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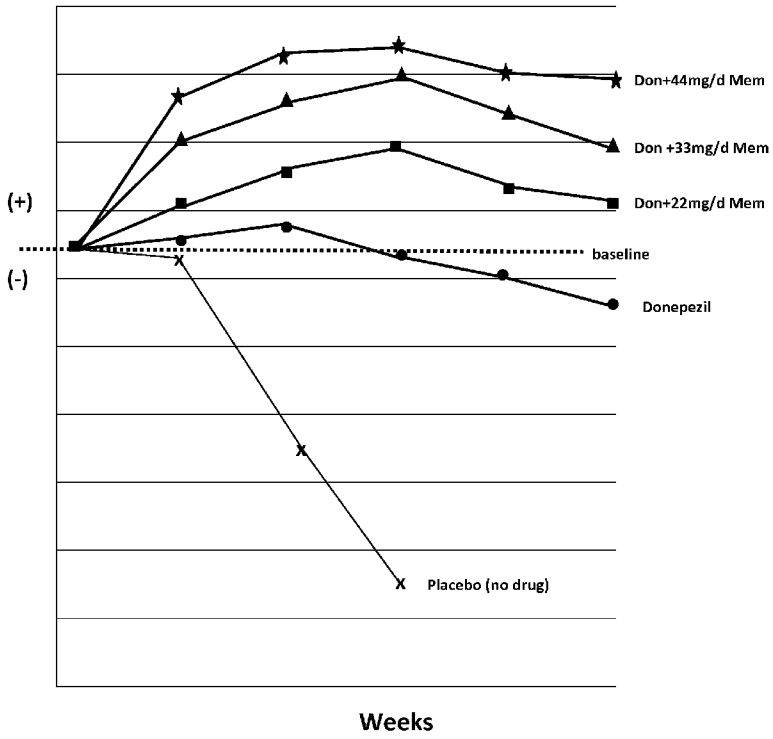
(54) Title: TREATMENT OF MILD DEMENTIA OF THE ALZHEIMER'S DISEASE TYPE

FIGURE 1




(57) Abstract: Methods, compositions, and kits for slowing progression of Alzheimer's disease symptoms in a patient with mild Alzheimer's disease are described.

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# Treatment of Mild Dementia of the Alzheimer's Disease Type

## Background of the Invention

[001] The field of the invention is the combined use of a cholinesterase inhibitor and memantine for the treatment of mild dementia of the Alzheimer's type.

[002] Donepezil, rivastigmine, galantamine, and tacrine are reversible cholinesterase inhibitors that have been approved in the United States for the treatment of dementia of the Alzheimer's type. This class of drugs can have significant positive effects on global function, cognition, activities of daily living (ADL), and behavioral symptoms in patients with Alzheimer's disease (see e.g. Seow and Gauthier, Can J Psychiatry (2007) 52:620-9; and Rogers et al., Neurology (1998) 50:136-45). However, patient dropout rates due to adverse events are significant (Lanctot et al, CMAJ. (2003) 169:557-64), limiting the clinical utility of these drugs. Alzheimer's disease patients who are treated with cholinesterase inhibitors, on average, return to their pre-treatment status between 9 and 12 months of initiation of treatment (Johannsen P, CNS Drugs (2004) 18:757-68).

[003] Memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has been approved in the United States for the treatment of moderate to severe dementia of the Alzheimer's type. Placebo-controlled trials of memantine in patients with mild to moderate dementia of the Alzheimer's type have been conducted, but reports have been mixed as to whether the drug has any statistically significant effect at this stage of the disease, and the FDA has not approved memantine for this indication (Schneider, Alzheimer's & Dementia (2007) 3:18-20). The following references discuss the use of memantine to treat mild to moderate Alzheimer's disease: Doody et al., Alzheimer's & Dementia (2007) 3:7-17; Pomara et al., Alzheimer Dis Assoc Disord. (2007) 21:60-4; Peskind et al., Am J Geriatr Psychiatry (2006) 14:704-715; Knopman, Alzheimer's & Dementia (2007) 3:21-22); Görtelmeyer and Erbler, Arzneimittelforschung (1992) 42:904-13); Bakchine and Loft, J Alzheimer's Dis 11: 471-479; and McDonald et al., US 2006/0020042.

