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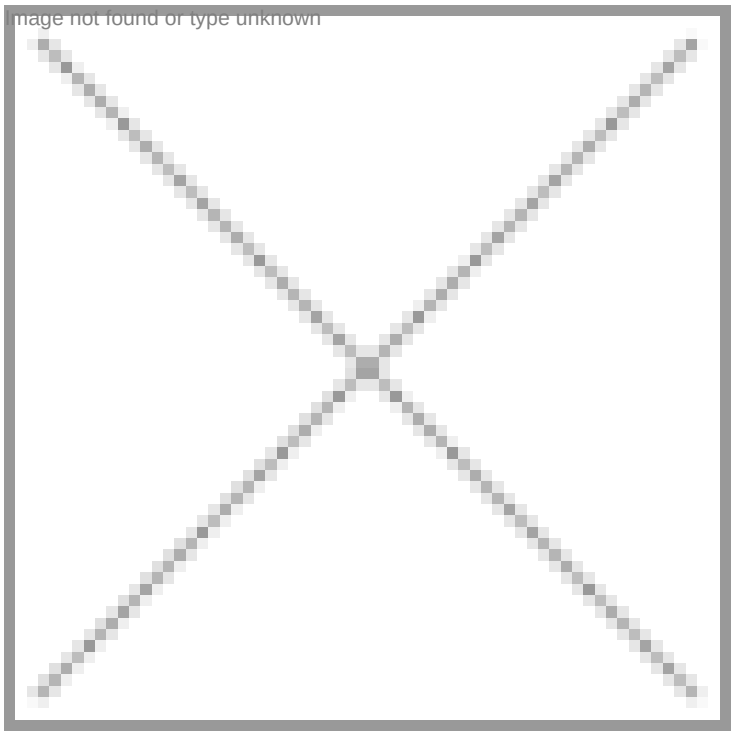

Obesity Management Converges Diverse Approaches

With exciting fields opening up, obesity management is now being looked upon as a booming market by companies.

It has been denounced as what has been rightly termed as an outbreak of an epidemic called obesity. However, scientists may term it as a losing battle but life sciences companies are cashing on to this challenge as an opportunity considering the huge populace that the “disorder” (as it is supposedly termed) embraces. And why not? The market for obesity drugs by 2012 will look lucrative with the expected populace expected to hit the 600 million mark (with 2 billion slated as overweight) thus opening up whole new vistas.

Country-wise, the US is presently the biggest market for weight loss drugs with around 68 percent of its population either overweight or obese. The US is followed by the UK and other European countries. In future, emerging economies, China, Russia, India and Brazil are also expected to become a huge market for weight loss products. With China’s obesity and overweight levels touching 665-670 million by 2015, the country will emerge as the most potential weight loss market. Yet, the million dollar question popping up is will the scientific community and the industry as a whole be able to catch up with this pace? Hopefully yes, if we have a cursory glance at the pipeline of products which are slated to come out in the market by 2015.

Evolution and major breakthrough

Breakthroughs in obesity are a recent phenomenon and this included the discovery, in 1994, of leptin, a hormone that appeared to provide negative feedback. Later studies showed that appetite regulation is an immensely complex process involving the gastrointestinal tract, many hormones, and both the central and autonomic nervous systems.

The phenomenon of obesity was observed much earlier. This was done by studying mutant obese mice that arose at random within a mouse colony at the Jackson Laboratory in 1950.These mice were massively obese and excessively voracious|.

Leptin itself was discovered in 1994 by Jeffrey M. Friedman and colleagues at the Rockefeller University through the study of such mice. To date, only leptin and insulin are known to act as an adiposity signal. Although leptin is a circulating signal that reduces appetite, in general, obese people have an unusually high circulating concentration of leptin. These people are said to be resistant to the effects of leptin, in much the same way that people with type 2 diabetes are resistant to the effects of insulin. It was also discovered that the high sustained concentrations of leptin from the enlarged adipose stores result in leptin desensitization. The pathway of leptin control in obese people might be flawed at some point so the body doesn't adequately receive the satiety feeling subsequently to eating. Early anorectics were fenfluramine and phentermine. A more recent addition is sibutramine which increases serotonin and noradrenaline levels in the central nervous system. In addition, recent reports on recombinant PYY 3-36 suggest that this agent may contribute to weight loss by suppressing appetite.

