Some schizophrenia patients have shown significant improvements in positive and negative symptoms when my colleagues and I added acetylcholinesterase inhibitors (AChEIs) to their antipsychotic regimens. We cannot rule out these benefits as placebo effects, but nevertheless they have been sustained over time. When patients appear to have benefited from AChEIs but stopped them, the benefits rapidly disappeared. Then, when these patients restarted the medications, the benefits recurred.

Unfortunately, recent well-controlled clinical studies have not supported these anecdotal findings or the results of approximately 20 preliminary trials. Thus, this article explains:

- why we don’t recommend using off-label AChEIs as a “first choice” augmentation strategy in schizophrenia patients at this time
- under what circumstances the adjunctive use of these agents might be reasonable.

**Why Alzheimer’s medications?**

Schizophrenia and Alzheimer’s disease (AD) have dramatically different onset, symptoms, course, and pathophysiology. As reviewed below, schizophrenia patients are no more likely to develop AD than the general population, and AChEIs—even when effective—have a short-term, limited benefit in AD.

So why are psychiatrists trying AD medications in patients with schizophrenia? The answer has to do with the intriguing effects of cholinergic agents on cognition.
Toward cognitive enhancement

Schizophrenia’s cognitive impairments may occur at a very early age, often before other overt symptoms, then may worsen—sometimes to dementia levels—when obvious psychotic symptoms emerge. Positive symptoms (hallucinations, delusions, thought disorder, etc.) and—to a lesser extent—negative symptoms (anhedonia, asociality, blunted affect, etc.) often improve when patients are treated with antipsychotics. Antipsychotics do not significantly improve cognitive symptoms (attention, reaction time, working memory, verbal fluency, etc.), however, and cognitive symptoms are the strongest predictors of poor functional outcomes in our patients.

Heterogeneous disorder. In 2000, Cummings summarized evidence from case reports and small studies that AChEIs were useful in treating neuropsychiatric conditions other than AD (Table 1). Cholinergic agents, Cummings noted, “affect many aspects of cognition, which suggests that the primary effect may be on an attentional or executive system with a secondary, pan-intellectual modulating influence on memory, language, and visuospatial skills.”

In schizophrenia, different patients have different types of cognitive impairment. Thus, broad-based cognitive enhancers such as AChEIs may be necessary for general use in this illness.

Acetyltransferase activity. Schizophrenia patients—even those meeting criteria for dementia—do not usually have typical AD neuropathology, and the incidence of AD is no different in elderly patients with or without comorbid schizophrenia. At autopsy, schizophrenia patients and normal controls have similar brain cortical choline acetyltransferase levels.

Nevertheless, persons with AD and those with schizophrenia show a similar, statistically significant negative correlation between premorbid Clinical Dementia Rating scale scores and brain cortical choline acetyltransferase activity (r = −0.36, P <0.0003 vs r = −0.29, P <0.005, respectively). Furthermore, studies have found cholinergic neurotransmission alterations in schizophrenia patients, including:

- a deficit in regulation of the low-affinity alpha-7 nicotinic receptor in those with impaired sensory gating
- altered high-affinity nicotinic receptor binding
- decreased hippocampal muscarinic receptor binding compared with matched normal controls
- reduced density of cholinergic interneurons in the ventral striatum.

These findings—plus the presumably “nonspecific” benefits of AChEIs in many illnesses—suggest that some patients with schizophrenia may have deficits in nicotinic and/or muscarinic cholinergic neurophysiology, which might be amenable to pharmacologic supplementation.

