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(54) Title: COMPOSITIONS FOR CONTROLLING FOOD INTAKE AND USES THEREFOR

(57) Abstract: The present invention is directed to a combination treatment for: individuals who meet the definition of food addiction; individuals that are overweight or obese (e.g., a BMI > 25); individuals that have a binge eating disorder; or individuals who engage in a binge eating behavior. In particular embodiments, the combination therapy reduces the intake of fatty foods, sugar rich foods, or foods that are both fatty and sugar-rich (e.g., such as fast foods).



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## DESCRIPTION

## COMPOSITIONS FOR CONTROLLING FOOD INTAKE AND USES THEREFOR

## CROSS REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Provisional Patent Application Serial Number 61/560,356, filed November 16, 2011, the disclosure of which is hereby incorporated by reference in its entirety, including all figures, tables and nucleic acid sequences.

## TECHNICAL FIELD

The present invention relates to a combination therapy for the treatment of food addiction, obesity, binge eating disorder, or binge eating behavior.

## BRIEF SUMMARY OF THE INVENTION

The present invention is directed to a combination treatment of an mu-opioid receptor antagonist and GABA B receptor agonist and, optionally a third therapeutic agent selected from CB-1 receptor antagonists, glycine reuptake inhibitors, dopamine augmenting compounds, nicotine receptor agonists, psychostimulants, mGlu2/3 agonists, mGlu5 antagonists, glycine-site partial agonists, cystine-glutamate exchangers, cystine-glutamate activators, glutamate transporter inhibitors, mGlu5 receptor agonists or NMDA receptor co-agonists for the treatment of individuals who meet the definition of food addiction; individuals that are overweight or obese (e.g., a BMI  $\geq 25$ ); individuals that have a binge eating disorder; or individuals who engage in a binge eating behavior. Specific combinations of these classes of compounds are provided in Table 1. Tables 2-3 provide exemplary combinations of specific compounds suitable for the treatment of individuals who meet the definition of food addiction; individuals that are overweight or obese (e.g., a BMI  $\geq 25$  or having a BMI between 25 and 35); individuals that have a binge eating disorder; or individuals who engage in a binge eating behavior. The invention may also be used for individuals who have difficulty in controlling the amounts of fast foods consumed during a given period of time.

## BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 - Baclofen (alone) has no effect on binge eating of sugar.

Figs. 2A-2B - Baclofen (alone) reduces intake of oil-containing palatable foods.

Figs. 3A-3C - Naltrexone has a trend toward reducing food intake in the oil containing groups, but has no effect on sugar-bingeing rats.

Figs. 4A-4C. The combination of baclofen/naltrexone at the higher doses (naltrexone at 1.0 mg/kg and baclofen at 1.8 mg/kg) robustly reduces intake of sugar, fat, or diets containing both fat and sugar.

Figs. 5A-5C. The effect of baclofen/naltrexone on suppressing palatable food intake is specific to palatable food regardless of the group tested. No effects were seen on the intake of plain chow.

Fig. 6. The Yale Food Addiction Scale (survey).

#### DETAILED DISCLOSURE OF THE INVENTION

The present invention is directed to a combination treatment of an mu-opioid receptor antagonist and GABA B agonist and, optionally a third therapeutic agent selected from CB-1 receptor antagonists, glycine reuptake inhibitors, dopamine augmenting compounds, nicotine receptor agonists, psychostimulants, mGlu2/3 agonists, mGlu5 antagonists, glycine-site partial agonists, cystine-glutamate exchangers, cystine-glutamate activators, glutamate transporter inhibitors, mGlu5 receptor agonists or NMDA receptor co-agonists for the treatment of individuals who meet the definition of food addiction; individuals that are overweight or obese (e.g., a BMI  $\geq 25$ ); individuals that have a binge eating disorder; or individuals who engage in a binge eating behavior. Specific combinations of these classes of compounds are provided in Table 1. Tables 2-3 provide exemplary combinations of specific compounds suitable for the treatment of individuals who meet the definition of food addiction; individuals that are overweight or obese (e.g., a BMI  $\geq 25$  or having a BMI between 25 and 35); individuals that have a binge eating disorder; or individuals who engage in a binge eating behavior. The invention may also be used for individuals who have difficulty in controlling the amounts of fast foods consumed during a given period of time.

The term “combination” as in the phrase “a first compound in combination with a second compound” includes co-administration of a first therapeutically effective compound and a second therapeutically effective compound, which for example, may be dissolved or intermixed in the same pharmaceutically acceptable carrier. The term “concurrently administered” when referring to the various compounds disclosed herein indicates that the compounds can be administered separately at the same time or sequentially in any order at

different points in time. The compounds, however, should be administered close in time so as to provide an effect suitable for the treatment of individuals who meet the definition of food addiction; individuals that are overweight or obese (e.g., a BMI  $\geq 25$ ); individuals that have a binge eating disorder; or individuals who engage in a binge eating behavior. Typically, concurrently administered compounds are administered within 60 minutes of one another.

The term "synergistic effect" as used herein refers to the combined effect of administering two (or three) therapeutic compounds where the overall response is greater than the sum of the two individual effects (e.g., the effects observed when each compound is administered alone as a monotherapy).

The dosage of the individual therapeutic compounds that are to be administered to individuals may be adjusted to provide the optimal therapeutic response. Thus, the specific dose level for any particular patient may vary depending upon a variety of factors, including but not limited to, the activity of the specific compound employed; the age, body weight, general health, sex and diet of the patient; the time of administration; the rate of excretion; drug combination; the severity of the particular disease being treated; and the form of administration. Typically, in vitro dosage-effect results provide useful guidance on the proper doses for patient administration. The considerations for determining the proper dose levels are well known in the art.

In one embodiment, naltrexone is coadministered or administered in combination with baclofen and, optionally additional therapeutic compounds. In certain cases, naltrexone, in an amount of about 25 to 100 milligrams per day, and baclofen, in an amount ranging between about 15 and about 120 milligrams per day (preferably between about 20 milligrams and about 80 milligrams per day) can be administered in combination or coadministered. As set forth in the Tables, a combination of three therapeutic compounds can be used in the disclosed methods. For example, a combination of naltrexone, baclofen and acamprosate or bupropion (or bupropion (extended release)) can be coadministered or administered in combination to a subject according to the disclosed methods. In such embodiments, naltrexone, in an amount of about 25 to 100 milligrams per day, baclofen, in an amount ranging between about 15 and about 120 milligrams per day (preferably between about 20 milligrams and about 80 milligrams per day), and acamprosate in an amount of between about 300 and 2500 milligrams per day (e.g., as two 333-mg tablets taken three times a day) can be coadministered or administered in combination. Alternatively, naltrexone, in an

amount of about 25 to 100 milligrams per day, baclofen, in an amount ranging between about 15 and about 120 milligrams per day (preferably between about 20 milligrams and about 80 milligrams per day), and bupropion (or bupropion extended release) in an amount of between 75 milligrams and 450 milligrams per day (or, preferably, between about 150 and about 300 milligrams per day) can be coadministered or administered in combination within the disclosed methods. Other combinations of therapeutic compounds and compositions according to the invention are set forth in Tables 2 and 3.

The therapeutic compounds used in the disclosed combination therapies can be administered in oral forms. These include, but are not limited to, tablets, capsules, pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. Rapid-release and time-controlled release (extended release) formulations of the disclosed therapeutic compounds can be used for the treatment of individuals who meet the definition of food addiction; individuals that are overweight or obese (e.g., a BMI  $\geq 25$ ); individuals that have a binge eating disorder; or individuals who engage in a binge eating behavior. The therapeutic compounds disclosed herein can, typically, be administered in "pharmaceutically acceptable carriers such as pharmaceutical diluents, pharmaceutical excipients or pharmaceutical carriers. For instance, tablets or capsules can comprise one or more of the disclosed therapeutic compounds and lactose, starch, sucrose, glucose, modified sugars, modified starches, methyl cellulose and its derivatives, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and other reducing and non-reducing sugars, magnesium stearate, steric acid, sodium stearyl fumarate, glyceryl behenate, calcium stearate and the like. Liquid formulations can comprise one or more therapeutic agent in combination with ethanol, glycerol, water and the like. Additionally, the compositions can contain binders, lubricants, disintegrating agents, coloring and/or flavoring agents as desired.

In the context of the present invention, the term "individual" refers to a mammal. In particular embodiments, the mammal can be a rodent, such as a mouse or rat. In other embodiments, the mammal is a human. Individuals to whom the methods disclosed herein can be applied can be identified by a variety of means, including the use of body mass index (BMI) or surveys that identify individuals exhibiting symptoms of food addiction (e.g., the Yale Food Addiction Scale (see Figure 6).

Thus, certain aspects of the disclosed invention provide methods for the treatment of individuals who meet the definition of food addiction; individuals that are overweight or obese (e.g., a BMI  $\geq 25$ ); individuals that have a binge eating disorder; or individuals who

engage in a binge eating behavior. These methods comprise the administration of a composition as set forth in any one of Tables 1-3 to an individual meeting the definition of food addiction, an individual who is obese or overweight, an individual who has a binge-eating disorder or individuals who engage in binge eating behavior in amounts effective to control or reduce the intake of food. In preferred embodiments of this aspect of the invention, the foods are fatty foods, sugar rich foods, or foods that are both fatty and sugar-rich.

It should be understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and the scope of the appended claims. In addition, any elements or limitations of any invention or embodiment thereof disclosed herein can be combined with any and/or all other elements or limitations (individually or in any combination) or any other invention or embodiment thereof disclosed herein, and all such combinations are contemplated with the scope of the invention without limitation thereto.

## EXAMPLES

### EXAMPLE 1

Drugs (2 doses/drug)

Baclofen (at 1.0 and 1.8 mg/kg, administered i.p.)

Naltrexone (at 0.1 and 1.0 mg/kg, administered i.p.)

Baclofen + naltrexone (mixed low and mixed high)

Saline

Groups (n=10/group)

1. Binge sugar (10% sucrose solution, w/v)

2. Binge Fat (35% oil emulsion, w/v)

3. Binge Sweet/Fat (10% sucrose, 35% oil emulsion, w/v)

Procedure

Groups of animals (rats) were maintained on their diets for 3 weeks to establish stable binge eating behavior. After this period of time, the rats were administered three days of daily i.p. injections of saline (to acclimate to the injection procedure), and sugar/chow intake was measured after the first hour of access and then hourly for the next 3 hours, as well as at the end of the 12-h access period. After this three day period, rats were given baclofen +

naloxone, and measurements taken as described above. Other dosage amounts of baclofen and naloxone were tested, as were the effects of these compounds alone (with measurements being performed as described above). Vehicle injections were performed between the various tests in order to allow for suitable clearance of compounds from the animals. Interestingly, the effect of baclofen/naltrexone on suppressing palatable food intake is specific to palatable food (fatty foods, sweet foods or foods choices that were both fatty and sweet, see Figures 1-5); no effects were seen on the rat's intake of plain chow. Thus, the treatment appears ideally suited for food addicts, hedonic overeaters and changes food choice but not appetite.

## EXAMPLE 2

### Materials and Methods

Male Sprague-Dawley rats, 250–300 g at the onset of the experiment, were obtained from Taconic Farms (Germantown, NY, USA). Rats were housed individually on a 12-h reversed light/dark cycle and given 1 wk to acclimate before diet training began.

### Diets

The rats were divided into groups (n=10/group) matched for body weight and assigned to one of the following dietary conditions: (1) Binge Sugar, (2) Binge Fat or (3) Binge Sugar-Fat. All rats received palatable diets and standard rodent chow (LabDiet #5001, PMI Nutrition International, Richmond, Indiana, USA; 10% fat, 20% protein, 70% carbohydrate, 3.02 kcal/g) for 12 h/day, starting 4 h after the onset of the dark cycle. Water was available ad libitum.

All palatable foods were mixed in the laboratory. The Binge Sugar group had access to a 10% (w/v) sucrose solution (Domino® Granulated Pure Cane Sugar, dissolved in tap water, 0.4 kcal/mL). The Binge Fat group had access to a 35% (w/v) fat emulsion (3.1 kcal/mL) and the Binge Sugar-Fat group had access to a 10% (w/v) sugar solution and 35% (w/v) fat emulsion (3.5 kcal/mL). Both emulsions were made with Wesson® Pure Vegetable Oil in tap water and 0.6% (w/v) Emplex, a commercially available emulsifier (American Ingredients Company, Kansas City, MO, USA). Palatable food intakes were recorded daily. Chow intake was recorded weekly. Body weights were taken at the beginning and end of the 21-day diet period.

