Donepezil and Related Cholinesterase Inhibitors as Mood and Behavioral Controlling Agents

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Acetylcholinesterase inhibitors (ChEIs) enhance neuronal transmission by increasing the availability of acetylcholine in muscarinic and nicotinic receptors. This effect is believed to be responsible for the beneficial and protective effects of ChEIs on cognition in patients with Alzheimer's disease (AD). Effects of ChEIs on mood and behavior have also been reported. Earlier observations were limited by the exclusive availability of intravenous forms of administration, the short half-life of the formulations, and the high frequency of peripheral side effects. The introduction, in recent years, of better tolerated and less invasive compounds has rekindled the interest in cholinergic central nervous system mechanisms and has given rise to studies in areas other than cognition. The ChEI donepezil has been involved in the largest number of studies and positive reports. Preliminary observations suggest the possible value of ChEIs in the management of behavioral dysregulation, apathy, irritability, psychosis, depression, mania, tics, and delirium and in the diagnosis of depression, panic, and personality disorders.

Introduction

Acetylcholine is a neurotransmitter distributed extensively throughout the central nervous system (CNS). It modulates neuronal activity through agonist effects on muscarinic and nicotinic receptors. Acetylcholinesterase inhibitors (ChEIs) enhance neuronal transmission by preventing the hydrolysis of acetylcholine by the enzyme acetylcholinesterase, thus increasing the availability of acetylcholine in muscarinic and nicotinic receptors.

Cholinergic neurons demonstrate extensive distribution throughout the CNS and the peripheral nervous system. In the CNS they are believed to be associated with cognitive functions. One of the hypotheses of the origin of Alzheimer's disease (AD) postulates loss of cholinergic neurons as the primary cause. ChEIs have been used successfully in the improvement of cognition and slowing of cognitive deterioration in AD patients. It is believed that increased cholinergic tone is responsible for the beneficial effect of ChEIs on cognition.

In addition to effects on cognition, sporadic reports, mainly in the latter half of the 20th century, have suggested that cholinergic mechanisms may have a role in the modulation of human mood and behavior. Anecdotal reports date back to as early as 1889 when Willoughby [1] reported the resolution of manic symptoms following intravenous administration of pilocarpine. In the 1950s use of cholinesterase inhibitors in the form of organophosphate insecticides was found to be associated with an unusual frequency of depressive and psychotic symptoms [2,3,4]. In 1972 Janowsky *et al.* [5,6] published a report describing the resolution of manic symptoms following intravenous administration of the ChEI physostigmine and postulated the cholinergic-adrenergic hypothesis of mania and depression. According to the hypothesis, cholinergic and adrenergic tone had reciprocating and balancing effects on mood, adrenergic tone being manicogenic or antidepressant, and cholinergic tone being depressogenic or antimanic. In further support of the hypothesis were observations that cholinergic antagonist such as scopolamine may induce euphoria, talkativeness, difficulties in concentration, and flight of ideas [7], and that cholinomimetics may cause changes in sleep patterns (*eg*, decrease REM latency) and hormone levels (*eg*, adrenocorticotropic hormone [ACTH], cortisol) similar to those found in patients with major depression [8,9].

Critics of the cholinergic-adrenergic hypothesis claimed that the behavioral effects observed with ChEIs are secondary and nonspecific reaction to the wide range of unpleasant peripheral side effects they generate and the stress and malaise that ensue [10,11]. The short half-life (10–20 minutes) of physostigmine, the presence of central as well as peripheral effects, and the obligatory intravenous administration, were considered significant obstacles to the testing of the effects of ChEIs on mood and behavior [12].

In the past decade, the advent of orally administered ChEIs, with longer half-life and a more tolerable side-effect

profile, developed mainly for the treatment of cognitive deficits in AD, has led to an increasing number of reports on the effects of ChEIs in mood and behavior. This review focuses mainly on advancements made in the field over the past 2 to 3 years.

Properties of Cholinesterase Inhibitors

As a class ChEIs share a propensity for certain side effects. These include nausea, vomiting, anorexia, diarrhea, insomnia, fatigue, muscle cramps, and headache. The frequency and severity of these side effects vary substantially from compound to compound and appear to be related to the rate at which the dose of the compound is increased.

