Meta Analysis: Donepezil in the Treatment of Cognitive Impairment and Dementia in Patients with Parkinson's Disease

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ABSTRACT

Objective. Evaluate the efficacy and safety of Donepezil in improving cognitive function of patients with Parkinson's disease diagnosed to have cognitive impairment or dementia.

Methods. Meta-analysis of randomized controlled trials comparing Donepezil versus placebo in the management of Parkinson's disease patients with cognitive impairment or dementia. Mean differences were computed using RevMan Version 5.1.

Results. Fifty-five studies were screened for inclusion in this meta-analysis. Only four studies met the inclusion and exclusion criteria. Administration of Donepezil 10 mg/tab for at least 4 weeks showed statistically significant improvement in the cognitive function of Parkinson's disease patients with dementia or cognitive impairment in terms of MMSE. There were no significant differences in the other scales measured. Incidence of adverse events was found to be higher in the Donepezil group, but this was not statistically significant.

Conclusion. This study successfully demonstrated the efficacy of Donepezil in cognitively impaired Parkinson's disease patient in the improvement of MMSE without significant impact on motor symptoms.

Key Words: Donepezil, Parkinson's Dementia, dementia, Parkinson's Disease, cognitive impairment

Introduction

Parkinson's disease (PD) affects almost 1% of the population aged 65 years old and above worldwide.[1] The range of incidence rate of PD dementia is from 4.2% to 9.5% per year.[2,3] The prevalence rate of PD dementia ranges from 10% to 40%, depending on the sample population and criteria used. On the other hand, due to the lack of universal criteria to detect mild cognitive impairment in PD, the prevalence of mild cognitive impairment (MCI) in PD remains unclear and ranges from 10% to 95%.[4-11]

Nevertheless, both forms of cognitive dysfunction in patients with PD imposes a great impact on the quality of life not only of the patient but also of the caregivers, family, and other members of the social support group of the patient.[12,13]

The neuropathophysiological substrate of cognitive dysfunction in PD involves interaction between neurotransmitters, as well as complex cerebral circuits. However, their interaction is not fully understood and not well established. Several pathologic findings have been deemed contributory to the cognitive impairment seen in some PD patients. These include (1) interruption of the frontal–subcortical dopaminergic circuits due to the progressive loss of dopaminergic neurons in the substantia nigra, (2) destruction of the neurons in the nucleus basalis of Meynert leading to decreased cholinergic activity both in cortical areas and in the basal telencephalon, (3) noradrenergic and serotonergic neurons degeneration.[14,15,16]

Among the three pathomechanisms mentioned above, pharmacologic management of PD dementia has drawn attention to cholinergic deficiency. In view of improving the quality of life of PD patients, the great need to halt or treat the progressive cognitive decline seen in PD has paved the way for studies focusing on cholinergic deficiency. Choline esterase inhibitors are one of the classes of drugs that have been experimented on dementia.[15] This class of drug includes donepezil and rivastigmine.

Donepezil has specific activity for AChE. The unique piperidine-based structure of Donepezil makes it chemically and pharmacologically distinct from other cholinesterase inhibitors making it highly selective for brain AChE and has no effect on cholinesterases from cardiac muscle or intestinal smooth muscle, and has only marginal effect on striatal muscle cholinesterase.[17,18,19] This makes donepezil very effective in increasing brain acetylcholine levels which has been associated with improved performance in behavioral, learning, and memory function tests in rats with experimentally induced cholinergic hypofunction.[20,19]

In terms of pharmacokinetics, once-daily administration of the drug allows achievement of significant AChE inhibition throughout the dosing interval, even after the first-dose administration. Steady-state concentrations of the

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drug are achieved after 14–21 days of once-daily administration.[21]

Donepezil has been proven effective in patients with Alzheimer's disease.[15] However, its role in the management of cognitive impairment in other neurodegenerative diseases such as Parkinson's disease and diffuse Lewy body dementia is not well established. Therefore, this meta-analysis aims to evaluate the efficacy of Donepezil in improving cognitive function of patients with Parkinson's disease diagnosed to have cognitive impairment or dementia.

Methods

Studies

Criteria for inclusion of published studies were (1) adequate allocation concealment, blinding of interventions, and assessment, (2) including patients older than 40 years of age (3) with a clinical diagnosis Parkinson's disease, (4) diagnosed to have cognitive impairment by baseline MMSE scores of 10-26 (5) given Donepezil of any dose for at least 10 weeks compared to placebo.

