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(54) **Title**: THERAPEUTIC COMBINATION OF MEMANTINE AND BACLOFEN AND PHARMACEUTICAL COMPOSITION CONTAINING THEM

(57) **Abstract**: The present invention relates to the combination of memantine and baclofen active ingredients, and also to the method for achieving body weight loss and thereby treating obesity and related co-morbidities by co-administration of baclofen and memantine.

Therapeutic combination of memantine and baclofen and pharmaceutical composition containing them

Field of the Invention

The present invention relates to the combination of memantine and baclofen active ingredients, wherein baclofen may also mean racemic baclofen, enantiomers and/or prodrugs of baclofen. The invention also relates to the use of such combinations in methods for treating overweight, obesity or related conditions or for achieving body weight loss, wherein memantine and baclofen are administered simultaneously or subsequently, preferably within a short period of time. The invention further relates to the pharmaceutical compositions comprising memantine and baclofen active ingredients and the use of such compositions in methods for treating overweight, obesity or related conditions or for achieving body weight loss. The treatment methods of the presented invention also mean a treatment regimen that is supplemented with other means such as dietary or life style modifications, dietary supplements, herbal or pharmaceutical remedies.

Background of the invention

Overweight and obesity are growing public health problems in the modern world. In medical practice overweight is defined as a body mass index (BMI) above 25 kg/m2, while obesity as BMI > 30 kg/m2. As of 2011, the prevalence of obesity more than doubled compared to 1980 (WHO Fact sheet N°311, 2011); http://www.who.int/mediacentre/factsheets/fs311/en/). In most parts of the world the prevalence of overweight and obesity grows progressively (Europe, USA, Middle East and Asia). According to the estimation of World Health Organisation (WHO), in 2008, the worldwide prevalence of overweight and obesity were 1.5 billion and 500 million, respectively. Both overweight and obesity, namely the increased body mass beyond healthy limits, increases the risk of several diseases in a severity dependent manner. In this description, hereafter obesity stands for both overweight and obesity categories. Obesity is a known risk factor for several diseases and medical conditions, such as diabetes, insulin resistance, metabolic syndrome, hypertension, atherosclerosis, coronary artery disease, cardiac failure, stroke, biliary tract diseases, such as cholecystitis and gallstones, osteoarthritis, orthopedic abnormalities, dyspnea, respiratory apnea, ovarian cysts, malignancies, such as mammary, prostate and colon tumors, anesthesiological complications,

heartburn, venous varicosities, infections and eczema (Kopelman Nature 404:635-643 2000; Rissanen et al. BMJ 301:835-837 1990). Obesity also has a negative effect on life expectancy, and along with smoking, hypertension and hypercholesterolemia, it is one of the major risk factors for several chronic diseases (James, Comparative Quantification of Health Risks Global and Regional Burden of Diseases Attributable to Selected Major Risk Factors, Chapter 8, WHO, Geneva, 2004).

Overweight and obesity is the fifth leading risk factor for mortality worldwide. At least 2.8 million adults die yearly as a consequence of being overweight or obese (WHO Fact sheet N°311, 2011). The medical need for weight loss in obese people is underlined by the fact that as small as 5% long term weight loss is able to significantly improve cardiovascular morbidity and mortality rates (Goldstein, Int. J. Obes. Relat. Metab. Disord. 16:397-415 1992). Therefore, an enormous unmet medical need exists for the treatment of obesity and related co-morbid conditions.

It is known that obesity can be alleviated with rigorous low calorie dieting and exercise. However, according to medical experience, these kind of lifestyle modifications are not effective on the long term and have limited utility in some patient populations (Powell et al. Am. Psychol. 62:234-246 2007; Sahoo, Obesity Drug Markets in the US and EU: Analysis of product pipelines and the competitive environment. Business Insights Ltd., 2008). Therefore, a large public demand exists for pharmacotherapies that can support hypocaloric dieting and can enhance the effectiveness of behavioral modifications (Witkamp Pharm. Res. 28:1792-1818 2011).

The progress of obesity is multifactorial, but at the end it always manifests as impairment in the regulation of energy intake and expenditure. Although the human body aims to maintain its weight, a moderate weight gain along with aging can be considered as a normal physiological process. However, in modern societies several environmental factors, such as sedentary lifestyle and the easy availability of energy-dense foods, severely affect the normal homeostatic control of body weight, which lead to increased storage of body fat (Bessesen Physiol. Behav. 104:599-607 2011). Accordingly, anti-obesity pharmacotherapies are aiming to reduce unutilized energy by (1) reducing energy absorption, (2) alleviating hunger / increasing satiety, thereby reducing energy-intake, or (3) increasing the utilization of stored energy (Witkamp Pharm. Res. 28:1792-1818 2011). Out of these three pharmacotherapeutic options the latter two can be achieved by using drugs acting in the central nervous system (CNS).

Some regions of the CNS play crucial role in the regulation of energy intake, energy expenditure and metabolism. For example, one main integrating center is the hypothalamus (Gao et al. Annu. Rev. Neurosci. 30:367-398 2007). More than 50 neurotransmitters have been identified in the hypothalamus that play a proven or potential role in the regulation of energy homeostasis. The neurotransmitters that are involved in the regulation of energy homeostasis provide potential targets for anti-obesity pharmacotherapies. However, since the development of obesity and the regulation of food intake and energy homeostasis is affected by various central and peripheral pathways - some of which are prone to fast adaptation and resistance – targeting only one pathway can hardly provide an effective pharmacotherapy (Aronne et al. Expert Opin. Emerg. Drugs 16:587-596 2011). Accordingly, targeting more pathways - e.g. by co-administering simultaneously more than one drug - might be needed to reach an optimal therapeutic effect. Nevertheless unpredictable interactions might occur when using combination therapies, especially if CNS mechanisms are involved. These interactions can range from antagonistic interaction through additive effect to supra-additive interaction (synergy).

Reaching sufficient efficacy is a fundamental requirement with regards to therapeutic utility. Namely, if the efficacy of an anti-obesity pharmacotherapy does not reach a certain limit, drug licensing agencies (Food and Drug Administration, FDA in the USA or European Medicines Agency, EMA in Europe) would not grant the approval of the drug. According to the actual FDA guidelines, the required mean primary efficacy endpoint is 5% weight loss (versus placebo-treated group) at 1 year, while the categorical primary efficacy endpoint requires that at least 35% of the treated population should lose more than 5% body weight (versus placebo-treated group) (Guidance for Industry Developing Products for Weight Management. U.S. Department of Health and Human Services, FDA (2007)). The desirable minimum weight loss specified by EMA is even higher: 10% (Guideline On Clinical Evaluation Of Medicinal Products Used In Weight Control. EMA (2008)).

However, it is not enough for an anti-obesity drug to be sufficiently effective. In addition, drug regulatory agencies set very high safety standards for these kinds of drugs. Therefore such drugs must be substantially devoid of side effects at therapeutic doses. Despite that efficient anti-obesity therapy may require centrally acting drugs, at the time of writing this application there are no approved drugs on the market which are indicated for long term use. This lack of CNS drugs is at least partly due to the high safety and tolerability standards. The only approved anti-obesity treatment for long term use is a non-CNS drug, orlistat, which blocks digestion and subsequent absorption of alimentary fat. However, efficacy of orlistat is

fairly less than desirable and its broad use is also limited by troublesome gastrointestinal side effects (Filippatos et al. Drug Saf. 31:53-65 2008). Achieving a sufficient therapeutic index, i.e. good separation of effective and side effect causing doses, is a particularly challenging task with CNS drugs. Two CNS drugs, rimonabant and sibutramine were recently withdrawn from the market due to unwanted side effects (Kennett et al. Pharmacol. Biochem. Behav. 97:63-83 2010). Consequently, achieving appropriate efficacy and sufficient lack of side effects, hence good tolerability and safety are critical and challenging issues in the pharmacotherapy of obesity. In another aspect, suitable separation between doses mediating efficacy and side effects is also an essential criterion in order to meet the requirements of good tolerability and safety.

Severely obese patients (BMI>35-40) with comorbid conditions (e.g. diabetes, hypertension) who are unresponsive to diet and pharmacotherapy are treated in some countries by gastrointestinal surgical interventions, called bariatric surgery (Powell et al. Am. Psychol. 62:234-246 2007). However, such surgical interventions have considerable risks, including mortality, severe postoperative side effects and high rate of postoperative complications (Encinosa et al. Med. Care 44:706-712 2006). Despite the substantial risks, the severely obese population can still benefit from surgical treatments, due to the high impact of obesity-related comorbidities on life expectancy and on the quality of life. Therefore, it is a reasonable assumption that a future pharmacotherapy providing high efficacy close to that of the surgery, i.e. 20-25% body weight loss (Bueter et al. Obes. Facts 2:325-331 2009) along with less risks and side effects, could offer a better treatment option for severely obese patients.

Recently, it turned out, that several drugs - that were originally developed to treat other diseases - have some body weight reducing effects in humans at their regular therapeutic doses (e.g. zonisamide, topiramate, bupropion, naltrexone (Kennett et al. Pharmacol. Biochem. Behav. 97:63-83 2010); atomoxetine (Gadde et al. Int. J. Obes. (Lond) 30:1138-1142 2006); baclofen (Arima et al. Intern. Med. 49:2043-2047 2010); betahistine (Barak et al. Int. J. Obes. (Lond) 32:1559-1565 2008); duloxetine (Guerdjikova et al. In.t J. Eat. Disord. Epub ahead of print 2011); fluoxetine (Serretti et al. J. Clin. Psychiatry 71:1259-1272 2010); memantine (Hermanussen et al. Econ. Hum. Biol. 3:329-337 2005); methylphenidate (Leddy et al. Obes. Res. 12:224-232 2004); sertraline (Serretti et al. J. Clin. Psychiatry 71:1259-1272 2010); venlafaxine (Malhotra et al. J. Clin. Psychiatry. 63:802-806 2002). On the other hand, these medications usually have modest efficacy, typically below 5% body weight loss compared to placebo or baseline. Furthermore, it is also questionable whether their side effect

profile would be acceptable in view of the high regulatory safety bars in the obesity indication.

It has also been known for quite a long time that amphetamines and similar drugs (e.g. phentermine, diethylpropion, phendimetrazine, phenylpropanolamine, mazindol) have anti-obesity effects. Nonetheless, the majority of these kinds of medications had been withdrawn from the market, due to cardiovascular risks, abuse potential and psychostimulant side effects (Ioannides-Demos et al. Drug Saf. 29:277-302 2006). Their therapeutic utility is also limited by their liability to development of tolerance, which leads to attenuation or cessation of efficacy over time during long-term treatment. Therefore, marketing authorization of most of these compounds has been withdrawn and the few commercially still available amphetamine-like compounds, like phentermine in the USA, are only permitted for short term treatment (Kennett et al. Pharmacol. Biochem. Behav. 97:63-83 2010).

In summary, several drugs exist with weak anti-obesity activity, which are either insufficiently effective or carry unacceptable side effect profiles when administered alone. However, it is absolutely not obvious that combinations of which drugs result in real summation of the effects (additive interaction) and which combinations do not lead to such summation (infra-additive interaction). Furthermore, it is even less obvious which drug combinations exhibit an even higher efficacy than would be expected from simple summation (i.e. supra-additive interaction or synergy) in terms of the desired action. It is also not obvious whether the components of the combinations will enhance or reduce each-others' side effects or ultimately the combination will have better or worse side effect profile and therapeutic index than the components alone. In the case of synergistic action for the desired action it is also questionable whether or not the synergy refers to the side effects as well. As a matter of fact, synergy for both main and side effects would not yield an improved therapeutic index. Hence, it is not obvious at all whether the combination of two drugs with known anti-obesity effects yields a combination that is favorable in terms of therapeutic utility and benefits as compared to solo use of its components.

Baclofen has been used for a long time as a centrally acting muscle relaxant drug. Its primary pharmacological action is an agonist effect on the gamma-aminobutyric acid B-type (GABA-B) receptors (Davidoff, Ann. Neurol. 17:107-116 1985). The drug used in medical practice is a racemic mixture of left-(S-) and right-handed (R-) enantiomers. Its oral form is used to alleviate spasticity associated with CNS injury related disorders which cause an increase in muscle-tone that is called 'spasticity'. Its most common side-effect is muscle weakness due to exaggerated muscle relaxation, for which its therapeutic index is rather narrow. In addition,

drowsiness and dizziness are also common side effects of baclofen. Therefore, for attaining an efficacious anti-spastic but well tolerable dose level individual dose titration is recommended. The effective therapeutic doses of oral baclofen for the treatment of spasticity fall typically in the range of 30-80 mg/day (Dario et al. Drug Saf. 27:799-818 2004). Similarly to humans, the anti-spastic and motor side effect-causing doses do also overlap in mice (Farkas et al. J. Pharmacol. Toxicol. Methods 52:264-273 2005).

It is known that baclofen decreases food intake and body weight in diet induced obese mice. Both enatiomers of baclofen had body weight reducing effects, however the R-enantiomer was more effective (Sato et al. FEBS Lett. 581:4857-4864 2007). The moderate effect of baclofen on body weight has also been proven in a small human study (10 obese patients), in which baclofen was administered at the dose of 30 mg/day, beginning with a 10 day gradual dose-increasing phase and lasting for 12 weeks. The study showed a mean 1.7% body weight loss. Out of the 10 participants only one had lost more than 5% body weight (Arima et al. Intern. Med. 49:2043-2047 2010). These limited data suggest that baclofen treatment alone at well tolerated doses would not meet the minimum efficacy criteria of drug regulatory agencies. It is known, for example, that a new drug candidate lorcaserin, which was entitled by the FDA (in its „complete response letter" of 2010) as having "marginal efficacy", caused 3.5-4% weight loss at 12 weeks and 5.8% after 1-year-long treatment relative to baseline. Hence, the less than 2% body-weight decreasing effect of 30 mg/day baclofen in 12 weeks can be considered as submarginal. There is another human baclofen study that refers to food intake reducing effect of baclofen, though that study was not designed to assess anti-obesity efficacy. Broft and her co-workers (Broft et al. Int J. Eat. Disord. 40:687-691 2007) investigated the effects of baclofen on binge eating in seven female participants. Binge eating disorder is not equivalent with obesity and out of the 7 patients only 2 were obese (BMI>30 kg/m^2) and 1 was overweight (BMI>25 kg/m^2). In this investigation there were no significant changes in mean body weight (0.9 kg body weight increase within 10 weeks) but only food craving and the number of binge eating episodes were decreased by baclofen. The targeted dose of baclofen was 60 mg/day and the most common side effect was sedation. Hence, these data indicate that baclofen has some moderate appetite reducing effects but this effect alone is not sufficient to cause a clinically meaningful body weight loss at doses associated with no side effects or at least with a tolerable side effect profile.

