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Beneficial Effect of Donepezil Augmentation for the Management of Comorbid Schizophrenia and Dementia

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Summary: Comorbid schizophrenia and dementia is a common clinical phenomenon; however, management of the coexisting illnesses remains incomplete. Donepezil, a cholinesterase inhibitor, may be beneficial for the management of symptoms of Alzheimer's disease, a disease in which cholinergic pathways in the cerebral cortex and basal forebrain are well known to be compromised. Furthermore, impaired cognition in elderly schizophrenic patients has been observed to be more than two thirds; however, there are no published controlled studies reporting the use of cholinesterase inhibitors in the management of schizophrenia in patients with associated dementia. In this study, six patients with chronic schizophrenia and comorbid dementia were administered donepezil, 5 mg, in single-blind fashion as augmentation to their standard antipsychotic medication for a 4-week period. Patients were evaluated with the Mini Mental State Examination (MMSE); Alzheimer's Disease Assessment Scale, Cognitive subscale; Positive and Negative Symptom Scale (PANSS); and the Clinical Global Impression (CGI) scales. A significant improvement was noted in MMSE scores ($p < 0.01$) and for CGI scores ($p < 0.01$). In addition, three patients demonstrated improvement on the PANSS. Donepezil appears to be an effective treatment for the management of symptoms of dementia accompanying patients with comorbid schizophrenia and dementia. Since cholinergic dysfunction may be present in some patients with schizophrenia, the authors' findings further demonstrate the possibility that this disorder may be managed with cholinergic medications as augmenting agents, at least in this specific subpopulation of patients with comorbid dementia. To confirm the findings of this preliminary trial, further investigation is mandated with a larger sample of subjects in the context of a double-blind medication trial. **Key Words:** Schizophrenia—Dementia—Donepezil

The comorbid expression of schizophrenia and dementia is frequently observed in clinical practice. While pharmacologic management of the separate conditions is improving, adequate therapy for the coexisting illnesses remains lacking. Furthermore, clinically significant cognitive impairments, including deficits in attention, memory, verbal skills, motor skills, and executive function, occur in approximately 85% of schizophrenic patients (1). This cognitive impairment often occurs at a very early age, frequently before any emergent overt clinical symptomatology (2,3), and in many patients, it worsens during the course of illness to the extent of dementia-like proportions (4,5). Interestingly, while it may be considered that cognitive dysfunction resulting in dementia later in life may be increased in those with schizophrenia, the incidence of Alzheimer's-type dementia in elderly schizophrenic patients is not known to be different from that of the general elderly population and, in fact, may be even less (6,7).

Donepezil is a centrally active relatively specific acetylcholinesterase inhibitor and has been shown to be beneficial for the management of symptoms of memory and cognitive dysfunction in patients with mild to moderately severe Alzheimer's disease (8). It is relatively well tolerated with few adverse effects. In addition, more recent observation suggests that neuropathology of Alzheimer's dementia does not have to be present for cognitive enhancement with donepezil to occur (9). Al-

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though the incidence of impaired cognition in elderly schizophrenia patients has been observed to be more than two thirds (10–12), studies investigating the use of cholinesterase inhibitors in the management of schizophrenia and associated dementia under blinded conditions do not exist. This is despite evidence demonstrating donepezil's safety, but uncertain efficacy, in two double-blind studies investigating its use for the management of cognitive dysfunction in patients with schizophrenia and schizoaffective disorder (13,14). The rationale for the use of a cholinesterase inhibitor such as donepezil in schizophrenia patients with dementia is twofold. First, there is the assumption that reduced cholinergic activity may contribute to the cognitive impairment in patients with schizophrenia, which may be alleviated by increasing cholinergic activity at muscarinic and nicotinic receptors. This is based on evidence indicating a correlation between decreases in postmortem brain choline acetyltransferase levels and ante mortem cognitive dysfunction (15), and receptor studies indicating decreased muscarinic (16) and nicotinic (17,18) receptors, critical to hippocampal cognitive functions, in brains of schizophrenic patients.

Considering the recent report from our group (19), demonstrating significant improvement of cognition and behavior following short-term treatment with donepezil in three schizophrenia patients with comorbid dementia, we hypothesize that donepezil may improve cognition in patients suffering from coexistent schizophrenia and dementia. Thus, in contrast to the two aforementioned studies (13,14), which investigated donepezil use for cognitive dysfunction in schizophrenia patients who did not necessarily demonstrate features of dementia, we conducted, to our knowledge, the first study investigating with a single-blind design the efficacy of donepezil addition to ongoing antipsychotic treatment of chronic schizophrenia patients who also met DSM-IV criteria for dementia.

