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Donepezil for memory dysfunction in schizophrenia

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A case is reported of a 54-year-old female patient with schizophrenia and cognitive impairment. Her memory dysfunction improved following the addition of donepezil to quetiapine. The possible implications for future studies are reviewed.

Key words: antipsychotic agents, cholinergic system, cholinesterase inhibitors, cognition

Introduction

Cognitive dysfunction in schizophrenia is increasingly recognized as an important target for pharmacotherapy, and a range of largely unstudied options are available (Friedman *et al.*, 1999). A preliminary report of a controlled study of the cholinesterase inhibitor donepezil as a cognitive enhancing agent was negative in patients with schizophrenia treated with risperidone (Friedman *et al.*, 2001). A detailed case study of donepezil augmentation of olanzapine was positive, and suggested increased activation of prefrontal cortex and basal ganglia (Risch *et al.*, 2001). The present case report is of a positive response to donepezil in schizophrenia, with consideration of possible unique features which could be taken into consideration in future studies.

Case report

The patient, a 54-year-old, single white premenopausal female with a 30-year history of schizophrenia, was referred for assistance in treating deteriorating behaviour at her boarding home. Increasing confusion, difficulty following directions and completing activities of daily living, bizarre delusions and incomprehensible speech were noted over the past year. There was no comorbid drug or alcohol abuse. Specifically, she was a non-smoker throughout her life. Compliance with medications was assured and her regimen was quetiapine 500 mg/day; haloperidol 5 mg/day, lorazepam 3 mg/day, methotrimeprazine (a medium potency phenothiazine antipsychotic) 75 mg/day and benztropine 4 mg/day.

She first experienced symptoms of mental illness at age 24 years. Before this, her level of function was good: she had finished grade 12 schooling, held several office jobs and worked with children with mental retardation in a day-care centre. After becoming psychotic, she required hospitalization and treatment with antipsychotic medications for several months. Subsequently, there were nine hospitalizations, with lengths of stay ranging from 2 weeks to 7 months. She was treated with adequate trials of chlorpromazine, methotrimeprazine, fluphenazine, thioridazine, haloperidol, risperidone, olanzapine, quetiapine and clozapine. Her best response was to clozapine, which was discontinued after 1 year of treatment when her neutrophil count dropped to 0.9×10^9 cells/litre on one measurement during a viral upper respiratory tract infection.

She presented in an alert and cooperative fashion, but was difficult to access as she was a challenge to comprehend. This was a consequence of her high-pitched speech, which would be coherent initially and then deteriorate into a mumble. Her reliability as a historian was very poor. She was agitated, fidgeting and rocking back and forth during the interview. At times, she giggled inappropriately, and her speech was slightly pressured. Her thought form was mildly loosened when she could be understood, and there was evidence in her thought content of delusions of reference (Jesus sending her messages), somatic passivity experiences and bizarre delusions (she believed she was carrying twins and had been for years). She described 'visions' as well as experiencing the 'king' and 'queen' talking to her.

There were no neurological abnormalities on physical examination, and she had enjoyed fairly good physical health. The clinical impression was of cognitive impairment out of proportion to psychosis. Investigations for reversible causes of dementia were negative. Laboratory studies were within normal limits, including complete blood count, electrolytes, renal function tests, liver function tests, calcium, thyroid function, B_{12}, folate, routine urinalysis and syphilis screen. Electrocardiogram was normal. Non-contrast computed tomography scan of the head demonstrated cortical atrophy and mild ventricular enlargement.

Her baseline Positive and Negative Syndrome Scale (PANSS) scores are shown in Fig. 1. Her best Global Assessment of Functioning score for the previous year was estimated at 20, on admission 14; her best Social and Occupational Functioning Assessment Scale score for the previous year was 20, on admission 17. Her Clinical Global Impression score on admission was 7 (among the most severely ill patients with schizophrenia). The DSM-IV diagnosis determined through a multi-disciplinary conference was chronic schizophrenia, disorganized subtype. All medications were tapered and discontinued except quetiapine, which was increased to 800 mg for 3 weeks, without any resulting change in her mental state.