[004] As severity of dementia progresses from mild to moderate to severe in Alzheimer's disease patients receiving monotherapy with cholinesterase inhibitors, memantine is routinely added to the pharmacotherapy. Tariot et al. (JAMA (2004) 291:317-24) reported that patients with moderate to severe Alzheimer's disease who were being treated with donepezil had significantly better outcome measures of cognition, ADL, global outcome, and behavior when memantine was added to the therapy compared to treatment with

donepezil alone. The following additional references describe the combined use of cholinesterase inhibitors with memantine: Wenk et al., Life Sci. (2000) 66:1079-83; Thomsen et al., WO 03/101458; Went et al., US 2006/0252788; Moebius, WO 2004/037234; Riepe et al., J. Clin Psychiatry (2006) 8:258-263; Grossberg et al., J Clin Pharmacol (2006) 46:17S-26S; and Kimura et al., US 2006/0246003.

**[005]** Effective therapeutic treatments for mild Alzheimer's disease having fewer side-effects and longer beneficial effects than current treatments are needed.

## Summary of the Invention

**[006]** One aspect of the invention is a method for slowing progression of Alzheimer's disease symptoms in a patient with mild Alzheimer's disease, comprising administering to the patient 25-60 mg/day memantine and a cholinesterase inhibitor. Another aspect of the invention is the use of 25-60 mg/day memantine and a cholinesterase inhibitor in the preparation of a medicament for slowing progression of Alzheimer's disease symptoms in a patient with mild Alzheimer's disease. In various embodiments of the invention the cholinesterase inhibitor is selected from the group consisting of donepezil, galantamine, rivastigmine, tacrine, and huperzine-A. In various embodiments the cholinesterase is donepezil and the daily dose is 0.5-9 mg/day or 0.5-4 mg day; and the daily dose of memantine is 30-50 or 35-45 mg/day. Preferably, the memantine is in an oral extended release dosage form.

**[007]** Another aspect of the invention is a starter kit for initiating memantine therapy in a patient in need thereof, comprising a plurality of a first unit dosage form comprising 5-35 mg memantine; and a plurality of a second unit dosage form comprising at least 10 mg more memantine than the first unit dosage form, wherein the memantine in the first and second unit dosage forms is in extended release form. In various embodiments, the second unit dosage form comprises at least 11 mg, 15 mg, or 20 mg more memantine than the first unit dosage form. The first and second unit dosage forms of the kit may further comprise 0.5-10 mg/day donepezil or the kit may further comprise a third unit dosage form comprising a cholinesterase inhibitor.

## Brief Description of the Figure

**[008]** **FIG 1** depicts changes in baseline MMSE score in patients treated with no drug, donepezil monotherapy, or donepezil plus memantine at 22, 33, or 44 mg/day.

**Detailed Description of the invention**

**[009]** The invention provides methods, compositions, and kits for slowing progression of Alzheimer's disease symptoms in a patient with mild Alzheimer's disease. As used herein, a patient is said to have Alzheimer's disease after a diagnosis of probable Alzheimer's disease or dementia of the Alzheimer's type based on acceptable medical practice such as the use of criteria established by the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRA; see McKhann et al., Neurology (1984) 34:939-44), DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th ed. American Psychiatric Association, 1994), or equivalent diagnostic methodology. Further, the severity of the patient's disease is determined to be "mild" using established diagnostic criteria such as a Mini Mental State Examination (MMSE; Folstein et al., J. Psychiat Res (1975) 12:189-198), the Alzheimer's Disease Assessment Scale—cognitive subscale (ADAS-Cog; Rosen et al., Am J Psychiatry (1984) 141:1356-1364); the Global Deterioration Scale (GDS; Reisberg et al., Am J Psychiatry (1982) 139:1136-1139); the Gottfries-Bråne-Steen (GBS) scale (Gottfries et al., Arch Gerontol Geriatr (1982) 1:311-330; Bråne et al, Dement Geriatr Cogn Disord (2001) 12:1-14), or equivalent tests.

**[010]** In the method of the invention, the patient is administered at least 25 mg/day memantine together with a cholinesterase inhibitor in an amount sufficient to slow progression of one or more Alzheimer's disease symptoms compared to no treatment or compared to monotherapy with the cholinesterase inhibitor. In a particular embodiment the rate of cognitive decline in the patient is slowed.

**[011]** Exemplary cholinesterase inhibitors that have a therapeutic effect in the treatment of Alzheimer's disease patients include donepezil, rivastigmine, galantamine, tacrine, and huperzine-A (see Li et al, Curr Alzheimer Res. (2007) 4:386-96). Preferred cholinesterase inhibitors are donepezil, rivastigmine, and galantamine. The dosage forms and strengths at which various cholinesterase inhibitors are currently used as monotherapy for Alzheimer's disease patients are provided in Table I.

