SUMMARY OF THE INVENTION

There remains a need for new treatments and therapies for Alzheimer's disease, and Alzheimer's disease-related disorders, such as dementia.

Thus, embodiments provided herein are methods of treating Alzheimer's disease as adjunctive therapy to acetylcholinesterase treatment comprising administering an effective daily dose of N-(2-(6-fluoro-lH-indol-3-yl)ethyl)-3-(2,2,3,3-tetrafluoropropoxy)benzylamine or a pharmaceutically acceptable salt to a patient in need of such treatment , wherein the effective daily dose administered to the patient is between about 30 and about 60 mg.

The ~~invention~~ embodiments further provides methods of treating Alzheimer's disease as adjunctive therapy to acetylcholinesterase treatment comprising administering an effective daily dose of N-(2-(6-fluoro-lH-indol-3-yl)ethyl)-3-(2,2,3,3-tetrafluoropropoxy)benzylamine or a pharmaceutically acceptable salt to a patient in need of such treatment , wherein the effective daily dose administered to the patient is between about 30 and about 60 mg.

Further provided is the use of a compound N-(2-(6-fluoro-lH-indol-3-yl)ethyl)-3-(2,2,3,3-tetrafluoropropoxy)benzylamine or a pharmaceutically acceptable salt in the manufacture of a medicament for ~~use in~~ treating Alzheimer's disease by improving or augmenting the effect of an acetylcholinesterase inhibitor, ~~comprising administering~~wherein an effective daily dose of said compound is to be administered to a patient in need of such treatment, and wherein the effective daily dose to be administered to the patient is between about 30 and about 60 mg.

The invention also provides the use of N-(2-(6-fluoro-lH-indol-3-yl)ethyl)-3-(2,2,3,3-tetrafluoropropoxy)benzylamine or a pharmaceutically acceptable salt in the preparation of a medicament for ~~use in~~ treating Alzheimer's disease, the medicament being for use as adjunctive therapy to acetylcholinesterase treatment, ~~comprising administering~~wherein an effective daily dose of N-(2-(6-fluoro-lH-indol-3-yl)ethyl)-3-(2,2,3,3-tetrafluoropropoxy)benzylamine or a pharmaceutically acceptable salt is to be administered to a patient in need of such treatment, and wherein the effective daily dose administered to the patient is between about 30 and about 60 mg.

One embodiment of the ~~invention~~ disclosure is directed to a method of treating mild to moderate Alzheimer's disease. In one embodiment, the pharmaceutically acceptable salt is the hydrochloride.

In another embodiment, the dose is administered as an immediate release formulation.

Yet another embodiment, the method is for treating mild to moderate Alzheimer's disease.

In another embodiment, the acetylcholineesterase inhibitor is donepezil.

In another embodiment, the acetylcholineesterase inhibitor is rivastigmine.

In another embodiment, the acetylcholineesterase inhibitor is galantamine.

In another embodiment, the dose is administered once daily.

The aforementioned embodiment ~~of the invention~~ pertaining to once daily administration of Compound I has clear advantages for patients. Such advantages include but are not limited to ease of administration, convenience, and patient compliance with consistent dosing. However, certain embodiments ~~of the invention~~ also include, based on the Applicants' data herein, administration of Compound I more than once daily in amounts equivalent to the amounts disclosed herein within a twenty-four hour period. Thus, embodiments of the ~~invention~~ disclosure also include the following:

In one embodiment, the effective daily dose is 30 mg.

In yet another embodiment, the dose is effective daily dose is 40 mg or less.

In one embodiment, the dose is effective daily dose is 50 mg or less.

In another embodiment, the dose is effective daily dose is 60 mg or less.