METHODS

Study Population

Patients who met DSM-IV criteria for schizophrenia and dementia were recruited from inpatient units of Beer-Yaakov Mental Health Center during 2000–2001. Two senior board-certified psychiatrists (Y. B. and F. B.) evaluated all subjects to confirm the DSM-IV diagnosis of schizophrenia and dementia. In addition, patients scored 24 points or below on the Mini Mental State Examination (MMSE) (20), widely accepted as the threshold for dementia (21). Patients or their legal guardians provided informed consent to participate. The patient and family members received full explanation regarding donepezil, its side effects, and possible benefits. They were also informed regarding the study design, its objective, and the option to continue receiving the drug. The study was approved by the local hospital Institutional Review Board.

All patients underwent a comprehensive physical and psychiatric evaluation, thus excluding the possibility of a reversible dementia. This included blood levels for thyroid function, vitamin B12, folic acid, and electrolytes including calcium, complete blood count, and renal and liver functions, electrocardiogram, and complete medical history and physical and neurologic examination. Patients unable to cooperate because of illiteracy, severe psychosis, restlessness, and suicidal or homicidal ideation were excluded from the study.

Study Design

All patients were stabilized with antipsychotic medication for at least 6 months prior to study entry. The medications remained unchanged during the 4-week trial. The study consisted of administration of donepezil, 5 mg/day, prior to bedtime for a 4-week period as an "add-on" medication to ongoing antipsychotic medication. Following the completion of the 4-week study, patients were offered the option to continue receiving the medication for an additional indefinite period of time.

Rating Scales

A neurologist experienced in the evaluation of patients with dementia (E. W.) performed the neurocognitive evaluation, consisting of the Alzheimer's Disease Assessment Scale, Cognitive subscale (ADAS-COG) (22) and the MMSE. These scales were selected since they are considered by many to be the "gold standard" in dementia evaluation by the clinician because they provide a good indication of overall functioning, are relatively simple to administer, and are able to provide an overall impression of improvement over time. The neurologist, as opposed to patients and their family members, remained blind to the nature of the study aims, study parameters, and treatment regimen. The patient being instructed not to reveal any study details in addition to being supervised during the examination by a staff member assured the single-blind nature of the study. The subjects' clinical symptoms were rated using the Positive and Negative Symptom Scale (PANSS) (23). The Clinical Global Impression-Severity of Illness (CGI-S) and -Improvement (CGI-I) scales (24), both scored on a 1–7 scale, were performed before and at the completion of the study by the treating physician.

Statistical Analysis

Data was analyzed by two-tailed Student paired *t*-test. All results are expressed as mean ± SD.

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RESULTS

The sample consisted of 6 patients (4 women, 2 men), aged 54–76 years (mean, 65 ± 35.6 years), with illness duration of 25–49 years (Table 1). The mean CGI-S level was 5.83 ± 0.75, and CGI-I was 3.17 ± 1.17. All but one of the patients showed an improvement on the MMSE as indicated by higher posttreatment compared with pretreatment results. The mean prestudy MMSE score was 18.16 ± 6.2 with the mean MMSE value increasing to 22 ± 6.8 after donepezil administration. The effect of treatment on the MMSE was significant ($t(5) = 4.39$, $p < 0.01$). There was a mean percentage change in the MMSE of 25% ± 24.4%, with the range of increase from 0% to 71%.

The effect of donepezil addition on the ADAS-COG was less robust. Four subjects showed improvement (reduction of posttreatment compared with pretreatment), one did not change, and another showed a decline. Thus, the difference between pretreatment and posttreatment data was not significant ($p = 0.26$). The mean prestudy ADAS-COG score was 26.5 ± 23.9 with the mean ADAS-COG value decreasing to 23.3 ± 14.7 after donepezil administration. The mean decrease was to a value of 87.6% ± 19.6% of the initial results, ranging from a 17% increase to a 34% decrease in scores.

