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METHOD TO AID SMOKING CESSATION

This invention relates to a method to aid smoking cessation. More particularly the method relates to treating a patient who wishes to stop smoking with an effective amount of a compound, in particular a phenylcyclobutylbutylamine, in order to aid the patient in overcoming the craving following smoking cessation. In addition, the method relates to preventing weight gain in a patient who ceases to smoke.

BACKGROUND OF THE INVENTION

Discontinuing the use of nicotine is extremely difficult for many smokers and many who seek help to cease smoking in formal programs return to smoking within a year. Although nicotine withdrawal causes symptoms that are most intense 48 – 72 hours after smoking is discontinued, such as increased anxiety, hostility and depression, in the long term the ex-smoker is at risk for weight gain and a craving to return to smoking.

Because of the adverse effects of smoking on health and the difficulty so many smokers have in giving up the habit of smoking entirely, it would be advantageous to have an effective method for smoking cessation.

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SUMMARY OF THE INVENTION

The present invention relates to compositions containing agents which selectively enhance noradrenergic effects and to a method of administering such compositions in order to take advantage of a noradrenergic agent's effect on appetites of various types.

In addition to an effect on nicotine craving following smoking cessation, it is advantageous for the agent to have a positive effect on other symptoms of smoking cessation such as an increased appetite and other nervous system activities associated with nicotine withdrawal. The present invention more particularly relates to the use of sibutramine to accomplish these objectives.

In one embodiment of this invention sibutramine is administered to individuals who are attempting to quit smoking in a quantity sufficient to ameliorate or prevent the mood disturbances and/or to suppress the weight gain frequently evident in individuals trying to give up smoking, as well as to reduce recidivism.

In another embodiment sibutramine is administered in conjunction with the patient's participation in a behavior modification program.

In yet another embodiment, administration of sibutramine is carried out in conjunction with the use of a nicotine patch and the patient's participation in a behavior modification program.

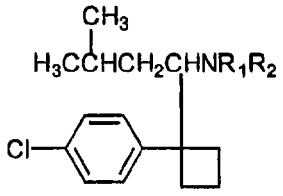
Administration of a noradrenergic compound according to the method of the present invention can be of great benefit to persons who experience withdrawal symptoms and increased appetite associated with giving up smoking because the compounds act to alleviate or prevent such adverse symptoms.

While the biochemistry of nicotine habituation and of cigarette withdrawal is not completely understood, a theoretical basis for treatment has been established. The abstinence syndrome produced by withdrawal or addictive substances is associated with an abrupt increase in sympathetic outflow from the brain stem. In particular, noradrenergic neurones in the locus coeruleus (containing half the noradrenergic neurons in the mammalian brain) show a marked increase in firing rate during withdrawal (Amaral and Sinnamon, 1978).

DETAILED DESCRIPTION OF THE INVENTION

The treatment of smoking withdrawal symptoms is provided by the method described below, and variations made possible through the optional steps.

More particularly, the present invention relates to a method of aiding smoking cessation by administration of a therapeutically effective amount of a compound of formula I



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including enantiomers and pharmaceutically acceptable salts thereof, in which R_1 and R_2 are independently H or methyl, is administered in conjunction with a pharmaceutically acceptable diluent or carrier to a human in need thereof.

A preferred compound of formula I is N,N-dimethyl-1-[1 -(4-chlorophenyl)cyclobutyl]-3-methylbutylamine or a pharmaceutically acceptable salt thereof, for example, the hydrochloride or hydrobromide salt and other salts as are known in the art.

A particularly preferred form of this compound is N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methyl-butylamine hydrochloride monohydrate (sibutramine hydrochloride) which is described in European Patent Number 230742.

When a compound of formula I contains a single chiral center it may exist in two enantiomeric forms. The present invention includes the use of the individual enantiomers and mixtures of the enantiomers. The enantiomers may be resolved by methods known to those skilled in the art, for example by formation of diastereoisomeric salts or complexes which may be separated, for example, by crystallisation; via formation of diastereoisomeric derivatives which may be separated, for example, by crystallisation, gas-liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic oxidation or reduction, followed by separation of the modified and

unmodified enantiomers; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support, for example silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step is required to liberate the desired enantiomeric form. Alternatively, specific enantiomers may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer to the other by asymmetric transformation.

