Cognitive dysfunctions in schizophrenia: potential benefits of cholinesterase inhibitor adjunctive therapy

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Objective: In schizophrenia, cognitive dysfunctions commonly affect attention, memory and executive function, interfere with functional outcome and remain difficult to treat. Previous studies have implicated the cholinergic system in cognitive functioning. In Alzheimer's disease, cholinergic agonists have shown modest clinical benefits on cognitive and behavioural symptoms. Impaired cholinergic activity might also be involved in schizophrenia. Hence the role of cholinesterase inhibitors (ChEI) as adjunctive therapy is under study. We aimed to review the literature and evaluate the overall effectiveness of ChEI adjunctive therapy for the management of cognitive dysfunctions in schizophrenia. **Methods:** We conducted a computer-based search using PubMed (up to February 15, 2006) and ISI Web of Science (conference proceeding abstracts from January 2003 to December 2005) databases. We used the search terms "schizophrenia," "cognition or memory" and "tacrine or donepezil or rivastigmine or galantamine." Studies included were critically analyzed for allocation, blindness, duration and study design, demographic data, and clinical and neuropsychological outcome assessments. We excluded studies that involved patients with psychiatric disorders other than schizophrenia-spectrum or if they involved animals or molecular investigations. We also excluded conference proceeding abstracts with no explicit neuropsychological battery and/or results. **Results:** Data on ChEI as adjunctive therapy for the cognitive impairments in schizophrenia are sparse and so far derived from small samples and mostly open uncontrolled studies. ChEI's potential in long-term management has barely been documented and remains to be fully explored. **Conclusion:** There is insufficient evidence on whether ChEI should be used for the treatment of cognitive dysfunctions in schizophrenia. Nevertheless, further studies with appropriate trial designs and outcome measures in homogenous schizophrenia populations are warranted.

Objectif : Dans les cas de schizophrénie, le dysfonctionnement cognitif affecte généralement l'attention, la mémoire et la fonction d'exécution, interfère avec le résultat fonctionnel et demeure difficile à traiter. Des études antérieures ont associé le système cholinergique au fonctionnement cognitif. Dans les cas de maladie d'Alzheimer, les agonistes cholinergiques ont montré des avantages cliniques modestes pour ce qui est des symptômes cognitifs et comportementaux. Une activité cholinergique diminuée est peut-être aussi liée à la schizophrénie. C'est pourquoi le rôle des inhibiteurs de la cholinestérase (IChE) comme thérapie d'appoint est à l'étude. Notre objectif était d'examiner les écrits scientifique et d'évaluer l'efficacité globale de l'emploi des IChE comme thérapie d'appoint pour la gestion du dysfonctionnement cognitif dans la schizophrénie. **Méthodes :** Nous avons effectué une recherche informatisée en utilisant les bases de données PubMed (jusqu'au 15 février 2006) et ISI Web of Science (les résumés des actes de congrès de janvier 2003 à décembre 2005). Nous avons utilisé les termes de recherche suivants "schizophrenia", "cognition or memory" et "tacrine or donepezil or rivastigmine or galantamine". Les études retenues ont été soumises à une analyse critique de l'attribution, du fonctionnement à l'insu, de la durée et de la conception, des données démographiques et des évaluations des résultats cliniques et neuropsychologiques. Nous avons exclu les études qui comprenaient des patients souffrant de problèmes psychiatriques autres que ceux qui appartiennent au spectre de la schizophrénie, des animaux ou des enquêtes au niveau moléculaire. Nous avons aussi exclu les résumés d'actes de congrès sans résultats ou sans batterie d'éléments neuropsychologiques explicites. **Résultats :** Il y a peu de données sur les IChE comme thérapie d'appoint pour les déficits de la cognition dans la schizophrénie et, jusqu'à maintenant, elles ont été tirées de petits échantillons et d'études

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pour la plupart ouvertes et non contrôlées. Le potentiel des IChE pour la gestion à long terme est à peine documenté et demeure peu exploré. **Conclusion :** Il n'y a pas suffisamment de données probantes pour permettre de déterminer si les IChE devraient être utilisés pour le traitement du dysfonctionnement cognitif dans la schizophrénie. Néanmoins, d'autres études dans des populations homogènes de patients schizophrènes, et comprenant des conceptions d'essais et des mesures des résultats appropriés, sont justifiées.

