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<p>(54) Title: METHOD FOR WEIGHT CONTROL</p> <p>(57) Abstract</p> <p>A method for reducing the weight of an obese subject which comprises the combined administration of leptin and/or a leptin mimetic and a synthetic organic appetite suppressing compound according to a dosage schedule which is based on: (a) administering an effective dose of an organic appetite suppressing compound alone or in combination with leptin and/or a leptin mimetic in an amount that will suppress the subjects appetite; and (b) administering an effective dose of said organic appetite suppressing compound and leptin and or/a leptin mimetic at an effective dose which will substantially maintain the subjects leptin level at a level of leptin which will sustain a continued weight reduction in said subject.</p>		

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METHOD FOR WEIGHT CONTROL

BACKGROUND OF THE INVENTION:

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The present invention relates to a method for reducing the weight of an obese patient using a combination of pharmacological agents. It is known that the ob gene elaborates a substance known as leptin which has been identified as a component in controlling body weight by acting as an agonist to receptors in the brain to regulate body weight and fat deposition. This substance appears to provide a negative afferent signal in a feedback loop which affects appetite and controls body weight.

In obese individuals, leptin levels are elevated which suggests that there is a resistance to effects of leptin which points to the conclusion that the level of leptin is involved in the obesity of the particular subject.

When humans lose weight, there is commonly observed a phenomenon of a weight loss plateau in which an individual reaches a weight below which they cannot lose weight despite substantial efforts. This is seen after a mean weight loss of 5 to 15% of total body weight. Some patients who have lost large amounts of weight exhibit symptoms which are similar to symptoms that are seen in animals having demonstrated leptin deficiencies. This has led to questions of whether or not weight loss plateau is due to a deficiency in the level of leptin in a subject.

Studies that have involved the administration of recombinant leptin have shown that exogenous leptin can initially induce some weight loss but eventually the continued administration of leptin fails to induce weight loss. The present inventor has discovered that if controlled amounts of leptin or a leptin mimetic are used in combination with a synthetic organic compound that is

known to inhibit the appetite, the problem of resistance to the effects of leptin can be reduced or eliminated.

SUMMARY OF THE INVENTION

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The present invention is directed to a method of reducing the weight of an obese subject which is based on the combined administration of leptin or a leptin mimetic and a synthetic organic appetite suppressing compound according to a dosage schedule which is based on:

(a) administering an effective dose of an organic appetite suppressing compound alone or in combination with leptin or a leptin mimetic in an amount that will suppress the subjects appetite;

(b) when the subjects rate of weight loss shows a detectable change, administering an effective dose of said leptin or a leptin mimetic at an effective dose which will substantially maintain the subjects total level of leptin, i.e. that which is produced endogenously and leptin or leptin mimetic which has been administered from an exogenous source at a level of total leptin which will sustain a continued weight reduction in said subject.

The total level of leptin should be maintained at a level which is no higher than the subjects original base level before any treatment is initiated although, if desired, maintaining a higher total level of leptin will still enable a subject to continue to lose weight.

It is a primary object of the invention to provide a method of inducing weight loss in an obese subject which utilizes leptin or a leptin mimetic in combination with a organic appetite suppressing compound.

It is also an object of the invention to provide a method of inducing weight loss in an obese subject which avoids the plateau syndrome and provide a means for continuous weight loss.

It is also an object of this invention to provide a improved means of controlling the dosing of leptin or a leptin mimetic for inducing continuous weight loss.

5 It is also an object of this invention to provide a means of reducing the dose of leptin or a leptin mimetic which is required to induce weight loss.

10 It is also an object of this invention to provide an improved method for achieving higher amounts of weight loss in patients as compared to the weight loss that is induced using organic appetite suppressing compounds.

These and other objects of the invention will become apparent from a review of the specification.

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DETAILED DESCRIPTION OF THE INVENTION

The invention is directed to a method of providing a therapeutic regimen which is based on the combined administration of leptin or a leptin mimetic and a organic appetite suppressing compound.

20 Leptin, which is also known as OB, is a peptide hormone which is a natural agonist for regulating body weight and fat deposition. Leptin is produced by adipose tissue and has been described by Zhang et al, Nature (Lond.), 372:425-431 (1994), which is incorporated by reference. The gene which codes for human leptin has been cloned and recombinant leptin is commercially available. In addition, an extended acting form of leptin may be employed which is glycolated leptin that is prepared by pegelation of leptin. Other leptin mimetics are described in U.S. 5,756,461, which is incorporated by reference. The initial dose of leptin or the leptin mimetic will be an effective amount for appetite suppression which will usually be between 0.05 to 0.5mg/kg given in divided doses, either 1 or 2 times per day parenterally, preferably by subcutaneous injection or at less frequent

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intervals when long acting leptin mimetic compounds are administered. When the maintenance phase of the combined leptin or leptin mimetic and organic appetite suppressant treatment is entered, where it is necessary to maintain a
5 determined level of leptin or leptin mimetic, then each patient must be titrated to determine the necessary maintenance dose within the broadly stated range.

The organic appetite suppressing compound may be administered initially with leptin or a leptin mimetic
10 or it may be used without leptin or a leptin mimetic for a short term, i.e. about 14-30 days during which a plateau in weight loss is detected or for a longer term up to about 3 to about 6 months at which time the plateau effect may be detected. The term plateau is used to
15 describe the phenomenon where an appetite suppressant is administered but the subject's rate of weight loss shows a detectable change and there is substantial failure to lose additional weight.

The organic appetite suppressing compounds
20 include sibutramine, fenfluramine, phentermine, dexfenfluramine, diethylpropion, phendimetrazine, ephedrine, caffeine and mixtures thereof. The preferred organic appetite suppressing compounds are those which are made synthetically rather than those which are
25 obtained from natural sources.

