BMJ open

Protocol for a randomized controlled trial: efficacy of donepezil against psychosis in Parkinson's disease (EDAP)

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-003533
Article Type:	Protocol
Date Submitted by the Author:	03-Jul-2013
Complete List of Authors:	Sawada, Hideyuki; Utano National Hospital, Clinical Research Center Oeda, Tomoko; Utano National Hospital, Clinical Research Center
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Neurology, Pharmacology and therapeutics
Keywords:	Parkinson-s disease < NEUROLOGY, Adult neurology < NEUROLOGY, NEUROLOGY

Protocol for a randomized controlled trial: efficacy of donepezil against psychosis in Parkinson's disease (EDAP)

Hideyuki Sawada[1], Tomoko Oeda[1]

Author Affiliations

[1]Clinical Research Center, National Hospital of Utano, Kyoto, Japan

Correspondence to Dr Hideyuki Sawada; sawada@unh.hosp.go.jp

8 Ondoyamacho, Narutaki, Ukyoku, Kyoto, Japan

Phone: +81-75-461-5121, Fax: +81-75-464-0027

Abstract

Introduction: Psychosis, including hallucinations and delusions, is one of the important non-motor problems in patients with Parkinson's disease (PD), and is possibly associated with cholinergic neuronal degeneration. The EDAP (Efficacy of Donepezil against Psychosis in PD) study will evaluate the efficacy of donepezil, a brain acetylcholine esterase inhibitor, for prevention of psychosis in PD.

Methods and analysis: Psychosis is assessed every 4 weeks using the Parkinson Psychosis Questionnaire (PPQ), and PD patients whose PPQ-B score (hallucinations) and PPQ-C score (delusions) have been zero for 8 weeks before enrollment are randomized to two arms: patients receiving donepezil hydrochloride, or patients receiving placebo. The subjects are then followed for 96 weeks. The primary outcome measure is the time to the event, defined as getting 2 points or more on the PPQ-B score or PPQ-C score, which is assessed using a survival time analysis. The hypothesis being tested is that donepezil prevents psychosis in patients with PD. Efficacy will be tested statistically using the intention-to-treat analysis including a Log-rank test and Cox proportional hazard models. Secondary outcomes, such as changes of PPQ scores and UPDRS scores from baseline will be assessed.

Ethics and dissemination: Ethics approval was received from the Central Review Board of the National Hospital Organization, Tokyo, Japan. The trial was declared and registered to the Pharmaceuticals and Medical Devices Agency (PMDA), Japan (No. 22-4018). All participants will receive a written informed consent that was approved by the Central Review. A completed written informed consent is required to enroll in the study. Severe adverse events will be monitored by investigators, and in cases where a severe adverse event was previously unreported, it will be reported to the PMDA.

Clinical Trial Registration Number: UMIN000005403

ARTICLE SUMMARY

Article focus

Given that psychosis is caused by the degeneration of brain cholinergic neurons in patients with Parkinson's disease (PD), an inhibitor of brain acetylcholine esterase such as donepezil hydrochloride may be efficacious in the prevention of psychosis. However, motor symptoms may become worse since central anticholinergic drugs improve motor symptoms.

A multi-center, randomized, placebo-controlled, double-blinded trial will be conducted to investigate the efficacy of donepezil in the prevention of psychosis. This protocol paper outlines the design, eligibility criteria, methods of data collection, and safety monitoring.

Key messages

The study is a long-term randomized placebo-controlled trial to investigate the prophylactic effects against psychosis in Parkinson disease. The occurrence of psychosis is monitored using the Parkinson Psychosis Questionnaire (PPQ) that is validated for assessment of hallucinations, illusions, and delusions in patients with PD.

Strengths and limitations of this study

In previous randomized controlled trials for psychosis the efficacy was investigated in patients who presented with psychosis, and the primary endpoint was improvement of psychotic symptoms. By comparison, this study is designed to evaluate the prophylactic effect in patients without current psychosis. Because psychosis may be overlooked and underestimated it is assessed using a questionnaire, Parkinson Psychosis Questionnaire (PPQ) every 4 weeks. The strength of this study is its prospective design using the preset definition of psychosis using PPQ (hallucinations/illusion and delusions). However, it could also be a limitation; because other types of psychosis cannot be evaluated. Another limitation is the sample size estimation. Because there have never been any randomized trials for the prevention of psychosis, previous data for sample size estimation were insufficient. To resolve this issue we estimated the sample size based on our previous retrospective cohort study.

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder presenting with motor disturbances, including muscular rigidity, tremor, bradykinesia or postural reflex disturbance. These motor symptoms are caused by the depletion of dopamine in the striatum. Dopamine replacement therapy can improve motor disturbances in PD. However, many patients suffer from psychiatric symptoms, such as hallucinations and delusions, during their long therapy process.[1 2]

In previous studies the efficacy of anti-dopaminergic drugs, including clozapine,[3 4] olanzapine,[5] quetiapine,[6 7] and risperidone[8] was investigated based on the possibility that psychosis may be caused by excessive dopamine replacement therapy. Although the efficacy of clozapine against psychosis without worsening of motor symptoms of PD was established in the French Clozapine Parkinson Study (FCPS)[4] and the PSYCHOPLOS study,[4] clozapine has a risk of granulocytepenia, and requires careful blood cell monitoring. Previous RCTs demonstrated that olanzapine improves psychosis, but there were no significant differences in improvement between the olanzapine groups and the placebo groups. In addition olanzapine worsened motor symptoms in PD compared with placebo.[5] Two other RCTs demonstrated that quetiapine does not worsen motor symptoms; however, its efficacy against psychosis was not superior to placebo.[6 7] A small-sized RCT comparing risperidone and clozapine demonstrated that risperidone improves psychosis as well as clozapine; however, risperidone worsened motor symptoms.[8] There have been no clinical trials regarding other anti-psychotic drugs against psychosis in PD. Taken together anti-dopaminergic drugs, except for clozapine, insufficiently improve psychosis.

Cholinergic neurons of the basal forebrain play an important role in cognitive function, and disruption of the cholinergic system has been proposed in Alzheimer's disease.[9 10] Previous reports demonstrated that the cholinergic neurons are degenerated, as are dopaminergic neurons in PD,[11] suggesting the possibility that psychosis could be caused by cholinergic neuronal damage, but not by dopaminergic replacement therapy.[12]

Previously we investigated the clinical risk factors for psychosis in a retrospective cohort study (unpublished data). In this study, 334 patients with PD were followed until the occurrence of psychosis in 24 months. PD psychosis was significantly associated with the severity of PD, PD duration, and cognitive function. These data demonstrated that psychosis is associated with the severity of the disease and cognitive function and the results are very consistent with previous reports.[13-15] In addition, the influence of medications were analyzed using a case-crossover study comparing medications at the endpoint (occurrence of psychosis or end of the study) and those for 1 or 3 months before the endpoint, and the analysis showed that the use of anti-cholinergic drugs was a significant risk factor for psychosis. In these results psychosis may have been caused by the degeneration of cholinergic neurons and deterioration of cognitive function.

Donepezil hydrochloride is an inhibitor of acetylcholine esterase in brain neurons[16-18] and activates cholinergic neurons.[16 19 20] In this context donepezil could reduce the risk of psychosis

in patients with PD.[21] In this study we will investigate the efficacy of donepezil against psychosis in a multi-center double-blinded placebo-controlled study.

Except for clozapine, in previous placebo-controlled RCTs against psychosis, the ratio of participants who dropped out from the trials was relatively high, ranging from 18%[5] to 50%[7]. A high drop-out ratio is possible due to patient anxiety to be worsened if assigned to placebo. In addition, psychosis may spontaneously improve even if assigned to placebo. These conditions make it difficult to demonstrate significant differences between active drugs and placebo. Therefore, in this study, the main outcome measure is the prophylactic efficacy of donepezil and the efficacy will be analyzed using a survival time analysis.

Because psychosis may be overlooked and underestimated, it is assessed using Parkinson Psychosis Questionnaire (PPQ)[22] given every 4 weeks. The PPQ consists of 4 categorical dimensions, sleep disturbance, hallucinations/illusions, delusions, and orientations. Eligible patients are those whose scores on the PPQ-B (hallucinations /illusion) and PPQ-C (delusion) are zero at least for 8 weeks before enrollment, and the primary endpoint is the occurrence of psychosis that is defined as PPQ-B ≥2 or PPQ-C ≥2, because the situations when PPQ-B or PPQ-C is ≥2 can result in clinically harmful conditions.

To exclude patients with dementia with Lewy bodies (DLB) and PD with dementia, patients with MMSE score less than 24 are excluded. The risk of psychosis is low in patients with an H-Y stage of 2 or less and the evaluation of psychosis is difficult in patients with H-Y stage of 5. Therefore, patients with H-Y stage of 1–2 or 5 are excluded. The length of time to the occurrence of psychosis is compared between subjects who were prescribed placebo and those who were prescribed donepezil.

Hypothesis to be examined in the study

Psychosis may be caused by dysfunction of brain cholinergic neurons. We examine the hypothesis that donepezil prevents psychosis in patients with PD.

METHODS AND ANALYSIS

Study design

A multicenter, double-blinded, placebo-controlled, randomized trial. A two arm study.

Sites where the study is performed

Eight hospitals of the National Hospital Organization: Utano National Hospital, Hokkaido Medical Center, Sagamihara National Hospital, Shizuoka Institute of Epilepsy and Neurological Disorders, Kyoto Medical Center, Minami Kyoto Hospital, Toneyama National Hospital, and Nagasaki Kawatana Medical Center.

Eligibility criteria

Eligibility

Eligible patients are those who satisfy all of the following criteria and who do not have any of the listed exclusion criteria.

