

Naltrexone/Bupropion ER for the treatment of obesity

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Abstract

Naltrexone/bupropion extended release (ER), a new drug for the management of obesity, will be available in Greece soon. The potential of the drug to reduce body weight is related to its ability to stimulate pro-opiomelanocortin (POMC) neurons. A number of clinical studies have shown that naltrexone/bupropion ER administration is associated with a decrease in body weight by 3.2-5.2% compared with placebo, while approximately half of treated patients experience a greater than 5% decrease in body weight. In diabetic patients a decrease of glycated hemoglobin by approximately 0.5% was also noticed. The most common adverse effects of the drug include nausea, vomiting and headache. Due to potential interactions with a number of drugs, special attention should be given in patients receiving concomitant medications.

Key words: naltrexone; bupropion; obesity; diabetes mellitus

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Introduction

The number of people who are considered overweight or obese is climbing.¹ Many factors contribute to obesity, such as dietary intake, inadequate exercise or sedentary lifestyles, various medical/metabolic conditions, or medications. Thus treatment of obesity needs a multifactorial approach. Obese patients usually have difficulties losing weight with diet alone and

maintaining their weight loss in the long term. Pharmacotherapy with antiobesity drugs assists to achieve greater weight loss and maintenance compared with diet alone.² However, in the recent past antiobesity drugs such as sibutramine and rimonabant, despite their beneficial effects on weight loss and associated cardiovascular risk factors, were withdrawn due to cardiovascular adverse effects and increased risk of

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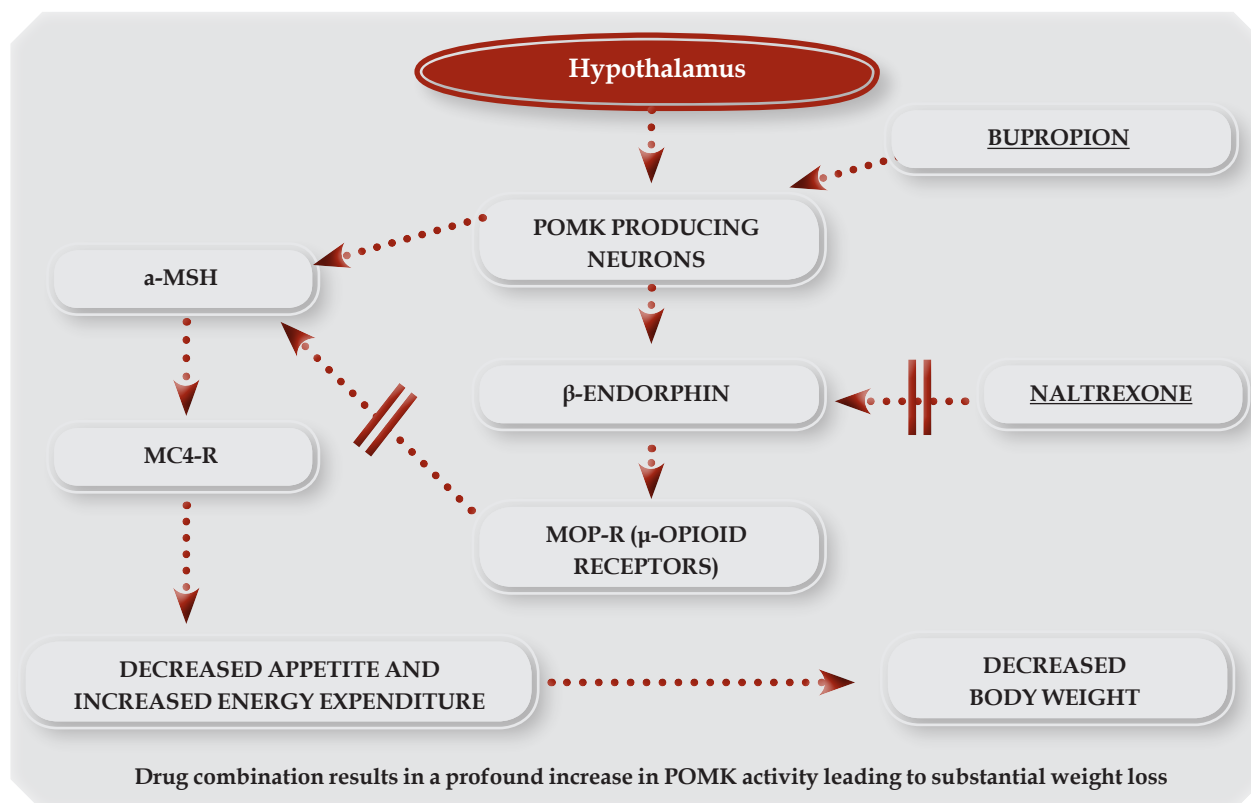


Figure 1. Mechanism of action of naltrexone/bupropion.