Technological upgradation today

The ideal road usually taken as a resort to tackle the issue of obesity is to pitch in for lifestyle modification through diet and exercise and the recent medical intervention being bariatric surgery (applicable as researchers confirm only for morbid obesity). Any eventual drug treatment for overweight and mild obesity is likely to involve combination therapy, i.e., the prescription of two or more drugs, in addition to lifestyle changes, in order for the patient to successfully lose the excess weight and keep it off. Today there is also a huge market for medical devices also mostly from the private sector. Moreover now there have been exciting fields opening up. Early research found that 30 percent of obese people were infected with Ad-36 virus, while only 11 percent of non-obese people were infected. New research finds that Ad-36 has a direct effect on human fat stem cells. The virus infects the fatty tissue and increases replication, differentiation, and accumulation of fat cells. Ultimately, this leads to larger fat cells. The virus also increases lipid sensitivity and decreases leptin secretion of the new fat cells.

Moreover it has been argued that obesity cannot just be a consequence of lifestyle disorders and that the existence of some kind of virus may go explain the speed with which the problem has progressed. If proven right then some people may be able to solve some of their weight problems with the application of an anti-viral, or some other treatment that attacks viruses. The past decade has seen tremendous advances in the understanding of the physiological regulation of energy balance and adiposity, and important insights into the pathogenesis of obesity. Today there is a comprehensive view of the adiposity hormone leptin, the subsequent identification of hypothalamic and other brain neuropeptide systems controlling energy balance, and the progress in understanding the molecular mechanisms by which cells can sense and respond to changes in metabolic state. Some of the most recent developments are prototypic compounds that manipulate fat metabolism, both in peripheral tissues and in the brain, to reduce body fat synthesis and storage and to increase fat oxidation, to reduce food intake, and to increase energy expenditure.

This apart, with FDA becoming all the more stringent over its guidelines, and drug manufacturers have not been lucky tokeep it in its good books. Recently the FDA has published a list of unapproved drugs which it described as "tainted" be pulled off from the market. The list includes rimonabant and sibutramine. Rimonabant was the active ingredient in Zimulti/Acomplia, the ill-fated obesity treatment that Sanofi-Aventis tried to get approved in the US. The FDA turned the application down.

Acomplia was marketed for a while in Europe but the European Medicines Authority scrapped off the drug over safety concerns.

Sibutramine is the active ingredient in Abbott Labs' Meridia, a prescription product. However in this case, the USFDA only asserted that the unapproved products that use Meridia as an ingredient be pulled off rather than the product as a whole being pulled off.

The list goes on, as obesity much like Alzheimer's has been like walking on a shaky bridge. The FDA recently also rejected Orexigen's Contrave pill because there was not enough difference between the placebo group and patients actually taking the pill. Others include Pfizer which halted its anti-fat drug, the unnamed "CP-945,598," for "regulatory" reasons, Merck in November pulled its fat pill, taranabant, from its pipeline,GlaxoSmithKline has had disappointing sales from Alli, Roche had negligible sales from Xenical, the Rx version of Alli, Wyeth abandoned fen-phen and Redux after they produced lawsuits.

Market potential

Realizing the staggering potential in this market, the pharmaceutical sector is very active in research and development forthe treatment of overweight, obesity and even morbid obesity. The main goal is to produce a drug or a combination of drugs which results in clinically significant weight loss over placebo, with as less side-effects. More companies have a drug in the pipeline for the treatment of overweight and obesity than for morbid obesity, although a few companies have set their sights on morbid obesity.

Some of the medical devices are in the development and testing stages. The world market for clinical management ofobesity is forecast to reach about $6.4 billion by 2015, on a revenue compound annual growth rate (CAGR) of 23.2 percent, and a unit CAGR of approximately 19 percent. The prices vary widely between the price for a year of pharmaceutical treatment and the price for the surgically implanted medical devices; the unit price in the table reflects the weighted average based upon the forecasted sales and prices for drugs and devices. The increase in sales is based upon the net effect of a number of factors, including, increasing attention paid by governments, public health systems, physicians and patients to the enormity of the obesity problem and to its growth rate, regulatory approvals and market launch of new, more effective drugs with relatively more acceptable adverse side effects.

