Review Article

Next Lipitor® will also be from metabolic therapy

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"Because such is the rate of prevalence of obesity and quite limited options that as soon as a successful antiobesity drug is launched (without side effects) in coming years, people will take it in no time and it will break the record of world's biggest blockbuster brand Lipitor®. Lipitor® till date is the world's largest sold drug; becoming the blockbuster brand containing Atrovastatin. There is an urgent need of exploring all the available options to address the menace of this metabolic disorder.

INTRODUCTION

At least one article is seen in newspaper on obesity on daily basis; no other disease is searched (and articles are read on) as frequently as obesity. Such is the menace of obesity that even fast food giant McDonald's has put an advice in few of its offices "not to eat too much fast-food". Obesity is defined as BMI (body mass index) 30kg\m^2 or more. A person with a BMI between 25 and 29.9 are considered over weight but not obese. BMI is a simple index of weight-for-height that is commonly used to classify overweight and obesity in humans. It is also defined as a person's weight in kilograms divided by the square of his height in meters (kg\m^2). As per world health organization (WHO), BMI greater than or equal to 25 is overweight and BMI greater than or equal to 30 is obese. Obesity is a foremost health problem not only in developed nations but also in developing countries. It increases the risk of other diseases like diabetes, cardiovascular ailments, fatty liver and some forms of cancer [1]. Obesity is no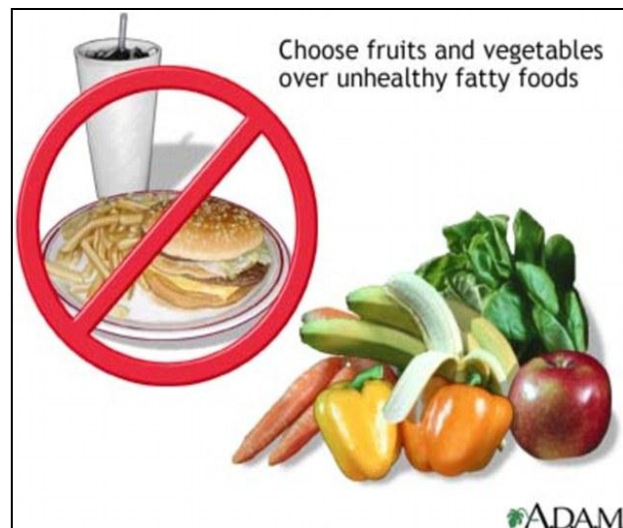w so common in various geographies that it is beginning to replace conditions arising from malnutrition and infectious diseases as the most significant contributor to ill health. Obesity is measured using BMI and further evaluated in terms of fat distribution via the waist–hip ratio and total cardiovascular risk factors [2]. BMI is closely related to both percentage body fat and total body fat [3]. The global epidemic of obesity results from an amalgamation of such factors as genetic susceptibility, increased availability of high-energy foods and diminished need of physical activity in prevailing situation in modern society.

"Obesity is no more a cosmetic issue affecting certain individuals, but a pandemic threatening global well being because it exacerbates a large number of health-related problems, both independently and in association with other ailments [4,5].

Obesity threat is replacing morbidity and mortality arising from malnutrition and infectious disease as most significant contributor to ill health. The rising incidence and prevalence of obesity, especially in developing countries will warrant involvement of governments and individuals. Plant treatments may be more culturally acceptable for some people and exploiting foodstuffs as obesity treatments may be easier to incorporate into a lifestyle than taking a tablet or injections. Obesity is often a lifelong problem. Many of the currently available treatments for obesity aim to reduce body weight or manage obesity for impermanent period; there is a need for some solution which can address obesity in a longer lasting or permanent way. Once excess weight is gained, it is not easy to lose. Once lost, you will have to work at maintaining your healthier weight. The continuing rise in occurrence of obesity worldwide will require new solutions to be found for treatment, management and prevention of obesity. Because humanity does not appear inclined to take more exercise or avoid opulent life style, the emphasis over the next few decades is likely to be on treating obesity and might be possible that next Lipitor® will be again from metabolic therapy. Because such is the rate of prevalence of obesity and quite limited options that as soon as a successful antiobesity drug is launched (without side effects) in coming years, people will take it in no time and it will break the record of world's biggest blockbuster brand Lipitor®. Lipitor® till date is the world's largest sold drug; becoming the blockbuster brand containing Atrovastatin. There is an urgent need of exploring all the available options to address the menace of this metabolic disorder.
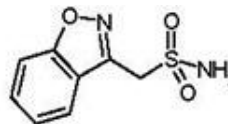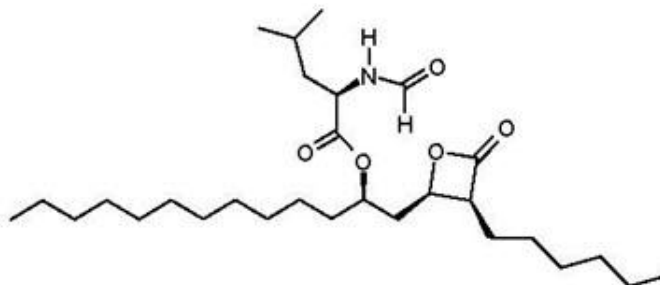

Advice put on the website[6,7]
● "It is hard to eat a healthy diet when you eat at fast-food restaurants often."
● "Many foods are cooked with a lot of fat, even if they are not trans fats. Many fast-food restaurants do not offer any lower-fat foods."
● "Eat at places that offer a variety of salads, soups and vegetables."