Memantine has been an approved drug for quite a long time. Initially (in 1978) it entered the market in Germany for the treatment of Parkinson's disease, spasticity and other neurological disorders. Later it was found that memantine blocks N-methyl-D-aspartate (NMDA) receptors

in a noncompetitive manner (Bormann, *Eur. J. Pharmacol.* 166:591-592 1989), shows neuroprotective effects and is also effective in preventing cognitive and histological damages in preclinical models of Alzheimer's disease (Parsons et al. *Neuropharmacology* 38:735-767 1999); Rammes et al. *Curr. Neuropharmacol.* 6:55-78 2008). Then its efficacy was proven also in clinical trials of vascular dementia and Alzheimer's disease (Raina et al. *Ann. Intern. Med.* 148:379-397 2008). Currently memantine is an approved and widely used drug for the treatment of Alzheimer's disease. Its general therapeutic dose is 20 mg/day in the clinical practice, which should be reached only by gradual dose-escalation. Its therapeutic window is narrow and side effects typical for NMDA antagonists, such as restlessness, confusion, or more seriously hallucination, may occur in case of too fast dose-escalation or administration of higher doses. Nevertheless, side effects of memantine are rare when administered according to the recommended dosing regimen: restlessness (1.3%), nausea (0.9%), dizziness (0.8%), tiredness (0.4%) (Mobius et al. *Drugs of Today* 40:685-695 2004). It is difficult to determine which dose in the animal experiments corresponds to the human therapeutic dose. However, the effective anti-Alzheimer dose range of memantine in mice can be estimated to be 5-30 mg/kg/day with oral administration based on plasma concentration data or cognitive and neurohistological effects in animal models of Alzheimer's disease (Dong et al. *Neuropsychopharmacology* 33:3226-3236 2008); Minkeviciene et al. *J. Pharmacol. Exp. Ther.* 311:677-682 2004); Rammes et al. *Curr. Neuropharmacol.* 6:55-78 2008).

In an open-label clinical trial on 5 obese female patients (Hermanussen et al. *Econ. Hum. Biol* 3:329-337 2005), memantine, at doses higher than the usual therapeutic dose (20-30 mg/day with dose adjustment if needed) was found to decrease the appetite, number binge eating episodes and body weight. However, the relevance of this observation with regards to assessment of utility for anti-obesity treatment is very limited, since all but one of these patients were treated only for a short period (21 or fewer days). Some patients experienced dizziness during the treatment. In a more extended open-label study, where memantine was administered to 16 obese, binge eater patients according to the dosing regimen recommended in labeling (i.e. the dose was gradually increased to 20 mg/day or left lower if needed for good tolerability), memantine decreased the number of binge episodes but not the body weight (Brennan et al. *Int. J. Eat. Disord.* 41:520-526 2008). Hence, these data suggest that although a slight decrease in appetite can be reached using memantine but the well-tolerated doses in current therapeutic use do not cause a substantial weight loss. This conclusion is in accordance with data from animal experiments where memantine decreased binge numbers in a rat model of binge eating disorder but did not decrease body weight (Popik et al. *Amino Acids* 40:477-485 2011).

Summary of the invention

This invention is based on the unexpected observation that combined application of memantine and baclofen exerted a surprisingly strong, apparently synergistic effect on weight loss in a mouse model of obesity. In contrast, combined administration of baclofen with phentermine, which is another drug with a known weight reducing effect, caused clearly an infra-additive interaction. Furthermore, as another unexpected finding, the synergistic and remarkable weight-reducing effects of memantine and baclofen were found at doses that were lower than the doses sufficient to detect their known therapeutic efficacy in relevant mouse models related to their current indications.

We have also surprisingly found that the combination of memantine and baclofen exhibited infra-additive interaction in terms of side effects and resulted in improvement of the therapeutic index.

The present invention relates to the combination of memantine and baclofen active ingredients, wherein baclofen may also mean racemic baclofen, enantiomers and/or prodrugs of baclofen.

The invention further relates to the pharmaceutical compositions comprising memantine and baclofen active ingredients.

The invention also relates to the use of combinations and compositions of memantine and baclofen active ingredients in methods for treating overweight, obesity or related conditions or for achieving body weight loss.

Brief description of the figures

Figure 1 depicts the efficacy of memantine, baclofen and their combination in the mouse DIO test.

Figure 2 shows the magnitudes of the weight reducing effects of memantine, baclofen and their combination in the mouse DIO test (pooled results of two studies).

Figure 3 shows the efficacy of phentermine, baclofen and their combination on the mouse diet-induced obesity test. The doses presented were administered per os twice daily.

Figure 4. shows the isobolographic analysis of the pharmacological interaction between memantine and baclofen in the rotarod test in mice.

Figure 5. shows the effect of memantine, baclofen and their combination on the horizontal motor activity of mice.

Detailed Description of the Invention

The present invention relates to the combination of memantine and baclofen active ingredients, wherein baclofen may also mean racemic baclofen, enantiomers and/or prodrugs of baclofen and to the use of such combinations in methods for treating overweight, obesity or related conditions or for achieving body weight loss, wherein memantine and baclofen are administered simultaneously or subsequently, preferably within a short period of time. The invention further relates to the pharmaceutical compositions comprising memantine and baclofen active ingredients and the use of such compositions in methods for treating overweight, obesity or related conditions or for achieving body weight loss. The treatment methods of the presented invention also mean a treatment regimen that is supplemented with other means such as dietary or life style modifications, dietary supplements, herbal or pharmaceutical remedies.

In course of our experiments, we have surprisingly found that the combination of memantine and baclofen cause a remarkable weight reduction even when applied at doses below their present human therapeutic dose. In addition, if a similar synergism is not found in their side effects, then the improvement of the side effect profile and therapeutic index can also be experienced by the combination of these drugs. We have proven that no synergy was present in terms of CNS side effects typical for baclofen, i.e. muscle weakness and dizziness, as measured by rotarod performance, when administered these drugs to mice at a dose combination that exerts an apparent synergistic effect in terms of weight reduction. Moreover, unexpectedly we observed that baclofen counteracted the locomotor activity-increasing effect of memantine, an effect that can be observed in mice after treatment with memantine and which is typical for NMDA antagonist compounds.

Based on the results of our experiments, the following key features of the new combination can be summarized:

(1) A weight reduction higher than the acceptable threshold value proposed by the FDA might be reached using the combination of memantine and baclofen.

(2) This efficacy can be reached at a dose of baclofen that is lower than its usual therapeutic dose or falls in the lower end of the recommended dose range according to current labeling (Summary of Product Characteristics). Accordingly the stipulated anti-obesity dose range for baclofen is 5-40 mg/day depending on the weight of the patient.

(3) In the case of memantine a successful weight reducing effect can be reached at its usual therapeutic dose (20 mg/day) or at lower doses (2-20 mg/day).

(4) Due to the lower doses and/or to counteracting effects of the components concerning side effects, a better therapeutic window and side effect profile can be observed with combination of memantine and baclofen.

(5) In cases of morbid obesity that carries higher health risks and may need very high efficacy, slightly inferior side effect profile is acceptable in the risk/benefit evaluation. Therefore in such cases the combination of these compounds can be applied at doses in the upper region of their usual therapeutic dose range. Moreover, in accordance with the clinical practice, there may be a need to adjust doses to higher body weights in the case of extremely heavy patients (>120 kg). Therefore application of higher doses than the above mentioned ones may be reasonable in certain cases, particularly in cases of morbid obesity (i.e. baclofen 20-160 mg, memantine 10-40 mg).

According to the present invention the combinations of memantine and baclofen active ingredients preferably contain memantine in the range of about 2 to about 40 mg/day and baclofen in the range of about 5 to about 160 mg/day. In a further preferred embodiment the combination contains memantine in the range of about 2 to about 20 mg/day and baclofen in the range of about 5 to about 40 mg/day. In case of serious need the combination may more preferably contains memantine in the range of about 10 to about 40 mg/day and baclofen in the range of about 20 to about 160 mg/day.

The invention also relates to the pharmaceutical compositions comprising memantine and baclofen combinations and pharmaceutically acceptable excipients.

Suitable routes of administration may, for example, include oral, rectal, transdermal administration or parenteral delivery. The pharmaceutical compositions of the invention can be formulated as liquids or solids, for example solutions, suspensions, emulsions, liposomes, granules, tablets, film-tablets or capsules.

The pharmaceutical compositions can be administered by variety of routes and dosage forms. The memantine and baclofen active ingredients can be formulated into a pharmaceutical composition either in combination or separately and the compositions can be administered in either single or multiple doses.

The dosage required to exert the therapeutic effect can vary within wide limits and will be fitted to the individual requirements in each of the particular case, depending on the stage of the disease, the condition and the bodyweight of the patient to be treated, as well as the sensitivity of the patient against the active ingredient, route of administration and number of

daily treatments. The actual dose of the active ingredient to be used can safely be determined by the attending physician skilled in the art in the knowledge of the patient to be treated.

For the sake of a simple administration it is suitable if the pharmaceutical compositions comprise dosage units containing the amount of the active ingredient to be administered once, or a few multiples or a half, third or fourth part thereof. Such dosage units are e.g. tablets, which can be powdered with grooves promoting the halving or quartering of the tablet in order to exactly administer the required amount of the active ingredient.

The pharmaceutical compositions containing the active ingredients according to the present invention usually contain 3 to 200 mg of active ingredients meaning preferably 1 to 40 mg of memantine and 2 to 160 mg of baclofen in a single dosage unit. In a further preferred embodiment the composition contains 1 to 20 mg of memantine and 2 to 40 mg of baclofen in each dosage unit. Depending on the stage of the disease the compositions may more preferably contain 5 to 40 mg of memantine and 10 to 160 mg of baclofen in each dosage unit.

It is, of course possible that the amount of the active ingredient in some compositions or combinations exceeds the upper or lower limits defined above.

The pharmaceutical compositions of the present invention may be manufactured in a manner that is itself known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or tabletting processes.

The aim of the pharmaceutical formulation procedure of the present invention is to develop a new weight-loss promoting, oral pharmaceutical composition containing the two active ingredients and to elaborate a procedure for the reproducible industrial production of the product assuring homogenous distribution of the two active ingredients in the composition and warranting the stability of the composition till the end of the expiration date, satisfying all the strict pharmaceutical regulatory, stability and safety demands. Through the suitable industrial procedures the active ingredients are formulated into capsules, tablets, filmtablets, capsules filled with pellets or tablets, filmtablets derived from pellets.

Pharmaceutical compositions for use in accordance with the present invention thus may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art.

The active ingredients can be mixed with for example lactose, cellulose, starch, sucrose, mannitol, sorbitol, calcium phosphate and calcium sulphate as commonly used diluents. The microcrystalline cellulose functions not only as a diluent; it has also some lubricant and disintegrant properties that make it beneficial. Calcium carboxymethyl amylopectin, sodium carboxymethyl amylopectin, croscarmellose sodium, polyvinylpyrrolidone, starches can be added among others as disintegrants; gelatin, hydroxypropyl cellulose, hydroxypropyl methylcellulose and polyvidone can be used among others as binders; and other excipients can be added to modify the solubility and/or release of the active ingredients.

To the powder or granule mixture, if necessary, at any operational steps additional excipients e.g. colloidal silicon dioxide, talc, calcium stearate, glyceryl monostearate, magnesium stearate, polyethylene glycol, sodium stearyl fumarate, stearic acid and zinc stearate are added as lubricants or glidants and/or different colouring and/or flavouring agents and/or additives modifying the drug release can be used. The compressed tablets or filled capsules can be film or sugar-coated.

The above described ingredients and different routes of manufacture are merely representative. Other materials as well as processing techniques and the like well known in the art can also be used.

The combinations and compositions of the present invention are useful for achieving body weight loss and for the treatment of overweight, obesity or related conditions. Consequently the invention relates to the method of treatment of overweight and obesity in a mammal, particularly in human by administering an effective amount of memantine and baclofen. The combinations of memantine and baclofen are administered simultaneously or subsequently.

Studies and results substantiating the invention

Studying the efficacy on weight loss using mouse diet-induced obesity test

The experiments were performed using a diet-induced obesity (DIO) test. The DIO test is a widely accepted animal model of human obesity well mimicking the development and course of the disease, its comorbidities as well as its response to pharmacological medications (Hariri and Thibault Nutr. Res. Rev. 23:270-299 2010). Young (22-25 g) male C57Bl6 mice were fed with high-fat diet (e.g. D12492, Research Diets Inc., New Brunswick, NJ, USA), thus these animals became obese compared to mice kept on a control diet. The body weights of control and obese mice were 31.84 ± 0.89 and 45.74 ± 0.78 g, respectively, in the first experiment

(n=8 per group, mean ± SEM). These values were 30.47 ± 0.58 and 45.38 ± 0.61 g (n=20 per group) in the second experiment, and 27.61 ± 0.34 and 41.00 ± 0.91 (n=8 per group) in the third experiment (Study 2). Then the animals were assigned to different groups and treated with different vehicles or test compounds. Test compounds were dissolved in water and administered *per os* twice daily in a volume of 10 ml/kg of body weight. The animals were weighed daily during the experiments. The percent weight loss of each animal compared the baseline body weight was calculated at the end of the two-week-long experiment. The average percent weight change of the vehicle group was subtracted from the percent weight change of each animal, thus the vehicle-corrected weight loss was calculated. The statistical evaluation of results included descriptive statistics (mean and standard error). Furthermore, statistical significance of differences between groups was evaluated using one-way or factorial ANOVA test followed by Duncan's post-hoc test. Interactions between different treatments (i.e. combination of drugs) were evaluated using factorial ANOVA test.

Study 1

Studying the effects of 2.5 mg/kg memantine and 2 mg/kg baclofen separately and in combination, we found that memantine did not influence the body weight of treated animals compared to vehicle controls (body weight loss: 0.1 %). Baclofen caused a body weight loss of 3.2 %, which was statistically non-significant. In contrast, treatment with the combination of memantine and baclofen caused 8.7 % decrease in the body weight. The body weight loss of the group treated with the combination was statistically significantly higher ($p < 0.05$, one-way ANOVA and Duncan's post hoc test) than in the vehicle, memantine alone or baclofen alone groups (Figure 1). The doses shown in Figure 1 were administered *per os* twice daily. The results are shown as mean ± SE of percent vehicle-corrected weight loss. There were no statistical differences between the other three groups. (Number of animals: n = 8 per group, except the memantine group, where n = 7.)

