials. *Obes Facts* 2012, 5:485-494.
88. Singh AK, Singh R: Pharmacotherapy in obesity: a systematic review and meta-analysis of randomized controlled trials of anti-obesity drugs. *Expert Review of Clinical Pharmacology* 2020, 13:53-64.
89. Tchang BG, Tarazi MS, Aras M, Shukla AP: An update on pharmacotherapeutic strategies for obesity. *Expert Opin Pharmacother* 2021, 22:1305-1318.
90. Bays H: Phentermine, topiramate and their combination for the treatment of adiposopathy ('sick fat') and metabolic disease. *Expert Rev Cardiovasc Ther* 2010, 8:1777-1801.
91. Li M-F, Cheung BM: Rise and fall of anti-obesity drugs. *World journal of diabetes* 2011, 2:19-23.
92. Nelson DL, Gehlert DR: Central nervous system biogenic amine targets for control of appetite and energy expenditure. *Endocrine* 2006, 29:49-60.
93. Verrotti A, Scaparrotta A, Agostinelli S, Di Pillo S, Chiarelli F, Grosso S: Topiramate-induced weight loss: a review. *Epilepsy Res* 2011, 95:189-199.
94. Jordan J, Astrup A, Engeli S, Narkiewicz K, Day WW, Finer N: Cardiovascular effects of phentermine and topiramate: a new drug combination for the treatment of obesity. *Journal of Hypertension* 2014, 32:1178-1188.
95. Klein S, Romijn JA: Chapter 36 - Obesity. In *Williams Textbook of Endocrinology (Thirteenth Edition)*. Edited by Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: Elsevier; 2016:1633-1659.
96. Qsymia Prescribing Information, Vivus Inc, Moutain View, California. Edited by; 2014. vol 2021.]
97. Garvey WT, Ryan DH, Look M, Gadde KM, Allison DB, Peterson CA, Schwiers M, Day WW, Bowden CH: Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study. *Am J Clin Nutr* 2012, 95:297-308.
98. Khera R, Pandey A, Chandar AK, Murad MH, Prokop LJ, Neeland IJ, Berry JD, Camilleri M, Singh S: Effects of Weight-Loss Medications on Cardiometabolic Risk Profiles: A Systematic Review and Network Meta-analysis. *Gastroenterology* 2018, 154:1309-1319.e1307.
99. Khera R, Murad MH, Chandar AK, Dulai PS, Wang Z, Prokop LJ, Loomba R, Camilleri M, Singh S: Association of Pharmacological Treatments for Obesity With Weight Loss and Adverse Events: A Systematic Review and Meta-analysis. *Jama* 2016, 315:2424-2434.
100. Siebenhofer A, Winterholer S, Jeitler K, Horvath K, Berghold A, Krenn C, Semlitsch T: Long-term effects of weight-reducing drugs in people with hypertension. *Cochrane Database Syst Rev* 2021, 1:Cd007654.
101. Lei XG, Ruan JQ, Lai C, Sun Z, Yang X: Efficacy and Safety of Phentermine/Topiramate in Adults with Overweight or Obesity: A Systematic Review and Meta-Analysis. *Obesity (Silver Spring)* 2021, 29:985-994.
102. Day C: Chapter 26 - New Therapies in Obesity. In *Practical Guide to Obesity Medicine*. Edited by Weaver JU: Elsevier; 2018:271-279.
103. Woloshin S, Schwartz LM: The New Weight-Loss Drugs, Lorcaserin and Phentermine-Topiramate: Slim Pickings? *JAMA Internal Medicine* 2014, 174:615-619.
104. Lewis KH, Fischer H, Ard J, Barton L, Bessesen DH, Daley MF, Desai J, Fitzpatrick SL, Horberg M, Koebnick C, et al.: Safety and Effectiveness of Longer-Term Phentermine Use: Clinical Outcomes from an Electronic Health Record Cohort. *Obesity (Silver Spring)* 2019, 27:591-602.
105. Agency EM: Refusal of the Marketing Authorisation for Qsiva (Phentermine/Topiramate). Outcome of re-examination. 2013.
106. Greenway FL, Whitehouse MJ, Guttadauria M, Anderson JW, Atkinson RL, Fujioka K, Gadde KM, Gupta AK, O'Neil P, Schumacher D, et al.: Rational design of a combination medication for the treatment of obesity. *Obesity (Silver Spring)* 2009, 17:30-39.