Outcome Measures

Primary Outcomes

Measure of cognitive improvement by any of the following scales: Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog), Mini-Mental Status Examination (MMSE), Clinician's Interview Based Impression Change (CIBC+), Brief Test of Attention (BTA).

Secondary Outcomes

Worsening of motor symptoms by UPDRS (Unified Parkinson's Disease Rating Scale) Motor Subsection. Adverse events were also taken into account.

Search strategy, study selection, and data extraction

Three independent reviewers searched, selected studies and extracted data. Online databases searched included PUBMED, Cochrane Central Register of Controlled Trials, LILACS were browsed to search for studies including 2002 up to the present year, 2012. In order to ensure data acquired was as complete as possible, authors were contacted through email and asked for raw data. Selection of studies and data extraction was done independently by the three reviewers and cross-checked for accuracy.

Statistical analyses

We performed five subgroup analyses. Data was analyzed using Review Manager Software Version 5.1 to generate forest plot for each of the five scales.

For the primary outcome, all four studies utilized MMSE, two of the four had ADAS-Cog, BTA, and CIBC. For the secondary outcome, all four studies utilized UPDRS Motor Subsection to measure affectation of the Parkinsonian symptoms. However, the study of Dubois et al. 2012 did not provide the UPDRS motor scores at the end of the trial (week 24).

Results

A total of 55 clinical studies were screened for possible inclusion in this meta-analysis (Figure 1). All 55 studies looked into the use of cholinesterase inhibitors in the management of cognitive impairment in patients with neurodegenerative disorders such as Parkinson's disease and diffuse Lewy body disease.
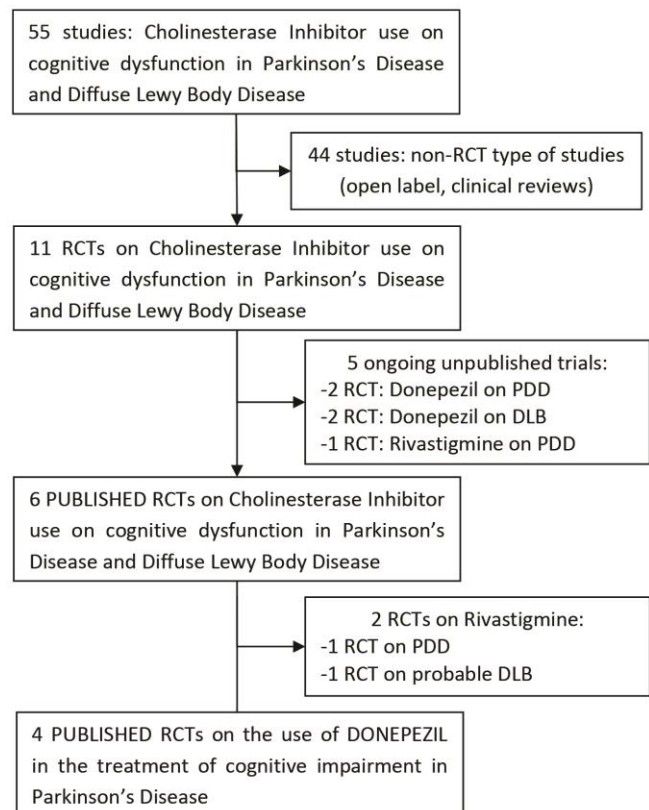
Figure 1. Literature Review Flow Diagram

Forty-three (43) studies were excluded because they were not RCTs. Six trials are still ongoing and remain unpublished. Of the six studies, two studies are RCTs investigating the efficacy of Donepezil on the management of PD dementia (Anon 2004a and Burn 2009) and were not included in this meta-analysis.

Of the six published RCTs on cholinesterase inhibitors, two studies used Rivastigmine as the treatment arm, hence was excluded. Of the four studies included, only Dubois 2012 responded and provided complete raw data for analysis.

Description of Studies

A total of four studies met our inclusion and exclusion criteria. All the studies used were randomized controlled trials which used Donepezil as the treatment arm compared to placebo on the other. Two studies, Ravina 2005 and Dubois 2012, included Parkinson's disease patients with dementia only while the other two studies, Leroi 2004 and Aarsland 2002, included those with mild cognitive impairment and dementia. The Dubois 2012 study is the final published version of Dubois 2007. Table 1 summarizes the characteristics of the studies included in this meta-analysis.