Inclusion criteria

1) PD: Diagnosis of PD according to Steps 1 and 2 of the United Kingdom Brain Bank Parkinson's Disease Diagnostic Criteria.[23]
2) Modified H-Y grades from 2.5 to 4.0, in 'ON' period if patients suffer from motor fluctuation.
3) Psychosis: During the 8 weeks before the study enrollment (V2), there has been no evidence of psychosis that is defined in the Parkinson Psychosis Questionnaire; the answers to questions B (hallucinations /illusions) and C (delusions) are none (score 0) at both Visit 1 (V1) and V2.
4) Cognitive function: The score on the MMSE is 24 or more at both V1 and V2.
5) Either in-patients or out-patients.
6) Sex: Males and females can be enrolled. Females of child-bearing age can be enrolled if a pregnancy test is negative and she agrees to avoid getting pregnant during the study.
7) Age: Patients are between the ages of 20 and 79 years (inclusive) when giving consent.
8) The purpose and methods of the trial are explained, and a written informed consent is obtained.
9) Patients who can follow the protocol, will consent to examination and will provide information on their symptoms.

Exclusion criteria

1) Patients who have previously taken donepezil hydrochloride.
2) Patients who took the following anti-cholinergic drugs in the preceding 4 weeks before V2; trihexyphenidyl, biperiden, profenamine, piroheptine, metixene, mazaticol, promethazine, or cyproheptadine.

3) Patients who took Tsumura No. 54 (Yoku-Kansan) in the preceding 4 weeks before V2.
4) Patients who took antipsychotics in the preceding 12 weeks before V2.
5) Patients who fulfill the criteria of probable DLB according to the revised criteria for the clinical diagnosis of DLB in the third report of the DLB consortium.
6) Patients who have previously been diagnosed with schizophrenia.
7) Patients who have previously had stereotactic brain surgery.
8) Patients who are or were allergic to piperidine derivatives.
9) Patients with severe hepatic or renal dysfunction.
10) Patients with sick sinus syndrome or cardiac conduction block in the atrium or of the atrioventricular junction (sinoatrial block or AV block of 2 degrees or more).
11) Patients with present or past severe bronchial asthma, severe peptic ulcer, or severe obstructive pulmonary disorders.
12) Patients with bradycardia <45/min in ECG at V1.
13) Patients with a QTc >460 msec in ECG at V1.
14) Patients who are pregnant.
15) Patients who participated in other clinical trials in 12 weeks before V2.
16) Patients who are diagnosed with a malignancy.
17) Patients who are judged as inappropriate for the study.

Concomitant medications and restricted medications

During the study periods the flowing drugs are not permitted:

1) Central anti-cholinergic drugs.
2) Anti-psychotic drugs.
3) Inhibitors of brain acetylcholine esterase.
4) NMDA receptor antagonists.
5) Tsumura kampo medicine No. 54 (Yoku-Kansan).
6) Study drugs except for the EDAP study drug.

Definition of psychosis

In this study, psychosis is monitored every 4 weeks using the PPQ-B (hallucinations/illusions) and PP-C (delusions). In determining the cut-off points for PPQ-B and PPQ-C, we think that the lower threshold (or mild psychosis) is better for this trial because of the following three reasons: 1) a lower threshold will allow for higher statistical power in the limited-size trials; 2) higher threshold (or severe psychosis) will make the interpretation of trial results difficult because investigators will reduce dopaminergic drugs even if mild psychosis occurs, prior to worsening of psychosis; 3) a higher threshold is difficult to set because of the concern over safety of the subjects (severe psychosis will be documented as a severe adverse event in the trial). A condition where the PPQ-B or PPQ-C score is 2 or higher is harmful to daily living. A condition with PPQ-B or PPQ-C ≥1 would not always be harmful to daily living and may also be encountered under healthy conditions. Therefore, in this study, psychosis is defined as PPQ-B or PPQ-C ≥2.

The first occurrence of psychosis:
To specify the date of the first occurrence of psychosis, patients and their care-givers are requested to fill a diary on visual or auditory hallucinations or illusions. If the date of the occurrence of psychosis cannot be specified by the diary, midpoint between the last visit and the current visit will be regarded as the date of psychosis occurrence.

Sample size calculation

In our previous study that followed patients with PD, about 20% patients required anti-psychotic medications because of psychosis that was defined as the use of anti-psychotics (unpublished data). In EDAP trial the definition of psychosis is defined according to the PPQ-B (Hallucinations /illusions) and PPQ-C (Delusions) because of a high inter-rater reliability of the PPQ. According to the definition of psychosis in this study (PPQ-B ≥2 or PPQ-C ≥2), we assumed that the cumulative occurrence of psychosis as 45% in the placebo group. According to the previous study, the use of donepezil hydrochloride will reduce the risk of psychosis occurrence by 0.5, and therefore, the cumulative occurrence of psychosis would be 22.5% in the active group. The sample size was calculated on the condition that alpha is 0.05 (bilateral), power is 0.8, and the statistical test is the Log rank test. The sample size was calculated as 84 in each group and 142 in the total subjects.

Allocation

Eligibility is checked at V1 according to inclusion and exclusion criteria. Additionally, scoring of PPQ-A, B, C, and D is performed at V2, and we will confirm eligibility, including that both the PPQ-B and PPQ-C scores are zero at V2. The allocation will be done with stratification of the subjects according to sex (male and female) and modified H-Y (2.5-3.0 and 4.0), because the rate of psychosis is associated with sex and H-Y grades.

Observations

V1 Screening

At V1 the following tests or examinations will be done:

1. PPQ.
2. Modified H-Y.
3. MMSE.
4. Peripheral blood sampling, urine analysis, and ECG.
5. Urine hCG pregnancy test if the participant is non-menopausal or within 1 year from menopause.
6. Body weight, height.
7. Onset of PD, history of hallucinations, delusions, or impulse control disorders.
8. Smoking.

V2 Enrollment

At V2 the following tests and examination will be done:

1. PPQ.
2. Epworth Sleeping Score (Japanese version).

3. UPDRS I, II, III and IV.

The following examinations will be performed between V2 and V3:

1. Frontal lobe Assessment Battery (FAB).
2. Revised version of Wechsler Memory Scale (WMS-R).

The following examinations will be performed limited to participants from Utano National Hospital between V2 and V3:

1. EEG.
2. Cerebral blood flow scintigram using ^{123}I-amphetamine.
3. MRI volumetry of the brain.

V3

At V3 the study drug (3mg) will be prescribed.

V4

At V4 PPQ will be examined. Study drug (5mg) will start to be prescribed after confirming safety.

V5

At V5 the following tests and examinations will be done:

1. PPQ.
2. UPDRS-III, and modified H-Y.
3. JESS.
4. Peripheral blood sampling, urinary analysis, ECG. Urinary pregnancy test if required.

V6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26

1. PPQ. PPQ can be performed by telephone interview.

V7, 11, 13, 17, 19, 23, 25

1. PPQ.
2. UPDRS-III, and modified H-Y.
3. JESS.
4. Peripheral blood sampling, urinary analysis, ECG. Urinary pregnancy test if required.

V9, 15, 21

1. PPQ.
2. UPDRS-III, and modified H-Y.
3. JESS.
4. Peripheral blood sampling, urinary analysis, ECG. Urinary pregnancy test if required.
5. MMSE, FAB, WMS-R.

V27

1. PPQ.
2. UPDRS-I, II, III, IV and modified H-Y.

3. JESS.
4. Peripheral blood sampling, urinary analysis, ECG. Urinary pregnancy test if required.
5. MMSE, FAB, WMS-R.

Apolipoprotein genotype will be examined if the subject gives consent for the genotyping, because the ε4 genotype may reduce the efficacy of donepezil in Alzheimer's disease.

Compliance rate of the investigational product will be monitored at every visit.

Study period and definition of endpoint

The study period is from the start of administration of the investigational product (donepezil or placebo) to the endpoint, and the longest observation period is 96 weeks.

Endpoint is the occurrence of psychosis or termination of observation. Psychosis is defined as a score of 2 or more on the PPQ-B or PPQ-C (if any answer to questions in PPQ-B or PPQ-C is yes, and the frequency or the severity is 2 or more) that is shown in the yellow area in Table 1.

Primary outcome measure and statistical analysis

Primary outcome measure is the time to the occurrence of psychosis from V2 during 48 weeks. The time length to the occurrence of psychosis will be compared between the placebo and the donepezil groups and the difference will be statistically examined using the log rank test. Kaplan-Meier survival curves will be obtained from the data of the placebo and donepezil groups.

Secondary outcome measures

The following data will be obtained and compared between the placebo and donepezil groups as secondary outcome measure:

1. Time to the occurrence of the first psychosis from V2 during 24 weeks.
2. The proportion of participants with psychosis to total participants. The comparison will be analyzed using a statistical model.
3. PPQ score, and the changes of MMSE, WMS-R, FAB from the baseline at V9.
4. PPQ score, and the changes of MMSE, WMS-R, FAB from the baseline at V15.
5. PPQ score, and the changes of MMSE, WMS-R, FAB from the baseline at V21.
6. PPQ score, and the changes of MMSE, WMS-R, FAB from the baseline at V27.
7. Subgroup analysis of the primary and secondary outcome measures by genotype of apolipoprotein E.
8. Secondary measure limited to Utano National Hospital
   - 8-1) I^{123}-iodo-amphetamine brain scintigram at the endpoint. The comparison will be performed by a 3D-SSP method.
   - 8-2) The grand total score of EEG at the endpoint.

Safety

Patients will be requested to report any adverse events. All adverse events that are still present must be followed up until their disappearance or no further requirement of follow-up. Severe adverse events will be monitored by investigators, and in cases where a severe adverse event was previously unreported, it will be reported to the PMDA. To detect QT time elongation ECG will be performed every 8 weeks. Complete blood cell count and laboratory data including hepatic and renal functions will be tested every 8 weeks.

ETHICS AND DISSEMINATION

Ethics approval was received from the Central Review Board of the National Hospital Organization. The trial was declared and registered to the Pharmaceuticals and Medical Devices Agency (PMDA), Japan (No. 22-4018). According to “Good Clinical Practice (GCP)” released from the Minister of Health, Labor and Welfare, all participants will receive a written informed consent that was approved by the Central Review. A completed written informed consent is required to enroll in the study.

