EXPERT OPINION

Assessing the prospect of donepezil in improving cognitive impairment in patients with schizophrenia

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Introduction: Even though cognitive impairment is manifested in almost all patients with schizophrenia, the Clinical Antipsychotic Trials for Intervention Effectiveness (CATIE) study showed no significant difference between first- and second-generation psychotropic drugs in improving cognitive abilities. Discovering new drugs that can improve impaired cognition, thus, is an attractive treatment target for patients with schizophrenia.

Areas covered: This article briefly reviews about donepezil, a highly selective (IC_{50} = 6.7 nM) centrally acting reversible acetylcholinesterase inhibitor that has been approved by FDA for treating cognitive deficit states such as in Alzheimer's disease and its uses in clinical trials for the treatment of schizophrenia. The literature search included PubMed and Cochrane library with the following words: donepezil, schizophrenia and cognitive impairments.

Expert opinion: The results of several clinical trials utilizing donepezil as an adjunct to second-generation antipsychotic drugs targeting cognitive deficits in schizophrenia subjects have been disappointing and would not lead clinicians to consider this as a potential treatment option. While longer randomized controlled trials, increase dosage and selected groups of patients at different stage of cognitive impairment may provide a better understanding of the potential for this drug in addressing cognitive deficits, results to date have not been encouraging.

Keywords: acetylcholinesterase inhibitor, atypical antipsychotics, cognitive impairments, donepezil, schizophrenia

Expert Opin. Investig. Drugs (2013) ***22****(2):259-265*

1. Introduction

Schizophrenia is a severe and chronic neuropsychiatric disorder with a lifetime prevalence of 1% [1]. It can be broadly divided into three categories: 'positive' symptoms, 'negative' symptoms and 'cognitive domain' symptoms. Positive symptoms include symptoms such as hallucinations and delusions. Negative symptoms are characterized by experiential (anhedonia, avolition and asociality) and expressive (affective flattening and alogia) symptoms. Unlike positive and negative symptoms that have more of an expressional phenotype, cognitive domain symptoms are primarily related to working memory, attention and information processing deficits [2].

Alongside negative symptoms, cognitive symptoms represent the greatest hurdle for patients with schizophrenia. They not only affect every aspect of patients' daily life, such as independent living skills, social functioning and occupational or

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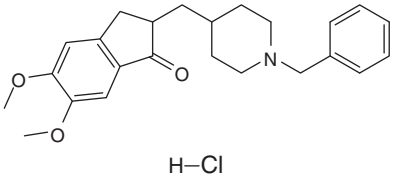
healthcare

Box 1. Drug summary.

Drug name	Donepezil
Phase	Phase II clinical trial
Indication	Schizophrenia
Pharmacology description	Acetylcholinesterase inhibitor
Route of administration	Oral
Chemical structure	
Pivotal trial(s)	Keefe *et al.* (n = 245) showed that donepezil is safe and well tolerated but not effective in improving cognitive impairment in schizophrenia patients taking antipsychotics

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educational performance, but also have a negative association with clinical and functional outcomes [3].

Introduction of first antipsychotic drug, chlorpromazine, in 1952 not only provided a tremendous advancement in treating schizophrenia but also instilled a strong belief in the scientific community that pharmaceutical interventions might hold a key in ultimately curing schizophrenia. Chlorpromazine and other psychotropic drugs have been shown to only slightly improve cognitive and negative symptoms.

Various studies had concluded that second-generation psychotropic provides modest cognitive benefit in patients with schizophrenia compared to first-generation psychotropic drugs. The Clinical Antipsychotic Trials for Intervention Effectiveness (CATIE) disputed previous findings and showed no significant difference between first- and second-generation psychotropic drugs in improving cognitive abilities [4-6]. Cognitive impairment and impaired functional outcomes are manifested in almost all patients with schizophrenia [7,8]. Thus, discovering new drugs that can improve impaired cognition is an essential treatment target for patients with schizophrenia [7,9].