Table 1. Summary of Studies on Donepezil in Parkinson's Disease with Cognitive Impairment

Study Name	DUBOIS	RAVINA	LEROI	AARSLAND
Publication Date	May 2012	2005	2004	2002
Title / Name	Donepezil in Parkinson's Disease Dementia: A Randomized, Double-Blind Efficacy and Safety Study	Donepezil for dementia in Parkinson's disease: a randomized, double blind, placebo controlled, crossover study	Randomized placebo-controlled trial of donepezil in cognitive impairment in Parkinson's disease	Donepezil for cognitive impairment in Parkinson's disease: a randomized controlled study
Authors	Bruno Dubois, MD, * Eduardo Tolosa, MD, PhD, Regina Katzenschlager, MD, Murat Emre, MD, Andrew J. Lees, MD, FRCP, Gu¨nther Schumann, MD, Emmanuelle Pourcher, MD, Julian Gray, MS, Gail Thomas, Jina Swartz, MD, PhD, Timothy Hsu, MD, and Margaret L. Moline, PhD10	B Ravina, M Putt, A Siderowf, J T Farrar, M Gillespie, A Crawley, H H Fernandez, M M Trieschmann, S Reichwein, T Simuni	Iracema Leroi *, Jason Brandt , Stephen G. Reich , Constantine G. Lyketsos , Stephen Grill , Richard Thompson4 and Laura Marsh2	D Aarsland, K Laake, J P Larsen, C Janvin
Research Center	108 centers in 13 countries	4 centers	2 centers	1 center
Site	Germany & Austria, Spain, Russia, UK, France, Australia, New Zealand, South Africa, Canada, Italy, Belgium, Portugal	NINDS (National Institute of Neurological Disorders and Stroke), Brown University, University of Pennsylvania and Northwestern University	Outpatient neurology clinics in John Hopkins and community-based neurology practices in Baltimore	Outpatient Clinic in Department of Neurology at the General Hospital of Rogaland, Stavanger, Norway
N	550	19	16	14
Inclusion Criteria				
Age	>40 years old	>40 years old		45-95 years old
Clinical Diagnosis of PD based on	Queen Square Brain Bank Criteria	Not mentioned	United Kingdom Brain Bank Criteria	Not mentioned
Hoeh & Yahr	II-IV	Not mentioned	<= IV	<V
Dementia based on DSM IV	Yes > 1 year	yes	Yes	yes
MMSE	10-26	17-26	>10	16-26
Cognitive Impairment			Yes	Clinical evidence of memory decline & at least 1 other category of cognitive function Onset should be >1 year
Exclusion Criteria	Major depression Dementia with Lewy Body Alzheimer's Disease Previous AchEI use allergy			Brain disease other than PD Taking anticholinergics or psychotropic agents
Intervention	Donepezil	Donepezil	Donepezil	Donepezil
Dose	5mg, 10mg	10mg	10mg	5-10mg
Duration of Treatment	24 weeks	10 weeks	18 weeks	10 weeks
Monitoring	Week 4, week 8, week 12, week 24	Week 1, week 7, week 10, week 16, week 23, week 26	Every 6 weeks	Week 6, week 10
Scales Used (Primary & Secondary Outcomes)	ADAS-Cog CIBC BTA D-KEFs MMSE DAD SE NPI UPDRS CGIC-PD	ADAS-Cog MMSE MDRS CGI BPRS UPDRS	NART MMSE DRS BTA TMT-A TMT-B HVLT VMI UPDRS CSDD	MMSE CIBC NPI UPDRS
Conclusion	Donepezil treatment improved cognitive function & global status in patients with PDD	There is modest benefit on aspects of cognitive function and that donepezil is well-tolerated	Donepezil has beneficial effect on memory and may improve other cognitive deficits in patients with PD and cognitive impairment. Tolerability is variable especially in increasing doses.	Donepezil improves cognition and seems to be well tolerated and does not worsen parkinsonism

