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QHG-IIAD - Quest for the Holy Grail: Inventing Ideal Anti-obesity Drug

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Abstract

THE FACT: Obesity is a chronic health-threatening disease and the potential of pharmacotherapy for obesity is enormous. Though incidence of obesity is high, only a small percentage of patients are treated with pharmacotherapy. The limiting factors are, firstly, the lack of long-term data on effect of medications on obesity-related morbidity and mortality; secondly, none of the currently available anti-obesity compounds approach the criteria of an ideal or nearly-ideal anti-obesity drug and need to be prescribed with caution and under medical supervision; and thirdly, their efficacy in reducing body weight (BW) is mild to modest. The desired loss of BW ~1 to 1.5 Kg per week is translated often into just ~0.25 kg per week, and a partial regain of BW occurs when the drugs are used for a long period. Fourthly, there are associated adverse effects ranging from mild and transient to serious and potentially life-threatening cardiovascular and psychiatric complications, which have led to withdrawal of many anti-obesity drugs in recent years.

THE PAST: The history of anti-obesity drugs is littered with approvals, pitfalls and withdrawals. The early drugs had severe side effects and serious consequences when used in practice. Thus, dinitrophenol was introduced in 1933 and withdrawn by 1938; the weight-losing regimens during 1930s included stimulants, such as amphetamines and thyroid hormone, diuretics, digitalis, laxatives, and barbiturate to suppress the side effects of the stimulants, were withdrawn by 1970s; phentermine and fenfluramine (approved by FDA in 1959 and in 1973 respectively), and their combination *Fen-phen,* developed in 1992, was withdrawn by 1997. Another drug, Ephedra was withdrawn in 2004 over concerns that it raises blood pressure and could lead to strokes and death. Rimonabant, a CB1 receptor antagonist, was withdrawn in 2008 due to psychiatric adverse effects. More recently, sibutramine, which acted by inhibiting deactivation of the neurotransmitters to decrease appetite was withdrawn in 2010 due to cardiovascular concerns. The currently available, orlistat acts by inhibiting pancreatic lipase. It has minor GI side effects but on the serious side few cases of liver damage have been reported. Other drugs in pipeline, Lorcaserin (approved by FDA in 2012) and Qsymia (a combination of phentermine and topirimate) cleared by the FDA during 2012. The latter has to undergo studies about the cardiovascular effects, and projected to be available by 2016.

THE QUEST: There is clearly a need for an efficient and safe pharmacological agent for treatment of obesity. Considering the history, inventing an ideal anti-obesity drug promising a sustained weight loss with minimal side effects may seem as difficult as tracking the Holy Grail. With the advancement of civilization, the food has evolved, by being available in abundance, calorie-rich and highly palatable. Compared to this, the neural mechanism concerning appetite is still at hunting-gathering stage as the neuropsychiatric component and the basic drive to eat and eating behavior seem to be linked to survival instinct and embedded with essential pathways in brain. Suppressing appetite or modifying absorption of fat, thus, affects other systems and has been linked to psychotic episodes, depression and suicidal thoughts, and serious effects like hypertension, valvulopathy and cardiovascular events.

THE TRENDS: Certain trends are evident clearly in the research and development of pharmacotherapy of obesity, which is poised to touch 2.6 billion $ by 2019. The advances in understanding of energy balance control have resulted in identification of new targets. A second major trend is targeting multiple mechanisms by drugs combinations. This approach widens safety margins by decreasing the effective dose, mutually balancing individual undesirable effects and offers increased efficacy.

Biography

Vinod Nikhra M.D. is Fellow of International Medical Sciences Academy and Fellow of Royal Society of Medicine. He is trained in internal medicine, endocrinology and clinical nephrology. He has authored 4 books, which include *The Anti-Obesity Guide* and *Aging slowly, Living longer*, and contributed more than 46 papers in reputed journals and has been an editor for Journal of Association for Health in Middle Aged and a reviewer for International Journal of Obesity (the Nature group) and Family Practice (the Oxford group). He is a senior consultant physician and on teaching faculty at Hindu Rao Hospital, Delhi, India. He can be found on www.vinodnikhra.com and www.nikhrafoundation.in.