914 107. Billes SK, Greenway FL: Combination therapy with naltrexone and bupropion for obesity.
915 *Expert Opin Pharmacother* 2011, 12:1813-1826.
916 108. Padwal R: Contrave, a bupropion and naltrexone combination therapy for the potential
917 treatment of obesity. *Curr Opin Investig Drugs* 2009, 10:1117-1125.
918 109. Chao AM, Wadden TA, Berkowitz RI, Quigley K, Silvestry F: The risk of cardiovascular
919 complications with current obesity drugs. *Expert opinion on drug safety* 2020, 19:1095-
920 1104.
921 110. Sposito AC, Bonilha I, Luchiari B, Benchimol A, Hohl A, Moura F, Cercato C, Geloneze B, Nadruz
922 W, Aguilar-Salinas C, et al.: Cardiovascular safety of naltrexone and bupropion therapy:
923 Systematic review and meta-analyses. *Obes Rev* 2021, 22:e13224.
924 111. Onakpoya IJ, Lee JJ, Mahtani KR, Aronson JK, Heneghan CJ: Naltrexone-bupropion (Mysimba) in
925 management of obesity: A systematic review and meta-analysis of unpublished clinical
926 study reports. *British journal of clinical pharmacology* 2020, 86:646-667.
927 112. Drucker DJ: Mechanisms of Action and Therapeutic Application of Glucagon-like Peptide-1. *Cell*
928 *Metab* 2018, 27:740-756.
929 113. Kanoski SE, Hayes MR, Skibicka KP: GLP-1 and weight loss: unraveling the diverse neural
930 circuitry. *Am J Physiol Regul Integr Comp Physiol* 2016, 310:R885-895.
931 114. Deacon CF, Nauck MA, Toft-Nielsen M, Pridal L, Willms B, Holst JJ: Both subcutaneously and
932 intravenously administered glucagon-like peptide I are rapidly degraded from the NH2-
933 terminus in type II diabetic patients and in healthy subjects. *Diabetes* 1995, 44:1126-1131.
934 115. Agersø H, Jensen LB, Elbrønd B, Rolan P, Zdravkovic M: The pharmacokinetics,
935 pharmacodynamics, safety and tolerability of NN2211, a new long-acting GLP-1 derivative,
936 in healthy men. *Diabetologia* 2002, 45:195-202.
937 116. Administration FaD: SAXENDA (liraglutide [rDNA origin] injection), solution for subcutaneous
938 use. 2014.
939 117. Davies MJ, Aronne LJ, Caterson ID, Thomsen AB, Jacobsen PB, Marso SP: Liraglutide and
940 cardiovascular outcomes in adults with overweight or obesity: A post hoc analysis from
941 SCALE randomized controlled trials. *Diabetes Obes Metab* 2018, 20:734-739.
942 118. O'Neil PM, Aroda VR, Astrup A, Kushner R, Lau DCW, Wadden TA, Brett J, Cancino AP, Wilding
943 JPH: Neuropsychiatric safety with liraglutide 3.0 mg for weight management: Results from
944 randomized controlled phase 2 and 3a trials. *Diabetes Obes Metab* 2017, 19:1529-1536.
945 119. Piccoli GF, Mesquita LA, Stein C, Aziz M, Zoldan M, Degobi NAH, Spiazzi BF, Lopes Junior GL,
946 Colpani V, Gerchman F: Do GLP-1 Receptor Agonists Increase the Risk of Breast Cancer? A
947 Systematic Review and Meta-analysis. *J Clin Endocrinol Metab* 2021, 106:912-921.
948 120. Knudsen LB, Lau J: The Discovery and Development of Liraglutide and Semaglutide. *Frontiers in*
949 *endocrinology* 2019, 10:155-155.
950 121. Lau J, Bloch P, Schäffer L, Pettersson I, Spetzler J, Kofoed J, Madsen K, Knudsen LB, McGuire J,
951 Steensgaard DB, et al.: Discovery of the Once-Weekly Glucagon-Like Peptide-1 (GLP-1)
952 Analogue Semaglutide. *Journal of Medicinal Chemistry* 2015, 58:7370-7380.
953 122. Capehorn MS, Catarig AM, Furberg JK, Janez A, Price HC, Tadayon S, Vergès B, Marre M: Efficacy
954 and safety of once-weekly semaglutide 1.0mg vs once-daily liraglutide 1.2mg as add-on to
955 1–3 oral antidiabetic drugs in subjects with type 2 diabetes (SUSTAIN 10). *Diabetes &*
956 *Metabolism* 2020, 46:100-109.
957 123. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, McGowan BM,
958 Rosenstock J, Tran MTD, Wadden TA, et al.: Once-Weekly Semaglutide in Adults with
959 Overweight or Obesity. *N Engl J Med* 2021, 384:989.
960 124. Davies M, Færch L, Jeppesen OK, Pakseresht A, Pedersen SD, Perreault L, Rosenstock J,
961 Shimomura I, Viljoen A, Wadden TA, et al.: Semaglutide 2·4 mg once a week in adults with
962 overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-
963 dummy, placebo-controlled, phase 3 trial. *Lancet* 2021, 397:971-984.
964 125. Wadden TA, Bailey TS, Billings LK, Davies M, Frias JP, Koroleva A, Lingvay I, O'Neil PM, Rubino
965 DM, Skovgaard D, et al.: Effect of Subcutaneous Semaglutide vs Placebo as an Adjunct to

