

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for a randomized controlled trial: efficacy of donepezil against psychosis in Parkinson's disease (EDAP)
AUTHORS	Sawada, Hideyuki; Oeda, Tomoko

VERSION 1 - REVIEW

REVIEWER	Manganelli, Fiore University Federico II of Naples, Department of Neurosciences, Reproductive and Odontostomatological Sciences
REVIEW RETURNED	03-Jul-2013

THE STUDY	<p>1) Page 3 line 14-15 the sentence "However, motor symptoms may become worse since central anticholinergic drugs improve motor symptoms" is unclear. The authors want to state that cognitive symptoms may become worse since central anticholinergic drugs improve motor symptoms?</p> <p>2) Page 4 line 40: the authors report that psychosis (i.e. visual hallucinations) could be related to cholinergic neuronal damage and not to dopaminergic therapy. To this regard Manganelli et al (Brain, 2009) have demonstrated by using a neurophysiologic technique, the short latency afferent inhibition (SAI) a functional involvement of central cholinergic circuits in PD patients with visual hallucinations.</p>
GENERAL COMMENTS	<p>It could be useful to add to the psychological assessment the evaluation of visuospatial functions.</p> <p>The authors should record at any visit the dose of l-dopa or dopaminergic drugs.</p>

REVIEWER	Stocchi, Fabrizio IRCCS San Raffaele Roma, Neurology
REVIEW RETURNED	03-Jul-2013

RESULTS & CONCLUSIONS	There are no results therefore no interpretation or discussion is just a study protocol.
GENERAL COMMENTS	<p>The authors report in the paper the design, eligibility criteria, methods of data collection, and safety monitoring of a multi-center, randomized, placebo-controlled, double-blinded trial to investigate the efficacy of donepezil in the prevention of psychosis.</p> <p>The paper report the study protocol which, I believe, can not be</p>

VERSION 1 – AUTHOR RESPONSE

Reviewer #1

1. Reviewer comment: page 3 line 14-15 the sentence “However, motor symptoms may become worse since central anticholinergic drugs improve motor symptoms” is unclear. The authors want to state that cognitive symptoms may become worse since central anticholinergic drugs improve motor symptoms?

Response: Anti-cholinergic drugs such as trihexyphenidyl are used to improve extrapyramidal sign of Parkinson’s disease. In this context, donepezil hydrochloride might worsen motor symptoms of Parkinson’s disease. We revised the sentence as follows: “However, motor symptoms may become worse by donepezil hydrochloride since central anticholinergic drugs such as trihexyphenidyl improve motor symptoms.” (Page 3, Lines 6-7)

2. Page 4 line 40: the authors report that psychosis (i.e. visual hallucinations) could be related to cholinergic neuronal damage and not to dopaminergic therapy. To this regard Manganelli et al (Brain, 2009) have demonstrated by using a neurophysiologic technique, the short latency afferent inhibition (SAI) a functional involvement of central cholinergic circuits in PD patients with visual hallucinations.

Response: According to the comment, we revised the sentences as follows: “Donepezil hydrochloride is an inhibitor of acetylcholine esterase in brain neurons¹⁶⁻¹⁸ 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.” (Page 4, Line 40 – Page 5, Line 1)

3. It could be useful to add to the psychological assessment the evaluation of visuospatial functions.

Response: Thank you for an important and useful suggestion. The protocol has been fixed and the study is going, and therefore we do not have baseline data of visuospatial functional assessment. However, we will evaluate visuospatial function and will compare the patients who were allocated to donepezil group and placebo group.

4. The authors should record at any visit the dose of l-dopa or dopaminergic drugs.

Response: Thank you for your suggestion. We are collecting drugs including L-Dopa, dopamine agonists at any visits. We added the following documentation. “Dose of drugs prescribed (including drugs for PD and other medical conditions) will be collected at every visit.” (Page 10, Lines 4-5)

Reviewer #2.

Reviewer: The authors report in the paper the design, eligibility criteria, methods of data collection, and safety monitoring of a multi-center, randomized, placebo-controlled, double-blinded trial to investigate the efficacy of donepezil in the prevention of psychosis.

The paper report the study protocol which, I believe, can not be discussed in this contest.

Response: Thank you for reviewing the protocol paper. We hope that we will report the results of the study in future.