Severe adverse events will be monitored by investigators. All severe adverse events will be reported to all investigators via a Web-based electric data capturing system and be discussed. In cases where a severe adverse event was previously unreported, it will be reported to the PMDA according to the GCP guideline. The trial was registered in UMIN Clinical Trials Registry (UMIN-CTR; UMIN000005403).

The key-code table that contains allocation data is made by a key-holder who will not participate in the study, using a computer program. It is concealed from other personnel until key-opening by the key-holder.

Table Multiplicative PPQ score

A Early symtoms /sleep disturbnace

severity	Frequency: Up to once per week	Several times per week	Once or more per day
Not or slightly affecting well-being	1	2	3
Moderately affecting well-being	2	4	6
Severely affecting well-being	3	6	9

B. Hallucinations /illusions

severity	Frequency: Only during the night	During the night & occasionally during the day	Almost every day & night
Insight retained	1	2	3
No full insight	2	4	6
Lacking insight	3	6	9

C. Dellusions

severity	Frequency: Up to once per week	Several times per week	Once or more per day
Withoug affecting the social enviroment	1	2	3
Affecting the patient by emotional distress	2	4	6
Affecting the patient by accusation, agression, or lack of cooperation	3	6	9

D. Orientation

severity	Frequency: Up to once per week	Several times per week	Once or more per day
No requirement of supervision	1	2	3
Temporal requirement of supervision	2	4	6
Permanent requirement of supervision	3	6	9

Contributorship statement: Drs. Sawada and Oeda designed the study and Dr. Sawada wrote the protocol.

Funding: This research received no specific funding.

References

1. Adler CH. Nonmotor complications in Parkinson's disease. *Mov Disord* 2005;20 Suppl 11:S23-9.
2. Maetzler W, Liepelt I, Berg D. Progression of Parkinson's disease in the clinical phase: potential markers. *Lancet neurology* 2009;8(12):1158-71.
3. Clozapine in drug-induced psychosis in Parkinson's disease. The French Clozapine Parkinson Study Group. *Lancet* 1999;353(9169):2041-2.
4. Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. The Parkinson Study Group. *The New England journal of medicine* 1999;340(10):757-63.
5. Breier A, Sutton VK, Feldman PD, Kadam DL, Ferchland I, Wright P, et al. Olanzapine in the treatment of dopamimetic-induced psychosis in patients with Parkinson's disease. *Biological psychiatry* 2002;52(5):438-45.
6. Ondo WG, Tintner R, Voung KD, Lai D, Ringholz G. Double-blind, placebo-controlled, unforced titration parallel trial of quetiapine for dopaminergic-induced hallucinations in Parkinson's disease. *Mov Disord* 2005;20(8):958-63.
7. Rabey JM, Prokhorov T, Miniovitz A, Dobronevsky E, Klein C. Effect of quetiapine in psychotic Parkinson's disease patients: a double-blind labeled study of 3 months' duration. *Mov Disord* 2007;22(3):313-8.
8. Ellis T, Cudkowicz ME, Sexton PM, Growdon JH. Clozapine and risperidone treatment of psychosis in Parkinson's disease. *The Journal of neuropsychiatry and clinical neurosciences* 2000;12(3):364-9.
9. Mesulam MM. Alzheimer plaques and cortical cholinergic innervation. *Neuroscience* 1986;17(1):275-6.
10. Whitehouse PJ, Price DL, Clark AW, Coyle JT, DeLong MR. Alzheimer disease: evidence for selective loss of cholinergic neurons in the nucleus basalis. *Annals of neurology* 1981;10(2):122-6.
11. Bohnen NI, Kaufer DI, Ivanco LS, Lopresti B, Koeppe RA, Davis JG, et al. Cortical cholinergic function is more severely affected in parkinsonian dementia than in Alzheimer disease: an in vivo positron emission tomographic study. *Archives of neurology* 2003;60(12):1745-8.
12. Jellinger KA. Pathology of Parkinson's disease. Changes other than the nigrostriatal pathway. *Molecular and chemical neuropathology / sponsored by the International Society for Neurochemistry and the World Federation of Neurology and research groups on neurochemistry and cerebrospinal fluid* 1991;14(3):153-97.
13. Goetz CG, Leurgans S, Pappert EJ, Raman R, Stemer AB. Prospective longitudinal assessment of hallucinations in Parkinson's disease. *Neurology* 2001;57(11):2078-82.

14. Williams DR, Lees AJ. Visual hallucinations in the diagnosis of idiopathic Parkinson's disease: a retrospective autopsy study. *Lancet neurology* 2005;4(10):605-10.
15. Merims D, Shabtai H, Korczyn AD, Peretz C, Weizman N, Giladi N. Antiparkinsonian medication is not a risk factor for the development of hallucinations in Parkinson's disease. *J Neural Transm* 2004;111(10-11):1447-53.
16. Kawakami Y, Inoue A, Kawai T, Wakita M, Sugimoto H, Hopfinger AJ. The rationale for E2020 as a potent acetylcholinesterase inhibitor. *Bioorganic & medicinal chemistry* 1996;4(9):1429-46.
17. Giacobini E, Zhu XD, Williams E, Sherman KA. The effect of the selective reversible acetylcholinesterase inhibitor E2020 on extracellular acetylcholine and biogenic amine levels in rat cortex. *Neuropharmacology* 1996;35(2):205-11.
18. Nochi S, Asakawa N, Sato T. Kinetic study on the inhibition of acetylcholinesterase by 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl]methylpiperidine hydrochloride (E2020). *Biological & pharmaceutical bulletin* 1995;18(8):1145-7.
19. Kosasa T, Kuriya Y, Matsui K, Yamanishi Y. Effect of donepezil hydrochloride (E2020) on basal concentration of extracellular acetylcholine in the hippocampus of rats. *European journal of pharmacology* 1999;380(2-3):101-7.
20. Kosasa T, Kuriya Y, Yamanishi Y. Effect of donepezil hydrochloride (E2020) on extracellular acetylcholine concentration in the cerebral cortex of rats. *Japanese journal of pharmacology* 1999;81(2):216-22.
21. Manganelli F, Vitale C, Santangelo G, Pisciotta C, Iodice R, Cozzolino A, et al. Functional involvement of central cholinergic circuits and visual hallucinations in Parkinson's disease. *Brain* 2009;132(Pt 9):2350-5.
22. Brandstaedter D, Spieker S, Ulm G, Siebert U, Eichhorn TE, Krieg JC, et al. Development and evaluation of the Parkinson Psychosis Questionnaire A screening-instrument for the early diagnosis of drug-induced psychosis in Parkinson's disease. *Journal of neurology* 2005;252(9):1060-6.
23. Daniel SE, Lees AJ. Parkinson's Disease Society Brain Bank, London: overview and research. *Journal of neural transmission* 1993;39:165-72.

BMJ open

Protocol for a randomized controlled trial: efficacy of donepezil against psychosis in Parkinson's disease (EDAP)

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-003533.R1
Article Type:	Protocol
Date Submitted by the Author:	30-Aug-2013
Complete List of Authors:	Sawada, Hideyuki; Utano National Hospital, Clinical Research Center Oeda, Tomoko; Utano National Hospital, Clinical Research Center
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Neurology, Pharmacology and therapeutics
Keywords:	Parkinson-s disease < NEUROLOGY, Adult neurology < NEUROLOGY, NEUROLOGY

Protocol for a randomized controlled trial: efficacy of donepezil against psychosis in Parkinson's disease (EDAP)

Hideyuki Sawada[1], Tomoko Oeda[1]

Author Affiliations

[1]Clinical Research Center, National Hospital of Utano, Kyoto, Japan

Correspondence to Dr Hideyuki Sawada; sawada@unh.hosp.go.jp

8 Ondoyamacho, Narutaki, Ukyoku, Kyoto, Japan

Phone: +81-75-461-5121, Fax: +81-75-464-0027

Abstract

Introduction: Psychosis, including hallucinations and delusions, is one of the important non-motor problems in patients with Parkinson's disease (PD), and is possibly associated with cholinergic neuronal degeneration. The EDAP (Efficacy of Donepezil against Psychosis in PD) study will evaluate the efficacy of donepezil, a brain acetylcholine esterase inhibitor, for prevention of psychosis in PD.

Methods and analysis: Psychosis is assessed every 4 weeks using the Parkinson Psychosis Questionnaire (PPQ), and PD patients whose PPQ-B score (hallucinations) and PPQ-C score (delusions) have been zero for 8 weeks before enrollment are randomized to two arms: patients receiving donepezil hydrochloride, or patients receiving placebo. The subjects are then followed for 96 weeks. The primary outcome measure is the time to the event, defined as getting 2 points or more on the PPQ-B score or PPQ-C score, which is assessed using a survival time analysis. The hypothesis being tested is that donepezil prevents psychosis in patients with PD. Efficacy will be tested statistically using the intention-to-treat analysis including a Log-rank test and Cox proportional hazard models. Secondary outcomes, such as changes of PPQ scores and UPDRS scores from baseline will be assessed.

Ethics and dissemination: Ethics approval was received from the Central Review Board of the National Hospital Organization, Tokyo, Japan. The trial was declared and registered to the Pharmaceuticals and Medical Devices Agency (PMDA), Japan (No. 22-4018). All participants will receive a written informed consent that was approved by the Central Review. A completed written informed consent is required to enroll in the study. Severe adverse events will be monitored by investigators, and in cases where a severe adverse event was previously unreported, it will be reported to the PMDA.

Clinical Trial Registration Number: UMIN000005403

ARTICLE SUMMARY

Article focus

Given that psychosis is caused by the degeneration of brain cholinergic neurons in patients with Parkinson's disease (PD), an inhibitor of brain acetylcholine esterase such as donepezil hydrochloride may be efficacious in the prevention of psychosis. However, motor symptoms may become worse by donepezil hydrochloride since central anticholinergic drugs such as trihexyphenidyl improve motor symptoms.

