

Cholinesterase Inhibitors: A New Class of Psychotropic Compounds

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Objective: This article reviews evidence indicating that acetylcholinesterase inhibitors have psychotropic properties. **Method:** The author reviewed the English-language literature pertinent to the response of neuropsychiatric symptoms in Alzheimer's disease and related conditions to cholinergic agents. **Results:** The cholinergic system originates in the basal forebrain and projects diffusely to the cerebral cortex; the limbic and paralimbic regions receive the most abundant cholinergic projections. The basal forebrain nuclei are positioned at the interface of the limbic system and cerebral cortex, where they play a role in mediating emotional responses. The basal forebrain nuclei are atrophic in Alzheimer's disease, leading to a widespread cholinergic deficit. The cholinergic disturbance may contribute to neuropsychiatric manifestations of the disease. The treatment of patients with Alzheimer's disease with acetylcholinesterase inhibitors reduces neuropsychiatric symptoms, particularly apathy and visual hallucinations. In some studies, a variety of other neuropsychiatric symptoms have been reported to respond to treatment with acetylcholinesterase inhibitors. Response profiles vary among acetylcholinesterase inhibitors. **Conclusions:** Acetylcholinesterase inhibitors have psychotropic effects and may play an important role in controlling neuropsychiatric and behavioral disturbances in patients with Alzheimer's disease. These agents also may contribute to the management of other disorders with cholinergic system abnormalities and neuropsychiatric symptoms. The beneficial response is most likely mediated through limbic cholinergic structures.

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Acetylcholinesterase inhibitors have recently been introduced as cognition-enhancing agents in the treatment of patients with mild to moderate Alzheimer's disease. Tacrine (1–3) and donepezil (4–6) have been approved by the U.S. Food and Drug Administration (FDA); metrifonate (7, 8), and rivastigmine (9–11) are under review as possible marketable compounds, and long-acting physostigmine (12), eptastigmine (13), huperzine (14), galantamine (15), and velnacrine (16) have been investigated as acetylcholinesterase inhibitors with potential therapeutic benefit in Alzheimer's disease. These agents exert their beneficial effect on intellectual functioning by blocking acetylcholinesterase and enhancing cholinergic function. They have been developed to improve the neuropsychological deficits of Alzheimer's disease, as shown in most clinical trials by improved scores or superior performance compared to patients receiving placebo on the cogni-

tive subscale of the Alzheimer's Disease Assessment Scale (17), the Mini-Mental State examination (18), and a global scale such as the Clinician Interview-Based Impression (19).

Evidence has accrued that acetylcholinesterase inhibitors ameliorate behavioral disturbances as well as enhance cognition. These observations have implications for understanding the pathophysiological basis of neuropsychiatric symptoms in Alzheimer's disease (20, 21) and for developing therapeutic options for clinicians involved in managing behavioral alterations in patients with the disease. This review presents the available data concerning the psychotropic effects of acetylcholinesterase inhibitors and describes the neurobiological basis for these neuropsychiatric alterations.

CENTRAL CHOLINERGIC SYSTEMS

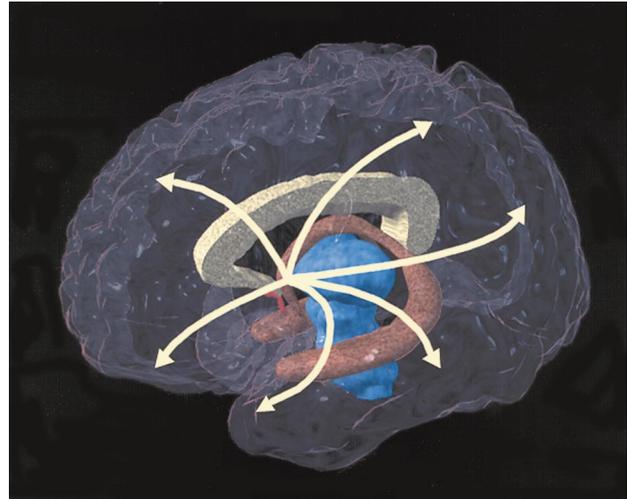
Anatomy of the Cholinergic System

Acetylcholinesterase, the substrate of acetylcholinesterase inhibitors, is located in the synaptic space (soluble form) and in the synaptic membranes (membrane-bound form) of the neurons of the cholinergic system (22, 23). Thus, the anatomy of the cholinergic system determines the pharmacology of the response to acetylcholinesterase inhibitors.

Mesulam (24) identified eight cholinergic cell groups that form the origins of projections to other central nervous system (CNS) structures. The medial septal nucleus and the vertical nucleus of the diagonal band constitute the major cholinergic projections to the hippocampal formation, cingulate cortex, olfactory bulb, and hypothalamus. The horizontal limb of the diagonal band nucleus projects to the olfactory bulb, whereas the nucleus basalis of Meynert provides the major innervation of the cerebral cortex and amygdala (figure 1). The pedunculopontine nucleus and the laterodorsal tegmental nucleus of the brainstem project to the thalamus; the medial habenula innervates the interpeduncular nucleus; and the paraventricular nucleus projects to the superior colliculus. Cholinergic neurons manufacture choline acetyltransferase, which is transported to projection targets, where it catalyzes the synthesis of acetylcholine. All of the cholinergic innervation of the human cerebral cortex and thalamus arises from these extrinsic cholinergic sources.