Donepezil

Donepezil hydrochloride is a reversible inhibitor of the enzyme acetylcholinesterase. The elimination half-life of donepezil is about 70 hours and pharmacokinetics are linear. It is approximately 96% bound to plasma proteins, although it was not found to have any significant effects on the binding of other highly protein bound drugs, including warfarin, digoxin, and furosemide. Nor do these drugs significantly affect donepezil. Donepezil is both excreted in the urine intact and extensively metabolized by CYP 450 isoenzymes 2D6 and 3A4 and by undergoing glucuronidation. Donepezil has greater selectivity for acetylcholinesterase (AChE), the type of ChE prevalent in the CNS, than it has for butylcholinesterase (BChE), the type of ChE which is primarily active outside of the blood brain barrier. The AChE:BChE ratio of donepezil (1200:1) is the highest available in this class of agents. This leads to increased central versus peripheral cholinergic specificity and is believed to be responsible for the favorable side effect profile of donepezil [13].

Tacrine

Tacrine hydrochloride is a reversible inhibitor of the enzyme acetylcholinesterase. Tacrine inhibits both AChE and BChE; but it is more selective for AChE than physostigmine. Tacrine undergoes extensive hepatic metabolism by the cytochrome P450 1A2 isoenzyme to at least three metabolites. The major metabolite, 1-hydroxy-tacrine (velnacrine), is active. Metabolites are excreted in the urine. Elimination half-life is between 1.5 and 4 hours. Tacrine is known to produce significant elevations in liver enzymes, notably the transaminases. These elevations are generally reversible and tend to be higher in women.

Rivastigmine

Rivastigmine is a carbamate–type pseudo–irreversible ChEI. Rivastigmine is not metabolized by the hepatic cytochrome P450 oxidative enzyme system and it exhibits approximately 40% protein-binding. Thus, drug interactions with rivastigmine are unlikely. Rivastigmine is rapidly and extensively metabolized primarily at CNS receptor sites via cholinesterase. The plasma half-lives of rivastigmine and the major metabolite are roughly 1 hour and 2 hours, respectively; however, the cholinesterase inhibition in the CNS lasts much longer (average 10 hours) than the short plasma half-life would predict. This is due to the fact that when rivastigmine's phenolic ZNN-666 metabolite is formed, it leaves behind a carbamate moiety that stays attached to the AChE receptor for up to 10 hours, which prevents the hydrolysis of ACh. Renal excretion of the metabolite is the major route of elimination.

Metrifonate

Metrifonate differs from other AChE inhibitors in that it is a prodrug that is nonenzymatically converted in vivo to the active moiety 2,2-dichlorovinyl dimethylphosphate (DDVP). DDVP administered alone has a very short plasma elimination half-life, but small amounts released from metrifonate are sufficient to inhibit AChE activity in vivo. DDVP is an irreversible inhibitor of AChE and activity is maintained for several weeks. It also inhibits BChE. Metrifonate has been withdrawn from marketing consideration due to safety concerns.

Galantamine

Galantamine is a reversible, competitive cholinesterase inhibitor. In addition, it allosterically modulates nicotinic acetylcholine receptors. Galantamine is approximately 50 times more effective against human AChE than against human BChE at therapeutic doses.

Controlled Release Physostigmine

A new extended-release formulation of physostigmine salicylate that yields sustained blood levels, permitting twice-daily dosing. It inhibits both AChE and BChE. It is associated with high frequency of gastrointestinal side effects.

Effect of Cholinesterase Inhibitors on Mood and Behavior in Alzheimer's Disease

Most available cholinesterase inhibitors exhibit a similar beneficial effect on cognition in AD patients. Patients with AD, however, typically present with a variety of neuropsychiatric symptoms including depression, apathy, agitation, hallucinations and psychosis. In addition, patients' ability to perform activities of daily living (ADL) is a crucial factor in the assessment of their disability, the burden on caregivers, and whether they require placement in a nursing facility or not. As a consequence, studies of ChEIs in AD started to include, in addition to measures of cognitive function, also measures of mood and behavior, such as the Neuropsychiatric Inventory (NPI) [14].