Due to her extensive cognitive impairment, a more detailed

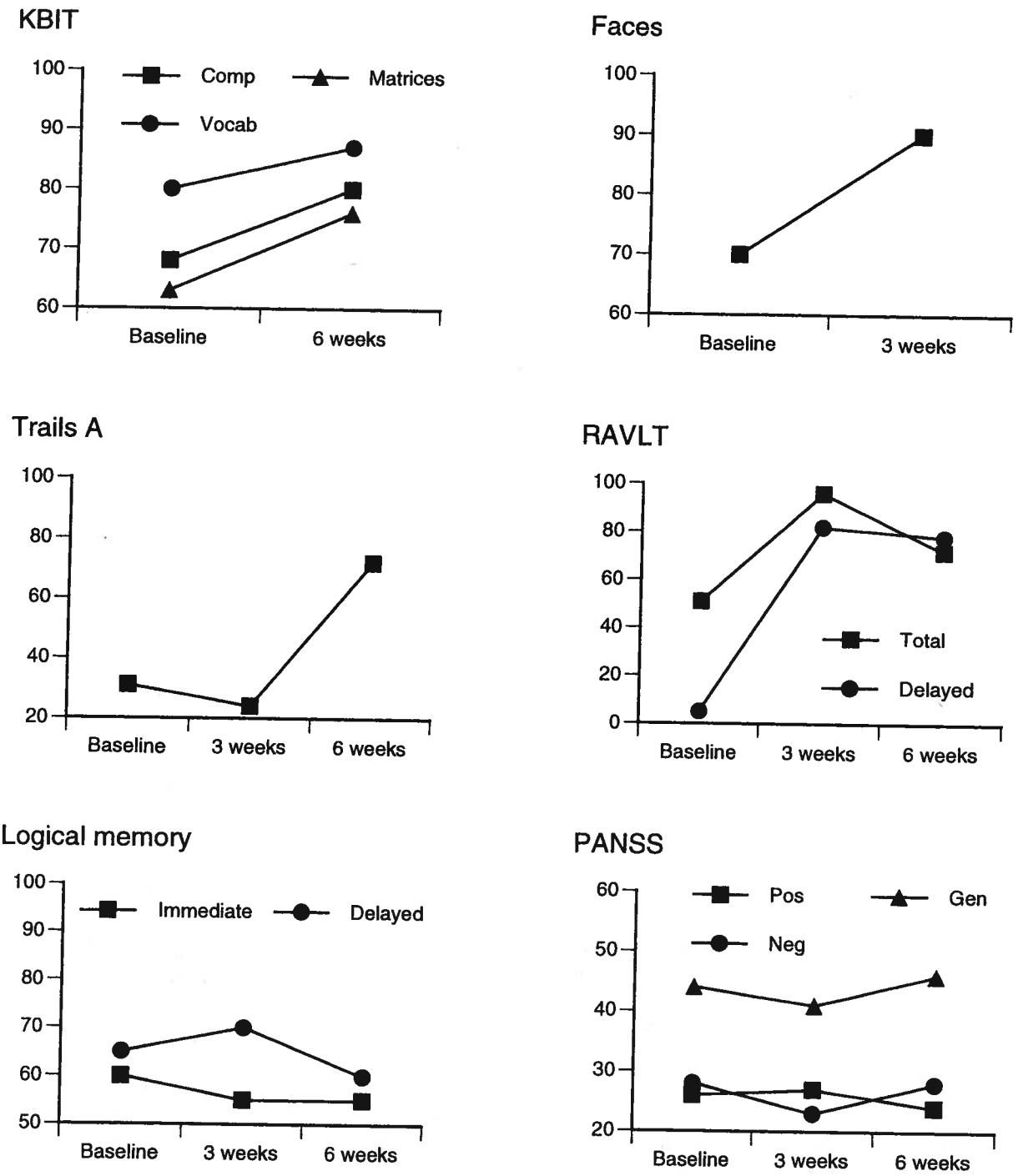

Figure 1 Psychological tests administered at baseline and following 3 and/or 6 weeks of augmentation of quetiapine with donepezil 5 mg. All neuropsychological measures are reported in standard score units with a mean of 100 and a standard deviation of 15. The PANSS positive and negative scales have a range of 7–49, the general scale 16–112. K-BIT, Kaufman Brief Intelligence test; Comp, Composite IQ score; Vocab, K-BIT Vocabulary score; Matrices, K-BIT Matrices score; Faces, Immediate Face Memory score from the Wechsler Memory Scale (3rd edition); Trails A, Trail Making test (Form A); RAVLT, Rey Auditory Verbal Learning test, total refers to total recall (five trials); Logical Memory, Logical Memory score from the Wechsler Memory Scale (3rd revision); PANSS, Positive and Negative Syndrome Scale

neuropsychological battery was performed (Fig. 1). The baseline assessments were carried out following 4 weeks of quetiapine 500 mg/day as monotherapy. Using the Wide-Range Achievement Test, her premorbid intelligence quotient (IQ) was estimated as 91, consistent with her education and good level of function prior to becoming ill. When tested at age 38 years, her IQ was estimated at 69. The present composite IQ score of 68 was consistent with this, and indicated significant intellectual impairment associated with her illness. This longstanding, static impairment was unlikely to be related to a progressive form of dementia, such as Alzheimer's

disease. A trial of donepezil 5 mg/day was initiated, with quetiapine kept constant at 500 mg/day. She was retested at 3 and 6 weeks. No side-effects to donepezil were noted and, specifically, no Parkinsonism.

In terms of her baseline neuropsychological functioning, she was noted to be disoriented to date and personal information and scored in the deficient range (standard score = 61) on a Working Memory Index Subtest of the Wechsler Memory Scale (3rd edition). Figure 1 illustrates the results from all tests with at least two valid assessment points, and demonstrates several selective improvements in neurocognitive functioning after 3 and 6 weeks augmentation with donepezil. Not all testing is reported because of the patient's inability to complete tests, such as Trails B, or response