## Injection Procedures

After 21 days on these diets, drug testing began. During testing, diet regimens were maintained. Approximately 3.5 h into the dark cycle, animals were weighed and intraperitoneal (i.p.) injections of drug were given (according to the schedule below). 30-min later (4 h into the dark cycle) palatable food and chow were made available to the rats. For the first 3 days, rats were acclimated to handling and injections with daily vehicle injections (0.9% saline, Lakeforest, IL, USA, Hospira, i.p. 1 mL/kg). For days 4-16 of drug testing, either vehicle or drug was alternatively administered, starting with drug on day 4. Drug injections included combinations of R-baclofen (Tocris, Ellisville, Missouri, USA) and naltrexone hydrochloride (Sigma, St. Louis, MO, USA); 0.1 mg/kg naltrexone and 1.0 mg/kg baclofen, or 1.0 mg/kg naltrexone and 1.8 mg/kg baclofen. Or, either drug was tested alone: 0.1 and 1.0 mg/kg naltrexone, or 1.0 and 1.8 mg/kg baclofen. Intake of palatable food and chow was measured hourly after injection for 4 h and again at the end of the 12-h access period.

## Analysis and Statistics

Palatable food and standard chow intakes following saline injections between days 4-16 were averaged. All data were analyzed using one-way ANOVAs with post hoc Multiple Comparisons, when appropriate. In Tables 4-7, values having the same letter superscript are statistically different from one another.

## Results

At the beginning of the study, the groups were weight-matched [ $F(2,29) \leq 0.001$ , 6 p=n.s.;  $280.0 \pm 3.6$  g (Binge Sugar),  $280.1 \pm 3.4$  g (Binge Fat),  $280.0 \pm 3.6$  g (Binge Sugar-Fat)]. There was still no difference in body weight among groups after 21 days on their respective diets [ $F(2,29)=0.39$ , p=n.s.;  $387.2 \pm 7.2$  g (Binge Sugar),  $396.7 \pm 5.7$  g (Binge Fat), and  $393.83 \pm 10.0$  g (Binge Sugar-Fat)], or at the completion of injections [ $F(2,29)=1.68$ , p=n.s.;  $419.9 \pm 9.3$  g (Binge Sugar),  $442.4 \pm 6.5$  g (Binge Fat),  $438.3 \pm 11.2$  g (Binge Sugar-Fat)].

### *Effects of Naltrexone, Baclofen or the Combination on Palatable Food Intake*

Table 4 shows a summary of palatable food intake in response to the drugs tested as a percent of each groups' saline injections. Naltrexone significantly decreased 1 h



( $F(2,29)=3.66$ ,  $p<0.05$ , Table 5) and 12- h intake in the Binge Sugar group ( $F(2,29)=5.94$ ,  $p<0.01$ ), with the greatest suppression of intake seen following the higher dose ( $p<0.05$ ). Similar to previous reports {Berner, 2009 #597; Corwin, 2009 #607}, there was no effect of baclofen on sugar intake at 1 h ( $F(2, 29)=0.79$ ,  $p=n.s.$ ) or at 12 h ( $F(2,29)=0.13$ ,  $p=n.s.$ ). The combination of naltrexone and baclofen decreased sugar intake at 1 h ( $F(2,29)=4.067$ ,  $p<0.05$ ), with the strongest suppression seen at the high-dose combination ( $p<0.05$ ). However, this effect was not apparent at 12 h ( $F(2,29)=0.28$ ,  $p=n.s.$ ).

For the Binge Fat group, there was no significant effect of naltrexone at 1 h ( $F(2,29)=2.55$ ,  $p=n.s.$ ) or 12 h ( $F(2,29)=0.96$ ,  $p=n.s.$ ). Baclofen decreased fat intake at 1 h ( $F(2,29)=6.85$ ,  $p<0.01$ ) and 12 h ( $F(2,29)=8.15$ ,  $p<0.01$ ), with the strongest suppression seen following the higher dose ( $p<0.01$ ). The combination of naltrexone and baclofen also decreased fat intake at 1 h ( $F(2,29)=12.11$ ,  $p<0.0001$ ) and 12 h ( $F(2,29)=8.41$ ,  $p<0.01$ ), again with the strongest suppression seen following the high-dose combination ( $p<0.01$ ).

In terms of the sugar-fat combination, naltrexone had no effect on palatable food intake at 1 h ( $F(2,29)=1.84$ ,  $p=n.s.$ ) or 12 h ( $F(2,29)=1.27$ ,  $p=n.s.$ ). Baclofen significantly decreased intake at 1 h ( $F(2,29)=9.69$ ,  $p<0.01$ ) at both doses tested ( $p<0.01$ ). At 12 h, baclofen suppressed intake ( $F(2,29)=4.25$ ,  $p<0.05$ ), with the strongest effect seen following the higher dose ( $p<0.05$ ). Lastly, there was an effect of the naltrexone and baclofen combination on sugar-fat intake at 1 h ( $F(2,29)=13.29$ ,  $p<0.0001$ ), with the strongest suppression seen at the higher dose ( $p<0.01$ ), but no effect was observed at 12 h ( $F(2,29)=0.82$ ,  $p=n.s.$ ).

#### *Effects of Naltrexone, Baclofen or the Combination on Standard Chow Intake*

There was no effect of naltrexone ( $F(2,29)=3.31$ ,  $p=n.s.$ ; Table 6) or baclofen ( $F(2,29)=1.07$ ,  $p>0.05$ ) on standard chow intake in the sugar group at 1 h. However, at 12 h, naltrexone ( $F(2,29)=6.18$ ,  $p<0.01$ ) and baclofen ( $F(2,28)=4.56$ ,  $p<0.05$ ) both stimulated chow intake. The combination of naltrexone and baclofen had a significant effect on standard chow intake in the sugar group at 1 h ( $F(2,29)=5.34$ ,  $p<0.05$ ), with the high dose reducing intake compared to the low dose ( $p<0.01$ ). At 12 h ( $F(2,28)=9.32$ ,  $p<0.01$ ), the combination stimulated intake of standard rodent chow at both drug doses ( $p<0.01$ , for each) compared to saline.

There was no effect of naltrexone or baclofen alone on standard chow intake in the fat group at 1 h (naltrexone:  $F(2,29)=2.01$ ,  $p=n.s.$ ; baclofen  $F(2,29)=0.44$ ,  $p>0.05$  or 12 h

(naltrexone:  $F(2,29)=0.28$ ,  $p=n.s.$ ; baclofen:  $F(2,29)=0.27$ ,  $p>0.05$ ; Table 7). There was, however, an effect of the combination of naltrexone and baclofen 1 h ( $F(2,29)=10.92$ ,  $p<0.0001$ ), with less chow intake at the high dose compared to the other two groups ((saline:  $p<0.05$ ) and low dose:  $p<0.0001$ ). This effect did not persist, as no significant effect was seen at 12 h ( $F(2,29)=0.47$ ,  $p=n.s.$ ).

There was no effect of naltrexone on chow intake in the Binge Sugar-Fat group at 1 h ( $F(2,29)=0.65$ ,  $p=n.s.$ ) or at 12 h ( $F(2,29)=0.85$ ,  $p=n.s.$ ). Baclofen had a significant effect at 1 h ( $F(2,29)=3.58$ ,  $p<0.05$ ), with less chow intake at the high dose compared to the low dose ( $p<0.05$ ), but not at 12 h ( $F(2,28)=0.05$ ,  $p=n.s.$ ). There was no effect of the naltrexone and baclofen combination 1 h ( $F(2,29)=1.07$ ,  $p=n.s.$ ) or 12 h ( $F(2,29)=0.46$ ,  $p=n.s.$ ).

#### *Effects of Naltrexone, Baclofen or the Combination on Total Caloric Intake*

Naltrexone significantly increased total caloric intake in the Sugar group at 1 h ( $F(2,29)=4.53$ ,  $p<0.05$ ; low dose compared to saline  $p<0.05$ ). However, at 12 h, differences were no longer evident ( $F(2,27)=3.15$ ,  $p=n.s.$ ). Baclofen had no effect on total caloric intake in the sugar group at 1 h ( $F(2,29)=1.63$ ,  $p=n.s.$ ) or 12 h ( $F(2,26)=3.22$ ,  $p=n.s.$ ). The combination of naltrexone and baclofen, however, did significantly reduce total caloric intake 1 h ( $F(2,29)=8.11$ ,  $p<0.01$ ; high dose ( $p<0.01$ )). An effect was still apparent at 12 h ( $F(2,26)=6.52$ ,  $p<0.01$ ), but this time, caloric intake was increased in rats given both the low ( $p<0.01$ ) and high dose ( $p<0.05$ ), of the drug.

In the fat group, naltrexone had no effect on total caloric intake at 1 h ( $F(2,29)=3.25$ ,  $p=n.s.$ ) or 12 h ( $F(2,29)=1.13$ ,  $p=n.s.$ ). Baclofen, however, significantly reduced total caloric intake at 1 h ( $F(2,29)=6.73$ ,  $p<0.01$ ) and 12 h ( $F(2,29)=4.96$ ,  $p<0.05$ ), at the high dose, at each time point ( $p<0.05$ ). Likewise, the combination of naltrexone and baclofen reduced total caloric intake at 1 h ( $F(2,29)=22.07$ ,  $p<0.0001$ ) and 12 h ( $F(2,29)=8.02$ ,  $p<0.01$ ), at the high dose at each time point ( $p<0.05$ ).

In the Sugar-Fat group, naltrexone had no effect on total caloric intake at 1 h ( $F(2,29)=2.17$ ,  $p=n.s.$ ) or 12 h ( $F(2,27)=1.16$ ,  $p=n.s.$ ). Conversely, baclofen reduced total caloric intake in the sugar-fat group at 1 h ( $F(2,29)=15.02$ ,  $p<0.0001$ ), at the high dose ( $p<0.01$ ), but this effect was not apparent at 12 h ( $F(2,27)=2.435$ ,  $p=n.s.$ ). Likewise, the combination of naltrexone and baclofen reduced total caloric intake at 1 h ( $F(2,29)=13.46$ ,  $p<0.0001$ ), with less intake at the high dose ( $p<0.01$ ), but this effect was not seen at 12 h ( $F(2,27)=0.76$ ,  $p=n.s.$ ).

| Table 1. Triple Combination Compound Classes                            |
|-------------------------------------------------------------------------|
| GABA-B agonists and Mu antagonists and CB-1 Antagonists                 |
| GABA-B agonists and Mu antagonists and Glycine reuptake inhibitors      |
| GABA-B agonists and Mu antagonists and Dopamine augmenting compounds    |
| GABA-B agonists and Mu antagonists and Nicotine receptor agonists       |
| GABA-B agonists and Mu antagonists and Psychostimulants                 |
| GABA-B agonists and Mu antagonists and mGlu2/3 agonists                 |
| GABA-B agonists and Mu antagonists and mGlu5 antagonists                |
| GABA-B agonists and Mu antagonists and Glycine-site partial agonists    |
| GABA-B agonists and Mu antagonists and Cystine-glutamate exchangers     |
| GABA-B agonists and Mu antagonists and Cystine-glutamate activators     |
| GABA-B agonists and Mu antagonists and Glutamate transporter inhibitors |
| GABA-B agonists and Mu antagonists and mGlu5 receptor agonists          |
| GABA-B agonists and Mu antagonists and NMDA receptor co-agonists        |

| Table 2. Two Compound Combinations          |
|---------------------------------------------|
| baclofen and naltrexone                     |
| baclofen and naloxone                       |
| baclofen and nalorphine                     |
| baclofen and levallorphan                   |
| baclofen and buprenorphine                  |
| baclofen and extended release naltrexone    |
| baclofen and TAN-67                         |
| baclofen and SNC80                          |
| lesogaberan and naltrexone                  |
| lesogaberan and naloxone                    |
| lesogaberan and nalorphine                  |
| lesogaberan and levallorphan                |
| lesogaberan and buprenorphine               |
| lesogaberan and extended release naltrexone |
| lesogaberan and TAN-67                      |
| lesogaberan and SNC80                       |
| gabapentin and naltrexone                   |
| gabapentin and naloxone                     |
| gabapentin and nalorphine                   |
| gabapentin and levallorphan                 |
| gabapentin and buprenorphine                |
| gabapentin and extended release naltrexone  |
| gabapentin and TAN-67                       |
| gabapentin and SNC80                        |
| pregabalin and naltrexone                   |
| pregabalin and naloxone                     |
| pregabalin and nalorphine                   |
| pregabalin and levallorphan                 |
| pregabalin and buprenorphine                |
| pregabalin and extended release naltrexone  |
| pregabalin and TAN-67                       |
| pregabalin and SNC80                        |