**[012]** Table I.

| Active ingredient | Trade name | Dosage strengths | Dosage form /route | Dosing frequency | Total daily dose |
|---|---|---|---|---|---|
| donepezil | ARICEPT® | 5mg, 10mg | Tablet / oral | q.d. | 5 or 10mg |
| donepezil | ARICEPT ODT® | 5mg, 10mg | Orally disintegrating | q.d. | 5 or 10mg |

| | | | | | |
|---|---|---|---|---|---|
| | | | tablet / oral | | |
| rivastigmine | EXELON® | 1.5mg, 3mg, 4.5mg, 6mg | Capsule /oral | b.i.d. | 6 or 12mg |
| rivastigmine | EXELON® | 2 mg/ml | Solution / oral | b.i.d. | 6 or 12mg |
| rivastigmine | EXELON® | 4.6mg/24hr; 9.5mg/24hr | ER Film / transdermal | q.d. | 9.5 mg |
| galantamine | RAZADYNE® | 4mg, 8mg, 12mg | Tablet / oral | b.i.d. | 16 or 24mg |
| galantamine | RAZADYNE® | 4 mg/ml | Solution / oral | b.i.d. | 16 or 24mg |
| galantamine | RAZADYNE ER® | 8mg , 16mg, 24mg | ER capsule / oral | q.d. | 16 or 24mg |
| tacrine | COGNEX® | 10mg, 20mg, 30mg, 40mg | capsule / oral | q.i.d. | 80, 120, or 160mg |

**[013]** The cholinesterase inhibitor is administered at a dose that is the same as, and preferably less than the dose demonstrated to be effective as a monotherapy in the treatment of mild Alzheimer's disease. In preferred embodiments the dose of donepezil is 0.5-9 mg/day, and more preferably 0.5-4 mg/day. In specific embodiments, the dose of donepezil is 0.5 mg/day, 0.75 mg/day, 1 mg/day, 1.5 mg/day, 2 mg/day, 2.5 mg/day, 3 mg/day, or 4 mg/day administered q.d. When the cholinesterase inhibitor is rivastigmine, the daily dose is preferably less than 10 mg/day, and preferably 6mg/day or less. In specific embodiments, the rivastigmine is administered once daily at a dose of 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, or 5 mg. When the cholinesterase inhibitor is galantamine, the daily dose is preferably less than 15 mg, and more preferably less than 12 mg. In one embodiment, the dose of galantamine is 10mg/day or less. In specific embodiments, the galantamine is administered b.i.d. or q.d. for a total daily dose of 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8mg, 9mg, or 10mg.

**[014]** The dose of memantine is at least 25 mg/day, and preferably 25-80 mg/day, 25-60 mg/day, 30-60 mg/day, 30-50 mg/day, or 35-45 mg/day. The memantine is preferably administered orally once daily in an extended release (ER) unit dosage form. In some cases, extended release memantine may be taken by the patient less frequently, e.g. every other day or every third day, provided that the daily dose released into the patient is at least 25 mg/day. Suitable ER memantine dosage forms are described by Went et al., US 2006/0142398, incorporated herein by reference. Preferred dosage forms provide a Tmax of 12-24 hours, and more preferably 16-24 or 18-22 hours.

[015] The memantine and cholinesterase inhibitor may be provided to the patient in a combination dosage form, or in separate dosage forms. When administered as separate dosage forms, the type of dosage forms for the memantine and cholinesterase inhibitor may be the same or different. For example, a patient may be administered the memantine in the form of an orally administered tablet or capsule, and the cholinesterase inhibitor, such as rivastigmine, in the form of an orally administered solution or ER film that is administered transdermally. In a preferred embodiment, the patient is administered a single unit dosage form administered b.i.d. or q.d. (or even less frequently, e.g. once every 2 or 3 days), that contains both the memantine and the cholinesterase inhibitor. In one such embodiment, the dosage form is a capsule that contains memantine-containing pellets (also referred to in the art as "beads") that have an ER coating, and cholinesterase inhibitor-containing pellets that are formulated for either immediate release (IR) or extended release (ER). Suitable such dosage forms are described by Went et al., US 2006/0252788, incorporated herein by reference.