α-MSH: A melanocyte stimulating hormone. MC4-R: Melanocortin-4 receptors. POMC neurons: Pro-opiomelanocortin neurons
MOP-R: μ-opioid receptors

suicide, respectively.³⁻⁸ Until recently, orlistat, an intestinal lipase inhibitor, was the only antiobesity drug available.⁹⁻¹⁴ Nowadays, a number of newer generation antiobesity drugs have been developed, such as naltrexone/bupropion combination, liraglutide, lorcaserin, and phentermine/topiramate combination.² Naltrexone/bupropion Extended Release (ER) combination will be available soon in Greece.¹⁵⁻¹⁷ It is a combination of naltrexone and bupropion, which have been previously used for other indications. Thus, bupropion (a dopamine and norepinephrine reuptake inhibitor) is used as antidepressant and smoking cessation agent, while naltrexone (an opioid receptor antagonist) has been used for the management of alcohol and opioid dependence.¹⁷⁻¹⁹ The aim of this short review is to describe the mechanisms of action, the effects on body weight and cardiovascular risk factors and the adverse effects of naltrexone/bupropion ER combination.

Mechanism of action

Bupropion can stimulate the hypothalamic pro-opiomelanocortin (POMC)-producing neurons resulting in the release of α-melanocyte stimulating hormone (α-MSH), which then binds to melanocortin-4 receptor (MC4R) leading to reduced energy intake but also to increased energy expenditure.¹⁹ However, when α-MSH is released, POMC neurons also release β-endorphin, which is an endogenous agonist of the μ-opioid receptors on POMC neurons, resulting in a reduction of α-MSH release (negative feedback loop). The simultaneous administration of naltrexone can block this inhibitory feedback loop¹⁸, thus a more potent and longer-lasting activation of POMC neurons is observed leading to a greater effect on body weight regulation (synergistic action of the two drugs) (Figure 1).¹⁹

Pharmacokinetic properties of the drug

The pharmacokinetic data of the drug are sum-

Table 1. Pharmacokinetic profile of naltrexone/bupropion extended release

Absorption (>90%) in the gastrointestinal tract
Increased blood levels with a high-fat meal are observed (the drug should not be administered with high fat meals)
Protein binding: naltrexone 21% /bupropion 84%
The half-life of naltrexone is 5h and its active metabolite 6-β-naltrexone 13h, while the half -life of bupropion is 21 hours, and its active metabolites 20-37 hours.
Naltrexone: undergoes extensive metabolism by non-cytochrome-mediated dehydrogenase; the main metabolite (6-β-naltrexone) contributes to the total drug activity. The drug and its metabolites undergo renal excretion.
Bupropion: undergoes extensive metabolism to three active metabolites; the cytochrome 2B6 is the main enzyme involved in the production of hydroxybupropion. Furthermore, bupropion is also a strong CYP2D6 inhibitor. The drug is also excreted by the kidneys and the feces.

marized in **table 1**. The pharmacokinetics of this drug are not affected by age and sex. Since there are limited data in elderly patients careful administration is suggested in patients > 65 years of age, while the drug should not be given in patients > 75 years who are more sensitive to the central nervous system adverse effects. Pharmacokinetic studies in patients with renal or hepatic failure are lacking. Thus, in the EU, the drug is contraindicated in patients with end-stage renal failure, in those with severe renal or liver impairment and is not recommended in patients with moderate renal disease or mild/moderate hepatic disease. However, according to the manufacturer recommendations, 1 tablet in the morning and evening can be administered in patients with moderate renal impairment, while 1 tablet in the morning is suggested in patients with liver impairment. Furthermore, the drug is contraindicated during pregnancy or in nursing mothers or in patients younger than 18 years of age.^{20,21}