These data suggested a striking synergistic effect. Therefore, we repeated the experiment with larger group sizes (n = 20 per group) in order to statistically assess the likelihood of this apparent synergy.

Synergy is considered to be statistically proven if the factorial ANOVA test with the two drug treatments as two factors indicates a significant interaction between the two factors (Slinker J. Mol. Cell. Cardiol. 30:723-731 1998). The null hypothesis of the interaction is that the two drugs exert their effect independently from each other, therefore these effects are summed up when the drugs are administered in combination (linear additivity). Rejection of the null hypothesis (significant interaction) means a significant difference between the sum of the

effect of the two drugs (administered alone) and the effect of the combination (contra- or supraadditivity, depending on the direction of deviation). If the data were obtained from more than one experiment, then the experimental tier makes a third factor in the statistical analysis. Therefore, the results of the first (small group size, n=8) and second (n=20) experiment were pooled in the final analysis and a factorial ANOVA was performed on these data with the following three factors: 1: memantine treatment; 2: baclofen treatment; 3: experimental tier. Pooling of the datasets from the two experiments is justified because the experimental tier as factor did not produce significant alteration either alone (p=0.648), or in interaction with any of the treatments (memantine x experiment: p = 0.429; baclofen x experiment: p = 0.648). In contrast, both memantine and baclofen treatments as factors showed a highly significant effect (memantine: p = 0.010; baclofen: p<0.001). The probability of the absence of interaction between memantine and baclofen treatments was p=0.058. This result confirms a strong, at least additive interplay between the effects of the two drugs, and also implies with a high probability (94.2 %) the potential presence of a supra-additive interplay (synergy) (Figure 2). The data in Figure 2 are presented as mean ± SE of percent vehicle-corrected weight loss. The statistical analysis of the synergistic interaction was performed using factorial ANOVA (Slinker J. Mol. Cell. Cardiol. 30:723-731 1998). Group sizes: n=28 per group (except the memantine group, where n=27), In this kind of graph (Figure 2), parallel lines would represent additivity, rightward divergent lines indicate synergistic interaction.

These experimental results indicate an apparent interaction whereby memantine alone does not exert a considerable weight-reducing effect but potentiates the weight reducing effect of baclofen. This interpretation was supported by the finding that weight loss of memantine-treated group did not differ significantly from the weight loss of vehicle-treated group either in the first experiment, or in the pooled dataset (first experiment: p=0.957, pooled dataset: p=0.449, Duncan's post hoc test). In contrast, when memantine was administered in combination with baclofen, it increased the effect of baclofen significantly, as the weight loss of the group receiving the combination was significantly higher than the weight loss of the group receiving baclofen alone (first experiment: p=0.019, pooled dataset: p=0.005, Duncan's post hoc test).

Study 2

We have also tested the combination of phentermine and baclofen. In the study investigating the effects of 2.5 mg/kg phentermine and 2 mg/kg baclofen, both drugs decreased the body weight moderately (by 5.4% and 3.6%, respectively). However, the body weight loss of animals receiving the combination of these drugs (4.9 %) did not exceed the body weight loss

caused by phentermine alone. There was no significant difference between the groups (including the vehicle group as well). Although the group sizes (n=8 per group) were relatively small, these results clearly showed an infra-additive interaction between the two drugs when applied in combination (Figure 3). Data in Figure 3 are presented as mean ± SE of percent vehicle-corrected weight loss.

In conclusion, studying the efficacy of combined treatments on weight loss showed that there is a synergistic (supra-additive) or at least additive interaction between memantine and baclofen in terms of their weight-reducing effect. On the other hand, it has also been shown that combining two drugs having moderate weight-reducing effects does not necessarily result in additive or synergistic interaction.

Studies on side effects in mice

Examination of rotarod performance impairing effects in mice

The rotarod test is a widely used simple and objective method to detect the side effects affecting motor function in rodents. This method is also capable for sensitive detection of a central muscle relaxant effect, which is a pharmacological feature of both memantine and baclofen (Farkas et al. J. Pharmacol. Toxicol. Methods 52:264-273 2005). However, other CNS side effects (e.g. sleepiness, disturbances in coordination) also impair rotarod performance. Therefore this method was used to assess liability of the combination memantine and baclofen to produce unwanted side effects.

Mice were placed on a rod rotating with a constant speed of 12rpm. After training, i.e. after habituation to the rotarod three times for 120 seconds on the previous day, the mice are usually able to run on the rod for 120 seconds without falling down. Immediately before the treatment with the test compounds, the mice were tested and only those able to stay on the rod for 120 seconds were involved to the experiment. Test compounds were dissolved in distilled water (vehicle) and administered orally to groups of ten male NMRI mice (20-24 g). One group was treated with vehicle in each experimental session. Dose-response relationships for memantine, baclofen and their combination were investigated in three separate experimental sessions. We calculated the mean latency to fall in each group and the percent change relative to the latency in the vehicle group. ED_{50} values (effective doses causing 50 % failure rate) were calculated for each compound and treatment type using logistic regression in order to characterize the effect of the compounds. The statistical analysis of the latency to fall was

performed using ANOVA test followed by Duncan's post hoc test. In order to reveal whether the effect of the combination is higher than the effect of the compounds alone and also to clarify whether a supra-additive or infra-additive interaction is present, we performed an isobolographic analysis (Tallarida et al. Psychopharmacology (Berlin) 133:378-382 1997). The results are presented in Table 1 and Figure 4.

TABLE 1

The time to falling (mean and SE) in the rotarod test

Memantine [mg/kg]	0	5	10	20	
Mean latency to fall (sec)	120	112.7	96.3	41.8**	
SE	0.0	7.3	12.5	10.1	
Baclofen [mg/kg]	0	5	10	20	
Mean latency to fall (sec)	118.1	106.7	94.2	53.7**	
SE	2	9	12.4	13.5	
Memantin [mg/kg]	0	2.5	5	10	20
+Baclofen [mg/kg]	0	2	4	8	16
Mean latency to fall (sec)	120	120	106.9	85.8**	7.6**
SE	0	0	9.1	12.7	0.9

All latency values presented in Table 1 show means (and SE – standard error of mean) from 10 animals. The dose "0" stands for the group receiving only vehicle (distilled water). Measurements were performed 60 minutes after treatment. **: $p<0.01$ (ANOVA followed by Dunnett's post hoc test; no asterisks: $p>0.05$).

Memantine at a dose of 20mg/kg significantly decreased the latency to fall compared to the vehicle group. However, the doses of 5 and 10mg/kg did not significantly decrease the latency to fall. The ED_{50} for memantine was 16.1±1.7 mg/kg (mean±SE). Baclofen caused a significant effect also only at the dose of 20 mg/kg and its ED_{50} (18.3±3.3 mg/kg) was comparable to that of memantine. In the case of groups treated with one of the four 1.25 : 1 fixed dose-ratio (1.25 : 1) combinations of memantine and baclofen, the two highest doses (memantine and baclofen: 10 and 8; 20 and 16 mg/kg, respectively) caused significant effect.

The calculated ED_{50} of the combination was 21.6±1.5 mg/kg (in terms of summed equieffective doses), which was significantly higher than the theoretical ED_{50} (17.0±1.7mg/kg) calculated assuming additivity (Figure 4).

It was concluded that the dose of baclofen that provided an efficient weight reducing effect in the mouse DIO test in combination with memantine (2 mg/kg/treatment) is below the dose that is eliciting muscle relaxation or other side-effects. Moreover, the dose combination showing synergy or additivity in terms of body weight reducing effects does not show synergy but an infra-additive interaction in terms of motor side effects.

Studying the effect on spontaneous motor activity of mice

NMDA receptor antagonists are known to cause dose-dependent behavioral activation in rodents, which is manifested in increased locomotor activity (Sukhanov et al. Behav. Pharmacol. 15:263-271 2004). This behavior may correspond to side effects observed in the clinical practice, such as agitation and restlessness, which are rarely seen with memantine. We have studied the modulating effect of baclofen on the locomotor activity increasing effect of memantine when administered to mice in combination. Groups of male C57Bl6J mice (25-32 g; Wobe-Harlan, Hungary; 8-10 mice/group) were treated orally with 2 mg/kg baclofen, 2.5 mg/kg memantine or their combination or vehicle (distilled water) twice daily during the light phase of diurnal light-dark cycle. After one day of habituation, the activity of the animals was recorded continuously for 24 hours on the first and 14th day of treatment using an automated behavioral activity measurement system (LABORAS, Metris, Netherlands).. However, only the data from the light phase (12 hours) are shown. The animals were housed individually during the whole experiment in their home cages, which enabled the activity recording as well. The mechanical vibrations and gravity related static signals evoked by the movement of the animals were transformed to an electrical signal by the system, and these recorded signals were evaluated off-line by a computer algorithm (Quinn et al. J. Neurosci. Methods 130:83-92 2003). The behavior of the mice was categorized by the software as locomotor activity, immobility, climbing and grooming. Figure 5 shows the mean and SEM of time spent with horizontal motor activity during the 12-hour light phase. Statistical analysis was performed using ANOVA followed by Tukey's post hoc test. The statistical significance of effects of drug treatments was calculated compared to vehicle and also compared to other drug-treated groups.

Studying the effects of 2.5 mg/kg memantine and 2 mg/kg baclofen alone and in combination, memantine statistically significantly ($p < 0.05$) increased the horizontal motor activity on the

14th day of treatment (an effect that is typical for NMDA antagonists). This effect of memantine did not reach statistical significance on the first day. In contrast, neither baclofen alone, nor the combination altered the motor activity either on the first or on the 14th day of treatment (Figure 5).

In conclusion, the dose-combination showing a synergistic effect in terms of weight reduction does not show a synergistic effect in terms of side effects related to spontaneous motor activity. On the contrary, baclofen apparently attenuated the locomotor activity increasing effect of memantine.

Claims

1. Combination of memantine and baclofen active ingredients.

2. The combination of Claim 1 for the treatment of overweight and obesity.

3. The combination according to Claim 1 or Claim 2, wherein the therapeutically effective amount of memantine is in the range of about 2 to about 40 mg/day and the therapeutically effective amount of baclofen is in the range of about 5 to about 160 mg/day.

4. The combination according to any of Claims 1-3, wherein the therapeutically effective amount of memantine is in the range of about 10 to about 40 mg/day and the therapeutically effective amount of baclofen is in the range of about 20 to about 160 mg/day.

5. The combination according to any of Claims 1-3, wherein the therapeutically effective amount of memantine is in the range of about 2 to about 20 mg/day and the therapeutically effective amount of baclofen is in the range of about 5 to about 40 mg/day.

6. A pharmaceutical composition comprising the combination of Claim 1 and pharmaceutically acceptable excipients.

7. The composition of Claim 6 for use in the treatment of overweight and obesity.

8. The composition according to Claim 6 or Claim 7, which contains about 1 to 40 mg of memantine and about 2 to 160 mg of baclofen in each dosage unit.

9. The composition according to any of Claims 6-8, wherein the composition contains about 5 to 40 mg of memantine and about 10 to 160 mg of baclofen in each dosage unit.

10. The composition according to any of Claims 6-8, wherein the composition contains about 1 to 20 mg of memantine and about 2 to 40 mg of baclofen in each dosage unit.

11. Method of treatment of overweight and obesity in a mammal, particularly in human characterized by administering the therapeutically effective amount of memantine and baclofen in combination simultaneously or subsequently to the mammal to be treated.

12. The method according to Claim 11, wherein the therapeutically effective amount of memantine is in the range of about 2 to about 40 mg/day and the therapeutically effective amount of baclofen is in the range of about 5 to about 160 mg/day.

13. The method according to Claim 11 or Claim 12, wherein the therapeutically effective amount of memantine is in the range of about 10 to about 40 mg/day and the therapeutically effective amount of baclofen is in the range of about 20 to about 160 mg/day.

14. The method according to Claim 11 or Claim 12, wherein the therapeutically effective amount of memantine is in the range of about 2 to about 20 mg/day and the therapeutically effective amount of baclofen is in the range of about 5 to about 40 mg/day.

15. Method of treatment according to Claims 11-14 characterized by administering the pharmaceutical composition according to Claim 6 to the subject to be treated.

16. The method according to Claim 15, wherein the pharmaceutical composition contains memantine in the range of about 1 to about 40 mg in each dosage unit and baclofen in the range of about 2 to about 160 mg in each dosage unit.

17. The method according to Claim 15 or Claim 16, wherein the pharmaceutical composition contains memantine in the range of about 5 to about 40 mg in each dosage unit and baclofen in the range of about 10 to about 160 mg in each dosage unit.

18. The method according to Claim 15 or Claim 16, wherein the pharmaceutical composition contains memantine in the range of about 1 to about 20 mg in each dosage unit and baclofen in the range of about 2 to about 40 mg in each dosage unit.

