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ORIGINAL ARTICLE

Pharmacotherapy for Weight Reduction: Bupropion/Naltrexone Drugs for Obesity

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ABSTRACT

Background: There is no valid and accurate documentation on the combination therapy of bupropion along with naltrexone. The experimentations on these actions of combination drugs have resulted in rare success.
Methods: A complex interaction occurs in the central and peripheral nervous system for reducing weight loss. It is difficult to find out the major mechanism of action of these drugs on weight reduction. Naltrexone and bupropion is the experimental combination for reducing the weight. For obesity, the combination of naltrexone/bupropion therapy's mechanism working is still unknown.
Results: The attempts for weight loss rarely have a long-term effect. It is an outcome of more likely some complex interaction between various peripheral and Central Nervous systems, and an overwhelming lack of real obesity treatment may be explained. Based on the evidence that obesity involves a change in the hypothalamic melanocortin system in addition to a brain reward system, which causes food craving and mood swings, this investigational combination therapy of NB was developed. Naltrexone and bupropion work in an interesting way.
Conclusion: It affects the parts of the brain that influences food craving, food intake, eating behaviors, and loss of body weight. We will have a review on the working of naltrexone, and bupropion separately, and Vivo, current in vitro, and clinical evidence will be provided, describing how NB affects food intake and food craving.
Keywords: CNS, obesity, medicine, weight lose, NB, therapy.

INTRODUCTION

The risk of cardiovascular diseases, osteoarthritis, diabetes, and cancer at early age increases due to obesity[1]. Adult obesity has doubled since the 1970s, while overweight/obesity has tripled in children, young adults, and adolescents[2,3]. A heavy percentage of children and adults are obese in the USA. Approximately, 17% of children and 36% of adults are currently obese in the US[4,5].

Despite health advice and awareness on the benefits of exercise, this uncontrolled obesity is still occurring. 16 to 18% of the US health care costs account for the increased prevalence of obesity and its comorbidities and may be the first to initiate the decrease in life expectancy in the History of the US[6]. The most common treatments are behavioral interventions such as exercise and diet consciousness, but very few people can lose weight by this method.

Link of the Brain with Obesity: Energy intake and expenditure affect body weight, and they are regulated by the brain. **[7]** In most individual, the energy intake and the expenditure, balanced by the brain, is biased toward weight conservation. This makes a clear sense that the energy conservation property protects the body from getting food deficient. Weight loss is associated with less energy expenditure, **[8]** which requires reduced caloric intake to maintain lesser body fat. In addition, more than necessary calorie consumption, promoted by the intrinsic reward of food, results in weight gain with time.

Naltrexone and Bupropion Individual Effects on Energy Balance: A combination of NB, an investigational therapy, was used to target the neural pathway which regulated the homeostatic food consumption, and energy expenditure[9,10] in addition to Hedonic eating and decision making. According to clinical and preclinical studies, these agents interact in the homeostatic and reward pathways and eventually influence the weight of the body and food consumption.

Naltrexone: With a very high affinity for u-opioid receptors, Naltrexone is an opioid antagonist. Naltrexone is approved for the treatment of opioid-addicted patients and alcoholism[11,12,13]. Naltrexone acts on the improvement of eating behaviors in animals. Opioid neurons are contained by hypothalamic melanocortin and reward systems[14,15] which eventually affect food intake and body weight. However, there are many opioid receptors, the u-opioid receptors are associated with the eating behaviors in animals by genetic and pharmaceutical studies[16].

Bupropion: For aid in smoking cessation, depression treatment, and seasonal defective disorder, this bupropion is approved as an atypical antidepressant[17,18,19]**.** Bupropion constrains reuptake of the catecholamine dopamine and norepinephrine and is a weak nicotinic acetylcholine receptor antagonist[20]. A transient alteration in extracellular dopamine and norepinephrine concentration in the brain is produced by this acute peripheral treatment with bupropion. It works by blocking the excretion of synaptic and dopamine and norepinephrine, **[21, 22]** and may also vary the activity of neurons in the excretion of dopamine and norepinephrine[23].