All layers of the cerebral cortex receive cholinergic innervation; the density of cholinergic projections is highest in layers 1 and 2 and the upper regions of layer 3. Muscarinic cortical input disinhibits the cortical pyramidal cells that enhance the intralaminar transfer of information between cortical columns; in contrast, nicotinic input augments inhibition (25). There is regional variability in the cholinergic innervation of the human cortex (26): limbic areas that include the amygdala and hippocampus have the highest density of cholinergic axons; paralimbic regions have the next

FIGURE 1. Cholinergic Projections From the Nucleus Basalis to the Cerebral Cortex and Related Structures^a



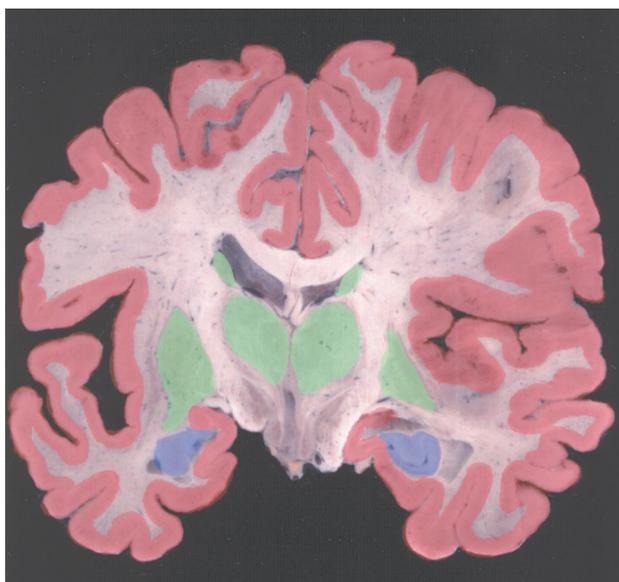
^a Image provided by the UCLA Laboratory of Neuroimaging; courtesy of Andrew Lee, John Bachelor, and Arthur Toga.

highest density of cholinergic fibers; the unimodal and heteromodal association cortices have intermediate densities of cholinergic innervation; and the primary visual cortex has the least abundant cortical cholinergic projections.

The neurons of the nucleus basalis and basal forebrain complex do not receive reciprocal projections from many of the cortical regions that they innervate. The afferent input to the nucleus basalis is largely from limbic brain regions, including the prepyriform cortex, orbitofrontal cortex, anterior insula, temporal pole, medial temporal cortex, entorhinal cortex, septal nuclei, nucleus accumbens, and hypothalamus (27). The virtually unique limbic origin of afferents to the nucleus basalis, coupled with its widespread cortical, limbic, and paralimbic projections, position this structure to determine the emotional valence of stimuli, influence the impact of emotionally relevant information on cortical function, and play a major role in emotionally relevant brain function (20, 27).

Cholinergic Receptors

Two classes of cholinergic receptors are recognized on the basis of their responses to specific agonists and antagonists (28)—muscarinic and nicotinic. Three types of muscarinic receptors have been identified pharmacologically, and five types have been shown to exist on the basis of molecular cloning experiments. Two major nicotinic receptor types have been identified in the CNS by using α -bungarotoxin and neuronal bungarotoxin (29). Muscarinic receptors use G proteins for signal transduction (28) and are metabotropic; nicotinic receptors are ionotropic and use ligand-gated ion channels for signal transduction (28, 30).

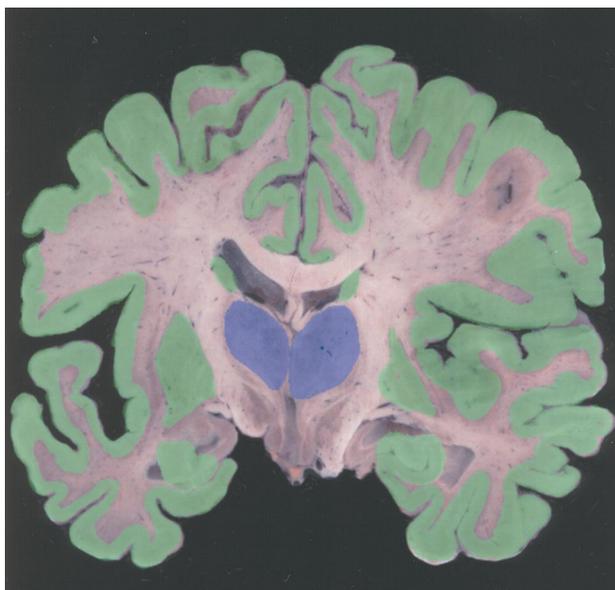
FIGURE 2. Regional Concentrations of M₁ Muscarinic Cholinergic Receptors^a

^a High=green, low=blue. Image provided by the UCLA Laboratory of Neuroimaging; courtesy of Andrew Lee, John Bachelor, and Arthur Toga.

