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Combination Pharmaceutical Therapies for Obesity

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Obesity has emerged as a global epidemic. It is estimated that about a billion people worldwide are overweight or obese and at least 300 million are obese. Obesity increases the risk for type 2 diabetes, cardiovascular disease, hypertension, and many other major illnesses, with resultant decrease in longevity. For severely obese patients, bariatric surgery has been demonstrated to achieve significant long-term weight loss as well as decrease overall mortality (1). Whereas intensive lifestyle intervention has been demonstrated to improve glycaemic control as well as cardiovascular disease risk factors in overweight and obese patients with type 2 diabetes (2), such interventions are not available to most obese individuals due to factors such as limited accessibility and affordability. Somewhat less intensive diet and lifestyle therapies achieve <5 kg weight loss after 2–4 years and about 1 in 5 are able to maintain meaningful weight loss for 3–5 years (3–4).

In the United States, primary care physicians (PCPs) are the primary providers of treatment of obesity, accounting for 76%–84% of the patient visits (5). It is important to recognise this because there is a chasm between how clinical research is conducted and how clinical care is delivered in real life. While research studies that combine dietary, exercise and behavioural therapy interventions show good results, PCPs lack the training, reimbursement incentives and time, and as such have very little enthusiasm for administering such interventions.

Pharmacotherapy targeted for weight reduction is indicated for patients with a body mass index (BMI) of ≥ 30 kg/m² and also for those with a BMI of at least 27 kg/m² in the presence of obesity-related diseases or risk factors. Pharmacological interventions have a role in obesity management because many obese patients are unsuccessful in their attempts to lose weight with diets, exercise and lifestyle modifications. Further, pharmacological interventions could enhance adherence to a weight loss programme (6).

Of the currently available antiobesity medications, sibutramine and orlistat are the only ones approved for long-term use in the US and Europe. These two drugs have modest efficacy with a weight loss of 4.2kg for sibutramine and 2.9kg for orlistat after one-year treatment, in excess of the weight loss achieved by diet and lifestyle management (7). Such modest results are disappointing for many obese individuals, whose expectations are often in excess of 25% weight loss at one year (8). Thus, it is not surprising that less than 10% of obese patients prescribed sibutramine and orlistat persist with these treatments at one year, and about 2%

after two years (9). There was much enthusiasm for the potential weight loss and cardiovascular benefits of cannabinoid receptor 1 (CB1) antagonists when the first drug in this class, rimonabant was approved in Europe in 2006. Yet, weight loss efficacy of rimonabant was modest and there was a significantly higher incidence of psychiatric adverse events in phase III trials (10,11), which led to non-approval by the US Food and Drug Administration (FDA). In October 2008, consequent to ongoing review of safety by the European Medicine Agency (EMA), rimonabant was withdrawn from the European Union (EU), because of concern that the margin of benefits over risks for the drug is narrow (12). Merck, Pfizer and other pharmaceutical companies have also announced suspension of further development of their CB-1 antagonist candidates.

In the past few years, considerable knowledge has been gained regarding regulation of food intake and energy homeostasis to assist identification and development of potential antiobesity drugs. Body weight regulation is a highly complex process that involves many central nervous system (CNS) pathways that are integrated into a network of neurotransmitters, neuropeptides, gut hormones and adiposity signals (13). Some of the notable peptides and hormones proposed to have catabolic and/or anorectic effects include corticotropin-releasing hormone (CRH), thyrotropin-releasing hormone (TRH), α -melanocyte-stimulating hormone (α -MSH), serotonin, cocaine- and amphetamine-regulated transcript (CART), somatostatin, bombesin, cholecystokinin, neurotensin, calcitonin-gene-related peptide, peptide YY₃₋₃₆ (PYY₃₋₃₆) and glucagon-like peptide-1 (GLP-1). Purported anabolic signals include neuropeptide Y (NPY), melanin concentrating hormone (MCH), agouti-related protein (AgRP), growth hormone-releasing hormone (GRH), norepinephrine, orexins A and B (also known as hypocretins 1 and 2), endocannabinoids, dynorphin, β -endorphin, galanin and ghrelin (14). Drugs that enhance the effects of endogenous catabolic signals via structural similarity (analogues) or receptor agonism could potentially be useful tools to promote weight loss. Similarly, agents that antagonise endogenous anabolic signals via receptor blockade or other pathways might be therapeutic tools in managing obesity. However, agents that demonstrated potential therapeutic signals when tested using animal models, have often failed when tested in large randomised clinical trials (RCTs) in humans. For example, although animal studies as well as a short-term phase II study in humans suggested anorectic and weight loss efficacy, MK-0557, a potent and selective antagonist of Y5 receptor that mediates the anabolic effects of NPY, failed to demonstrate clinically meaningful efficacy in a larger phase III trial (15). Disappointing results have also been observed with other agents targeting novel specific and discrete sites in the circuits and networks that regulate energy homeostasis, suggesting that endogenous compensatory mechanisms might overcome pharmaceutical manipulations.