Introduction

Schizophrenia remains, despite recent treatment advances, one of the most disabling mental disorders,[1] characterized by a broad range of emotional, ideational and cognitive impairments.[2] Regarding cognitive impairments, deficits are observed in controlled and active information processing, such as speed of processing, attention/vigilance, working memory, verbal learning and memory, visual learning and memory, reasoning and problem solving, and verbal comprehension.[3] Performance deficit can be between 1.5 and 2 standard deviations (SD) below that of healthy control subjects.[4] A large body of evidence ascribes cognitive dysfunctions to a combination of neurochemical and neuropathological changes. Although dopamine has conventionally been regarded as the key neurotransmitter involved in the pathogenesis of schizophrenic symptoms, several studies have established that the cholinergic neurotransmitter system, involving both nicotinic and muscarinic receptors, is important for the neuromodulation of cognitive processes in schizophrenia.[5]

Acetylcholine (ACh) acts in many cognitive functions, such as cortical modulation of sensory information processing, attention, memory and learning.[6] This relation between ACh and cognition has been relatively well established in animals and healthy humans and in Alzheimer's disease (AD). In rodents,[7] monkeys[8] and humans,[9] administration of antimuscarinic agents (e.g., scopolamine and atropine) and nicotinic-cholinergic antagonists (e.g., mecamylamine) have brought about cognitive impairments. In AD, it is widely acknowledged that cognitive dysfunctions have been correlated with cholinergic deficiency, and cholinergic agonists have shown modest clinical benefits on cognitive symptoms.[10,11]

In schizophrenia, several studies have also reported anomalies in the cholinergic pathway. Although the degeneration of cholinergic neurons in the basal forebrain and the associated loss of cerebral cholinergic neurotransmission as seen in AD are absent in schizophrenia,[12,13] post mortem and in vivo studies[14–16] have shown alterations in the central cholinergic system, such as reduced numbers of muscarinic[17–19] (especially M1) and nicotinic[20] receptors (such as α-7 nicotinic receptors) in the cortex and hippocampus, that may be implicated in cognitive dysfunctions observed in schizophrenia. Moreover, from animal studies, it has been hypothesized that cognitive advantages, albeit modest, of some atypical antipsychotic drugs on cognitive functioning, compared with typical antipsychotic drugs,[21] are secondary to their ability to increase ACh release in the medial prefrontal cortex.[22] The above data fit with the cholinergic hypothesis, which proposes that hypocholinergic cortical transmission is linked to the development of cognitive dysfunctions in schizophrenia.[23,24]

Whereas the physiopathological mechanisms of cholinergic dysfunction in schizophrenia remain elusive, most authors agree that cholinergic projections to the cortex and basal forebrain play an important role in compromised cognitive constructs in schizophrenia (for review, see[3,23,25–28]). Therefore, drugs that act on cholinergic pathways may improve cognitive dysfunctions in schizophrenia. The possible existence of cholinergic deficits in schizophrenia provides the rationale for examining the efficacy of cholinesterase inhibitor (ChEI) adjunctive therapy for the treatment of cognitive dysfunctions in patients with schizophrenia.