The M₁ receptor is the most common muscarinic receptor subtype in the cerebral cortex (figure 2). Its highest concentrations are found in the dentate gyrus, hippocampus, anterior olfactory nucleus, cerebral cortex, olfactory tubercle, and nucleus accumbens. Moderate concentrations are found in the olfactory bulb and amygdala. The M₂ receptor is found in brain areas with abundant cholinergic neurons, including the interpeduncular nucleus and basal forebrain. The M₂ receptor is a presynaptic autoreceptor that governs cholinergic release (31). M₃ receptors are concentrated primarily in the diencephalic and brainstem regions, and M₄ receptors are found mainly in the striatum and olfactory tubercle (32). Nicotinic receptors are most abundant in the thalamus, periaqueductal gray, and substantia nigra (figure 3). Intermediate levels are found in the cerebral cortex and striatum. Relatively low levels are found in the hippocampus and amygdala (33).

Acetylcholinesterase

There are two cholinesterases in the CNS—acetylcholinesterase and butyrylcholine esterase. The latter is found also in the liver and plasma. The active site of acetylcholinesterase resides in a deep, narrow gorge within the three-dimensional structure of the enzyme (34, 35). Acetylcholinesterase inhibitors interact with the anionic or the esteratic (catalytic) site of the enzyme. Monomeric, dimeric, and tetrameric molecular forms of acetylcholinesterase arise from the posttranslational modification of the expressed protein. A single gene at chromosomal location 7q23 encodes acetyl-

FIGURE 3. Regional Concentrations of Nicotinic Cholinergic Receptors^a

^a High=green, medium=pink, low=blue. Image provided by the UCLA Laboratory of Neuroimaging; courtesy of Andrew Lee, John Bachelor, and Arthur Toga.

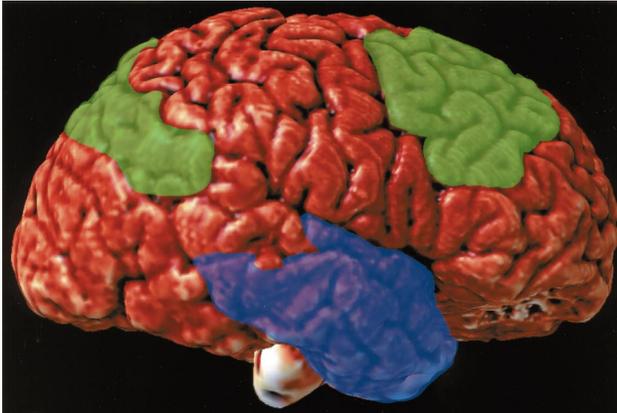
cholinesterase in humans (30, 34). The membrane-bound tetrameric form and the soluble monomeric form are the predominant enzyme species in humans (22, 23, 36).

CHOLINERGIC ABNORMALITIES IN ALZHEIMER'S DISEASE

Alzheimer's disease is a complex neurodegenerative disease with characteristic histological changes, including neuritic plaques, neurofibrillary tangles, and a variety of neurochemical deficits that affect the serotonergic, noradrenergic, and cholinergic systems (37). The cholinergic deficit of Alzheimer's disease is well documented; there is a marked loss of neurons in the basal forebrain nuclei that usually exceeds 75% of the total neuronal population at the time of an autopsy (38, 39). There are abundant neurofibrillary tangles in the remaining neurons of the basal nucleus (40). The death of cholinergic neurons leads to reductions in choline acetyltransferase of 80%–90% in the hippocampus and temporal cortex and 40%–75% in the parietal cortex and frontal convexity (figure 4 and figure 5). Less marked reductions occur in the mammillary bodies, cingulate gyrus, priming motor and sensory cortices, and caudate. Normal levels are present in the pons, midbrain, thalamus, hypothalamus, nucleus accumbens, and cerebellum (41, 42).

M₁ receptors are preserved or modestly reduced in Alzheimer's disease, presynaptic M₂ autoreceptors are decreased, and M₃ receptor levels are normal or up-

FIGURE 4. Regional Reductions of Cholinergic Markers in Alzheimer's Disease in the Lateral (Left) Brain Region^a



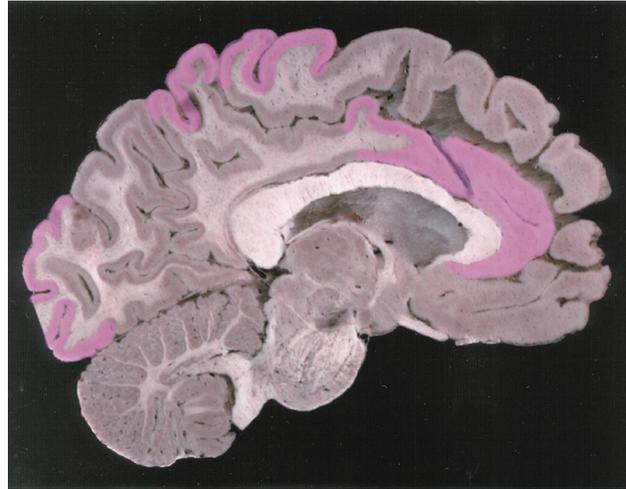
^a Marked=blue, medium=green. Image provided by the UCLA Laboratory of Neuroimaging; courtesy of Andrew Lee, John Bachelor, and Arthur Toga.

regulated (31, 43). The decreased M₁ receptor immunoreactivity suggests that the M₁ receptor function may be altered despite near-normal receptor numbers (31). Nicotinic receptors also are decreased in Alzheimer's disease (44). Studies of acetylcholinesterase reveal that there is a preferential loss of the tetrameric membrane-bound form compared to the monomeric soluble form (36).