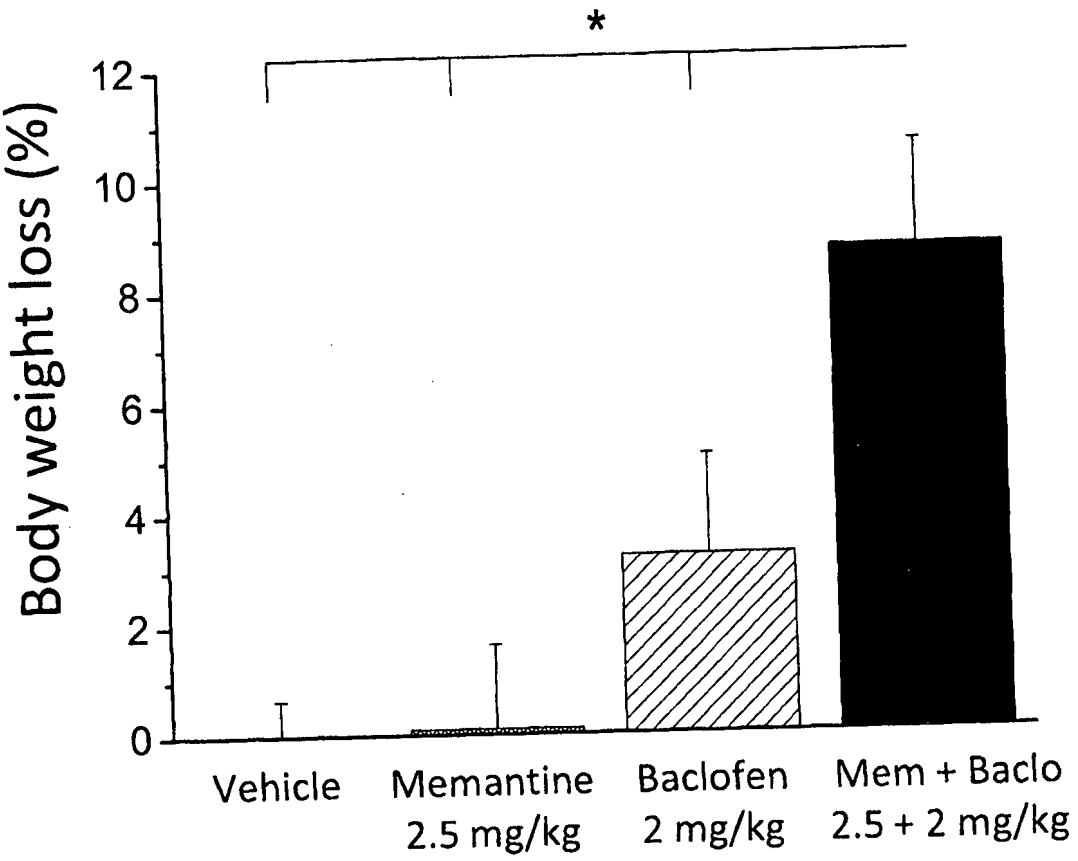
*
Body weight loss (%)
12
10
8
6
4
2
0
Vehicle
Memantine 2.5 mg/kg
Baclofen 2 mg/kg
Mem + Baclo 2.5 + 2 mg/kg

Figure 1

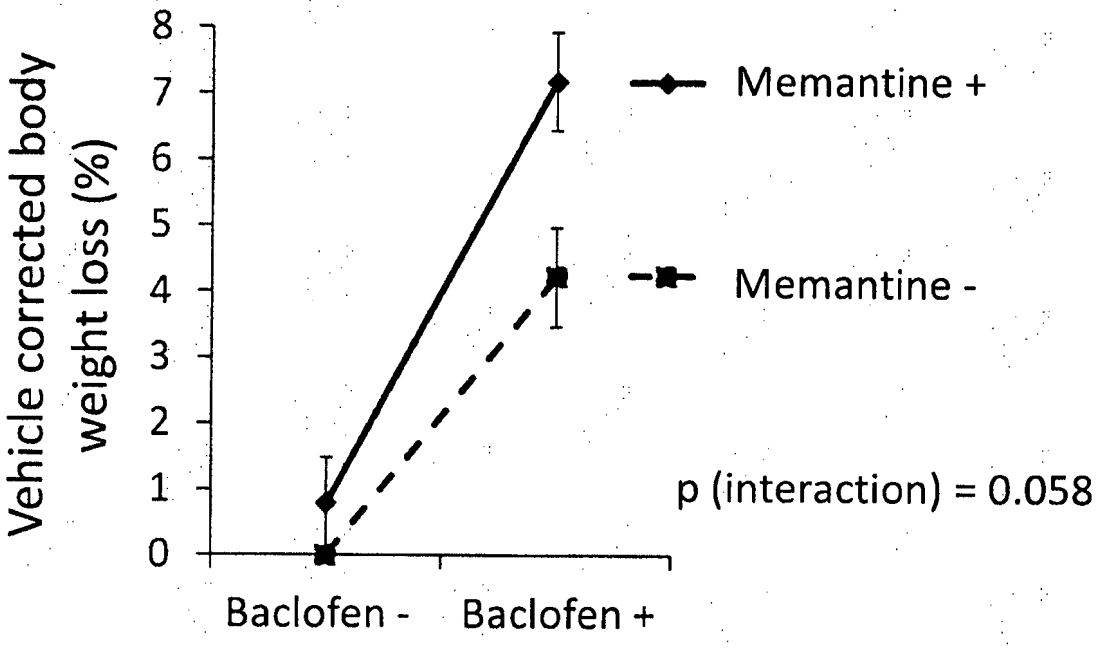
Vehicle corrected body weight loss (%)
8
7
6
5
4
3
2
1
0
Baclofen -
Baclofen +
Memantine +
Memantine -
p (interaction) = 0.058

Figure 2

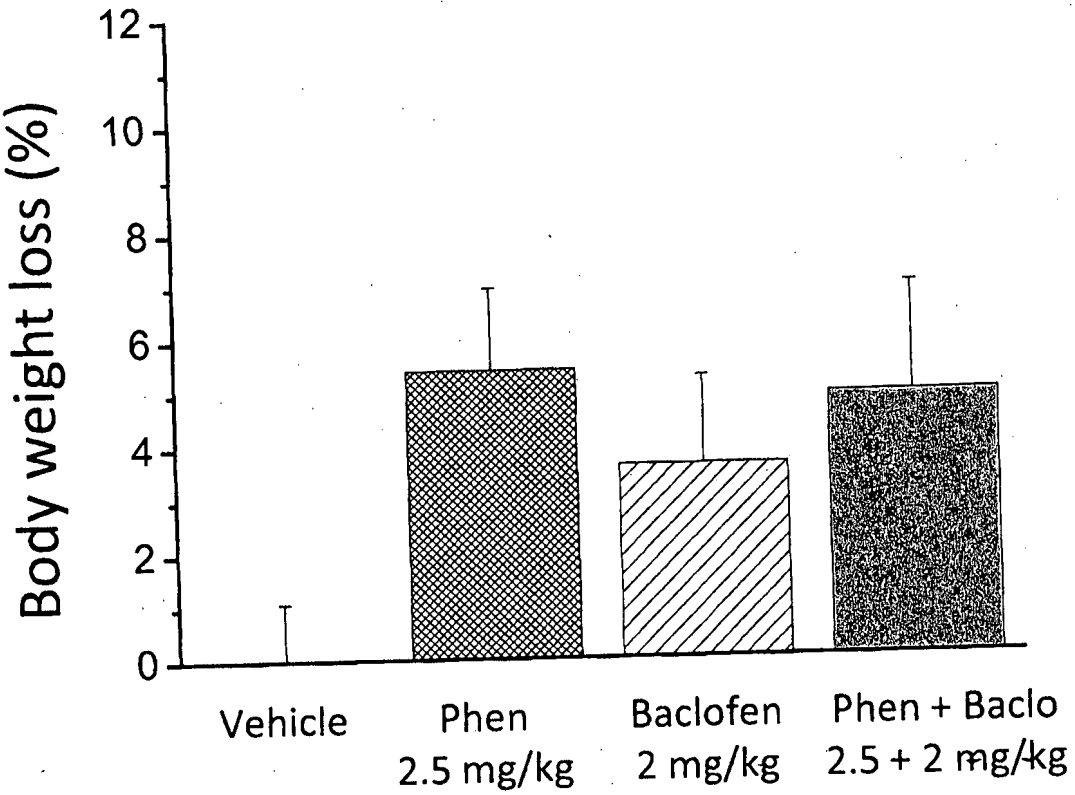
Body weight loss (%)
12
10
8
6
4
2
0
Vehicle
Phen
2.5 mg/kg
Baclofen
2 mg/kg
Phen + Baclo
2.5 + 2 mg/kg

Figure 3

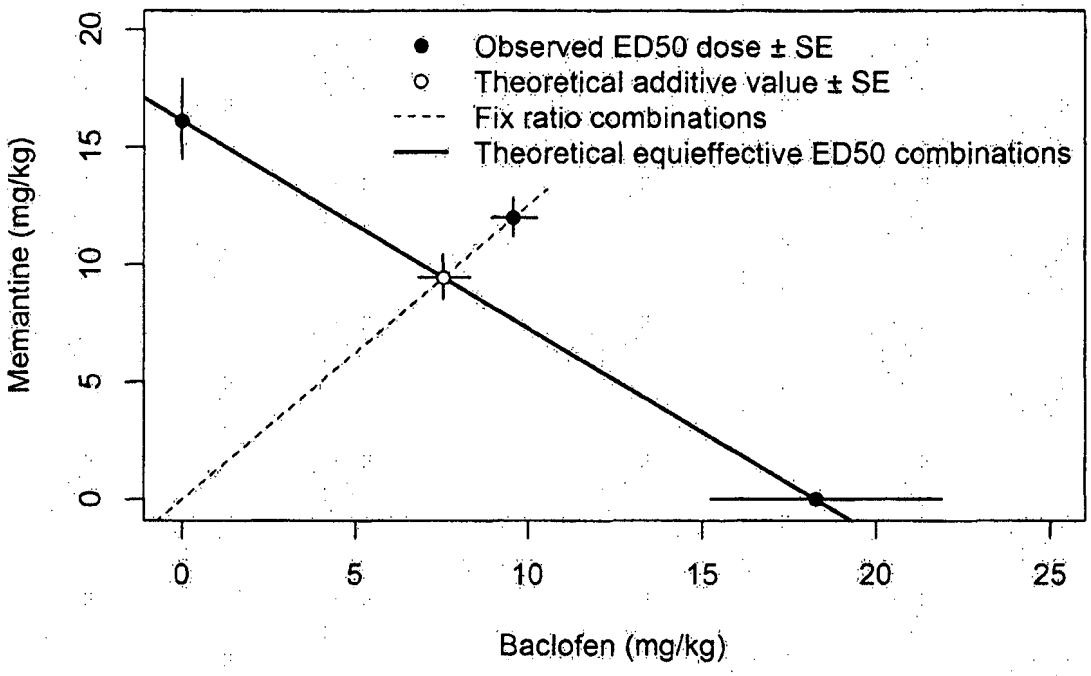
Observed ED50 dose ± SE
Theoretical additive value ± SE
Fix ratio combinations
Theoretical equieffective ED50 combinations
Memantine (mg/kg)
Baclofen (mg/kg)
0
5
10
15
20
25

Figure 4

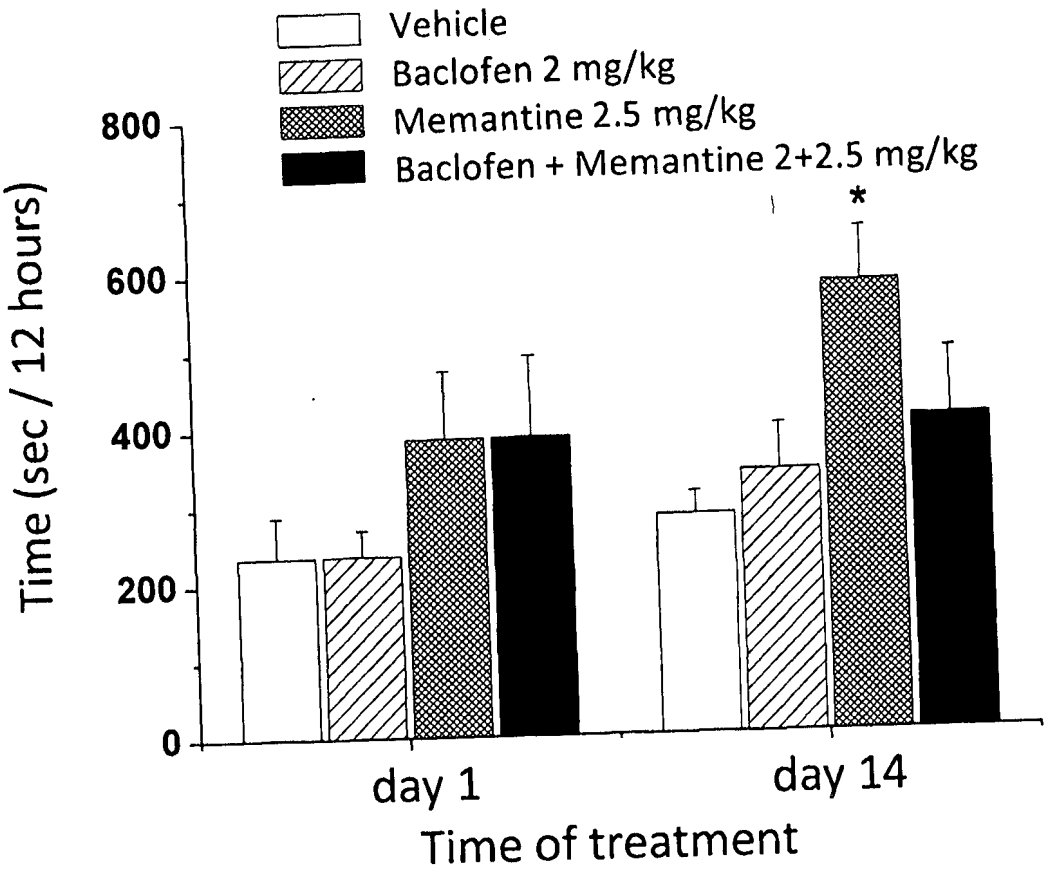
Vehicle
Baclofen 2 mg/kg
Memantine 2.5 mg/kg
Baclofen + Memantine 2+2.5 mg/kg
Time (sec / 12 hours)
800
600
400
200
0
*
day 1
day 14
Time of treatment

Figure 5

INTERNATIONAL SEARCH REPORT

International application No
PCT/HU2012/000119

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/13 A61K31/195 A61P3/04
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, SCISEARCH, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 2 058 008 A1 (UNIV NAGOYA NAT UNIV CORP [JP]) 13 May 2009 (2009-05-13) claims; examples	1-18
Y	PIOTR POPIK ET AL: "Memantine reduces consumption of highly palatable food in a rat model of binge eating", AMINO ACIDS ; THE FORUM FOR AMINO ACID AND PROTEIN RESEARCH, SPRINGER-VERLAG, VI, vol. 40, no. 2, 23 June 2010 (2010-06-23), pages 477-485, XP019873224, ISSN: 1438-2199, DOI: 10.1007/S00726-010-0659-3 discussion	1-18
Y	US 2004/102525 A1 (KOZACHUK WALTER E [US]) 27 May 2004 (2004-05-27) paragraph [0224] - paragraph [0230]	1-18

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 December 2012	08/01/2013

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1

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/HU2012/000119

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 2058008 A1	13-05-2009	EP 2058008 A1	13-05-2009
		US 2010197789 A1	05-08-2010
		WO 2008018275 A1	14-02-2008
US 2004102525 A1	27-05-2004	US 2004102525 A1	27-05-2004
		US 2010076075 A1	25-03-2010

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A61P 3/04(2006.01)

权利要求书1页 说明书11页 附图3页

(54)发明名称

美金刚胺和巴氯芬的治疗组合以及含有该组合的药物组合物

(57)摘要

本发明涉及美金刚胺和巴氯芬活性成分的组合，并且还涉及通过共同给药巴氯芬和美金刚胺实现体重减轻并且由此治疗肥胖和相关共存病的方法。

CN 103930099 A

1. 美金刚胺和巴氯芬活性成分的组合。

2. 权利要求 1 的组合，用于治疗超重和肥胖。

3. 根据权利要求 1 或权利要求 2 的组合，其中治疗有效量的美金刚胺的范围为约 2 至约 40mg/ 天和治疗有效量的巴氯芬的范围为约 5 至约 160mg/ 天。