Despite the repeated failures, pharmaceutical companies and research scientists are not deterred. The recent buzz about obesity equated to an inflectional virus can bring out a revolutionary change for the segment. Though in its animal study phase, if proven on humans, it could probably lead to a paradigm shift in dynamics. The analysis brought out by the Department of Nutrition and Food Science and the Center for Molecular Medicine and Genetics, Wayne State University, Detroit mentions, “Although obesity has multiple etiologies, an overlooked possibility is obesity of an infectious origin. Six pathogens are reported to cause obesity in animals. Canine distemper virus was the first virus reported to cause obesity in mice, followed by Rous-associated virus-7, an avian retrovirus, which has been shown to cause stunting, obesity and hyperlipidemia in chickens. Next, the obesity-promoting effect of Borna disease virus was demonstrated in rats. Scrape agents were reported to induce obesity in mice and hamsters. The final two reports were of SMAM-1, an avian adenovirus, and Ad-36, a human adenovirus that caused obesity in animals. Additionally, an association with human obesity is the unique feature of SMAM-1 and Ad-36. Although the exact mechanism of pathogen-induced obesity is unclear, infection attributable to certain organisms should be included in the long list of potential etiological factors for obesity. In addition, the involvement of some pathogens in etiology of obesity suggests the possibility of a similar role for additional pathogens. If proven this could be a major breakthrough and we can have vaccine products in the future,” added a well known name in the field.

Repeated failures in coming up with clinically successful drugs has again not deterred companies from walking thepreferably untrodden path. Wyeth will pay $120 million to Thiakis to obtain its anti-obesity drug candidate, TKS1225. In doing so, Wyeth has taken its first, expensive step into a disease category that many drug companies have entered.

Galapagos announced that it has entered into a multi-year global strategic alliance with Merck & Co., Inc. to developpotential new therapies in obesity and diabetes.

Galapagos will be responsible for the discovery and pre-clinical development of new small molecule candidate drugs based on novel Galapagos targets. Merck will have the exclusive option to license each candidate for clinical development and commercialization on a worldwide basis. The alliance will make use of Galapagos’ proprietary SilenceSelect target discovery platform for identification of novel targets in obesity and diabetes. After validation, targets will be selected by a joint steering committee and entered into screening and chemistry by Galapagos. Merck has the option to acquire an exclusive license to each candidate drug and upon exercise of such an option, Merck will be responsible for the development and commercialization of the candidate drug. Galapagos may execute phase I clinical studies and will have the right to further develop and commercialize certain compounds for which Merck does not exercise its exclusive option. Under the terms of the agreement, Galapagos will receive an upfront fee of EUR 1.5 million from Merck. In addition Galapagos is eligible to receive discovery, development and regulatory milestone payments that could potentially exceed EUR 170 million total for multiple products, as well as specific sales milestones and royalties upon commercialization of any products covered under the agreement.

Despite its previous failures and challenges, however, the future potential for obesity drugs is huge with booming pipeline drugs in late phase-II and Phase-III pipelines. With the number of overweight and obese patients expected to reach 2 billion and 600 million respectively by 2012, the opportunity in this market is tremendous.

Future trends for obesity

The future of obesity treatment and management is moving towards adopting a combination of genomic, surgical and pharmaceutical approaches to manage the disease.

While the largely followed bariatric surgery addresses issues with regard to intake of food, an increasing focus is expected around the genetic pathways controlling obesity which would give rise to potential therapeutic targets.

For instance, it is a well researched observation that obesity is a complex disease wherein there are strong genetic and environmental factors that impact the penetration and expressivity of obesity. Research so far has indicated high linkage of genes located on five chromosomes including chromosome 2p, 3q, 4p, 5 cen-q,6q,8p,10p,12q,17p,20q and Xq23.

The high LOD scores of gene linkages such as those coding for adiponectin,GLUT2 and PI3K,PPAR ALPHA and GLUT-4 indicate the extensive impact of genetics upon obesity.

Being interplay of genetic and environmental factors implies that management of obesity would see growth and convergence of three diverse approaches including:

Genomics: Advances can be expected around the space of pharmacogenomics and nutrigenomics, wherein treatment for the disease would be based on the drugs suitable for the genomic constitution of the patient and the nutritional content that matches their genomic constitution respectively.

Therapeutics: Opportunities to tap the biochemical and genetic pathway of obesity to identify new targets would be theway forward and in that direction, the most promising candidates for obesity therapy to look forward to in the near future include Leptin, GLP-1, extending, Peptide YY 3- 36, NPY and the melanocortin receptor.

Source: Bhuvaneashwar S, senior research analyst, technical insights, Healthcare, Frost & Sullivan

Biotech research can make a difference

“In the area of obesity it is only biotech research can make a revolutionary difference. Because all this while, for obesity, the root cause of the disease was not identified and biotech will go to that root cause. This is because obesity is not just caused by lifestyle disorders, it goes beyond that. We will be seeing companies working big time on R&D because there is potential in the market.”

Muralidharan Nair, partner, Advisory Services, Ernst & Young

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