CLASSES OF CHOLINESTERASE INHIBITORS

Table 1 provides comparative information on the principal acetylcholinesterase inhibitors that are currently approved or under investigation. These drugs represent different classes of agents: physostigmine is a carbamate, tacrine and velnacrine are acridines, donepezil is a piperidine, rivastigmine and eptastigmine are carbamates, metrifonate is an organophosphate, and galantamine is a phenanthrene alkaloid. They differ principally in the type of bond they form with acetylcholinesterase. Tacrine, velnacrine, donepezil, and huperzine are high-affinity, noncovalent inhibitors; metrifonate forms an irreversible covalent bond with the substrate. Tacrine and velnacrine are noncompetitive inhibitors, donepezil has noncompetitive and competitive properties, galantamine is a competitive inhibitor, and metrifonate begins with competitive inhibition and becomes a noncompetitive inhibitor over time (34). Differences in the duration of action and metabolism determine the dosing regimen and the likelihood of drug interactions. Galantamine is an acetylcholinesterase inhibitor and an allosteric modulator of nicotinic cholinergic receptors (45). The last activity may increase acetylcholine release by activating presynaptic nicotinic receptors. Tacrine and velnacrine are associated with a high frequency of hepatotoxicity; eptastigmine produces neutropenia (46).

FIGURE 5. Regional Reductions of Cholinergic Markers in Alzheimer's Disease in the Medial (Right) Brain Region^a



^a Modest cholinergic reductions in areas shown in purple. Image provided by the UCLA Laboratory of Neuroimaging; courtesy of Andrew Lee, John Bachelor, and Arthur Toga.

BEHAVIORAL RESPONSES TO CHOLINESTERASE INHIBITORS

Table 2 summarizes the available information derived from standardized rating scales on the neuropsychiatric changes observed after treatment with acetylcholinesterase inhibitors.

Physostigmine

Physostigmine was the acetylcholinesterase inhibitor most studied in the early phases of the development of antidementia drugs. Many studies did not include behavioral measures, but Harrell and colleagues (47) included the Sandoz Clinical Assessment—Geriatric Scale (48) and reported that in the group of patients who had responded to physostigmine, as evidenced by cognitive improvement or correct identification of group membership by the patient's family or physician, there was significantly greater behavioral improvement than in patients receiving placebo or those designated as nonresponders. Schwartz and Kohlstaedt (49) reported that four of 11 patients who received intramuscular physostigmine had dramatic behavioral improvements lasting up to 3 days after drug administration. There was decreased restlessness and depression and improved sociability and initiative. In contrast, Wirkowski and colleagues (50) reported two cases of "physostigmine syndrome" in which patients became anxious, irritable, and uncooperative and one experienced extreme fatigue. The doses in this study exceeded considerably those administered by Schwartz and Kohlstaedt (49).

Four studies have specifically investigated the neuropsychiatric effects of physostigmine. Molchan and colleagues (51) used a double-blind, placebo-controlled,

TABLE 1. Pharmacologic Characteristics of Cholinesterase Inhibitors

Name	Class	Selectivity	Reversibility	Enzymatic Site of Action	Competitive Inhibition	Bioavailability (%)
Tacrine	Acridine ^b	Butyrylcholine esterase > acetylcholinesterase	Reversible	Anionic	Noncompetitive	17–33
Donepezil	Piperidine	Butyrylcholine esterase > acetylcholinesterase	Reversible	Anionic	Mixed	100
Rivastigmine	Carbamate	Acetylcholinesterase > butyrylcholine esterase	Pseudo-irreversible	Esteratic	— ^c	40
Physostigmine	Carbamate	Butyrylcholine esterase > acetylcholinesterase	Reversible	Esteratic	— ^c	3–8
Metrifonate	Organophosphate	Butyrylcholine esterase > acetylcholinesterase	Irreversible	Esteratic	Competitive changing to noncompetitive	— ^c
Galantamine	Phenanthrene alkaloid	Acetylcholinesterase > butyrylcholine esterase	Reversible	— ^c	Competitive	85
Eptastigmine	Carbamate	Butyrylcholine esterase > acetylcholinesterase	Reversible	— ^c	— ^c	— ^c

^a CYP=cytochrome P450 enzyme. ^b Acetylcholinesterase. ^c Information not available to author.

