related kinase family of receptor tyrosine kinases. Activation of tropomyosin-related kinase B triggers the phosphatidylinositol-3-OH-kinase-Akt pathway,[1] inactivating glycogen synthase kinase-3β, which is linked to the production of β-amyloid plaques and the hyperphosphorylation of tau, the two pathogenic features of Alzheimer's disease. Insulin signaling acts through this same intracellular pathway. It has also been shown that insulin signaling deficiency is related to Alzheimer's disease pathology.[2] Moreover, it seems that insulin signaling regulates the expression of the insulin-degrading enzyme, a protein implicated in β-amyloid degradation.[3]

Thiazolidinediones that are used to treat insulin resistance in type II diabetes mellitus patients work to activate peroxisome proliferator-activated receptor-γ, which in turn up-regulates proteins and enzymes related to insulin signaling such as insulin receptor substrates 1 and 2, and phosphatidylinositol-3-OH-kinase. Fuenzalida et al.[4] showed that nerve growth factor signaling pathway activated peroxisome proliferator-activated receptor-γ and that this protects rat hippocampal neurons against β-amyloid toxicity. They speculate that this could be mediated by tropomyosin-related kinase A activation. Even more, peroxisome proliferator-activated receptor-γ inhibited glycogen synthase kinase-3β.[4]

Recently, Reger et al.[5] showed beneficial effects of intranasal insulin in memory performance and β-amyloid levels in Alzheimer's disease patients. Further research with insulin and insulin sensitizers are needed to find a better comprehensive approach for Alzheimer's disease patients.

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Neurometabolic Correlations of Donepezil and Rivastigmine in Dementia Patients: A Different Neuroprotective Effect

To the Editor: Alzheimer's disease is the most frequently encountered type of primary degenerative dementia, which is the primary cause of morbidity and mortality in the elderly population. Recent studies have shown that functionality is preserved much longer in patients who received therapy in the early phases of dementia.[1] This increased the importance of rapid initiation of choline esterase inhibitors widely used in the treatment of Alzheimer's disease.

The evidence for the neuroprotective role of acetylcholine esterase inhibitors is rapidly replicating.[2,3] Rivastigmine is an effective cholinesterase inhibitor of acetyl and butyrylcholine esterase. Studies examining its superiority to donepezil revealed similar efficiency in the improvement of cognitive functions.

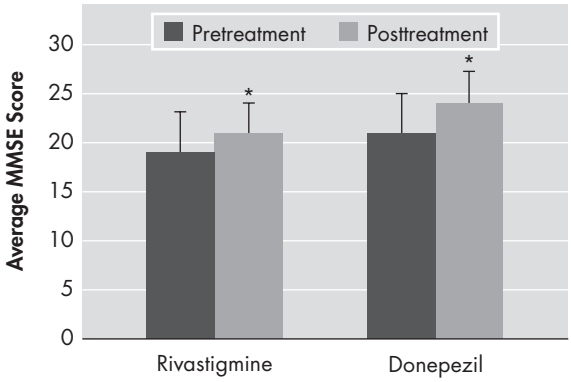
However, the existing clinical data were not combined with magnetic resonance spectroscopy (MRS) in any of these studies. MRS can provide quantitative analysis, unlike a subjective radiological evaluation limited with MRI and CT. In light of these findings, we compared the neurometabolic and the clinical correlations of rivastigmine and donepezil simultaneously.

Each group included 10 patients (five men and five women for the rivastigmine group; four men and six women for the donepezil group). The average age for rivastigmine and donepezil groups was 68.9±8.6 and 63.5±6.4 years old, respectively, and the target dose was determined as 12 mg/day and 10 mg/day for rivastigmine tartrate and donepezil hydrochloride, respectively. The Mini-Mental State Examination (MMSE), and MRS assays were repeated after 12 weeks of therapy.

Discussion

We found similar significant posttreatment improvements in cognitive function scores (Figure 1) in both of the treatment groups as well as strong correlations with the cerebral metabolite values. However, although rivastigmine and donepezil caused similar significant increases in *N*-acetylaspartate/choline level (rivastigmine: pretreatment 0.70±36, posttreat-

FIGURE 1. Posttreatment Improvements in Cognitive Function Scores



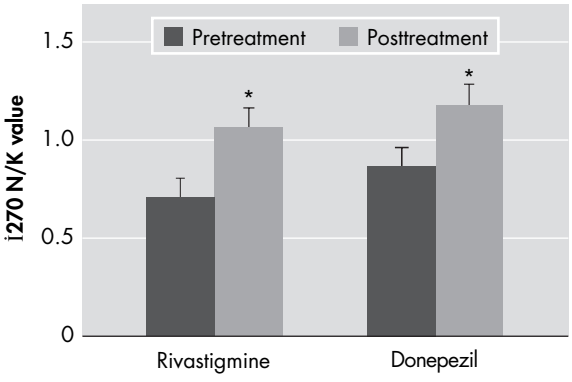
The posttreatment Mini-Mental State Examination (MMSE) scores were statistically significantly higher in the donepezil and rivastigmine groups (paired t test, $p=0.029$ and $p=0.001$, respectively).
*Significantly different ($p\leq0.05$).

ment 1.06±0.33; donepezil: pretreatment 0.86±0.40, posttreatment 1.17±0.27) (Wilcoxon rank sum test, $p<0.05$) (Figure 2), there was relatively more increasing effect of rivastigmine on İ 270 *N*-acetylaspartate levels than donepezil (rivastigmine: pretreatment 15.1±7.7, posttreatment 19.9±7.7; donepezil: pretreatment 20.0±7.9, posttreatment 22.6±4).