ChEI mode of action

Tacrine, donepezil, rivastigmine and galantamine have been used in clinical trials that target cognitive symptoms. All are known to be effective in treating the core cognitive symptoms of AD.[29–33] Two types of cholinesterases, acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), are present in a wide variety of tissues and are broadly distributed in the brain. Inhibition of cholinesterase increases the synaptic concentration of ACh, thereby enhancing and prolonging the action of ACh on both muscarinic and nicotinic receptors. Both receptors are known to be involved in cognition.[34] ChEIs differ among themselves in their selectivity for AChE and BChE, in their mechanism of inhibition and in their reversibility. Tacrine, the first available ChEI, is a reversible AChE inhibitor, which is slightly more potent toward BChE than toward AChE. A short half-life, a high incidence of side effects and, especially, liver toxicity have largely eliminated it from the market.[35] The new generation of ChEI, including donepezil, rivastigmine and galantamine, are free of these limitations. Donepezil is reversible, long-acting and highly AChE selective. Rivastigmine is a pseudo-irreversible inhibitor with a dual inhibition of AChE and BChE,[36] making it potentially more effective.[37] Its mechanism of inhibition is irreversible (covalent modification of the enzyme) but transient because of a rapid metabolism. Galantamine is interesting because of its dual mechanism of action, including selective competitive inhibition of AChE[38] and allosteric potentiation of nicotinic receptor response.[39,40] Galantamine interacts directly with nicotinic receptors at sites close to, but distinct from, the ACh and nicotine binding sites. It modulates nicotinic receptor allosteric configuration, which diminishes nicotinic receptor desensitization, therefore increasing nicotinic receptor channel openings induced by nicotinic agonists, at a presynaptic and postsynaptic level. Galantamine may act mainly by its sensitizing and potentiating action on nicotinic receptors rather than by general cholinergic enhancement due to cholinesterase inhibition.

Methods

We performed a search in PubMed (up to February 15, 2006) and ISI Web of Science (conference proceeding abstracts from January 2003 to the end of December 2005) databases. We used the search terms "schizophrenia," "cognition or memory" and "tacrine or donepezil or rivastigmine or galantamine." Selected clinical trials had been critically analyzed (allocation, blindness, duration and study design, demographic data, and clinical and neuropsychological outcome assessments). Case reports were excluded. We excluded trials that involved patients with psychiatric disorders other than schizophrenia-spectrum or if they involved animals or molecular investigations. We also excluded articles and conference proceeding abstracts with no explicit neuropsychological battery and/or results. One exception to the systematic review method used needs to be mentioned: because there is no peer-reviewed clinical trial related to galantamine adjunctive therapy in schizophrenia, one case series reference was found to be relevant and was included.[41]

Results

Tacrine

To date, there are no data available with tacrine. This may be related to its pharmacological profile: short duration of action, narrow dosing range and liver toxicity.[35]

Donepezil

In 2002, Buchanan and colleagues[42] conducted a 6-week open-label study of 15 non-geriatric patients with schizophrenia, evaluating the effects of donepezil given as adjunctive treatment to olanzapine. This study has shown significant improvement in manual dexterity (Grooved Pegboard Test [GPT[43]], $p < 0.01$), promising trends (not statistically significant) in verbal recall memory, visual memory and processing speed but no effect on an attention task. These promising initial results have stimulated further research. Since then, there has been 1 open-label study[44] and 6 randomized placebo-controlled clinical studies[45–50] with donepezil, involving a total of 105 non-geriatric and 23 elderly schizophrenia patients (from 6 up to 36 patients per study) with treatment duration of 4–24 weeks.[44–50] The doses of donepezil studied were 5 mg and 10 mg per day. Donepezil was added to the antipsychotic treatment, consisting most often of olanzapine or risperidone monotherapy. All studies concluded that the addition of donepezil did not improve psychopathological measures (Brief Psychiatric Rating Scale [BPRS[51]],[42] Positive and Negative Syndrome Scale [PANSS[52]],[44–50] Scale for the Assessment of Negative Symptoms [SANS[53]][42,46]). Neurocognitive examination covered a wide range of neurocognitive tests, including motor skills, attention, verbal and nonverbal fluency, executive skills and visual tracking. In elderly patients with schizophrenia, although some improvement was found in a brief measure of mental status (Mini Mental State Examination [MMSE[54]], $p < 0.01$),[44] no positive effect was found on a second measure (Alzheimer's Disease Assessment Scale-cognitive subscale [ADAS-cog[55]]) under either open-label[44] or double-blind conditions.[48] Summarizing the results in non-geriatric schizophrenia patients, with respect to verbal learning, significant positive changes versus baseline were found in a controlled study by Erickson and colleagues (Rey Auditory Verbal Learning Test [RAVLT[56]], $p < 0.05$),[45] but this was not replicated in 1 open-label study (RAVLT)[42] and 3 double-blind trials (RAVLT,[47] Wechsler Memory Scale-Revised [WMS-R[57]] logical memory and verbal paired associates[50]). Further, manual dexterity as measured by the GPT[43] improved in a study by Buchanan and others ($p < 0.05$),[42] but no improvement was reported in a controlled condition.[46] Concerning visual learning, in an open-label study, no benefit was found using Benton Visual Retention Test (BVRT[43]),[42] whereas under double-blind conditions,[50] although WMS-R figural memory was improved ($p < 0.05$), WMS-R visual reproduction and paired associates showed no benefit. Lastly, no improvements were observed on measures of attention (Digit Span,[46,47] Digit Symbol[42]), vigilance (Continuous Performance Task [CPT[58]]),[42,47] motor speed (Trail Making Tests [TMT[56]] A),[45–47,50] executive functions (TMT B,[45–47,50] Winsconsin Card Sorting Test [WCST[59]][47,50]), verbal fluency (Benton Oral Word Association Test [BOWAT[60]],[46] Controlled Oral Word Associate Task [COWAT[43]],[49] World Health Organization verbal fluency test,[50] unspecified[47]) and visuospatial skills (Simple Spatial Working Memory Test [SSWMT[61]]),[47] Wechsler Adult Intelligence Scale [WAIS[62]]-Block design[50]). Characteristics of included studies are presented in Table 1.