TABLE 2. Studies of Cholinesterase Inhibitors That Used Structured Assessments of Behavioral Effects^a

Agent	Assessment	Behavioral Response
Physostigmine	Sandoz Clinical Assessment—Geriatric Scale Behavioral Pathology in Alzheimer’s Disease Rating Scale	Behavioral improvement Decreased delusions and agitation
Tacrine	Noncognitive portion of the Alzheimer’s Disease Assessment Scale	Improved cooperation, delusions, and pacing
Velnacrine	Neuropsychiatric Inventory Relative’s Assessment of Global Symptomatology	Diminished apathy, anxiety, disinhibition, and aberrant motor activity No increase in behavioral symptoms (versus increasing symptoms in placebo group)
Donepezil	Neuropsychiatric Inventory	Improved total score
Metrifonate	Neuropsychiatric Inventory	Improved total score, visual hallucinations, apathy, depression, anxiety, and aberrant motor behavior
Eptastigmine	Spontaneous Behavior Interview	Significant behavioral improvement
Rivastigmine	Neuropsychiatric Inventory	Reduced psychosis

^a References in text.

single-case study design to assess changes in psychiatric symptoms produced by physostigmine in a patient with Alzheimer’s disease who exhibited psychotic symptoms. During the period of drug administration, there was a marked diminution in the occurrence of hallucinations and delusions and a modest increase in depressive symptoms. My colleagues and I (52) used a double-blind, active-comparator study design to investigate the relative effects of physostigmine and haloperidol in two patients with Alzheimer’s disease and psychosis. Physostigmine reduced delusions and hallucinations in both patients without effects on their mood. We also performed a double-blind crossover trial of haloperidol and physostigmine (53) in 13 patients with advanced Alzheimer’s disease and behavioral disturbances. Psychosis and agitation scores on the Behavioral Pathology in Alzheimer’s Disease Rating Scale (54) declined comparably in response to treatment with the two agents. In a study of long-acting, controlled-release physostigmine, Thal and colleagues (12) found that agitation was observed in 50% fewer patients treated with the active agent than with placebo.

Tacrine

The noncognitive portion of the Alzheimer’s Disease Assessment Scale (17) was used in three pivotal dou-

ble-blind, placebo-controlled studies of tacrine (1–3). This scale includes a variety of items, including questions regarding mood, psychosis, appetite, and tremor. No statistically significant effects on the total score on this scale were observed in any of the studies, although nonsignificant trends in favor of tacrine were reported by both Farlow and colleagues (2) and Davis et al. (1). A meta-analysis of all of the randomized, double-blind, placebo-controlled trials of tacrine revealed a significant but small beneficial effect on behavior (55). In a post hoc analysis of the patient group studied by Knapp and colleagues (3), Raskind et al. (56) found that a significantly larger percentage of the patients who received tacrine had improvement or stabilization on scores for three of the scale items: cooperation, delusions, and pacing. This difference in outcome conclusions on the basis of total score compared to individual item analysis suggests that investigating the effects of acetylcholinesterase inhibitors on individual symptoms and syndromes is important; the analysis of total rating scale scores may obscure important effects. In an open-label study, my colleagues and I (57), using the Neuropsychiatric Inventory (58), documented statistically significant improvements in anxiety and disinhibition. In a follow-up study with a larger study group (59), significant changes were seen in total Neuropsy-

Time to Maximum Serum Concentration	Food Interferes With Absorption	Serum Half-Life	Protein Binding (%)	Metabolism ^a	Dose (mg/day)	Daily Dosings	Hepato-toxicity
1–2 hours	Yes	1.3–2.0 hours	75	CYP1A2, CYP2D6	80–160	4	Yes
3–5 hours	No	70–80 hours	96	CYP2D6, CYP3A4	5–10	1	No
0.5–2.0 hours	Yes	10 hours	40	Nonhepatic	6–12	2	No
— ^c	— ^c	0.5 hours (short-acting form)	— ^c	Nonhepatic	6–12	Every 2 hours (short-acting form)	No
26 minutes	No	Metrifonate=2 hours; DDVP ^d =4 hours	0	Nonhepatic	50–80	1	No
30–60 minutes	— ^c	5–7 hours	0	CYP2D6	30–50	3	No
1.0–1.4 hours	— ^c	12.1 hours	— ^c	— ^c	30–60	2–3	No

^d DDVP=dichlorovinyl dimethyl phosphate (active metabolite of metrifonate); duration of enzyme inhibition=1 month.

chiatric Inventory scores, as well as reductions in apathy, disinhibition, and aberrant motor behavior.

Velnacrine

Antuono et al. (16) observed that the patients who received placebo had increasing symptoms on the Relative's Assessment of Global Symptomatology (60) (which rates 21 psychiatric symptoms and behavioral disturbances), whereas those treated with high doses (225 mg/day) of velnacrine did not. The patients who received velnacrine also required less caregiving time, a measure that was significantly correlated with the noncognitive score on the Alzheimer's Disease Assessment Scale. Finally, patients treated with velnacrine were less likely to have emergent periods of agitation in the course of the 24-week study (1% versus 4% for patients who received placebo).

Donepezil

There have been few studies of the behavioral effects of donepezil in Alzheimer's disease. Kaufer and co-workers (61) reported a significant reduction in total Neuropsychiatric Inventory scores in a group of 40 patients with Alzheimer's disease who were capable of walking and were enrolled in an open-label study. My colleagues and I (62) found no statistically significant effect of donepezil on the items assessed by the Neuropsychiatric Inventory; two subgroups of patients were identified in post hoc analyses—one that improved and one that had no changes in response to treatment. Small et al. (63) reported that compared to patients not treated with donepezil, those receiving donepezil were significantly less likely to be administered antidepressant, antipsychotic, and sedative medications. Shea and colleagues (64) observed behavioral improvement in eight of nine patients with dementia with Lewy bodies, a syndrome closely related to Alzheimer's disease (65). Aarsland et al. (66) described a patient with dementia with Lewy bodies whose psy-

chosis responded to treatment with donepezil, and Kaufer et al. (67) reported two patients with dementia with Lewy bodies who had beneficial responses.