Table 1

<table>
<thead>
<tr>
<th>Cholinesterase inhibitors have shown benefit in many neuropsychiatric conditions</th>
</tr>
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<tbody>
<tr>
<td>Alcoholism with Wernicke’s encephalopathy</td>
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<tr>
<td>Attention-deficit/hyperactivity disorder</td>
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<tr>
<td>Autism</td>
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<tr>
<td>Bipolar disorder</td>
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<tr>
<td>Creutzfeldt-Jakob disease</td>
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<tr>
<td>Dementia pugilistica</td>
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<tr>
<td>Dementia with Lewy bodies</td>
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<tr>
<td>Olivopontocerebellar atrophy</td>
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<tr>
<td>Parkinson’s disease with dementia</td>
</tr>
<tr>
<td>Parkinsonism dementia complex of Guam</td>
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<tr>
<td>Pick’s disease</td>
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<tr>
<td>Progressive supranuclear palsy</td>
</tr>
<tr>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Sleep disorders</td>
</tr>
<tr>
<td>Subacute sclerosing panencephalitis</td>
</tr>
<tr>
<td>Traumatic brain injury</td>
</tr>
<tr>
<td>Vascular dementia</td>
</tr>
</tbody>
</table>

* Data from case reports and small studies. Cholinesterase inhibitors are FDA-approved only for Alzheimer’s dementia.

Source: Reference 3

AChE I augmentation

Mixed results. A number of investigators—including myself—have published
Cognition in schizophrenia

Clinical Point
In a large 12-week controlled trial, donepezil was no more effective than placebo in improving cognition in patients with schizophrenia

Data indicating that adding AChEIs—most often donepezil, but also rivastigmine or galantamine—to antipsychotic regimens may improve some schizophrenia patients’ symptoms and general functioning. These benefits were modest, however, when they were seen in these relatively small case reports and studies (Box). Other studies of AChEI augmentation of typical or atypical antipsychotics have been:

- equivocal, reporting benefits in some but not all patients (with no clear statistical or clinical conclusions) or in schizophrenia patients with comorbid dementia
- decisively negative, showing no benefits, particularly in comparatively larger, randomized, placebo-controlled trials

Meta-analysis power. In an attempt to understand these wide-ranging results, Chouinard et al. performed an elegant meta-analysis of oral AChEI augmentation therapies for cognitive enhancement in schizophrenia. This review emphasized the available studies’ complexity, small number and sample sizes, and small benefit effect sizes.

The authors concluded that—based on preliminary data—adjunctive AChEIs seemed to have “some beneficial effects” on attention and memory for schizophrenia patients.

Box

Early studies: Modest benefit from AChEIs in schizophrenia

Approximately 20 published studies have reported clinically significant benefits (positive symptom, negative symptom, and/or cognitive improvement) when schizophrenia patients received cholinesterase inhibitors with their antipsychotic regimens. These include case reports, case series, and double-blind, placebo-controlled, crossover or parallel-design studies, most with relatively small numbers of subjects.

Recent studies, however, have failed to show a clinically or statistically significant benefit from cholinesterase inhibitor augmentation in schizophrenia (Table 2). Some included larger sample sizes than earlier investigations and a placebo-active drug parallel design.

fMRI findings. A few crossover design studies of schizophrenia patients taking antipsychotics included functional magnetic resonance imaging (fMRI) at baseline and after cholinesterase inhibitor and placebo augmentation. Of interest, the basal “abnormal” pattern of the baseline fMR image became more “normal” when subjects were treated with donepezil.

Source: For reference citations, see this article at CurrentPsychiatry.com

The last word? Within weeks, however, results of a large multicenter trial by Keefe et al. showed that donepezil augmentation was no more effective than placebo in improving cognition in patients with schizophrenia or schizoaffective disorder. In this 38-center, randomized, double-blind, placebo-controlled, parallel design study, 250 patients with mild to moderate cognitive impairment received adjunctive donepezil—5 mg/d for 6 weeks, then 10 mg/d for 6 weeks—or placebo for 12 weeks.

Both the treatment and placebo groups experienced statistically and clinically significant benefits from baseline in measures of cognition, positive symptoms, and negative symptoms. For all measures, placebo augmentation was equal to or superior to donepezil augmentation.

Analyzing trial results

The large, well-designed clinical trial by Keefe et al. suggests conclusively that donepezil augmentation is not more effective than placebo in most stable schizophrenia or schizoaffective disorder patients with mild to moderate cognitive impairment.