Preferred compounds of formula I are N,N-dimethyl-1-[1-(4-chlorophenyl)- cyclobutyl]-3-methylbutylamine, N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N- methylamine, and 1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine including racemates, individual enantiomers and mixtures thereof, and pharmaceutically acceptable salts thereof

The compound of formula I may be administered in any of the known pharmaceutical dosage forms. The amount of the compound to be administered will depend on a number of factors including the age of the patient, the severity of the condition and the past medical history of the patient and always lies within the sound discretion of the administering physician but it is generally envisaged that

the dosage of the compound to be administered will be in the range 0. 1 to 50 mg, preferably 1 to 30 mg per day given in one or more doses.

Oral dosage forms are the preferred compositions for use in the present invention and these are the known pharmaceutical forms or such administration, for example tablets, capsules, granules, syrups and aqueous or oil suspensions. The excipients used in the preparation of these compositions are the excipients known in the pharmacist's art. Tablets may be prepared from a mixture of the active compound with fillers, for example calcium phosphate; disintegrating agents, for example maize starch; lubricating agents, for example magnesium stearate; binders, for example microcrystalline cellulose or polyvinylpyrrolidone and other optional ingredients known in the art to permit tableting the mixture by known methods. The tablets may, if desired, be coated using known methods and excipients which may include enteric coating using for example hydroxypropylmethylcellulose phthalate.

The tablets may be formulated in a manner known to those skilled in the art so as to give a sustained release of the compounds of the present invention. Such tablets may, if desired, be provided with enteric coatings by known methods, for example by the use of cellulose acetate phthalate. Similarly, capsules, for example hard or soft gelatin capsules, containing the active compound with or without added excipients, may be prepared by known methods and, if desired, provided with enteric coatings in a known manner. The contents of the capsule may be formulated using known methods so as to give sustained release of the

active compound. The tablets and capsules may conveniently each contain 1 to 50 mg of the active compound.

Other dosage forms for oral administration include, for example, aqueous suspensions containing the active compound in an aqueous medium in the presence of a non-toxic suspending agent such as sodium carboxy-methycellulose, and oily suspensions containing a compound of the present invention in a suitable vegetable oil, 5 for example arachis oil. The active compound may be formulated into granules with or without additional excipients. The granules may be ingested directly by the patient or they may be added to a suitable liquid carrier (for example, water) before ingestion. The granules may contain disintegrants, eg an effervescent couple formed from an acid and a carbonate or bicarbonate salt to facilitate dispersion in the liquid medium.

The therapeutically active compounds of formula I may be formulated into a composition which the patient retains in his mouth so that the active compound is administered through the mucosa of the mouth.

Dosage forms suitable for rectal administration are the known pharmaceutical forms for such administration, for example, suppositories with cocoa butter or polyethylene glycol bases.

Dosage forms suitable for parenteral administration are the known pharmaceutical forms for such administration, for example sterile suspensions or sterile solutions in a suitable solvent.

Dosage forms for topical administration may comprise a matrix in which the pharmacologically active compounds of the present invention are dispersed so that the compounds are held in contact with the skin in order to administer the compounds transdermally. A suitable transdermal composition may be prepared by mixing the pharmaceutically active compound with a topical vehicle, such as a mineral oil petrolatum and/or a wax, e.g. paraffin wax or beeswax, together with a potential transdermal accelerant such as dimethyl sulphoxide or propylene glycol. Alternatively the active compounds may be dispersed in a pharmaceutically acceptable cream, gel or ointment base. The amount of active compound contained in a topical formulation should be such that a therapeutically effective amount of the compound is delivered during the period of time for which the topical formulation is intended to be on the skin.

The therapeutically active compound of formula I may be formulated into a composition which is dispersed as an aerosol into the patients oral or nasal cavity. Such aerosols may be administered from a pump pack or from a pressurized pack containing a volatile propellant.

The therapeutically active compounds of formula I used in the method of the present invention may also be administered by continuous infusion either from an external source, for example by intravenous infusion or from a source of the compound placed with the body. Internal sources include implanted reservoirs containing the compound to be infused which is continuously released for

example by osmosis and implants which may be (a) liquid such as an oily suspension of the compound to be infused for example in the form of a very sparingly water-soluble derivative such a dodecanoate salt or a lipophillic ester or (b) solid in the form of an implanted support, for example of a synthetic resin or waxy material, for the compound or a series of several bodies each containing part of the compound to be delivered. The amount of active compound present in an internal source should be such that a therapeutically effective amount of the compound is delivered over a long period of time.

In some formulations it may be beneficial to use the compounds of the present invention in the form of particles of very small size, for example as obtained by fluid energy milling.

In carrying out the method of the invention a behavior modification program may also be offered to the patient who is attempting to quit smoking. There are many behavior modification programs known to one skilled in the art. The programs include self-help programs and programs that are taught by others as well as programs that combine both methods.