Intensive Behavioral Therapy on Body Weight in Adults With Overweight or Obesity: The STEP 3 Randomized Clinical Trial. *Jama* 2021, 325:1403-1413.
126. Rubino D, Abrahamsson N, Davies M, Hesse D, Greenway FL, Jensen C, Lingvay I, Mosenzon O, Rosenstock J, Rubio MA, et al.: Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity: The STEP 4 Randomized Clinical Trial. *Jama* 2021, 325:1414-1425.
127. Tsapas A, Karagiannis T, Kakotrichi P, Avgerinos I, Mantsiou C, Tousinas G, Manolopoulos A, Liakos A, Malandris K, Matthews DR, et al.: Comparative efficacy of glucose-lowering medications on body weight and blood pressure in patients with type 2 diabetes: A systematic review and network meta-analysis. *Diabetes, Obesity and Metabolism* 2021, 23:2116-2124.
128. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, et al.: Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med* 2016, 375:1834-1844.
129. Huvenne H, Dubern B, Clément K, Poitou C: Rare Genetic Forms of Obesity: Clinical Approach and Current Treatments in 2016. *Obes Facts* 2016, 9:158-173.
130. Stutzmann F, Tan K, Vatin V, Dina C, Jouret Ba, Tichet J, Balkau B, Potoczna N, Horber F, O'Rahilly S, et al.: Prevalence of Melanocortin-4 Receptor Deficiency in Europeans and Their Age-Dependent Penetrance in Multigenerational Pedigrees. *Diabetes* 2008, 57:2511-2518.
131. Clément K, van den Akker E, Argente J, Bahm A, Chung WK, Connors H, De Waele K, Farooqi IS, Gonneau-Lejeune J, Gordon G, et al.: Efficacy and safety of setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or POMC deficiency: single-arm, open-label, multicentre, phase 3 trials. *The Lancet Diabetes & Endocrinology* 2020, 8:960-970.
132. Pharmaceuticals. R: Rhythm Pharmaceuticals announces positive topline results from pivotal phase 3 clinical trial evaluating setmelanotide in Bardet-Biedl and Alström syndromes. 2020.
133. Markham A: Setmelanotide: First Approval. *Drugs* 2021, 81:397-403.
134. Bannuru RR, Osani MC, Vaysbrot EE, Arden NK, Bennell K, Bierma-Zeinstra SMA, Kraus VB, Lohmander LS, Abbott JH, Bhandari M, et al.: OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage* 2019, 27:1578-1589.
135. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, Callahan L, Copenhaver C, Dodge C, Felson D, et al.: 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. *Arthritis Care Res (Hoboken)* 2020, 72:149-162.
136. Ryan DH, Yockey SR: Weight Loss and Improvement in Comorbidity: Differences at 5%, 10%, 15%, and Over. *Current Obesity Reports* 2017, 6:187-194.
137. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: executive summary. Expert Panel on the Identification, Evaluation, and Treatment of Overweight in Adults. *Am J Clin Nutr* 1998, 68:899-917.
138. Christensen R, Bartels EM, Astrup A, Bliddal H: Effect of weight reduction in obese patients diagnosed with knee osteoarthritis: a systematic review and meta-analysis. *Annals of the Rheumatic Diseases* 2007, 66:433-439.
139. Inam SHA, Riaz B, Jamil H, Rafique D, Siddiqi UA, Iqbal M, Sherwani NZF, Khan W: Do Patients With Osteoarthritis get Weight Loss Counseling? *Cureus* 2020, 12:e11502-e11502.
140. Puhl RM, Heuer CA: The stigma of obesity: a review and update. *Obesity (Silver Spring)* 2009, 17:941-964.
141. Kanj A, Levine D: Overcoming obesity: Weight-loss drugs are underused. *Cleve Clin J Med* 2020, 87:602-604.
142. Chen J, Xie J-J, Shi K-S, Gu Y-T, Wu C-C, Xuan J, Ren Y, Chen L, Wu Y-S, Zhang X-L, et al.: Glucagon-like peptide-1 receptor regulates endoplasmic reticulum stress-induced

apoptosis and the associated inflammatory response in chondrocytes and the progression of osteoarthritis in rat. *Cell Death & Disease* 2018, 9:212.
143. Que Q, Guo X, Zhan L, Chen S, Zhang Z, Ni X, Ye B, Wan S: The GLP-1 agonist, liraglutide, ameliorates inflammation through the activation of the PKA/CREB pathway in a rat model of knee osteoarthritis. *J Inflamm (Lond)* 2019, 16:13.
**144. Gudbergsen H, Overgaard A, Henriksen M, Wæhrens EE, Bliddal H, Christensen R, Nielsen SM, Boesen M, Knop FK, Astrup A, et al.: Liraglutide after diet-induced weight loss for pain and weight control in knee osteoarthritis: a randomized controlled trial. *Am J Clin Nutr* 2021, 113:314-323.
(The first phase-3 RCT examining the effects of liraglutide in patients with knee OA and obesity, revealing a significant weight loss at >52 wk but no improvement in knee pain)
145. Ganguly R, Tian Y, Kong SX, Hersloev M, Hobbs T, Smolarz BG, Ramasamy A, Haase CL, Weng W: Persistence of newer anti-obesity medications in a real-world setting. *Diabetes Res Clin Pract* 2018, 143:348-356.
146. Association AD: 8. Obesity Management for the Treatment of Type 2 Diabetes: Standards of Medical Care in Diabetes—2020. *Diabetes Care* 2019, 43:S89-S97.
147. Canuto R, Garcez A, de Souza RV, Kac G, Olinto MTA: Nutritional intervention strategies for the management of overweight and obesity in primary health care: A systematic review with meta-analysis. *Obes Rev* 2021, 22:e13143.
148. Hall KD, Kahan S: Maintenance of Lost Weight and Long-Term Management of Obesity. *Med Clin North Am* 2018, 102:183-197.
149. Tak YJ, Lee SY: Long-Term Efficacy and Safety of Anti-Obesity Treatment: Where Do We Stand? *Current obesity reports* 2021, 10:14-30.
150. Salari N, Jafari S, Darvishi N, Valipour E, Mohammadi M, Mansouri K, Shohaimi S: The best drug supplement for obesity treatment: a systematic review and network meta-analysis. *Diabetol Metab Syndr* 2021, 13:110.
151. Patel DK, Stanford FC: Safety and tolerability of new-generation anti-obesity medications: a narrative review. *Postgrad Med* 2018, 130:173-182.
152. Acosta A, Streett S, Kroh MD, Cheskin LJ, Saunders KH, Kurian M, Schofield M, Barlow SE, Aronne L: White Paper AGA: POWER - Practice Guide on Obesity and Weight Management, Education, and Resources. *Clin Gastroenterol Hepatol* 2017, 15:631-649.e610.
153. Acosta A, Camilleri M, Abu Dayyeh B, Calderon G, Gonzalez D, McRae A, Rossini W, Singh S, Burton D, Clark MM: Selection of Antiobesity Medications Based on Phenotypes Enhances Weight Loss: A Pragmatic Trial in an Obesity Clinic. *Obesity (Silver Spring, Md.)* 2021, 29:662-671.
154. Tak YJ, Lee SY: Anti-Obesity Drugs: Long-Term Efficacy and Safety: An Updated Review. *World J Mens Health* 2021, 39:208-221.
155. Chao AM, Wadden TA, Berkowitz RI, Quigley K, Silvestry F: The risk of cardiovascular complications with current obesity drugs. *Expert Opin Drug Saf* 2020, 19:1095-1104.
156. Wadden TA, Hollander P, Klein S, Niswender K, Woo V, Hale PM, Aronne L: Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. *Int J Obes (Lond)* 2013, 37:1443-1451.
157. Torgerson JS, Hauptman J, Boldrin MN, Sjöström 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.
158. Garvey WT, Ryan DH, Look M, Gadde KM, Allison DB, Peterson CA, Schwiers M, Day WW, Bowden CH: Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study. *The American Journal of Clinical Nutrition* 2011, 95:297-308.