As used herein, Compound I is N-(2-(6-fluoro-lH-indol-3-yl)ethyl)-3-(2,2,3,3-tetrafluoro-propoxy)benzylamine and accordingly, the invention further provides a pharmaceutical composition comprising Compound I wherein the composition when administered to a human provides a blood plasma concentration of Compound I in a range of about 56 ng/mL to about 310 ng/mL at steady-state plasma level and when the composition is administered to provide an effective daily dose of Compound I of about 60 mg or less.

Further provided is a pharmaceutical composition comprising Compound I wherein the composition provides when administered to a human a receptor occupancy of Compound I greater than or equal to about 90 % at the 5HT-6 receptor at a steady-state plasma level and when the composition is administered to provide an effective daily dose of Compound I of about 60 mg or less.

Further provided is a pharmaceutical composition comprising Compound I wherein the composition provides when administered to a human a receptor occupancy of Compound I greater than or equal to about 80 % at the 5HT-6 receptor at a steady-state plasma level and when the composition is administered to provide an effective daily dose of Compound I or about 60 mg of less.

The ~~invention~~ disclosure further provides a pharmaceutical composition comprising 60 mg or less of Compound I, wherein the composition when administered to a human provides a blood plasma concentration of Compound I in a range of about 56 ng/mL to about 310 ng/mL at steady-state plasma level.

In one embodiment, the composition is an immediate release formulation.

In one embodiment, the effective daily dose is 30 mg.

In yet another embodiment, the effective daily dose is 40 mg or less.

In one embodiment, the effective daily dose is 50 mg or less.

The ~~invention~~ disclosure describes novel methods for treating and preventing dementia caused by vascular diseases; dementia associated with Parkinson's disease; Lewy Body dementia; AIDS dementia; mild cognitive impairments; age-associated memory impairments; cognitive impairments and/or dementia associated with neurologic and/or psychiatric conditions, including epilepsy, brain tumors, brain lesions, multiple sclerosis, Down's syndrome, Rett's syndrome, progressive supranuclear palsy, frontal lobe syndrome, and schizophrenia and related psychiatric disorders; cognitive impairments caused by traumatic brain injury, post coronary artery by-pass graft surgery, electroconvulsive shock therapy, and chemotherapy, comprising administering a therapeutically effective amount of N-(2-(6-fluoro-lH-indol-3-yl)ethyl)-3-(2,2,3,3-tetrafluoropropoxy)benzylamine to improve or augment the effect of a acetylcholinesterase inhibitor.

The ~~invention~~ disclosure also describes novel methods for treating and preventing delirium, Tourette's syndrome, myasthenia gravis, attention deficit hyperactivity disorder, autism, dyslexia, mania, depression, apathy, and myopathy associated with or caused by diabetes comprising administering a therapeutically effective amount N-(2-(6-fluoro-lH-indol-3-yl)ethyl)-3-(2,2,3,3-tetrafluoropropoxy)benzylamine to improve or augment the effect of a acetylcholinesterase inhibitor. The ~~invention~~ disclosure further describes novel methods for delaying the onset of Alzheimer's disease, for enhancing cognitive functions, for treating and preventing sleep apnea, for alleviating tobacco withdrawal syndrome, and for treating the dysfunctions of Huntington's disease comprising administering a therapeutically effective amount of N-(2-(6-fluoro-lH-indol-3-yl)ethyl)-3-(2,2,3,3-tetrafluoropropoxy)benzylamine to improve or augment the effect of a cholinesterase inhibitor.

Provided herein are methods of treating Alzheimer's disease by improving or augmenting the effect of a acetylcholinesterase inhibitor comprising administering a dose of N-(2-(6-fluoro-lH-indol-3-yl)ethyl)-3-(2,2,3,3-tetrafluoropropoxy)benzylamine at least once daily. In one embodiment, the dose is administered every two days.

The invention is described in more detail below.