The following examples are illustrative only and are not meant to limit the invention in any manner.

EXAMPLE 1

The invention will be used by patients who desire to quit smoking and who have decided upon a quit date. Sibutramine 15 mg orally once daily (or 1 0 mg daily) in the morning will be initiated one week before the planned quit date. Sibutramine will be continued at this daily dose until six months after the planned quit date. A behavior modification program will be offered in conjunction with sibutramine. This program may consist of individual counseling sessions or group counseling sessions. Patients will be seen by the treating physician two weeks before the planned quit date, one month after the planned quit date, three months after the planned quit date, six months after the planned quite date, and nine months after the planned quit date.

EXAMPLE 2

The invention will be used by patients who desire to quit smoking and who have decided upon a quit date. Sibutramine 15 mg orally once daily (or 10 mg daily) in the morning will be given for the two weeks before the planned quite date. Sibutramine will be continued at this daily dose until six months after the planned quit date. A behavior modification program will be offered in conjunction with sibutramine. This program may consist of individual counseling

sessions or group counseling sessions. Beginning on the planned quit date, a nicotine patch will also be applied for two months. Patients will be seen by the treating physician two weeks before the planned quit date, one month after the planned quit date, three months after the planned quit date, six months after the planned quite date, and nine months after the planned quit date.

EXAMPLE 3

The invention was used by patients who desired to quit smoking and who had decided upon a quit date. Sibutramine 15 mg orally once daily in the morning was initiated two weeks before the planned quit date. Sibutramine was continued at this daily dose until four weeks after the planned quit date. A behavior modification program was given in conjunction with sibutramine. This program consisted of giving each patient a self-help pamphlet on smoking cessation at the start of the program and 5- to 10-minute structured lifestyle modification sessions designed to enhance their efforts to abstain from smoking at all visits and during telephone contacts. This clinical intervention, which was based on ACHPR guidelines, included advice on successful quitting/continued abstinence (e.g. abstinence form alcohol, other smoker in the household), explaining the relevance of smoking (e.g., impact on family, social, health, and prior quitting experience,

identifying the risks of smoking (acute, long-term, risks to spouse and children), explaining that low-tar cigarettes do not eliminate these risks, and explaining the rewards of quitting.

The following data were obtained.

Sibutramine (15 mg) v. placebo

	Placebo (n=212)	Sibutramine (n=211)	ρ value
4-week quit rate	11.8%	10.9%	--
Mean weight change	0.8 kg	-1.0 kg	<0.0001
Mean weight change in quitters	2.2 kg	-0.4 kg	< 0.005
% of quitters who did not gain weight	16%	52%	<0.02

EXAMPLE 4

The invention was used by patients who desire to quit smoking and who decided upon a quit date. Sibutramine 15 mg orally once daily in the morning was initiated two weeks before the planned quite date. Sibutramine was continued at this daily dose until four weeks after the planned quit date. A

behavior modification program was given in conjunction with sibutramine. This program consisted of giving each patient a self-help pamphlet on smoking cessation at the start of the program and 5- to 10-minute structured lifestyle modification sessions designed to enhance their efforts to abstain from smoking at all visits and during telephone contacts. This clinical intervention, which was based on ACHPR guidelines, included advice on successful quitting/continued abstinence (e.g. abstinence form alcohol, other smoker in the household), explaining the relevance of smoking (e.g., impact on family, social, health, and prior quitting experience, identifying the risks of smoking (acute, long-term, risks to spouse and children), explaining that low-tar cigarettes do not eliminate these risks, and explaining the rewards of quitting.

Beginning on the planned quit date, a nicotine patch was also applied for one month. Patients were seen by the treating physician two weeks before the planned quit date and one month after the planned quit date.

The following data were obtained.

Sibutramine (15 mg) plus patch v. Placebo plus patch

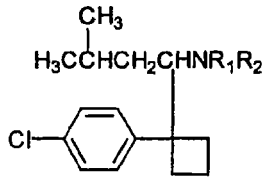
	Placebo plus patch (n=190)	Sibutramine plus patch (n=189)	ρ value
4-Week quit rate	24.7%	33.3%	0.063
Mean weight change	0.7 kg	-0.5 kg	<0.0001
Mean weight change in quitters	0.5 kg	-0.2 kg	<0.02
% of quitters who did not gain weight	28%	33.3%	<0.005

5

The invention has been described with reference to various specific embodiments. However, many variations and modifications may be made while remaining within the scope and spirit of the invention.