Table 3. Three Compound Combinations

|                                                                           |
|---------------------------------------------------------------------------|
| baclofen and naltrexone and rimonabant                                    |
| baclofen and naltrexone and am-251                                        |
| baclofen and naltrexone and org24598                                      |
| baclofen and naltrexone and acamprosate                                   |
| baclofen and naltrexone and bupropion                                     |
| baclofen and naltrexone and bupropion (extended release)                  |
| baclofen and naltrexone and nicotine                                      |
| baclofen and naltrexone and varenicline                                   |
| baclofen and naloxone and rimonabant                                      |
| baclofen and naloxone and am-251                                          |
| baclofen and naloxone and org24598                                        |
| baclofen and naloxone and acamprosate                                     |
| baclofen and naloxone and bupropion                                       |
| baclofen and naloxone and bupropion (extended release)                    |
| baclofen and naloxone and nicotine                                        |
| baclofen and naloxone and varenicline                                     |
| baclofen and nalorphine and rimonabant                                    |
| baclofen and nalorphine and am-251                                        |
| baclofen and nalorphine and org24598                                      |
| baclofen and nalorphine and acamprosate                                   |
| baclofen and nalorphine and bupropion                                     |
| baclofen and nalorphine and bupropion (extended release)                  |
| baclofen and nalorphine and nicotine                                      |
| baclofen and nalorphine and varenicline                                   |
| baclofen and levallorphan and rimonabant                                  |
| baclofen and levallorphan and am-251                                      |
| baclofen and levallorphan and org24598                                    |
| baclofen and levallorphan and acamprosate                                 |
| baclofen and levallorphan and bupropion                                   |
| baclofen and levallorphan and bupropion (extended release)                |
| baclofen and levallorphan and nicotine                                    |
| baclofen and levallorphan and varenicline                                 |
| baclofen and buprenorphine and rimonabant                                 |
| baclofen and buprenorphine and am-251                                     |
| baclofen and buprenorphine and org24598                                   |
| baclofen and buprenorphine and acamprosate                                |
| baclofen and buprenorphine and bupropion                                  |
| baclofen and buprenorphine and bupropion (extended release)               |
| baclofen and buprenorphine and nicotine                                   |
| baclofen and buprenorphine and varenicline                                |
| baclofen and extended release naltrexone and rimonabant                   |
| baclofen and extended release naltrexone and am-251                       |
| baclofen and extended release naltrexone and org24598                     |
| baclofen and extended release naltrexone and acamprosate                  |
| baclofen and extended release naltrexone and bupropion                    |
| baclofen and extended release naltrexone and bupropion (extended release) |
| baclofen and extended release naltrexone and nicotine                     |

Table 3. Three Compound Combinations

|                                                               |
|---------------------------------------------------------------|
| baclofen and extended release naltrexone and varenicline      |
| baclofen and tan-67 and rimonabant                            |
| baclofen and tan-67 and am-251                                |
| baclofen and tan-67 and org24598                              |
| baclofen and tan-67 andacamprosate                            |
| baclofen and tan-67 and bupropion                             |
| baclofen and tan-67 and bupropion (extended release)          |
| baclofen and tan-67 and nicotine                              |
| baclofen and tan-67 and varenicline                           |
| baclofen and snc80 and rimonabant                             |
| baclofen and snc80 and am-251                                 |
| baclofen and snc80 and org24598                               |
| baclofen and snc80 andacamprosate                             |
| baclofen and snc80 and bupropion                              |
| baclofen and snc80 and bupropion (extended release)           |
| baclofen and snc80 and nicotine                               |
| baclofen and snc80 and varenicline                            |
| lesogaberan and naltrexone and rimonabant                     |
| lesogaberan and naltrexone and am-251                         |
| lesogaberan and naltrexone and org24598                       |
| lesogaberan and naltrexone andacamprosate                     |
| lesogaberan and naltrexone and bupropion                      |
| lesogaberan and naltrexone and bupropion (extended release)   |
| lesogaberan and naltrexone and nicotine                       |
| lesogaberan and naltrexone and varenicline                    |
| lesogaberan and naloxone and rimonabant                       |
| lesogaberan and naloxone and am-251                           |
| lesogaberan and naloxone and org24598                         |
| lesogaberan and naloxone andacamprosate                       |
| lesogaberan and naloxone and bupropion                        |
| lesogaberan and naloxone and bupropion (extended release)     |
| lesogaberan and naloxone and nicotine                         |
| lesogaberan and naloxone and varenicline                      |
| lesogaberan and nalorphine and rimonabant                     |
| lesogaberan and nalorphine and am-251                         |
| lesogaberan and nalorphine and org24598                       |
| lesogaberan and nalorphine andacamprosate                     |
| lesogaberan and nalorphine and bupropion                      |
| lesogaberan and nalorphine and bupropion (extended release)   |
| lesogaberan and nalorphine and nicotine                       |
| lesogaberan and nalorphine and varenicline                    |
| lesogaberan and levallorphan and rimonabant                   |
| lesogaberan and levallorphan and am-251                       |
| lesogaberan and levallorphan and org24598                     |
| lesogaberan and levallorphan andacamprosate                   |
| lesogaberan and levallorphan and bupropion                    |
| lesogaberan and levallorphan and bupropion (extended release) |
| lesogaberan and levallorphan and nicotine                     |

Table 3. Three Compound Combinations

|                                                                              |
|------------------------------------------------------------------------------|
| lesogaberan and levallorphan and varenicline                                 |
| lesogaberan and buprenorphine and rimonabant                                 |
| lesogaberan and buprenorphine and am-251                                     |
| lesogaberan and buprenorphine and org24598                                   |
| lesogaberan and buprenorphine andacamprosate                                 |
| lesogaberan and buprenorphine and bupropion                                  |
| lesogaberan and buprenorphine and bupropion (extended release)               |
| lesogaberan and buprenorphine and nicotine                                   |
| lesogaberan and buprenorphine and varenicline                                |
| lesogaberan and extended release naltrexone and rimonabant                   |
| lesogaberan and extended release naltrexone and am-251                       |
| lesogaberan and extended release naltrexone and org24598                     |
| lesogaberan and extended release naltrexone andacamprosate                   |
| lesogaberan and extended release naltrexone and bupropion                    |
| lesogaberan and extended release naltrexone and bupropion (extended release) |
| lesogaberan and extended release naltrexone and nicotine                     |
| lesogaberan and extended release naltrexone and varenicline                  |
| lesogaberan and tan-67 and rimonabant                                        |
| lesogaberan and tan-67 and am-251                                            |
| lesogaberan and tan-67 and org24598                                          |
| lesogaberan and tan-67 andacamprosate                                        |
| lesogaberan and tan-67 and bupropion                                         |
| lesogaberan and tan-67 and bupropion (extended release)                      |
| lesogaberan and tan-67 and nicotine                                          |
| lesogaberan and tan-67 and varenicline                                       |
| lesogaberan and snc80 and rimonabant                                         |
| lesogaberan and snc80 and am-251                                             |
| lesogaberan and snc80 and org24598                                           |
| lesogaberan and snc80 andacamprosate                                         |
| lesogaberan and snc80 and bupropion                                          |
| lesogaberan and snc80 and bupropion (extended release)                       |
| lesogaberan and snc80 and nicotine                                           |
| lesogaberan and snc80 and varenicline                                        |
| gabapentin and naltrexone and rimonabant                                     |
| gabapentin and naltrexone and am-251                                         |
| gabapentin and naltrexone and org24598                                       |
| gabapentin and naltrexone andacamprosate                                     |
| gabapentin and naltrexone and bupropion                                      |
| gabapentin and naltrexone and bupropion (extended release)                   |
| gabapentin and naltrexone and nicotine                                       |
| gabapentin and naltrexone and varenicline                                    |
| gabapentin and naloxone and rimonabant                                       |
| gabapentin and naloxone and am-251                                           |
| gabapentin and naloxone and org24598                                         |
| gabapentin and naloxone andacamprosate                                       |
| gabapentin and naloxone and bupropion                                        |
| gabapentin and naloxone and bupropion (extended release)                     |
| gabapentin and naloxone and nicotine                                         |

Table 3. Three Compound Combinations

|                                                                             |
|-----------------------------------------------------------------------------|
| gabapentin and naloxone and varenicline                                     |
| gabapentin and nalorphine and rimonabant                                    |
| gabapentin and nalorphine and am-251                                        |
| gabapentin and nalorphine and org24598                                      |
| gabapentin and nalorphine and acamprosate                                   |
| gabapentin and nalorphine and bupropion                                     |
| gabapentin and nalorphine and bupropion (extended release)                  |
| gabapentin and nalorphine and nicotine                                      |
| gabapentin and nalorphine and varenicline                                   |
| gabapentin and levallorphan and rimonabant                                  |
| gabapentin and levallorphan and am-251                                      |
| gabapentin and levallorphan and org24598                                    |
| gabapentin and levallorphan and acamprosate                                 |
| gabapentin and levallorphan and bupropion                                   |
| gabapentin and levallorphan and bupropion (extended release)                |
| gabapentin and levallorphan and nicotine                                    |
| gabapentin and levallorphan and varenicline                                 |
| gabapentin and buprenorphine and rimonabant                                 |
| gabapentin and buprenorphine and am-251                                     |
| gabapentin and buprenorphine and org24598                                   |
| gabapentin and buprenorphine and acamprosate                                |
| gabapentin and buprenorphine and bupropion                                  |
| gabapentin and buprenorphine and bupropion (extended release)               |
| gabapentin and buprenorphine and nicotine                                   |
| gabapentin and buprenorphine and varenicline                                |
| gabapentin and extended release naltrexone and rimonabant                   |
| gabapentin and extended release naltrexone and am-251                       |
| gabapentin and extended release naltrexone and org24598                     |
| gabapentin and extended release naltrexone and acamprosate                  |
| gabapentin and extended release naltrexone and bupropion                    |
| gabapentin and extended release naltrexone and bupropion (extended release) |
| gabapentin and extended release naltrexone and nicotine                     |
| gabapentin and extended release naltrexone and varenicline                  |
| gabapentin and tan-67 and rimonabant                                        |
| gabapentin and tan-67 and am-251                                            |
| gabapentin and tan-67 and org24598                                          |
| gabapentin and tan-67 and acamprosate                                       |
| gabapentin and tan-67 and bupropion                                         |
| gabapentin and tan-67 and bupropion (extended release)                      |
| gabapentin and tan-67 and nicotine                                          |
| gabapentin and tan-67 and varenicline                                       |
| gabapentin and snc80 and rimonabant                                         |
| gabapentin and snc80 and am-251                                             |
| gabapentin and snc80 and org24598                                           |
| gabapentin and snc80 and acamprosate                                        |
| gabapentin and snc80 and bupropion                                          |
| gabapentin and snc80 and bupropion (extended release)                       |
| gabapentin and snc80 and nicotine                                           |

Table 3. Three Compound Combinations

|                                                                             |
|-----------------------------------------------------------------------------|
| gabapentin and snc80 and varenicline                                        |
| pregabalin and naltrexone and rimonabant                                    |
| pregabalin and naltrexone and am-251                                        |
| pregabalin and naltrexone and org24598                                      |
| pregabalin and naltrexone andacamprosate                                    |
| pregabalin and naltrexone and bupropion                                     |
| pregabalin and naltrexone and bupropion (extended release)                  |
| ppregabalin and naltrexone and nicotine                                     |
| pregabalin and naltrexone and varenicline                                   |
| pregabalin and naloxone and rimonabant                                      |
| pregabalin and naloxone and am-251                                          |
| pregabalin and naloxone and org24598                                        |
| pregabalin and naloxone andacamprosate                                      |
| pregabalin and naloxone and bupropion                                       |
| pregabalin and naloxone and bupropion (extended release)                    |
| pregabalin and naloxone and nicotine                                        |
| pregabalin and naloxone and varenicline                                     |
| pregabalin and nalorphine and rimonabant                                    |
| pregabalin and nalorphine and am-251                                        |
| pregabalin and nalorphine and org24598                                      |
| pregabalin and nalorphine andacamprosate                                    |
| pregabalin and nalorphine and bupropion                                     |
| pregabalin and nalorphine and bupropion (extended release)                  |
| pregabalin and nalorphine and nicotine                                      |
| pregabalin and nalorphine and varenicline                                   |
| pregabalin and levallorphan and rimonabant                                  |
| pregabalin and levallorphan and am-251                                      |
| pregabalin and levallorphan and org24598                                    |
| pregabalin and levallorphan andacamprosate                                  |
| pregabalin and levallorphan and bupropion                                   |
| pregabalin and levallorphan and bupropion (extended release)                |
| pregabalin and levallorphan and nicotine                                    |
| pregabalin and levallorphan and varenicline                                 |
| pregabalin and buprenorphine and rimonabant                                 |
| pregabalin and buprenorphine and am-251                                     |
| pregabalin and buprenorphine and org24598                                   |
| pregabalin and buprenorphine andacamprosate                                 |
| pregabalin and buprenorphine and bupropion                                  |
| pregabalin and buprenorphine and bupropion (extended release)               |
| pregabalin and buprenorphine and nicotine                                   |
| pregabalin and buprenorphine and varenicline                                |
| pregabalin and extended release naltrexone and rimonabant                   |
| pregabalin and extended release naltrexone and am-251                       |
| pregabalin and extended release naltrexone and org24598                     |
| pregabalin and extended release naltrexone andacamprosate                   |
| pregabalin and extended release naltrexone and bupropion                    |
| pregabalin and extended release naltrexone and bupropion (extended release) |
| pregabalin and extended release naltrexone and nicotine                     |



