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A 12-week open-label pilot study of donepezil for cognitive functioning and instrumental activities of daily living in late-life bipolar disorder

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Abstract

Objective—To determine whether donepezil is effective in enhancing cognitive functioning and instrumental activities of daily living (IADLs) in older adults with bipolar disorder.

Methods—Twelve elderly patients with bipolar I or II disorder, with evidence of mild cognitive decrements, were administered donepezil 5–10 mg daily for 3 months. Participants had cognitive and functional evaluation pre-, on-, and 3-months post donepezil administration.

Results—Three subjects dropped out of the study. In the remaining nine subjects, no significant effects were observed in cognitive and functional measures. Seven of the nine participants asked to resume the medication after completion of the study because of the perceived beneficial effects.

Conclusions—In this small pilot study of older adults with bipolar disorder, acute treatment with donepezil was not associated with improvements in cognitive and IADL functioning. Given limitations of the study design, placebo effects could not be ruled out in the subjects who asked to resume donepezil.

Keywords

aged; bipolar disorder; cognition; IADLs; cholinesterase inhibitors

INTRODUCTION

We have previously reported on cognitive dysfunction in late-life bipolar disorder (Gildengers *et al.*, 2004, 2007). We have observed that elders with bipolar disorder have worse information processing speed and executive functioning than age-matched comparators without history of mental illness, and that cognitive functioning is highly correlated with ability to perform Instrumental Activities of Daily Living (IADLs) (Gildengers *et al.*, 2007). A case report has suggested that the cholinesterase-inhibitor galantamine may be beneficial in improving chronic

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cognitive impairment in middle-aged adults with bipolar disorder (Schrauwen and Ghaemi, 2006). Based on a retrospective chart review, cognitive changes of four cases (three women, one man; ages 34–59 years) were rated using the Clinical Global Impression scale: two patients were judged to have improved on galantamine (24 mg/ day); the two other patients discontinued galantamine due to lack of benefit at low doses. To date, no prospective study has examined the effects of cholinesterase inhibitors in elderly adults with bipolar disorder on mood stability, cognition, or IADL functioning.

We follow this case report with a case series on 12 older adults treated openly for cognitive impairment with donepezil. In these patients, cognition was assessed prospectively as part of a pilot study to examine the effects of donepezil on cognition and on mood-stability in patients 60 years and older with bipolar I or II disorder. Reports have shown that cholinesterase inhibitors improve attention and working memory in older non-demented adults (Cummings, 2000; Yesavage *et al.*, 2002; Mumenthaler *et al.*, 2003; Freo *et al.*, 2005). Based on these reports and our pilot work (Gildengers *et al.*, 2004, 2007) showing decrements in attention and executive control of working memory, we hypothesized that donepezil would improve cognitive functioning and IADL performance.

METHODS

As described elsewhere (Fagiolini *et al.*, 2005; Gildengers *et al.*, 2005), all patients sought treatment at Western Psychiatric Institute and Clinic (Pittsburgh, PA) and participated in intervention studies of bipolar disorder conducted within the Intervention Research Center for Late-Life Mood Disorders (IRC/LLMD) at the University of Pittsburgh School of Medicine with funding from the NIMH or from the Commonwealth of Pennsylvania. The protocol was approved by the Institutional Review Board at the University of Pittsburgh and all participants provided writteninformed consent. Inclusion criteria were: age 60 years or older; current bipolar I or II disorder diagnosis; clinical euthymia for four weeks preceding neuropsychological (NP) and IADL assessment with scores of 10 or less on both the Hamilton Rating Scale for Depression-17 item (HRSD-17) and Young Mania Rating Scale (YMRS) (APA, 2000) at the time of assessment; ability to speak English; corrected visual ability to read newspaper headlines and hearing capacity adequate to respond to a raised conversational voice; and some cognitive dysfunction demonstrated by a score 1 SD or more below age and gender-adjusted norms on the Mini Mental State Examination (MMSE), Dementia Rating Scale (DRS) total, or any sub-scale, or 1 SD or more above age and gender-adjusted norms on the Executive Interview (EXIT). Exclusion criteria were: pre-existing diagnosis of dementia, history of neurological disorder affecting the central nervous system (for example, Parkinson's disease, traumatic brain injury, or multiple sclerosis), current use of a cholinesterase inhibitor, alcohol abuse or dependence within past 12 months, and contraindications to the use of donepezil.