Combination therapies are commonly used in the treatment of hypertension, diabetes, cancer and many other major illnesses. Combination therapies could have additive effects, thereby enhancing clinical efficacy. Agents combined with scientific rationale could have synergistic effects and/or promote endogenous synergies. Combination therapies that target different sites and/or different pathways might be more successful in overcoming the natural compensatory mechanisms involved in energy homeostasis. Further, combination therapies facilitate administration of lower doses of the individual components, thereby potentially

mitigating the burden of adverse events. Lastly, carefully chosen agents with dissimilar side effect profiles, when combined, could improve tolerability.

Combination drug therapies have been tested for treatment of obesity. The combination of ephedrine/caffeine (20mg/200mg) demonstrated more weight loss than ephedrine (20mg), caffeine (200mg) or placebo, all given three times a day over 24 weeks in obese subjects who also received dietary intervention (16). Ephedrine in the form of dietary supplements was banned in the US in April 2004 due to concerns of the FDA regarding hypothesized adverse effects including myocardial infarction and stroke, though a recent report casts doubt on the extent to which such concerns were well-founded (17).

About 25 years ago, Weintraub et al compared a combination of fenfluramine (30mg) and phentermine (15mg) to fenfluramine (60mg) alone, phentermine (30mg) alone or placebo for 24 weeks in conjunction with dietary intervention (18). Weight loss with lower-dose combination (8.4kg) was about the same as with higher doses of phentermine (10.0kg) and fenfluramine (7.5kg), with all active drugs superior to placebo (4.4kg). In a subsequent RCT, after 6 weeks of lifestyle intervention, 121 obese subjects were treated with the combination of fenfluramine 60 mg and phentermine 15 mg or placebo for an additional 28 weeks. Subjects receiving the combination drug therapy lost 14.2kg whereas those treated with placebo lost 4.6kg (6). In 1997, fenfluramine and dexfenfluramine were withdrawn from markets due to an association with valvular heart disease.

At least, four different drug combinations are currently in clinical investigations for weight reduction in obese non-diabetic and diabetic patients.

Bupropion plus naltrexone

Bupropion, marketed as an antidepressant has been shown to promote modest weight loss in obese patients in three RCTs (19). Naltrexone, an opioid receptor antagonist, marketed to treat alcoholism, has anorectic effect in animals, but failed to demonstrate meaningful weight loss in humans. In a 16-week proof-of-concept trial, bupropion/naltrexone (300mg/50mg) combination was shown to cause more weight loss in obese subjects than bupropion (300mg), naltrexone (50mg), or placebo (20). Because nausea was a frequent adverse effect in subjects receiving naltrexone or the combination, lower doses of naltrexone were tested in a subsequent 24-week, phase IIb trial. In this randomised trial, all three doses of naltrexone (48mg, 32mg, 16mg) combined with bupropion resulted in significant weight loss (4.3%, 5.4%, 5.4%, respectively) with better tolerability for the lower doses (21). Four phase III trials are underway investigating this combination for weight loss in obese patients with or without type 2 diabetes. In three trials, the investigational drug is a fixed dose combination of bupropion 360mg/naltrexone 32mg while one trial also compares this combination to bupropion 360mg/naltrexone 16mg. The most common side effect, nausea, is primarily related to naltrexone.

Bupropion plus zonisamide

Zonisamide, marketed as an antiepileptic, has been shown to promote weight loss in obese subjects (22). Further, in a small study, a combination of zonisamide and bupropion led to

more weight loss than zonisamide alone (23). In a 24-week RCT (24), bupropion/zonisamide (300mg/400mg) achieved more weight loss than zonisamide (400mg), bupropion (300mg), or placebo (−9.2%, −6.6%, −3.6%, −0.4%, respectively). In a subsequent 24-week RCT comparing various doses of bupropion and zonisamide in the combination, all six different ratio combinations achieved significantly greater weight loss than placebo, with zonisamide 360mg/bupropion 360mg having the largest effect (21). There was no clear demonstration of differences in tolerability. Another phase IIb RCT is underway. Adverse effects include anxiety, dizziness, insomnia and fatigue.