A multi-center, randomized, placebo-controlled, double-blinded trial will be conducted to investigate the efficacy of donepezil in the prevention of psychosis. This protocol paper outlines the design, eligibility criteria, methods of data collection, and safety monitoring.

Key messages

The study is a long-term randomized placebo-controlled trial to investigate the prophylactic effects against psychosis in Parkinson disease. The occurrence of psychosis is monitored using the Parkinson Psychosis Questionnaire (PPQ) that is validated for assessment of hallucinations, illusions, and delusions in patients with PD.

Strengths and limitations of this study

In previous randomized controlled trials for psychosis the efficacy was investigated in patients who presented with psychosis, and the primary endpoint was improvement of psychotic symptoms. By comparison, this study is designed to evaluate the prophylactic effect in patients without current psychosis. Because psychosis may be overlooked and underestimated it is assessed using a questionnaire, Parkinson Psychosis Questionnaire (PPQ) every 4 weeks. The strength of this study is its prospective design using the preset definition of psychosis using PPQ (hallucinations/illusion and delusions). However, it could also be a limitation; because other types of psychosis cannot be evaluated. Another limitation is the sample size estimation. Because there have never been any randomized trials for the prevention of psychosis, previous data for sample size estimation were insufficient. To resolve this issue we estimated the sample size based on our previous retrospective cohort study.

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder presenting with motor disturbances, including muscular rigidity, tremor, bradykinesia or postural reflex disturbance. These motor symptoms are caused by the depletion of dopamine in the striatum. Dopamine replacement therapy can improve motor disturbances in PD. However, many patients suffer from psychiatric symptoms, such as hallucinations and delusions, during their long therapy process.[1 2]

In previous studies the efficacy of anti-dopaminergic drugs, including clozapine,[3 4] olanzapine,[5] quetiapine,[6 7] and risperidone[8] was investigated based on the possibility that psychosis may be caused by excessive dopamine replacement therapy. Although the efficacy of clozapine against psychosis without worsening of motor symptoms of PD was established in the French Clozapine Parkinson Study (FCPS)[4] and the PSYCHOPLOS study,[4] clozapine has a risk of granulocytepenia, and requires careful blood cell monitoring. Previous RCTs demonstrated that olanzapine improves psychosis, but there were no significant differences in improvement between the olanzapine groups and the placebo groups. In addition olanzapine worsened motor symptoms in PD compared with placebo.[5] Two other RCTs demonstrated that quetiapine does not worsen motor symptoms; however, its efficacy against psychosis was not superior to placebo.[6 7] A small-sized RCT comparing risperidone and clozapine demonstrated that risperidone improves psychosis as well as clozapine; however, risperidone worsened motor symptoms.[8] There have been no clinical trials regarding other anti-psychotic drugs against psychosis in PD. Taken together anti-dopaminergic drugs, except for clozapine, insufficiently improve psychosis.

Cholinergic neurons of the basal forebrain play an important role in cognitive function, and disruption of the cholinergic system has been proposed in Alzheimer's disease.[9 10] Previous reports demonstrated that the cholinergic neurons are degenerated, as are dopaminergic neurons in PD,[11] suggesting the possibility that psychosis could be caused by cholinergic neuronal damage, but not by dopaminergic replacement therapy.[12]

Previously we investigated the clinical risk factors for psychosis in a retrospective cohort study (unpublished data). In this study, 334 patients with PD were followed until the occurrence of psychosis in 24 months. PD psychosis was significantly associated with the severity of PD, PD duration, and cognitive function. These data demonstrated that psychosis is associated with the severity of the disease and cognitive function and the results are very consistent with previous reports.[13-15] In addition, the influence of medications were analyzed using a case-crossover study comparing medications at the endpoint (occurrence of psychosis or end of the study) and those for 1 or 3 months before the endpoint, and the analysis showed that the use of anti-cholinergic drugs was a significant risk factor for psychosis. In these results psychosis may have been caused by the degeneration of cholinergic neurons and deterioration of cognitive function.

Donepezil hydrochloride is an inhibitor of acetylcholine esterase in brain neurons[16-18] and activates cholinergic neurons.[16 19 20] Manganelli et al. have demonstrated by using a

neurophysiologic technique, the short latency afferent inhibition, a functional involvement of central cholinergic circuits in PD patients with visual hallucinations. [21] In this context donepezil could reduce the risk of psychosis in patients with PD. In this study we will investigate the efficacy of donepezil against psychosis in a multi-center double-blinded placebo-controlled study.

Except for clozapine, in previous placebo-controlled RCTs against psychosis, the ratio of participants who dropped out from the trials was relatively high, ranging from 18%[5] to 50%[7]. A high drop-out ratio is possible due to patient anxiety to be worsened if assigned to placebo. In addition, psychosis may spontaneously improve even if assigned to placebo. These conditions make it difficult to demonstrate significant differences between active drugs and placebo. Therefore, in this study, the main outcome measure is the prophylactic efficacy of donepezil and the efficacy will be analyzed using a survival time analysis.

Because psychosis may be overlooked and underestimated, it is assessed using Parkinson Psychosis Questionnaire (PPQ)[22] given every 4 weeks. The PPQ consists of 4 categorical dimensions, sleep disturbance, hallucinations/illusions, delusions, and orientations. Eligible patients are those whose scores on the PPQ-B (hallucinations /illusion) and PPQ-C (delusion) are zero at least for 8 weeks before enrollment, and the primary endpoint is the occurrence of psychosis that is defined as PPQ-B ≥2 or PPQ-C ≥2, because the situations when PPQ-B or PPQ-C is ≥2 can result in clinically harmful conditions.

To exclude patients with dementia with Lewy bodies (DLB) and PD with dementia, patients with MMSE score less than 24 are excluded. The risk of psychosis is low in patients with an H-Y stage of 2 or less and the evaluation of psychosis is difficult in patients with H-Y stage of 5. Therefore, patients with H-Y stage of 1–2 or 5 are excluded. The length of time to the occurrence of psychosis is compared between subjects who were prescribed placebo and those who were prescribed donepezil.

Hypothesis to be examined in the study

Psychosis may be caused by dysfunction of brain cholinergic neurons. We examine the hypothesis that donepezil prevents psychosis in patients with PD.

METHODS AND ANALYSIS

Study design

A multicenter, double-blinded, placebo-controlled, randomized trial. A two arm study.

Sites where the study is performed

Eight hospitals of the National Hospital Organization: Utano National Hospital, Hokkaido Medical Center, Sagamihara National Hospital, Shizuoka Institute of Epilepsy and Neurological Disorders, Kyoto Medical Center, Minami Kyoto Hospital, Toneyama National Hospital, and Nagasaki Kawatana Medical Center.

Eligibility criteria

Eligibility

Eligible patients are those who satisfy all of the following criteria and who do not have any of the listed exclusion criteria.

Inclusion criteria

1) PD: Diagnosis of PD according to Steps 1 and 2 of the United Kingdom Brain Bank Parkinson's Disease Diagnostic Criteria.[23]
2) Modified H-Y grades from 2.5 to 4.0, in 'ON' period if patients suffer from motor fluctuation.
3) Psychosis: During the 8 weeks before the study enrollment (V2), there has been no evidence of psychosis that is defined in the Parkinson Psychosis Questionnaire; the answers to questions B (hallucinations /illusions) and C (delusions) are none (score 0) at both Visit 1 (V1) and V2.
4) Cognitive function: The score on the MMSE is 24 or more at both V1 and V2.
5) Either in-patients or out-patients.
6) Sex: Males and females can be enrolled. Females of child-bearing age can be enrolled if a pregnancy test is negative and she agrees to avoid getting pregnant during the study.
7) Age: Patients are between the ages of 20 and 79 years (inclusive) when giving consent.
8) The purpose and methods of the trial are explained, and a written informed consent is obtained.
9) Patients who can follow the protocol, will consent to examination and will provide information on their symptoms.

Exclusion criteria

1) Patients who have previously taken donepezil hydrochloride.
2) Patients who took the following anti-cholinergic drugs in the preceding 4 weeks before V2; trihexyphenidyl, biperiden, profenamine, piroheptine, metixene, mazaticol, promethazine, or cyproheptadine.

3) Patients who took Tsumura No. 54 (Yoku-Kansan) in the preceding 4 weeks before V2.
4) Patients who took antipsychotics in the preceding 12 weeks before V2.
5) Patients who fulfill the criteria of probable DLB according to the revised criteria for the clinical diagnosis of DLB in the third report of the DLB consortium.
6) Patients who have previously been diagnosed with schizophrenia.
7) Patients who have previously had stereotactic brain surgery.
8) Patients who are or were allergic to piperidine derivatives.
9) Patients with severe hepatic or renal dysfunction.
10) Patients with sick sinus syndrome or cardiac conduction block in the atrium or of the atrioventricular junction (sinoatrial block or AV block of 2 degrees or more).
11) Patients with present or past severe bronchial asthma, severe peptic ulcer, or severe obstructive pulmonary disorders.
12) Patients with bradycardia <45/min in ECG at V1.
13) Patients with a QTc >460 msec in ECG at V1.
14) Patients who are pregnant.
15) Patients who participated in other clinical trials in 12 weeks before V2.
16) Patients who are diagnosed with a malignancy.
17) Patients who are judged as inappropriate for the study.

Concomitant medications and restricted medications

During the study periods the flowing drugs are not permitted:

1) Central anti-cholinergic drugs.
2) Anti-psychotic drugs.
3) Inhibitors of brain acetylcholine esterase.
4) NMDA receptor antagonists.
5) Tsumura kampo medicine No. 54 (Yoku-Kansan).
6) Study drugs except for the EDAP study drug.