Twenty-one patients were screened and completed baseline testing. Fifteen patients met all the inclusion and none of the exclusion criteria. Twelve patients provided informed consent. Following baseline assessment of attention and IADLs these 12 participants initiated donepezil 5 mg daily to be titrated to 10 mg daily after four weeks. After receiving donepezil for a total of 12 weeks, attention and IADLs were reassessed. Participants then discontinued donepezil and had attention and IADLs reassessed 3 months later. Side effects were assessed with the UKU rating scale (Lingjaerde *et al.*, 1987). Participants were tested when euthymic. If a participant experienced mood symptoms, follow-up testing was delayed until the participant returned to euthymia. In this study, cognition was assessed with the Digit Span Subtest of the Wechsler Memory Scale-III (Attention), Trail Making Test A and Digit Symbol Subtest of the WAIS-3 (Information Processing Speed); Trail Making Test B and Stroop Interference Test (Executive Functions) (Lezak, 2004). At the completion of the study, subjects were provided donepezil if they wanted to restart it.

IADLs were assessed with a criterion-referenced, performance-based instrument, the Performance Assessment of Self-Care Skills (PASS) as previously described (Gildengers *et al.*, 2007). Assistance was provided only when needed, with the least assistive prompt used first followed by progressively more assistive and intrusive prompts. Assistive prompts progress from verbal (scores of 1, 2, 3) to gestures, task/environmental rearrangement and demonstration, (scores of 4, 5, 6) to physical (scores of 7, 8, 9). The highest prompt needed represents the assistance level for that item. All PASS assessments were performed by the same rater (DC).

We computed the mean, standard deviation, and median for each test administered to the subjects. We compared testing results from Time 1 (pre) and Time 2 (post), and Time 2 and Time 3 (follow-up) using the Wilcoxon matched-pairs signed rank test.

RESULTS

The demographic and clinical characteristics of the 12 these participants are reported in Table 1. Nine participants were able to continue donepezil for 3 months; eight of them tolerated the 10 mg/day dose; one subject remained on the 5 mg dose. The nine participants who received donepezil for 12 weeks remained euthymic. However, two participants (#5 and #8) experienced re-emergence of depressive symptoms after discontinuing donepezil; participant #8 required a 4-month delay in testing off donepezil until she re-established euthymia. Three of the 12 participants who initiated donepezil 5 mg daily discontinued the medication within the first two weeks: one participant because of nausea and two because of manic activation.

Although there were some numerical improvements (and decrements) in the measures of cognitive and IADL functioning from Time 1 to Time 2, overall the positive (or negative) effects were small to medium, not consistent across all subjects, and not statistically significant. Mean (SD) total UKU scores were not significantly different across time points: Time 1, 6.2 (4.1); Time 2, 6.6 (4.5); Time 3, 7.7 (3.0).

Seven of the participants asked to resume donepezil after completing the study because they felt it improved their concentration and attention and IADL functioning. The two subjects (1, 8) who did not restart donepezil were both female and the youngest members of the group. Additionally, these two subjects scored higher than the other six subjects on the cognitive and functional tests at baseline and follow-up.

DISCUSSION

In this pilot study, 12 patients with bipolar disorder with mild cognitive decrements were treated with donepezil and assessed prospectively. We observed no significant improvements in cognitive or IADL functioning as had been hypothesized. Given the small to medium effect sizes observed, 0.04 to 0.5, roughly 50 to 100 participants would have been needed to detect a statistically significant effect of donepezil on cognitive or IADL functioning.