Table 3. Three Compound Combinations

|                                                            |
|------------------------------------------------------------|
| pregabalin and extended release naltrexone and varenicline |
| pregabalin and tan-67 and rimonabant                       |
| pregabalin and tan-67 and am-251                           |
| pregabalin and tan-67 and org24598                         |
| pregabalin and tan-67 and acamprosate                      |
| pregabalin and tan-67 and bupropion                        |
| pregabalin and tan-67 and bupropion (extended release)     |
| pregabalin and tan-67 and nicotine                         |
| pregabalin and tan-67 and varenicline                      |
| pregabalin and snc80 and rimonabant                        |
| pregabalin and snc80 and am-251                            |
| pregabalin and snc80 and org24598                          |
| pregabalin and snc80 and acamprosate                       |
| pregabalin and snc80 and bupropion                         |
| pregabalin and snc80 and bupropion (extended release)      |
| pregabalin and snc80 and nicotine                          |
| pregabalin and snc80 and varenicline                       |
| baclofen and naltrexone and phentermine                    |
| baclofen and naltrexone and dexmethylphenidate             |
| baclofen and naltrexone and dextroamphetamine              |
| baclofen and naltrexone and dexedrine                      |
| baclofen and naltrexone and adderall                       |
| baclofen and naltrexone and methylphenidate                |
| baclofen and naltrexone and modafanil                      |
| baclofen and naltrexone and lisdexamfetamine               |
| baclofen and naloxone and phentermine                      |
| baclofen and naloxone and dexmethylphenidate               |
| baclofen and naloxone and dextroamphetamine                |
| baclofen and naloxone and dexedrine                        |
| baclofen and naloxone and adderall                         |
| baclofen and naloxone and methylphenidate                  |
| baclofen and naloxone and modafanil                        |
| baclofen and naloxone and lisdexamfetamine                 |
| baclofen and nalorphine and phentermine                    |
| baclofen and nalorphine and dexmethylphenidate             |
| baclofen and nalorphine and dextroamphetamine              |
| baclofen and nalorphine and dexedrine                      |
| baclofen and nalorphine and adderall                       |
| baclofen and nalorphine and methylphenidate                |
| baclofen and nalorphine and modafanil                      |
| baclofen and nalorphine and lisdexamfetamine               |
| baclofen and levallorphan and phentermine                  |
| baclofen and levallorphan and dexmethylphenidate           |
| baclofen and levallorphan and dextroamphetamine            |
| baclofen and levallorphan and dexedrine                    |
| baclofen and levallorphan and adderall                     |
| baclofen and levallorphan and methylphenidate              |
| baclofen and levallorphan and modafanil                    |

Table 3. Three Compound Combinations

|                                                                  |
|------------------------------------------------------------------|
| baclofen and levallorphan and lisdexamfetamine                   |
| baclofen and buprenorphine and phentermine                       |
| baclofen and buprenorphine and dexamethylphenidate               |
| baclofen and buprenorphine and dextroamphetamine                 |
| baclofen and buprenorphine and dexedrine                         |
| baclofen and buprenorphine and adderall                          |
| baclofen and buprenorphine and methylphenidate                   |
| baclofen and buprenorphine and modafanil                         |
| baclofen and buprenorphine and lisdexamfetamine                  |
| baclofen and extended release naltrexone and phentermine         |
| baclofen and extended release naltrexone and dexamethylphenidate |
| baclofen and extended release naltrexone and dextroamphetamine   |
| baclofen and extended release naltrexone and dexedrine           |
| baclofen and extended release naltrexone and adderall            |
| baclofen and extended release naltrexone and methylphenidate     |
| baclofen and extended release naltrexone and modafanil           |
| baclofen and extended release naltrexone and lisdexamfetamine    |
| baclofen and tan-67 and phentermine                              |
| baclofen and tan-67 and dexamethylphenidate                      |
| baclofen and tan-67 and dextroamphetamine                        |
| baclofen and tan-67 and dexedrine                                |
| baclofen and tan-67 and adderall                                 |
| baclofen and tan-67 and methylphenidate                          |
| baclofen and tan-67 and modafanil                                |
| baclofen and tan-67 and lisdexamfetamine                         |
| baclofen and snc80 and phentermine                               |
| baclofen and snc80 and dexamethylphenidate                       |
| baclofen and snc80 and dextroamphetamine                         |
| baclofen and snc80 and dexedrine                                 |
| baclofen and snc80 and adderall                                  |
| baclofen and snc80 and methylphenidate                           |
| baclofen and snc80 and modafanil                                 |
| baclofen and snc80 and lisdexamfetamine                          |
| lesogaberan and naltrexone and phentermine                       |
| lesogaberan and naltrexone and dexamethylphenidate               |
| lesogaberan and naltrexone and dextroamphetamine                 |
| lesogaberan and naltrexone and dexedrine                         |
| lesogaberan and naltrexone and adderall                          |
| lesogaberan and naltrexone and methylphenidate                   |
| lesogaberan and naltrexone and modafanil                         |
| lesogaberan and naltrexone and lisdexamfetamine                  |
| lesogaberan and naloxone and phentermine                         |
| lesogaberan and naloxone and dexamethylphenidate                 |
| lesogaberan and naloxone and dextroamphetamine                   |
| lesogaberan and naloxone and dexedrine                           |
| lesogaberan and naloxone and adderall                            |
| lesogaberan and naloxone and methylphenidate                     |
| lesogaberan and naloxone and modafanil                           |

Table 3. Three Compound Combinations

|                                                                    |
|--------------------------------------------------------------------|
| lesogaberan and naloxone and lisdexamfetamine                      |
| lesogaberan and nalorphine and phentermine                         |
| lesogaberan and nalorphine and dexmethylphenidate                  |
| lesogaberan and nalorphine and dextroamphetamine                   |
| lesogaberan and nalorphine and dexedrine                           |
| lesogaberan and nalorphine and adderall                            |
| lesogaberan and nalorphine and methylphenidate                     |
| lesogaberan and nalorphine and modafanil                           |
| lesogaberan and nalorphine and lisdexamfetamine                    |
| lesogaberan and levallorphan and phentermine                       |
| lesogaberan and levallorphan and dexmethylphenidate                |
| lesogaberan and levallorphan and dextroamphetamine                 |
| lesogaberan and levallorphan and dexedrine                         |
| lesogaberan and levallorphan and adderall                          |
| lesogaberan and levallorphan and methylphenidate                   |
| lesogaberan and levallorphan and modafanil                         |
| lesogaberan and levallorphan and lisdexamfetamine                  |
| lesogaberan and buprenorphine and phentermine                      |
| lesogaberan and buprenorphine and dexmethylphenidate               |
| lesogaberan and buprenorphine and dextroamphetamine                |
| lesogaberan and buprenorphine and dexedrine                        |
| lesogaberan and buprenorphine and adderall                         |
| lesogaberan and buprenorphine and methylphenidate                  |
| lesogaberan and buprenorphine and modafanil                        |
| lesogaberan and buprenorphine and lisdexamfetamine                 |
| lesogaberan and extended release naltrexone and phentermine        |
| lesogaberan and extended release naltrexone and dexmethylphenidate |
| lesogaberan and extended release naltrexone and dextroamphetamine  |
| lesogaberan and extended release naltrexone and dexedrine          |
| lesogaberan and extended release naltrexone and adderall           |
| lesogaberan and extended release naltrexone and methylphenidate    |
| lesogaberan and extended release naltrexone and modafanil          |
| lesogaberan and extended release naltrexone and lisdexamfetamine   |
| lesogaberan and tan-67 and phentermine                             |
| lesogaberan and tan-67 and dexmethylphenidate                      |
| lesogaberan and tan-67 and dextroamphetamine                       |
| lesogaberan and tan-67 and dexedrine                               |
| lesogaberan and tan-67 and adderall                                |
| lesogaberan and tan-67 and methylphenidate                         |
| lesogaberan and tan-67 and modafanil                               |
| lesogaberan and tan-67 and lisdexamfetamine                        |
| lesogaberan and snc80 and phentermine                              |
| lesogaberan and snc80 and dexmethylphenidate                       |
| lesogaberan and snc80 and dextroamphetamine                        |
| lesogaberan and snc80 and dexedrine                                |
| lesogaberan and snc80 and adderall                                 |
| lesogaberan and snc80 and methylphenidate                          |
| lesogaberan and snc80 and modafanil                                |

Table 3. Three Compound Combinations

|                                                                   |
|-------------------------------------------------------------------|
| lesogaberan and snc80 and lisdexamfetamine                        |
| gabapentin and naltrexone and phentermine                         |
| gabapentin and naltrexone and dexmethylphenidate                  |
| gabapentin and naltrexone and dextroamphetamine                   |
| gabapentin and naltrexone and dexedrine                           |
| gabapentin and naltrexone and adderall                            |
| gabapentin and naltrexone and methylphenidate                     |
| gabapentin and naltrexone and modafanil                           |
| gabapentin and naltrexone and lisdexamfetamine                    |
| gabapentin and naloxone and phentermine                           |
| gabapentin and naloxone and dexmethylphenidate                    |
| gabapentin and naloxone and dextroamphetamine                     |
| gabapentin and naloxone and dexedrine                             |
| gabapentin and naloxone and adderall                              |
| gabapentin and naloxone and methylphenidate                       |
| gabapentin and naloxone and modafanil                             |
| gabapentin and naloxone and lisdexamfetamine                      |
| gabapentin and nalorphine and phentermine                         |
| gabapentin and nalorphine and dexmethylphenidate                  |
| gabapentin and nalorphine and dextroamphetamine                   |
| gabapentin and nalorphine and dexedrine                           |
| gabapentin and nalorphine and adderall                            |
| gabapentin and nalorphine and methylphenidate                     |
| gabapentin and nalorphine and modafanil                           |
| gabapentin and nalorphine and lisdexamfetamine                    |
| gabapentin and levallorphan and phentermine                       |
| gabapentin and levallorphan and dexmethylphenidate                |
| gabapentin and levallorphan and dextroamphetamine                 |
| gabapentin and levallorphan and dexedrine                         |
| gabapentin and levallorphan and adderall                          |
| gabapentin and levallorphan and methylphenidate                   |
| gabapentin and levallorphan and modafanil                         |
| gabapentin and levallorphan and lisdexamfetamine                  |
| gabapentin and buprenorphine and phentermine                      |
| gabapentin and buprenorphine and dexmethylphenidate               |
| gabapentin and buprenorphine and dextroamphetamine                |
| gabapentin and buprenorphine and dexedrine                        |
| gabapentin and buprenorphine and adderall                         |
| gabapentin and buprenorphine and methylphenidate                  |
| gabapentin and buprenorphine and modafanil                        |
| gabapentin and buprenorphine and lisdexamfetamine                 |
| gabapentin and extended release naltrexone and phentermine        |
| gabapentin and extended release naltrexone and dexmethylphenidate |
| gabapentin and extended release naltrexone and dextroamphetamine  |
| gabapentin and extended release naltrexone and dexedrine          |
| gabapentin and extended release naltrexone and adderall           |
| gabapentin and extended release naltrexone and methylphenidate    |
| gabapentin and extended release naltrexone and modafanil          |