BRIEF DESCRIPTION OF THE FIGURES

FIGURE 1: Time-activity curves (TACs) of selected brain regions, as means of baseline scans of Part B (Panel A) and 3 H post-dose (B) scans. Putamen and caudate nucleus showed

~~CLAIMS:~~

1. N-(2-(6-fluoro-lH-indol-3-yl)ethyl)-3-(2,2,3,3-tetrafluoropropoxy)benzylamine or a pharmaceutically acceptable salt for use in treating Alzheimer's disease by improving or augmenting the effect of an acetylcholinesterase inhibitor comprising administering an effective daily dose of said compound to a patient in need of such treatment, wherein the effective daily dose administered to the patient is between about 30 and about 60 mg.

2. N-(2-(6-fluoro-lH-indol-3-yl)ethyl)-3-(2,2,3,3-tetrafluoropropoxy)benzylamine or a pharmaceutically acceptable salt for use in treating Alzheimer's disease as adjunctive therapy to acetylcholinesterase treatment comprising administering an effective daily dose of N-(2-(6-fluoro-lH-indol-3-yl)ethyl)-3-(2,2,3,3-tetrafluoropropoxy)benzylamine or a pharmaceutically acceptable salt to a patient in need of such treatment, wherein the effective daily dose administered to the patient is between about 30 and about 60 mg.

3. N-(2-(6-fluoro-lH-indol-3-yl)ethyl)-3-(2,2,3,3-tetrafluoropropoxy)benzylamine according to claim 1 or 2, wherein the pharmaceutically acceptable salt is the hydrochloride.

4. N-(2-(6-fluoro-lH-indol-3-yl)ethyl)-3-(2,2,3,3-tetrafluoropropoxy)benzylamine according to anyone of claims 1-3, wherein the dose is administered as an immediate release formulation.

5. N-(2-(6-fluoro-lH-indol-3-yl)ethyl)-3-(2,2,3,3-tetrafluoropropoxy)benzylamine according to anyone of claims 1-4 for treating mild to moderate Alzheimer's disease.

6. N-(2-(6-fluoro-lH-indol-3-yl)ethyl)-3-(2,2,3,3-tetrafluoropropoxy)benzylamine according to anyone of claims 1-5, wherein the acetylcholineesterase inhibitor is donepezil.

7. N-(2-(6-fluoro-lH-indol-3-yl)ethyl)-3-(2,2,3,3-tetrafluoropropoxy)benzylamine according to anyone of claims 1-5, wherein the acetylcholineesterase inhibitor is rivastigmine.

8. N-(2-(6-fluoro-lH-indol-3-yl)ethyl)-3-(2,2,3,3-tetrafluoropropoxy)benzylamine according to anyone of claims 1-5, wherein the acetylcholineesterase inhibitor is galatamine.

9. N-(2-(6-fluoro-lH-indol-3-yl)ethyl)-3-(2,2,3,3-tetrafluoropropoxy)benzylamine according to anyone of claims 1-8, wherein the effective daily dose is 30 mg.

10. N-(2-(6-fluoro-lH-indol-3-yl)ethyl)-3-(2,2,3,3-tetrafluoropropoxy)benzylamine according to ~~anyone of claims 1-8, wherein the effective daily dose is 40 mg or less.~~

~~11. N-(2-(6-fluoro-lH-indol-3-yl)ethyl)-3-(2,2,3,3-tetrafluoropropoxy)benzylamine according to~~ anyone of claims 1-8, wherein the effective daily dose is 50 mg or less.

12. N-(2-(6-fluoro-lH-indol-3-yl)ethyl)-3-(2,2,3,3-tetrafluoropropoxy)benzylamine according to anyone of claims 1-8, wherein the effective daily dose is 60 mg or less.

13. N-(2-(6-fluoro-lH-indol-3-yl)ethyl)-3-(2,2,3,3-tetrafluoropropoxy)benzylamine according to anyone of claims 1-8, wherein the effective daily dose is 60 mg.