159. le Roux CW, Astrup A, Fujioka K, Greenway F, Lau DCW, Van Gaal L, Ortiz RV, Wilding JPH, Skjøth TV, Manning LS, et al.: 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. *Lancet* 2017, 389:1399-1409.
160. Field AE, Camargo CA, Jr., Ogino S: The merits of subtyping obesity: one size does not fit all. *Jama* 2013, 310:2147-2148.
161. DerSarkissian M, Bhak RH, Huang J, Buchs S, Vekeman F, Smolarz BG, Brett J, Ganguly R, Duh MS: Maintenance of weight loss or stability in subjects with obesity: a retrospective longitudinal analysis of a real-world population. *Current Medical Research and Opinion* 2017, 33:1105-1110.
162. Hartmann-Boyce J, Theodoulou A, Oke JL, Butler AR, Scarborough P, Bastounis A, Dunnigan A, Byadya R, Hobbs FDR, Sniehotta FF, et al.: Association between characteristics of behavioural weight loss programmes and weight change after programme end: systematic review and meta-analysis. *Bmj* 2021, 374:n1840.
163. Ahmad NN, Robinson S, Kennedy-Martin T, Poon JL, Kan H: Clinical outcomes associated with anti-obesity medications in real-world practice: A systematic literature review. *Obesity Reviews* 2021, 22:e13326.
164. Hainer V, Aldhoon-Hainerová I: Tolerability and safety of the new anti-obesity medications. *Drug Saf* 2014, 37:693-702.
165. Elangovan A, Shah R, Smith ZL: Pharmacotherapy for Obesity-Trends Using a Population Level National Database. *Obes Surg* 2021, 31:1105-1112.
166. Jiang L, Xie X, Wang Y, Wang Y, Lu Y, Tian T, Chu M, Shen Y: Body mass index and hand osteoarthritis susceptibility: an updated meta-analysis. *Int J Rheum Dis* 2016, 19:1244-1254.
167. Jiang L, Rong J, Wang Y, Hu F, Bao C, Li X, Zhao Y: The relationship between body mass index and hip osteoarthritis: a systematic review and meta-analysis. *Joint Bone Spine* 2011, 78:150-155.
168. Magnusson K, Slatkowsky-Christensen B, van der Heijde D, Kvien TK, Hagen KB, Haugen IK: Body mass index and progressive hand osteoarthritis: data from the Oslo hand osteoarthritis cohort. *Scand J Rheumatol* 2015, 44:331-336.
169. Visser AW, de Mutsert R, le Cessie S, den Heijer M, Rosendaal FR, Kloppenburg M: The relative contribution of mechanical stress and systemic processes in different types of osteoarthritis: the NEO study. *Ann Rheum Dis* 2015, 74:1842-1847.
170. Silvestre MP, Rodrigues AM, Canhão H, Marques C, Teixeira D, Calhau C, Branco J: Cross-Talk between Diet-Associated Dysbiosis and Hand Osteoarthritis. *Nutrients* 2020, 12:3469.
171. Robson EK, Hodder RK, Kamper SJ, O'Brien KM, Williams A, Lee H, Wolfenden L, Yoong S, Wiggers J, Barnett C, et al.: Effectiveness of Weight-Loss Interventions for Reducing Pain and Disability in People With Common Musculoskeletal Disorders: A Systematic Review With Meta-Analysis. *Journal of Orthopaedic & Sports Physical Therapy* 2020, 50:319-333.
172. Polidori D, Sanghvi A, Seeley RJ, Hall KD: How Strongly Does Appetite Counter Weight Loss? Quantification of the Feedback Control of Human Energy Intake. *Obesity* 2016, 24:2289-2295.
173. Löffler MC, Betz MJ, Blondin DP, Augustin R, Sharma AK, Tseng YH, Scheele C, Zimdahl H, Mark M, Hennige AM, et al.: Challenges in tackling energy expenditure as obesity therapy: From preclinical models to clinical application. *Mol Metab* 2021, 51:101237.
174. DONNELLY JE, BLAIR SN, JAKICIC JM, MANORE MM, RANKIN JW, SMITH BK: Appropriate Physical Activity Intervention Strategies for Weight Loss and Prevention of Weight Regain for Adults. *Medicine & Science in Sports & Exercise* 2009, 41:459-471.
175. Pontzer H, Durazo-Arvizu R, Dugas Lara R, Plange-Rhule J, Bovet P, Forrester Terrence E, Lambert Estelle V, Cooper Richard S, Schoeller Dale A, Luke A: Constrained Total Energy Expenditure and Metabolic Adaptation to Physical Activity in Adult Humans. *Current Biology* 2016, 26:410-417.

