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Cholinesterase Inhibitors as Adjunctive Therapy in Patients with Schizophrenia and Schizoaffective Disorder

A Review and Meta-Analysis of the Literature

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Abstract

Background: Cognitive deficits have been described in patients with schizophrenia from the first descriptions of dementia praecox to current concepts of cognitive dysmetria. Nevertheless, little is known about how to deal with them. In Alzheimer disease, cholinergic deficit is found and cholinesterase inhibitors have been used to delay the progression of memory and cognitive dysfunction. Several lines of evidence suggest that the cholinergic system may be disrupted in schizophrenia.

Objective: To evaluate cognitive and clinical effects of adjunctive cholinesterase inhibitors in patients with schizophrenia and schizoaffective disorder.

Method: We conducted a literature search on PubMed and EMBASE (up to December 2008) for articles that investigated adjunctive cholinesterase inhibitors in patients with schizophrenia. The terms 'schizophrenia', 'acetylcholinesterase inhibitors', 'rivastigmine', 'donepezil', 'galantamine' and 'cognitive deficit' were searched with restriction for English language and without a year limit. All articles that presented original data from randomized, double-blind, placebo-controlled trials with donepezil, rivastigmine or galantamine in patients with schizophrenia or schizoaffective disorder were included in the meta-analysis. Studies were excluded for the following reasons: (i) case study/letter/correspondence/review; (ii) animal study; (iii) molecular/genetic investigation; and (iv) inclusion of patients with schizophrenia and co-morbid dementia.

Few appropriate data for meta-analysis were found because of the large heterogeneity of the assessment instruments used. Nevertheless, effects of cholinesterase inhibitors in some cognitive domains (executive function, memory and language), psychopathology (using the Positive and Negative Syndrome Scale) and extrapyramidal symptoms could be analysed.

Results: Six open-label and 24 double-blind studies were found. In five open-label studies there was an improvement in memory, attention and executive functions. Thirteen double-blind studies (four with rivastigmine, six with donepezil and three with galantamine) contributed to the meta-analysis.

Significant improvement was found in this analysis for memory and the Trail Making test part A.
Conclusions: The reviewed studies suggest that specific cognitive deficits (memory, and the motor speed and attention part of executive function) of patients with schizophrenia and schizoaffective disorder are responsive to rivastigmine, donepezil and galantamine as adjunctive therapy. Confirmatory studies are needed to determine the clinical utility of this treatment strategy.

Background

Cognitive dysfunction has been recognized as a core feature of schizophrenia from the first descriptions of dementia praecox[1] to current concepts of cognitive dysmetria.[2] Cognitive deficit in schizophrenic patients is not merely a medication adverse effect. It occurs at a very early age, often before overt clinical symptoms appear.[3] With the onset of overt psychotic symptoms, cognitive impairments may worsen and, in some patients, continue to worsen during the course of the illness, at times to dementia-like proportions.[3] Deficits in various cognitive measures such as memory, attention, executive function, verbal fluency and motor skills have been consistently shown.[4,5] Furthermore, cognitive deficits predict poor social outcome in schizophrenia patients, often to a greater degree than other indices of illness severity.[6]

Several lines of evidence suggest that the cholinergic system may be disrupted in schizophrenia. Postmortem studies have demonstrated alterations in muscarinic receptor and nicotinic receptor availability or expression.[7-13]

Alterations in nicotinic cholinergic receptor function may also contribute to cognitive impairment in schizophrenic patients. Nicotinic receptor stimulation may increase arousal, improve attention and influence a number of cognitive functions. Schizophrenic patients have been shown to have a reduced number of nicotinic receptors (including the low-affinity α_7-receptor subtype), especially in the hippocampus,[14] and a reduced number of high-affinity (containing β_4- and β_2-subunits) nicotinic receptors in the hippocampus, cortex, striatum and thalamus.[15]