In light of recent developments suggesting *N*-acetylaspartate as a marker for neuronal loss and rapidly replicating evidences about the neuroprotective role of acetylcholine esterase inhibitors,[3,4] we can hypothesize that this difference in *N*-acetylaspartate levels can be attributed to the dual effect of rivastigmine on cholinergic neurotransmission (acetyl and butyrylcholine esterase inhibition), which can contribute to its possible neuroprotective effect.

This is suggested by preclinical studies which indicated the enhancing effect of cholinergic activity in neuroprotection as well as the reversal of such effect under cholinergic blockage in different models of traumatic brain injury.[5]

FIGURE 2. Posttreatment Improvements in Cognitive Function Scores



In both treatment groups, the posttreatment increase in İ 270 *N*-acetylaspartate levels was found to be statistically significant.
*Significantly different ($p\leq0.05$).

From this point of view, we think that this is an interesting study that compares not only the neuropsychological effects of two different groups of acetylcholine esterase inhibitors but also their effect on the quantitative neurometabolic assay that can reflect their possible underlying antiapoptotic and/or antinecrotic effect. This was also suggested by recent MRI hippocampal volumetric studies with donepezil.[3]

Further experiments to evaluate the underlying neuroprotective mechanisms as well as long- and short-term clinical reflections of such neuroprotective effects using MRS and positron emission tomography studies would be the logical future steps in the field of psychiatry research.

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Improvement in Pisa Syndrome and Tardive Dyskinesia Following Aripiprazole Treatment

To the Editor: Tardive dystonia and tardive dyskinesia, parts of a group of delayed-onset neuroleptic-induced movement disorders, may coexist but are postulated to be different in prevalence, demographic profiles, clinical presentations, and to have different neurochemical mechanisms.[1] Drug-induced Pisa syndrome, manifesting as a tonic lateral flexion of trunk after exposure to neuroleptics, consists of both acute and persistent types. Thus, Pisa syndrome can also be viewed as an atypical subtype of tardive dystonia.[1,2] Aripiprazole exerts a therapeutic effect by partial D2 agonism rather than D2 receptor blockage,[3] implying its possibly beneficial effect to delayed-onset extrapyramidal symptoms. Previous reports often focused on the issue relevant to either one of the tardive syndromes. We report on a patient whose Pisa syndrome and tardive dyskinesia were improved following aripiprazole treatment.

Case Report

Ms. Y, a 31-year-old schizophrenia patient (DSM-IV criteria), had psychotic symptoms onset at the age of 20. Her symptoms were rapidly alleviated after 6 months of sulpiride therapy with trihexyphenidyl. She had received treatment with trifluoperazine, haloperidol, clotiapine, and zotepine in the following years for intermittent relapsing symptoms. Oral-buccal-lingual dyskinesia was first noticed after she had been treated with risperidone for 2 years. Her antipsychotic was then switched to olanzapine. Moreover, she developed left-tilting of her trunk and right-sided rotation of her neck with subjective stiffness in her chin and shoulders during olanzapine treatment. A diagnosis of tardive dystonia was made according to Burke and colleagues' criteria.[4] Her dystonic reaction showed no improvement after high-dose anticholinergic medication (biperiden, 8 mg) was added on and olanzapine was withdrawn. Lingual dyskinesia was partially ameliorated after replacement of olanzapine by amisulpride for 2 months, but Pisa syndrome did not improve. Eventually, aripiprazole and amantadine were substituted for amisulpride and biperiden, respectively. Tardive dyskinesia disappeared in one month, and Pisa syndrome was improved significantly after 2 months' administration of aripiprazole, 30 mg/day, and amantadine, 200 mg/day.

Discussion

Despite the sharing dopamine blockade in the pathogenesis of Pisa syndrome and tardive dyskinesia, cholinergic-dopaminergic imbalance may better account for the former whereas dopamine receptor hypersensitivity may account for the latter.[2] Our patient developed persistent motor symptoms insidiously after long-term conventional and atypical antipsychotics, which excluded an acute tonic reaction.[2] This patient's tardive syndromes were neither resolved by withdrawal of olanzapine (a multi-acting receptor-targeted antipsychotic with high 5HT2/D2 ratio), nor treatment of amisulpride (a D2/D3 receptor antagonist with high D3/D2 ratio).[3] Unlike other atypical antipsychotics, aripiprazole shows higher affinity at D2 receptors than at 5-HT2 receptors, and its weak partial $5HT_{1A}$ agonism is demonstrated in a recent study.[5] Thus, aripiprazole successfully improved both tardive dyskinesia and Pisa syndromes, possibly because it can reverse D2 receptor hypersensitivity and restore cholinergic-dopaminergic balance via D2 partial agonism. As for amantadine, there has been no substantial evidence regarding its effect on treating tardive dystonia. The role played by amantadine in this patient was unclear.

In summary, we suggest that aripiprazole is a potential drug for the management of Pisa syndrome coexistent with tardive dyskinesia. Aripiprazole is also a drug candidate to study the differential neurochemical mechanism of various subtypes of tardive syndromes.

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