Table 3. Three Compound Combinations

|                                                                 |
|-----------------------------------------------------------------|
| gabapentin and extended release naltrexone and lisdexamfetamine |
| gabapentin and tan-67 and phentermine                           |
| gabapentin and tan-67 and dexmethylphenidate                    |
| gabapentin and tan-67 and dextroamphetamine                     |
| gabapentin and tan-67 and dexedrine                             |
| gabapentin and tan-67 and adderall                              |
| gabapentin and tan-67 and methylphenidate                       |
| gabapentin and tan-67 and modafanil                             |
| gabapentin and tan-67 and lisdexamfetamine                      |
| gabapentin and snc80 and phentermine                            |
| gabapentin and snc80 and dexmethylphenidate                     |
| gabapentin and snc80 and dextroamphetamine                      |
| gabapentin and snc80 and dexedrine                              |
| gabapentin and snc80 and adderall                               |
| gabapentin and snc80 and methylphenidate                        |
| gabapentin and snc80 and modafanil                              |
| gabapentin and snc80 and lisdexamfetamine                       |
| pregabalin and naltrexone and phentermine                       |
| pregabalin and naltrexone and dexmethylphenidate                |
| pregabalin and naltrexone and dextroamphetamine                 |
| pregabalin and naltrexone and dexedrine                         |
| pregabalin and naltrexone and adderall                          |
| pregabalin and naltrexone and methylphenidate                   |
| pregabalin and naltrexone and modafanil                         |
| pregabalin and naltrexone and lisdexamfetamine                  |
| pregabalin and naloxone and phentermine                         |
| pregabalin and naloxone and dexmethylphenidate                  |
| pregabalin and naloxone and dextroamphetamine                   |
| pregabalin and naloxone and dexedrine                           |
| pregabalin and naloxone and adderall                            |
| pregabalin and naloxone and methylphenidate                     |
| pregabalin and naloxone and modafanil                           |
| pregabalin and naloxone and lisdexamfetamine                    |
| pregabalin and nalorphine and phentermine                       |
| pregabalin and nalorphine and dexmethylphenidate                |
| pregabalin and nalorphine and dextroamphetamine                 |
| pregabalin and nalorphine and dexedrine                         |
| pregabalin and nalorphine and adderall                          |
| pregabalin and nalorphine and methylphenidate                   |
| pregabalin and nalorphine and modafanil                         |
| pregabalin and nalorphine and lisdexamfetamine                  |
| pregabalin and levallorphan and phentermine                     |
| pregabalin and levallorphan and dexmethylphenidate              |
| pregabalin and levallorphan and dextroamphetamine               |
| pregabalin and levallorphan and dexedrine                       |
| pregabalin and levallorphan and adderall                        |
| pregabalin and levallorphan and methylphenidate                 |
| pregabalin and levallorphan and modafanil                       |

Table 3. Three Compound Combinations

|                                                                   |
|-------------------------------------------------------------------|
| pregabalin and levallorphan and lisdexamfetamine                  |
| pregabalin and buprenorphine and phentermine                      |
| pregabalin and buprenorphine and dexmethylphenidate               |
| pregabalin and buprenorphine and dextroamphetamine                |
| pregabalin and buprenorphine and dexedrine                        |
| pregabalin and buprenorphine and adderall                         |
| pregabalin and buprenorphine and methylphenidate                  |
| pregabalin and buprenorphine and modafanil                        |
| pregabalin and buprenorphine and lisdexamfetamine                 |
| pregabalin and extended release naltrexone and phentermine        |
| pregabalin and extended release naltrexone and dexmethylphenidate |
| pregabalin and extended release naltrexone and dextroamphetamine  |
| pregabalin and extended release naltrexone and dexedrine          |
| pregabalin and extended release naltrexone and adderall           |
| pregabalin and extended release naltrexone and methylphenidate    |
| pregabalin and extended release naltrexone and modafanil          |
| pregabalin and extended release naltrexone and lisdexamfetamine   |
| pregabalin and tan-67 and phentermine                             |
| pregabalin and tan-67 and dexmethylphenidate                      |
| pregabalin and tan-67 and dextroamphetamine                       |
| pregabalin and tan-67 and dexedrine                               |
| pregabalin and tan-67 and adderall                                |
| pregabalin and tan-67 and methylphenidate                         |
| pregabalin and tan-67 and modafanil                               |
| pregabalin and tan-67 and lisdexamfetamine                        |
| pregabalin and snc80 and phentermine                              |
| pregabalin and snc80 and dexmethylphenidate                       |
| pregabalin and snc80 and dextroamphetamine                        |
| pregabalin and snc80 and dexedrine                                |
| pregabalin and snc80 and adderall                                 |
| pregabalin and snc80 and methylphenidate                          |
| pregabalin and snc80 and modafanil                                |
| pregabalin and snc80 and lisdexamfetamine                         |
| baclofen and naltrexone and n-acetylcysteine                      |
| baclofen and naltrexone and d-cycloserine                         |
| baclofen and naltrexone and ceftriaxone                           |
| baclofen and naloxone and n-acetylcysteine                        |
| baclofen and naloxone and d-cycloserine                           |
| baclofen and naloxone and ceftriaxone                             |
| baclofen and nalorphine and n-acetylcysteine                      |
| baclofen and nalorphine and d-cycloserine                         |
| baclofen and nalorphine and ceftriaxone                           |
| baclofen and levallorphan and n-acetylcysteine                    |
| baclofen and levallorphan and d-cycloserine                       |
| baclofen and levallorphan and ceftriaxone                         |
| baclofen and buprenorphine and n-acetylcysteine                   |
| baclofen and buprenorphine and d-cycloserine                      |
| baclofen and buprenorphine and ceftriaxone                        |

Table 3. Three Compound Combinations

|                                                                  |
|------------------------------------------------------------------|
| baclofen and extended release naltrexone and n-acetylcysteine    |
| baclofen and extended release naltrexone and d-cycloserine       |
| baclofen and extended release naltrexone and ceftriaxone         |
| baclofen and tan-67 and n-acetylcysteine                         |
| baclofen and tan-67 and d-cycloserine                            |
| baclofen and tan-67 and ceftriaxone                              |
| baclofen and snc80 and n-acetylcysteine                          |
| baclofen and snc80 and d-cycloserine                             |
| baclofen and snc80 and ceftriaxone                               |
| lesogaberan and naltrexone and n-acetylcysteine                  |
| lesogaberan and naltrexone and d-cycloserine                     |
| lesogaberan and naltrexone and ceftriaxone                       |
| lesogaberan and naloxone and n-acetylcysteine                    |
| lesogaberan and naloxone and d-cycloserine                       |
| lesogaberan and naloxone and ceftriaxone                         |
| lesogaberan and nalorphine and n-acetylcysteine                  |
| lesogaberan and nalorphine and d-cycloserine                     |
| lesogaberan and nalorphine and ceftriaxone                       |
| lesogaberan and levallorphan and n-acetylcysteine                |
| lesogaberan and levallorphan and d-cycloserine                   |
| lesogaberan and levallorphan and ceftriaxone                     |
| lesogaberan and buprenorphine and n-acetylcysteine               |
| lesogaberan and buprenorphine and d-cycloserine                  |
| lesogaberan and buprenorphine and ceftriaxone                    |
| lesogaberan and extended release naltrexone and n-acetylcysteine |
| lesogaberan and extended release naltrexone and d-cycloserine    |
| lesogaberan and extended release naltrexone and ceftriaxone      |
| lesogaberan and tan-67 and n-acetylcysteine                      |
| lesogaberan and tan-67 and d-cycloserine                         |
| lesogaberan and tan-67 and ceftriaxone                           |
| lesogaberan and snc80 and n-acetylcysteine                       |
| lesogaberan and snc80 and d-cycloserine                          |
| lesogaberan and snc80 and ceftriaxone                            |
| gabapentin and naltrexone and n-acetylcysteine                   |
| gabapentin and naltrexone and d-cycloserine                      |
| gabapentin and naltrexone and ceftriaxone                        |
| gabapentin and naloxone and n-acetylcysteine                     |
| gabapentin and naloxone and d-cycloserine                        |
| gabapentin and naloxone and ceftriaxone                          |
| gabapentin and nalorphine and n-acetylcysteine                   |
| gabapentin and nalorphine and d-cycloserine                      |
| gabapentin and nalorphine and ceftriaxone                        |
| gabapentin and levallorphan and n-acetylcysteine                 |
| gabapentin and levallorphan and d-cycloserine                    |
| gabapentin and levallorphan and ceftriaxone                      |
| gabapentin and buprenorphine and n-acetylcysteine                |
| gabapentin and buprenorphine and d-cycloserine                   |
| gabapentin and buprenorphine and ceftriaxone                     |

Table 3. Three Compound Combinations

|                                                                 |
|-----------------------------------------------------------------|
| gabapentin and extended release naltrexone and n-acetylcysteine |
| gabapentin and extended release naltrexone and d-cycloserine    |
| gabapentin and extended release naltrexone and ceftriaxone      |
| gabapentin and tan-67 and n-acetylcysteine                      |
| gabapentin and tan-67 and d-cycloserine                         |
| gabapentin and tan-67 and ceftriaxone                           |
| gabapentin and snc80 and n-acetylcysteine                       |
| gabapentin and snc80 and d-cycloserine                          |
| gabapentin and snc80 and ceftriaxone                            |
| pregabalin and naltrexone and n-acetylcysteine                  |
| pregabalin and naltrexone and d-cycloserine                     |
| pregabalin and naltrexone and ceftriaxone                       |
| pregabalin and naloxone and n-acetylcysteine                    |
| pregabalin and naloxone and d-cycloserine                       |
| pregabalin and naloxone and ceftriaxone                         |
| pregabalin and nalorphine and n-acetylcysteine                  |
| pregabalin and nalorphine and d-cycloserine                     |
| pregabalin and nalorphine and ceftriaxone                       |
| pregabalin and levallorphan and n-acetylcysteine                |
| pregabalin and levallorphan and d-cycloserine                   |
| pregabalin and levallorphan and ceftriaxone                     |
| pregabalin and buprenorphine and n-acetylcysteine               |
| pregabalin and buprenorphine and d-cycloserine                  |
| pregabalin and buprenorphine and ceftriaxone                    |
| pregabalin and extended release naltrexone and n-acetylcysteine |
| pregabalin and extended release naltrexone and d-cycloserine    |
| pregabalin and extended release naltrexone and ceftriaxone      |
| pregabalin and tan-67 and n-acetylcysteine                      |
| pregabalin and tan-67 and d-cycloserine                         |
| pregabalin and tan-67 and ceftriaxone                           |
| pregabalin and snc80 and n-acetylcysteine                       |
| pregabalin and snc80 and d-cycloserine                          |
| pregabalin and snc80 and ceftriaxone                            |



| <b>Table 4: Palatable food intake following drug injections as a percent of intake after saline injections</b> |                   |           |                 |           |                            |           |
|----------------------------------------------------------------------------------------------------------------|-------------------|-----------|-----------------|-----------|----------------------------|-----------|
| <b>1-H Intake (%)</b>                                                                                          |                   |           |                 |           |                            |           |
| <b>Group</b>                                                                                                   | <b>Naltrexone</b> |           | <b>Baclofen</b> |           | <b>Naltrexone-Baclofen</b> |           |
|                                                                                                                | low dose          | high dose | low dose        | high dose | low dose                   | high dose |
| <b>Binge Sugar</b>                                                                                             | 158               | 92        | 131             | 96        | 115                        | <b>51</b> |
| <b>Binge Fat</b>                                                                                               | 70                | 59        | 106             | 38        | 110                        | <b>26</b> |
| <b>Binge Sugar-Fat</b>                                                                                         | 74                | 75        | 100             | <b>37</b> | 106                        | 44        |

| <b>12-H Intake (%)</b> |                   |           |                 |           |                            |           |
|------------------------|-------------------|-----------|-----------------|-----------|----------------------------|-----------|
| <b>Group</b>           | <b>Naltrexone</b> |           | <b>Baclofen</b> |           | <b>Naltrexone-Baclofen</b> |           |
|                        | low dose          | high dose | low dose        | high dose | low dose                   | high dose |
| <b>Binge Sugar</b>     | 92                | 85        | 88              | 90        | 85                         | <b>82</b> |
| <b>Binge Fat</b>       | 85                | 91        | 93              | <b>56</b> | 83                         | 59        |
| <b>Binge Sugar-Fat</b> | 92                | 109       | 85              | <b>75</b> | 94                         | 89        |

| Table 5: Palatable food intake following drug injections (Kcals) |                           |                      |                      |                       |                        |                         |
|------------------------------------------------------------------|---------------------------|----------------------|----------------------|-----------------------|------------------------|-------------------------|
| 1-H Palatable Food Intake (Kcal)                                 |                           |                      |                      |                       |                        |                         |
| Group                                                            | Saline                    | Naltrexone           |                      | Baclofen              |                        | Naltrexone-Baclofen     |
|                                                                  |                           | low dose             | high dose            | low dose              | high dose              | low dose                |
| Binge Sugar                                                      | 2.8±0.5                   | 4.4±0.7 <sup>a</sup> | 2.6±0.4 <sup>a</sup> | 3.6±0.8               | 2.7±0.5                | 3.2±0.6 <sup>b</sup>    |
| Binge Fat                                                        | 16.8±3.0 <sup>c,h,i</sup> | 11.7±1.9             | 9.9±2.0              | 17.9±2.4 <sup>d</sup> | 6.5±2.0 <sup>c,d</sup> | 18.5±2.3 <sup>g</sup>   |
| Binge Sugar-Fat                                                  | 23.5±2.7 <sup>k,m</sup>   | 17.3±1.7             | 17.6±3.5             | 23.5±3.9 <sup>j</sup> | 8.6±1.6 <sup>j,k</sup> | 24.9±1.9 <sup>n</sup>   |
|                                                                  |                           |                      |                      |                       |                        | 10.4±2.5 <sup>m,n</sup> |

