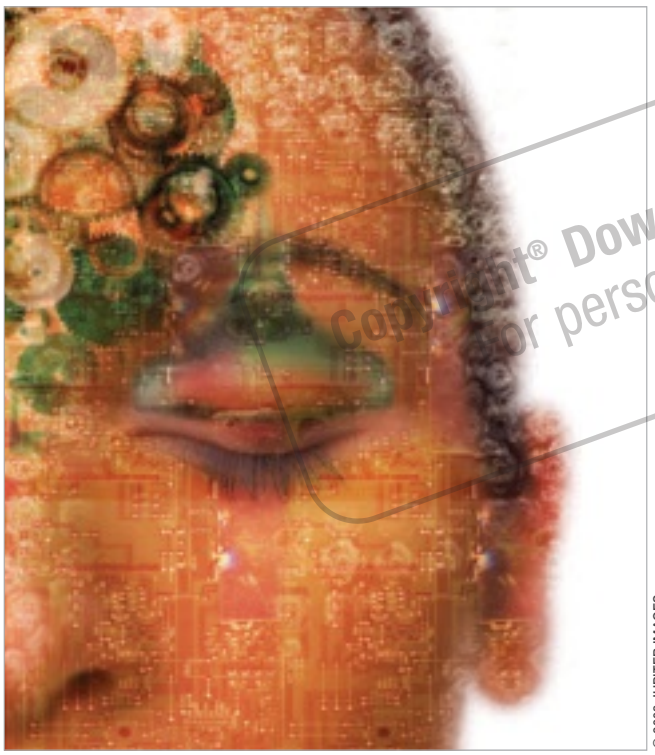
Current PSYCHIATRY

Do cholinesterase inhibitors enhance cognition in schizophrenia?



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Disorder's heterogeneity may help explain why the answer is unclear

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,[1] then may worsen—sometimes to dementia levels—when obvious psychotic symptoms emerge.[2]

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[3] 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, panintellectual modulating influence on memory, language, and visuospatial skills."[4]

In schizophrenia, different patients have different types of cognitive impairment.[5] 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.[6] 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).[6] Furthermore, studies have found

Table 1

Cholinesterase inhibitors have shown benefit in many neuropsychiatric conditions*

Alcoholism with Wernicke's encephalopathy
Attention-deficit/hyperactivity disorder
Autism
Bipolar disorder
Creutzfeldt-Jakob disease
Dementia pugilistica
Dementia with Lewy bodies
Olivopontocerebellar atrophy
Parkinson's disease with dementia
Parkinsonism dementia complex of Guam
Pick's disease
Progressive supranuclear palsy
Schizophrenia
Sleep disorders
Subacute sclerosing panencephalitis
Traumatic brain injury
Vascular dementia

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

Source: Reference 3

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[7]
- altered high-affinity nicotinic receptor binding[8]
- decreased hippocampal muscarinic receptor binding compared with matched normal controls[9]
- reduced density of cholinergic interneurons in the ventral striatum.[10]

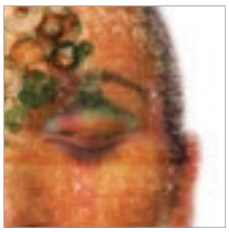
These findings—plus the presumably "nonspecific" benefits of AChEIs in many illnesses[3]—suggest that some patients with schizophrenia may have deficits in nicotinic and/or muscarinic cholinergic neurophysiology, which might be amenable to pharmacologic supplementation.

AChEI augmentation

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

Clinical Point

Neurologic studies suggest cholinergic neurotransmission deficits found in schizophrenia might be amenable to supplementation



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

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.[a-o]

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

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[11-14]
- decisively negative, showing no benefits, particularly in comparatively larger, randomized, placebo-controlled trials (***Table 2***).[15-19]

Meta-analysis power. In an attempt to understand these wide-ranging results, Chouinard et al[20] 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.

The last word? Within weeks, however, results of a large multicenter trial by Keefe et al[21] 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[21] 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.

Table 2

Controlled trials: No benefit from AChEIs in schizophrenia

Study design	Subjects	Drug (dosage)	Results
Friedman et al (2002),[15] 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),[16] 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),[17] 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),[18] 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),[19] 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),[21] 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[22] 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 pathophysiologies among patients, but these technologies are not yet clinically available.

Recommendations

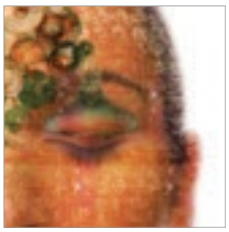
Clinical experience, case reports, and small case series indicate that occasional patients may benefit from AChEI augmentation. On the other hand, the only large, multicenter, placebo-controlled, parallel-design study found no difference between donepezil and placebo augmentation of atypical antipsychotics.[21]

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:

Clinical Point

Many augmentation agents have efficacy in schizophrenia, but only in a minority of patients



Clinical Point

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

- when other adjuncts have failed
- as a supplement to other augmentation strategies, such as cognitive-behavioral therapy or family therapy.

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Related Resources

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Drug Brand Names

Donepezil • Aricept
Galantamine • Reminyl, Razadyne
Rivastigmine • Exelon
Ziprasidone • Geodon

Disclosure

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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.