Dopamine has been regarded as the key neurotransmitter involved in the pathogenesis of schizophrenia symptoms [10]. The currently available antipsychotic drugs are effective in improving the positive symptoms of schizophrenia by antagonizing various dopamine receptors. However only 20% of patients treated with antipsychotic drugs appear to recover completely, while most of them continue to experience symptoms throughout their whole lives [11]. Therefore, the need for therapies that can address all three domains of schizophrenia as well as exhibit effects via mechanism other than the dopamine receptor blockade are necessary.

Although the obvious pathology of the cholinergic system as seen in Alzheimer's disease is absent from the brains of schizophrenia patients [12], some studies show a possible role of cholinergic neurons in schizophrenia as well. For example, a correlation has been found at postmortem examination between decrease in brain choline acetyltransferase levels and the severity of ante-mortem cognitive impairments in patients with schizophrenia [13]. Furthermore, patients with schizophrenia show cognitive deficits in learning and verbal memory [14] which correlates with the established finding that the cholinergic neurotransmitter system plays an important role in attention, memory and learning, involving both the nicotinic and the muscarinic system [15-17].

Both direct and indirect evidence support the involvement of muscarinic and nicotinic receptors in schizophrenia. A postmortem study found a decreased mRNA of M1 receptors [18] and a single-photon emission computed tomography (SPECT) imaging study also found decreased availability of muscarinic receptor [19]. Similarly, nicotinic receptors which are involved in sensory gating are reduced in the hippocampus of patients with schizophrenia [20]. Indirect evidence includes the high rates of cigarette smoking in patients with schizophrenia [21,22]. Levin *et al.* [23] showed that nicotine can cause dose-related reversal of the haloperidol-induced impairments in memory performance and complex reaction time. Taken together these data suggest that enhancing the cholinergic activity at nicotinic receptors may alleviate some of the cognitive impairment associated with schizophrenia.

Winkler *et al.* showed that the neurotransmitter acetylcholine also plays an important role in cognition. They found that impaired cholinergic transmission contributes to the cognitive deficits in Alzheimer's disease [24]. Thus, increasing the availability of acetylcholine at the synaptic cleft by inhibiting acetylcholinesterase may improve cognitive impairments in patients with schizophrenia.

In order to increase the level as well as the duration of action of acetylcholine, various inhibitors have been developed to inhibit acetylcholinesterase. One such inhibitor,

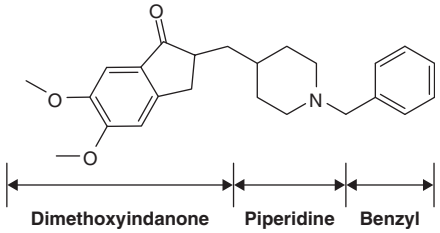

Figure 1. Chemical structure of donepezil, (±)-2,3-dihydro-5, 6-dimethoxy2-[[1-(phenylmethyl)-4-piperidinyl]-1H-inden-1-one. It contains three distinct moieties, dimethoxyindanone, piperidine and benzyl.

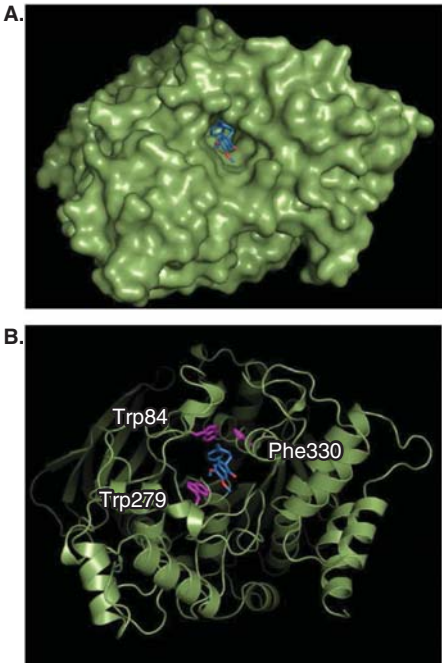

Figure 2. Crystal structure of donepezil bound to *Torpedo californica* acetylcholinesterase (Protein Data Bank (PDB) accession code:1EVE). Surface (**A**) and the cartoon (**B**) representation of the enzyme bound to donepezil shows that the donepezil binds to the active-site gorge of the enzyme through its three major functional groups: the benzyl moiety, the piperidine nitrogen and the dimethoxyindanone moiety which make specific interactions with residues Trp84, Phe330 and Trp279, respectively.