[016] When an ER unit dosage form of memantine is used, a memantine-naïve patient may initiate therapy without dose titration. However, and particularly for treatment with daily memantine dosages of about 30 mg or more, the therapy may be preceded by a dose titration regimen of one-, two-, three-, or more steps. The daily dose of memantine administered in the initial step of the titration is at least 5 mg/day, 10 mg/day, and preferably11 mg/day in an ER unit dosage form. In one embodiment of the invention, the daily dose administered during one of the steps (e.g. the second, third, or subsequent step, or the final (i.e. final dose) step) of the titration schedule is at least 10 mg/day more than the preceding step, and preferably at least 11 mg/day, 15 mg/day, or 20 mg/day more than the preceding step. In a specific embodiment, the patient is dose titrated with 5-20 mg/day and preferably 10-20 mg/day ER memantine for 1-2 weeks and then is administered a final daily dose of 30-60 mg/day or 35-45 mg/day ER memantine.

[017] Table II shows six exemplary dose titration schedules, A-F. Each step of the titration typically lasts 1-7 days and preferably 1-5 or 1-3 days.

[018] Table II

| | Total daily dose (mg) and dosing frequency | | | | |
|---|---|---|---|---|---|
| | **Step 1** | **Step 2** | **Step 3** | **Step 4** | **Final dose** |
| **A** | 5 q.d. | 10 q.d. | 20 q.d. | 30 q.d. | 40 q.d. |
| **A** | 5.5 q.d. | 11 q.d. | 22 q.d. | 33 q.d. | 44 q.d. |

| | | | | | |
|---|---|---|---|---|---|
| B | 12.5 q.d. | 25 q.d. | 37.5 q.d. | | 50 q.d. |
| C | 15 q.d. | 30 q.d. | | | 45 q.d. |
| D | 15 q.d. | 30 q.d. | 45 q.d or b.i.d. | | 60 q.d or b.i.d. |
| E | 16.5 q.d. | 33 q.d. | | | 50 q.d. |
| F | 22 q.d. | 33 q.d. | | | 45 q.d. |
| G | 22 q.d. | | | | 45 q.d. |

**[019]** The patient may be stabilized on a cholinesterase inhibitor therapy prior to initiating memantine therapy. Alternatively, the patient may be both cholinesterase inhibitor- and memantine- naïve, and initiate treatment with both drugs simultaneously. In some cases, the patient may be stabilized on memantine prior to initiating treatment with a cholinesterase inhibitor. When memantine dose titration is used in a patient who is cholinesterase inhibitor-naïve, treatment with the cholinesterase inhibitor may be initiated at the beginning of the titration, or after the patient is memantine-stabilized. In some cases, the patient is one who has previously initiated monotherapy with a cholinesterase inhibitor, but discontinued treatment due to adverse advents. The cholinesterase inhibitor dropout patient may later initiate monotherapy with memantine, then, after becoming stable on memantine, re-initiate treatment with a cholinesterase inhibitor. In this embodiment, the cholinesterase inhibitor may be the same as or different from the one that caused the adverse events. If it is the same cholinesterase inhibitor, it is typically administered at a lower dose in combination with memantine compared to the dose that caused the adverse events. Starter kits that facilitate patient compliance with various dose titration regimens are described further below. For example, a starter kit designed to facilitate patient compliance with the dose titration schedule E of Table II is depicted in Table III below.

**[020]** Prior to initiating treatment, the patient is typically assessed for degree of disease severity using a standardized examination such as the MMSE, the ADAS-Cog test, the GDS test (collectively referred to herein as "disease severity tests") and given a baseline score. In a specific embodiment the patient is given an MMSE and assigned a baseline score of at least 20, e.g. 20-26, indicative of mild Alzheimer's disease. Preferably the patient is brought in for assessment at an early stage of the disease and has an MMSE baseline score of at least 21, 22, or 23 (Folstein et al, *supra*). Treatment with the memantine and cholinesterase inhibitor combination therapy delays progression of Alzheimer's disease. This can be demonstrated using double-blind, placebo-controlled trials, as described in Example 1 below, to show that patients who are treated with the combination of memantine

and the cholinesterase inhibitor score at or above baseline on a disease severity test for a longer period than patients on cholinesterase inhibitor monotherapy. For example, on average, a patient on combination memantine-cholinesterase inhibitor therapy will score at or above baseline for at least 42 weeks, 48 weeks, 52 weeks, 64 weeks, 72 weeks, or 84 weeks. In a specific embodiment of the invention, the patient maintains an MMSE score at or above the baseline MMSE score for at least 52 weeks after initiating the combination therapy. In contrast, patients diagnosed with mild Alzheimer's disease who are treated with cholinesterase inhibitor monotherapy drop below their baseline levels approximately 36 weeks to 52 weeks after initiation of treatment (Johannsen, *supra*).