176. Foster-Schubert KE, Alfano CM, Duggan CR, Xiao L, Campbell KL, Kong A, Bain CE, Wang C-Y, Blackburn GL, McTiernan A: Effect of Diet and Exercise, Alone or Combined, on Weight and Body Composition in Overweight-to-Obese Postmenopausal Women. *Obesity* 2012, 20:1628-1638.
177. Hall M, Castelein B, Wittoek R, Calders P, Van Ginckel A: Diet-induced weight loss alone or combined with exercise in overweight or obese people with knee osteoarthritis: A systematic review and meta-analysis. *Semin Arthritis Rheum* 2019, 48:765-777.
178. Singh N, Stewart RAH, Benatar JR: Intensity and duration of lifestyle interventions for long-term weight loss and association with mortality: a meta-analysis of randomised trials. *BMJ open* 2019, 9:e029966-e029966.
179. Look ARG: Eight-year weight losses with an intensive lifestyle intervention: the look AHEAD study. *Obesity (Silver Spring, Md.)* 2014, 22:5-13.
180. Kuczmarski RJ, Flegal KM: Criteria for definition of overweight in transition: background and recommendations for the United States. *Am J Clin Nutr* 2000, 72:1074-1081.
181. Wolfe BM, Kvach E, Eckel RH: Treatment of Obesity: Weight Loss and Bariatric Surgery. *Circulation research* 2016, 118:1844-1855.
182. Yermilov I, McGory ML, Shekelle PW, Ko CY, Maggard MA: Appropriateness criteria for bariatric surgery: beyond the NIH guidelines. *Obesity (Silver Spring)* 2009, 17:1521-1527.
183. Lawley J: Weighing up the evidence: a meta-analysis and therapeutic audit of the treatments for obesity. *Bioscience Horizons: The International Journal of Student Research* 2014, 7.
184. O'Brien PE, Hindle A, Brennan L, Skinner S, Burton P, Smith A, Crosthwaite G, Brown W: Long-Term Outcomes After Bariatric Surgery: a Systematic Review and Meta-analysis of Weight Loss at 10 or More Years for All Bariatric Procedures and a Single-Centre Review of 20-Year Outcomes After Adjustable Gastric Banding. *Obes Surg* 2019, 29:3-14.
185. Franz MJ, VanWormer JJ, Crain AL, Boucher JL, Histon T, Caplan W, Bowman JD, Pronk NP: Weight-loss outcomes: a systematic review and meta-analysis of weight-loss clinical trials with a minimum 1-year follow-up. *J Am Diet Assoc* 2007, 107:1755-1767.
186. Khera R, Murad MH, Chandar AK, Dulai PS, Wang Z, Prokop LJ, Loomba R, Camilleri M, Singh S: Association of Pharmacological Treatments for Obesity With Weight Loss and Adverse Events: A Systematic Review and Meta-analysis. *JAMA* 2016, 315:2424-2434.
187. Vosoughi K, Atieh J, Khanna L, Khoshbin K, Prokop LJ, Davitkov P, Murad MH, Camilleri M: Association of glucagon-like peptide 1 analogs and agonists administered for obesity with weight loss and adverse events: a systematic review and network meta-analysis. *EClinicalMedicine* 2021, 42.
188. Gloy VL, Briel M, Bhatt DL, Kashyap SR, Schauer PR, Mingrone G, Bucher HC, Nordmann AJ: Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomised controlled trials. *BMJ : British Medical Journal* 2013, 347:f5934.
189. Courcoulas AP, Christian NJ, Belle SH, Berk PD, Flum DR, Garcia L, Horlick M, Kalarchian MA, King WC, Mitchell JE, et al.: Weight change and health outcomes at 3 years after bariatric surgery among individuals with severe obesity. *Jama* 2013, 310:2416-2425.
190. Arterburn DE, Telem DA, Kushner RF, Courcoulas AP: Benefits and Risks of Bariatric Surgery in Adults: A Review. *Jama* 2020, 324:879-887.
191. Jakobsen GS, Småstuen MC, Sandbu R, Nordstrand N, Hofsø D, Lindberg M, Hertel JK, Hjelmesæth J: Association of Bariatric Surgery vs Medical Obesity Treatment With Long-term Medical Complications and Obesity-Related Comorbidities. *Jama* 2018, 319:291-301.
192. Ha J, Kwon Y, Kwon JW, Kim D, Park SH, Hwang J, Lee CM, Park S: Micronutrient status in bariatric surgery patients receiving postoperative supplementation per guidelines: Insights from a systematic review and meta-analysis of longitudinal studies. *Obes Rev* 2021, 22:e13249.
193. Avenell A, Robertson C, Skea Z, Jacobsen E, Boyers D, Cooper D, Aceves-Martins M, Retat L, Fraser C, Aveyard P, et al.: Bariatric surgery, lifestyle interventions and orlistat for severe