4. 根据权利要求 1-3 任一项的组合，其中治疗有效量的美金刚胺的范围为约 10 至约 40mg/ 天和治疗有效量的巴氯芬的范围为约 20 至约 160mg/ 天。

5. 根据权利要求 1-3 任一项的组合，其中治疗有效量的美金刚胺的范围为约 2 至约 20mg/ 天和治疗有效量的巴氯芬的范围为约 5 至约 40mg/ 天。

6. 一种药物组合物，其包含权利要求 1 的组合和药物学上可接受的赋形剂。

7. 权利要求 6 的组合物，用于超重和肥胖的治疗中。

8. 根据权利要求 6 或权利要求 7 的组合物，其在每个剂量单位中含有约 1 至 40mg 的美金刚胺和约 2 至 160mg 的巴氯芬。

9. 根据权利要求 6-8 任一项的组合物，其中组合物在每个剂量单位中含有约 5 至 40mg 美金刚胺和约 10 至 160mg 巴氯芬。

10. 根据权利要求 6-8 任一项的组合物，其中组合物在每个剂量单位中含有约 1 至 20mg 美金刚胺和约 2 至 40mg 巴氯芬。

11. 治疗哺乳动物，特别是人超重和肥胖的方法，其特征在于将治疗有效量的美金刚胺和巴氯芬组合同时或相继给药于待治疗的哺乳动物。

12. 根据权利要求 11 的方法，其中治疗有效量的美金刚胺的范围为约 2 至约 40mg/ 天和治疗有效量的巴氯芬的范围为约 5 至约 160mg/ 天。

13. 根据权利要求 11 或权利要求 12 的方法，其中治疗有效量的美金刚胺的范围为约 10 至约 40mg/ 天和治疗有效量的巴氯芬的范围为约 20 至约 160mg/ 天。

14. 根据权利要求 11 或权利要求 12 的方法，其中治疗有效量的美金刚胺的范围为约 2 至约 20mg/ 天和治疗有效量的巴氯芬的范围为约 5 至约 40mg/ 天。

15. 根据权利要求 11-14 的治疗方法，其特征在于将根据权利要求 6 的药物组合物给药于待治疗的患者。

16. 根据权利要求 15 的方法，其中药物组合物在每个剂量单位中含有约 1 至 40mg 的美金刚胺和约 2 至 160mg 的巴氯芬。

17. 根据权利要求 15 或权利要求 16 的方法，其中药物组合物在每个剂量单位中含有约 5 至 40mg 的美金刚胺和约 10 至 160mg 的巴氯芬。

18. 根据权利要求 15 或权利要求 16 的方法，其中药物组合物在每个剂量单位中含有约 1 至 20mg 的美金刚胺和约 2 至 40mg 的巴氯芬。

美金刚胺和巴氯芬的治疗组合以及含有该组合的药物组合物

发明领域

[0001] 本发明涉及美金刚胺(memantine)和巴氯芬(baclofen)活性成分的组合物，其中巴氯芬还表示外消旋巴氯芬、巴氯芬的对映异构体和/或前药。本发明还涉及这样的组合物在用于治疗超重、肥胖或相关病症或用于实现体重减轻的方法中的用途，其中同时或按序(优选在短的时间段内)给药美金刚胺和巴氯芬。本发明进一步涉及包含美金刚胺和巴氯芬活性成分的药物组合物以及这样的组合物在用于治疗超重、肥胖或相关病症或用于实现体重减轻的方法中的用途。所提及的本发明的治疗方法还表示补充其他手段的治疗方案，所述其他手段如饮食或生活方式改变、饮食补充剂、草药或药物治疗。

[0002] 发明背景

[0003] 超重和肥胖是现代世界中日益增长的公众健康问题。在医学实践中，将超重限定为高于25kg/m^{2}的体重指数(BMI)，而肥胖为BMI>30kg/m^2。到2011年为止，与1980年相比，肥胖的发病率多出一倍多(WHO Fact sheet N° 311,2011);http://www.who.int/mediacentre/factsheets/fs311/en/)。在世界的大部分地区，超重和肥胖的发病率逐步增长(欧洲、USA、中东和亚洲)。根据世界卫生组织(WHO)在2008年的估计，超重和肥胖的全世界发病率分别为15亿和5亿。超重和肥胖，即，超过健康极限的增加的体重指数，以严重性依赖方式提高了几种疾病的风险。在本发明的描述中，下文的肥胖将表示超重和肥胖两个类别。肥胖是几种疾病和医学状况的已知风险因素，所述疾病和医学状况如糖尿病、胰岛素抗性、代谢综合症、高血压、动脉粥样硬化、冠心病、心力衰竭、中风、肠道疾病(如，胆囊炎和胆结石)、骨关节炎、矫正术异常(orthopedic abnormalities)、呼吸困难、呼吸暂停、卵巢囊肿、恶性肿瘤(如，乳腺、前列腺和结肠肿瘤)、麻醉并发症、烧心、静脉曲张、感染和湿疹(Kopelman Nature404:635-6432000;Rissanen等，BMJ301:835-8371990)。肥胖对生活期望也具有负面影响，并且与吸烟、高血压和高胆固醇血症一起，其是几种慢性疾病的主要风险因素之一(James,Comparative Quantification of Health Risks Global and Regional Burden of Diseases Attributable to Selected Major Risk Factors,Chapter8,WHO,Geneva,2004)。

[0004] 超重和肥胖是全世界死亡率的第五大风险因素。每年至少2.8百万承认因为超重或肥胖的结果而死亡(WHO Fact sheet N° 311,2011)。对肥胖人群体重减轻的医学需求以少如5%的长期体重减轻能够显著改善心血管发病率和死亡率的事实为基础(Goldstein,Int.J.Obes.Relat.Metab.Disord.16:397-4151992)。因此，对于肥胖和相关的共同存在的病症的治疗存在巨大的尚未满足的医学需求。

[0005] 已知通过严格的低卡里路饮食和锻炼可以减轻肥胖。然而，根据医学经验，这些类型的生活方式改变长期而言是无效的并且在一些病人群体中具有有限的实用性(Powell等，Am.Psychol.62:234-2462007;Sahoo,Obesity Drug Markets in the US and EU:Analysis of product pipelines and the competitive environment.Business Insights Ltd.,2008)。因此，对于可以支持低热量饮食和可以增强行为改变有效性的药物

存在很大的公众需求 (Witkamp Pharm. Res. 28:1792-18182011)。

[0006] 肥胖的进展是多因素的，但最终总是呈现为能量摄入和消耗的调控的损伤。尽管人体目的在于维持其体重，但随着年龄增长适度的体重增加被认为是正常的生理过程。然而，在现代社会中，几个环境因素，如久坐的生活方式和高能量食物的易获得性，严重地影响了正常的体重体内平衡控制，这导致提高的身体脂肪的存储 (Bessesen Physiol. Behav. 104:599-6072011)。因此，抗肥胖药物疗法的目的在于通过 (1) 降低能量吸收，(2) 降低饥饿感 / 提高饱腹感，由此降低能量摄入，或 (3) 提高存储能量的利用，从而降低未利用的能量 (Witkamp Pharm. Res. 28:1792-18182011)。在这三种药物疗法选项中，通过使用在中枢神经系统 (CNS) 中作用的药物来实现后两者。

[0007] CNS 的一些区域在能量摄入、能量消耗和代谢的调控中起着关键作用。例如，一个主要的综合中心是下丘脑 (Gao 等，Annu. Rev. Neurosci. 30:367-3982007)。在下丘脑中已经鉴定出超过 50 种的在能量体内平衡的调控中起着已经证实的或潜在作用的神经递质。涉及能量提供平衡调控的神经递质给抗肥胖药物疗法提供了潜在的目标。然而，由于肥胖的发展以及食物摄入和能量体内平衡的调控受到多个中枢和外周途径的影响 - 其中一些倾向于快速适应和抵抗 - 仅靶向一个途径难以提供有效的药物疗法 (Aronne 等，Expert Opin. Emerg. Drugs16:587-5962011)。因此，为了实现最佳治疗效果，可能需要靶向更多途径 - 例如，通过同时共同给药超过一种药物。然而，当使用组合疗法时，可能会产生不可预测的相互作用，尤其是如果涉及 CNS 机理。这些相互作用从通过叠加作用的拮抗相互作用到超叠加的相互作用 (协同作用)。

[0008] 获得足够的功效是关于治疗实用性的基本要求。即，如果抗肥胖药物疗法的功效没有达到特定的极限，药物许可机构 (食品和药品管理局，USA 的 FDA 和欧洲药物机构，欧洲的 EMA) 将不会同意批准药物。根据实际的 FDA 方针，所需的平均初步功效终点为 1 年使 5% 体重减轻 (vs. 安慰剂治疗组)，同时绝对的初步功效终点需要至少 35% 的治疗群体应当减掉超过 5% 的体重 (vs. 安慰剂治疗组)(Guidance for Industry Developing Products for Weight Management. U. S. Department of Health and Human Services, FDA(2007))。EMA 规定的理想最小体重减轻甚至更高 :10% (Guideline On Clinical Evaluation Of Medicinal Products Used In Weight Control. EMA(2008))。

[0009] 然而，抗肥胖药物足够有效还是不够的。此外，药物管理机构对于这些种类的药物设定了非常高的安全性标准。因此，这样的药物在治疗剂量下必须基本上没有副作用。尽管有效的抗肥胖疗法需要在中枢起作用的药物，在书写本申请时，在市场上还不存在批准的表明用于长期使用的药物。这种 CNS 药物的缺乏至少部分是由于高安全性和耐受性标准。唯一批准用于长期使用的抗肥胖治疗是非 -CNS 药物奥利司他 (orlistat)，其阻断食物性脂肪的消化以及随后的吸收。然而，奥利司他的功效比理想的低得多，并且麻烦的胃肠道副作用也限制了其的广泛使用 (Filippatos 等，Drug Saf. 31:53-652008)。使用 CNS 药物获得足够的治疗指数，即，有效的和引起副作用的剂量的良好分离，是一个特别有挑战性的任务。两种 CNS 药物，利莫那班 (rimonabant) 和西布曲明 (sibutramine)，由于不希望的副作用，最近撤出了市场 (Kennett 等，Pharmacol. Biochem. Behav. 97:63-832010)。因此，获得合适的功效和足够小的副作用，因此良好的耐受性和安全性在肥胖的药物疗法中是关键的和具有挑战性的问题。在另一个方面中，介导功效和副作用的剂量之间的合适分离也是必

需的标准，以满足良好耐受性和安全性的需求。

[0010] 在一些国家中，通过胃肠道手术干预（称为肥胖（bariatric）外科手术），治疗对节食和药物疗法无应答的具有并存（comorbid）病症（例如，糖尿病、高血压）的严重肥胖病人（BMI>35-40）(Powell 等，Am. Psychol. 62:234-2462007)。然而，这样的外科手术干预具有相当大的风险，包括死亡率、严重的手术后副作用和高比率的手术后并发症(Encinosa 等，Med. Care44:706-7122006)。尽管存在实质性的风险，但由于肥胖相关的并存病对生活期望和生活质量的严重影响，严重肥胖的人群仍然得益于外科手术治疗。因此，将来的药物疗法提供接近于外科手术的高功效（即 20-25％体重减轻 (Bueter 等，Obes. Facts2:325-3312009)）并且较少风险和副作用的合理假设可以给严重肥胖的病人提供更好的治疗选择。

[0011] 最近，出现了几种药物－最初研发用于治疗其他疾病－以常规治疗剂量在人类中具有一定的体重减轻作用（例如，唑尼沙胺 (zonisamide)、托吡酯 (topiramate)、安非他酮 (bupropion)、那曲酮 (naltrexone)(Kennett 等，Pharmacol. Biochem. Behav. 97:63-832010)；阿托莫西汀 (atomoxetine)(Gadde 等，Int. J. Obes. (Lond)30:1138-11422006)；巴氯芬 (Arima 等，Intern. Med. 49:2043-20472010)；倍他司汀 (betahistine)(Barak 等，Int. J. Obes. (Lond)32:1559-15652008)；度洛西汀 (duloxetine)(Guerdjikova 等，In. t J. Eat. Disord. Epub ahead of print2011)；氟西汀 (fluoxitein)(Serretti 等，J. Clin. Psychiatry71:1259-12722010)；美金刚胺 (Hermanussen 等，Econ. Hum. Biol. 3:329-3372005)；哌醋甲酯 (Leddy 等，Obes. Res. 12:224-2322004)；舍曲林 (sertraline)(Serretti 等，J. Clin. Psychiatry71:1259-12722010)；文拉法辛 (venlafaxine)(Malhotra 等，J. Clin. Psychiatry. 63:802-8062002)。另一方面，这些药物通常具有适度功效，通常与安慰剂或基线相比，低于5％的体重减轻。此外，鉴于肥胖适应症中的高调控安全棒，它们的副作用谱是否是可接受的也是个问题。

[0012] 很长时间以来，还知道安非他命 (amphetamine) 和相似药物（例如，芬特明 (phentermine)、二乙胺苯丙酮 (diethylpropion)、苯甲曲秦、苯丙醇胺 (phenylpropanolamine)、吗吲哚 (mazindol)）具有抗肥胖作用。然而，由于心血管风险、滥用的可能和精神兴奋副作用，这些种类药物中的大部分已经退出市场 (Ioannides-Demos 等，Drug Saf. 29:277-3022006)。它们的治疗实用性还受限于它们产生耐药性的倾向性，这导致长期治疗过程中随着时间的功效减弱或停止。因此，这些化合物中的大部分已经撤回了销售许可，在 USA，商业上仍然可以获得的少数安非他命－样化合物，如芬特明，只允许用于短期治疗 (Kennett 等，Pharmacol. Biochem. Behav. 97:63-832010)。

[0013] 总之，存在几种具有微弱抗肥胖活性的药物，其单独给药时，不够有效或带有不可接受的副作用谱。然而，哪些药物的组合导致真实总和的作用（叠加相互作用）并且哪些组合没有导致这样的总和（低于叠加相互作用）绝对不是显而易见的。此外，就所需作用而言，哪些药物组合呈现出甚至比简单总和预期的更高的功效（即，高于叠加相互作用或协同作用），甚至更不明显。组合物的组分是否将增强或降低彼此的作用或最终组合物将具有比单独的组分更好或更差的副作用谱和治疗指数，也是不明显的。在对于所需作用的协同作用的情况中，协同作用是否也涉及副作用也是个问题。事实上，对于主要作用和副作用