Effects of the drug in clinical trials

A number of clinical trials (**table 2**) have clearly shown that long-term treatment (56 weeks) with naltrexone/bupropion ER (32/360mg/d) reduced body weight by 3.2-5.2% compared with placebo in obese or overweight adults; thus signif-

icantly more drug-treated patients experienced a >5% decrease in body weight compared with placebo-treated patients (44.5%-66.4% *vs.* 16%-18.9%, respectively).²²⁻²⁵ No significant by group interactions for sex, ethnicity baseline body mass index (BMI), hypertension, dyslipidemia, or smoking status were noticed in these trials. A pooled analysis of the 4 phase III trials (*n*=3,362) showed that naltrexone/bupropion ER decreased body weight by 4.7% compared with placebo, while over half of the treated patients experienced a greater than 5% decrease in body weight at week 56 (53% *vs.* 21%).²⁶ Interestingly, patients with an early response (a decrease in body weight >5% at week 16) exhibited an additional decrease in body weight (by 11.7% at week 56) compared with patients without such a response.²⁷

Drug treatment is associated with a significant decrease in waist circumference, insulin levels and homeostasis model assessment of insulin resistance (HOMA) index.²²⁻²⁵ In COR-1 and II trials a significant reduction in high-sensitivity C-reactive protein (hsCRP) by 12.3% and 20.5% was observed. However, no significant changes in hsCRP was found in the other trials of naltrexone/bupropion ER. Small favorable change in serum lipid parameters have been also noticed (an increase in high-density lipoprotein cholesterol by 3-5mg/dl and a decrease of

Table 2. Key Phase III Trials of naltrexone/bupropion extended release

TRIAL	NUMBER OF PATIENTS	PATIENTS (TREATMENT DURATION)	BODY REDUCTION (NB32) FROM BASELINE (vs PLACEBO)	MAIN SIDE EFFECTS IN DRUG GROUP
COR-I	1,742	Obese or overweight patients with dyslipidemia or controlled hypertension (56 weeks)	-6.1% (<i>vs.</i> -1.3%)	Nausea (32%)
COR-II	1,496	Obese or overweight patients with dyslipidemia or controlled hypertension (56 weeks)	-6.4% (<i>vs.</i> -1.2%)	Nausea (29.2%) 1 episode of seizures 1 acute myocardial infarction
COR-BMOD	793	Obese or overweight patients with dyslipidemia or controlled hypertension (56 weeks)	-9.3% (<i>vs.</i> -5.1%)	Nausea (34.1%) 2 episodes of cholecystitis
COR-DIABETES	505	Type 2 diabetes mellitus with BMI 27-45kg/m ² , HbA _{1c} 7-10% and fasting blood glucose <270mg/dl (56 weeks)	-5% (<i>vs.</i> -1.8%) (a decrease in HbA _{1c} by 0.5% was also shown)	Nausea (42.3%)

NB32: 32mg of naltrexone / 360mg of bupropion

BMI: body mass index

HbA_{1c}: glycated hemoglobin

triglycerides by 11-15mg/dl and low-density lipoprotein cholesterol by 1-4mg/dl).²²⁻²⁵

Interestingly, in the COR-Diabetes trial a significant decrease in glycated hemoglobin (HbA_{1c}) by 0.5% compared with placebo was observed in patients received naltrexone/bupropion ER, resulting in the achievement of HbA_{1c} < 7% in a significant greater proportion of treated patients compared with placebo (44.1% *vs.* 26.3%).²⁵ The decrease in HbA_{1c} correlated significantly with the decrease in body weight ($r=0.509$). Furthermore, fewer diabetic patients receiving naltrexone/bupropion ER required modifications of the antidiabetic drugs to achieve HbA_{1c} < 7% compared with placebo treated patients (22.3% *vs.* 35.2%).²⁵

A pooled analysis of patient-level data from four randomized controlled Phase 3 studies of naltrexone/bupropion ER ($n= 3362$) evaluated the changes at 56 weeks in quality of life, measured by the Impact of Weight on Quality of Life-Lite

(IWQOL-Lite) questionnaire.²⁸ The total Improvements in IWQOL-Lite Total Score were greater in subjects treated with naltrexone/bupropion ER compared with placebo [11.9 points, standard error (SE) 0.3 *vs.* 8.2 points, SE 0.3, $p < 0.001$], corresponding to weight loss of 7.0% (SE 0.2) and 2.3% (SE 0.2), respectively. The improvement in quality of life was associated with weight loss since subjects who lost $\geq 15\%$ of their baseline body weight experienced the greatest improvement in IWQOL-Lite Total Score in both groups. A greater percentage of patients treated with naltrexone/bupropion ER compared with placebo achieved clinically meaningful improvements in IWQOL-Lite Total Score (50% *vs.* 32.3%, odds ratio 2.09, 95% confidence interval 1.79-2.44).²⁸