That two participants experienced manic activation shortly after initiating donepezil adds an important note of caution to this report, given prior report of mania associated with donepezil (Benazzi, 1999). Benazzi describes manic activation with donepezil in four elderly patients with dementia, two with bipolar I disorder, one with major depressive disorder, and one with delusional disorder. Manic activation occurred in close temporal association with the start of donepezil and resolved spontaneously with discontinuation of donepezil in 1 to 7 days. A second trial of donepezil in the two non-bipolar patients resulted in the same pattern of manic activation. He suggests that cholinesterase inhibitor activation of the central cholinergic system can cause noradrenergic and dopaminergic system activation, resulting in rebound mania. Note,

in contrast to our report, neither patient described with bipolar disorder was on an anti-manic mood stabilizer.

A number of limitations need to be highlighted. First, these findings reflect open, naturalistic, treatment with donepezil; assessors were un-blinded to the time-point of assessment, there was no control group, and no ability to control for practice effects. Second, there were 'ceiling effects' and overall small effect sizes in a limited number of subjects, likely related to the broadly defined inclusion criteria for cognitive dysfunction. Third, the assessment instruments employed may have arguably been insensitive to examining the cognitive/functional improvements experienced by the participants, given that seven of the nine participants asked to resume the medication after completion of the study. Last, the subjective concerns regarding cognitive functioning in the study participants may have made them susceptible to a placebo effect of donepezil.

Cholinesterase Inhibitors have been examined for cognitive dysfunction other than dementia in patients with schizophrenia with mixed evidence of benefit (Chouinard *et al.*, 2007; Stip *et al.*, 2007). Cognition in middle aged and older adults with schizophrenia is impaired in a variety of domains that overlap with decrements in bipolar disorder (Depp *et al.*, 2007). To date there have been various published trials examining donepezil, galantamine, and rivastigmine. In a quantitative systematic review of studies examining the effects of cholinesterase inhibitors on various cognitive domains, Chouinard *et al*. (2007) find support for beneficial effects on attention and memory. However, they qualify their findings by noting that few data appropriate for the meta-analysis were found, and that their findings need to be substantiated by larger trials.

Considering the limitations described above, our data might suggest further examination of donepezil (or galantamine, noting its different pharmacologic effects) for cognitive dysfunction associated with bipolar disorder in a larger, randomized controlled trial employing more precise measures of cognition and more advanced measures of IADLs. Studying the utility of employing donepezil or other cholinesterase inhibitors in this population long term will be problematic, since it is unclear if the cognitive deficits in bipolar disorder are progressive (Robinson and Ferrier, 2006). Further, cholinesterase inhibitors may be more efficacious in patients with more significant deficits when used long term, for example, mild to moderate Alzheimer's disease, than when used acutely in patients with mild cognitive decrements (Petersen *et al.*, 2005; Loy and Schneider, 2006). If treatments can be demonstrated to improve cognitive functioning in bipolar elders, this would clearly be beneficial to patients and their caregivers, enhancing patients' day to day independence and potentially quality of life.

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CONFLICT OF INTEREST

Dr Ariel G. Gildengers has participated in scientific advisory board meetings for Shire Pharmaceuticals.

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Table 1

Demographic and clinical characteristics of 12 elders with bipolar disorder administered donepezil