bias (Face Recognition Delayed). Although a subset of cognitive test scores were improved, there was no detectable improvement in the ordinary clinical setting at this time. The PANSS scores shown in Fig. 1 indicated that the cognitive improvements were not associated with improvement in psychosis and, as a consequence, quetiapine was discontinued and another trial of clozapine attempted. Donepezil was increased to 10 mg/day after 3 months on clozapine. At this point, although the total PANSS scores was unchanged, there was enough overall clinical improvement to permit discharge from hospital back to the boarding home.

Discussion

Cognitive disability in schizophrenia has a significant impact on the prognosis of the illness (Cuesta *et al.*, 1998) and the level of functioning (Green, 1996). The effects of cognitive decline after illness onset may have a larger effect on level of functioning than the baseline severity of cognitive impairment or the degree of symptomatology (Harvey *et al.*, 1999). The neurocognitive deficits in schizophrenia may affect two-thirds or more of patients, and include impairments in attention, executive functioning, memory, language, intellectual ability, motor performance and spatial ability (Heinrichs and Zakzanis, 1998). Intellectual impairment that approximates dementia in severity was reported as a possible complication of schizophrenia (de Vries *et al.*, 2001). Eight patients with schizophrenia under the age of 65 years were found to have a mean decrease in their IQ scores of 29.3 points from their estimated premorbid level. Our patient suffered an estimated decrease in this range (23 points), although the rate and timing of her cognitive decline are uncertain. She did manifest symptoms of disorganization that were poorly controlled early in her course, and her cognitive impairment was present for at least 15 years.

Atypical antipsychotics have been suggested to possibly improve the intellectual compromise in schizophrenia (Meltzer and McGurk, 1999). There are numerous other proposed pharmacological strategies for augmenting cognitive performance including serotonin 1A agonists, glutamatergic agonists, noradrenergic α_2 receptor agonists, and cholinomimetics (muscarinic M1/M4 agonists and acetylcholinesterase inhibitors) (Friedman *et al.*, 1999; Sumiyoshi *et al.*, 2001).