Principles of drug administration

The drug is available in extended-release tablets containing 8mg naltrexone HCL and 90mg bupropion HCL, which should be taken in the morning and evening. A careful dose titration is recommended

Table 3. Drugs metabolized by the CYP2D6 with increased possibility of interaction with naltrexone/bupropion extended release

Selective Serotonin Reuptake Inhibitors
Tricyclic antidepressants
Antipsychotics (haloperidol, risperidone, thioridazine)
β -blockers (metoprolol)
Antiarrhythmic drugs (type IC) [propafenone/flecainide]

within 4 weeks to avoid nausea. Thus, one tablet in the morning for week 1 is followed by one tablet twice for week 2, two tablets in the morning and 1 in the evening for week 3 and two tablets twice daily for week 4 and onward. However, if 16 weeks after drug initiation a decrease in body weight > 5% has not been achieved, drug treatment should be discontinued.^{20,21} According to the EU label, annual re-assessment of the need of continuation of treatment is necessary.^{16,20,29}

Side effects and drug interactions

The most common side effect of the drug is nausea (observed in up to 32.5% of patients in clinical trials). Nausea is usually observed at the initiation of therapy, is transient and has mild to moderate intensity.³⁰ Metformin-treated patients are more sensitive to experience nausea in clinical trials. Other common side effects include vomiting and headache (up to 10.7% and 17.6%, respectively). Other side effects are constipation or diarrhea, dizziness, insomnia, anxiety, hot flush, dry mouth, fatigue, tinnitus and tremor.²²⁻²⁵

A randomized controlled trial which assessed the cardiovascular safety of the drug was unfortunately terminated early.³¹ However, in this high risk overweight/obese patients no evidence of an increased cardiovascular morbidity or mortality was noticed after 50% of the planned events was recorded. It should be mentioned that a small increase in systolic and diastolic blood pressure by approximately 1mmHg was found, which was decreased to baseline values by week 12 and then decreased by 1mmHg by weeks 24-56 compared

with baseline. At the same time a weight loss-induced decrease in BP by 2-3mmHg was observed in the placebo group^{31,32}. Furthermore, in the COR trials an increase in SBP by 1.1 to 2.6mmHg was noticed compared with placebo, while heart rate also increased with naltrexone/bupropion (+0.8 to 1.1 beats/min). Thus, the drug is contraindicated in patients with uncontrolled hypertension; blood pressure and pulse rate should be measured during treatment at regular intervals especially in hypertensive patients.^{20,21,33} The drug is also contraindicated in patients with a history of seizures, since bupropion has been previously related with seizures. Concurrent administration of drugs that lower the threshold of seizures, such as antidepressants, antipsychotics, systemic corticosteroids and theophylline should be carefully assessed.^{20,21,33} The drug is contraindicated in patients receiving monoamine oxidase inhibitors (MAOI) (due to an increased risk of hypertensive reactions) or long-term opioid analgetics. Additionally, the drug is contraindicated in patients receiving opioid agonists or partial agonist therapy (including antitussives and antidiarrheal medication) or undergoing opioid analgesics withdrawal. It has been emphasized that MAOI should be discontinued for at least 14 days before naltrexone/bupropion initiation. Furthermore, after drug discontinuation the patients are sensitive to even small doses of opioids.³⁴

The bupropion and its active metabolite can inhibit CYP2D6 and thus can increase the concentration of certain drugs (table 3). Thus, in patients treated with naltrexone/bupropion ER the lowest dose of drugs metabolized by the CYP2D6 should

be administered at the initiation of treatment and a careful titration of the dose should be attempted. Furthermore, careful monitoring is advised in patients receiving drugs that are transported by the renal organic cation transporters 2(OCT-2), such as amantadine, dopamine, metformin and ranitidine. Bupropion and its metabolite are inhibitors of this transporter leading to decreased renal clearance and increased concentrations of drugs transported by the renal OCT-2.^{20,21} On the other hand, since bupropion is primarily metabolized by CYP2B6, inhibitors, such as ticlopidine or clopidogrel, can increase the concentrations of bupropion. In such cases, accordingly to the USA label the dose of the drug should be reduced to one tablet twice daily. It should be acknowledged that CYP2B6 inducers (ritonavir, lopinavir, efavirenz) can decrease bupropion levels and thus should be avoided or used with caution. Since in diabetic patients a decrease in blood glucose levels is observed, careful monitoring of insulin and oral antidiabetic drugs is indicated to avoid the risk of hypoglycemia and seizures. Finally, since decreased alcohol tolerance and even neuropsychiatric adverse effects have been observed in patients consuming alcohol beverages during drug administration, alcohol drinking is contraindicated. Naltrexone/bupropion ER should not be given in individuals undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates or antiepileptic drugs.