Definition of psychosis

In this study, psychosis is monitored every 4 weeks using the PPQ-B (hallucinations/illusions) and PP-C (delusions). In determining the cut-off points for PPQ-B and PPQ-C, we think that the lower threshold (or mild psychosis) is better for this trial because of the following three reasons: 1) a lower threshold will allow for higher statistical power in the limited-size trials; 2) higher threshold (or severe psychosis) will make the interpretation of trial results difficult because investigators will reduce dopaminergic drugs even if mild psychosis occurs, prior to worsening of psychosis; 3) a higher threshold is difficult to set because of the concern over safety of the subjects (severe psychosis will be documented as a severe adverse event in the trial). A condition where the PPQ-B or PPQ-C score is 2 or higher is harmful to daily living. A condition with PPQ-B or PPQ-C ≥1 would not always be harmful to daily living and may also be encountered under healthy conditions. Therefore, in this study, psychosis is defined as PPQ-B or PPQ-C ≥2.

The first occurrence of psychosis:
To specify the date of the first occurrence of psychosis, patients and their care-givers are requested to fill a diary on visual or auditory hallucinations or illusions. If the date of the occurrence of psychosis cannot be specified by the diary, midpoint between the last visit and the current visit will be regarded as the date of psychosis occurrence.

Sample size calculation

In our previous study that followed patients with PD, about 20% patients required anti-psychotic medications because of psychosis that was defined as the use of anti-psychotics (unpublished data). In EDAP trial the definition of psychosis is defined according to the PPQ-B (Hallucinations /illusions) and PPQ-C (Delusions) because of a high inter-rater reliability of the PPQ. According to the definition of psychosis in this study (PPQ-B ≥2 or PPQ-C ≥2), we assumed that the cumulative occurrence of psychosis as 45% in the placebo group. According to the previous study, the use of donepezil hydrochloride will reduce the risk of psychosis occurrence by 0.5, and therefore, the cumulative occurrence of psychosis would be 22.5% in the active group. The sample size was calculated on the condition that alpha is 0.05 (bilateral), power is 0.8, and the statistical test is the Log rank test. The sample size was calculated as 84 in each group and 142 in the total subjects.

Allocation

Eligibility is checked at V1 according to inclusion and exclusion criteria. Additionally, scoring of PPQ-A, B, C, and D is performed at V2, and we will confirm eligibility, including that both the PPQ-B and PPQ-C scores are zero at V2. The allocation will be done with stratification of the subjects according to sex (male and female) and modified H-Y (2.5-3.0 and 4.0), because the rate of psychosis is associated with sex and H-Y grades.

Observations

V1 Screening

At V1 the following tests or examinations will be done:

1. PPQ.
2. Modified H-Y.
3. MMSE.
4. Peripheral blood sampling, urine analysis, and ECG.
5. Urine hCG pregnancy test if the participant is non-menopausal or within 1 year from menopause.
6. Body weight, height.
7. Onset of PD, history of hallucinations, delusions, or impulse control disorders.
8. Smoking.

V2 Enrollment

At V2 the following tests and examination will be done:

1. PPQ.
2. Epworth Sleeping Score (Japanese version).

3. UPDRS I, II, III and IV.

The following examinations will be performed between V2 and V3:

1. Frontal lobe Assessment Battery (FAB).
2. Revised version of Wechsler Memory Scale (WMS-R).

The following examinations will be performed limited to participants from Utano National Hospital between V2 and V3:

1. EEG.
2. Cerebral blood flow scintigram using ^{123}I-amphetamine.
3. MRI volumetry of the brain.

V3

At V3 the study drug (3mg) will be prescribed.

V4

At V4 PPQ will be examined. Study drug (5mg) will start to be prescribed after confirming safety.

V5

At V5 the following tests and examinations will be done:

1. PPQ.
2. UPDRS-III, and modified H-Y.
3. JESS.
4. Peripheral blood sampling, urinary analysis, ECG. Urinary pregnancy test if required.

V6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26

1. PPQ. PPQ can be performed by telephone interview.

V7, 11, 13, 17, 19, 23, 25

1. PPQ.
2. UPDRS-III, and modified H-Y.
3. JESS.
4. Peripheral blood sampling, urinary analysis, ECG. Urinary pregnancy test if required.

V9, 15, 21

1. PPQ.
2. UPDRS-III, and modified H-Y.
3. JESS.
4. Peripheral blood sampling, urinary analysis, ECG. Urinary pregnancy test if required.
5. MMSE, FAB, WMS-R.

V27

1. PPQ.
2. UPDRS-I, II, III, IV and modified H-Y.

3. JESS.
4. Peripheral blood sampling, urinary analysis, ECG. Urinary pregnancy test if required.
5. MMSE, FAB, WMS-R.

Apolipoprotein genotype will be examined if the subject gives consent for the genotyping, because the ε4 genotype may reduce the efficacy of donepezil in Alzheimer's disease.

Compliance rate of the investigational product will be monitored at every visit. Dose of drugs prescribed (including drugs for PD and other medical conditions) will be collected at every visit.

Study period and definition of endpoint

The study period is from the start of administration of the investigational product (donepezil or placebo) to the endpoint, and the longest observation period is 96 weeks.

Endpoint is the occurrence of psychosis or termination of observation. Psychosis is defined as a score of 2 or more on the PPQ-B or PPQ-C (if any answer to questions in PPQ-B or PPQ-C is yes, and the frequency or the severity is 2 or more) that is shown in the yellow area in Table 1.

Primary outcome measure and statistical analysis

Primary outcome measure is the time to the occurrence of psychosis from V2 during 48 weeks. The time length to the occurrence of psychosis will be compared between the placebo and the donepezil groups and the difference will be statistically examined using the log rank test. Kaplan-Meier survival curves will be obtained from the data of the placebo and donepezil groups.

Secondary outcome measures

The following data will be obtained and compared between the placebo and donepezil groups as secondary outcome measure:

1. Time to the occurrence of the first psychosis from V2 during 24 weeks.
2. The proportion of participants with psychosis to total participants. The comparison will be analyzed using a statistical model.
3. PPQ score, and the changes of MMSE, WMS-R, FAB from the baseline at V9.
4. PPQ score, and the changes of MMSE, WMS-R, FAB from the baseline at V15.
5. PPQ score, and the changes of MMSE, WMS-R, FAB from the baseline at V21.
6. PPQ score, and the changes of MMSE, WMS-R, FAB from the baseline at V27.
7. Subgroup analysis of the primary and secondary outcome measures by genotype of apolipoprotein E.
8. Secondary measure limited to Utano National Hospital
   - 8-1) I^{123}-iodo-amphetamine brain scintigram at the endpoint. The comparison will be performed by a 3D-SSP method.
   - 8-2) The grand total score of EEG at the endpoint.

Safety

Patients will be requested to report any adverse events. All adverse events that are still present must be followed up until their disappearance or no further requirement of follow-up. Severe adverse events will be monitored by investigators, and in cases where a severe adverse event was previously unreported, it will be reported to the PMDA. To detect QT time elongation ECG will be performed every 8 weeks. Complete blood cell count and laboratory data including hepatic and renal functions will be tested every 8 weeks.

ETHICS AND DISSEMINATION

Ethics approval was received from the Central Review Board of the National Hospital Organization. The trial was declared and registered to the Pharmaceuticals and Medical Devices Agency (PMDA), Japan (No. 22-4018). According to “Good Clinical Practice (GCP)” released from the Minister of Health, Labor and Welfare, all participants will receive a written informed consent that was approved by the Central Review. A completed written informed consent is required to enroll in the study.

Severe adverse events will be monitored by investigators. All severe adverse events will be reported to all investigators via a Web-based electric data capturing system and be discussed. In cases where a severe adverse event was previously unreported, it will be reported to the PMDA according to the GCP guideline. The trial was registered in UMIN Clinical Trials Registry (UMIN-CTR; UMIN000005403).

The key-code table that contains allocation data is made by a key-holder who will not participate in the study, using a computer program. It is concealed from other personnel until key-opening by the key-holder.

Table Multiplicative PPQ score

A Early symtoms /sleep disturbnace

severity	Frequency: Up to once per week	Several times per week	Once or more per day
Not or slightly affecting well-being	1	2	3
Moderately affecting well-being	2	4	6
Severely affecting well-being	3	6	9

B. Hallucinations /illusions

severity	Frequency: Only during the night	During the night & occasionally during the day	Almost every day & night
Insight retained	1	2	3
No full insight	2	4	6
Lacking insight	3	6	9

C. Dellusions

severity	Frequency: Up to once per week	Several times per week	Once or more per day
Withoug affecting the social enviroment	1	2	3
Affecting the patient by emotional distress	2	4	6
Affecting the patient by accusation, agression, or lack of cooperation	3	6	9

D. Orientation

severity	Frequency: Up to once per week	Several times per week	Once or more per day
No requirement of supervision	1	2	3
Temporal requirement of supervision	2	4	6
Permanent requirement of supervision	3	6	9

Funding

This paper received no specific funding.

Competing interest

There are no competing interests.

Contributoship statement

Drs. Sawada and Oeda designed the study and Dr. Sawada wrote the protocol.

References

1. Adler CH. Nonmotor complications in Parkinson's disease. *Mov Disord* 2005;20 Suppl 11:S23-9.
2. Maetzler W, Liepelt I, Berg D. Progression of Parkinson's disease in the clinical phase: potential markers. *Lancet neurology* 2009;8(12):1158-71.
3. Clozapine in drug-induced psychosis in Parkinson's disease. The French Clozapine Parkinson Study Group. *Lancet* 1999;353(9169):2041-2.
4. Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. The Parkinson Study Group. *The New England journal of medicine* 1999;340(10):757-63.
5. Breier A, Sutton VK, Feldman PD, et al. Olanzapine in the treatment of dopamimetic-induced psychosis in patients with Parkinson's disease. *Biological psychiatry* 2002;52(5):438-45.
6. Ondo WG, Tintner R, Voung KD, et al. Double-blind, placebo-controlled, unforced titration parallel trial of quetiapine for dopaminergic-induced hallucinations in Parkinson's disease. *Mov Disord* 2005;20(8):958-63.
7. Rabey JM, Prokhorov T, Miniovitz A, et al. Effect of quetiapine in psychotic Parkinson's disease patients: a double-blind labeled study of 3 months' duration. *Mov Disord* 2007;22(3):313-8.
8. Ellis T, Cudkowicz ME, Sexton PM, et al. Clozapine and risperidone treatment of psychosis in Parkinson's disease. *The Journal of neuropsychiatry and clinical neurosciences* 2000;12(3):364-9.
9. Mesulam MM. Alzheimer plaques and cortical cholinergic innervation. *Neuroscience* 1986;17(1):275-6.
10. Whitehouse PJ, Price DL, Clark AW, et al. Alzheimer disease: evidence for selective loss of cholinergic neurons in the nucleus basalis. *Annals of neurology* 1981;10(2):122-6.
11. Bohnen NI, Kaufer DI, Ivanco LS, et al. Cortical cholinergic function is more severely affected in parkinsonian dementia than in Alzheimer disease: an in vivo positron emission tomographic study. *Archives of neurology* 2003;60(12):1745-8.
12. Jellinger KA. Pathology of Parkinson's disease. Changes other than the nigrostriatal pathway. *Molecular and chemical neuropathology / sponsored by the International Society for Neurochemistry and the World Federation of Neurology and research groups on neurochemistry and cerebrospinal fluid* 1991;14(3):153-97.