PHARMATUTOR
PHARMACY INFOPEDIA

MECHANISM OF CURRENTLY AVAILABLE OR RECALLED DRUGS

MOST OF THE DRUGS THAT HAVE ENTERED THE MARKET FOR TREATING OBESITY WERE ORIGINALLY DEVELOPED TO TREAT PSYCHIATRIC PROBLEMS.

During the past decade, understanding of the hypothalamus functions that control food intake has increased considerably. Different factors like meal termination, meal initiation and overconsumption of highly rewarding and palatable foods are modulated by different neuroanatomical structures. Integration of the action of many signaling chemicals like hormones, neurotransmitters and neuropeptides is central to feeding behavior. Currently available drugs and ongoing research act on somewhat overlapping systems that manage food intake[8]. Phentermine increases the serotonin levels, noradrenalin and dopamine in the brain, although its anti-obesity activity is thought to occur mainly by increasing noradrenalin levels in the hypothalamus, thereby leading to an increased sympathetic activity. Orlistat is a long time solution for obese person, permitted by US Food and Drug Administration. In the intestinal mucosa, orlistat binds to and blocks the activity of lipase enzyme, released by the pancreas in response to fat intake, thereby inhibiting the breakdown of fat molecules and their absorption. Sibutramine blocks serotonin noradrenalin re-uptake in the synapse. Rimonabant, a cannabinoid 1 (CB1) receptor inverse agonist, obstructs the signaling of endogenous cannabinoids (such as 2-arachidonoylglycerol (2-AG))[9].

Structure of some commonly talked about anti obesity drugs [10]

Phentermine (α, α, - dimethylphenethylamine hydrochloride)

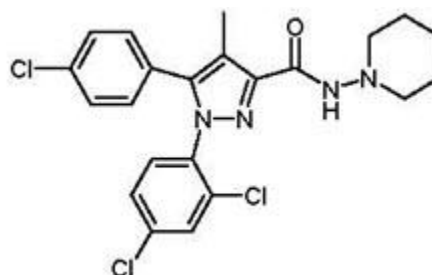Topiramate (2,3:4,5-Di-*O*-isopropylidene-β-D-fructopyranose sulfamate)

Zonisamide (benzo[d]isoxazol-3-ylmethanesulfonamide)

Orlistat ((S)-2-formylamino-4-methyl-pentanoic acid (S)-1-[[(2S, 3S)-3-hexyl-4-oxo-2-oxetanyl] methyl]-dodecyl ester)

Rimonabant (5-(4-chlorophenyl)-1-(2,4-dichloro-phenyl)-4-methyl-*N*-(piperidine-1-yl)-*1H*-pyrazole-3-carboxamide)

Sibutramine Hydrochloride (cyclobutanemethanamine, 1-(4-chlorophenyl)-N,N-dimethyl-α-(2-methylpropyl)-,hydrocholoride)
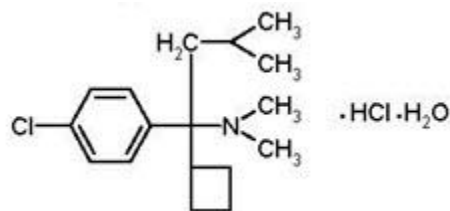
WHAT ARE THE MAJOR LEG PULLERS/CONSTRAINTS IN OBESITY MANAGEMENT: TENTATIVE REASONS?

● Perhaps the only disease where person has to interrupt his daily assignment (taking meal) fixed by the God, which is a daunting task.

● Preclinical models or clinical designs are not robust enough to analyze and predict real time effect in obese persons.

● Placebo or will power seems to be more effectual than well designed clinical studies.

● With technology spreading and sliding in every household, obesity victim becomes helpless and hapless notwithstanding his willingness to shed those extra pounds.

● Side effects of approved antiobesity molecules led to frequent suspension of marketing authorization by regulatory authorities in one or more part of world.

● Moreover, this is among those rare diseases in which medication alone does not improve the conditions significantly and permanently. Person has to follow strict dietary regimen.

● Treatment and change in food habits are frustrating.

● Treatment involves interplay of at least three major systems of body: Nervous, Endocrine and Digestive systems.

● Though a bit successful, but traditional treatment single drug therapy to treat obesity is not effective impressively because of multiplicity and redundancy of mechanism

involved in appetite regulation and energy homeostasis.

● Even treatment is on but ready availability of palatable food with a high fat content is not supporting the therapy.

● Side effects are probably due to the fact that body is being forced to not absorb/assimilate basic building blocks i. e. fatty acids.

● So many chemicals are involved that it seems difficult to completely control the system.

● From the physiology of weight control, it is evident that there are many potential targets for obesity treatment, but there is high degree of redundancy in the system.

● So far there is no proof or success indicating that pharmacological treatment is effective in the absence of changes to diet and lifestyle.

● Intense behavioral interventions are mandatory for effective weight loss and health improvements in obese patients [11].

CONCLUSION

One thing is still sure and challenging, at least based on the available literature that pharmacotherapy for obesity is unlikely to provide a magic bullet and that diet and life style changes are expected to remain the centre of treatment for the predictable future. Much stress is being focused on endpoints (reduced food intake/body weight) and possibly not enough on process. To accomplish full-fledged and foolproof success in obesity treatment, a deepest and penetrating understanding of molecular, physiological, and psychological mechanisms are warranted. Looking at the ever increasing number of obese person, this is not an overstatement that an obesity panacea stands a good chance of becoming next Lipitor®.

↓ REFERENCES

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