14. A pharmaceutical composition comprising Compound I wherein the composition when administered to a human provides a blood plasma concentration of Compound I in a range of about 56 ng/mL to about 310 ng/mL at steady-state plasma level and when the composition is administered to provide an effective daily dose of Compound I of about 60 mg or less; and wherein Compound I is N-(2-(6-fluoro-lH-indol-3-yl)ethyl)-3-(2,2,3,3-tetrafluoropropoxy)benzylamine.

15. A pharmaceutical composition comprising Compound I wherein the composition provides when administered to a human a receptor occupancy of Compound I greater than or equal to about 90 % at the 5HT-6 receptor at a steady-state plasma level and when the composition is administered to provide an effective daily dose of Compound I of about 60 mg of less; and wherein Compound I is N-(2-(6-fluoro-lH-indol-3-yl)ethyl)-3-(2,2,3,3-~~tetrafluoropropoxy)benzylamine.~~

CLAIMS:

1. Use of a compound N-(2-(6-fluoro-lH-indol-3-yl)ethyl)-3-(2,2,3,3-tetrafluoropropoxy)benzylamine or a pharmaceutically acceptable salt in the preparation of a medicament for treating Alzheimer's disease by improving or augmenting the effect of an acetylcholinesterase inhibitor, wherein an effective daily dose of said compound is to be administered to a patient in need of such treatment, and wherein the effective daily dose to be administered to the patient is between about 30 and about 60 mg.

2. Use of a compound N-(2-(6-fluoro-lH-indol-3-yl)ethyl)-3-(2,2,3,3-tetrafluoropropoxy)benzylamine or a pharmaceutically acceptable salt in the manufacture of a medicament for treating Alzheimer's disease, said medicament being for use as adjunctive therapy to acetylcholinesterase treatment ,wherein an effective daily dose of N-(2-(6-fluoro-lH-indol-3-yl)ethyl)-3-(2,2,3,3-tetrafluoropropoxy)benzylamine or a pharmaceutically acceptable salt is to be administered to a patient in need of such treatment, and wherein the effective daily dose to be administered to the patient is between about 30 and about 60 mg.

3. The use according to claim 1 or 2, wherein the pharmaceutically acceptable salt is the hydrochloride.

4. The use according to any one of claims 1-3, wherein the dose is administered as an immediate release formulation.

5. The use according to any one of claims 1-4 for treating mild to moderate Alzheimer's disease.

6. The useaccording to any one of claims 1-5, wherein the acetylcholineesterase inhibitor is donepezil.

7. The use according to any one of claims 1-5, wherein the acetylcholineesterase inhibitor is rivastigmine.

8. The use according to anyone of claims 1-5, wherein the acetylcholineesterase inhibitor is galatamine.

9. The use according to any one of claims 1-8, wherein the effective daily dose is 30 mg.

10. The use according to any one of claims 1-8, wherein the effective daily dose is 40 mg or less.

11. The use according to any one of claims 1-8, wherein the effective daily dose is 50 mg or less.

12. The use according to any one of claims 1-8, wherein the effective daily dose is 60 mg or less.

13. The use according to any one of claims 1-8, wherein the effective daily dose is 60 mg.

14. A pharmaceutical composition comprising Compound I wherein the composition when administered to a human provides a blood plasma concentration of Compound I in a range of about 56 ng/mL to about 310 ng/mL at steady-state plasma level and when the composition is administered to provide an effective daily dose of Compound I of about 60 mg or less; and wherein Compound I is N-(2-(6-fluoro-lH-indol-3-yl)ethyl)-3-(2,2,3,3-tetrafluoropropoxy)benzylamine.

15. A pharmaceutical composition comprising Compound I wherein the composition provides when administered to a human a receptor occupancy of Compound I greater than or equal to about 90 % at the 5HT-6 receptor at a steady-state plasma level and when the composition is administered to provide an effective daily dose of Compound I of about 60 mg of less; and wherein Compound I is N-(2-(6-fluoro-lH-indol-3-yl)ethyl)-3-(2,2,3,3-tetrafluoropropoxy)benzylamine.