| 12-H Palatable Food Intake (Kcal) |                         |                       |                       |                       |                         |                     |
|-----------------------------------|-------------------------|-----------------------|-----------------------|-----------------------|-------------------------|---------------------|
| Group                             | Saline                  | Naltrexone            |                       | Baclofen              |                         | Naltrexone-Baclofen |
|                                   |                         | low dose              | high dose             | low dose              | high dose               | low dose            |
| Binge Sugar                       | 12.8±2.3                | 18.7±2.4 <sup>r</sup> | 10.8±1.8 <sup>r</sup> | 11.3±2.5              | 11.4±2.4                | 10.8±2.3            |
| Binge Fat                         | 58.6±6.3 <sup>e,i</sup> | 49.9±3.6              | 53.3±4.5              | 54.5±4.5 <sup>t</sup> | 32.6±4.9 <sup>e,t</sup> | 48.7±3.8            |
| Binge Sugar-Fat                   | 76.4±5.8 <sup>p</sup>   | 70.6±3.4              | 83.3±8.1              | 64.9±6.6              | 57.4±4.1 <sup>p</sup>   | 71.8±6.5            |
|                                   |                         |                       |                       |                       |                         | 67.9±4.5            |

| Table 6: Chow intake following drug injections (Kcals) |                       |            |           |                       |                      |                       |                        |
|--------------------------------------------------------|-----------------------|------------|-----------|-----------------------|----------------------|-----------------------|------------------------|
| 1-H Chow Intake (Kcal)                                 |                       |            |           |                       |                      |                       |                        |
| Group                                                  | Saline                | Naltrexone |           | Baclofen              |                      | Naltrexone-Baclofen   |                        |
|                                                        |                       | low dose   | high dose | low dose              | high dose            | low dose              | high dose              |
| Binge Sugar                                            | 18.2±1.7              | 25.5±3.2   | 20.1±1.3  | 23.0±1.5              | 19.3±3.4             | 23.0±1.8 <sup>d</sup> | 15.7±1.7 <sup>d</sup>  |
| Binge Fat                                              | 11.3±1.3 <sup>g</sup> | 8.5±1.1    | 10.1±1.2  | 12.2±1.7              | 10.6±1.0             | 13.1±0.8 <sup>h</sup> | 8.1±0.7 <sup>g,h</sup> |
| Binge Sugar-Fat                                        | 8.2±1.4               | 6.6±1.0    | 7.1±0.9   | 11.3±1.7 <sup>i</sup> | 6.3±1.0 <sup>i</sup> | 10.1±1.1              | 7.5±1.6                |

| 12-H Chow Intake (Kcal) |                               |                       |                       |                       |           |                       |                       |
|-------------------------|-------------------------------|-----------------------|-----------------------|-----------------------|-----------|-----------------------|-----------------------|
| Group                   | Saline                        | Naltrexone            |                       | Baclofen              |           | Naltrexone-Baclofen   |                       |
|                         |                               | low dose              | high dose             | low dose              | high dose | low dose              | high dose             |
| Binge Sugar             | 58.5±2.7 <sup>a,b,c,e,f</sup> | 73.7±5.1 <sup>a</sup> | 78.6±4.7 <sup>b</sup> | 73.5±4.5 <sup>c</sup> | 62.5±3.8  | 77.0±3.2 <sup>e</sup> | 75.4±4.5 <sup>f</sup> |
| Binge Fat               | 38.0±3.4                      | 34.1±4.3              | 37.0±3.4              | 34.1±3.3              | 35.0±5.0  | 35.1±3.8              | 33.3±3.3              |
| Binge Sugar-Fat         | 23.6±2.5                      | 26.4±1.9              | 27.4±2.6              | 24.6±2.2              | 24.1±3.1  | 26.3±2.2              | 24.8±1.9              |

| Table 7: Total caloric intake following drug injections (Kcals) |                         |                       |           |                       |                         |                       |                         |
|-----------------------------------------------------------------|-------------------------|-----------------------|-----------|-----------------------|-------------------------|-----------------------|-------------------------|
| 1-H Total Caloric Intake (Kcal)                                 |                         |                       |           |                       |                         |                       |                         |
| Group                                                           | Saline                  | Naltrexone            |           | Baclofen              |                         | Naltrexone-Baclofen   |                         |
|                                                                 |                         | low dose              | high dose | low dose              | high dose               | low dose              | high dose               |
| Binge Sugar                                                     | 20.9±2.2 <sup>a</sup>   | 29.9±3.9 <sup>a</sup> | 22.6±1.7  | 26.7±2.3              | 21.9±4.4                | 26.2±2.4 <sup>b</sup> | 17.1±2.1 <sup>b</sup>   |
| Binge Fat                                                       | 28.2±3.4 <sup>e,h</sup> | 20.2±3.0              | 19.9±3.2  | 30.1±4.1 <sup>f</sup> | 17.0±3.0 <sup>e,f</sup> | 31.6±3.1 <sup>i</sup> | 12.4±2.1 <sup>h,i</sup> |
| Binge Sugar-Fat                                                 | 31.7±4.1 <sup>k,n</sup> | 23.9±2.7              | 24.8±4.4  | 34.8±5.6 <sup>m</sup> | 15.0±2.6 <sup>k,m</sup> | 35.0±3.0 <sup>o</sup> | 17.9±4.0 <sup>n,o</sup> |

| 12-H Total Caloric Intake (Kcal) |                         |            |            |          |                       |                       |                       |
|----------------------------------|-------------------------|------------|------------|----------|-----------------------|-----------------------|-----------------------|
| Group                            | Saline                  | Naltrexone |            | Baclofen |                       | Naltrexone-Baclofen   |                       |
|                                  |                         | low dose   | high dose  | low dose | high dose             | low dose              | high dose             |
| Binge Sugar                      | 71.3±5.0 <sup>c,d</sup> | 85.4±7.5   | 89.4±6.4   | 84.8±7.0 | 74.0±6.3              | 87.9±5.5 <sup>e</sup> | 85.9±7.3 <sup>d</sup> |
| Binge Fat                        | 96.6±9.6 <sup>g,j</sup> | 84.0±7.9   | 90.3±8.3   | 88.6±7.8 | 67.7±9.9 <sup>g</sup> | 83.7±7.5              | 68.1±6.4 <sup>j</sup> |
| Binge Sugar-Fat                  | 100.0±8.3               | 97.0±5.7   | 110.7±10.7 | 89.5±8.8 | 81.4±7.3              | 98.1±8.7              | 92.7±6.3              |

## CLAIMS

We claim:

1. A pharmaceutical composition comprising a therapeutically effective amount of: a first compound selected from baclofen, lesogaberan, gabapentin, pregabalin or a pharmaceutically acceptable salt, isomer, prodrug, analog or derivative thereof; and a second compound selected from naltrexone, naloxone, nalorphine, levallorphan, buprenorphine, extended release naltrexone, TAN-67, SNC80 or a pharmaceutically acceptable salt, isomer, prodrug, analog or derivative thereof.

2. The composition of claim 1, wherein said composition further comprises a therapeutically effective amount of a third compound selected from rimonabant, AM-251, extended release bupropion, bupropion, acamprosate, nicotine, varenicline, phentermine, dextmethylphenidate, dextroamphetamine, adderall, dexedrine, methylphenidate, dextroamphetamine, modafanil, lisdexamfetamine or a pharmaceutically acceptable salt, isomer, prodrug, analog or derivative thereof.

3. The composition of claim 2, wherein said combination of compounds is selected from those set forth in Table 2 or Table 3 or a pharmaceutically acceptable salt, isomer, prodrug, analog or derivative thereof, particularly naltrexone and baclofen.

4. The composition according to claim 1, wherein the composition comprises the naltrexone, in an amount of about 25 to 100 milligrams and baclofen, in an amount between about 15 and about 120 milligrams per day.

5. The composition according to claim 2, wherein the composition comprises:

a) naltrexone, in an amount of about 25 to 100 milligrams, baclofen, in an amount between about 15 and about 120 milligrams and acamprosate in an amount of between about 300 and 2500 milligrams; or

b) naltrexone, in an amount of about 25 to 100 milligrams, baclofen, in an amount between about 15 and about 120 milligrams and bupropion or bupropion extended release in an amount of between 75 milligrams and 450 milligrams.

6. The use of a composition according to any one of claims 1, 2, 3, 4 or 5 for the treatment of individuals who meet the definition of food addiction; individuals that are overweight or obese (e.g., a BMI  $\geq 25$ ); individuals that have a binge eating disorder; or individuals who engage in a binge eating behavior.

7. A method for the treatment of individuals who meet the definition of food addiction; individuals that are overweight or obese (e.g., a BMI  $\geq 25$ ); individuals that have a binge eating disorder; or individuals who engage in a binge eating behavior comprising the administration of a composition according to any one of claims 1, 2, 3, 4 or 5 to an individual meeting the definition of food addiction, an individual who is obese or overweight, an individual who has a binge-eating disorder or an individual who engages in binge eating behavior.

8. A method for reducing the intake of fatty foods, sugar rich foods, or foods that are both fatty and sugar-rich comprising the administration of a composition according to any one of claims 1, 2, 3, 4 or 5 to an individual whose diet includes fatty foods, sugar rich foods, or foods that are both fatty and sugar-rich.

9. The method according to claim 8, wherein said individual is an individual meeting the definition of food addiction, an individual who is obese or overweight, has a binge-eating disorder or an individual that engages in binge eating behavior.

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### Baclofen on Palatable Food Sugar Group (1 h Intake)

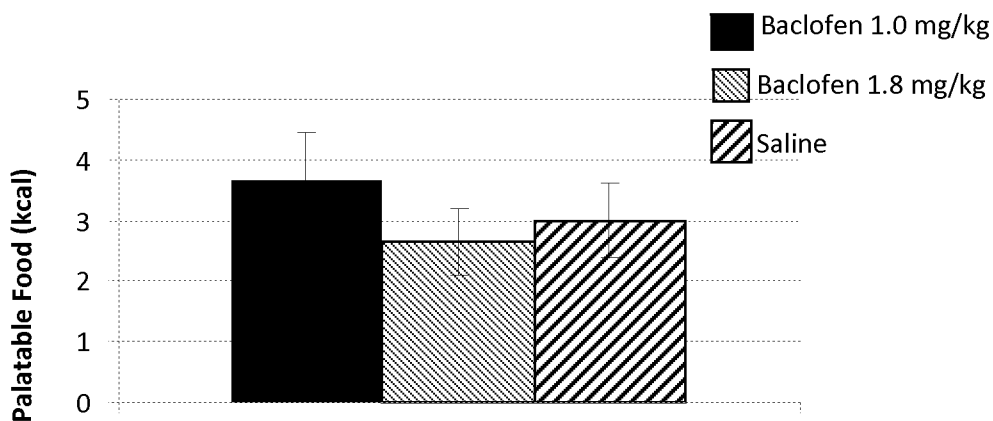


FIG. 1

### Baclofen on Palatable Food Oil Group (1 h Intake)

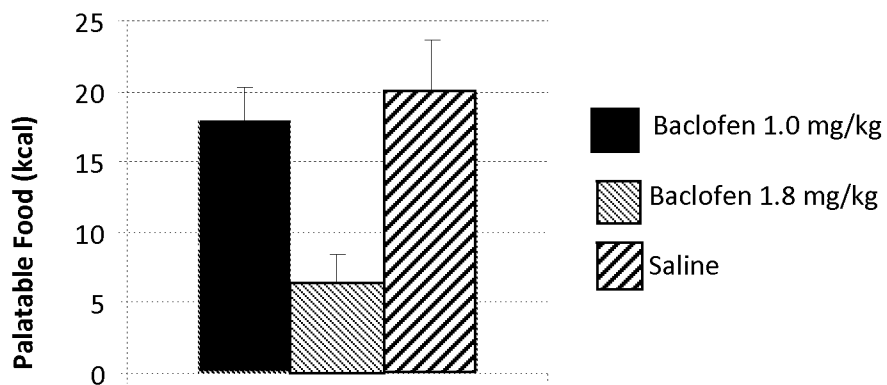


FIG. 2A

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### Baclofen Palatable Food Sugar-Oil Group (1 h Intake)