Rivastigmine

Four reports of rivastigmine adjunctive therapy in schizophrenia have been published: 2 open-label studies[67,68] and 2 controlled trials (1 peer-reviewed study[69] and 1 conference proceeding abstract[70]) for a total of 50 non-geriatric and 13 geriatric schizophrenia patients, with a treatment duration of 12–52 weeks. The measure of psychopathological issues (PANSS) showed improvement in one open-label study[68] ($p < 0.01$), but this was not replicated under double-blind conditions.[69] In addition, a second psychopathological measure (BPRS)[67,68] showed no benefit. Rivastigmine adjunctive therapy in non-geriatric and elderly patients with schizophrenia resulted in significant improvements in mental status, as measured by the MMSE ($p < 0.05$,[67] $p < 0.01$[68]) and the ADAS-cog ($p < 0.01$),[68] and in quality of life, as measured by the Satisfaction with Life Domains Scale[71] ($p < 0.05$)[67] and the Lawton-Brody Activity of Daily Living Scale[72] ($p < 0.01$).[68] In non-geriatric patients, learning and memory (WMS) were significantly enhanced in one open-label study ($p < 0.001$).[67] With respect to attentional measure, although benefits were reported at 8 and 12 weeks in Lenzi and colleagues' study,[67] consistent with the positive trend in the controlled study by Aasen and others,[69] this result was not sustained to 12 months.[67] Lastly, in one controlled study,[70] no significant improvements between baseline and study end were observed in visual tracking (Rapid Visual processing[43]), reaction time, verbal learning (Paired Associates Learning[43]), executive

functions (Stocking of Cambridge[43]) and visuospatial skills (Spatial Working Memory[43]). Characteristics of included studies are presented in Table 2.

Galantamine

To date, data on the effectiveness of galantamine in enhancing cognitive functions in schizophrenia are available from 1 peer-reviewed case series[41] and 1 conference proceeding abstract.[73] The open-label trial conducted by Bora and colleagues [41] examined the effects of galantamine given as adjunctive treatment to clozapine. A total of 5 subjects (mean age 27.6; SD 8.5 yr) received 16 mg per day of galantamine for a period of 8 weeks. In this case series, data are presented in terms of the number of cases out of 5 that demonstrated any improvement. No significant changes in psychopathological measures (PANSS) were found. A few of the cases showed small improvements, not significant, on test of attention (Conners Continuous Performance Task-II,[74] 3 patients), selective attention and response inhibition (Stroop task,[75] 3 patients), working memory (Auditory Consonant Trigrams [ACP[76]], 1 patient), verbal learning (RAVLT, 3 patients), mo-