两者的协同作用将不会产生提高的治疗指数。因此，就治疗实用性和益处而言，与单独使用组分相比，具有已知抗肥胖作用的两种药物的组合是否产生有利的组合物根本就不是显而易见的。

[0014] 巴氯芬长期以来用作中枢作用肌肉松弛药物。其主要的药理学作用是对 γ-氨基丁酸 B-型 (GABA-B) 受体的激动剂作用 (Davidoff, Ann. Neurol. 17:107-1161985)。医学实践中所用的药物是左-(S-) 和右手 (R-) 对映异构体的外消旋混合物。使用其口服形式来减轻与 CNS 损伤相关病症有联系的痉挛状态，CNS 损伤相关疾病引起称为“痉挛状态”的肌紧张性。其最常见的副作用是由于过大的肌肉放松引起的肌肉虚弱，为此，其治疗指数相当窄。此外，瞌睡和眩晕也是巴氯芬的常见副作用。因此，为了获得有效的抗痉挛但充分耐受的剂量水平，推荐了剂量滴定。用于治疗痉挛状态的口服巴氯芬的有效治疗剂量通常落入 30-80mg/ 天的范围中 (Dario 等，Drug Saf. 27:799-8182004)。与人类相似，小鼠中的抗痉挛和引起运动神经副作用的剂量也是重叠的 (Farkas 等，J. Pharmacol. Toxicol. Methods52:264-2732005)。

[0015] 已知巴氯芬降低饮食诱发的肥胖小鼠的食物摄入和体重。巴氯芬的两种对映异构体都具有体重减轻作用，然而 R-对映异构体更有效 (Sato 等，FEBS Lett. 581:4857-48642007)。在小的人类研究 (10 名肥胖病人) 中也已经证明了巴氯芬对体重的适度作用，其中以 30mg/ 天的剂量给药巴氯芬，从 10 天开始剂量递增期，并持续 12 周。研究显示出平均 1.7% 体重减轻。10 名参与者中，只有一名减掉超过 5% 的体重 (Arima 等，Intern. Med. 49:2043-20472010)。这些有限的数据表明充分耐受剂量的巴氯芬的单独治疗不能满足药物管理机构的最小功效标准。已知，例如，新药候选物绿卡色林 (lorcasetin)，其由 FDA (在其 2010 年的“完整答复信”中) 称为具有“最低限度的功效”，相对于基线，在 12 周时引起 3.5-4% 体重减轻，在 1 年长的治疗后，体重减轻 5.8%。因此，12 周的 30mg/ 天巴氯芬的低于 2% 体重降低作用可以认为是低于最低限度的。存在另一个人类巴氯芬研究，其涉及巴氯芬的食物摄入减少作用，尽管该研究不是为了评价抗肥胖功效而设计的。Broft 和她的同事 ((Broft 等，Int J. Eat. Disord. 40:687-6912007) 在七名女性参与者中研究了巴氯芬对过食症的作用。过食症不等同于肥胖，并且 7 名病人中只有 2 名是肥胖的 (BMI>30kg/m^2) 和 1 名是超重的 (BMI>25kg/m^2)。在这个研究中，平均体重不存在显著的变化 (10 周内增加 0.9kg 体重)，但巴氯芬仅降低了食物渴望和过食情况的次数。巴氯芬的目标剂量为 60mg/ 天，并且最常见的副作用是镇静。因此，这些数据表明巴氯芬具有适度的食欲降低作用，但这种单独的作用在与没有副作用相关的剂量下或至少具有可耐受副作用谱的剂量下不足以引起临床上有意义的体重减轻。

[0016] 美金刚胺是已经批准了很长时间的药物。最初 (1978 年)，其在德国进入市场，用于帕金森病、痉挛状态和其他神经疾病的治疗。之后，发现了美金刚胺以非竞争性方式阻断 N-甲基 -D-天冬氨酸 (NMDA) 受体 (Bormann, Eur. J. Pharmacol. 166:591-5921989)，显示出神经保护作用，并且在阿尔茨海默病的临床前模型中，能有效防止认知和组织学损伤 (Parsons 等，Neuropharmacology38:735-7671999) ;Rammes 等，Curr. Neuropharmacol. 6:55-782008)。然后，在血管性痴呆和阿尔茨海默病的临床试验中也证明了其功效 (Raina 等，Ann. Intern. Med. 148:379-3972008)。目前，美金刚胺是批准的并且广泛用于阿尔茨海默病治疗的药物。其通常在临床实践中的治疗剂量为 20mg/ 天，这

应当仅仅通过逐渐的剂量增加来达到。其治疗窗口狭窄，并且在剂量增加太快或给药较高剂量的情况中，可能会产生 NMDA 拮抗剂典型的副作用，如烦躁、混乱，或更严重的幻觉。然而，根据推荐的定量给药方案给药时，美金刚胺的副作用是罕见的：烦躁（1.3％）、恶心（0.9％）、眩晕（0.8％）、疲劳（0.4％）(Mobius 等，Drugs of Today40:685-6952004)。难以确定动物实验中的哪个剂量对应于人治疗剂量。然而，估算小鼠中使用口服给药的有效的抗－阿尔茨海默病剂量范围为 5-30mg/kg/ 天，基于阿尔茨海默病动物模型中的血浆浓度数据或认知和神经组织学作用 (Dong 等，Neuropsychopharmacology33:3226-32362008)；Minkeviciene 等，J. Pharmacol. Exp. Ther. 311:677-6822004)；Rammes 等，Curr. Neuropharmacol. 6:55-782008)。

[0017] 在对 5 名肥胖女性病人的开放标签临床试验中 (Hermanussen 等，Econ. Hum. Biol3:329-3372005)，发现剂量高于常规治疗剂量 (20-30mg/ 天，如果需要，使用剂量调节）的美金刚胺降低食欲、过食事件次数和体重。然而，关于抗肥胖治疗实用性的评价，这种观察的关联性非常有限，因为这些病人中除了一名全部只治疗了短的时间段 (21 天或更短时间）。一些病人在治疗过程中经历了眩晕。在更长期的开放标签研究中，其中根据标签中推荐的定量给药方案，将美金刚胺给药于 16 名肥胖的暴食者（即，将剂量逐渐提高至 20mg/kg，或为了良好耐受性的需要，保持较低剂量），美金刚胺降低了暴食事件的数量，但是没有引起体重降低 (Brennan 等，Int. J. Eat. Disord. 41:520-5262008)。因此，这些数据表明使用美金刚胺尽管能够轻微降低食欲，但在目前治疗中充分耐受的剂量没有引起实质性的体重减轻。这个结论与来自其中美金刚胺降低了暴食症大鼠模型中的暴食数量但没有降低体重的数据相一致 (Popik 等，Amino Acids40:477-4852011)。

[0018] 发明概述

[0019] 本发明是基于出乎预料的观察：美金刚胺和巴氯芬的组合应用在肥胖的小鼠模型中对体重减轻发挥了出人意料的强烈的、明显的协同作用。相反，巴氯芬与芬特明（其是另一种具有已知体重减轻作用的药物）的组合给药明显地引起了低于叠加的相互作用。此外，作为另一个出乎预料的发现，发现了美金刚胺和巴氯芬的协同且明显的体重减轻作用的剂量低于足以在涉及其现有适应症的相关小鼠模型中检测其已知治疗功效的剂量。

[0020] 我们还出人意料地发现了就副作用而言，美金刚胺和巴氯芬的组合呈现出低于叠加的相互作用，并且导致了治疗指数的提高。

[0021] 本发明涉及美金刚胺和巴氯芬活性成分的组合，其中巴氯芬也可以表示外消旋巴氯芬、巴氯芬的非对映异构体和／或前药。

[0022] 本发明进一步涉及包含美金刚胺和巴氯芬活性成分的药物组合物。

[0023] 本发明还涉及美金刚胺和巴氯芬活性成分的组合和组合物在用于治疗超重、肥胖或相关病症或用于实现体重减轻的方法中的用途。

[0024] 附图简述

[0025] 图 1 描绘了美金刚胺、巴氯芬及其组合在小鼠 DIO 测试中的功效。

[0026] 图 2 显示了美金刚胺、巴氯芬及其组合物在小鼠 DIO 测试中的体重减轻作用的大小（两个研究集合的结果）。

[0027] 图 3 显示了芬特明、巴氯芬及其组合对小鼠饮食诱发的肥胖测试中的功效。每天经口给药所示剂量两次。

[0028] 图 4 显示了美金刚胺和巴氯芬在小鼠的转棒 (rotarod) 测试中的药理学相互作用的等辐射 (isobolographic) 分析。

[0029] 图 5 显示了美金刚胺、巴氯芬及其组合对小鼠的水平运动活动的作用。

[0030] 发明详述

[0031] 本发明涉及美金刚胺和巴氯芬活性成分的组合，其中巴氯芬也可以表示外消旋巴氯芬、巴氯芬的对映异构体和 / 或前药，并且涉及这样的组合在用于治疗超重、肥胖或相关病症或用于实现体重减轻的方法中的用途，其中同时或按序（优选在短的时间段内）给药美金刚胺和巴氯芬。本发明进一步涉及包含美金刚胺和巴氯芬活性成分的药物组合物以及这样的组合物在用于治疗超重、肥胖或相关病症或用于实现体重减轻的方法中的用途。所提及的本发明的治疗方法还表示补充其他手段的治疗方案，所述其他手段如饮食或生活方式改变、饮食补充剂、草药或药物治疗。

[0032] 在我们的实验过程中，我们出人意料地发现了美金刚胺和巴氯芬的组合引起了显著的体重减轻，即使以低于其现有的人治疗剂量的剂量应用时。此外，如果在它们的副作用中没有发现相似的协同作用，那么这些药物的组合还可以呈现出副作用谱和治疗指数的提高。我们已经证明了将这些药物以就体重减轻而言发挥出明显的协同作用的剂量组合给药于小鼠时，就巴氯芬典型的 CNS 副作用（即，肌肉弱化和眩晕）而言，不存在协同作用，如通过转棒性能测量的。此外，出乎预料地，我们观察到了巴氯芬中和了美金刚胺的运动活动提高作用，这是小鼠中用美金刚胺治疗后可以观察到的作用并且这是 NMDA 拮抗剂化合物典型的。

[0033] 基于我们的实验结果，可以概括出新组合的以下关键特征：

[0034] (1) 使用美金刚胺和巴氯芬的组合可以达到高于 FDA 提出的可接受阈值的体重减轻。

[0035] (2) 在低于常用治疗剂量或落入根据目前的标签（产品特征概述 (Summary of Product Characteristics)）推荐的剂量范围下限的巴氯芬剂量可以实现这一功效。因此，规定的巴氯芬的抗肥胖剂量范围为 5-40mg/ 天，这取决于病人的体重。

[0036] (3) 在美金刚胺的情况中，在其常用治疗剂量 (20mg/ 天）或较低剂量 (2-20mg/ 天）下，可以获得成功的体重减轻作用。

[0037] (4) 由于较低剂量和 / 或涉及副作用的成分的中和作用，使用美金刚胺和巴氯芬的组合可以观察到更好的治疗窗口和副作用谱。

[0038] (5) 在携带较高风险因素并且可能需要非常高功效的病态肥胖中，在风险 / 益处评价中，略微弱的副作用谱是可接受的。因此，在这样的情况中，可以以其常用治疗剂量范围上限的剂量来应用这些化合物的组合。此外，根据临床实践，在非常严重的病人的情况中 (>120kg)，需要将剂量调整至较高体重。因此，在特定的情况中，使用高于上述剂量的剂量是合理的，特别是在病态肥胖的情况中（即，巴氯芬 20-160mg，美金刚胺 10-40mg）。

[0039] 根据本发明，美金刚胺和巴氯芬活性成分的组合优选含有约 2 至约 40mg/ 天范围的美金刚胺和约 5 至约 160mg/ 天范围的巴氯芬。在进一步优选的实施方案中，组合物含有约 2 至约 20mg/ 天范围的美金刚胺和约 5 至约 40mg/ 天范围的巴氯芬。在严重需要的情况中，组合可以更优选含有约 10 至约 40mg/ 天范围的美金刚胺和约 20 至约 160mg/ 天的巴氯芬。

[0040] 本发明还涉及包含美金刚胺和巴氯芬组合以及药物学上可接受的赋形剂的药物组合物。

[0041] 合适的给药途径可以例如包括口服、直肠、经皮给药或非肠道传送。本发明的药物组合物可以配制成液体或固体，例如，溶液、悬浮液、乳液、脂质体、颗粒、片剂、膜－片或胶囊。

[0042] 药物组合物可以通过各种途径和剂型来给药。美金刚胺和巴氯芬活性成分可以配制成组合或分开的药物组合物，并且可以以单剂量或多剂量来给药组合物。

[0043] 发挥治疗作用所需的剂量可以在宽范围内变化，并且将适合每个特定情况中的个体需求，这取决于疾病的阶段、待治疗病人的状况和体重，以及病人对活性成分的敏感性、给药途径和每日治疗的数量。可以通过本领域的主治医生根据待治疗病人的认识，安全地确定待使用的活性成分的实际剂量。

[0044] 为了简单给药，如果药物组合物包含含有一次给药的活性成分含量的剂量单位、或几个剂量单位或其一半、三分之一或四分之一，是合适的。这样的剂量单位例如是片剂，其可以弄成粉末，其具有利于将片剂分成一半或四分之一的凹痕，以精确地给药所需量的活性成分。

[0045] 根据本发明的含有活性成分的药物组合物通常含有 3 至 200mg 活性成分，表示优选单个剂量单位中 1 至 40mg 美金刚胺和 2 至 160mg 巴氯芬。在进一步优选的实施方案中，组合物在每个剂量单位中含有 1 至 20mg 美金刚胺和 2 至 40mg 巴氯芬。根据疾病的阶段，组合物可以更优选地在每个剂量单位中含有 5 至 40mg 美金刚胺和 10 至 160mg 巴氯芬。

[0046] 当然，一些组合物或组合中的活性成分的含量超出以上限定的上限或下限是可能的。

[0047] 可以以本身已知的方法来制备本发明的药物组合物，例如，通过常规混合、溶解、造粒、包糖衣、磨细、乳化、包胶、包裹或压片操作来制备。

[0048] 本发明的药物配制程序的目的在于研发新的促进体重减轻的含有两种活性成分的口服药物组合物，以及详细阐述用于可重复工业生产产品的程序，确保两种活性成分均匀地分布在组合物中并且确保组合物的稳定性直至有效期结束，满足所有严格的药物管理、稳定性和安全性要求。通过合适的工业程序，将活性成分配制成胶囊、片剂、膜片、装满丸剂或片剂的胶囊、源自丸剂的膜片。

