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ANALYSIS OF COMBINATION OF NALTREXONE WITH BUPROPION FOR WEIGHT LOSS

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Abstract:

An estimated 34% of American adults were obese, and an additional 34% were overweight in 2007–2008. Obesity is associated with diabetes, hypertension, hyperlipidemia, stroke, heart disease, respiratory problems, osteoarthritis, and several types of cancer. The basic aim of the study is to analyze the combination of naltrexone with bupropion for weight loss. Obesity is associated with alterations in neural signaling. Differences in neural responses to hunger and satiation are documented in obese vs. lean individuals and women appear to exhibit lower cognitive control of brain responses to food stimuli than men. Naltrexone is reformulated as a sustained release (SR) dosage form in this combination product, which has bioequivalent exposure to naltrexone immediate release (IR). Naltrexone/bupropion should be used with caution in patients who are elderly or have moderate or severe renal impairment. It should be avoided in patients with severe hepatic disease. Bupropion reduces short-term food intake in lean and obese rodent models and increases energy expenditure by increasing heat production, although the overall effect of bupropion on body weight in animals is modest. It is concluded that naltrexone/bupropion is an effective agent for weight management. Further studies are necessary to determine the effect of naltrexone/ bupropion on cardiovascular outcomes.

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INTRODUCTION:

An estimated 34% of American adults were obese, and an additional 34% were overweight in 2007–2008. Obesity is associated with diabetes, hypertension, hyperlipidemia, stroke, heart disease, respiratory problems, osteoarthritis, and several types of cancer. Across all insurance sectors medical spending for an obese patient is approximately 42% higher annually compared to that for an individual with normal body weight [1]. Obesity increases the risk for diabetes, cardiovascular disease, osteoarthritis, cancer, and early mortality. Since the mid-1970s, the incidence of adult obesity has doubled, while the incidence of overweight/obesity in children, adolescents and young adults has tripled. Currently, 36% of adults and 17% of children in the United States are considered obese. This has occurred in spite of public health advice about the benefits of exercise and reducing caloric intake. The increasing prevalence of obesity and its comorbidities has been predicted to account for 16–18% of US health care costs by 2030 and to initiate the first decrease in life expectancy in modern history [2]. Behavioral interventions such as diet and exercise are the most common treatments for weight loss, but many overweight and obese individuals are unable to achieve moderate weight loss with behavioral intervention alone. The increase in the prevalence of obesity is a clear indication of the failure of behavioral intervention to produce sustained and meaningful weight loss in today's obesogenic environment, and highlights the need for additional methods of weight loss [3].

Obesity is generally regarded as a chronic disease requiring continuous intervention to maintain ideal body weight. Of the few treatments available for obesity, bariatric surgery is the most effective, resulting in weight loss of about 25% at 2 years post-surgery and improvements in many cardio metabolic risk factors [4]. Common limitations of bariatric surgery include peri- and post-operative complications, cost, and access. Bariatric surgery is associated with a 7.3% peri-operative complication rate, a 1.6–3.5% incidence of serious complications, conversions and reoperations, weight regain, and recurrent binge-eating [5].

Theoretical background

Pharmacological treatments for obesity offer a less invasive alternative to bariatric surgery but the field has been hampered by few treatment options, limited efficacy, and uncertainty about the safety of long-term use in the general population. In recent years, the high-profile withdrawal of obesity drugs (e.g., sibutramine) from the market due to safety issues has left physicians with few treatment options, increased concern about the safety of pharmacotherapy options, and caused confusion about how to effectively manage obesity. Recent approval of 2 new obesity drugs by the FDA in 2012 increased the total to 3 FDA-approved long-term pharmacological treatments for obesity: orlistat, lorcaserin, and the combination of phentermine and topiramate [6].

Objectives of the study

The basic aim of the study is to analyze the combination of naltrexone with bupropion for weight loss.

Background of obesity

Obesity is associated with alterations in neural signaling. Differences in neural responses to hunger and satiation are documented in obese vs. lean individuals and women appear to exhibit lower cognitive control of brain responses to food stimuli than men. Persistence of abnormal neural responses to a meal in formerly obese individuals, a group at high risk for relapse, indicates that a tendency to obesity may involve areas of the brain that control complex aspects of eating behavior including anticipation and reward, chemosensory perception, autonomic control of digestion, and memory [7]. Weight loss is also associated with increases in neural activity in brain regions involved in reward processing and valuation of food stimuli, as well as decreased activity in regions involved in restraint in response to food. These changes likely drive the delayed satiation, decreased perception of caloric intake, and increased hunger observed after a 10% weight loss. Furthermore, dieting is associated with increases in food preoccupation and food craving. Consequently, significant and sustained weight loss in overweight or obese individuals is often accomplished by significant increases in dietary restraint or eating control [8]. Considering the broad availability of aggressively marketed, highly palatable food in developed countries, obesity drugs that reduce hedonic feeding behavior may be especially helpful. Some of the currently available obesity therapies are thought to produce weight loss by influencing reward-mediated eating behavior through a variety of CNS mechanisms, though further study is needed.