Table 1: Donepezil in schizophrenia: characteristics of included studies

		Patients				Treatment				
Reference	Study design	Diagnosis	No. of patients	Mean age (and SD), yr	Nicotine use, %	Duration, wk	Dose ChEI, mg/d	Antipsychotic agent use with ChEI	Anti-cholinergic medications*	Outcome measures†
Buchanan et al[42]	OPrT	Schz. Schz-aff	14	43.1 (7.2)	?	6	10	Olanzapine	Not clearly reported	BPRS, SANS, Digit Symbol, RAVLT, BVRT, CPT, GPT‡
Stryjer et al[44]	OPrT	Schz. comorbid dementia	6	65 (?)	?	4	5	Clotiapine, haloperidol, olanzapine, risperidone	Allowed	MMSE,§ PANSS,[NS] ADAS-cog, CGI (S&I)§
Erickson et al[45]	RCT	Schz. Schz-aff	15	43 (5.2)	?	18	5	Chlorpromazine, clozapine, fluphenazine, haloperidol, olanzapine, quetiapine, risperidone	Allowed	PANSS,[NS] TMT[NS] (A&B), RAVLT‡
Freudenreich et al[46]	RCT	Schz.	36	48.7 (?)	80	8	10	Aripiprazole, fluphenazine, haloperidol, olanzapine, quetiapine, risperidone, ziprazidone	NA	PANSS, SANS,CDSS, Digit Span, TMT (A&B), HVLT-R, BOWAT, GPT
Friedman et al[47]	RCT	Schz.	36	48.8 (11.1)	78	12	5 or 10	Risperidone	NA	PANSS, CPT,[NS] Digit Span, SSWMT, TMT (A&B), WCST, RAVLT Verbal fluency
Mazeh et al[48]	RCT (Crossover)	Schz. comorbid dementia	17	70.2 (6.51)	?	24	10	Clozapine, fluphenazine, haloperidol, olanzapine, penfluridol, perphenazine, risperidone, ziprasidone, zuclopenthixol	Allowed	PANSS, ADAS-cog, CGI
Nahas et al[49]	RCT (Crossover) fMRI	Schz. Schz-aff	6	36.8 (11)	?	12	10	Olanzapine, risperidone	NA	PANSS, COWAT[NS]
Tugal et al[50]	RCT (Crossover)	Schz.	12	38 (10.2) 29.2 (5.9)	?	12	5	Fluphenazine, pimozide	NA	PANSS, CDSS WMS-R,¶ TMT (A&B), WCST, WAIS-Block design, WHO-verbal fluency

ADAS-cog[55] = Alzheimer's Disease Assessment Scale-cognitive subscale; BOWAT[60] = Benton Oral Word Association Test; BPRS[51] = Brief Psychiatric Rating Scale; BVRT[43] = Benton Visual Retention Test; CDSS[63] = Calgary Depression Scale for Schizophrenia; CGI (S&I) [64]= Clinical Global Impression (severity and improvement); ChEI = cholinesterase inhibitor; COWAT[43] = Controlled Oral Word Associate Task; CPT[58] = Continuous Performance Task; DSPT[55,57] = Digital Span Distraction Test; fMRI = functional magnetic resonance imaging; GPT[43] = Grooved-Pegboard Test; HVLT-R [65]= Hopkins Verbal Learning Test (Revised); MMSE[54] = Mini Mental State Examination; NA = not allowed; NS = modest trend toward improvement not statistically significant; OPrT = open prospective trial; PANSS[52] = Positive and Negative Syndrome Scale; RCT = randomized, placebo-controlled trial; RAVLT[56] = Rey Auditory Verbal Learning Test; SANS[53] = Scale for the Assessment of Negative Symptoms; Schz. = schizophrenia; Schz-aff = schizo-affective disorder; SSWMT[61] = Simple Spatial Working Memory Test; SD = standard deviation; TMT (A&B)[56] = Trail Making Test (part A and B); WAIS[62] = Wechsler Adult Intelligence Scale; WSCT[59] = Winsconsin Card Sorting Test; WMS-R[57] = Wechsler Memory Scale (Revised); WHO-verbal fluency[66] = World Health Organization-verbal fluency test.