Effects of Intervention

Comparison of the mean change in ADAS-Cog, as shown in Figure 2 (higher score in ADAS-Cog indicates a more severe cognitive dysfunction), between Donepezil and placebo showed a trend favoring Donepezil (WMD=–1.31, CI –2.69–0.06). However, this was not statistically significant (p=0.06). On the other hand, the change in MMSE, as shown in Figure 3 (higher score indicates better cognitive function),

between the two interventions was statistically significant (p<0.00001) favoring Donepezil (WMD=1.53, CI 1.06–2.06). BTA (Figure 4) showed that the interventions had no effect (WMD=1.01, CI 0.57, 1.45) with p <0.00001. Other scales such as CIBC (Figure 5) and UPDRS (Figure 6) were not statistically significant with p values of 0.010 and 0.91, respectively.
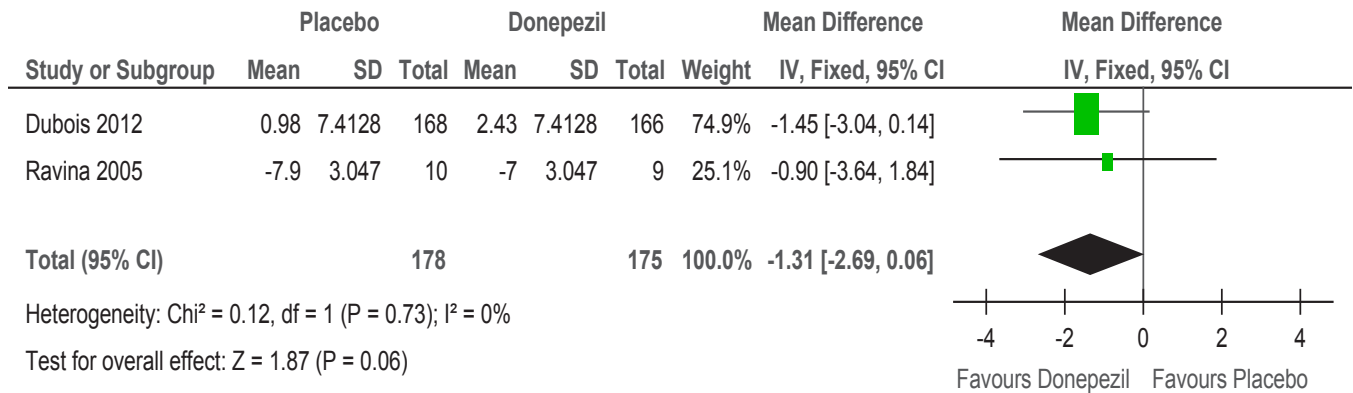
Study or Subgroup	Placebo Mean	SD	Total	Donepezil Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Dubois 2012	0.98	7.4128	168	2.43	7.4128	166	74.9%	-1.45 [-3.04, 0.14]
Ravina 2005	-7.9	3.047	10	-7	3.047	9	25.1%	-0.90 [-3.64, 1.84]
Total (95% CI)			178			175	100.0%	-1.31 [-2.69, 0.06]

Heterogeneity: Chi² = 0.12, df = 1 (P = 0.73); I² = 0%
Test for overall effect: Z = 1.87 (P = 0.06)

Figure 2. Comparison of the Mean Change in ADAS-Cog Scores

Study or Subgroup	Placebo Mean	SD	Total	Donepezil Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Aarsland 2002	0.3	3.2	9	2.1	2.7	8	2.9%	-1.80 [-4.61, 1.01]
Ravina 2005	1.1	5.801	10	1.4	4.061	9	1.1%	-0.30 [-4.77, 4.17]
Leroi 2004	0.12	5.008	9	-0.67	4.467	7	1.0%	0.79 [-3.86, 5.44]
Dubois 2012	1.72	2.3007	173	0.06	2.3007	170	95.0%	1.66 [1.17, 2.15]
Total (95% CI)			201			194	100.0%	1.53 [1.06, 2.00]

Heterogeneity: Chi² = 6.43, df = 3 (P = 0.09); I² = 53%
Test for overall effect: Z = 6.32 (P < 0.00001)

Figure 3. Comparison of the Mean Change MMSE Scores

Study or Subgroup	Placebo Mean	SD	Total	Donepezil Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Dubois 2012	-0.39	2.1737	111	0.61	2.1737	105	97.2%	-1.00 [-1.58, -0.42]
Leroi 2004	-1.43	3.962	7	0.22	2.709	9	2.8%	-1.65 [-5.08, 1.78]
Total (95% CI)			118			114	100.0%	-1.02 [-1.59, -0.45]