**[021]** Other aspects of the invention are compositions and kits that can be used in treating a patient with mild Alzheimer's disease in accordance with the methods described herein. Kits can be designed to ensure patient compliance with dose titration regimens. For example, a starter kit may be provided to the patient that comprises a plurality of a first unit dosage form comprising 5-35, and preferably 10-35 mg extended release memantine; and a plurality of a second unit dosage form comprising at least 10 mg more extended release memantine than the first unit dosage form. In some embodiments, the kit further comprises a plurality of a third unit dosage form comprising at least 10 mg more memantine than the second unit dosage form. In specific embodiments, the second unit dosage form comprises at least 10 mg, 12.5, 15 mg, or 20mg more memantine than the first unit dosage form. For example, the second unit dosage form may comprise 11 mg or 22 mg more memantine than the first unit dosage form. In another specific embodiment, the kit comprises a plurality of first unit dosage forms comprising 12.5 mg extended release memantine, and a plurality of second unit dosage forms comprising 25 mg extended release memantine. The kits are clearly marked to allow the patient (or caregiver) to easily identify which dose or doses are to be taken on a given day. Such kits can also be used to transition a patient currently being treated with 20 mg/day IR memantine (administered in two divided doses) to higher daily doses of ER memantine administered once daily. An exemplary kit is depicted in Table III, which represents a 2-step memantine titration blister pack. The blister pack is imprinted with the words Day 1 – Day 7 across the top, and with the words Week 1 – Week 4 down the left side of the pack, as shown. Each of the remaining cells in the table represents a single blister within the pack that contains a single unit dosage form. Row one contains a plurality (i.e. 7 units) of a first unit dosage form that comprises 22 mg ER memantine, row two contains 7 units of a second unit dosage form that comprises 33 mg ER memantine, and

rows three and 4 together contain a total of 14 units of a third unit dosage form that comprises 45 mg ER memantine, which is the final maintenance dose of memantine.

**[022]** Table III

| | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 |
|---|---|---|---|---|---|---|---|
| **Week 1** | (22mg M) | (22mg M) | (22mg M) | (22mg M) | (22mg M) | (22mg M) | (22mg M) |
| **Week 2** | (33mg M) | (33mg M) | (33mg M) | (33mg M) | (33mg M) | (33mg M) | (33mg M) |
| **Week 3** | (45mg M) | (45mg M) | (45mg M) | (45mg M) | (45mg M) | (45mg M) | (45mg M) |
| **Week 4** | (45mg M) | (45mg M) | (45mg M) | (45mg M) | (45mg M) | (45mg M) | (45mg M) |

**[023]** An exemplary 1-step memantine titration kit is depicted in Table IV. In this example, the kit comprises a plurality of 3 unit doses of 22 mg ER memantine that the patient takes once daily for the first 3 days, and 4 unit doses of 33 mg ER memantine that the patient takes on days 4-7. Thereafter the patient may be maintained on a dose of 33mg/day ER memantine, or may begin treatment with a higher maintenance dose of 45 mg/day.

**[024]** Table IV

| | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 |
|---|---|---|---|---|---|---|---|
| **Week 1** | (22mg M) | (22mg M) | (22mg M) | (33mg M) | (33mg M) | (33mg M) | (33mg M) |

**[025]** Another exemplary 1-step memantine titration kit is depicted in Table V. in this example, the kit comprises a blister pack containing 7 unit doses of 12.5 mg ER memantine that the patient takes once daily for the first 7 days of treatment. Thereafter, the patient may be maintained on a dose of 25 mg/day ER memantine.

**[026]** Table V

| Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 |
|---|---|---|---|---|---|---|
| (12.5mg M) | (12.5mg M) | (12.5mg M) | (12.5mg M) | (12.5mg M) | (12.5mg M) | (12.5mg M) |

**[027]** The unit dosage forms in the kits of the invention may further comprise a cholinesterase inhibitor. In a specific embodiment, the first and second (and, if applicable, third, etc.) unit dosage forms further comprise 0.5-10 mg/day, preferably 0.5-9 mg/day, donepezil. The amount of the cholinesterase inhibitor in the second unit dosage form, may be greater than in the first (i.e. there is dose titration), but more typically the amount in the first and second dosage forms will be the same. For example, in the blister packs depicted

in Tables III and IV above, each of the dosage forms may further comprise 4 mg donepezil. In alternative embodiments, the kit will comprise a plurality of first and second unit dosage forms that contain memantine as the only active ingredient, and a plurality of a third unit dosage form that contains a cholinesterase inhibitor as the only active ingredient. For example, in the blister packs depicted in Tables III and IV above, each of the blisters may contain an additional unit dosage form (e.g. another tablet or capsule) that contains 4 mg donepezil.