*Concomitant use of antipsychotic drugs or other medications considered as strongly anticholinergic, such as anticholinergic agents (e.g., biperiden, trihexyphenidyl), low-potency conventional antipsychotic drugs (e.g., chlorpromazine), clozapine and tricyclic antidepressants.

†Outcomes measures focusing on mental state and neuropsychological assessments.

‡$p < 0.05$

§$p < 0.01$

¶Figural memory $p < 0.05$, visual reproduction and paired associates, logical memory, verbal paired associates.

tor speed (TMT A, 2 patients), executive functions (TMT B, 4 patients) and verbal fluency (Animal Naming,[43] 3 patients). In Allen and colleagues' poster,[73] presented 3 years earlier but as yet unpublished, in double-blind condition, although significant benefits were reported in verbal fluency (COWAT, $p < 0.05$) and on one measure of attention (CPT errors of commission, $p < 0.05$), no changes were observed on a second measure of attention (Symbol Coding[77]) or in measure of working memory (Digit Sequencing[77]), verbal memory (List Learning[77]), manual dexterity (Token Motor[77]) and executive functions (Tower of London[77]). Characteristics of included studies are presented in Table 3.

Discussion

For an effective evaluation of adjunctive strategies or a comparative analysis of available studies, a consistent trial design (inclusion and exclusion criteria, outcome measures, ChEI treatment durations, as well as concomitant medications) must be adhered to.[78] We have summarized clinical trials that investigated the cognitive enhancing potential of ChEI therapy in patients with schizophrenia. Some have provided evidence that, indeed, ChEI may have a beneficial effect in enhancing cognitive functions. However, most of the double-blind controlled trials sug-

Table 2: Rivastigmine in schizophrenia: characteristics of included studies

		Patients				Treatment				
Reference	Study design	Diagnosis	No. of patients	Mean age (and SD), yr	Nicotine use, %	Duration, wk	Dose ChEI, mg/d	Antipsychotic agent use with ChEI	Anti-cholinergic medications*	Outcome measures†
Lenzi et al[67]	OPrT	Schz.	10	?	?	52	3, 6 or 12	Not clearly reported	Allowed	BPRS,[NS] MMSE,‡ WMS,§ CPT,[NS] SLDS‡
Mendelsohn et al[68]	OPrT	Schz. comorbid dementia	13	65.5 (4.8)	?	12	3, 6, 9 or 12	Not clearly reported	Allowed	PANSS,¶ BPRS, MMSE,¶ ADAS-cog,¶ B-D ADL¶
Aasen et al[69]	RCT fMRI	Schz. Schz-aff	20	42.55 (8.81)	66	12	12	Olanzapine quetiapine risperidone	Not clearly reported	PANSS Attention task[NS]
Chouinard et al[70]**	RCT (Cross-over)	Schz.	20	30.0 (8.0)	?	24	6 up to 9	Atypical antipsychotics	Not clearly reported	CANTAB

ADAS-cog[55] = Alzheimer's Disease Assessment Scale—cognitive subscale; B-D ADL[72] = Lawton and Brody's Activity of Daily Living scale; BPRS[51] = Brief Psychiatric Rating Scale; CANTAB[43] = Cambridge Neuropsychological Test Automated Battery; ChEI = cholinesterase inibitor; CPT[58] = Continuous Performance Task; MMSE[54] = Mini Mental State Examination; NS = modest trend toward improvement not statistically significant; OPrT = open prospective trial; PANSS[52] = Positive and Negative Syndrome Scale; RCT = randomized placebo-controlled trial; Schz. = schizophrenia; Schz-aff = schizo-affective disorder; SD = standard deviation; SLDS[71] = Satisfaction with Life Domains Scale; WMS[57] = Wechsler Memory Scale.
*Concomitant use of antipsychotic drugs or others medications considered as strongly anticholinergic, such as anticholinergic agents (e.g., biperiden, trihexyphenidyl), low-potency conventional antipsychotic drugs (e.g., chlorpromazine), clozapine and tricyclic antidepressants.
†Outcomes measures focusing on mental state and neuropsychological assessments.
‡$p < 0.05$
§$p < 0.001$
¶$p < 0.01$
**Conference proceeding abstract.