13. Goetz CG, Leurgans S, Pappert EJ, et al. Prospective longitudinal assessment of hallucinations in Parkinson's disease. *Neurology* 2001;57(11):2078-82.
14. Williams DR, Lees AJ. Visual hallucinations in the diagnosis of idiopathic Parkinson's disease: a retrospective autopsy study. *Lancet neurology* 2005;4(10):605-10.
15. Merims D, Shabtai H, Korczyn AD, et al. Antiparkinsonian medication is not a risk factor for the development of hallucinations in Parkinson's disease. *J Neural Transm* 2004;111(10-11):1447-53.
16. Kawakami Y, Inoue A, Kawai T, et al. The rationale for E2020 as a potent acetylcholinesterase inhibitor. *Bioorganic & medicinal chemistry* 1996;4(9):1429-46.
17. Giacobini E, Zhu XD, Williams E, et al. The effect of the selective reversible acetylcholinesterase inhibitor E2020 on extracellular acetylcholine and biogenic amine levels in rat cortex. *Neuropharmacology* 1996;35(2):205-11.
18. Nochi S, Asakawa N, Sato T. Kinetic study on the inhibition of acetylcholinesterase by 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl]methylpiperidine hydrochloride (E2020). *Biological & pharmaceutical bulletin* 1995;18(8):1145-7.
19. Kosasa T, Kuriya Y, Matsui K, et al. Effect of donepezil hydrochloride (E2020) on basal concentration of extracellular acetylcholine in the hippocampus of rats. *European journal of pharmacology* 1999;380(2-3):101-7.
20. Kosasa T, Kuriya Y, Yamanishi Y. Effect of donepezil hydrochloride (E2020) on extracellular acetylcholine concentration in the cerebral cortex of rats. *Japanese journal of pharmacology* 1999;81(2):216-22.
21. Manganelli F, Vitale C, Santangelo G, et al. Functional involvement of central cholinergic circuits and visual hallucinations in Parkinson's disease. *Brain* 2009;132(Pt 9):2350-5.
22. Brandstaedter D, Spieker S, Ulm G, et al. Development and evaluation of the Parkinson Psychosis Questionnaire A screening-instrument for the early diagnosis of drug-induced psychosis in Parkinson's disease. *Journal of neurology* 2005;252(9):1060-6.
23. Daniel SE, Lees AJ. Parkinson's Disease Society Brain Bank, London: overview and research. *Journal of neural transmission* 1993;39:165-72.

Protocol for a randomized controlled trial: efficacy of donepezil against psychosis in Parkinson's disease (EDAP)

Hideyuki Sawada[1], Tomoko Oeda[1]

Author Affiliations

[1]Clinical Research Center, National Hospital of Utano, Kyoto, Japan

Correspondence to Dr Hideyuki Sawada; sawada@unh.hosp.go.jp

8 Ondoyamacho, Narutaki, Ukyoku, Kyoto, Japan

Phone: +81-75-461-5121, Fax: +81-75-464-0027

Abstract

Introduction: Psychosis, including hallucinations and delusions, is one of the important non-motor problems in patients with Parkinson's disease (PD), and is possibly associated with cholinergic neuronal degeneration. The EDAP (Efficacy of Donepezil against Psychosis in PD) study will evaluate the efficacy of donepezil, a brain acetylcholine esterase inhibitor, for prevention of psychosis in PD.

Methods and analysis: Psychosis is assessed every 4 weeks using the Parkinson Psychosis Questionnaire (PPQ), and PD patients whose PPQ-B score (hallucinations) and PPQ-C score (delusions) have been zero for 8 weeks before enrollment are randomized to two arms: patients receiving donepezil hydrochloride, or patients receiving placebo. The subjects are then followed for 96 weeks. The primary outcome measure is the time to the event, defined as getting 2 points or more on the PPQ-B score or PPQ-C score, which is assessed using a survival time analysis. The hypothesis being tested is that donepezil prevents psychosis in patients with PD. Efficacy will be tested statistically using the intention-to-treat analysis including a Log-rank test and Cox proportional hazard models. Secondary outcomes, such as changes of PPQ scores and UPDRS scores from baseline will be assessed.

Ethics and dissemination: Ethics approval was received from the Central Review Board of the National Hospital Organization, Tokyo, Japan. The trial was declared and registered to the Pharmaceuticals and Medical Devices Agency (PMDA), Japan (No. 22-4018). All participants will receive a written informed consent that was approved by the Central Review. A completed written informed consent is required to enroll in the study. Severe adverse events will be monitored by investigators, and in cases where a severe adverse event was previously unreported, it will be reported to the PMDA.

Clinical Trial Registration Number: UMIN000005403

ARTICLE SUMMARY

Article focus

Given that psychosis is caused by the degeneration of brain cholinergic neurons in patients with Parkinson's disease (PD), an inhibitor of brain acetylcholine esterase such as donepezil hydrochloride may be efficacious in the prevention of psychosis. However, motor symptoms may become worse by donepezil hydrochloride since central anticholinergic drugs such as trihexyphenidyl improve motor symptoms.

A multi-center, randomized, placebo-controlled, double-blinded trial will be conducted to investigate the efficacy of donepezil in the prevention of psychosis. This protocol paper outlines the design, eligibility criteria, methods of data collection, and safety monitoring.

Key messages

The study is a long-term randomized placebo-controlled trial to investigate the prophylactic effects against psychosis in Parkinson disease. The occurrence of psychosis is monitored using the Parkinson Psychosis Questionnaire (PPQ) that is validated for assessment of hallucinations, illusions, and delusions in patients with PD.

Strengths and limitations of this study

In previous randomized controlled trials for psychosis the efficacy was investigated in patients who presented with psychosis, and the primary endpoint was improvement of psychotic symptoms. By comparison, this study is designed to evaluate the prophylactic effect in patients without current psychosis. Because psychosis may be overlooked and underestimated it is assessed using a questionnaire, Parkinson Psychosis Questionnaire (PPQ) every 4 weeks. The strength of this study is its prospective design using the preset definition of psychosis using PPQ (hallucinations/illusion and delusions). However, it could also be a limitation; because other types of psychosis cannot be evaluated. Another limitation is the sample size estimation. Because there have never been any randomized trials for the prevention of psychosis, previous data for sample size estimation were insufficient. To resolve this issue we estimated the sample size based on our previous retrospective cohort study.

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder presenting with motor disturbances, including muscular rigidity, tremor, bradykinesia or postural reflex disturbance. These motor symptoms are caused by the depletion of dopamine in the striatum. Dopamine replacement therapy can improve motor disturbances in PD. However, many patients suffer from psychiatric symptoms, such as hallucinations and delusions, during their long therapy process.[1 2]

In previous studies the efficacy of anti-dopaminergic drugs, including clozapine,[3 4] olanzapine,[5] quetiapine,[6 7] and risperidone[8] was investigated based on the possibility that psychosis may be caused by excessive dopamine replacement therapy. Although the efficacy of clozapine against psychosis without worsening of motor symptoms of PD was established in the French Clozapine Parkinson Study (FCPS)[4] and the PSYCHOPLOS study,[4] clozapine has a risk of granulocytepenia, and requires careful blood cell monitoring. Previous RCTs demonstrated that olanzapine improves psychosis, but there were no significant differences in improvement between the olanzapine groups and the placebo groups. In addition olanzapine worsened motor symptoms in PD compared with placebo.[5] Two other RCTs demonstrated that quetiapine does not worsen motor symptoms; however, its efficacy against psychosis was not superior to placebo.[6 7] A small-sized RCT comparing risperidone and clozapine demonstrated that risperidone improves psychosis as well as clozapine; however, risperidone worsened motor symptoms.[8] There have been no clinical trials regarding other anti-psychotic drugs against psychosis in PD. Taken together anti-dopaminergic drugs, except for clozapine, insufficiently improve psychosis.

Cholinergic neurons of the basal forebrain play an important role in cognitive function, and disruption of the cholinergic system has been proposed in Alzheimer's disease.[9 10] Previous reports demonstrated that the cholinergic neurons are degenerated, as are dopaminergic neurons in PD,[11] suggesting the possibility that psychosis could be caused by cholinergic neuronal damage, but not by dopaminergic replacement therapy.[12]

Previously we investigated the clinical risk factors for psychosis in a retrospective cohort study (unpublished data). In this study, 334 patients with PD were followed until the occurrence of psychosis in 24 months. PD psychosis was significantly associated with the severity of PD, PD duration, and cognitive function. These data demonstrated that psychosis is associated with the severity of the disease and cognitive function and the results are very consistent with previous reports.[13-15] In addition, the influence of medications were analyzed using a case-crossover study comparing medications at the endpoint (occurrence of psychosis or end of the study) and those for 1 or 3 months before the endpoint, and the analysis showed that the use of anti-cholinergic drugs was a significant risk factor for psychosis. In these results psychosis may have been caused by the degeneration of cholinergic neurons and deterioration of cognitive function.