Pharmacokinetics

Naltrexone is reformulated as a sustained release (SR) dosage form in this combination product, which has bioequivalent exposure to naltrexone immediate release (IR). Naltrexone/bupropion should be used with caution in patients who are elderly or have moderate or severe renal impairment. It should be

avoided in patients with severe hepatic disease [9].

Individual effects of naltrexone and bupropion on energy balance

The naltrexone/bupropion combination (NB) is an investigational obesity therapy that was developed to target neural pathways that regulate homeostatic food intake and energy expenditure as well as hedonic eating behavior and decision making. Preclinical and clinical
studies with naltrexone and bupropion indicate that these agents may act in homeostatic and reward pathways to influence food intake and body weight [8].

Naltrexone

Naltrexone is an opioid antagonist with a high affinity for the μ-opioid receptor. Approved for treatment of alcoholism and opioid addiction, naltrexone influences eating behavior in animals. The hypothalamic melanocortin and reward systems contain opioid neurons, hence naltrexone activity may influence food intake and body weight via these dual systems.

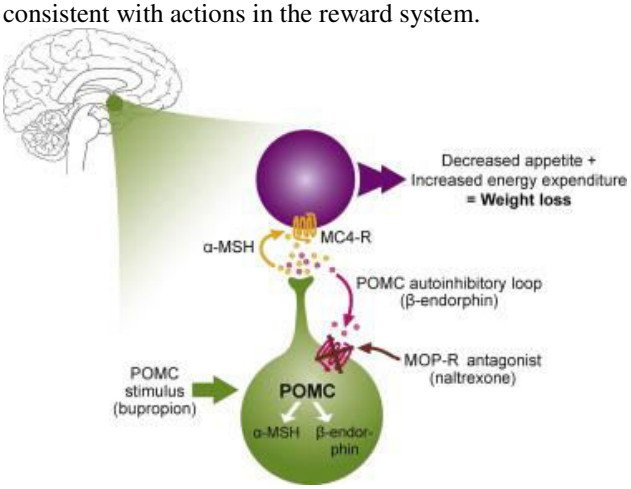
Although there are several opioid receptors, genetic and pharmacological preclinical studies implicate the μ-opioid receptor in eating behavior. Mice engineered to lack the μ-opioid receptor are resistant to obesity induced by a high fat diet. Chronic administration of naltrexone increases POMC mRNA; this would be expected to restore activity of POMC neurons and melanocortin satiety systems. These results are consistent with the hypothesis that naltrexone blocks β-endorphin action at the μ-opioid receptor, thus preventing autoinhibition of POMC neurons.

Human studies also demonstrate that opioids can influence ingestive behavior by modulating subjective palatability. Consistent with the role of opioids in the rewarding aspects of eating, naltrexone reduces the subjective pleasantness, or liking, of certain foods (especially palatable foods); this effect is independent of nausea, a common side effect of naltrexone [8].

Bupropion

Bupropion is an atypical antidepressant currently approved as an aid in smoking cessation and for the treatment of depression and seasonal affective disorder. Bupropion inhibits reuptake of the catecholamines dopamine and norepinephrine, and is a weak nicotinic acetylcholine receptor antagonist. By blocking the removal of synaptic dopamine and norepinephrine, acute peripheral treatment with bupropion produces transient changes in extracellular dopamine and norepinephrine concentrations in the brain and may also alter the activity of the neurons that release dopamine and norepinephrine [10].

Activity of the melanocortin system is influenced by both dopamine and norepinephrine, and reduced dopaminergic tone in the hypothalamus is associated with various elements of obesity. Thus, the hypothalamic melanocortin system is a potential site of bupropion action. Indeed, bupropion stimulates activity of POMC cells in vitro and increases α-MSH secretion. In addition, bupropion's antidepressant effects and efficacy as a smoking cessation aid are consistent with actions in the reward system.



Mechanism of POMC

Bupropion reduces short-term food intake in lean and obese rodent models and increases energy expenditure by increasing heat production, although the overall effect of bupropion on body weight in animals is modest.

Dosage and Administration

Naltrexone/bupropion is formulated as 4/90 mg and 8/90 mg tablets. One 4/90 mg tablet daily may be considered as a conservative initial dose. The recommended initial dose titration schedule for 8/90 mg tablets is as follows: one tablet in the morning for week 1, one tablet twice daily for week 2, two tablets in the morning and one in the evening for week 3, and two tablets twice daily starting on week 4. The maintenance dose is 16 mg of naltrexone SR and 180 mg of bupropion SR (taken as two 8/90 mg tablets) twice daily. It can be taken with or without food[11].

CONCLUSION:

It is concluded that naltrexone/bupropion is an effective agent for weight management. Further studies are necessary to determine the effect of naltrexone/ bupropion on cardiovascular outcomes.

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