donepezil (see drug summary **Box 1**), has been approved by FDA for treating cognitive deficit states such as Alzheimer's disease [25]. Recently, acetylcholinesterase inhibitors have been studied for the treatment of schizophrenia. This review will assess the effects of using donepezil together with antipsychotic drugs in the treatment of cognitive deficits in schizophrenia.

2. Donepezil

Donepezil is a highly selective (IC_{50} = 6.7 nM) centrally acting reversible acetylcholinesterase inhibitor whose chemical structure is shown in **Figure 1**. Chemically it is known as (±)-2, 3-dihydro-5, 6-dimethoxy2-[[1-(phenylmethyl)-4-piperidinyl]-1H-inden-1-one.

The affinity of donepezil for human acetylcholinesterase is ~ 1000-fold greater than for human butyrylcholinesterase, whereas another centrally acting cholinesterase inhibitor, tacrine, has a similar affinity for the two enzymes [26-28]. Although tacrine and donepezil share the same target, tacrine must be administered up to four times a day and is associated with hepatotoxicity, slow pharmacokinetics and a high incidence of side effects. On the other hand donepezil, whose half life is 70 h, is administered only once daily and has fewer side effects [29].The three-dimensional crystal structure of donepezil bound to *Torpedo californica* acetylcholinesterase has been solved (**Figure 2**) [26]. As seen in **Figure 2A and B**, donepezil makes principle interactions along the active-site gorge of the enzyme through its three major functional groups: dimethoxyindanone moiety, the piperidine nitrogen and the benzyl moiety (**Figures 1** and **2**).

At the top of the gorge, the indanone ring stacks against the indole ring of Trp279 by a classical π–π interaction (**Figure 2B**) [26]. Halfway up the gorge, the charged nitrogen of the piperidine ring makes a cation–π interaction with the phenyl ring of Phe330, and near the bottom of the gorge, one face of the benzyl ring displays classic parallel π–π stacking with the six-membered ring of the Trp84 indole [26]. Interactions of donepezil with these functional groups along with discrete water-mediated contacts (not shown) are crucial for its binding and specificity to acetylcholinesterase [26].

3. How effective is donepezil in improving cognitive impairment in patients with schizophrenia?

Various randomized trials that utilized donepezil along with atypical antipsychotic drugs to address cognitive impairment in patients with schizophrenia did not show significant benefit over atypical antipsychotics and placebo. Representative literatures are listed in **Table 1** [30-38]. Using cognitive battery that primarily measured six major domains (attention, working memory, executive function, verbal memory, visual memory and construction), Akhondzadeh *et al.* found no differences between donepezil and placebo groups on any neurocognitive assessments (sample size, n = 30, duration of study 12 weeks). However, they were able to see some improvements in the negative symptoms [30]. Likewise, Fagerlund *et al.* assessed psychomotor coordination, motor speed, reasoning and planning abilities, memory and attention and found no evidence of improved cognition after treatment with donepezil (n = 11, duration of study 16 weeks) [31]. Freudenreich *et al.* conducted an 8-week

Table 1. Summary of representative references that used donepezil and atypical antipsychotics for the trial.