Donepezil hydrochloride is an inhibitor of acetylcholine esterase in brain neurons[16-18] and activates cholinergic neurons.[16 19 20] Manganelli et al. have demonstrated by using a neurophysiologic technique, the short latency afferent inhibition, a functional involvement of central cholinergic circuits in PD patients with visual hallucinations. [21] In this context donepezil

could reduce the risk of psychosis in patients with PD.[21] In this study we will investigate the efficacy of donepezil against psychosis in a multi-center double-blinded placebo-controlled study.

Except for clozapine, in previous placebo-controlled RCTs against psychosis, the ratio of participants who dropped out from the trials was relatively high, ranging from 18%[5] to 50%[7]. A high drop-out ratio is possible due to patient anxiety to be worsened if assigned to placebo. In addition, psychosis may spontaneously improve even if assigned to placebo. These conditions make it difficult to demonstrate significant differences between active drugs and placebo. Therefore, in this study, the main outcome measure is the prophylactic efficacy of donepezil and the efficacy will be analyzed using a survival time analysis.

Because psychosis may be overlooked and underestimated, it is assessed using Parkinson Psychosis Questionnaire (PPQ)[22] given every 4 weeks. The PPQ consists of 4 categorical dimensions, sleep disturbance, hallucinations/illusions, delusions, and orientations. Eligible patients are those whose scores on the PPQ-B (hallucinations /illusion) and PPQ-C (delusion) are zero at least for 8 weeks before enrollment, and the primary endpoint is the occurrence of psychosis that is defined as PPQ-B ≥2 or PPQ-C ≥2, because the situations when PPQ-B or PPQ-C is ≥2 can result in clinically harmful conditions.

To exclude patients with dementia with Lewy bodies (DLB) and PD with dementia, patients with MMSE score less than 24 are excluded. The risk of psychosis is low in patients with an H-Y stage of 2 or less and the evaluation of psychosis is difficult in patients with H-Y stage of 5. Therefore, patients with H-Y stage of 1–2 or 5 are excluded. The length of time to the occurrence of psychosis is compared between subjects who were prescribed placebo and those who were prescribed donepezil.

Hypothesis to be examined in the study

Psychosis may be caused by dysfunction of brain cholinergic neurons. We examine the hypothesis that donepezil prevents psychosis in patients with PD.

METHODS AND ANALYSIS

Study design

A multicenter, double-blinded, placebo-controlled, randomized trial. A two arm study.

Sites where the study is performed

Eight hospitals of the National Hospital Organization: Utano National Hospital, Hokkaido Medical Center, Sagamihara National Hospital, Shizuoka Institute of Epilepsy and Neurological Disorders, Kyoto Medical Center, Minami Kyoto Hospital, Toneyama National Hospital, and Nagasaki Kawatana Medical Center.

Eligibility criteria

Eligibility

Eligible patients are those who satisfy all of the following criteria and who do not have any of the listed exclusion criteria.

Inclusion criteria

1) PD: Diagnosis of PD according to Steps 1 and 2 of the United Kingdom Brain Bank Parkinson's Disease Diagnostic Criteria.[23]
2) Modified H-Y grades from 2.5 to 4.0, in 'ON' period if patients suffer from motor fluctuation.
3) Psychosis: During the 8 weeks before the study enrollment (V2), there has been no evidence of psychosis that is defined in the Parkinson Psychosis Questionnaire; the answers to questions B (hallucinations /illusions) and C (delusions) are none (score 0) at both Visit 1 (V1) and V2.
4) Cognitive function: The score on the MMSE is 24 or more at both V1 and V2.
5) Either in-patients or out-patients.
6) Sex: Males and females can be enrolled. Females of child-bearing age can be enrolled if a pregnancy test is negative and she agrees to avoid getting pregnant during the study.
7) Age: Patients are between the ages of 20 and 79 years (inclusive) when giving consent.
8) The purpose and methods of the trial are explained, and a written informed consent is obtained.
9) Patients who can follow the protocol, will consent to examination and will provide information on their symptoms.

Exclusion criteria

1) Patients who have previously taken donepezil hydrochloride.
2) Patients who took the following anti-cholinergic drugs in the preceding 4 weeks before V2; trihexyphenidyl, biperiden, profenamine, piroheptine, metixene, mazaticol, promethazine, or cyproheptadine.
3) Patients who took Tsumura No. 54 (Yoku-Kansan) in the preceding 4 weeks before V2.

4) Patients who took antipsychotics in the preceding 12 weeks before V2.
5) Patients who fulfill the criteria of probable DLB according to the revised criteria for the clinical diagnosis of DLB in the third report of the DLB consortium.
6) Patients who have previously been diagnosed with schizophrenia.
7) Patients who have previously had stereotactic brain surgery.
8) Patients who are or were allergic to piperidine derivatives.
9) Patients with severe hepatic or renal dysfunction.
10) Patients with sick sinus syndrome or cardiac conduction block in the atrium or of the atrioventricular junction (sinoatrial block or AV block of 2 degrees or more).
11) Patients with present or past severe bronchial asthma, severe peptic ulcer, or severe obstructive pulmonary disorders.
12) Patients with bradycardia <45/min in ECG at V1.
13) Patients with a QTc >460 msec in ECG at V1.
14) Patients who are pregnant.
15) Patients who participated in other clinical trials in 12 weeks before V2.
16) Patients who are diagnosed with a malignancy.
17) Patients who are judged as inappropriate for the study.

Concomitant medications and restricted medications

During the study periods the flowing drugs are not permitted:

1) Central anti-cholinergic drugs.
2) Anti-psychotic drugs.
3) Inhibitors of brain acetylcholine esterase.
4) NMDA receptor antagonists.
5) Tsumura kampo medicine No. 54 (Yoku-Kansan).
6) Study drugs except for the EDAP study drug.

Definition of psychosis

In this study, psychosis is monitored every 4 weeks using the PPQ-B (hallucinations/illusions) and PP-C (delusions). In determining the cut-off points for PPQ-B and PPQ-C, we think that the lower threshold (or mild psychosis) is better for this trial because of the following three reasons: 1) a lower threshold will allow for higher statistical power in the limited-size trials; 2) higher threshold (or severe psychosis) will make the interpretation of trial results difficult because investigators will reduce dopaminergic drugs even if mild psychosis occurs, prior to worsening of psychosis; 3) a higher threshold is difficult to set because of the concern over safety of the subjects (severe psychosis will be documented as a severe adverse event in the trial). A condition where the PPQ-B or PPQ-C score is 2 or higher is harmful to daily living. A condition with PPQ-B or PPQ-C ≥1 would not always be harmful to daily living and may also be encountered under healthy conditions. Therefore, in this study, psychosis is defined as PPQ-B or PPQ-C ≥2.

The first occurrence of psychosis:

To specify the date of the first occurrence of psychosis, patients and their care-givers are requested to fill a diary on visual or auditory hallucinations or illusions. If the date of the occurrence of psychosis cannot be specified by the diary, midpoint between the last visit and the current visit will be regarded as the date of psychosis occurrence.

Sample size calculation

In our previous study that followed patients with PD, about 20% patients required anti-psychotic medications because of psychosis that was defined as the use of anti-psychotics (unpublished data). In EDAP trial the definition of psychosis is defined according to the PPQ-B (Hallucinations /illusions) and PPQ-C (Delusions) because of a high inter-rater reliability of the PPQ. According to the definition of psychosis in this study (PPQ-B ≥2 or PPQ-C ≥2), we assumed that the cumulative occurrence of psychosis as 45% in the placebo group. According to the previous study, the use of donepezil hydrochloride will reduce the risk of psychosis occurrence by 0.5, and therefore, the cumulative occurrence of psychosis would be 22.5% in the active group. The sample size was calculated on the condition that alpha is 0.05 (bilateral), power is 0.8, and the statistical test is the Log rank test. The sample size was calculated as 84 in each group and 142 in the total subjects.

Allocation

Eligibility is checked at V1 according to inclusion and exclusion criteria. Additionally, scoring of PPQ-A, B, C, and D is performed at V2, and we will confirm eligibility, including that both the PPQ-B and PPQ-C scores are zero at V2. The allocation will be done with stratification of the subjects according to sex (male and female) and modified H-Y (2.5-3.0 and 4.0), because the rate of psychosis is associated with sex and H-Y grades.

Observations

V1 Screening

At V1 the following tests or examinations will be done:

1. PPQ.
2. Modified H-Y.
3. MMSE.
4. Peripheral blood sampling, urine analysis, and ECG.
5. Urine hCG pregnancy test if the participant is non-menopausal or within 1 year from menopause.
6. Body weight, height.
7. Onset of PD, history of hallucinations, delusions, or impulse control disorders.
8. Smoking.

V2 Enrollment

At V2 the following tests and examination will be done:

1. PPQ.
2. Epworth Sleeping Score (Japanese version).
3. UPDRS I, II, III and IV.

The following examinations will be performed between V2 and V3:

1. Frontal lobe Assessment Battery (FAB).
2. Revised version of Wechsler Memory Scale (WMS-R).

The following examinations will be performed limited to participants from Utano National Hospital between V2 and V3:

1. EEG.
2. Cerebral blood flow scintigram using ^{123}I-amphetamine.
3. MRI volumetry of the brain.

V3

At V3 the study drug (3mg) will be prescribed.

V4

At V4 PPQ will be examined. Study drug (5mg) will start to be prescribed after confirming safety.

V5

At V5 the following tests and examinations will be done:

1. PPQ.
2. UPDRS-III, and modified H-Y.
3. JESS.
4. Peripheral blood sampling, urinary analysis, ECG. Urinary pregnancy test if required.

V6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26

1. PPQ. PPQ can be performed by telephone interview.

V7, 11, 13, 17, 19, 23, 25

1. PPQ.
2. UPDRS-III, and modified H-Y.
3. JESS.
4. Peripheral blood sampling, urinary analysis, ECG. Urinary pregnancy test if required.