**[028]** **Example 1:** A Randomized, Placebo-Controlled, Double-Blind Study of the Efficacy and Safety of Treatment with Memantine and Donepezil Combination Therapy in Subjects with Mild Alzheimer's Disease

**[029]** The design for this 52-week, 4-arm randomized, double-blinded, placebo-controlled clinical study was adapted from a previously reported study (Winblad et al., Neurology (2001) 57:489-95). The study is conducted at 25-50 sites in the U.S.

**[030]** Study design: Patients are randomized to one of the following:

**Arm 1**: Placebo, patients maintained at 5 mg/day donepezil.

**Arm 2**: 5mg/day donepezil + 11 mg/day ER memantine during the first week; 5mg/day donepezil + 22 mg/day ER memantine thereafter.

**Arm 3**: 5mg/day donepezil + 11 mg/day ER memantine during the first week; 5mg/day donepezil + 22 mg/day ER memantine during the second week; 5mg/day donepezil + 33 mg/day ER memantine thereafter.

**Arm 4**: 5mg/day donepezil + 11 mg/day ER memantine during the first week; 5mg/day donepezil + 22 mg/day ER memantine during the second week; 5mg/day donepezil + 33 mg/day ER memantine 5g/day donepezil during the third week; and 5 mg/day donepezil + 45 mg/day ER memantine thereafter.

**[031]** Efficacy measures are performed at screening, baseline, and weeks 4, 12, 24, 36, and 52. Safety and compliance are also assessed at these time points and at week 6.

**[032]** Patient selection: Men and women of any race between 50 and 90 years of age who fulfill all the inclusion and none of the exclusion criteria are accepted for enrollment in the study.

**[033]** Inclusion criteria: Diagnosis of Alzheimer's disease (AD) is consistent with the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria and National Institute of Neurologic and Communicative Disorders and Stroke–AD and Related

Disorders Association (NINCDS-ADRDA) criteria for possible or probable AD. Patients have mild AD, confirmed by a Mini-Mental State Examination (MMSE) score of at least 20. If not performed within the last 12 months, CT or MRI scans are obtained at screening. Patients are otherwise healthy and ambulatory or ambulatory aided (i.e., walker or cane), with vision and hearing sufficient for compliance with the testing procedures. Laboratory test values have to be within normal limits or considered to be clinically insignificant by the investigator. All patients have to have a reliable caregiver.

Exclusion criteria: Patients are excluded if they have evidence of clinically significant and unstable, active gastrointestinal, renal, hepatic, endocrine, or cardiovascular system disease, primary neurologic or psychiatric diseases other than AD (notably DSM-IV–defined depression or vascular dementia), newly treated hypothyroidism, or a known or suspected history (within the past 10 years) of alcoholism or drug abuse. Additional reasons for exclusion include evidence of neoplasm, insulin-dependent diabetes or diabetes not stabilized by diet or oral hypoglycemic agents, obstructive pulmonary disease or asthma, recent (<2 years) hematologic/oncologic disorders, pernicious anemia, vitamin B12 or folate deficiency as evidenced by blood concentrations below the lower normal limit, or recent (< 3 months) use of ginkgo biloba. The use of selective serotonin reuptake inhibitors, neuroleptics in small daily doses, and short-acting benzodiazepines is permitted provided that they have been given in stable doses for at least 2 months before entering the study. Medications with major anticholinergic effects, such as high doses of neuroleptics, tricyclic antidepressants, and medications for PD, are not permitted. Patients with a known hypersensitivity to cholinesterase inhibitors as well as those treated with cholinomimetics, including tacrine, within 30 days of screening are excluded. Prescription or over-the-counter sympathomimetic amines and antihistamines are to be stopped temporarily for 48 hours before each clinic visit. Written informed consent is obtained from the patient (if possible), the caregiver, and the patient's representative (if applicable) before beginning detailed screening activities.

**[034]** Outcome measures: Primary outcomes are measured using the GBS scale, MMSE, ADAS-cog, and GDS. The study demonstrates memantine-donepezil combination therapies that significantly delay disease progression in patients with mild Alzheimer disease compared to donepezil monotherapy.