Authors	Study	Demographic				Donepezil dosage	Conclusions
		n	Age (years)	Illness duration (years)	Medication		
Akhondzadeh *et al.* 2008	12-Week, double-blind, placebo-controlled	30, M = 19, F = 11	Placebo group: 33.86 ± 6.05; donepezil group: 32.33 ± 6.47 (mean)	Placebo group: 85.6 ± 46.6; donepezil group: 89.2 ± 50.2 (mean)	Risperidone	5 mg/day for 4 weeks, then 10 mg/day for 8 weeks	No significant difference on cognition. Significantly greater improvement in the negative symptoms
Fagerlund *et al.* 2007	4-month, longitudinal, double-blind, placebo-controlled	11, M = 8, F = 3	Placebo group 27.2 – 40.9; donepezil group: 23.2 – 43 (range)	Placebo group: 0.7 – 14.9; donepezil group: 1.4 – 17 (range)	Ziprasidone	5 or 10 mg/day	No significant effects on either psychopathology or cognitive scores
Freudenreich *et al.* 2005	8-week double-blind placebo-controlled	36, M = 91.7%, F = 8.3%	48.7 (mean) (range, 24 – 64)	25 years (mean)(range, 1 – 43 years)	Olanzapine or risperidone	5 mg/day for 4 weeks, then 10 mg/day for 4 weeks	Donepezil did not improve measures of cognition or psychopathology
Friedman *et al.* 2002	12-week, double-blind, placebo-controlled	36, M = 8, F = 3	placebo group = 48.8, donepezil group = 50.3 (mean)	Placebo group = 25.9, donepezil group = 26.9 (mean)	Risperidone	5 or 10 mg/day	No significant difference on any cognitive measure
Keefe *et al.* 2007	Prospective 12-week, randomized, double-blind, placebo-controlled, multicentric study with two parallel groups	245, M =172, F = 73	18 – 55 (range)	Placebo group = 14.8, donepezil group = 18 (mean)	Risperidone, olanzapine, quetiapine, ziprasidone or aripiprazole – alone or in combination	5 mg for 6 weeks, then 10 mg for 6 weeks	Donepezil was not effective compared to placebo as a cotreatment for the improvement of cognitive impairment
Kohler *et al.* 2007	16-week, double-blind, placebo-controlled	26, M =18, F =8	18 – 40 (range)	< 10 years	Second-generation antipsychotics	5 mg for 4 weeks, then 10 mg for 12 weeks	No significant improvements in neurocognition and social cognition
Nahas *et al.* 2003	12-week pilot double-blind placebo-controlled BOLD fMRI	M = 6	22 – 53 (range)	Not specified	Antipsychotic	Up to 10 mg	Donepezil addition provided a functional normalization with an increase in left frontal lobe and cingulated activity
Tugal *et al.* 2004	12-week double-blind, placebo-controlled, crossover	12, M = 6, F = 6	18 – 45 (range)	Placebo–donepezil: 16 (mean) donepezil–placebo 6.3 (mean)	Fluphenazine or pimozide	5 mg/day for 6 weeks, then subjects were crossed over to the alternate condition for 6 additional weeks	Donepezil has not affected cognitive performance on a variety of neurocognitive tasks
Tuma *et al.* 2003	112-day double-blind, placebo-controlled	16 (gender not specified)	32 ± 8.6 (mean)	not specified	risperidone	5 mg for 30 days, then 10 mg for 82 days	Donepezil did not improve measures of cognition or psychopathology

All of the studies were placebo-controlled trial. The sample size (n), duration of study, age, gender (F: Female, M: Male), donepezil's dose and the effects of donepezil on cognition are shown.

