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Modern Trends in Managing Obesity - Evolution of a New Drug: Sibutramine (MERIDIA TM)

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## Introduction

Production of pharmacological weight reducing agents has been favored by the same evolutionary mechanism that has predisposed humans towards weight gain. Perhaps at some point in our evolution, it was phylogenetically more advantageous to favor genetic changes that allowed for weight gain. Today, obesity is regarded as a chronic disease increasing in prevalence, and together with its associated comorbidities (i.e., hyperlipidemia, cardiovascular diseases, diabetes, and gout), accounts for up to 10% of health costs. Realizing that these mediatory complications require intense treatments, and that these conditions are improved by losing as little as 5 % of body weight, management of obesity suddenly poses as a sensible solution. Yet, weight loss is notoriously difficult to achieve and maintain following classical life-style recommendations. Moreover, the genetic and physiological component of this disease are great, suggesting that this rather metabolic disorder should be treated with a combination of pharmacotherapy and classical recommendations.

There is a great deal of controversy as to whether pharmacological treatment of obesity is safe, since pharmaceutical companies and inventors have vested interest in making available "the ideal drug." In 1950s when amphetamines were used as anorexigenic drugs, the short term weight loss efficacy of the drug was of primary concern. Soon its psychogenic and addictive side effects undermined its efficacy. Widely used in 80s and 90s, Phentermine/Fenfluramine (Phen/Fen), followed a similar path as clinical findings illustrated a number of cardiopulmonary and long-term neurotoxic problems. Today a newly approved drug Sibutramine (Meridia TM) is taking the center stage, promising a higher benefit-to-risk ratio. Perhaps it is too early to make any accurate conclusions regarding the safety, since long term side effects are not well established. However, scientists do share some common views as to how an ideal leptogenic (leptos = slim) drug should induce its effects.

An ideal pharmaceutical agent for the treatment of obesity should exhibit chronic effectiveness, and high benefit-to-risk ratio. Moreover, the agent should have both anorexigenic and thermogenic effects, in order to increase metabolism (expenditure) in response to the lower metabolic rates resulting from the reduced food intake. It has been shown that sibutramine (Meridia TM) encompasses all these qualities and more. The goal of this report is to examine the evolution of some common diet pills, sibutramine's mechanism, benefits, and possible side effects in treating obesity. In order to do so, it is imperative to briefly consider other common anorectic and leptogenic drugs.

### Pharmacological Target of Leptogenic Drugs

It is now known that energy and organic matter balance is under significant regulation by the central nervous system (CNS). A variety of signals such as gut distension, glucagon like peptides, and adipose mass signals serve as feedback input to CNS, which in turn regulates satiety and sense of hunger. There are also known appetite centers, especially localized to the lateral and ventromedial hypothalamus. For instance animal experiments have illustrated that a lesion to the lateral hypothalamus causes hypophagia. It is this CNS regulatory mechanism, and central activation of sympathetic outflow to adipocyte that are targets of anorexigenic and thermogenic medications. These drugs exert their effect indirectly through neuromodulation of neurotransmitter release involved in such appetite and metabolic regulatory centers.

### Mechanisms and Side-effects of Commonly Used Weight Reducing Drugs:

#### Amphetamine, Phentermine, Fenfluramine, and Dexfenfluramine (Redux TM)

Amphetamine (alpha-methyl (b)-phenethylamine), the first anorexigenic compound, acts by stimulating the release of norepinephrine (NE) and dopamine. The appetite suppressant effect is attributed to release of NE, while dopamine release produces addictiveness and psychogenic properties. Dopamine imbalance is a cause of many affective mood disorders. Phentermine has sympathomimetic appetite suppressing effects, by stimulating the release of NE. It is postulated that phentermine exhibits dopaminergic effects by stimulating the dopaminergic receptors, but lacks the addictiveness of amphetamine in lower doses.

Later, with the discovery of fenfluramine in 1960s, prescribing it in combination with phentermine (Phen/Fen) created a more potent weight loss treatment, as illustrated in a four year clinical trial by Michael Weintrub in 1992. The logic was that co-prescription phentermine would not only reverse the dopamine antagonist effects of l-fenfluramine that caused tiredness, but also increase metabolism by releasing NE. Also this would allow for a lower dose prescription of each medication, thus avoiding any dose dependent side effects. In a 3 year clinical trials conducted in 1997 by Atkinson et al., Phen/Fen's efficacy was supported by demonstrating an average weight loss of 16% in 1388 patients. However, in 1997 Phen/Fen was recalled, when long term studies illustrated increased valvular disease, pulmonary hypertension, and neurotoxicity.,

This directed attention towards dexfenfluramine (Redux TM), the purified d-isomer of fenfluramine, known to act by increasing serotonin release by stimulating the raphe nucleus in the brain, inhibiting presynaptic serotonin reuptake, and causing a small increase in calorie utilization. However, doses above 16 mg/Kg exhibited neurotoxicity in some studies and long term effects are not well established.