Metrifonate

In a randomized, double-blind, parallel-group, placebo-controlled, safety and cognitive efficacy study that lasted 26 weeks (8), patients who were treated with metrifonate manifested significant improvement or significantly less behavioral deterioration as shown by differences between metrifonate and placebo in total Neuropsychiatric Inventory scores and hallucination subscores. In a pooled analysis (68) of three prospective multicenter, randomized, double-blind, parallel-group, placebo-controlled trials of metrifonate that resulted in a total study group of 2,218 (411 patients taking placebo and 1,807 taking metrifonate), there were statistically significant differences between the placebo and active agent groups in favor of metrifonate on the total Neuropsychiatric Inventory score and on the scores for the hallucinations and apathy. There was a trend toward improvement in depression, anxiety, and aberrant motor behavior. Metrifonate improved or prevented the worsening of psychiatric and behavioral symptoms in 60% of the symptomatic patients. More than 50% of the patients with symptoms at baseline had clinically relevant (e.g., at least 30%) reductions in depression, anxiety, and apathy subscale scores. Raskind and colleagues (69) found that treatment with metrifonate (50 mg/day) reduced agitation and aberrant motor behavior as measured by the Neuropsychiatric Inventory; no statistically significant change was found in the same population by using the noncognitive portion of the Alzheimer's Disease Assessment Scale. Similarly, Becker and colleagues (70, 71) found no behavioral effects of metrifonate in studies using the noncognitive portion of the Alzheimer's Disease Assessment Scale or the Brief Psychiatric Rating Scale (BPRS) (72).

Eptastigmine

Imbimbo and colleagues (13) assessed the safety and efficacy of two doses (30 mg/day and 45 mg/day) of eptastigmine in a double-blind, placebo-controlled study. Using the Spontaneous Behavior Interview (73), a caregiver-based instrument that assesses a wide range of neuropsychiatric symptoms, they documented significant behavioral improvement in those who received 30 mg/day.

Rivastigmine

Jan and McKeith (74) reported that Neuropsychiatric Inventory scores that reflected the presence of psychosis were reduced by treatment with rivastigmine.

DISCUSSION

The principal conclusion of this review is that there is substantial and growing evidence that acetylcholinesterase inhibitors exert beneficial psychotropic effects in patients with Alzheimer's disease. Changes in neuropsychiatric symptoms should be among the clinical outcomes assessed in clinical trials of cholinergic agents, and clinicians should monitor psychiatric and behavioral responses in patients as an indication of drug effect when prescribing acetylcholinesterase inhibitors. Limbic and paralimbic cortices normally receive robust cholinergic innervation and have cholinergic deficits in Alzheimer's disease. Restoration of function in these brain regions that are critical to the mediation of emotion may underlie the behavioral response to acetylcholinesterase inhibitors.

Visual hallucinations and apathy are the most predictably responsive symptoms in most investigations. Anxiety, disinhibition, agitation, depression, delusions, and aberrant motor behavior have improved in some studies but not in others. The observation that several acetylcholinesterase inhibitors have similar effects on behavior suggests that this may be a class effect that reflects cholinergic enhancement in behaviorally relevant areas of the brain. However, acetylcholinesterase inhibitors may differ in their neuropsychiatric potency, and assessments of the psychotropic effects of individual agents are necessary.

Neurobiological Basis of the Response to Cholinergic Agents

Similarities between the neuropsychiatric symptoms of Alzheimer's disease and anticholinergic toxicity, the response of these symptoms to acetylcholinesterase inhibitors in conditions with cholinergic deficits, and the anatomic distribution of the cholinergic deficits all link cholinergic abnormalities to neuropsychiatric disturbances (20).

Anticholinergic agents induce changes in mental status that are similar to the neuropsychiatric symptoms of Alzheimer's disease, including thought disorganiza-

tion, visual hallucinations, and variable mood changes. Patients with Alzheimer's disease are unusually sensitive to the adverse effects of anticholinergic compounds (75). Neuropsychiatric symptoms induced by anticholinergics can be ameliorated by acetylcholinesterase inhibitors, including tacrine and physostigmine (76).

Patients with neurologic disorders with concomitant cholinergic deficits have been reported to respond to acetylcholinesterase inhibitors with reduced neuropsychiatric symptoms. Patients with dementia with Lewy bodies improve behaviorally in response to treatment with acetylcholinesterase inhibitors (64, 66, 67), and patients with Parkinson's disease and dementia with delusions and hallucinations may exhibit a beneficial neuropsychiatric response to therapy with acetylcholinesterase inhibitors (77). Cholinergic disturbances are present in the limbic and paralimbic cortices, which mediate functions critical to emotion (24, 27, 41) this regional deficiency may provide the substrate for some of the emotional disturbances of Alzheimer's disease and their response to cholinergic therapy.