V9, 15, 21

1. PPQ.
2. UPDRS-III, and modified H-Y.
3. JESS.
4. Peripheral blood sampling, urinary analysis, ECG. Urinary pregnancy test if required.
5. MMSE, FAB, WMS-R.

V27

1. PPQ.
2. UPDRS-I, II, III, IV and modified H-Y.
3. JESS.
4. Peripheral blood sampling, urinary analysis, ECG. Urinary pregnancy test if required.

5. MMSE, FAB, WMS-R.

Apolipoprotein genotype will be examined if the subject gives consent for the genotyping, because the ε4 genotype may reduce the efficacy of donepezil in Alzheimer's disease.

Compliance rate of the investigational product will be monitored at every visit. Dose of drugs prescribed (including drugs for PD and other medical conditions) will be collected at every visit.

Study period and definition of endpoint

The study period is from the start of administration of the investigational product (donepezil or placebo) to the endpoint, and the longest observation period is 96 weeks.

Endpoint is the occurrence of psychosis or termination of observation. Psychosis is defined as a score of 2 or more on the PPQ-B or PPQ-C (if any answer to questions in PPQ-B or PPQ-C is yes, and the frequency or the severity is 2 or more) that is shown in the yellow area in Table 1.

Primary outcome measure and statistical analysis

Primary outcome measure is the time to the occurrence of psychosis from V2 during 48 weeks. The time length to the occurrence of psychosis will be compared between the placebo and the donepezil groups and the difference will be statistically examined using the log rank test. Kaplan-Meier survival curves will be obtained from the data of the placebo and donepezil groups.

Secondary outcome measures

The following data will be obtained and compared between the placebo and donepezil groups as secondary outcome measure:

1. Time to the occurrence of the first psychosis from V2 during 24 weeks.
2. The proportion of participants with psychosis to total participants. The comparison will be analyzed using a statistical model.
3. PPQ score, and the changes of MMSE, WMS-R, FAB from the baseline at V9.
4. PPQ score, and the changes of MMSE, WMS-R, FAB from the baseline at V15.
5. PPQ score, and the changes of MMSE, WMS-R, FAB from the baseline at V21.
6. PPQ score, and the changes of MMSE, WMS-R, FAB from the baseline at V27.
7. Subgroup analysis of the primary and secondary outcome measures by genotype of apolipoprotein E.
8. Secondary measure limited to Utano National Hospital
   - 8-1) I^{123}-iodo-amphetamine brain scintigram at the endpoint. The comparison will be performed by a 3D-SSP method.
   - 8-2) The grand total score of EEG at the endpoint.

Safety

Patients will be requested to report any adverse events. All adverse events that are still present must be followed up until their disappearance or no further requirement of follow-up. Severe adverse events will be monitored by investigators, and in cases where a severe adverse event was previously unreported, it will be reported to the PMDA. To detect QT time elongation ECG will be performed every 8 weeks. Complete blood cell count and laboratory data including hepatic and renal functions will be tested every 8 weeks.

ETHICS AND DISSEMINATION

Ethics approval was received from the Central Review Board of the National Hospital Organization. The trial was declared and registered to the Pharmaceuticals and Medical Devices Agency (PMDA), Japan (No. 22-4018). According to “Good Clinical Practice (GCP)” released from the Minister of Health, Labor and Welfare, all participants will receive a written informed consent that was approved by the Central Review. A completed written informed consent is required to enroll in the study.

Severe adverse events will be monitored by investigators. All severe adverse events will be reported to all investigators via a Web-based electric data capturing system and be discussed. In cases where a severe adverse event was previously unreported, it will be reported to the PMDA according to the GCP guideline. The trial was registered in UMIN Clinical Trials Registry (UMIN-CTR; UMIN000005403).

The key-code table that contains allocation data is made by a key-holder who will not participate in the study, using a computer program. It is concealed from other personnel until key-opening by the key-holder.

Table Multiplicative PPQ score

A Early symtoms /sleep disturbnace

		Frequency		
		Up to once per week	Several times per week	Once or more per day
severity	Not or slightly affecting well-being	1	2	3
	Moderately affecting well-being	2	4	6
	Severely affecting well-being	3	6	9

B. Hallucinations /illusions

		Frequency		
		Only during the night	During the night & occasionally during the day	Almost every day & night
severity	Insight retained	1	2	3
	No full insight	2	4	6
	Lacking insight	3	6	9

C. Dellusions

		Frequency		
		Up to once per week	Several times per week	Once or more per day
severity	Withoug affecting the social enviroment	1	2	3
	Affecting the patient by emotional distress	2	4	6
	Affecting the patient by accusation, agression, or lack of cooperation	3	6	9

D. Orientation

		Frequency		
		Up to once per week	Several times per week	Once or more per day
severity	No requirement of supervision	1	2	3
	Temporal requirement of supervision	2	4	6
	Permanent requirement of supervision	3	6	9

References

1. Adler CH. Nonmotor complications in Parkinson's disease. *Mov Disord* 2005;20 Suppl 11:S23-9.
2. Maetzler W, Liepelt I, Berg D. Progression of Parkinson's disease in the clinical phase: potential markers. *Lancet neurology* 2009;8(12):1158-71.
3. Clozapine in drug-induced psychosis in Parkinson's disease. The French Clozapine Parkinson Study Group. *Lancet* 1999;353(9169):2041-2.
4. Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. The Parkinson Study Group. *The New England journal of medicine* 1999;340(10):757-63.
5. Breier A, Sutton VK, Feldman PD, Kadam DL, Ferchland I, Wright P, et al. Olanzapine in the treatment of dopamimetic-induced psychosis in patients with Parkinson's disease. *Biological psychiatry* 2002;52(5):438-45.
6. Ondo WG, Tintner R, Voung KD, Lai D, Ringholz G. Double-blind, placebo-controlled, unforced titration parallel trial of quetiapine for dopaminergic-induced hallucinations in Parkinson's disease. *Mov Disord* 2005;20(8):958-63.
7. Rabey JM, Prokhorov T, Miniovitz A, Dobronevsky E, Klein C. Effect of quetiapine in psychotic Parkinson's disease patients: a double-blind labeled study of 3 months' duration. *Mov Disord* 2007;22(3):313-8.
8. Ellis T, Cudkowicz ME, Sexton PM, Growdon JH. Clozapine and risperidone treatment of psychosis in Parkinson's disease. *The Journal of neuropsychiatry and clinical neurosciences* 2000;12(3):364-9.
9. Mesulam MM. Alzheimer plaques and cortical cholinergic innervation. *Neuroscience* 1986;17(1):275-6.
10. Whitehouse PJ, Price DL, Clark AW, Coyle JT, DeLong MR. Alzheimer disease: evidence for selective loss of cholinergic neurons in the nucleus basalis. *Annals of neurology* 1981;10(2):122-6.
11. Bohnen NI, Kaufer DI, Ivanco LS, Lopresti B, Koeppe RA, Davis JG, et al. Cortical cholinergic function is more severely affected in parkinsonian dementia than in Alzheimer disease: an in vivo positron emission tomographic study. *Archives of neurology* 2003;60(12):1745-8.
12. Jellinger KA. Pathology of Parkinson's disease. Changes other than the nigrostriatal pathway. *Molecular and chemical neuropathology / sponsored by the International Society for Neurochemistry and the World Federation of Neurology and research groups on neurochemistry and cerebrospinal fluid* 1991;14(3):153-97.
13. Goetz CG, Leurgans S, Pappert EJ, Raman R, Stemer AB. Prospective longitudinal assessment of hallucinations in Parkinson's disease. *Neurology* 2001;57(11):2078-82.
14. Williams DR, Lees AJ. Visual hallucinations in the diagnosis of idiopathic Parkinson's disease: a retrospective autopsy study. *Lancet neurology* 2005;4(10):605-10.
15. Merims D, Shabtai H, Korczyn AD, Peretz C, Weizman N, Giladi N. Antiparkinsonian medication is not a risk factor for the development of hallucinations in Parkinson's disease. *J Neural Transm* 2004;111(10-11):1447-53.

16. Kawakami Y, Inoue A, Kawai T, Wakita M, Sugimoto H, Hopfinger AJ. The rationale for E2020 as a potent acetylcholinesterase inhibitor. *Bioorganic & medicinal chemistry* 1996;4(9):1429-46.
17. Giacobini E, Zhu XD, Williams E, Sherman KA. The effect of the selective reversible acetylcholinesterase inhibitor E2020 on extracellular acetylcholine and biogenic amine levels in rat cortex. *Neuropharmacology* 1996;35(2):205-11.
18. Nochi S, Asakawa N, Sato T. Kinetic study on the inhibition of acetylcholinesterase by 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl]methylpiperidine hydrochloride (E2020). *Biological & pharmaceutical bulletin* 1995;18(8):1145-7.
19. Kosasa T, Kuriya Y, Matsui K, Yamanishi Y. Effect of donepezil hydrochloride (E2020) on basal concentration of extracellular acetylcholine in the hippocampus of rats. *European journal of pharmacology* 1999;380(2-3):101-7.
20. Kosasa T, Kuriya Y, Yamanishi Y. Effect of donepezil hydrochloride (E2020) on extracellular acetylcholine concentration in the cerebral cortex of rats. *Japanese journal of pharmacology* 1999;81(2):216-22.
21. Manganelli F, Vitale C, Santangelo G, Pisciotta C, Iodice R, Cozzolino A, et al. Functional involvement of central cholinergic circuits and visual hallucinations in Parkinson's disease. *Brain* 2009;132(Pt 9):2350-5.
22. Brandstaedter D, Spieker S, Ulm G, Siebert U, Eichhorn TE, Krieg JC, et al. Development and evaluation of the Parkinson Psychosis Questionnaire A screening-instrument for the early diagnosis of drug-induced psychosis in Parkinson's disease. *Journal of neurology* 2005;252(9):1060-6.
23. Daniel SE, Lees AJ. Parkinson's Disease Society Brain Bank, London: overview and research. *Journal of neural transmission* 1993;39:165-72.