Cholinergic treatments were developed for use in patients with Alzheimer's disease but may be applicable to patients with other disorders involving cholinergic abnormalities. Preliminary evidence suggests that patients who have dementia with Lewy bodies or Parkinson's disease with dementia may exhibit a behavioural response to treatment with cholinesterase inhibitors.[16] Cortical cholinergic deficits have been identified in a variety of other neurological disorders, including some cases of Pick's disease, olivoponto-cerebellar atrophy, progressive supranuclear palsy, the parkinsonism dementia complex of Guam, alcoholism with Wernicke's encephalopathy, Creutzfeldt-Jakob disease, subacute sclerosing panencephalitis, dementia pugilistica and traumatic brain injury.[16] 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 renders them potentially responsive to cholinesterase inhibitors.[16] Neuropsychiatric disturbances in these conditions might be reduced with the use of cholinesterase inhibitors.[16]

Cholinesterase inhibitors include physostigmine,[17,18] tacrine,[17,18] rivastigmine,[17,18] donepezil[17,18] and galantamine.[18,19] The use of tacrine and the carbamate physostigmine was limited due to potentially serious adverse effects. Both exert detrimental effects on hepatic and cardiovascular functions.[17] The amelioration of apathy and reduction of visual hallucinations are the most reproducible effects of cholinesterase inhibitors on neuropsychiatric symptoms in Alzheimer's disease; however, impacts on other neuropsychiatric symptoms have been reported

in some studies.[20,21] The beneficial effects of cholinesterase inhibitors on emotion and behaviour are most likely mediated through cholinergic influences on limbic and paralimbic brain structures. Patients who exhibit substantial cognitive improvement typically exhibit a concomitant behavioural response; however, behavioural and cognitive responses may be dissociated.[16]

Cholinergic agents affect many aspects of cognition, including attentional or executive systems, and have a pan-intellectual modulating influence on memory, language and visuospatial skills.[22] Improvement in attention may underlie the reductions in apathy that are commonly associated with cholinesterase inhibitors, possibly explaining why apathy is among the most responsive of neuropsychiatric symptoms to cholinergic therapy and why it correlates highly with cognitive improvement.[16]

Thus, cholinesterase inhibitors may contribute to the management of other disorders with cholinergic system abnormalities and neuropsychiatric symptoms, such as schizophrenia.[16]

Considering this evidence, it is reasonable to speculate that increasing cholinergic activity at muscarinic and nicotinic receptors may alleviate some of the cognitive deficits associated with schizophrenia. Treatment with a cholinesterase inhibitor is an effective method of stimulating nicotinic and muscarinic receptor activity since inhibition of acetylcholinesterase increases the synaptic level of the natural agonist acetylcholine.

Objective

Our objective was to evaluate the cognitive and clinical effects of cholinesterase inhibitors administered to patients with schizophrenia or schizoaffective disorder.

Methods

In this article, we present a systematic and critical review of the literature and the results of published trials that evaluated the use of cholinesterase inhibitors as add-on therapy for cognitive enhancement in patients with schizophrenia and schizoaffective disorder, as well as their effects on psychopathology. Eligible papers were additionally submitted to meta-analysis.

Data Sources

A literature search of the PubMed and EMBASE databases was performed (up to December 2008) to investigate the use of cholinesterase inhibitors in patients with schizophrenia/schizoaffective disorder and cognitive deficit. The terms 'schizophrenia', 'acetylcholinesterase inhibitors', 'rivastigmine', 'donepezil', 'galantamine' and 'cognitive deficit' were searched, with a restriction for English language and without a year limit.

Only original articles were included. Additionally, we reviewed the bibliographic data of all included publications for further studies and conference proceedings abstracts. First authors of trials were contacted to obtain more information on particular aspects of trials. All articles that presented original data from randomized, double-blind, placebo-controlled, crossover and open-label trials with rivastigmine, donepezil or galantamine in patients with schizophrenia or schizoaffective disorder were included in the qualitative review.

Meta-Analysis

Each article identified by the literature search was reviewed by one author (S.R.I. Ribeiz) and all articles fulfilling the inclusion criteria were selected for the meta-analysis.