obesity: the REBALANCE mixed-methods systematic review and economic evaluation. *Health Technol Assess* 2018, 22:1-246.
194. Noparatayaporn P, Thavorncharoensap M, Chaikledkaew U, Bagepally BS, Thakkinstian A: Incremental Net Monetary Benefit of Bariatric Surgery: Systematic Review and Meta-Analysis of Cost-Effectiveness Evidences. *Obes Surg* 2021, 31:3279-3290.
195. Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A, Marczak L, Mokdad AH, Moradi-Lakeh M, Naghavi M, et al.: Health Effects of Overweight and Obesity in 195 Countries over 25 Years. *N Engl J Med* 2017, 377:13-27.
196. Franz MJ, Boucher JL, Rutten-Ramos S, VanWormer JJ: Lifestyle weight-loss intervention outcomes in overweight and obese adults with type 2 diabetes: a systematic review and meta-analysis of randomized clinical trials. *J Acad Nutr Diet* 2015, 115:1447-1463.
197. Hamman RF, Wing RR, Edelstein SL, Lachin JM, Bray GA, Delahanty L, Hoskin M, Kriska AM, Mayer-Davis EJ, Pi-Sunyer X, et al.: Effect of weight loss with lifestyle intervention on risk of diabetes. *Diabetes care* 2006, 29:2102-2107.
198. Gummesson A, Nyman E, Knutsson M, Karpefors M: Effect of weight reduction on glycated haemoglobin in weight loss trials in patients with type 2 diabetes. *Diabetes Obes Metab* 2017, 19:1295-1305.
199. Haase CL, Lopes S, Olsen AH, Satylganova A, Schnecke V, McEwan P: Weight loss and risk reduction of obesity-related outcomes in 0.5 million people: evidence from a UK primary care database. *International Journal of Obesity* 2021, 45:1249-1258.
200. Zomer E, Gurusamy K, Leach R, Trimmer C, Lobstein T, Morris S, James WPT, Finer N: Interventions that cause weight loss and the impact on cardiovascular risk factors: a systematic review and meta-analysis. *Obesity Reviews* 2016, 17:1001-1011.
201. Bell K, Parasuraman S, Shah M, Raju A, Graham J, Lamerato L, D'Souza A: Economic implications of weight change in patients with type 2 diabetes mellitus. *Am J Manag Care* 2014, 20:e320-329.
202. Fridman M, Lucas ME, Paprocki Y, Dang-Tan T, Iyer NN: Impact of Weight Change in Adults with Type 2 Diabetes Mellitus: A Literature Review and Critical Analysis. *Clinicoecon Outcomes Res* 2020, 12:555-566.
203. Amundsen MO, Engdahl B, Berg C, Nordeng H: Cardiovascular co-medication among users of antiobesity drugs: a population-based study. *Pharm World Sci* 2010, 32:752-758.
204. Counterweight Project T: The impact of obesity on drug prescribing in primary care. *The British journal of general practice : the journal of the Royal College of General Practitioners* 2005, 55:743-749.
205. Lau DC, Teoh H: Impact of Current and Emerging Glucose-Lowering Drugs on Body Weight in Type 2 Diabetes. *Can J Diabetes* 2015, 39 Suppl 5:S148-154.
206. Maher RL, Hanlon J, Hajjar ER: Clinical consequences of polypharmacy in elderly. *Expert Opin Drug Saf* 2014, 13:57-65.
207. Kim B-Y, Kang SM, Kang J-H, Kim KK, Kim B, Kim SJ, Kim Y-H, Kim J-H, Kim JH, Nam GE, et al.: Current Long-Term Pharmacotherapies for the Management of Obesity. *Journal of obesity & metabolic syndrome* 2020, 29:99-109.

## Figures

**Figure 1. Central and peripheral mechanisms of anti-obesity drugs.**

AGRP, agouti-related peptide; ARC, arcuate nucleus; CART, cocaine- and amphetamine-regulated transcript; DAT, dopamine active transporter; D1R, dopamine 1-class receptor; D2R, dopamine 2-class receptor; GABA, gamma-aminobutyric acid; GABAAR, γ-aminobutyric acid type A receptor; GLP-1R, glucagon-like peptide-1 receptor; MC3R, melanocortin-3 receptor; MC4R, melanocortin-4 receptor; MOPR, μ-opioid receptor; NAc, nucleus accumbens; NPY, neuropeptide Y; POMC, proopiomelanocortin; VTA, ventral tegmental area; Y1R, neuropeptide Y receptor type 1 (**Ref 72**)

**Figure 2. The efficacy of currently approved anti-obesity drugs in weight loss.**

BMOD, behaviour modification; CONQUER, Controlled-Release Phentermine plus Topiramate Combination in Overweight and Obese Adults; COR, Contrave Obesity Research; D, Diabetes; EQUATE, evaluation of phentermine and topiramate versus phentermine/topiramate extended-release in obese adults; EQUIP, controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial; LIGHT, long-term intervention with group-wise dietary consulting supported by meal replacements maintain weight loss in patients with concomitant obesity and knee osteoarthritis; O, obesity; SCALE, Satiety and Clinical Adiposity—Liraglutide Evidence in Nondiabetic and Diabetic Individuals; SEQUEL, 2-year Sustained Weight Loss and Metabolic Benefits with Controlled-release Phentermine/Topiramate in Obese and Overweight Adults; STEP, Semaglutide Treatment Effect for People with obesity; XENDOS, Xenical in the Prevention of Diabetes in Obese Subjects.

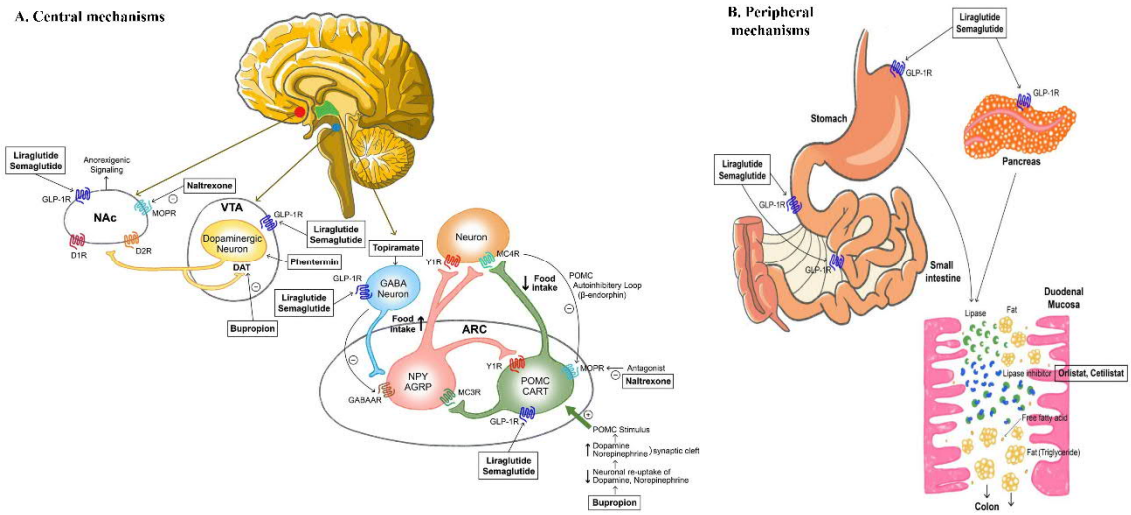
**Figure 3. The efficacy of life-style modifications, pharmacological and surgical interventions in weight loss extracted from meta-analyses**