Subject	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10***	**11***	**12***	**mean**	**SD**	**median**	**Wilcoxon z =, effect size (es)**	***p***
Age	64	79	64	75	81	76	75	63	82	68	86	80	74.4	7.86	75.5		
Education	16	9	18	20	18	12	20	14	12	20	12	12	15.6	3.93	16.0		
Gender	F	F	F	M	M	F	M	F	F	M	F	M					
Race	C	C	C	C	C	C	C	C	AA	SA	C	C					
CIRS-G total	10	7	8	4	15	13	9	19	8	9	4	7	9.4	4.38	8.5		
CIRS-G count	8	5	5	4	9	7	6	10	4	5	2	5	5.8	2.29	5.0		
MMSE	30	26	30	25	27	28	29	28	24	29	24	24	27.0	2.34	27.5		
DRS total score	139	122	135	129	139	139	138	137	124	139	126	118	132.1	7.81	136.0		
EXIT	8	16	14	8	12	13	6	9	13	6	10	20	10.8	3.49	11.0		
Pharmacotherapy	Li SSRI	VLP SSRI	SNRI	SNRI	SSRI	CBZ	LMT SSRI	VLP SSRI	VLP SNRI	Li SSRI	CBZ	Li MRT					
ATTENTION																	
Digit span total – pre	17	9	16	15	16	18	16	23	12				15.8	3.87	16.0		
																z=−0.419 es=0.15	0.6749
Post	19	9	13	14	18	19	21	22	11				16.2	4.60	18.0		
																z=−0.119 es=0.04	0.9050
Follow-up	18	11	12	17	14	19	25	18	13				16.3	4.36	17.0		
INFORMATION PROCESSING SPEED																	
Trails A – pre	0.73	2.69	2.14	0.95	1.95	2.27	2.62	1.63	3.43				2.05	0.85	2.14		
																z=0.770 es=0.26	0.4413
Post	0.76	2.99	1.70	0.87	2.64	1.38	1.60	1.71	3.35				1.89	0.91	1.70		
																z=−0.534 es=0.19	0.5936
Follow-up	0.87	2.25	2.65	0.73	2.54	1.59	1.67	1.57	5.43				2.14	1.40	1.67		
Digit symbol – pre	78	30	30	76	34	33	33	44	28				42.89	19.87	33.00		
																z=−0.595 es=0.21	0.5515
Follow-up	79	29	30	62	39	51	57	45	9				44.56	20.73	45.00		
																z=−1.011 es=0.34	0.3122
Post	86	33	30	64	49	46	42	50	16				46.22	20.28	46.00		
EXECUTIVE FUNCTIONING																	
Trails B – pre	1.56	14.29	6.11	2.24	9.16	9.43	6.27	5.21	23.00				8.59	6.65	6.27		
																z=−0.718 es=0.06	0.8590
Post	2.00	10.78	8.76	2.37	5.03	9.98	3.22	5.91	50.00				10.89	15.02	5.91		
																z=1.481 es=0.46	0.1386
Follow-up	1.65	7.98	7.70	1.80	5.72	10.31	4.20	3.65	42.80				9.53	12.81	5.72		
STROOP – pre	2.50	3.69	3.96	2.83	3.64	2.83	2.40	2.23	3.09				3.02	0.62	2.83		
																z=−0.119 es=0.04	0.9056
Follow-up	2.54	3.49	4.66	2.79	2.63	2.49	3.04	1.83	7.87				3.48	1.82	2.79		
																z=1.051 es=0.35	0.2930
Post	2.28	3.38	4.57	2.60	3.56	2.60	2.38	1.45					2.85	0.95	2.60		
IADL FUNCTIONING																	
PASS assists – pre	1.00	2.00	1.80	1.10	1.30	1.10	0.00	0.20	7.90				1.82	2.37	1.10		
																z=1.007 es=0.34	0.3139
Post	0.00	2.10	1.40	0.90	1.40	0.00	1.70	0.30	5.70				1.50	1.74	1.40		

Subject	1	2	3	4	5	6	7	8	9	10*	11*	12*	mean	SD	median	Wilcoxon z =, effect size (es)	p
																z=−1.718 es=0.52	0.0858
Follow-up	0.30	3.60	3.20	1.70	0.50	1.00	1.10	0.80	9.00				2.36	2.75	1.10		
Restart donepezil(Y/N)	N	Y	Y	Y	Y	Y	Y	N	Y								

*Subjects 10–12 exited the study.

Tests highlighted in gray are "reverse-coded" - higher scores indicate worse performance.

Abbreviations: RACE: W (Caucasian), AA (African-American), SA (Southeast Asian); CIRS-G = Cumulative Illness Rating Scale - Geriatric; MMSE = Mini Mental State Examination; DRS = Dementia Rating Scale; EXIT = Executive Interview; Li = lithium, VLP = valproate, LMT = lamotrigine, SSRI = selective serotonin reuptake inhibitor; SNRI = Serotonin Norepinephrine Reuptake Inhibitor; CBZ = carbamazepine, MRT = mirtazapine; Digit Span Total = number of digits retained forward and backward; Trails A = Number of seconds per completed connection; Trails B = Number of seconds per completed connection; PASS Assists = Performance Assessment of Self-Care Skills – Level of Assistance Provided.