Preclinical Studies of Naltrexone/Bupropion Combination:

Naltrexone/bupropion Action in the Melanocortin System: In mouse hypothalamus studies in vitro, the combination does naltrexone and bupropion was developed. The researchers found out that bupropion fastens the activity of POMC cells that shows enhanced green fluorescent protein (POMC-EGFP). It was

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hypothesized that modest effects of bupropion monotherapy on weight loss and caloric intake were a result of the limited effect of bupropion on increasing the POMC activity, caused by the u-opioid receptors, which mediates autoinhibition of POMC cells by β-endorphin.

Action of Naltrexone/bupropion in the Reward System: Independent introduction of naltrexone or bupropion decreases the intake of food when administered through injection directly into the reward system of hungry mice. Studies also show the combined effect by introduction of both naltrexone and bupropion in reward system has been greater than their independent effect in decreasing food intake. This supports the indication of a synergistic relation between co-administration of naltrexone and bupropion as well as their independent effect in the reward system.

Systemic Effects of Combination Therapy: The reduction of food intake in hungry mice and rats by the administration of naltrexone and bupropion depends upon the dosage and health of the subject. The combined administration of bupropion and naltrexone has shown greater effect in decreasing food intake than independent administration of both medicines independently. These medicines help reduce fat from Diet-Induced Obese (DOI) mice and rats. When naltrexone and bupropion are administered independently in DIO they decrease the intake of food, reduce hunger in obese mice[24] and rats while in combination both medicines boost each other effects in reducing fat mass and body weight in DIO rats and mice.

METHODOLOGY

Naltrexone and bupropion influence the energy balance system of the brain by affecting two regions of the brain as displayed in preclinical trials. Bupropion and naltrexone synergistically stimulate different systems which complement their independent effects and amplify the results. POMC cells in the melanocortin system are influenced by bupropion while the opioid-mediated brake is stopped by naltrexone boosting the effect of bupropion. All these processes with time help in decreasing food intake with high energy consumption of the body which results in decrease weight in mice and rats. The other path of action of bupropion and naltrexone display is through the reward system. Increasing the food value and food consumption activity in the reward system helps directly in reducing weight in obese mice and rats.

Clinical Studies with the Naltrexone/Bupropion Combination: To test the preclinical trial test clinical treatments with phases 2 and 3 were given to obese mice and rats. In phase 2 the co-administration and independent administration of naltrexone and bupropion were monitors whereas the control group with placebo was also observed. The experiment was conducted for 24 to 48 weeks.[24] The clinical trials complimented the preclinical trial with amplified results with co-administration of bupropion and naltrexone as compared to independent administration o bupropion or naltrexone. In phase 3 the co-administration of naltrexone and bupropion showed reduced visceral fat as well as whole-body fat mass which resulted in twice in weight reduction than independent administration of either one.

RESULTS

The administration period for phase 3 was set from 4 weeks to 56 weeks with the combination of bupropion and naltrexone as 360 mg/day bupropion SR with 32 mg/day naltrexone sustained-release (SR) named as NB32. The clinical trial in Contrave Obesity Research (COR) used placebo and NB 2 for 56 weeks in obese and overweight mice and rats (Table 1).

Table 1. Weight decreases by NB32 in 3rd trial phase in participants who took 56 weeks therapy.

Trial	Study description	Random subjects N	%age of people in whole population[a]	(%) [Weight loss[a]		Subjects with greater than and equal to 5% Weight Reduction [a]		Subjects with greater than/ qual to 10% weight loss[a](%)	
				NB32	Placebo	NB32	Placebo	NB32	Placebo
Study COR-I	Weeks= 56 placebo or NB32 in obese and overweight adults[b]	1741	49%	8.2±0.5*	1.79±0.49	61.9%*	22.9%	33.9%*	10.9%
Study COR-II	Weeks= 56 placebo or NB32 in obese and overweight adults [b]	1497	55%	8.1±0.41*	1.39±0.49	64.5%*	21.9%	38.9%*	7.9%
Study COR-life style MOD	lifestyle modification and Weeks= 56 placebo or NB32 in obese and overweight adults [b]	794	52%	11.6±0.59*	7.29± 1.0	79.9%*	59.9%	554.9%*	29.9%
Study COR-Diabetes Mellitus	Weeks= 56 placebo or NB32 in obese and overweight adults [b] and type 2 diabetic patients	506	53%	6.0±0.49*	2.19±0.59	52.9%*	23.9%	25.9%*	7.9%