**[035]** **Example 2:** A Randomized, Placebo-Controlled, Double-Blind Study of the Efficacy and Safety of Treatment with Memantine and Donepezil Combination Therapy in Subjects with Mild Alzheimer's Disease

**[036]** The design for this 52-week, 4-arm randomized, double-blinded, placebo-controlled clinical study was adapted from a previously reported study (Winblad et al., Neurology (2001) 57:489-95). The study is conducted at 25-50 sites in the U.S.

**[037]** Study design: Patients are randomized to one of the following:

**Arm 1**: Placebo, patients maintained at 5 mg/day donepezil.

**Arm 2**: 5mg/day donepezil + 12.5 mg/day ER memantine during the first week; 5mg/day donepezil + 25 mg/day ER memantine thereafter.

**Arm 3**: 5mg/day donepezil + 12.5 mg/day ER memantine during the first week; 5mg/day donepezil + 25 mg/day ER memantine during the second week; 5mg/day donepezil + 37.5 mg/day ER memantine thereafter.

**Arm 4**: 5mg/day donepezil + 12.5 mg/day ER memantine during the first week; 5mg/day donepezil + 25 mg/day ER memantine during the second week; 5mg/day donepezil + 37.5 mg/day ER memantine 5g/day donepezil during the third week; and 5 mg/day donepezil + 50 mg/day ER memantine thereafter.

**[038]** Efficacy measures are performed at screening, baseline, and weeks 4, 12, 24, 36, and 52. Safety and compliance are also assessed at these time points and at week 6.

**[039]** The patient selection, inclusion criteria, exclusion criteria, and outcome measures used in the study are described in Example 1 above.

**WHAT IS CLAIMED IS:**

1. A method for slowing progression of Alzheimer's disease symptoms in a patient with mild Alzheimer's disease, comprising:

administering to the patient 25-60 mg/day memantine and a cholinesterase inhibitor.

2. The method of claim 1 wherein the cholinesterase inhibitor is selected from the group consisting of donepezil, galantamine, rivastigmine, tacrine, and huperzine-A.

3. The method of claim 1 wherein the patient is administered 0.5-9 mg/day donepezil.

4. The method of claim 1 wherein the patient is administered 0.5-4 mg/day donepezil.

5. The method of claim 1 wherein the patient is administered 30-50 mg/day memantine.

6. The method of claim 1 wherein the patient is administered 35-45 mg/day memantine.

7. The method of claim 1 wherein the memantine is orally administered in an extended release dosage form.

8. The method of claim 1 wherein the patient is orally administered donepezil in an immediate release dosage form.

9. The method of claim 1 wherein the patient is orally administered a unit dosage form that contains both memantine and donepezil.

10. The method of claim 1 wherein prior to the administering step, the patient is donepezil-naïve.

11. The method of claim 1 wherein prior to the administering step, the patient is memantine-naïve.

12. The method of claim 1 wherein prior to the administering step, the patient is memantine-and donepezil-naïve.

13. The method of claim 1, wherein prior to the administering step, the patient discontinued cholinesterase inhibitor monotherapy.

14. The method of claim 1 wherein prior to the administering step, the patient is given a Mini-Mental State Examination (MMSE) and assigned a baseline MMSE score of at least 20.

15. The method of claim 14 wherein the patient maintains an MMSE score at or above the baseline MMSE score for at least 52 weeks after initiating the administering step.

16. The method of claim 1 wherein for 1-2 weeks prior to the administering step, the patient is dose-escalated with 5-20 mg/day memantine.

17. A starter kit for initiating memantine therapy in a patient in need thereof, comprising:

a plurality of a first unit dosage form comprising 5-35 mg memantine; and

a plurality of a second unit dosage form comprising at least 10 mg more memantine than the first unit dosage form, wherein the memantine in the first and second unit dosage forms is in extended release form.

18. The kit of claim 17 wherein the second unit dosage form comprises at least 11 mg more memantine than the first unit dosage form.

19. The kit of claim 17 wherein the second unit dosage form comprises at least 15 mg more memantine than the first unit dosage form.

20. The kit of claim 17 wherein the second unit dosage form comprises at least 20 mg more memantine than the first unit dosage form.

21. The kit of claim 17 wherein the second unit dosage form comprises 22 mg more memantine than the first unit dosage form.

22. The kit of claim 17 further comprising:

a plurality of a third unit dosage form comprising at least 10 mg more memantine than the second unit dosage form.