placebo-controlled trial of 36 patients with schizophrenia to investigate the effect of donepezil on attention, short-term memory, verbal learning, set-shifting abilities, verbal fluency, visuospatial function and motor speed. They found no statistically significant differences in cognitive measures between the control group and the drug group [32]. Friedman *et al.* showed similar results. Neither donezepil 5 mg nor donezepil 10 mg produced significant improvements in cognition (attention, working memory and executive functions) compared to placebo [33]. Keefe *et al.* showed that donepezil, although safe and well tolerated, was not effective compared with placebo in improving cognitive impairment in patients with schizophrenia (neurocognitive composite battery, Clinical Global Impression – Severity [CGI-S], Brief Assessment of Cognition in Schizophrenia [BACS], Wide Range Achievement Test Reading subset [WRAT-R] and positive and negative sign and symptom [PANSS] for both treatment groups; n = 245) [34]. Similarly, Kohler *et al.* whose cognitive battery included selected test of abstraction, attention, verbal and spatial memory, and spatial abilities also found no significant effects on any areas of cognitive function or clinical symptoms in placebo and donepezil groups [35]. Interestingly, using blood oxygen level-dependent (BOLD) functional MRI (fMRI) while performing verbal fluency tasks (VFT), Nahas *et al.* showed that the administration of donepezil provided a functional normalization with an increased activity in the left frontal lobe and the cingulated gyrus indicating improved regional brain activity [36]. Apparent limitations of the above study are the brief duration (12 weeks) and the small number of participants (n = 6). Tugal *et al.* used a cognitive battery consisting of 11 tests to measure 7 major domains (attention, working memory, executive function, verbal memory, visual memory, verbal fluency and construction). They showed no significant effect of donepezil in neither the cognitive measures nor the PANSS and depression scores (n = 12, duration of the study = 12 weeks) [37]. Tuma *et al.* also found that donepezil did not produce significant improvements in memory functions, attention, learning, executive functions compared with placebo (n = 16, duration of study 16 weeks) [38].

Galantamine, an acetylcholinesterase inhibitor that allosterically modulates nicotinic receptors preventing their desensitization, has also been studied in schizophrenia patients with cognitive impairment. Small studies and case reports have shown modest benefits in treating cognitive dysfunction in schizophrenia [39,40]. However, other double-blind, placebo-controlled studies have shown that galantamine did not exhibit significant global benefits [41-43].

4. Expert opinion

The results of several clinical trials utilizing donepezil and targeting cognitive deficits in schizophrenia subjects have been disappointing and would not lead clinicians to consider this as a potential treatment option to address cognitive deficits in schizophrenia. As mentioned in the Cochrane meta-analysis titled 'Acetylcholinesterase inhibitors for schizophrenia', longer trial duration might be necessary to truly assess the effect of donepezil in cognitive impairment [44]. While longer randomized controlled trials may provide a better understanding of the potential for this drug in addressing cognitive deficits, results to date have not been encouraging. Even though donepezil has been shown to modestly improve cognitive deficits in Alzheimer's disease, it is possible that the abnormalities of the cholinergic system found in Alzheimer's disease might be different or absent in patients with schizophrenia. A large percentage of patients with schizophrenia smoke cigarettes [45,46]. Hence it is also reasonable to postulate that nicotine itself may positively affect the cholinergic system in these patients. This may also be a confounding factor in patients treated with acetylcholinesterase inhibitors such as donepezil.

The dosage as well as the stage of cognitive impairment in patients with schizophrenia enrolled in the future studies should be also taken into consideration. In all the studies described in this review the maximum dose of donepezil administered was 10 mg/day, a dose used in Alzheimer's disease population. Patients with schizophrenia may require a higher dosage to observe significant response. The stage of cognitive impairment may play an important role in patients' response to acetylcholinesterase inhibitors. Unlike in Alzheimer's disease, donepezil might not show any significant effect in chronically or moderately ill patients, but it might show cognitive improvement or prevent cognitive symptoms in patients who are beginning to experience cognitive dysfunction. To date, no study has been conducted in early episode schizophrenia or in patients who exhibit prodromal symptoms. Thus, future research on donepezil and cognitive dysfunction in patients with schizophrenia should focus on the duration of the study, increase dosage and selected groups of patients at different stage of cognitive impairment.

Declaration of interest

D Hendersen has previously worked with Alke emes, NuPathe, Otsuka, the NIMH and the Stanley Foundation. None of the remaining authors have any competing interests to declare and no funding was received in support of this article.

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