Table 3: Galantamine in schizophrenia: characteristics of included studies

		Patients				Treatment				
Reference	Study design	Diagnosis	No. of patients	Mean age (and SD), yr	Nicotine use, %	Duration, wk	Dose ChEI, mg/d	Antipsychotic agent use with ChEI	Anti-cholinergic medications*	Outcome measures†
Bora et al[41]	OPrT	Schz.	5	27.6 (8.5)	20	8	16	Clozapine	Allowed	PANSS, Stroop task,[NS] ACP, CPT,[NS] TMT (A&B),[NS] RAVLT,[NS] Animal naming[NS]
Allen et al[73]‡	RCT	Schz.	24	?	100	4	16, 24 or 32	Not clearly reported	Not clearly reported	BPRS, BACS, CPT§, Verbal fluency§

ACT[76] = Auditory Consonant Trigrams; BACS[77] = Brief Assessment of Cognition in Schizophrenia; BPRS = Brief Psychiatric Rating Scale; ChEI = cholinesterase inhibitor; CPT[58] = Continuous Performance Task; NS = modest trend toward improvement not statistically significant; OPrT = open prospective trial; PANSS[52] = Positive and Negative Syndrome Scale; RAVLT[56] = Rey Auditory Verbal Learning Test; RCT = randomized placebo-controlled trial; Schz. = schizophrenia; TMT (A&B)[56] = Trail Making Test (part A and B).
*Concomitant use of antipsychotic drugs or other medications considered as strongly anticholinergic, such as anticholinergic agents (e.g., biperiden, trihexyphenidyl), low-potency conventional antipsychotic drugs (e.g., chlorpromazine), clozapine and tricyclic antidepressants.
†Outcome measures focusing on mental state and neuropsychological assessments.
‡Conference proceeding abstract.
§$p < 0.05$

gested no efficacy of this add-on strategy. One should be cautious in interpreting this discrepancy, given that trial designs were not optimal.

First, the population heterogeneity in these studies is of concern. Some trials studied schizophrenia only,[41,46,47,50,67,70,79] others studied schizophrenia with comorbid dementia or at least prominent cognitive decline,[44,48,68] and still others studied schizophrenia and schizo-affective disorders.[42,45,49,69] Even if these patients share a similar pattern of cognitive impairments, studies of potential cognitive enhancers should initially include only schizophrenia patients.[78] Moreover, the series reported by Erickson and others,[45] Friedman and others,[47] Mazeh and others[48] and Stryjer and others[44] included some inpatients, which suggests that the sample may be heterogeneous regarding the severity of schizophrenia with treatment-refractory cases. This may be another limitation in a negative trial.[78] Also, the smoker status of patients should be revealed. The nicotinic receptor desensibilization due to chronic nicotine use[80] may weaken donepezil and rivastigmine's cognitive impact, whereas galantamine would theoretically be less affected by this (see ChEI mode of action). Thus, in view of the heterogeneity of the populations in the published studies, it is premature to draw definitive conclusions on the basis of these data. Further clinical trials with larger and stratified samples are warranted.