Naltrexone has been used for the treatment of alcohol dependence; thus, the use of naltrexone/bupropion may be particularly useful in obese patients who also consume large amounts of alcohol.³⁵ Moreover, in two open-label studies complete tobacco abstinence with naltrexone/bupropion ER was reported in a considerable proportion of smokers (30-40%), along with minimization of the tobacco abstinence-associated weight gain.^{36,37}


It should be mentioned that in clinical trials the incidence of suicidality was not different between naltrexone/bupropion and placebo treated patients. However, both FDA and EMA have provided box warnings concerning the risk of neuropsychiatric reactions, including suicidal thoughts and

behaviors in patients treated with bupropion. On the other hand, an open-label pilot study showed that the drug can improve depressive symptoms in obese patients with major depressive disorders.³⁸

Discussion

The use of antiobesity drugs offers a considerable weight loss in addition to dietary treatment. Naltrexone/bupropion ER assists obese patients to achieve greater weight loss compared with placebo and to maintain this loss at least for two years as placebo-controlled trials have shown.³⁹ Weight loss is associated with improvement of cardiovascular risk factors and possibly of cardiovascular events.⁴⁰ In this context, naltrexone/bupropion ER may be beneficial in terms of cardiovascular risk, but data specifically examining this matter are not currently available since the relevant trial has been terminated early. It should be mentioned that data assessing the effects on cardiovascular events of the other currently available antiobesity drugs are also missing. Another concern is the effects of centrally-acting antiobesity drugs on the mood and suicidality. Although placebo-controlled trials have not shown an increased risk of suicidality with naltrexone/bupropion ER, the drug should be used with caution in patients with symptoms or history of depression. Placebo-controlled trials have shown that naltrexone/bupropion ER is generally safe if it is avoided in patients with uncontrolled hypertension, a history of seizures or receiving certain medications, such as MAOi or long-term opioid analgetics.^{20,21,33} If these precautions are followed, naltrexone/bupropion ER may be a very useful drug for obese patients, especially those with diabetes mellitus.

Conclusions

The careful administration of naltrexone/bupropion ER could be a particular useful therapy for the management of obese patients, including patients with diabetes mellitus. 

Conflict of interest

All authors declare no conflict of interest.

Περίληψη

Ναλτρεξόνη/Βουπροπιόνη για τη φαρμακευτική αντιμετώπιση της παχυσαρκίας

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Η naltrexone/bupropion extended release είναι ένα νέο φάρμακο για την αντιμετώπιση της παχυσαρκίας, το οποίο θα κυκλοφορήσει σύντομα και στη χώρα μας. Η δυνατότητα των δύο δραστικών ουσιών του να προκαλούν αξιοσημείωτη μείωση του σωματικού βάρους συσχετίζεται κυρίως με τη διέγερση των POMC νευρώνων, οι οποίοι εκκρίνουν την προ-οπιομελανοκορτίνη. Κλινικές μελέτες έδειξαν ότι το φάρμακο μειώνει το σωματικό βάρος κατά 3,2 - 5,2% σε παχύσαρκα ή υπέρβαρα άτομα σε σύγκριση με το εικονικό φάρμακο, ενώ περίπου οι μισοί ασθενείς εμφάνισαν μια μείωση του σωματικού βάρους μεγαλύτερη από 5%. Σε διαβητικούς ασθενείς η χορήγηση της naltrexone/bupropion είχε ως αποτέλεσμα μείωση της γλυκοζυλιωμένης αιμοσφαιρίνης κατά περίπου 0,5%. Οι πιο συχνές ανεπιθύμητες ενέργειες του φαρμάκου είναι η ναυτία, οι έμετοι και η κεφαλαλγία. Επειδή υπάρχει δυνατότητα αλληλεπίδρασης με άλλα φάρμακα απαιτείται προσοχή στην εξατομίκευση της θεραπείας.

Λέξεις ευρετηρίου: ναλτρεξόνη, βουπροπιόνη, παχυσαρκία, διαβήτης

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