Donepezil

Donepezil was associated with the largest number of positive observations supporting a beneficial effect on mood

and behavior in AD patients. Weiner *et al.* [15] found that donepezil administration was associated with prevention of worsening depression and behavioral dysregulation over a 12-month period in AD patients. [15] Cummings *et al.* [16] reported that AD patients taking donepezil had lower lever of behavioral disturbances, were less threatening, and needed fewer sedatives than those not on donepezil as reported by caregivers after a 6-month treatment period. In an open-label study of 2092 patients with mild-moderate AD donepezil improved ADL, mood, social behavior, and disturbing behavior, as well as memory after 3 months when compared with baseline. Improvements were specifically reported in urinary incontinence, nighttime restlessness, irritability, aggressive behavior, stubbornness, wandering, and bowel control [17]. Hecker [18] reported improvement with donepezil in depression, anxiety, and apathy areas of the NPI when compared with placebo over 4 and 24 weeks in 191 moderate-severe AD patients. In a retrospective study in 86 AD patients Mega *et al.* [19] observed significant improvement from baseline in delusions, agitation, anxiety, disinhibition, and irritability in responders to donepezil. The behavioral changes were dose-dependent. They concluded that donepezil has psychotropic properties, and pretreatment behaviors help predict patients' responses to treatment. The same group also demonstrated that AD patients that responded to donepezil with reduction of irritability, delusions, hallucinations, agitation, euphoria, and aberrant motor behavior, also demonstrated lower regional perfusion in the dorsolateral parietal, orbital frontal, and anterior cingulated bilaterally [20]. More recently they reported that AD patients who responded to ChEI therapy had significantly more pretreatment irritability, disinhibition, and euphoria than nonresponders on the NPI, and significantly lower lateral orbital frontal ($P < 0.00001$) and dorsolateral frontal ($P < 0.0005$) perfusion bilaterally as evidenced by 99m labelled D, L-hexamethyly-propylene amine oxime (99m Tem-HMPAO) single photon emission computed tomography. They concluded that a pretreatment orbitofrontal syndrome may predict behavioral response to ChEI therapy in AD [21•].

Metrifonate in Alzheimer's disease

Several studies have demonstrated the efficacy of metrifonate in improving neuropsychiatric symptoms in AD patients. Kaufer [22•] reported beneficial effects of metrifonate in AD patients on the NPI total score, aberrant motor behavior, and in symptoms of depression, apathy and hallucinations when compared with placebo in a 26-week trial. In a study by Morris *et al.* [23] metrifonate was associated with improvements in behavioral and global functioning as well as cognitive functioning in mild-moderate AD patients over a 36-week period when compared with placebo. Cummings *et al.* [24] and Raskind *et al.* [25] reported similar results in mild-moderate AD patients over a 6-month period as measured by the NPI. In a negative study, Becker *et al.* [26] reported that although metrifonate was associated with slowing the severity of cognitive symptoms in AD patients over a 6-month period, it did not affect noncognitive behaviors measured by the AD Assessment Scale noncognitive subscale (ADAS-N), Global Improvement Scale, or the ADL Checklist.

Other acetylcholinesterase inhibitors in Alzheimer's disease

Tacrine was associated with a higher percentage of patients exhibiting improvement on the Alzheimer's Disease Assessment Scale (ADAS) noncognitive items: cooperation, delusions, and pacing, as well as improvement in cognition when compared with placebo in a 30-week trial [27].

Rivastigmine was associated with significant improvement in activities of daily living, and global evaluation ratings in addition to cognitive functioning when compared with placebo in mild-moderate AD patients over a 6-month period. Twenty three percent of patients taking rivastigmine discontinued due to adverse events compared with 7% in the placebo group [28].