Second, the heterogeneity of the neuropsychological assessments is a major impediment (Table 1, Table 2 and Table 3). The MMSE, which was often used, has limiting floor and ceiling effects.[81,82] MMSE scores are affected by both age and education.[83] Although the MMSE has been chosen as an outcome measure in several trials,[44,67,68] its best use should be for defining severity of cognitive impairments for inclusion.[45] However, in specific study populations, such as chronic schizophrenia patients with comorbid dementia,[44,48,68] the MMSE remains useful as a secondary outcome measure.[84,85] The cognitive section of the ADAS-cog, a word-learning task with delay recall, and a maze task may also be useful additions.[84,85] In schizophrenia, many sensitive, reliable, objective and valid psychometric tasks are available to assess cognitive functions and psychomotor performance. This may explain the heterogeneity of neuropsychological batteries administered in published studies. For pragmatic and statistical reasons, it would be important to limit the number of neuropsychological outcome measures. Neurocognitive examination should include valid and reliable tests without ceiling or floor effects that cover a range of cognitive functions and are short enough to allow successful completion by patients. The use of a minimal standard in neuropsychological batteries needs be promoted. For instance, the joint Food and Drug Administration, (FDA), National Institutes of Mental Health (NIMH) and Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) workshop has produced guidelines[3] for cognitive assessment in trials, selecting few tests for each cognitive domain (speed of processing, attention/vigilance, working memory, verbal learning and memory, visual learning and memory, reasoning and problem solving, and verbal comprehension).

Third, ChEI treatment duration as well as concomitant medication is of major concern. In all studies, the dosage of ChEI matches the recommended dosage for other pathologies (e.g., AD). However, published studies in schizophrenia average 10 weeks in duration,[41,42,44,46,47,49,50,68,69,73] except 2 randomized studies with donepezil reaching 18[45] and 24[48] weeks and 2 trials with rivastigmine reaching 24[70] and 52[67] weeks. A trial lasting less than 12 weeks is considered to be short-term.[85] When assessing cognitive measures, the trial duration is recommended to be at least 6 months.[78] Therefore, evidence of long-term effectiveness and safety for add-on ChEI treatment in schizophrenia is currently lacking. The question of concomitant psychotropic use in available trials is also important. Of particular concern is the concomitant use of antipsychotic drugs or other medications considered to be strongly anticholinergic,[41,44,45,67,68] such as anticholinergic agents (e.g., biperiden, trihexyphenidyl), low-potency conventional antipsychotic drugs[86] (e.g., chlorpromazine), clozapine[86] and tricyclic antidepressants. Interestingly, trials where concomitant medications with anticholinergic properties were disallowed for the duration of the study have mainly negative findings,[46,47,49,50] whereas trials where anticholinergic medications were allowed have the most positive results,[41,44,45,67,68] except Mazeh et al,[48] who had negative results. Thus, it appears that when the use of concomitant anticholinergic medications is not clearly reported,[42,69,70,73] data may not be interpreted. Concomitant use of medications with anticholinergic profile is perhaps the most confounding factor. Indeed, the observed benefits of ChEI may then only reflect a reversal of the anticholinergic toxicity of concomitant drugs. In addition, some studies[41,42,44,45] have allowed benzodiazepine, valproate and/or antidepressant medications. All these drugs are possible confounding factors to interpreting cognitive function assessments.[78] Polypharmacy is relatively common, and excluding all concomitant medications may not be realistic. Nevertheless, concomitant medication in clinical trials should be limited regarding pharmacological profile of the study drug.

Conclusion

In summary, our review highlights the insufficiency of evidence to prove ChEI efficacy in the treatment of cognitive dysfunctions in schizophrenia. There are findings that support the idea that ChEI may have a beneficial effect in enhancing cognitive functions. However, most of the double-blind controlled trials suggest no efficacy of this add-on strategy. At this stage, any definitive conclusions arising from all these studies should be considered preliminary. Larger trials with sufficient duration (at least 6 months) and a better control of concomitant psychotropic drugs are needed to resolve this issue.

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Contributors: All authors designed the review. Drs. Ferreri and Agbokou acquired and analyzed the data and wrote the article. Dr. Gauthier critically reviewed the article. All authors gave final approval for its publication.

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Correction

The following note should have accompanied Dr. Selby's article "Psychopharmacology of smoking cessation in patients with mental illness" in the last issue of the *Journal of Psychiatry and Neuroscience* (2006;31[5]:360).

Competing interests: Dr. Selby has acted as a paid consultant for Pfizer Consumer and Pfizer Inc, Health Canada and the Ontario Ministry of Health Promotion. He has received funds for a study sponsored by GlaxoSmithKline, speaker fees from Pfizer Consumer Health and travel assistance from the American College of Cardiology.