Disturbances in the dopaminergic system with subsequent effects on the cholinergic system are thought to be a central pathophysiological mechanism in schizophrenia (Tandon and Greden, 1989; Sarter, 1994). Decreased post-mortem cortical choline acetyltransferase activity appeared to correlate with more severe antemortem dementia in patients with schizophrenia (Powchik *et al.*, 1998). Recently, variations in patterns of nicotine binding in the striatum (Court *et al.*, 2000), deficits in striatal cholinergic interneurons (Holt *et al.*, 1999) and altered sensitivity of nicotinic receptors in patients with schizophrenia (Mihailescu and Drucker-Colin, 2000) have also suggested manipulation of the cholinergic system as a potential therapeutic avenue.

A modest dose-related improvement with donepezil compared to placebo was demonstrated in Alzheimer's disease patients using cognitive scores on an Alzheimer's assessment scale at 12, 18 and 24 weeks (Rogers *et al.*, 1998). Confirmation of these phase III trials in a community sample showed improved cognition as early as 6 weeks with donepezil compared to placebo (Greenberg *et al.*, 2000). Quality of life measures have not been shown to yield a difference. The effects of cholinesterase inhibition may not be specific to Alzheimer's disease; donepezil improved moderate to severe cognitive impairment associated with multiple sclerosis as well (Greene *et al.*, 2000).

The marked improvement in our patient's performance on intelligence, verbal learning efficiency and retention was not likely to be entirely attributable to a practice effect, although practice may have made a modest contribution to her improvement. An alternate form of the word list learning showed improvement at 6 weeks. While we have no precise means of estimating typical practice in patients with severe psychosis, it is likely that this effect in individuals with such significantly compromised abilities would be attenuated, and carry-over from earlier sessions would be minimal.

An effort was made to repeat tests under similar circumstances; however, not all tests were repeated at each sitting. It is also unclear why memory for prose passages (tests in logical memory) did not reflect improvements seen on other tasks. She may have been confused by the inherent structure of the passage as a consequence of the disorganization associated with her psychotic symptoms. In fact, the marked improvement seen in verbal acquisition and retention was for unrelated word items that lack such structure. Tasks that involved more logical associations such as recalling stories appeared to be more of a challenge.

Similar to studies in the dementia population, side-effects did not limit continuation of our trial, and global functioning measures remained unchanged. We noted improvements in test performance at 3 weeks, which is earlier than documented in Alzheimer's patients. The neuropsychological battery we used was more likely to detect subtle changes in performance than the more general cognitive measures frequently used in the dementia population.

Two features of the present case may be worth considering in future studies. First, as noted above, the history and test results were consistent with dementia as a complication of schizophrenia. At baseline, she showed global cognitive impairments affecting memory and information processing speed most profoundly. These impairments were marked even when compared with other patients with schizophrenia (Heinrichs and Zakzanis, 1998). Donepezil may not be as valuable in patients with less severe cognitive impairment, or in patients who have premorbid cognitive impairment. Second, she had never smoked. Nicotine can improve cognitive performance in patients with schizophrenia, at least when also treated with haloperidol (Levin *et al.*, 1996). Non-smokers with schizophrenia may have more severe cognitive impairments in some domains than smokers (George *et al.*, 2001). It is possible that smokers already have maximal cholinergic augmentation,

and/or their nicotinic receptors may be less sensitive to cholinergic enhancement mediated through cholinesterase inhibition.

In summary, we report a case involving a marked cognitive deficit in a psychotic patient that appeared to improve with donepezil, despite no improvement in psychosis. Specifically, improvement in verbal acquisition and retention skills may be dissociable from change in other aspects of cognition, and in overall severity of psychosis. Clearly, additional work is required to establish this finding with an adequate degree of certainty. Ultimately, this line of inquiry may increase our understanding of the contribution of the cholinergic system to the pathophysiology of schizophrenia.

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