In a 5-month placebo-controlled study in mild to moderate AD patients, galantamine was associated with improvement in behavior and functioning as measured by the Clinician's Interview-Based Impression of Change, Caregiver Input, and AD Cooperative Study ADL Inventory, as well as improvement in cognition as measured by the AD Assessment Scale cognitive subscale [29]. In another study in mild-moderate AD patients, improvements in functioning and cognition were observed at 6 months on galantamine versus placebo [30].

In two studies involving extended release physostigmine there was a significant improvement in global functioning as well as cognitive functioning when compared with placebo in mild-moderate AD patients, but the treatment was also associated with a high incidence of adverse events (in one study 78.6% of patients experienced nausea, 61.5% vomiting; in the other study 37.6% of patients discontinued the study due to adverse events) [31, 32].

In view of the beneficial effect of ChEIs on cognition, and considering the relationship between cognition, mood, and behavior, on biologic, psychologic, and social levels, the primary effect of ChEIs on mood and behavior needs to be established especially in patients with preexisting cognitive deficits. For example, improved cognition may in itself be responsible for improvement in mood and behavior: patients with impaired skills that are necessary for ADL and social integration may be observed to demonstrate less disruptive behavior and irritable mood simply because improved cognition has led to better social integration and reduced environmental stress.

Cholinesterase Inhibitors in Mood Disorders and Schizophrenia

In both mood disorders and schizophrenia cognitive deficits are common as well as are behavioral and mood disturbances [33]. Whereas in mood disorders the primary focus was on the ability of cholinergic systems to normalize depression or mania, in schizophrenia the main focus was on the association of cognitive and functional deficits.

Burt *et al*. [34•] reported a case series of 11 patients with treatment-resistant bipolar disorder who received donepezil for a period of 6 weeks or more. Six patients had an improvement of two points or more on the Clinical Global Impression-Severity of Illness (CGI-S) [35], a seven-point scale. Five of the patients that improved demonstrated improvement within the first 2 weeks. Of note, one of the patients suffered from bipolar depression and demonstrated a three-point improvement on the CGI-S. Improvement of depression with ChEIs can be explained by the agonistic effect on nicotinic receptors. Nicotine may posses antidepressant effects as is suggested by the comorbidity of depression and nicotine dependence, as well as by the demonstrated efficacy of antidepressants in the treatment of nicotine dependence (*eg*, bupropion). If, in addition, ChEIs exert antimanic effects as well, through agonist activity on muscarinic receptors, ChEIs may be considered true bimodal mood-stabilizing agents.

In schizophrenia, Risch *et al*. [36] reported improvements in verbal fluency and attention in six patients on donepezil. Concurrent activation of the right dorsolateral prefrontal cortex and anterior cingulated on functional magnetic vesonance imaging was also observed. Bergman *et al*. [37] reported a case study of a patient with schizophrenia, resistant to clozapine, haloperidol, and fluphenazine, and partially responding to risperidone, that experienced improvement in psychotic symptoms and cognitive function within 4 weeks of starting donepezil. The patient maintained these improvements at a 6-month follow-up. Donepezil treatment was also associated with improved behavioral functioning and performance in neurocognitive test batteries in two treatment refractory patients with schizophrenia, in an open-label treatment [38]. Burke *et al*. [39] reported the resolution of postoperative visual hallucinations in a 74-year-old man after starting donepezil.

Cholinesterase Inhibitors in Tourette's Disorder and Attention Deficit Hyperactivity Disorder

Recent literature on tic disorders has focused on serotonin and dopamine, although reports of improvement in tics with nicotine treatment suggest a role for acetylcholine as well. Tacrine was associated with a significant decline in self-rated attentional deficits, a significant improvement in objective measures of sustained attention, and a near-significant decrease in examiner-rated tics in an open-label study involving six patients with Tourette's disorder [40]. Hoopes *et al*. [41] reported on two patients, 11 and 13 years old, both with Tourette's disorder and attention deficit hyperactivity disorder (ADHD), resistant to standard therapy who experienced a decrease in frequency and intensity of tics within days of starting donepezil, and maintained improvement in both tics and attention-related symptoms for 8 months. Because dopamine is known to inhibit acetylcholine interneurons in the striatum, a relationship evident in extrapyramidal syndrome as a result of dopamine blockade by neuroleptics, these reports suggest that acetylcholine may reciprocally decrease dopamine tone and thus improve some tics [41].