Heterogeneity: Chi² = 0.13, df = 1 (P = 0.71); I² = 0%
Test for overall effect: Z = 3.49 (P = 0.0005)
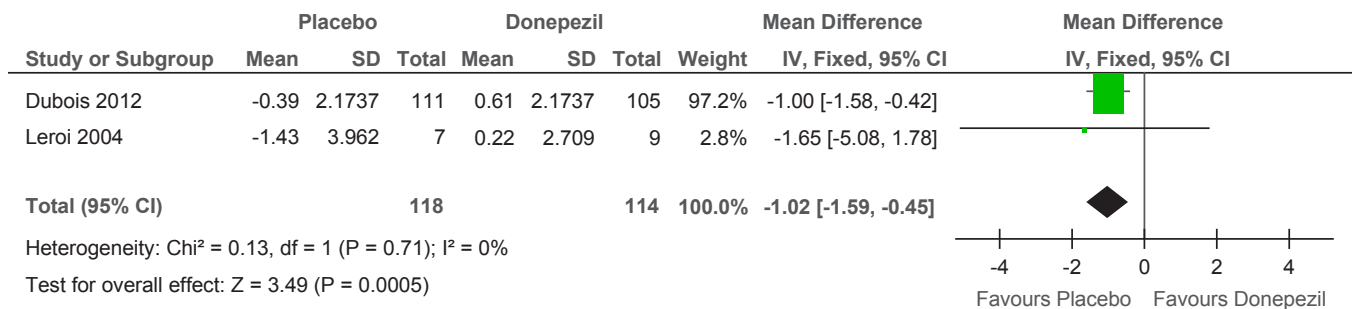
Figure 4. Comparison of the Mean Change in Brief Test of Attention Scores

Study or Subgroup	Placebo			Donepezil			Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total			
Aarsland 2002	3.3	0.9	8	4.1	0.8	6	8.5%	-0.80 [-1.69, 0.09]	
Dubois 2012	3.6	1.29	170	3.9	1.27	170	91.5%	-0.30 [-0.57, -0.03]	
Total (95% CI)			178			176	100.0%	-0.34 [-0.60, -0.08]	
Heterogeneity: Chi² = 1.10, df = 1 (P = 0.29); I² = 9%									
Test for overall effect: Z = 2.58 (P = 0.010)									

Favours Placebo Favours Donepezil
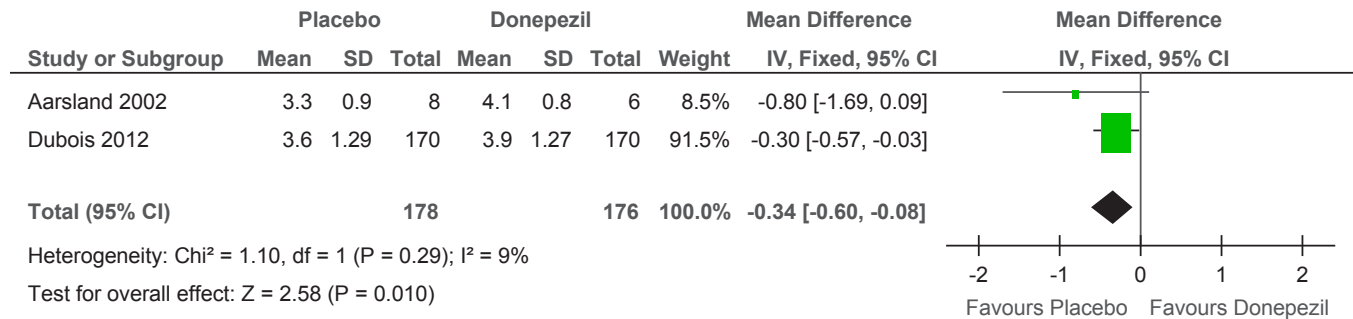
Figure 5. Comparison of the Mean Change in CIBC Scores

Study or Subgroup	Placebo			Donepezil			Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total			
Aarsland 2002	3	17.224	6	-0.3	21.638	8	0.6%	3.30 [-17.07, 23.67]	
Dubois 2012	-1.08	7.445	160	0.03	7.046	165	98.3%	-1.11 [-2.69, 0.47]	
Leroi 2004	2.78	17.766	9	4.43	24.455	7	0.5%	-1.65 [-23.17, 19.87]	
Ravina 2005	-0.7	22.304	10	-0.9	22.084	9	0.6%	0.20 [-19.78, 20.18]	
Total (95% CI)			185			189	100.0%	-1.08 [-2.64, 0.48]	
Heterogeneity: Chi² = 0.20, df = 3 (P = 0.98); I² = 0%									
Test for overall effect: Z = 1.35 (P = 0.18)									