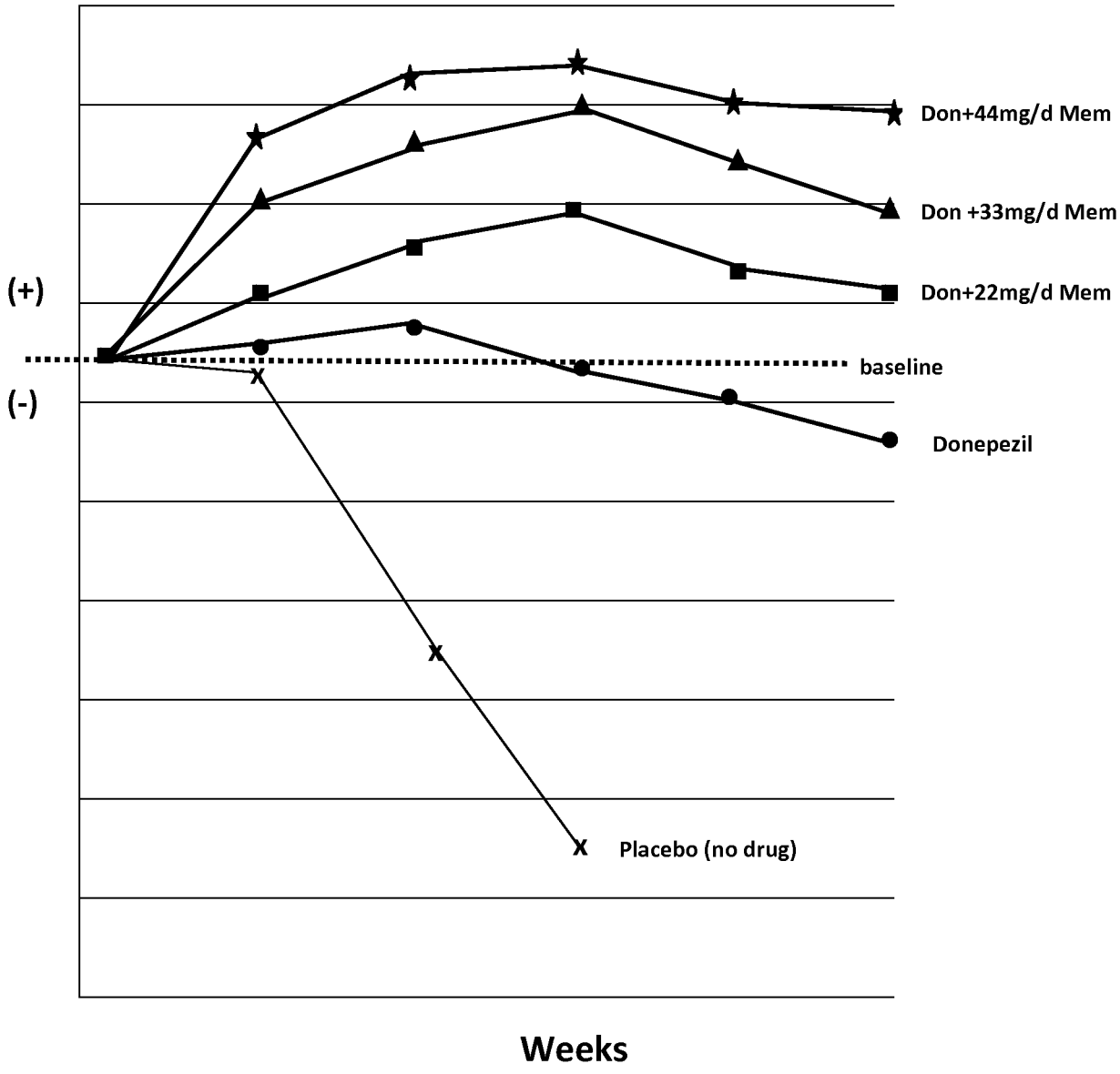
23. The kit of claim 17, wherein the first and second unit dosage forms further comprise 0.5-10 mg/day donepezil.

24. The kit of claim 23 wherein the amount of donepezil in the first and second unit dosage forms is the same.

25. The kit of claim 17 further comprising a third unit dosage form comprising a cholinesterase inhibitor.

26. The kit of claim 17 further comprising a third unit dosage form comprising 0.5-10 mg/day donepezil.

**FIGURE 1**


(+)
(-)
Don+44mg/d Mem
Don +33mg/d Mem
Don+22mg/d Mem
baseline
Donepezil
Placebo (no drug)
Weeks