The PANSS total scores indicated that the treatment was effective globally for only three subjects, while the other subjects did not indicate any change. This effect was not significant ($p = 0.16$). The mean prestudy PANSS score was 108.6 ± 17.4, with the mean PANSS value decreasing to 90.8 ± 28.9 after donepezil administration. The mean decrease was to 83.8% ± 22.3% of the initial PANSS results, ranging from no change to 67% decrease. To exclude the possibility that changes in MMSE may have been accounted for by changes in positive, negative, or general symptoms of the illness, covariate analysis was performed. The change of MMSE with donepezil treatment remained significant when total, positive, and general scores were used as covariates (all p's < 0.05). With the negative subscale, the change approached significance, $p = 0.054$. Thus, no support in the data appears to exist, suggesting that changes in MMSE may have been accounted for by changes in positive, negative, or general symptoms of the PANSS.

There was a strong correlation between the change in the CGI-I scale and the proportional change in PANSS and ADAS-COG scores ($r = 0.99$, $r = 0.73$, respectively). The correlation indicates that the greater the clinical improvement, the greater the decrease of the variables. CGI-S correlated with ADAS-COG change ($r = -0.76$), indicating that high baseline severity was associated with greater change in ADAS-COG scores. Continuation of donepezil was decided on the basis of clinical improvement.

Medication Continuation Poststudy

The three patients (patients 1, 2, and 4) who improved clinically on the CGI continued to receive donepezil. Patient 2 continued a further 4-week trial of donepezil at a dose of 10 mg/day. A second evaluation of this patient showed a further improvement of MMSE

TABLE 1. *Patient demographic data, medications received, and clinical rating scores*

Number	Age, sex	Illness duration (years)	Current medications	MMSE pre-trial	MMSE post-trial	ADASS-Cog pre-trial	ADASS-Cog post-trial	PANSS pre-trial	PANSS post-trial	CGI severity pre-trial	CGI improvement
1	65, F	25	haloperidol 10 mg, haloperidol 100 mg depot IM monthly, trihexyphenidyl 5 mg, lorazepam 2 mg	24	28	13	9	119	51	6	1
2	54, F	25	risperidone 3 mg	7	12	75	50	118	95	7	3
3	61, M	30	risperidone 4 mg, clotiapine 40 mg, trihexiphenidyl 10 mg	15	15	21	21	101	101	6	4
4	67, M	49	risperidone 4 mg, biperiden 4 mg, haloperidol 100 mg depot IM monthly	22	28	20	16	78	62	6	3
5	67 F	40	clotiapine 40 mg, risperidone 6 mg, fluvastatin 40 mg, aspirin 100 mg, captopril 37.5 mg	21	24	17	20	109	109	5	4
6	76, F	45	olanzapine 10 mg, glibenclamide 2.5 mg, metphormin 850 mg, cilazapril 5 mg	20	25	13	12	127	127	5	4

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from 12 points to 13 points and an improvement of ADAS-COG from 50 points to 49 points without additional improvement on PANSS and CGI. The family requested to stop donepezil with the explanation that they wanted "the least possible drugs." The two other patients (1 and 4) continued treatment with donepezil with no change of the dose. Patient 4 requested termination of donepezil after a further 45 days of poststudy donepezil administration due to complaints of fatigue and weakness. Patient 1 continued to take donepezil, and on follow-up examination 18 months poststudy, she remained unhospitalized, while her medication remained unchanged. Her husband reported improvement with respect to self-care and basic daily living skills with full antipsychotic medication compliance. This is particularly noteworthy since in the past when her cognitive decline was progressive, she was noncompliant with medication and had unremitting psychosis that caused her frequent exacerbations and multiple hospitalizations at a rate of almost 1 every 3 months.

Side Effects

Only one patient (4) stopped the medication because of side effects with complaints of general weakness and fatigue. This occurred 45 days after continuation of 5 mg donepezil following the completion of the single-blind trial. Laboratory tests and physical and neurologic examination remained unremarkable. No patient demonstrated worsening of extrapyramidal side effects during the trial.

