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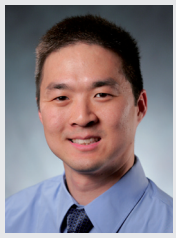

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"Given that the WHO estimates that there are currently over 300 million obese adults worldwide, the need for additional pharmacologic options remains unfulfilled."

In October 2008, two promising obesity treatments were essentially eliminated from future clinical application. Merck & Co., Inc. announced that the clinical development of taranabant was halted due to an unfavorable safety profile [101]. Approximately 3 weeks later, the Committee for Medicinal Products for Human Use (CHMP) of the EMEA concluded that the benefits of rimonabant (Acomplia®) no longer outweigh its risks, and recommended the suspension of the marketing authorization of Acomplia [102]. Thus, orlistat and sibutramine are the only remaining medications approved for the long-term treatment of obesity. Given that the WHO estimates that there are currently over 300 million obese adults worldwide [103], the need for additional pharmacologic options remains unfulfilled. What safety, efficacy and ethical issues need to be addressed to order to improve such an unsatisfactory situation?

Safety & efficacy

The pharmacologic treatment of obesity has resulted historically in the questionable use of various medications, with often significant adverse effects. Dinitrophenol was used in the 1930s to increase metabolic rate; overdoses lead to fatal hyperthermia. 'Rainbow pills', popular from the 1940s to the 1960s, were composed of amphetamines, thyroid hormone, digitalis, and diuretics. The anorectic stimulant aminorex was introduced in Europe in 1965, but soon withdrawn due to reports of resultant pulmonary hypertension. Excess thyroid hormone supplementation, widely used until the 1980s, often resulted in iatrogenic hyperthyroidism. The serotonergic agent fenfluramine was removed from the market in 1997 after being linked to valvular heart disease. Phenylpropanolamine, a sympathomimetic compound subsequently associated with hemorrhagic stroke in young women, was taken off the market in 2000.

"...adverse effects should not be unexpected when a pharmacologic treatment ... targets a specific pathway."

It is also increasingly apparent that the physiological mechanisms regulating caloric intake and bodyweight are highly integrated, complex and redundant [1]. Short-acting signals in response to meals include gut hormones (e.g., cholecystokinin, ghrelin, glucagon-like peptide 1 and peptide YY_{3-36}) and signals from vagal afferent neurons within the GI tract. Long-acting signals regarding adipose tissue mass are provided by leptin and insulin. Hypothalamic and hindbrain integration of such neural and humoral signals results in precise regulation of appetite and energy expenditure.

Within the context of such interrelated systems, adverse effects should not be unexpected when a pharmacologic treatment of obesity targets a specific pathway. For example, cannabinoid (CB) type 1 receptors are located in both central structures (e.g., the hypothalamus) and peripheral organs (e.g., adipose tissue). CB1 receptor antagonists, such as the aforementioned rimonabant and taranabant, were found to regulate food

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intake and adipose tissue metabolism, resulting in weight loss and favorable blood lipid changes. Unfortunately, CB1 receptor inhibition also increased the incidence of psychiatric adverse effects, such as anxiety and depression [2]. Other centrally acting small-molecule anorectics in development will undoubtedly face similar safety concerns; as detailed below, the US FDA addresses such issues in its most recent Guidance for Industry statement.

> "While these recommendations will probably result in safer weight-management products, fewer medications will receive US FDA approval in the near future."

In February 2007, the FDA updated guidance to industry regarding the development of products for weight management. Key efficacy and safety recommendations were as follows [104]:

"…weight loss and weight maintenance should be demonstrated over the course of at least 1 year before a product can be considered effective for weight management."

"The difference in mean weight loss between the active-product and placebo-treated groups is at least 5% and the difference is statistically significant," or "The proportion of subjects who lose greater than or equal to 5% of baseline body weight in the active-product group is at least 35%, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant."

"A reasonable estimation of the safety of a weight-management product upon which to base approval can be made when a total of approximately 3000 subjects are randomized to active doses of the product and no fewer than 1500 subjects are randomized to placebo for 1 year of treatment."

"In addition to routine safety monitoring, it may be appropriate for the development programs of some weight-management products to have specialized safety assessments" (e.g., neuropsychiatric function and abuse liability studies for centrally acting products)

While these recommendations will probably result in safer weight-management products, fewer medications will receive FDA approval in the near future. Enrolling over 4500 research individuals in clinical trials requires significant expense and planning. Retention of such individuals (particularly those in the placebo group) for at least 1 year will be a difficult challenge for the primary investigators and study sponsors, as weight-management studies often have high dropout rates. Centrally acting compounds will also have to meet a higher standards of safety monitoring; in contrast, peripheral peptide hormones (e.g., glucagon-like peptide 1) may carry less risk for significant adverse effects.

Ethical issues

Assuming that future obesity treatments meet reasonable levels of efficacy and safety, societal consideration must then be given to the equitable distribution of such pharmacologic therapies. Given the worldwide obesity epidemic, which patient populations would receive the most benefit from the finite treatments available?

For additional guidance, one could look at the risk-assessment tools used in the evaluation of cardiovascular disease and osteoporosis. The American Framingham risk score incorporates age, gender, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, blood pressure, diabetes and smoking to derive an estimated risk of developing coronary heart disease within 10 years (in Europe, the SCORE model serves a similar purpose) [3]. In 2008, a WHO task force introduced the Fracture Risk Assessment Tool (FRAX®), which estimates the 10-year probability of fracture based on clinical risk factors and the bone mineral density at the femoral neck [105]. Both the Framingham Risk Score and FRAX have subsequently been used to determine intervention thresholds for statin and bisphosphonate therapy, respectively.

> "Assuming that future obesity treatments meet reasonable levels of efficacy and safety, societal consideration must then be given to the equitable distribution of such pharmacologic therapies."

Clinical tools, such as BMI calculation and the diagnosis of metabolic syndrome, do identify those at risk for cardiovascular disease and Type 2 diabetes, but may lack precise long-term predictive value. While a new obesity risk-assessment tool might include components of metabolic syndrome (e.g., waist circumference and blood lipid values), it should aim to provide 10-year probabilities of developing specific obesity-related end points. If such a risk model could be developed and was comparable in accuracy to Framingham and FRAX, then cost-effective and country-specific criteria for the pharmacologic treatment of obesity could be established.

Conclusion

The development of safe and effective obesity treatments remains both vital and difficult. Since healthcare resources are inherently scarce, additional obesity risk-assessment tools will be necessary to develop effective treatment guidelines.

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The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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