

Bupropiona & Naltrexona

Associação para o tratamento da obesidade



DESCRIÇÃO

A **Bupropiona** é um inibidor da recaptção de dopamina e norepinefrina atualmente aprovado para o tratamento da depressão e como coadjuvante da cessação do tabagismo. Seu efeito como agente redutor do peso em monoterapia já foi testado previamente, obtendo resultados modestos.

A **Naltrexona** é um antagonista de receptor opioide, inicialmente aprovado como tratamento da dependência aos opiáceos e, posteriormente, da dependência ao álcool. Diversos estudos clínicos têm demonstrado que a associação de **Naltrexona** e **Bupropiona** pode ser útil na redução de peso corporal e no manejo da obesidade.

MECANISMO DE AÇÃO

A despeito de essas drogas apresentarem uma eficácia discreta, quando utilizadas isoladamente, o entendimento atual das complexas vias de regulação central e periférica do apetite permitiu que se postulasse um efeito sinérgico da sua associação. O aumento dos níveis de dopamina e norepinefrina mediado pela Bupropiona estimula a atividade neural da pró-opiomelanocortina (POMC). Os neurônios produtores da POMC, localizados no núcleo do hipotálamo, ao serem estimulados, levam à clivagem de dois peptídeos principais: o hormônio estimulador do alfa-melanócito (alfa-MSH) e a beta-endorfina. O aumento do alfa-MSH leva à ativação do MC4R (receptor largamente encontrado no hipotálamo) e das vias de sinalização secundárias que levam ao aumento do gasto energético e à diminuição do apetite. Em contrapartida, foi demonstrado que a beta-endorfina, um opioide endógeno, é responsável por um mecanismo de autoinibição da via da POMC, resultando em um aumento da ingestão alimentar em roedores.

Ao inibir os receptores opioides, a Naltrexona libera os neurônios da POMC da inibição pela beta-endorfina e, portanto, potencializa os efeitos ativadores dessa via pela Bupropiona. Estudos clínicos recentes e de larga escala têm descrito os benefícios na redução do peso pela associação destas duas drogas.

INDICAÇÃO

- Tratamento de perda de peso para pacientes com sobrepeso e obesos.

DOSE USUAL

A recomendação de uso oral de **Naltrexona** é de até 32 mg ao dia.

A recomendação de uso oral de **Bupropiona** é de até 360 mg ao dia.



Sugestões de Fórmulas

Naltrexona 8 mg
Bupropiona 90 mg

Modo de uso: uma cápsula, duas vezes ao dia, podendo ser aumentada para até duas cápsulas, duas vezes ao dia, de acordo com a orientação médica.

Indicação: redução de peso.

Naltrexona 4 mg
Bupropiona 90 mg

Modo de uso: uma cápsula, duas vezes ao dia, podendo ser aumentada para até duas cápsulas, duas vezes ao dia, de acordo com a orientação médica.

Indicação: redução de peso.

PRINCIPAIS REFERÊNCIAS

APOVIAN, Caroline M. et al. A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). *Obesity*, v. 21, n. 5, p. 935-943, 2013.
GREENWAY, Frank L. et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet*, v. 376, n. 9741, p. 595-605, 2010.

ESTUDOS



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ESTUDOS

Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial.