Neurobiological Basis of Variations in Response to Cholinergic Therapy

Variations in the cholinergic deficit may account for some of the observed neuropsychiatric heterogeneity of Alzheimer's disease and the differences in response to treatment with cholinergic agents. A few patients with histopathological changes typical of Alzheimer's disease do not show a loss of neurons in the nucleus basalis or a cortical cholinergic deficit at autopsy (78). Some investigators have found greater preservation of the nucleus basalis neurons in patients with onset of the disease after age 65—the most typical age at onset—than in those whose symptoms began earlier in life (79). Davis and colleagues (80) reported that cortical cholinergic deficits were not present in elderly patients with mild to moderate Alzheimer's disease, although they were notable in patients with advanced disease. Patients with the apolipoprotein E-4 genotype have less brain choline acetyltransferase and nicotinic receptor binding than patients with the E-3 or E-2 genotype (81, 82). In one study (83), women with Alzheimer's disease had more cytoskeletal changes in the nucleus basalis than men with Alzheimer's disease. Moreover, women who receive estrogen replacement therapy and those without the E-4 genotype have been shown to respond most favorably to tacrine (84, 85). Thus, differences in age, disease severity, or genotype may influence the cholinergic deficit and the response to therapy with acetylcholinesterase inhibitors.

Additional variability in the behavioral symptoms of Alzheimer's disease and the responsiveness to cholinergic therapy may reflect dynamic interactions between the cholinergic changes and other transmitter systems involved in Alzheimer's disease (20, 37). The cholinergic system interacts with a variety of other transmitters or neuromodulators, including norepinephrine,

dopamine, serotonin, γ -aminobutyric acid, opioid peptides, galanin, substance P, and angiotensin II (86).

Relationship of Behavioral and Cognitive Changes

Acetylcholinesterase inhibitors were developed to enhance cognition in patients with Alzheimer's disease. In patients with mild to moderate cognitive impairment, they temporarily improve, stabilize, or reduce the rate of decline in memory and other intellectual functions relative to the results with placebo. A few studies have investigated the relationship between cognitive and behavioral responses. My colleagues and I (57), in a study of the neuropsychiatric effects of tacrine, noted that of 10 subjects who had at least a 3-point improvement in Mini-Mental State examination scores, all also had an improvement in neuropsychiatric symptoms as reflected by lower scores on the Neuropsychiatric Inventory. Of the nine patients in the study who met the stringent criteria of at least a 9-point reduction in scores on the Neuropsychiatric Inventory, six met the criteria for improved cognitive function; three patients showed a substantial behavioral benefit from therapy without a coincident improvement in cognition. In a follow-up article (59), we noted that patients with moderate cognitive impairment (Mini-Mental State examination scores between 11 and 20) had the most consistent improvement in behavior; mildly affected patients exhibited fewer behaviors and had less robust treatment effects; and patients with severe dementia (Mini-Mental State examination scores of 10 or lower) exhibited an improvement in some symptoms (delusions, anxiety, apathy, and disinhibition) and a worsening of others (hallucinations, agitation, dysphoria, euphoria, irritability, and aberrant motor behavior). The available data suggest that behavioral improvement is not contingent upon cognitive changes, and some patients exhibit behavioral responses without concurrent improvements in cognition.

Cholinergic agents 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 (87). Conversely, anticholinergics have disproportionately adverse effects on attention, immediate memory, and executive processes (88–90). Improvement in attention may underlie the reductions in apathy that are commonly associated with acetylcholinesterase inhibitors, possibly explaining why apathy is among the most responsive of neuropsychiatric symptoms to cholinergic therapy and why it correlates highly with cognitive improvement.

Regulatory Issues

FDA guidelines specify that a claim of efficacy in dementia can arise only 1) if a drug beneficially affects a core symptom or sign of dementia (i.e., has cognitive effects) or 2) if the effect of the drug is expressed only or is differentially expressed in patients with dementia who exhibit the symptom, sign, or behavior (91). It is

likely that cholinergic agents will benefit only patients who have disturbances of cholinergic function, and, thus, a specific indication for the treatment of neuropsychiatric symptoms in Alzheimer's disease may be allowable under the second FDA criterion. These considerations are important since cholinergic agents sometimes have emotional benefits for patients who do not improve cognitively; cholinergic agents may reduce neuropsychiatric symptoms late in the course of the disease, when cognitive enhancement may be limited; subpopulations of patients with behaviors that are specifically responsive to cholinergic agents may be identified; and agents may differ substantially in their efficacy regarding the treatment of neuropsychiatric symptoms. Thus, acetylcholinesterase inhibitors may have a psychotropic role that is independent of their cognitive effects and deserves regulatory recognition.

Clinical Importance

Reducing behavioral disturbances in patients with Alzheimer's disease is an important treatment goal. Neuropsychiatric disturbances are distressing to the patient who experiences fear, sadness, or anxiety; they are a source of marked distress for the caregiver (92); and they may precipitate institutionalization (93). Thus, the treatment of behavioral disturbances in Alzheimer's disease may ameliorate a patient's emotional distress and have secondary beneficial effects on the caregiver and on the opportunity for the patient to remain at home. Cholinergic agents may play an important role in these treatment goals.