Inclusion Criteria

Studies meeting the following criteria were included: (i) randomized, controlled trials of the use of a cholinesterase inhibitor (rivastigmine, donepezil or galantamine) as an adjunctive treatment to antipsychotic treatment (typical or atypical); (ii) participants' doses of antipsychotic medication must have been stable for at least 1 month prior to the trial; (iii) cognitive/clinical assessment was performed using validated rating scales; (iv) data were available on group means and standard deviations for baseline and post-intervention cognitive/clinical tests; and (v) the sample constituted patients with schizophrenia or schizoaffective disorder.

Crossover design trials were included if it was possible to extract first-segment data from these trials. Every effort was made to use all extractable data.

Exclusion Criteria

Studies were excluded because of the following: (i) case study/letter/correspondence/review; (ii) animal study; (iii) molecular/genetic investigation; and (iv) inclusion of patients with schizophrenia/schizoaffective disorders and comorbid dementia.

Categorization of Neuropsychological/ Psychopathological/ Clinical Tests

Different instruments were used to assess cognition, psychopathology and extrapyramidal symptoms in the studies, which made comparison difficult.

In order to compare information, neuropsychological tests were grouped into the following cognitive or clinical domains: executive function; language; memory; motor function; and attention. Meta-analysis was conducted for outcome domains for which at least three measures were available. Data were not sufficient to analyse motor function and attention. The classification was conducted based on neuropsychological assessment tools. The Trail Making test part A was used in various trials and could be analysed separately. Psychopathology was evaluated by a specific scale, the Positive and Negative Syndrome Scale [PANSS] (subscales: total, positive and negative). We also analysed extrapyramidal symptoms. Some domains were evaluated with more than one scale, for example, extrapyramidal symptoms were evaluated with the Abnormal Involuntary Movement Scale (AIMS) and the Simpson-Angus Scale (SAS). Therefore, in the analysis, the results were corrected for the number of scales in each study.

Statistical Methods

Meta-analyses were performed using the software R: A Language and Environment for Statistical Computing Version 2.4.1 (R Foundation for Statistical Computing, Vienna, Austria) and standardized mean difference methodology with Hedge's correction for bias for small samples.[23] A Q test was performed to test for heterogeneity of the mean values of the scales (or cognitive domains) between the studies and the significance level was set at $\alpha = 5\%$. Random or fixed effect was used based on the statistical evidence of heterogeneity. In this meta-analysis, schizophrenia/schizoaffective disorder patients were compared after treatment with a control group (receiving placebo).

Results

Qualitative Review of the Studies

Six open-label studies were found for the present review (table I).[24-29] In these studies, the length of the treatment varied from 4 to 48 weeks and the number of patients included varied from 5 to 20. All studies included patients with a diagnosis of schizophrenia or schizoaffective disorder according to DSM-IV criteria (except for one study that did not specify the diagnostic criteria) and two of these studies[24,26] included patients with Alzheimer's disease (according to the Mini Mental State Examination or Alzheimer's Disease Assessment Scale-cognitive subscale [ADAS-cog score]).[30] Different instruments were used by each trial to assess cognitive or psychopathological changes. Cognitive improvement was found in five studies.

The results of 24 placebo-controlled studies (23 of which were randomized) investigating the use of cholinesterase inhibitors in schizophrenia/schizoaffective patients are summarized in table II.[31-54] In these trials,[31-54] the duration of treatment varied from 8 to 24 weeks. The number of patients included per study varied from 6 to 245, with a total of 796 patients. Twenty studies included patients with a diagnosis of schizophrenia or schizoaffective disorder according to DSM-IV criteria, one study according to ICD-10,[48] and three studies[32,47,53] did not report the criteria used. All trials combined several different instruments to assess treatment efficacy.

To evaluate the clinical global impression before and after treatment, the Clinical Global

Impression-Improvement (CGI-I) scale was used in eight studies,[31,33,39,41,43,45,48,49] but the mean and standard deviation were not described. Clinical global improvement was not found in any of these studies.