[0049] 因此可以使用一种或多种生理学上可接受的载体以常规方式来配制根据本发明使用的药物组合物，所述载体包含赋形剂和助剂，其促进活性化合物加工成药物学上可以使用的制备物。合适的制剂取决于所选择的给药途径。可以使用本领域合适的和了解的任何公知的技术、载体和赋形剂。

[0050] 可以将活性成分与例如作为常用稀释剂的乳糖、纤维素、淀粉、蔗糖、甘露糖醇、山梨糖醇、磷酸钙和硫酸钙混合。微晶纤维素不仅作为稀释剂；还具有一定的润滑剂和崩解剂特性，这使得其是有益的。羧甲基支链淀粉钙、羧甲基支链淀粉钠、交联羧甲基纤维素钠、聚乙烯吡咯烷酮、淀粉可以作为崩解剂加入；明胶、羟丙基纤维素、羟丙基甲基纤维素和聚维酮可以作为粘合剂使用；并且可以加入其他赋形剂，以改变活性成分的溶解性和／或释放。

[0051] 如果需要，在任何操作步骤中，向粉末或颗粒混合物中，加入其他赋形剂，例如，胶体二氧化硅、滑石、硬脂酸钙、单硬脂酸甘油酯、硬脂酸镁、聚乙二醇、硬脂富马酸钠、硬脂酸

和硬脂酸锌作为润滑剂或助流剂，和 / 或还可以使用不同的着色剂和 / 或调味剂和 / 或改变药物释放的添加剂。压制的片剂或填充的胶囊可以是膜或糖 - 覆盖的。

[0052] 以上描述的成分和不同的制造途径仅仅是代表性的。本领域公知的其他材料以及加工技术等也可以使用。

[0053] 本发明的组合和组合物可以用于实现体重减轻和用于治疗超重、肥胖或相关病症。因此，本发明涉及通过给药有效量的美金刚胺和巴氯芬治疗哺乳动物，特别是人的超重和肥胖的方法。同时或相继给药美金刚胺和巴氯芬的组合。

[0054] 证实本发明的研究和结果

[0055] 使用小鼠饮食诱发的肥胖测试研究对体重减轻的功效

[0056] 使用饮食诱发的肥胖 (DIO) 测试进行了实验。DIO 测试是广泛接受的人肥胖的动物模型，其充分模拟了疾病的发展和过程、其并存病症及其对药理学药物治疗的应答 (Hariri 和 Thibault Nutr. Res. Rev. 23:270-2992010)。给年轻 (22-25g) 雄性 C57B16 小鼠饲喂高脂肪饲料 (例如，D12492，Research Diets Inc.，New Brunswick，NJ，USA)，因此这些动物与饲喂对照饲料的小鼠相比，变得肥胖。在第一个实验中 (n = 8/ 组，平均 ±SEM)，对照和肥胖小鼠的体重各自为 31.84±0.89 和 45.74±0.78g。在第二个实验中，这些值为 30.47±0.58 和 45.38±0.61(n = 20/ 组)，在第三个实验 (研究 2) 中，为 27.61±0.34 和 41.00±0.91(n = 8/ 组)。然后，将动物分配给不同的组并且用不同的载体或测试化合物治疗。将测试化合物溶解于水中，并且以 10ml/kg 体重的体积每日经口给药两次。在实验过程中，给动物每日称重。在两周长的实验结束时，计算与基线体重相比每只动物的体重减轻百分比。从每只动物的体重变化百分比减去载体组的平均体重变化百分比，由此计算载体校正的体重减轻。结果的统计学评价包括描述统计学 (平均和标准误差)。此外，使用单向或阶乘 ANOVA 测试，接着 Duncan' s post-hoc 测试，来评价组之间差异的统计学显著性。使用阶乘 ANOVA 测试评价了不同治疗 (即，药物组合) 之间的相互作用。

[0057] 研究 1

[0058] 研究分开的和组合的 2.5mg/kg 美金刚胺和 2mg/kg 巴氯芬的作用，我们发现了与载体对照相比，美金刚胺没有影响所治疗动物的体重 (体重减轻 :0.1%)。巴氯芬引起 3.2% 的体重减轻，其在统计学上是非显著的。相反，使用美金刚胺和巴氯芬组合的治疗引起 8.7% 的体重降低。用组合治疗的组的体重减轻在统计学上是显著高于 ($p<0.05$，单向 ANOVA 和 Duncan' s post hoc 检验) 载体、单独的美金刚胺或单独的巴氯芬组 (图 1)。图 1 中所示的剂量每日经口给药两次。结果显示为载体校正的体重减轻百分比的平均 ±SE。其他三个组之间不存在统计学差异。(动物的数量 :n = 8/ 组，除了美金刚胺组，其中 n = 7)。

[0059] 这些数据表明显著的协同作用。因此，我们使用较大的组大小 (n = 20/ 组) 重复了实验，以在统计学上评定这种明显的协同作用的可能性。

[0060] 如果使用两种药物治疗作为两个因素的阶乘 ANOVA 测试表明两个因素之间的显著相互作用，则在统计学上证明了协同作用 (Slinker J. Mol. Cell. Cardiol. 30:723-7311998)。相互作用的零假设是两种药物彼此独立地发挥其作用，因此当药物组合给药时，这些作用总和 (线性叠加)。零假设的否决 (显著的相互作用) 意味着两种药物的作用总和 (单独给药) 与组合的作用之间的显著差异 (低于叠加或高于叠加，取

决于偏离的方向）。如果数据获自超过一个实验，那么实验等级在统计学分析中成为第三个因素。因此，第一个（小的组大小，n = 8）和第二个（n = 20）实验的结果在最终分析中集合，并且使用以下的三个因素对这些数据进行了阶乘 ANOVA：1：美金刚胺治疗；2：巴氯芬治疗；3：实验等级。证明了来自两个实验的数据集的集合，因为实验等级作为因素没有产生显著的改变，不管是单独的（p = 0.648）或是与任何治疗相互作用的（美金刚胺 x 实验：p = 0.429；巴氯芬 x 实验：p = 0.648）。相反，美金刚胺和巴氯芬治疗两者作为因素显示出明显高的作用（美金刚胺：p = 0.010；巴氯芬：p<0.001）。美金刚胺和巴氯芬治疗之间不存在相互作用的可能性为 p = 0.058。这一结果证实了两种药物作用之间强烈的，至少叠加的相互影响，并且还暗示潜在存在高于叠加的相互作用（协同作用）的高可能性（94.2%）（图 2）。图 2 中的数据呈现为载体校正的体重减轻百分比的平均 ±SE。使用阶乘 ANOVA 进行了协同相互作用的统计学分析（Slinker J. Mol. Cell. Cardiol. 30:723-7311998）。组大小：n = 28/ 组（除了美金刚胺组，其中 n = 27）。在这种图中（图 2），平行线表示叠加作用，向右的分叉线表示协同相互作用。

[0061] 这些实验结果表明明显的相互作用，由此单独的美金刚胺没有发挥出值得考虑的体重减轻作用，但加强了巴氯芬的体重减轻作用。这一解释得到第一个实验或集合数据集中美金刚胺治疗组的体重减轻没有显著不同于载体治疗组的发现的支持（第一个实验：p = 0.957，集合数据集：p = 0.449，Duncan's post hoc 检验）。相反，美金刚胺结合巴氯芬给药时，其显著提高了巴氯芬的作用，因为接受组合的组的体重减轻显著高于接受单独的巴氯芬的组的体重减轻（第一个实验：p = 0.019，集合的数据集：p = 0.005，Duncan's post hoc 检验）。

[0062] 研究 2

[0063] 我们还测试了芬特明和巴氯芬的组合。在该研究中，研究了 2.5mg/kg 芬特明和 2mg/kg 巴氯芬的作用，两种药物都适度地降低了体重（分别为 5.4%和 3.6%）。然而，接受这些药物组合的动物的体重减轻（4.9%）没有超过单独的芬特明引起的体重减轻。组之间不存在显著差异（也包括载体组）。尽管组大小（n = 8/ 组）相对小，但这些结果清楚地显示出组合使用时，两种药物之间低于叠加相互作用（图 3）。图 3 中的数据也呈现为载体校正的体重减轻百分比的平均 ±SE。

[0064] 总之，研究组合治疗对体重减轻的功效显示出就体重减轻作用而言美金刚胺和巴氯芬之间存在协同（高于叠加作用）或至少叠加相互作用。另一方面，还已经显示出组合具有适度体重减轻作用的两种药物不是必定导致叠加或协同相互作用。

[0065] 对小鼠中副作用的研究

[0066] 小鼠中转杆性能减弱的检测

[0067] 转杆测试是广泛使用的简单且客观的方法，用于检测啮齿动物中影响运动功能的副作用。这种方法也能够灵敏地检测中央肌松弛作用，其是美金刚胺和巴氯芬两者的药理学特征（Farkas 等，J. Pharmacol. Toxicol. Methods52:264-2732005）。然而，其他 CNS 副作用（例如，嗜睡、协调障碍）也损伤了转杆性能。因此，这种方法用于评价美金刚胺和巴氯芬组合产生不需要的副作用的可能性。

[0068] 将小鼠放在以 12rpm 恒速旋转的杆上。训练后，即，在前一天适应转杆三次 120 秒后，小鼠通常能够在杆上奔跑 120 秒，而没有跌落。就在用测试化合物治疗前，测试小鼠并

且只有那些能够停留在杆上 120 秒的参与实验。将测试化合物溶解于蒸馏水（载体）中，并且口服给药十只雄性 NMRI 小鼠 (20-24g) 的组。在每个实验部分，一组用载体处理。在三个分开的实验部分中，研究了美金刚胺、巴氯芬及其组合的剂量 - 应答相关性。我们计算出每组跌落的平均时间以及相对于载体组时间的变化百分比。使用逻辑回归计算出每种化合物和治疗类型的 ED_{50} 值（引起 50％失效率的有效剂量），以表征化合物的作用。使用 ANOVA 测试接着 Duncan's post hoc 进行了跌落时间的统计学分析。为了揭示组合的作用是否高于单独的化合物的作用并且还为了阐明是否存在高于叠加或低于叠加的相互作用，我们进行了等辐射分析 (Tallarida 等，Psychopharmacology（柏林）133 :378-382，1997)。这些结果呈现于表 1 和图 4 中。

[0069] 表 1

[0070]

转杆测试中的跌落时间(平均和 SE)

美金刚胺 [mg/kg]	0	5	10	20	
平均跌落时间 (sec)	120	112.7	96.3	41.8**	
SE	0.0	7.3	12.5	10.1	
巴氯芬 [mg/kg]	0	5	10	20	
平均跌落时间 (sec)	118.1	106.7	94.2	53.7**	
SE	2	9	12.4	13.5	
美金刚胺 [mg/kg]	0	2.5	5	10	20
+巴氯芬 [mg/kg]	0	2	4	8	16
平均跌落时间 (sec)	120	120	106.9	85.8**	7.6**
SE	0	0	9.1	12.7	0.9

[0071] 表 1 中呈现的所有时间值表示来自 10 只动物的平均（和 SE- 平均的标准误差）。剂量“0”表示只接受载体（蒸馏水）的组。在治疗后 60 分钟进行了测量。** :$p<0.01$ (ANOVA，接着 Dunnett's post hoc 检验；无星号 :$p>0.05$)。

[0072] 20mg/kg 剂量的美金刚胺与载体组相比显著降低了跌落时间。然而，5 和 10mg/kg 的剂量没有显著降低跌落时间。美金刚胺的 ED_{50} 为 16.1±1.7mg/kg（平均 ±SE）。巴氯芬仅在 20mg/kg 的剂量下也引起了显著作用并且其 ED_{50}(18.3±3.3mg/kg) 与美金刚胺的相当。在用美金刚胺和巴氯芬的四个 1.25:1 固定剂量 - 比例 (1.25:1) 之一治疗的组的情况中，两个最高剂量（美金刚胺和巴氯芬分别为 :10 和 8 ;20 和 16mg/kg) 引起了显著作用。

[0073] 计算的组合的 ED_{50} 为 21.6±1.5mg/kg（就总和的等效剂量而言），这显著高于假

定叠加作用而计算的理论 ED_{50}(17.0±1.7mg/kg)(图 4)。

[0074] 推断出在小鼠 DIO 测试中结合美景刚胺 (2mg/kg/ 治疗) 提供有效体重减轻作用的巴氯芬的剂量低于引发肌肉松弛或其他副作用的剂量。此外,就体重减轻作用而言显示出协同作用或叠加作用的剂量组合就运动功能副作用而言没有显示出协同作用而是显示出低于叠加的相互作用。

[0075] 研究对小鼠的自发性运动活动的作用

[0076] 已知 NMDA 受体拮抗剂在啮齿动物中引起剂量依赖性行为活动,其呈现出提高的运动活动 (Sukhanov 等, Behav. Pharmacol. 15:263-2712004)。这种行为对应于临床实践中观察到的副作用,如兴奋和坐立不安,这在使用美金刚胺的情况中很少看到。我们研究了组合给药于小鼠时,巴氯芬对美金刚胺的运动活动提高作用的调节作用。每日用 2mg/kg 巴氯芬、2.5mg/kg 美金刚胺或其组合或载体 (蒸馏水) 治疗雄性 C57B16J 小鼠组 (25-32g ; Wobe-Harlan, Hungary ;8-10 鼠 / 组),在每日亮 - 暗循环的光照期间过程中,每日给予两次。在适应一天后,使用自动化行为活动测量系统 (LABORAS, Metris,荷兰) 在治疗的第 1 天和第 14 天,连续记录动物活动 24 小时。然而,只显示了来自光照期间 (12 小时) 的数据。在整个实验过程中,将动物单独圈养在饲养笼子中,其也能够记录活动。将动物移动产生的机械振动和重力相关静止信号通过系统转化成电子信号,并且通过计算机算法脱机评价这些记录的信号 (Quinn 等, J. Neurosci. Methods130:83-922003)。通过软件将小鼠的行为归类为运动活动、静止、攀登和理毛。图 5 显示了在 12- 小时光照期间水平运动活动花费的时间的平均和 SEM。使用 ANOVA 接着 Tukey's post hoc 检验进行了统计学分析。计算了与载体比较以及还与其他药物治疗组比较的药物治疗作用的统计学显著性。

[0077] 研究单独和组合的 2.5mg/kg 美金刚胺和 2mg/kg 巴氯芬的作用,美金刚胺在治疗的第 14 天在统计学上显著 ($p<0.05$) 提高了水平运动活动 (NMDA 拮抗剂的典型作用)。美金刚胺的这一作用在第 1 天没有达到统计学显著性。相反,单独的巴氯芬和组合在治疗的第 1 天或第 14 天都没有改变运动活动 (图 5)。