CLAIMS

1. A method of causing smoking cessation which comprises administering a therapeutically effective amount of a compound of formula I



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or pharmaceutically acceptable salts and hydrates thereof, in which R_1 and R_2 are independently H or methyl.

2. The method as claimed in claim 1 wherein the compound of formula I comprises N,N-dimethyl-1 [1 -(4-chlorophenyl)cyclobutyl]-3-methybutylamine hydrochloride.

3. The method as claimed in claim 1 wherein the compound of formula I is N,N-dimethyl-1-[1 -(4-chlorophenyl)cyclobutyl]-3-methybutylamine in the form of its monohydrate.

4. The method as recited in claim 1 wherein the compound of formula I is administered in conjunction with the patient participating in a behavior modification program related to smoking cessation.

5. The method of claim 4 wherein the compound of formula I is administered in conjunction with the patient participating in a behavior modification program related to smoking cessation and in conjunction with the administration of nicotine replacement therapy.

6. A method as claimed in claim 1, 3 or 4 wherein the compound of formula 1 is (+)N-[1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N-methylamine.

7. A method as claimed in claim 1, 3 or 4 wherein the compound of formula 1 is (-)-N-{1-[1-(4-chlorophenyl)cyclobutyl-3-methylbutyl}-N-methylamine.

8. A method as claimed in claim 1, 3 or 4 wherein the compound of formula 1 is (+)-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine.

9. A method as claimed in claim 1, 3 or 4 wherein the compound of formula 1 is (-)-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine.

10 A method as claimed in claim 1, 3 or 4 wherein the compound of formula 1 is (+)-N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N-N-dimethylamine.

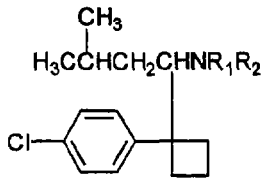
11. The method as claimed in claim 1, 3 or 4 wherein the compound of formula I is (-)-N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N-N-dimethylamine.

12. The method as claimed in claim 1, 3 or 4 wherein the compound of formula I is (±)-N-{1-[1-(4-chlorophenyl)cyclobutyl-3-methylbutyl}-N-methylamine.

13. The method as claimed in claim 1, 3 or 4 wherein the compound of formula I is (±)-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine.

14. The method as claimed in claim 1, 3 or 4 wherein the compound of formula I is (±)-N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N-N-dimethylamine.

15. A method of controlling weight gain in a patient who is undergoing a program for smoking cessation which comprises administering a therapeutically effective amount of a compound of formula I



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or pharmaceutically acceptable salts thereof, in which R_1 and R_2 are independently H or methyl.

16. The method as claimed in claim 15 wherein the compound of formula I comprises N,N-dimethyl-1 [1 -(4-chlorophenyl)cyclobutyl]-3-methybutylamine hydrochloride.

17. The method as claimed in claim 15 wherein the compound of formula I is N,N-dimethyl-1-[1 -(4-chlorophenyl)cyclobutyl]-3-methybutylamine in the form of its monohydrate.

18. The method as recited in claim 15 wherein the compound of formula I is administered in conjunction with the patient participating in a behavior modification program related to smoking cessation.

19. The method of claim 15 wherein the compound of formula I is administered in conjunction with the patient participating in a behavior modification program related to smoking cessation and in conjunction with the administration of nicotine replacement therapy.

20. A method as claimed in claim 15, 18 or 19 wherein the compound of formula 1 is (+)N-[1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N-methylamine.

21. A method as claimed in claim 15, 18 or 19 wherein the compound of formula 1 is (-)-N-{1-[1-(4-chlorophenyl)cyclobutyl-3-methylbutyl}-N-methylamine.

22. A method as claimed in claim 15, 18 or 19 wherein the compound of formula 1 is (+)-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine.

23. A method as claimed in claim 15, 18 or 19 wherein the compound of formula 1 is (-)-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine.

24. A method as claimed in claim 15, 18 or 19 wherein the compound of formula 1 is (+)-N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N-N-dimethylamine.

25. The method as claimed in claim 15, 18 or 19 wherein the compound of formula I is (-)-N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N-N-dimethylamine.

26. The method as claimed in claim 15, 18 or 19 wherein the compound of formula I is (±)-N-{1-[1-(4-chlorophenyl)cyclobutyl-3-methylbutyl}-N-methylamine.

27. The method as claimed in claim 15, 18 or 19 wherein the compound of formula I is (±)-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine.

28. The method as claimed in claim 15, 18 or 19 wherein the compound of formula I is (±)-N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N-N-dimethylamine.