A New Hope?

Sibutramine (MeridiaTM)

The side effects of these NE and serotonin secreting drugs geared scientists' curiosity to drugs that may inhibit the reuptake of these neurotransmitter. Such mechanism may avoid neurotoxic side effects, since it is not stimulating brain serotonergic and catecholaminergic centers to release neurotransmitter. Sibutramine, made from a racemic mixture of cyclobutanemethanamine, is a tertiary amine. Upon administration to animals and humans, it is rapidly demethylated to a secondary, and primary amine, Metabolite 1 and 2 which exhibit a more potent state of this novel drug. This drug and its metabolites exert their effects via decreasing food intake and increasing metabolic rate.

Unlike the drugs described previously, sibutramine and its metabolites do not enhance the neuronal release of NE, serotonin, or dopamine. They instead inhibit serotonin and norepinephrine synaptic reuptake (ibid.). This action is predicted to be restricted to monoamine reuptake inhibition, since they show negligible affinity for a wide range of neurotransmitter receptors.

Sibutramine reduces food intake by enhancing satiety, by advancing the "natural physiological process of satiety" (ibid.). The appetite suppressing effect of sibutramine is more natural than amphetamine. In mice experiments, when rats stop eating they spend more time resting and grooming, whereas the amphetamine treated rat's eating behavior is replaced by abnormal increased locomotory activity, perhaps due to increased levels of NE. What further sets sibutramine apart from dexfenfluramine, is the synergistic cooperative interaction between NE and serotonin caused by this drug, resulting in more effective food intake reduction. Two compounds, nisoxetine and fluoxetine, inhibit reuptake of NE and serotonin selectively. Whereas neither drug decrease food intake alone, combination of both potently inhibits food intake, when given in low doses to obese rats. The implication of this synergistic effect is high potency of anorexigenic effect of this drug, even with low elevations in serotonin levels. This could mean less side effects.

Moreover the sustained weight reducing effect of sibutramine over longer periods of time alluded to another mechanism at work: increased thermogenesis or increased energy expenditure. Evidence in mice show that raising serotonin levels stimulates the central activation of sympathetic outflow to brown adipose tissue (BAT), increasing diet-induced thermogenesis. Thermogenesis is due to sympathetic activation of  $\beta_3$ -adrenoreceptor on brown adipocytes by NE. This was illustrated by monitoring labeled 2-deoxy-D-glucose utilization in rats, showing 18 fold increase in thermogenesis with sibutramine treated rats.

Clinical Efficacy and Side Effects of Sibutramine

Controlled clinical studies have shown that sibutramine produces dose related weight loss, between the range of 5-30 mg per day, optimal at 10-15 mg per day. 69% of the patients treated with 15 mg dose, achieved a 5% or greater weight loss in 6 months. In a dose dependent long-term study of 485 patients,

those who lost greater than 5% body mass, were 29% placebo, 56% with 10 mg sibutramine, and 65% with 15 mg sibutramine (ibid.). This significant reduction was correlated with decrease in waist/hip ratio. Clinical trials have also illustrated other associated benefits, such as, an average of 10 mg/dl reduction in triglycerides, and 6 mg/dl in total cholesterol levels. Insignificant increase in HDL cholesterol has also been shown, but the mechanism is unclear.

Negative side effects of sibutramine has been only established up to one year. 18% of patients have exhibited dry mouth, 15% constipation, 11% insomnia, compared to 5% controls. The drug is also known to increase the pulse by an average of 5 beats/min, and blood pressure by 3-4 mmHg, as expected due to the sympathetic stimulation. This effect contradicts the usage of the drug, since some loose weight to reduce their blood pressure.

Sibutramine is prescribed to those with BMI of over 30, or over 27 with a risk factor. There is great evidence for its efficacy, especially when matched with life-style modifications; however, one must be careful about unknown side effects. Since metabolites 1 and 2 are cleared through hepatic metabolism, one must be cautious of long-term liver damage. Moreover, safety against mutagenicity, carcinogenicity, and impairment of fertility in humans have not been illustrated. There are also questions as to whether this drug is safe to use for women on estrogen therapy, for nursing mothers, or elderly population.

#### Discussion

There is yet a lot to be established regarding long term safety of sibutramine. It is also imperative to realize that treatment with sibutramine, without life style changes have proved to be inefficient. Knowing the history of leptogenic pills, one may be skeptical of any agent that results in weight reduction with minimal side effects. However, recent molecular techniques are enabling scientists to discover more about satiety regulation. For instance, a newly discovered gene in mice (*ob/ob* gene) is known to produce protein called leptin, triggered by adipose tissue metabolites, to inhibit satiety center in hypothalamus by activating ATP sensitive potassium channels. This mechanism could possibly be targeted for future treatment of obesity. In conclusion, it is crucial to evaluate pharmacological treatment of obesity critically, and encourage classical life-style modifications, regardless of being treated with a weight reducing agent.