Favours Placebo Favours Donepezil
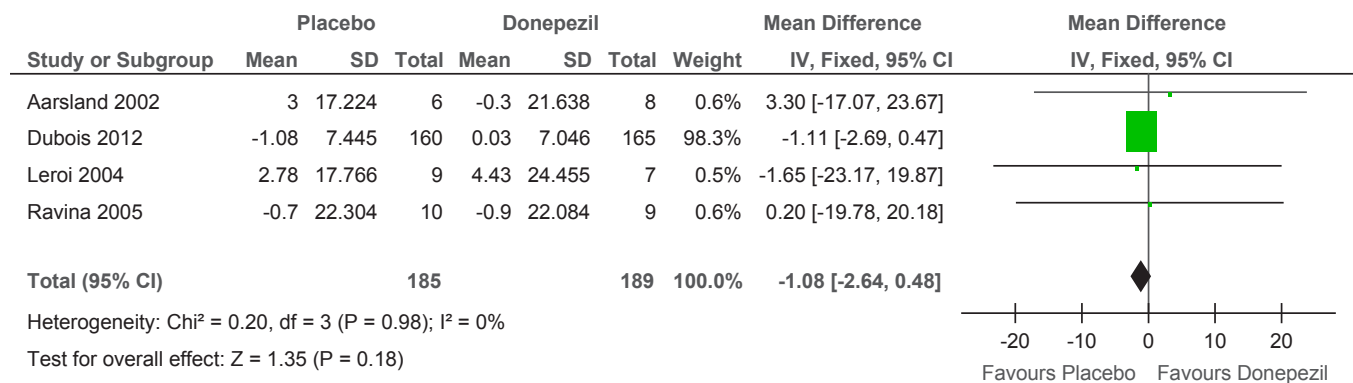
Figure 6. Comparison of the Mean Change in UPDRS Motor Scores

Discussion

Donepezil has been shown to be effective in improving cognitive function of patients with MCI and dementia as measured by change in MMSE. ADAS-Cog also showed a trend favoring Donepezil although this was not statistically significant. Furthermore, measurement of cognitive improvement by other scales such as BTA and CIBC failed to show statistically significant difference. Hence, Donepezil still has not yet established a firm ground in the management of cognitive dysfunction in Parkinson's disease patients with dementia or MCI. There are several points that can be discerned in this study explaining such claim.

Each of the cognitive scales mentioned above measures similar but not identical cognitive factors. ADAS-Cog tends to emphasize the domains of memory and language. These two domains are more severely affected in Alzheimer's disease than in Parkinson's disease. This may be the reason why ADAS-Cog failed to show statistical significance in this study. The same goes for BTA which mainly measures the ability to concentrate.[22,23]

On the other hand, MMSE is more commonly used as a screening tool for detecting cognitive impairment because it spans most of the cognitive domains. It may have been more sensitive in detecting change in cognitively impaired Parkinson's patients. The CIBC does not provide an objective means for detecting improvement. Hence, it is of no high value even if it were statistically significant.[22, 23, 24]

The incidence of adverse events reported was higher in donepezil compared to placebo in all of the four studies; however, none were statistically significant. Adverse events reported were nausea, vomiting, dizziness, diarrhea, hallucinations, psychosis, agitation, and arrhythmia. All the included studies concluded that Donepezil did not significantly affect the UPDRS Motor scale.

Variable cognitive scales used in the measurement of cognitive function of Parkinson's disease patients pose a big challenge for researchers to generalize results and clinicians to choose which scale can effectively monitor their patients' cognitive status. Therefore, a universally accepted cognitive assessment tool tailored especially to Parkinson's disease patients may be developed in the future.

Conclusion

This study demonstrated the efficacy of Donepezil in cognitively impaired Parkinson's disease patients in the improvement of MMSE. Consequently, the demonstration of the drug having no significant impact on the motor symptoms of PD patients as measured by the change in UPDRs makes it acceptable to administer it to such patients. However, the presence of side effects such as nausea,

headache, insomnia, dizziness, and diarrhea, should remain a factor in a clinician's decision to administer Donepezil or not.

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