Despite increasing public health concerns regarding obesity, few safe and effective drug treatments are available. Combination treatment with sustained-release naltrexone and bupropion was developed to produce complementary actions in CNS pathways regulating bodyweight. The Contrave Obesity Research I (COR-I) study assessed the effect of such treatment on bodyweight in overweight and obese participants. Men and women aged 18-65 years who had a body-mass index (BMI) of 30-45 kg/m² and uncomplicated obesity or BMI 27-45 kg/m² with dyslipidaemia or hypertension were eligible for enrolment in this randomised, double-blind, placebo-controlled, phase 3 trial undertaken at 34 sites in the USA. Participants were prescribed mild hypocaloric diet and exercise and were randomly assigned in a 1:1:1 ratio to receive sustained-release naltrexone 32 mg per day plus sustained-release bupropion 360 mg per day combined in fixed-dose tablets (also known as NB32), sustained-release naltrexone 16 mg per day plus sustained-release bupropion 360 mg per day combined in fixed-dose tablets (also known as NB16), or matching placebo twice a day, given orally for 56 weeks. The trial included a 3-week dose escalation. Randomisation was done by use of a centralised, computer-generated, web-based system and was stratified by study centre. Co-primary efficacy endpoints at 56 weeks were percentage change in bodyweight and proportion of participants who achieved a decrease in bodyweight of 5% or more. The primary analysis included all randomised participants with a baseline weight measurement and a post-baseline weight measurement while on study drug (last observation carried forward). This study is registered with ClinicalTrials.gov, number NCT00532779. 1742 participants were enrolled and randomised to double-blind treatment (naltrexone 32 mg plus bupropion, n=583; naltrexone 16 mg plus bupropion, n=578; placebo, n=581). 870 (50%) participants completed 56 weeks of treatment (n=296; n=284; n=290, respectively) and 1453 (83%) were included in the primary analysis (n=471; n=471; n=511). Mean change in bodyweight was -1.3% (SE 0.3) in the placebo group, -6.1% (0.3) in the naltrexone 32 mg plus bupropion group (p<0.0001 vs placebo) and -5.0% (0.3) in the naltrexone 16 mg plus bupropion group (p<0.0001 vs placebo). 84 (16%) participants assigned to placebo had a decrease in bodyweight of 5% or more compared with 226 (48%) assigned to naltrexone 32 mg plus bupropion (p<0.0001 vs placebo) and 186 (39%) assigned to naltrexone 16 mg plus bupropion (p<0.0001 vs placebo). The most frequent adverse event in participants assigned to combination treatment was nausea (naltrexone 32 mg plus bupropion, 171 participants [29.8%]; naltrexone 16 mg plus bupropion, 155 [27.2%]; placebo, 30 [5.3%]). Headache, constipation, dizziness, vomiting, and dry mouth were also more frequent in the naltrexone plus bupropion groups than in the placebo group. A transient increase of around 1.5 mm Hg in mean systolic and diastolic blood pressure was followed by a reduction of around 1 mm Hg below baseline in the naltrexone plus bupropion groups. Combination treatment was not associated with increased depression or suicidality events compared with placebo. A sustained-release combination of naltrexone plus bupropion could be a useful therapeutic option for treatment of obesity.

A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II).

To examine the effects of naltrexone/bupropion (NB) combination therapy on weight and weight-related risk factors in overweight and obese participants. CONTRAVE Obesity Research-II (COR-II) was a double-blind, placebo-controlled study of 1,496 obese (BMI 30-45 kg/m²) or overweight (27-45 kg/m²) with dyslipidemia and/or hypertension) participants randomized 2:1 to combined naltrexone sustained-release (SR) (32 mg/day) plus bupropion SR (360 mg/day) (NB32) or placebo for up to 56 weeks. The co-primary endpoints were percent weight change and proportion achieving ≥ 5% weight loss at week 28. Significantly (P < 0.001) greater weight loss was observed with NB32 versus placebo at week 28 (-6.5% vs. -1.9%) and week 56 (-6.4% vs. -1.2%). More NB32-treated participants (P < 0.001) experienced ≥ 5% weight loss versus placebo at week 28 (55.6% vs. 17.5%) and week 56 (50.5% vs. 17.1%). NB32 produced greater improvements in various cardiometabolic risk markers, participant-reported weight-related quality of life, and control of eating. The most common adverse event with NB was nausea, which was generally mild to moderate and transient. NB was not associated with increased events of depression or suicidality versus placebo. NB represents a novel pharmacological approach to the treatment of obesity, and may become a valuable new therapeutic option.

Naltrexone/bupropion for obesity.

Naltrexone/bupropion (Mysimba- Orexigen Therapeutics Ireland Limited) is a fixed-dose combination product for the treatment of adults who are obese or overweight with at least one weight-related comorbidity, as an adjunct to diet and lifestyle modifications. Originally licensed by the European Medicines Agency (EMA) in 2015, it has recently been launched in the UK. Here, we review the evidence for its efficacy and safety and consider its place in therapy.

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