Meta-Analysis

Study Selection

Of the 34 articles that were identified in the literature search, 21 were excluded (figure 1). These consisted of 2 literature reviews, 2 meta-analyses and 17 studies (6 open-label studies [table I] and 11 double-blind trials that did not meet the inclusion criteria or did not present sufficient information [table III]). Thirteen studies[33,35-37,39,41,44-46,48-49,51,53] were included in the meta-analysis, including four crossover design trials (table IV).[33,35,41,44]

Results

The effect sizes and related statistics for the cognitive and clinical domains are provided in table V.

Executive function was evaluated, and the analysis of heterogeneity of results in six studies (n = 199).[35,36,46,49,51,53] was shown to be homogeneous. No significant improvement was found.

The *Trail Making test part A* was evaluated, and the analysis of heterogeneity of results in four studies (n = 93)[35,36,46,51] was shown to be homogeneous. A significant improvement was found; patients who received cholinesterase inhibitors performed 68.6% faster than those who received placebo.

Language was evaluated, and the analysis of heterogeneity of results in four studies (n = 63)[33,35,46,51] was shown to be homogeneous. No significant improvement was found.

Memory was evaluated, and the analysis of heterogeneity of results from three studies (n = 146)[36,49,51] was shown to be homogeneous. A significant improvement of 28% was found.

Extrapyramidal symptoms were evaluated, and the analysis of heterogeneity of results of three studies (n = 158)[37,39,49] was shown to be heterogeneous. The experimental group showed a tendency to have a reduction (57%, p = 0.059) in

Table I. Open-label studies using cholinesterase inhibitors (ChEIs) for patients (pts) with schizophrenia/schizoaffective disorder

Study	ChEI	Dosage (mg/day)	No. of pts/dropouts	Smoker	Length of treatment (wk)	Mean age [y] (SD)	Inclusion criteria	Assessments	Results
Stryjer et al.[24]	Donepezil	5	6/1	NR	4	65 (35.6)	Schizophrenia (DSM-IV) and AD (DSM-IV)	Psych, cognition	Cognitive improvement (MMSE $p < 0.01$; CGI-I $p < 0.01$)
Buchanan et al.[25]	Donepezil	10	15/1	NR	6	43.1 (6.6)	Schizophrenia and schizoaffective disorder (DSM-IV)	Psych, cognition	Cognitive improvement (manual dexterity, visual memory)
Mendelsohn et al.[26]	Rivastigmine	9	13/2	NR	12	65.5 (4.8)	Schizophrenia (DSM-IV) and AD (DSM-IV)	Psych, cognition	Cognitive and psych improvements
Lenzi et al.[27]	Rivastigmine	12	16/6	NR	48	32 (8)	Schizophrenia (DSM-IV)	Psych, cognition	Cognitive improvement (learning and memory: WMS $p < 0.001$; MMSE $p < 0.05$). Psych improvement (anergia-BPRS $p < 0.05$)
Bora et al.[28]	Galantamine	16	5/0	1	8	27.6 (8.5)	Schizophrenia (DSM-IV)	Psych, cognition	Cognitive improvement (psychomotor speed and selective attention tasks)
Pérez et al.[29]	Donepezil	10	20/0	11	16	32.2 (10.8)	Schizophrenia (specific criteria NR)	Psych, cognition, EPS	Psych improvement

AD = Alzheimer's disease; **BPRS** = Brief Psychiatric Rating Scale; **CGI-I** = Clinical Global Impression-Improvement scale; **EPS** = extrapyramidal symptoms; **MMSE** = Mini Mental State Examination; **NR** = not reported; **psych** = psychopathology; **WMS** = Wechsler Memory Scale.

Table II. Double-blind, parallel group (pg) or crossover (co) clinical trials using cholinesterase inhibitors (ChEIs) in schizophrenia/schizoaffective patients (pts)

