Naltrexone/bupropion prolonged release

Notable Points:
- Obesity: A risk factor for many diseases including diabetes, cardiovascular disease and cancer. With 50% of the population predicted to be obese by 2030, obesity is a major public health problem. There are few effective management strategies in the treatment of obesity and even fewer pharmacological therapies. At present, the only licensed drug therapy in the UK is orlistat. A centrally acting anti-obesity agent comprised of prolonged release naltrexone and bupropion (NB) is available in the US and may soon be licensed in the UK.

Pharmacology
- Naltrexone is a μ-receptor antagonist, currently licensed in the treatment of drug and alcohol dependence. Bupropion is a dopamine and noradrenaline uptake inhibitor used as an adjunct in smoking cessation.
- Control of eating and energy expenditure resides in certain cells of the arcuate nucleus of the hypothalamus. Anorexigenic effects are mediated by stimulation of pro-opiomelanocortin (POMC) cells which produce various peptides including α-melanocyte-stimulating hormone (MSH) and β-endorphin. Alpha-MSH promotes reduced food intake, increasing energy expenditure and resultant weight loss while β-endorphin acts as an auto-inhibitor via μ-opioid receptors to reduce the activity of POMC cells. Bupropion increases the release of α-MSH and β-endorphin while naltrexone inhibits the actions of β-endorphin. The combination of both has a synergistic effect.

Figure 1. Pharmacological action of naltrexone/bupropion

Introduction
- Obesity is a risk factor for many diseases including diabetes, cardiovascular disease and cancer. With 50% of the population predicted to be obese by 2030, obesity is a major public health problem. There are few effective management strategies in the treatment of obesity and even fewer pharmacological therapies. At present, the only licensed drug therapy in the UK is orlistat. A centrally acting anti-obesity agent comprised of prolonged release naltrexone and bupropion (NB) is available in the US and may soon be licensed in the UK.

NOTES. Production of α-melanocyte-stimulating hormone (MSH) by pro-opiomelanocortin (POMC) cells in the arcuate nucleus promotes weight loss by reducing appetite and food intake and increasing energy expenditure. Auto-inhibitory feedback on POMC cells is mediated by β-endorphin. Bupropion increases the release of α-MSH and β-endorphin while naltrexone inhibits the actions of β-endorphin. The combination of both has a synergistic effect.
NB and its metabolites are predominantly excreted by the kidneys.

**Trials of efficacy and safety**

There have been four phase III trials evaluating the safety and efficacy of NB. Each was a randomised, double-blind, placebo controlled 56-week trial in obese (BMI >30kg/m²) or overweight (BMI >25kg/m²) patients. All participants were encouraged to increase physical activity and follow a hypocaloric diet (500kcal/day deficit) at each study visit (baseline, 12, 24, 36 and 48 weeks). Behavioural modification advice was also given. Baseline diet and lifestyle characteristics were not recorded nor was compliance with diet and exercise during the study.

COR-I was the first phase III trial and established the dose of naltrexone used in further studies. It compared 16mg vs 32mg of naltrexone with a fixed dose of 360mg bupropion in 802 participants. The higher dose of naltrexone with bupropion produced greater weight loss vs placebo (-1.3% in the placebo group, -6.1% and -5% in the naltrexone 32mg and naltrexone 16mg groups respectively, p<0.0001 vs placebo). The frequency of adverse effects was similar between each treatment group.

The effect of NB (32mg/360mg) vs placebo on weight and cardiometabolic risk factors in obese and overweight patients (n=1496) was assessed in COR-II. Treatment with NB resulted in a significantly greater weight loss (-6.5% vs -1.9%, p<0.001) as well as an improvement in cardiovascular risk markers such as waist circumference, insulin, blood glucose, fasting triglyceride and HDL cholesterol.

COR-BMOD examined the combination of naltrexone and bupropion as an adjunct to intensive behaviour modification (BMOD). In all, 793 patients with uncomplicated obesity or BMI between 27–45kg/m² with dyslipidaemia and/or hypertension were randomised to BMOD with NB-32 or placebo. Primary endpoints were similar to COR-I and COR-II. Intention-to-treat analysis demonstrated weight losses of 11.5% vs 5.1% in the placebo group (p<0.001).

The most frequent adverse reactions seen with NB-32 have been gastrointestinal (i.e. nausea, constipation, vomiting, dizziness, and dry mouth) and were most common at the start of treatment.

Concerns regarding the cardiovascular safety were raised by bupropion-mediated minor increases in heart rate and blood pressure. A further two trials are still underway to assess cardiovascular safety. Interim results from the Contrave Light Study are reassuring, showing no significant adverse cardiovascular event in 8900 patients treated with NB.

**Specific evidence for use in diabetes**

COR-DIABETES (n=501) evaluated NB in overweight or obese patients with type 2 diabetes mellitus on no medication or on stable doses of oral hypoglycaemics. Only patients taking oral diabetes therapy (metformin, sulphonylureas, thiazolidinediones, DDP-4 inhibitors etc) were included but not insulin, potential weight gain associated with this considered to make any results more difficult to interpret. The duration of diabetes was not reported. Baseline HbA1c was 8±0.8% and 8±0.9% in the treatment and placebo groups respectively. NB resulted in a significantly greater weight loss compared to those in the placebo group (5% vs 1.8%; p<0.001) and a greater improvement in HbA1c (0.6% vs 0.1%, p<0.001). Current oral antidiabetic drugs produce reductions in HbA1c between 0.4–2.5%.

Additionally, there were significant improvements in HDL cholesterol and triglyceride levels as well as waist circumference reduction in NB treated patients. No significant differences were found in fasting blood glucose or insulin concentrations between groups. There was a reduced risk of hypoglycaemia with NB treated patients and they were less likely to require increased or additional oral antidiabetic therapy (22.3% vs 35.2%, p<0.01).

Interestingly, the percentage weight loss in the treatment group was less than in previous studies of NB in non-diabetic subjects. The reasons for this are not clear but may be due to insulin resistance, oral hypoglycaemics or altered lipid metabolism.

**Discussion**

Weight loss is an important target in the management of type 2 diabetes although one that patients find difficult to achieve and maintain. Weight loss is associated with improved glycaemic control, lower blood pressure and improved lipid parameters potentially reducing cardiovascular risk in those with diabetes. NB in combination with lifestyle modifications has demonstrated efficacy as an anti-obesity agent and produces weight loss similar to orlistat. Limited evidence suggests that NB may be a useful adjunct in the management of diabetes by virtue of its ability to reduce weight as well as improving cardiometabolic factors. Further research is needed to fully evaluate the therapeutic benefits of NB in type 2 diabetes and to establish its cardiovascular safety.

**Declaration of interests**

There are no conflicts of interest declared.

**References**