**Footnote:** As a note, the placebo-subtracted weight loss obtained from the RCTs of pharmacological agents should be viewed in the background that the diet and exercises were

used in the placebo arm as the comparator. For the non-pharmacological RCTs, the placebo arm included the education and support only.

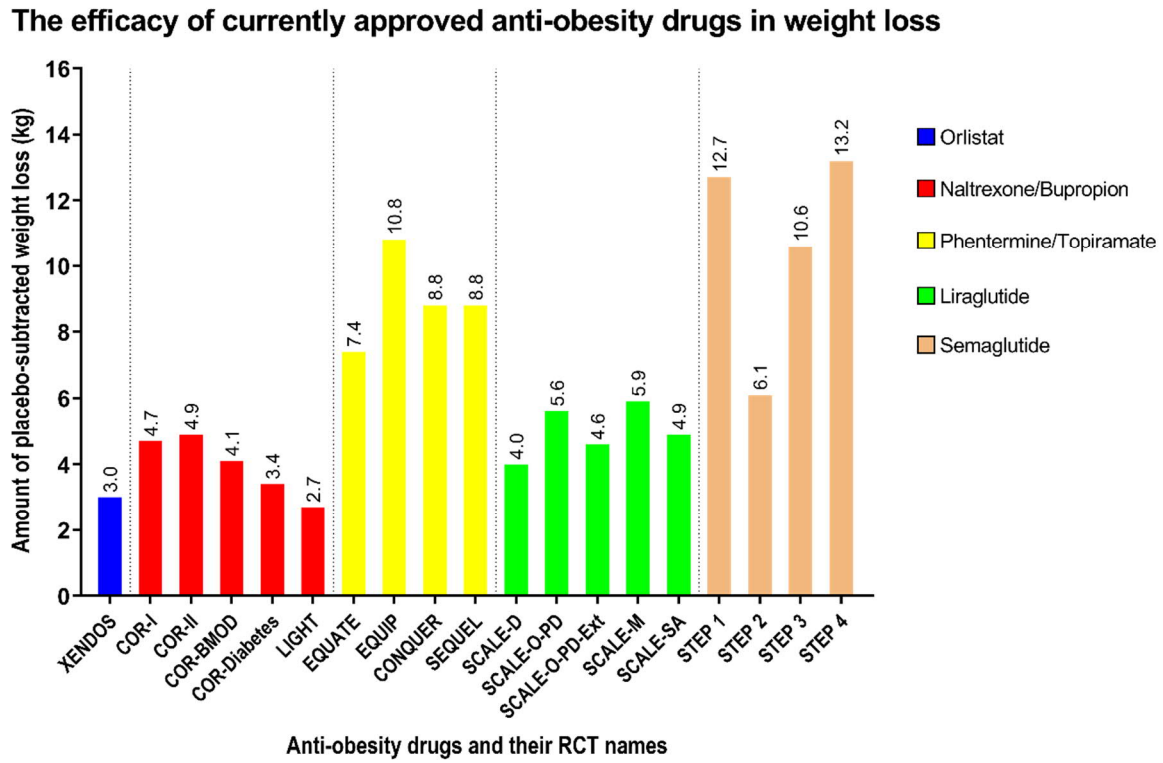
**Table 1. Mechanisms, dosage, adverse reactions, and contraindications of FDA-approved long-term anti-obesity medications.**

| Generic name | Year approved | Mechanisms of action | Dosage | Common adverse reactions | Contraindication |
|---|---|---|---|---|---|
| Orlistat | 1999 | Gastrointestinal and pancreatic lipase inhibitor; decrease lipid absorption | 60 or 120 mg TID during or within 1 hour of a fat-containing meal | Oily stools, oily spotting, faecal urgency, faecal incontinence, hyperdefecation, flatus with discharge, deficiency in vitamins A, D, E, and K | Pregnancy, chronic malabsorption syndrome, cholestasis and oxalate nephrolithiasis |
| Phentermine/ topiramate extended-release | 2012 | Sympathomimetic and carbonic anhydrase inhibitor | 3.75/23 mg QD for 14 days and then 7.5/46 mg QD; If <3% weight loss is achieved at 12 weeks, increase to 11.25/69 mg QD for 14 days, followed by 15/92 mg QD; discontinue gradually if <5% weight loss is achieved at 12 weeks with the highest dose | Paraesthesia, dizziness, dysgeusia, insomnia, constipation, dry mouth | Pregnancy, uncontrolled HTN, CVD, CKD, Glaucoma, hyperthyroidism, concurrent use with monoamine oxidase inhibitors within 14 days |
| Naltrexone/ bupropion sustained-release | 2014 | Opioid receptor antagonist/dopamine agonist and NE reuptake inhibitor; increase satiety, suppress appetite | 8/90 mg for 7 days; BID for 7 days; 2 tablets in the morning and 1 tablet in the evening for 7 days; and 2 tablets BID thereafter | Nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, diarrhea | Pregnancy, uncontrolled hypertension, seizures, eating disorders, chronic opioid use, concurrent use with monoamine oxidase inhibitors within 14 days |
| Liraglutide 3.0 mg | 2014 | Glucagon-like peptide-1 agonist; slow gastric emptying, increase satiety, decreases food reward | 0.6 mg subcutaneous injection QD, increase by 0.6 mg weekly to a daily target dose of 3 mg | Nausea, diarrhea, constipation, vomiting, dyspepsia | Pregnancy, personal or family history of medullary thyroid carcinoma or type 2 MEN |
| Semaglutide 2.4 mg | 2021 | Same as liraglutide | 0.25 mg subcutaneous injection once per week, escalate the dose every 4 weeks for 16 weeks, until the full maintenance dose of 2.4 mg is reached | Nausea, diarrhea, vomiting, constipation, abdominal pain, headache, dyspepsia, dizziness, abdominal distention, eructation, hypoglycaemia in patients with type 2 diabetes | Same as liraglutide |