Even so, it is arguably difficult to “prove a negative.” For example:

- Different dosages might have been more effective.
Controlled trials: No benefit from AChEIs in schizophrenia

<table>
<thead>
<tr>
<th>Study design</th>
<th>Subjects</th>
<th>Drug (dosage)</th>
<th>Results</th>
</tr>
</thead>
</table>
| Friedman et al (2002),
  double-blind, placebo-controlled    | 36 patients with schizophrenia                 | Donepezil, 5 or 10 mg/d for 12 weeks | Neither dose produced significant improvement in any cognitive measure |
| Tugal et al (2004),
  double-blind, placebo-controlled, crossover | 12 patients with stable schizophrenia          | Donepezil, 5 mg/d for 6 weeks, with crossover to placebo for 6 weeks | Treatment effect was not significant in any cognitive measure          |
| Freudenreich et al (2005),
  double-blind, placebo-controlled    | 36 stable outpatients with schizophrenia       | Donepezil, ≤10 mg/d for 8 weeks | No improvement in cognition or psychopathology measures                |
| Sharma et al (2006),
  randomized, double-blind, placebo-controlled | 21 patients with stable schizophrenia          | Rivastigmine, 12 mg/d for 24 weeks | No significant improvement in any cognitive measure                     |
| Fagerlund et al (2007),
  double-blind, placebo-controlled    | 21 patients enrolled, 11 completed            | Donepezil, 5 or 10 mg/d for 4 months added to ziprasidone | No differences in changes on PANSS scores or a global cognitive score |
| Keefe et al (2007),
  randomized, double-blind, placebo-controlled | 250 stable outpatients with schizophrenia or schizoaffective disorder | Donepezil, 5 mg for 6 weeks then 10 mg for 6 weeks | Donepezil was well-tolerated but did not improve cognition any more than placebo |

PANSS: Positive and Negative Syndrome Scale

- Longer treatment (>3 months) might have been necessary for donepezil to “surpass” the large placebo effect.
- Other AChEIs—such as galantamine, which stimulates nicotinic receptors—might be more effective than donepezil, which is predominantly muscarinic.

‘Subgroup’ hypothesis. Finally, if schizophrenia’s pathophysiology is extremely heterogeneous, AChEI augmentation might benefit only the small subgroup of patients with decreased cholinergic activity. Most other patients—without decreased cholinergic activity—would not benefit or might even worsen. In support of the “subgroup” hypothesis, Miller has reported that many augmentation agents have efficacy in schizophrenia—but only in a minority of patients.

If this hypothesis is true, clinicians would need to differentiate patients before giving them trials of AChEIs or other augmentation therapies. Genetic testing might identify different pathophysilogies among patients, but these technologies are not yet clinically available.

Recommendations

Clinical experience, case reports, and small case series indicate that occasional patients may benefit from AChEI augmentation. On the other hand, the only large, multicenter, placebo-controlled, parallel-design study found no difference between donepezil and placebo augmentation of atypical antipsychotics.

Thus this review of available evidence does not support the routine use of AChEI augmentation of typical or atypical antipsychotics as a viable psychopharmacologic strategy. Until more supportive evidence has been reported, this reviewer cannot recommend AChEIs as a “first line” augmentation strategy. Furthermore, because these medications do not have an FDA-approved indication in schizophrenia and are expensive, a cost-benefit appraisal also would not support their routine use.

Nevertheless, AChEIs are relatively safe and occasionally have been dramatically effective in a small subgroup of schizophrenia patients when used as augmentation. They may represent a reasonable approach:
• when other adjuncts have failed
• as a supplement to other augmentation strategies, such as cognitive-behavioral therapy or family therapy.

References

Related Resources

Drug Brand Names
Donepezil - Aricept
Galantamine - Reminyl, Razadyne
Rivastigmine - Exelon
Zaprisadone - Gedon

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Clinical Point
AChEIs may be a reasonable approach when other adjuncts have failed and as a supplement to cognitive-behavioral or family therapy.

Bottom Line
Available evidence and cost-benefit analysis suggest that acetylcholinesterase inhibitors (AChEIs) should not be high on your list as potential augmentation strategies for schizophrenia. Yet because schizophrenia is a heterogeneous brain disease, off-label AChEI augmentation might be a reasonable option for some patients when other add-on strategies fail to improve cognitive symptoms.