Study	Design/duration (wk)	Drug/dosage (mg/day)	No. of pts/smokers/ dropouts	Antipsychotics/ anticholinergic drugs	Mean age (SD) [y]	Inclusion criteria	Assessments	Results
Friedman et al.[31]	pg/12	DON/10	36/NR/2	Atypical (risperidone)/none	DON: 50.3 (10.1) PL: 48.8 (11.1)	Schizoaffective disorder (DSM-IV)	Psych, cognition	No improvement
Allen et al.[32]	pg//24	GAL/32	24/NR/NR	Atypical (risperidone)/NR	47 (NR)	NR	Psych, cognition	Cognitive improvement (CPT errors of commission and verbal fluency tests $p < 0.05$)
Nahas et al.[33]	co/12	DON/10	6/NR/0	Atypical (olanzapine, risperidone or both)/NR	36.8 (11)	Schizophrenia, schizoaffective disorder (DSM-IV)	Psych, cognition	No improvement
Stryjer et al.[34]	co/18	DON/10	8/NR/2	Atypical (clozapine)/NR	34.8 (5.4)	Schizophrenia (DSM-IV)	Psych, EPS, cognition	No improvement
Tuğal et al.[35]	co/12	DON/5	12/NR/NR	Typical (fluphenazine, pimozide)/none	DON: 29.2 (5.9) PL: 38 (10.2)	Schizophrenia (DSM-IV)	Psych, cognition	No improvement
Freudenreich et al.[36]	pg/8	DON/10	36/32/1	Typical, atypical/none	48.7 (NR)	Schizophrenia (DSM-IV); excluded if MMSE < 20	Psych	No improvement
Aasen et al.[37]	pg/12	RIV/6	36/8/20	Atypical (risperidone, olanzapine, quetiapine)/NR	RIV: 42.5 (8.81) PL: 44.11 (12.30)	Schizophrenia, schizoaffective disorder (DSM-IV)	Psych, EPS	No improvement
Erickson et al.[38]	co/18	DON/5	24/NR/9	Typical, atypical/none	43 (5.2)	Schizophrenia (DSM-IV)	Psych, cognition	Psych improvements: a significant effect of time for the total PANSS ratings ($p < 0.02$), a significant time effect across groups ($p < 0.01$) and a significant group by time effect period ($p < 0.02$)
Kumari et al.[39]	pg/12	RIV/6	36/17/15	Atypical/none	RIV: 42.55 (8.81) PL: 44.40 (11.64)	Schizophrenia (DSM-IV)	Psych, EPS	No improvement

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Table II. Contd

Study	Design/duration (wk)	Drug/dosage (mg/day)	No. of pts/smokers/ dropouts	Antipsychotics/ anticholinergic drugs	Mean age (SD) [y]	Inclusion criteria	Assessments	Results
Mazeh et al.[40]	co/12	DON/10	20/NR/3 (2 died of unrelated causes)	Typical, atypical/NR	70.2 (6.5)	Schizophrenia (DSM-IV) and cognitive decline (ADAS-Cog ≥14)	Psych, cognition	No improvement
Guillem et al.[41]	co/12	RIV/6–9	18/NR/0	Atypical/anticholinergics	RIV: 32.7 (8.6) PL: 25.1 (4.9)	Schizophrenia (DSM-IV)	Psych	Cognitive improvement
Schubert et al.[42]	pg/8	GAL/24	16/NR/3	Atypical (risperidone)/none	26–55[a]	Schizophrenia, schizoaffective disorder – depressive subtype (DSM-IV)	Psych, cognition, EPS	Overall improvement in cognitive performance (RBANS total scale score); RBANS attention and delayed memory subscale robustly improved (1 SD)
Lee et al.[43]	pg/12	DON/5	24/14/1	Typical (haloperidol 5–30 mg/d)/anticholinergics	DON: 42.2 (5.7) PL: 44.2 (4.0)	Schizophrenia (DSM-IV)	Psych, cognition	Cognitive improvement
Risch et al.[44]	co/12	DON/10	13/NR/0	Atypical/NR	34.7(10.0)	Schizophrenia, schizoaffective disorder (DSM-IV)	Psych, EPS	Psych improvement
Keefe et al.[45]	pg/12	DON/10	245/145/50	Atypical/none	DON: 40.9 (9.7) PL: 39.7 (9.0)	Schizophrenia, schizoaffective disorder (DSM-IV)	Psych, cognition, EPS	No improvement
Sharma et al.[46]	pg/24	RIV/12	21/17/18	Atypical (risperidone, olanzapine, quetiapine)/none	RIV: 42.64 (8.89) PL: 46.80 (13.02)	Schizophrenia (DSM-IV)	Cognition	No improvement
Risch et al.[47]	co/12	DON/10	13/NR/NR	Atypical (olanzapine, risperidone, clozapine)/NR	22–50[a]	Schizophrenia, schizoaffective disorder (NR)	Psych	Significant antidepressant effect