DISCUSSION

Our findings in this single-blind preliminary study suggest the efficacy of donepezil in the management of symptoms of dementia accompanying patients with comorbid schizophrenia and dementia. No additional effect reaching statistical significance was observed regarding overall psychotic symptoms, despite three of the six patients showing improvement. Furthermore, it should be noted that the effect on cognitive symptoms appeared to be more rapid than the improvement of cognitive function observed in patients with Alzheimer's disease who were administered donepezil (25). Thus, the modest enhancement of cognitive function with adjuvant donepezil administration suggests a specific and distinct effect of donepezil on cognitive improvement in this subpopulation of schizophrenia patients with dementia. The improvement in MMSE scores during the study duration suggests an overt beneficial effect on cognition as a direct result of donepezil administration on cognitive dysfunction, which in these patients may have been the result of superimposed dementia on long-term schizophrenia and intrinsic cognitive deficit typical of long-term schizophrenia in elderly patients. Although the significance of the findings indicating greater overall clinical improvement being correlated with greater improvement in cognitive function may be questionable considering the small sample sizes, we report them to indicate the phenomenon and recommend further study with larger sample sizes. While some have reported improvement of psychotic symptoms in patients who are administered donepezil for the management of Alzheimer's disease, our results were equivocal and demonstrated improvement of psychosis in only three of the patients. Obviously, a larger sample size would be required to confirm these observations. This apparent lack of effect on psychosis compared with patients with Alzheimer's disease may be because of the chronicity of schizophrenic illness or alternatively be related to the distinct pathophysiologic nature of the two illnesses.

It should be noted that there is evidence suggesting a neural substrate linking dysregulation of mesolimbic dopaminergic transmission to alterations in cortical cholinergic transmission. This evidence includes D_2 dopaminergic-mediated accumbens transmission regulating cortical acetylcholine release (26) and a decrease in the number or function of striatal cholinergic interneurons in schizophrenic patients (27). Studies also report decreases in choline acetyltransferase (ChAT) activity in the nucleus accumbens of schizophrenia patients and changes in acetylcholinesterase (AChE) activity in erythrocytes of schizophrenic patients (28). Others have implicated the prefrontal cortex as a potential site at which cholinergic dysfunction in schizophrenia patients may be manifested, as well as implicating cholinergic symptoms in the modulation of positive and negative symptoms (29). Additionally, ChAT and AChE activity appear to decrease in the cortex of schizophrenia patients who do not meet the criteria for Alzheimer's disease (28). Interestingly, regarding the subpopulation of schizophrenia patients with associated dementia, Powchik et al. (12) have reported that cognitive impairment is negatively correlated with ChAT activity to a similar degree as it is in persons with Alzheimer's disease.

Since, as we describe, cholinergic dysfunction may be present in some patients with schizophrenia (30), our findings further demonstrate the possibility that this disorder may be managed with cholinergic medications as augmenting agents, at least in this specific subpopulation of patients with comorbid dementia (9). Friedman et al. (31) have suggested that medications that increase cortical cholinergic activity may improve memory, language use, and constructional praxis in

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schizophrenia patients. Whether this may apply additionally to this subpopulation remains to be clarified.

We exclude antipsychotic medication as being a causative factor in the cognitive impairment because all the subjects received the medications for significant periods of time, and the consensus being from several studies that antipsychotic medications have, at most, minor deleterious effects on neuropsychologic test performance in healthy volunteers, and, if anything, they tend to improve performance in schizophrenia patients (32,33). Furthermore, while the possibility remains that long-term exposure to these drugs could have a cumulative toxic effect on intellectual function, Owens and Johnstone (34) found no correlation between intellectual test scores and lifetime neuroleptic exposure.

Regarding pharmacokinetic factors and interactions between donepezil and antipsychotic medication, it is important to recognize, for example, that CYP 2D6 is involved in the metabolism of risperidone and donepezil. This may become a factor in the emergence of extrapyramidal side effects as recently reported (35), which was, however, not observed in our patients. With regard to olanzapine, *in vitro* therapeutic doses of olanzapine have minimal inhibitory effects on other P-450 isoenzymes and, therefore, have low potential for interaction with metabolism of other drugs, including donepezil (36).

While we recognize that the small sample of patients, the short duration of treatment, and the single-blind nature of the study limit definitive conclusions that may be assumed from the results of the study, we suggest that donepezil may be effective treatment for the neurocognitive deficit in patients with comorbid diagnoses of schizophrenia and dementia. Regarding the effect of donepezil on psychosis, while speculative, we presume that donepezil may become an important and effective agent administered as adjuvant therapy to antipsychotic medication for a subgroup of schizophrenia patients with comorbid dementia. To confirm our observations, further investigation is mandated with a larger sample of subjects in the context of a double-blind medication trial.

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