Determining the magnitude of the psychotropic effect of acetylcholinesterase inhibitors is critical to establishing the clinical importance of these agents as treatments for neuropsychiatric symptoms. The psychotropic effects of individual cholinergic agents must be determined by prospective, randomized, controlled trials in which specific behavioral criteria are used for the selection of participants. The magnitude of the behavioral response can be anticipated by reviewing the change of symptoms in patients who were included from existing trials who were symptomatic at baseline. For example, of the patients treated with metrifonate, more than 50% had at least a 30% reduction in depression, anxiety, apathy, and total Neuropsychiatric Inventory scores (68). A 30% reduction in such symptoms is clinically relevant and comparable in magnitude to the changes observed with conventional psychotropic agents.

Role of Cholinergic Therapy in Other Conditions

Cholinergic treatments were developed for use in patients with Alzheimer's disease but may be applicable to patients with other disorders with cholinergic abnormalities. As already noted, preliminary evidence suggests that patients with dementia with Lewy bodies (64, 67) or Parkinson's disease with dementia (77) may exhibit a behavioral response to treatment with acetylcholinesterase inhibitors. Cortical cholinergic deficits

have been identified in a variety of other neurological disorders, including some cases of Pick's disease (94), olivopontocerebellar atrophy (95), progressive supranuclear palsy (96), the parkinsonism dementia complex of Guam (97), alcoholism with Wernicke's encephalopathy (98), Creutzfeldt-Jakob disease (99), subacute sclerosing panencephalitis (99), dementia pugilistica (100, 101), and traumatic brain injury (102). Patients with vascular dementia may have lesions that interrupt projections from the nucleus basalis and produce a cortical cholinergic deficit, or they may have mixed Alzheimer's disease plus cerebrovascular disease, which render them potentially responsive to acetylcholinesterase inhibitors (103). In addition, there are age-related changes in the nucleus basalis; cell numbers decline from approximately 450,000 in children to approximately 150,000 in elderly control subjects (104). Neuropsychiatric disturbances in these conditions might be reduced with the use of acetylcholinesterase inhibitors.

Open-label studies suggest that acetylcholinesterase inhibitors are of potential benefit in bipolar disorder (105), and cholinergic dysfunction may be present in some patients with schizophrenia (106). These findings raise the possibility that these disorders could be treated with cholinergic agents. Cholinesterase inhibitors also might benefit other disorders that putatively affect cholinergic systems, including attention deficit hyperactivity disorder, autism, and sleep disorders.

Behavioral Effects of Cholinergic Agonists

The hypothesis that cholinergic enhancement has psychotropic effects is strengthened by the observation that cholinergic agonists, as well as acetylcholinesterase inhibitors, have been reported to relieve neuropsychiatric symptoms. Xanomeline, an M₁- and M₄-selective muscarinic receptor agonist, was studied in a 6-month randomized, double-blind, placebo-controlled, parallel-group, multiple-dose trial (107). The agent exhibited substantial behavioral effects and significant dose-dependent reductions in vocal outbursts, suspiciousness, delusions, agitation, hallucinations, wandering, fearfulness, compulsiveness, tearfulness, mood swings, and threatening behaviors. The emergence of neuropsychiatric symptoms in patients in whom these were absent at baseline was suppressed. SB-202026, an M₁ partial agonist, produced an improvement in behavior, compared to the deterioration in behavior in the placebo group, when assessed with the noncognitive portion of the Alzheimer's Disease Assessment Scale (108).

The BPRS was used to assess behavioral responses to intravenous administration of the cholinergic agonist arecoline to patients with Alzheimer's disease (109). The anergia subscale of the BPRS showed a biphasic response, with decreases following low-dose infusions and increases following high-dose infusions. Similarly, the score on the thought disorder subscale increased with high-dose infusions.

Penn and colleagues (110) noted a trend toward decreased abnormal behavior scores during intraventricular administration of the cholinergic agonist bethanechol, whereas my colleagues and I (111) observed that two of five patients treated in the course of a dose-finding study exhibited distress, restlessness, agitation, and depression. Oxotremorine, a long-acting, direct cholinergic agonist, was administered to seven patients with Alzheimer's disease and was noted to precipitate depressive reactions in five (112). Intravenous nicotine has been used to assess the effect of nicotinic receptor stimulation in Alzheimer's disease, and Newhouse and colleagues (113) found that at the highest doses, patients exhibited significant elevations in scores for anxiety and depression.

Thus, whereas cholinergic agonists have produced improvement in neuropsychiatric symptoms in some studies of patients with Alzheimer's disease, the information available is limited, and the responses reported are less consistent than those observed with acetylcholinesterase inhibitors.

Summary

Acetylcholinesterase inhibitors have psychotropic as well as cognition-enhancing effects. The amelioration of apathy and reduction of visual hallucinations are the most reproducible effects on neuropsychiatric symptoms in Alzheimer's disease, but other neuropsychiatric symptoms have responded in some studies. There may be variations among acetylcholinesterase inhibitors in their psychotropic properties. The beneficial effects of acetylcholinesterase inhibitors on emotion and behavior are most likely mediated through cholinergic influences on limbic and paralimbic brain structures. Patients who exhibit substantial cognitive improvement usually have a concomitant behavioral response, but behavioral and cognitive responses may be dissociated. Clinical trials should be designed to clarify the neuropsychiatric effects of acetylcholinesterase inhibitors in Alzheimer's disease and to explore the potential use of these agents in other conditions.

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