Cholinesterase Inhibitors in Other Disorders

Lanctot *et al*. [42] reported on a case series of seven patients with dementia with Lewy bodies. These often neuroleptic-resistant patients with significant behavioral disturbances were treated with donepezil in an open label basis. Three patients demonstrated marked improvement as measured by the NPI and two more had improved minimally. Four patients did not complete the intended 8-week treatment period due to side effects or lack of response.

Wengel *et al*. [43] reported on a case of delirium complicating a preexisting dementia that resolved rapidly following initiation of donepezil. Because cholinergic dysfunction may play a role in the etiology of delirium a trial of donepezil may be appropriate in cases of unknown etiology.

In another anecdotal report, Kishnani *et al*. [44] described four patients with Down's syndrome treated for an average duration of therapy with donepezil of about 9 months. The following were observed: improvements in communication, expressive language, attention, mood stability, socialization, and adaptive behavior.

Green *et al*. [45] conducted a 12-week, open-pilot study in 17 patients with multiple sclerosis and cognitive impairment to assess the efficacy and tolerability of donepezil, and reported significant improvement in behavior, attention, memory, and executive functioning.

Cholinesterase Inhibitors as Diagnostic Tools

Abnormalities of CNS cholinergic tone have been found in a variety of psychiatric disorders [46]. The possibility that such abnormalities may constitute a biological marker and lend themselves to a quick, noninvasive, and inexpensive test such as the administration of a ChEI, led to a variety of studies in this area.

Major depression is reliably associated with REM sleep abnormalities, suggesting increased cholinergic activation, enhanced cholinergic sensitivity or imbalance in cholinergic and monoaminergic tone. Giles *et al*. [47•] reported that cholinergic challenge using donepezil distinguished between eight depressed patients and eight controls by significantly

reducing REM sleep latency in depressed patients but not in controls. These results suggest that donepezil can provide a pharmacologic probe of cholinergic tone.

Cooney *et al.* [48,49] examined the specificity of the growth hormone release in response to challenge with the ChEI pyridostigmine in a variety of psychiatric disorders and in healthy controls. Growth hormone response to the challenge was significantly greater in patients with major depression and panic disorder when compared with healthy controls. Responses in patients with schizophrenia and alcohol dependence did not differ from the control group. The test demonstrated a sensitivity of 63% for major depression.

Rubin *et al.* [50] used physostigmine challenge and measures of subsequent changes in plasma arginine vasopressin (AVP), ACTH, and cortisol to differentiate between groups of patients with major depression. Their results were consistent with a heightened cholinergic sensitivity in premenopausal women, but not in men with major depression.

Steinberg *et al.* [51] found a significant increase in depressive symptoms following physostigmine infusion when compared to placebo in patients with borderline personality disorder (BPD) but not other personality disorders, when compared with normal controls. The study was conducted in 34 patients with personality disorder (10 with BPD) and 11 normal controls [51].

Conclusions

Donepezil as well as other acetylcholinesterase inhibitors appear to have effects on human mood and behavior. Recent years have witnessed a growing number of preliminary observations with the newly introduced orally administered forms of cholinesterase inhibitors. Applications for cholinesterase inhibitors included both diagnostic and therapeutic interventions. Specifically, studies suggest that cholinesterase inhibitors may be useful in the diagnosis of depression and personality disorders, and that they may have mood and behavioral normalizing effects on symptoms such as depression, mania, apathy, delusions, hallucinations, and delirium, in conditions such as bipolar disorder, schizophrenia, Tourette's disorder, and delirium. Donepezil was involved in the largest number of studies and was associated with the largest number of positive results. In view of the established beneficial effect of ChEIs on cognition, and considering the close relationship between systems that regulate cognition, mood, and behavior in the CNS, further controlled studies are needed to establish a primary effect of ChEIs on mood and behavior and to clarify the diagnostic and therapeutic value of ChEIs as pharmacologic modulators of human mood and behavior.

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