The compound sibutramine is described in U.S. 4,929,629. This compound may be administered orally at a dose of 5 to 30mg per patient, daily, preferably in
1 to 2 divided doses.

30 The compound phentermine is described in U.S. 2,408,345. This compound may be administered orally at a dose of 8 to 30mg per patient, daily, preferably in 1 to 2 divided doses.

The compound diethylpropion is described in
35 U.S. 3,001,910. This compound may be administered orally at a dose of 25 to 75mg per patient, daily, preferably in 1 to 3 divided doses.

The compound fenfluramine is described in U.S. 3,198,833. This compound may be administered orally at a dose of 20 to 120mg per patient, daily, preferably in 1 to 3 divided doses.

5 The compound dexfluramine is described in U.S. 3,198,834. This compound may be administered orally at a dose of 15 to 30mg per patient, daily, preferably in 1 to 2 divided doses.

10 The compound mazindol is described in U.S. 3,763,178. This compound may be administered orally at a dose of 1 to 2mg per patient, daily, preferably in 1 to 2 divided doses.

15 The compound phendimetrazine is described in U.K. 791,416. This compound may be administered orally at a dose of 30 to 60mg per patient, daily, preferably in 1 to 2 divided doses.

Ephedrine may be administered orally at a dose of 12.5 to 75mg per patient, daily, preferably in 1 to 3 divided doses.

20 Compounds which are known serotonin reuptake inhibitors may also be utilized as synthetic organic appetite suppressants. It is understood that if the organic appetite suppressing compound is formulated in a 12 hour or 24 hour oral dosage forms, it will not be
25 necessary to take more than one or two doses per day.

All of the patents which are mentioned above are incorporated by reference.

EXAMPLE

30 An obese patient is treated as follows:
Therapy is commenced by administering leptin at a dose of 0.01 to 0.3mg/kg 1 to 2 times per day by subcutaneous injection and by administering sibutramine orally at a
35 dose of 10mg per day given orally as a single dose. After 14-30 days the serum leptin level is determined and the dose of leptin is adjusted to provide a level of which is

essentially the same as the base line level of leptin which is determined for each patient at the start of therapy. The treatment with sibutramine is continued with the adjusted dose of leptin. Subsequently, the level of
5 leptin is monitored on a monthly basis and the dose is adjusted to maintain a leptin level in the patients originally determined baseline level of serum leptin. serum while monitoring the patient for weight loss.

While certain preferred and alternative
10 embodiments of the invention have been set forth for purposes of disclosing the invention, modifications to the disclosed embodiments may occur to those who are skilled in the art. Accordingly, the appended claims are intended to cover all embodiments of the invention and
15 modifications thereof which do not depart from the spirit and scope of the invention.

I claim:

1. A method of reducing the weight of an obese subject which comprises the combined administration of leptin or a leptin mimetic and a synthetic organic appetite suppressing compound according to a dosage schedule which is based on:
 - (a) administering an effective dose of an organic appetite suppressing compound alone or in combination with leptin or a leptin mimetic in an amount that will suppress the subjects appetite; and
 - (b) administering an effective dose of said organic appetite suppressing compound and leptin at an effective dose which will substantially maintain the subjects leptin level at a level of leptin which will sustain a continued weight reduction in said subject.
2. A method of reducing the weight of an obese subject as defined in claim 1 wherein the organic appetite suppressing compound is sibutramine.
3. A method of reducing the weight of an obese subject as defined in claim 1 wherein the organic appetite suppressing compound is phentermine.
4. A method of reducing the weight of an obese subject as defined in claim 1 wherein the organic appetite suppressing compound is phendimetrazine.
5. A method of reducing the weight of an obese subject as defined in claim 1 wherein the organic appetite suppressing compound is fenfluramine.
6. A method of reducing the weight of an obese subject as defined in claim 1 wherein the organic appetite suppressing compound is dexfenfluramine.
7. A method of reducing the weight of an obese subject as

defined in claim 1 wherein the organic appetite
suppressing compound is caffeine.

8. A method of reducing the weight of an obese subject as
5 defined in claim 1 wherein the organic appetite
suppressing compound is ephedrine.

9. A method of reducing the weight of an obese subject as
defined in claim 1 wherein the organic appetite
10 suppressing compound is mazinol.

10. A method of reducing the weight of an obese subject
as defined in claim 1 wherein a combination of organic
suppressing compounds are employed.

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11. A method as defined in claim 1 wherein leptin derived
from recombinant DNA is employed.

12. A method as defined in claim 1 wherein a leptin
20 mimetic is employed.

INTERNATIONAL SEARCH REPORT

International application No.

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A. CLASSIFICATION OF SUBJECT MATTER		
IPC(7) : IPC(7): A61K 38/00, 31/535, 31/52, 31/415, 31/135, 31/13		
US CL : 514/2, 231.2, 264, 393, 646, 649, 659, 909, 910		
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)		
U.S. : 514/2, 231.2, 264, 393, 646, 649, 659, 909, 910		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
NONE		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
CAS ONLINE: leptin, sibutramine, phentermine, phendimetrazine, fenfluramine, dexfenfluramine, caffeine, ephedrine with weight, obes?, fat		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,594,101 A (BECKER et al) 14 January 1997, col. 2, lines 10-29.	1-12
Y	Database CA on STN (Columbus, OH, USA), No. 119:85876, 'D-fenfluramine in a rat model of dietary fat-induced obesity', abstract, Fislser et al., 1993.	1-12
Y	Database CA on STN (Columbus, OH, USA), No. 129:156775, 'Energy expenditure, body composition, and glucose metabolism in lean and obese rhesus monkeys treated with ephedrine and caffeine', abstract, Ramsey et al., 1998.	1-12
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
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