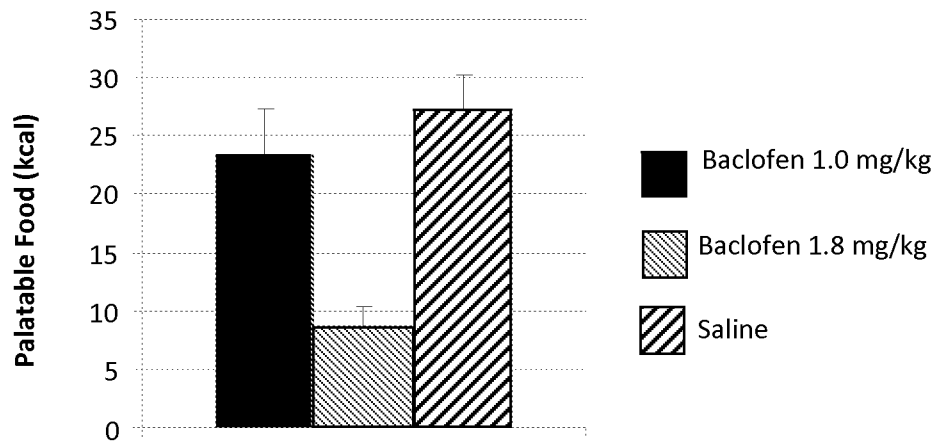


FIG. 2B

### Naltrexone on Palatable Food Sugar Group (1 h Intake)

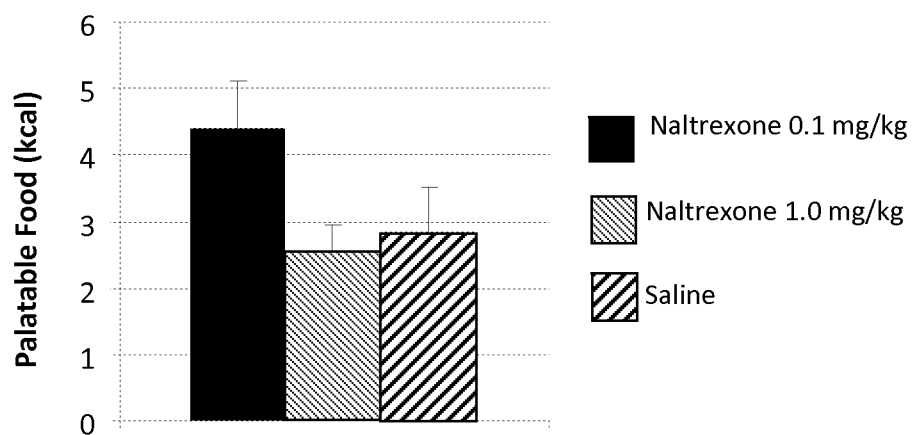


FIG. 3A

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### Naltrexone on Palatable Food Oil Group (1 h Intake)

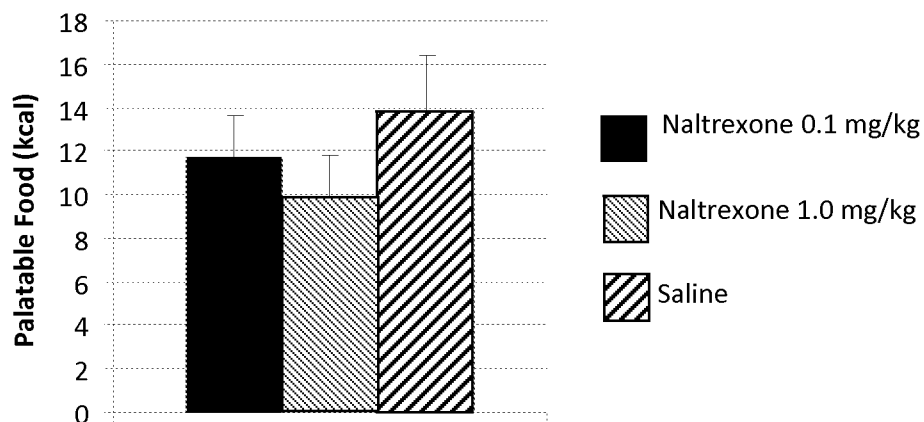


FIG. 3B

### Naltrexone on Palatable Food Sugar-Oil Group (1 h Intake)

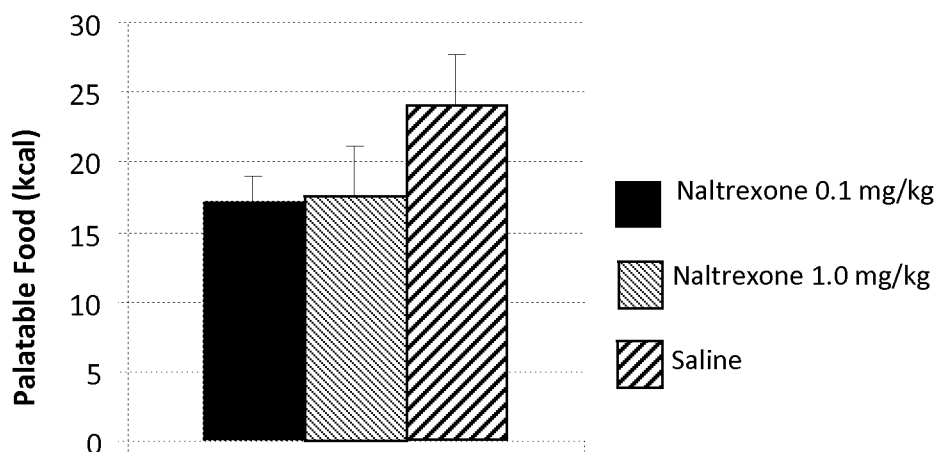


FIG. 3C



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### Combo on Palatable Food Sugar Group (1 h Intake)

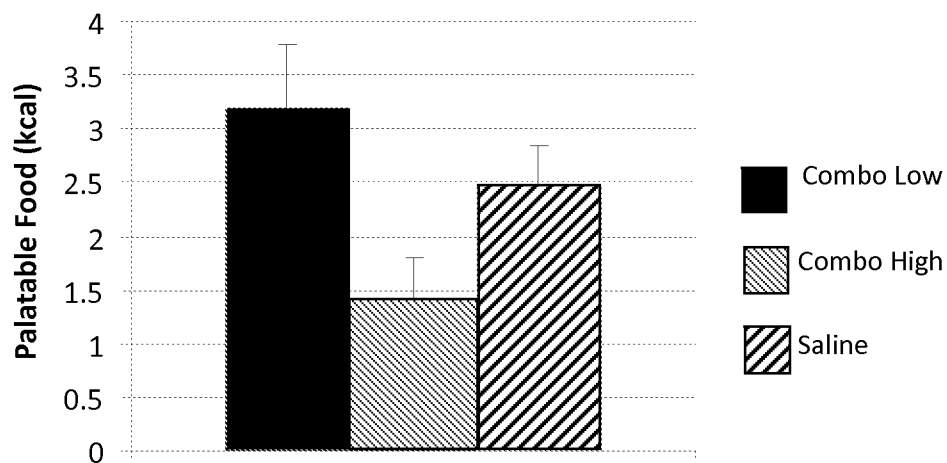


FIG. 4A

### Combo on Palatable Food Oil Group (1 h Intake)

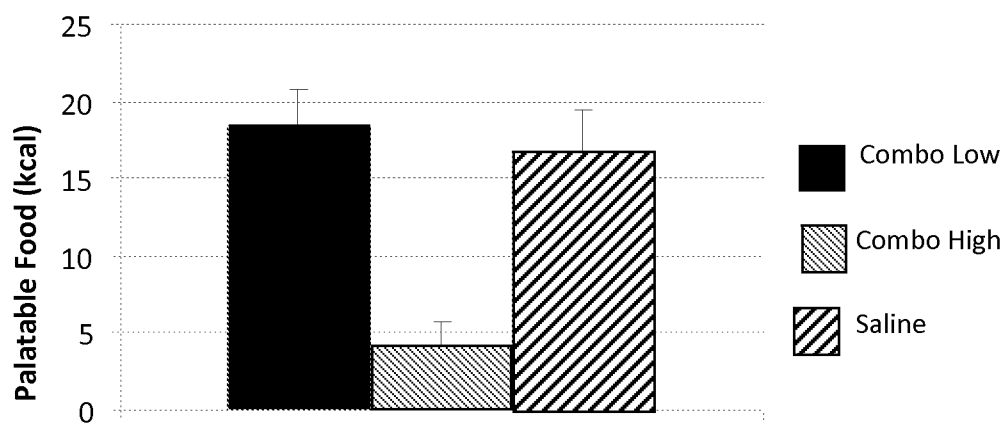


FIG. 4B

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### Combo on Palatable Food Sugar-Oil Group (1 h Intake)

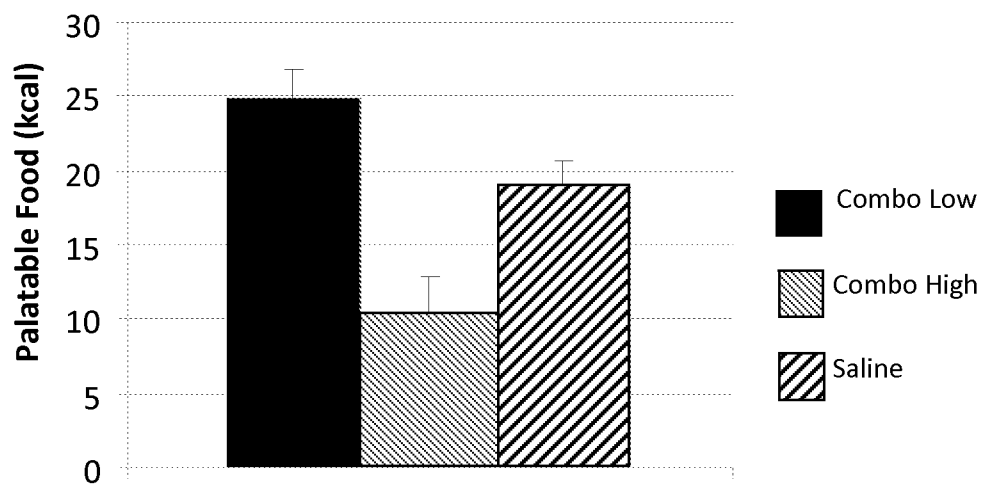


FIG. 4C

### Combo on Plain Chow Sugar Group (1 h Intake)

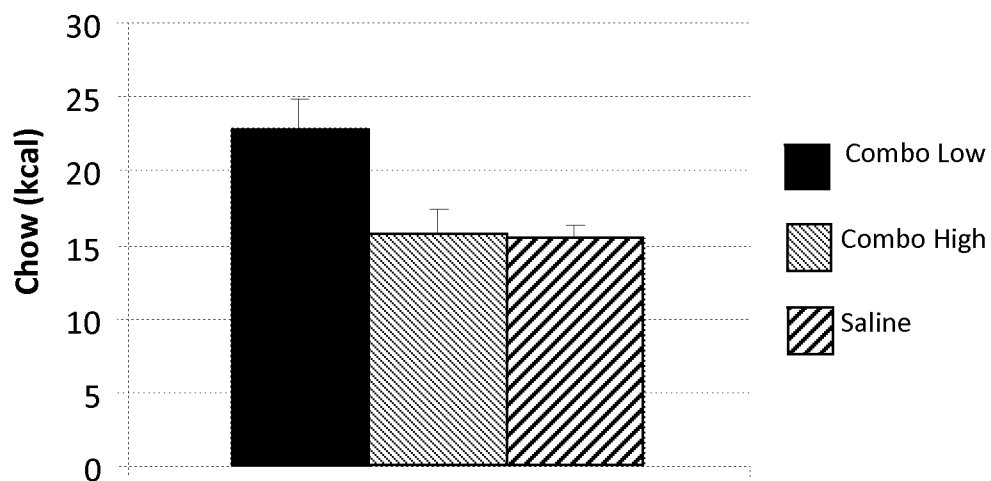


FIG. 5A

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### Combo on Plain Chow Oil Group (1 h Intake)