A. Central mechanisms
Liraglutide Semaglutide
Anorexigenic Signaling
GLP-1R
Naltrexone
NAc
MOPR
D1R
D2R
VTA
Dopaminergic Neuron
DAT
Phentermin
Topiramate
Bupropion
GABA Neuron
GABAAR
Neuron
MC4R
Y1R
Food intake
POMC Autoinhibitery Loop (β-endorphin)
ARC
NPY AGRP
MC3R
POMC CART
Antagonist
Naltrexone
POMC Stimulus
Dopamine Norepinephrine synaptic cleft
Neuronal re-uptake of Dopamine, Norepinephrine
B. Peripheral mechanisms
Stomach
Pancreas
Small intestine
Duodenal Mucosa
Lipase
Fat
Lipase inhibitor
Orlistat, Cetilistat
Free fatty acid
Fat (Triglyceride)
Colon

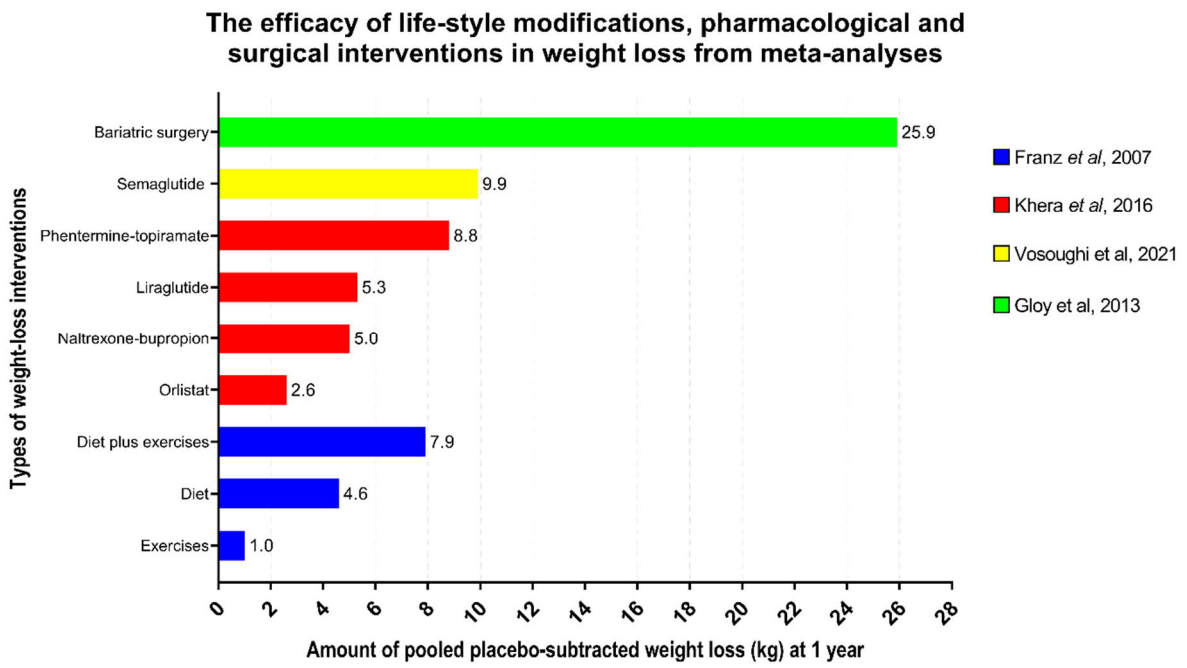
1249

1250


The efficacy of currently approved anti-obesity drugs in weight loss
Amount of placebo-subtracted weight loss (kg)
16
14
12
10
8
6
4
2
0
3.0
4.7
4.9
4.1
3.4
2.7
7.4
10.8
8.8
8.8
4.0
5.6
4.6
5.9
4.9
12.7
6.1
10.6
13.2
XENDOS
COR-I
COR-II
COR-BMOD
COR-Diabetes
LIGHT
EQUATE
EQUIP
CONQUER
SEQUEL
SCALE-D
SCALE-O-PD
SCALE-O-PD-Ext
SCALE-M
SCALE-SA
STEP 1
STEP 2
STEP 3
STEP 4
Anti-obesity drugs and their RCT names
Orlistat
Naltrexone/Bupropion
Phentermine/Topiramate
Liraglutide
Semaglutide

1251

1252


The efficacy of life-style modifications, pharmacological and surgical interventions in weight loss from meta-analyses
Types of weight-loss interventions
Bariatric surgery
Semaglutide
Phentermine-topiramate
Liraglutide
Naltrexone-bupropion
Orlistat
Diet plus exercises
Diet
Exercises
25.9
9.9
8.8
5.3
5.0
2.6
7.9
4.6
1.0
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
Amount of pooled placebo-subtracted weight loss (kg) at 1 year
Franz et al, 2007
Khera et al, 2016
Vosoughi et al, 2021
Gloy et al, 2013

1253