[0078] 总之,就体重减轻而言显示出协同作用的剂量组合就涉及自发性运动活动的副作用而言,没有显示出协同作用。相反,巴氯芬明显地减弱了美金刚胺的运动活动提高作用。

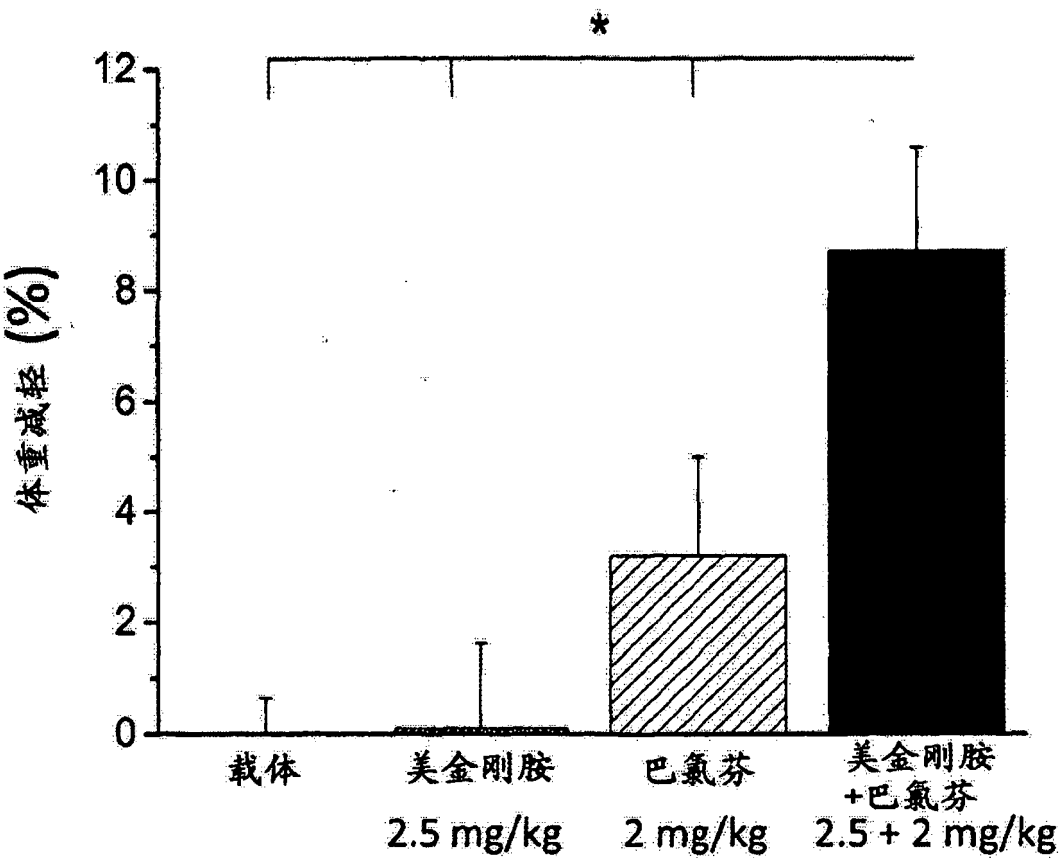
*
12
10
8
6
4
2
0
体重减轻 (%)
载体
美金刚胺
2.5 mg/kg
巴氯芬
2 mg/kg
美金刚胺
+巴氯芬
2.5 + 2 mg/kg

图 1

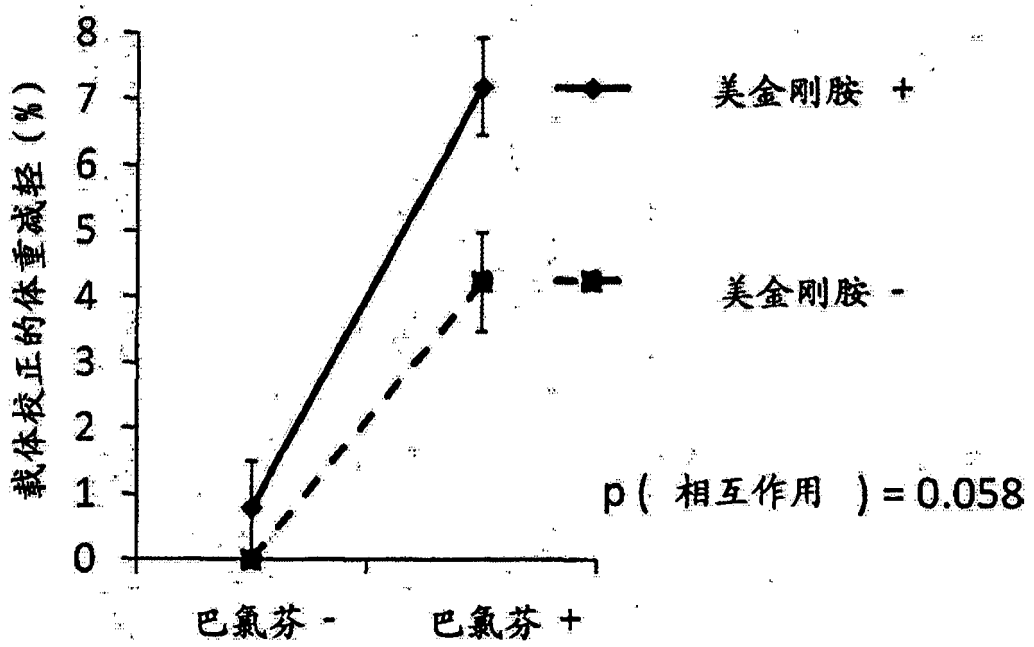
8
7
6
5
4
3
2
1
0
载体校正的体重减轻（%）
美金刚胺 +
美金刚胺 -
p (相互作用) = 0.058
巴氯芬 -
巴氯芬 +

图 2

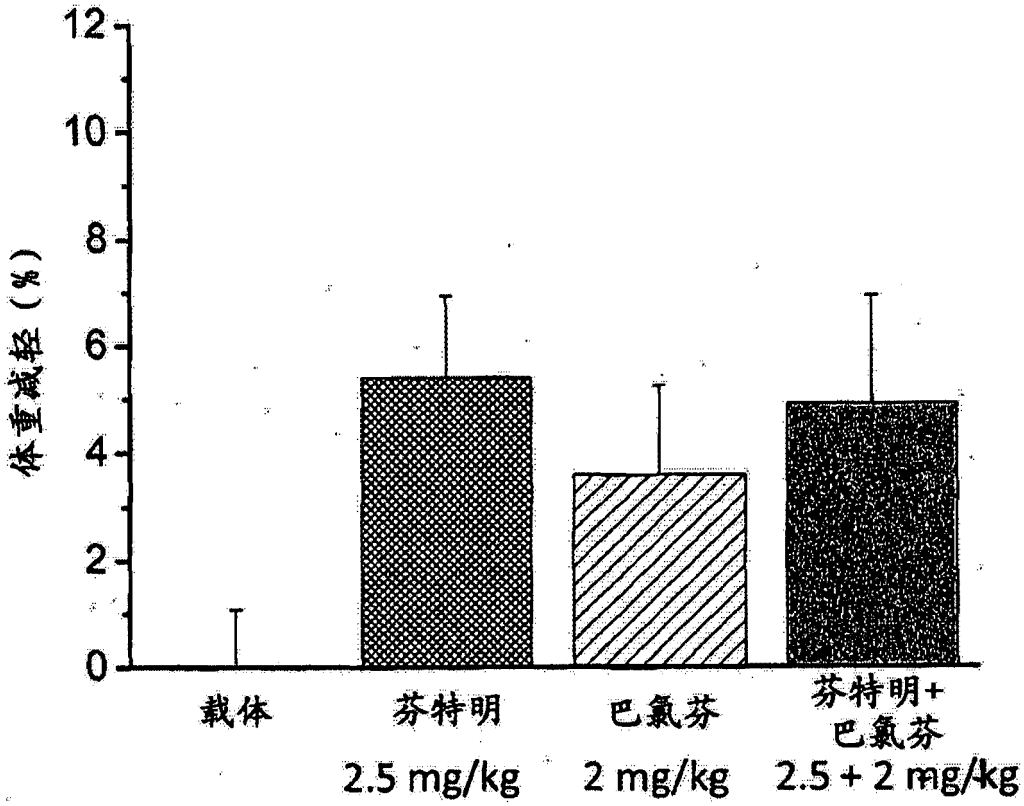
体重减轻（%）
12
10
8
6
4
2
0
载体
芬特明
2.5 mg/kg
巴氯芬
2 mg/kg
芬特明+
巴氯芬
2.5 + 2 mg/kg

图 3

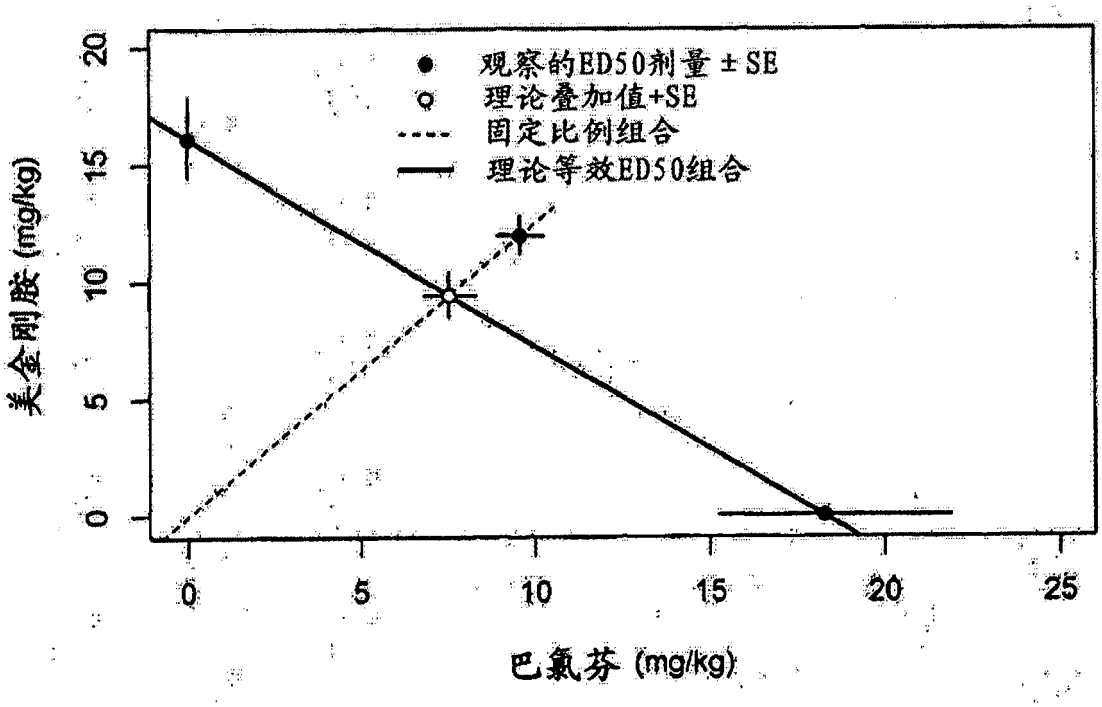
观察的ED50剂量 ± SE
理论叠加值+SE
固定比例组合
理论等效ED50组合
美金刚胺 (mg/kg)
0
5
10
15
20
0
5
10
15
20
25
巴氯芬 (mg/kg)

图 4

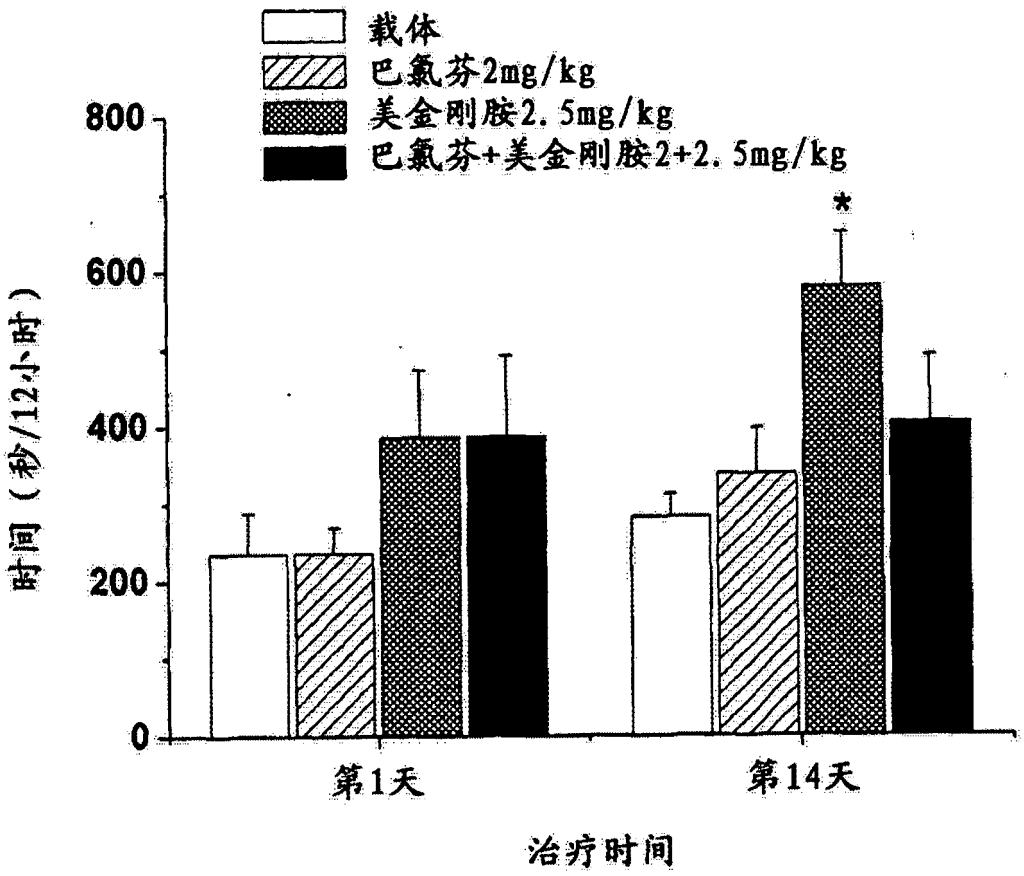
载体
巴氯芬2mg/kg
美金刚胺2.5mg/kg
巴氯芬+美金刚胺2+2.5mg/kg
800
600
400
200
0
时间（秒/12小时）
*
第1天
第14天
治疗时间

图 5