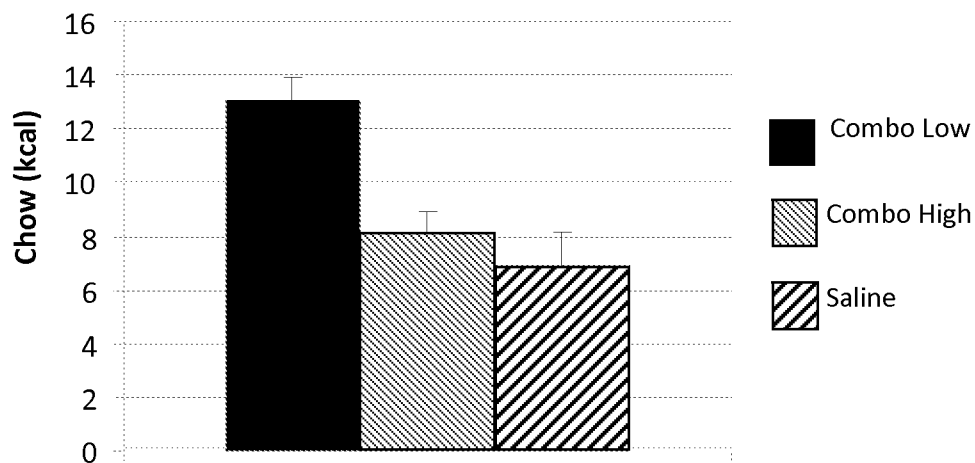


FIG. 5B

### Combo on Chow Sugar-Oil Group (1 h Intake)

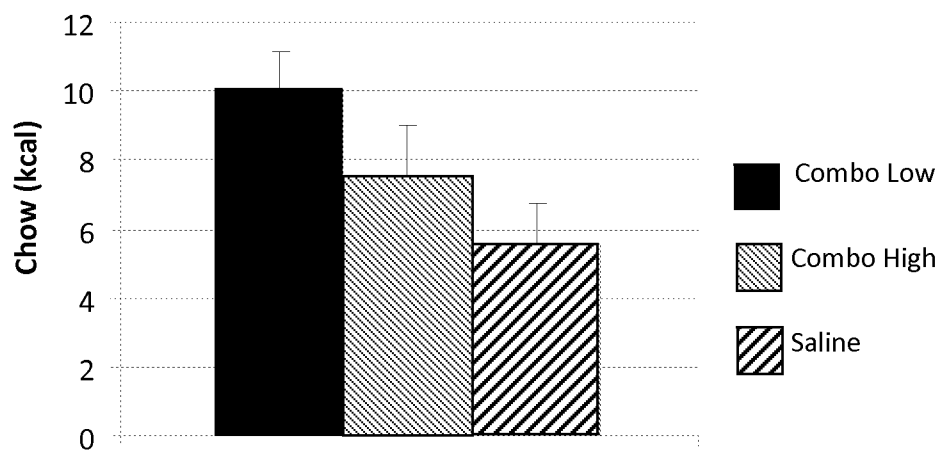


FIG. 5C

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## Yale Food Addiction Scale

Gearhardt, Corbin, Brownell, 2009  
Contact: ashley-gearhardt@yale.edu

This survey asks about your eating habits in the past year. People sometimes have difficulty controlling their intake of certain foods such as:

- Sweets like ice cream, chocolate, doughnuts, cookies, cake, candy, ice cream
- Starches like white bread, rolls, pasta, and rice
- Salty snacks like chips, pretzels, and crackers
- Fatty foods like steak, bacon, hamburgers, cheeseburgers, pizza, and French fries
- Sugary drinks like soda pop

When the following questions ask about "CERTAIN FOODS" please think of ANY food similar to those listed in the food group or ANY OTHER foods you have had a problem with in the past year

| IN THE PAST 12 MONTHS:                                                                                                                                                                                                                                                                                  |       |              |                   |                  |                          |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|--------------|-------------------|------------------|--------------------------|
|                                                                                                                                                                                                                                                                                                         | Never | Once a month | 2-4 times a month | 2-3 times a week | 4 or more times or daily |
| 1. I find that when I start eating certain foods, I end up eating much more than planned                                                                                                                                                                                                                | 0     | 1            | 2                 | 3                | 4                        |
| 2. I find myself continuing to consume certain foods even though I am no longer hungry                                                                                                                                                                                                                  | 0     | 1            | 2                 | 3                | 4                        |
| 3. I eat to the point where I feel physically ill                                                                                                                                                                                                                                                       | 0     | 1            | 2                 | 3                | 4                        |
| 4. Not eating certain types of food or cutting down on certain types of food is something I worry about                                                                                                                                                                                                 | 0     | 1            | 2                 | 3                | 4                        |
| 5. I spend a lot of time feeling sluggish or fatigued from overeating                                                                                                                                                                                                                                   | 0     | 1            | 2                 | 3                | 4                        |
| 6. I find myself constantly eating certain foods throughout the day                                                                                                                                                                                                                                     | 0     | 1            | 2                 | 3                | 4                        |
| 7. I find that when certain foods are not available, I will go out of my way to obtain them. For example, I will drive to the store to purchase certain foods even though I have other options available to me at home.                                                                                 | 0     | 1            | 2                 | 3                | 4                        |
| 8. There have been times when I consumed certain foods so often or in such large quantities that I started to eat food instead of working, spending time with my family or friends, or engaging in other important activities or recreational activities I enjoy.                                       | 0     | 1            | 2                 | 3                | 4                        |
| 9. There have been times when I consumed certain foods so often or in such large quantities that I spent time dealing with negative feelings from overeating instead of working, spending time with my family or friends, or engaging in other important activities or recreational activities I enjoy. | 0     | 1            | 2                 | 3                | 4                        |
| 10. There have been times when I avoided professional or social situations where certain foods were available, because I was afraid I would overeat.                                                                                                                                                    | 0     | 1            | 2                 | 3                | 4                        |
| 11. There have been times when I avoided professional or social situations because I was not able to consume certain foods there.                                                                                                                                                                       | 0     | 1            | 2                 | 3                | 4                        |
| 12. I have had withdrawal symptoms such as agitation, anxiety, or other physical symptoms when I cut down or stopped eating certain foods. (Please do NOT include withdrawal symptoms caused by cutting down on caffeinated beverages such as soda pop, coffee, tea, energy drinks, etc.)               | 0     | 1            | 2                 | 3                | 4                        |
| 13. I have consumed certain foods to prevent feelings of anxiety, agitation, or other physical symptoms that were developing. (Please do NOT include consumption of caffeinated beverages such as soda pop, coffee, tea, energy drinks, etc.)                                                           | 0     | 1            | 2                 | 3                | 4                        |
| 14. I have found that I have elevated desire for or urges to consume certain foods when I cut down or stop eating them.                                                                                                                                                                                 | 0     | 1            | 2                 | 3                | 4                        |
| 15. My behavior with respect to food and eating causes significant distress.                                                                                                                                                                                                                            | 0     | 1            | 2                 | 3                | 4                        |
| 16. I experience significant problems in my ability to function effectively (daily routine, job/school, social activities, family activities, health difficulties) because of food and eating.                                                                                                          | 0     | 1            | 2                 | 3                | 4                        |

FIG. 6

IN THE PAST 12 MONTHS:

17. My food consumption has caused significant psychological problems such as depression, anxiety, self-loathing, or guilt.

NO

YES

18. My food consumption has caused significant physical problems or made a physical problem worse.

0

1

19. I kept consuming the same types of food or the same amount of food even though I was having emotional and/or physical problems.

0

1

20. Over time, I have found that I need to eat more and more to get the feeling I want, such as reduced negative emotions or increased pleasure.

0

1

21. I have found that eating the same amount of food does not reduce my negative emotions or increase pleasurable feelings the way it used to.

0

1

22. I want to cut down or stop eating certain kinds of food.

0

1

23. I have tried to cut down or stop eating certain kinds of food.

0

1

24. I have been successful at cutting down or not eating these kinds of food

0

1

25. How many times in the past year did you try to cut down or stop eating certain foods altogether?

1 time

2 times

3 times

4 times

5 or more times

26. Please circle ALL of the following foods you have problems with:

|             |              |                   |           |              |         |            |                |
|-------------|--------------|-------------------|-----------|--------------|---------|------------|----------------|
| Ice cream   | Chocolate    | Apples            | Doughnuts | Broccoli     | Cookies | Cake       | Candy          |
| White Bread | Rolls        | Lettuce           | Pasta     | Strawberries | Rice    | Crackers   | Chips          |
| Pretzels    | French Fries | Carrots           | Steak     | Bananas      | Bacon   | Hamburgers | Cheese burgers |
| Pizza       | Soda Pop     | None of the above |           |              |         |            |                |

27. Please list any other foods that you have problems with that were not previously listed:

FIG. 6 (continued)

## INTERNATIONAL SEARCH REPORT

International application No.  
**PCT/US2012/065486****A. CLASSIFICATION OF SUBJECT MATTER****A61K 31/195(2006.01)i, A61K 31/185(2006.01)i, A61K 31/485(2006.01)i, A61K 31/44(2006.01)i, A61P 3/04(2006.01)i, A61P 3/00(2006.01)i**

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 31/195; A61K 31/137; A61K 9/50; A61K 31/41; A61K 38/33; B29C 47/78; A61K 31/4745; A61K 31/485; A61P 3/04

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

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal) &amp; keywords: baclofen, naltrexone, opioid antagonist, GABA B agonist, over-eating, obesity, eating addiction, bupropion, AM-251

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                                         | Relevant to claim No. |
|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X         | US 2007-0099947 A1 (DEAN III, R. L. et al.) 03 May 2007<br>See claims 1-4, 8-13, and 19; paragraph [0081]; and examples IX and VII.                                        | 1-4, 6                |
| Y         |                                                                                                                                                                            | 5                     |
| Y         | LIU, Y. et al. 'Food addiction and obesity: evidence from bench to bedside' Journal of Psychoactive Drugs, 2010, Vol. 42, No. 2, pp. 133-145.<br>See p. 141, right-column. | 5                     |
| A         | US 2007-0072899 A1 (JOHNSON, K. W. et al.) 29 March 2007<br>See claims 1, 2, 6-8, 17, 21, 22, and 43-45.                                                                   | 1-6                   |
| A         | US 2008-0293777 A1 (ERLANSON, D. A. et al.) 27 November 2008<br>See claims 1, 11, and 14-20.                                                                               | 1-6                   |
| A         | US 2007-0129283 A1 (MCKINNEY, A. A. et al.) 07 June 2007<br>See claims 1, 3, 8, 9, and 22.                                                                                 | 1-6                   |
| A         | US 2002-0044968 A1 (VAN Lengerich, B. H.) 18 April 2002<br>See claims 25 and 43.                                                                                           | 1-6                   |

☐ 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

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of 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

"&amp;" document member of the same patent family

Date of the actual completion of the international search

28 FEBRUARY 2013 (28.02.2013)

Date of mailing of the international search report

**28 FEBRUARY 2013 (28.02.2013)**

Name and mailing address of the ISA/KR



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Telephone No. 82-42-481-8740



**INTERNATIONAL SEARCH REPORT**

International application No.

**PCT/US2012/065486****Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 7-9  
because they relate to subject matter not required to be searched by this Authority, namely:  
Claims 7-9 pertain to a method for treatment of the human by therapy, and thus relate to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International application No.

**PCT/US2012/065486**

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
|-------------------------------------------|---------------------|----------------------------|---------------------|
| US 2007-0099947 A1                        | 03.05.2007          | WO 2007-056300 A2          | 18.05.2007          |
| US 2007-0072899 A1                        | 29.03.2007          | AU 2006-294758 A1          | 05.04.2007          |
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|                                           |                     | EP 1928438 A2              | 11.06.2008          |
|                                           |                     | JP 2009-509975 A           | 12.03.2009          |
|                                           |                     | US 7915285 B2              | 29.03.2011          |
|                                           |                     | WO 2007-038551 A2          | 05.04.2007          |
| US 2008-0293777 A1                        | 27.11.2008          | WO 2008-148064 A1          | 04.12.2008          |
| US 2007-0129283 A1                        | 07.06.2007          | TW 200803900 A             | 16.01.2008          |
|                                           |                     | US 2011-0028505 A1         | 03.02.2011          |
|                                           |                     | WO 2007-089318 A2          | 09.08.2007          |
| US 2002-0044968 A1                        | 18.04.2002          | AU 1997-49915 B2           | 14.02.2002          |
|                                           |                     | CA 2269806 A1              | 07.05.1998          |
|                                           |                     | CA 2269806 C               | 24.01.2006          |
|                                           |                     | EP 0935523 A1              | 25.06.2003          |
|                                           |                     | EP 0935523 B1              | 29.09.2004          |
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|                                           |                     | US 6190591 B1              | 20.02.2001          |
|                                           |                     | WO 98-18610 A1             | 07.05.1998          |