Topiramate plus phentermine

Phentermine is marketed for short-term treatment of obesity. Topiramate, a marketed antiepileptic drug, has been shown to promote weight loss in obese patients in numerous studies with a high incidence of neuropsychiatric adverse effects. Topiramate/phentermine (100mg/15mg) has been compared to topiramate (100mg), phentermine (15mg) or placebo in a 24-week RCT involving 200 obese subjects (25). The combination treatment led to weight loss of 11.4kg, which was significantly greater than weight loss achieved with topiramate (6.6kg), phentermine (5.3kg), or placebo (2.2kg). In a subsequent RCT with 7 treatment arms, 756 obese subjects were randomly assigned to placebo, or higher or lower doses of phentermine (15mg, 7.5mg), topiramate (92mg, 46mg), or the combination (15mg/92mg, 7.5mg/46mg) for 28 weeks (26). Higher-dose combination therapy led to 9.2% weight loss compared with 6.4% for higher-dose topiramate, 6.1% for higher-dose phentermine, and 1.7% for placebo. Lower-dose combination therapy was also effective with 8.5% weight loss relative to lower-dose topiramate (5.1%), phentermine (5.5%), and placebo (1.7%). Adverse effects (paresthesia, dry mouth, constipation) were somewhat less frequent with the lower-dose combination. Two one-year phase III trials are underway.

Pramlintide plus leptin

Leptin is an adipocyte-derived hormone that serves as a long-term signal of adiposity and energy intake. Recombinant leptin treatment causes modest weight loss in humans. Pancreatic hormone, amylin, is a short-term satiety signal. Pramlintide, an amylin analogue, marketed for treatment of diabetes, causes mild to modest weight loss. In a 24-week proof-of-concept study (27), 177 overweight or obese subjects were first treated with pramlintide and 40% energy restricted diet. After 21% subjects were withdrawn (9% to due to insufficient weight loss), the remaining subjects were randomised to pramlintide 360mg, leptin 5mg, or the combination for 20 weeks. Study drugs were given twice daily as subcutaneous injections. Weight change during the 20-week randomised period was −9.9kg for the combination, −7.2kg for pramlintide and −7.2kg for leptin. There was no placebo comparison. Adverse effects include nausea and injection site irritation.

Regulatory issues

For weight management drugs used in combination, FDA has stated as follows in its draft guidance document (28): “We recommend that the efficacy and safety of fixed-dose combinations be compared with the individual product components of the combination and placebo in phase 2 trials of sufficient duration to capture the maximal or near-maximal

weight-management effects of the products. We have not defined a minimum difference in weight loss between a fixed-dose combination and its individual component products that should be achieved for the combination to be considered more efficacious than either of its components when used alone. However, a fixed-dose combination that is associated with at least twice the weight loss observed with that of each of the individual components will be viewed more favorably than combinations that do not achieve this degree of relative weight loss. Once a fixed-dose combination has been deemed more effective than its individual components, the combination can then be examined versus placebo in phase 3 trials. This approach may preclude the need to include treatment groups for the individual components of the fixed-dose combination product in late-stage preapproval trials.”

Allison and Gadde (29) have commented that the suggestion asking for positive synergy might be an excessively high demand. “If *drug A* produces a weight loss of δ_A and *drug B* produces a weight loss of δ_B , this suggestion would imply that the combination of *drugs A and B*, should produce a weight loss of $2 \cdot \max(\delta_A, \delta_B)$. In contrast, even if the drugs were purely additive, the combination would only produce an effect of $(\delta_A + \delta_B)$. A combination product that fails to demonstrate a positive synergy might still offer greater efficacy than either drug alone and might also be superior to individual components in other aspects such as improved tolerability; we suggest that this could be a consideration for approval.” FDA has not issued the final version of the guidance document at the time of this writing.

Conclusions

Data available at the time of writing this paper suggest that drug combinations in development discussed in this article have achieved significantly greater weight loss than individual components and far greater weight loss than placebo. Data from phase III trials of longer duration and involving several thousand subjects will give us critical information regarding safety and tolerability. In light of the safety issues that surfaced with the phen-fen combination in the past, demonstration of safety is paramount.

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