NB32: 32 milligrams of sustained release naltrexone and sustained release bupropion once daily. The COR-I study included a group whose treatment was at a lower dose of naltrexone, NB16 shows the decreased dose was also given to some patients but it is not mentioned here. 16 shows 16mg of naltrexone and 369mg of bupropion once daily. Both drugs are in sustained release dosage form. In study of COR-II, participants were given 32 mg dose for 28 to 44 days. After that they were shifted to higher doses of 48mh naltrexone. Nb32 was provided to all of the 4 studies. There was an inclusion of life style modification in 3rd group. In the 4th group, the participants with diabetes mellitus were given this treatment for the reduction of obesity issues.

a: who completed whole 56 week time period

b: included the patients with body mass index of 30 to 47 along with controlled dyslipidemia and hypertension

*p greater than 0.01 for naltrexone/bupropion32 versus placebo.

DISCUSSION

Obesity is a severe problem and chronic state which needs commitment and long-term treatment to reduce and maintain the lower weight of the body. The best way to reduce and maintain low body weight is through lifestyle intervention, changes in diet and

exercise, but in some special cases these former mentioned steps aren't enough to cure obesity. Furthermore, regain of weight after cessation of obesity drugs and lifestyle intervention is quite common, and patients usually face some regain in weight, if not too much, after they stop taking obesity cessation drugs. Thus, obesity drugs aid in reducing weight and maintaining it, which proves very helpful in obesity linked sitautations like cardiovascular disease and diabetes.

In the research made upon pharmacotherapies available, that are currently in use in many states like orlistat, lorcaserin, and phentermine/ topiramate, a comparative evaluation was made among these and weight loss with NB32 in COR-I and COR-II. It was found after research that all these agents have the possibility to provide promising results of meaningful weight loss of 5%- 10% after appropriate treatment of 1 year. Just like the work of NB32, lorcaserin, and phentermine/ topiramate, also act in the CNS, the primary spot of action and suppress appetite which leads to efficient weight loss. However, some side effects have been reported of lorcaserin in form of headache, dizziness, fatigue, nausea, and of phentermine/topiramate in form of paresthesia, dizziness, dysgeusia, insomnia. These side effects are found consistent with their mode of action in the CNS. However, it was observed that consistent use of these drugs resolved the adverse effects.

Even though the rate of weight loss with only exercise and lifestyle intervention is minimum, still the usage of paharmacotherapies is quite low. It has been observed that the continuous rate of orlistat and sibutramine were below 10% for 1 year duration and 2% for 2 years, however, this drug has been removed from the market owing to its high risk rate of causing CVD. In the COR-I study, impacts of NB32 were tested along with lower dose of NB16 mg/day, naltrexone'bupropon. COR-I was also similar to COR-I research with the exception that the subjects treated with NB32 were re-randomized who failed to lose minimum 5% weight and its maintenance. These subjects were tested that either increasing the dose of NB32, NB48 will provide the desirable results. The results showed that weight loss was similar in both the tested subject categories. Moreover, results were also similar in COR-I and COR-II who continued using NB32 for 56 weeks, with 8.2% and 8.1% efficacy in comparison to placebo 1.7 and 1.39%, respectively. It was also observed that NB32 improved the factors, like lipids, insulin resistance, and waist circumference, associated with risks of developing cardiovascular disease.

Therefore, the utilization of these medicines along with the approval of lorcaserin and phentermine/topiramate depicts that multiple treatment options will be available for heterogeneous obesity patients. This in turn provides maximum positive results.

CONCLUSION

The reason why we see limited success rate of obesity medicines is because of the complex brain pathways that control hunger, food craving and eating patterns. It is just the beginning of developing some understanding about the strong effects of mood and emotions driven by hormones as well, upon eating pattern and gain of body weight. In the present era, where delicious but high fat food are readily available, hedonic drives handled by neural pathways definitely play significant role in gaining weight and setting a point in body to limit weight loss struggle.

Pre- and clinical trials have depicted that naltrexone/bupropion, combined, acts upon the hypothalamic region of brain from where hunger, energy expenditure and eating patterns are regulated. The weight loss achieved via NB is particularly due to dual action upon this region. It is observed that consistent use of NB32 in overweight and obese patients provide 5% to 10% reduction in weight. These losses are in those responders who are able to benefit from NB.

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