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Table II. Contd

Study	Design/duration (wk)	Drug/dosage (mg/day)	No. of pts/smokers/ dropouts	Antipsychotics/ anticholinergic drugs	Mean age (SD) [y]	Inclusion criteria	Assessments	Results
Fagerlund et al.[48]	pg/16	DON/10	11/7/10	Atypical (ziprasidone)/none	DON: 23.2–43[a] PL: 27.2–40.9[a]	Schizophrenia (ICD-10 criteria)	Psych, cognition	No improvement
Buchanan et al.[49]	pg/12	GAL/24	86/36/13	Atypical (other than clozapine), typical/none	GAL: 49.9 (9.2) PL: 49.5 (9.9)	Schizophrenia, schizoaffective disorder (DSM-IV)	Psych, cognition, EPS	Selective benefits for processing speed and verbal memory. Interference with practice effects during the performance of an attention task
Chouinard et al.[50]	co/12	RIV/9	20/14/4	Atypical, typical/anticholinergics	RIV: 32.8 (8.7) PL: 25.7 (6.0)	Schizophrenia, schizoaffective disorder (DSM-IV)	Psych, cognition	No improvement
Lee et al.[51]	pg/12	GAL/16	24/NR/2	Typical (mean dosage: 1390 mg/d chlorpromazine equivalent)/anticholinergics	GAL: 39.5 (3.2) PL: 41.5 (3.2)	Schizophrenia (DSM-IV)	Psych, cognition	No statistically significant differences between the two groups for any of the cognitive measures, except the score for recognition on the RCFT
Kohler et al.[52]	pg/16	DON/10	26/12/4	Atypical (olanzapine equivalents = 16.5 mg/d, SD = 9.5)/none	18–40[a]	Schizophrenia, schizoaffective disorder (DSM-IV)	Psych, cognition	No improvement
Dyer et al.[53]	pg/8	GAL/32	20/0/2	Atypical/none	GAL: 44.3 (11.9) PL: 50.5 (4.7)	Schizophrenia, schizoaffective disorder – depressive type (NR)	Psych, cognition	No improvement
Jacobo et al.[54]	pg/acute administration	GAL/4 and 8	21/12/0	NR/NR	NR	Schizophrenia (DSM-IV)	Psych, cognition	No improvement

a Age range.

ADAS-Cog = Alzheimer's Disease Assessment Scale, Cognitive subscale; **CPT** = Continuous Performance Test; **DON** = donepezil; **EPS** = extrapyramidal symptoms; **GAL** = galantamine; **MMSE** = Mini Mental State Examination; **NR** = not reported; **PANSS** = Positive and Negative Syndrome Scale; **PL** = placebo; **psych** = psychopathology; **RBANS** = Repeatable Battery for the Assessment of Neuropsychological Status; **RCFT** = Rey Complex Figure Test; **RIV** = rivastigmine.

extrapyramidal symptoms compared with the placebo group.

Total PANSS was evaluated, and the analysis of heterogeneity of results of six studies (n = 119)[33,35,37,39,41,48] was shown to be homogeneous. No significant improvement was found.

Negative symptoms from PANSS were evaluated, and the analysis of heterogeneity of results of eight studies (n = 377)[33,35,37,39,41,44,45,48] was shown to be heterogeneous. No significant improvement was found.

Positive symptoms from PANSS were evaluated, and the analysis of heterogeneity of results of seven studies (n = 364)[33,35,37,39,41,45,48] was shown to be homogeneous. Symptoms were significantly more intense (28.2%, p = 0.010) in the group that received a cholinesterase inhibitor than in the group that received placebo.

Discussion

Qualitative Review of the Literature

Six open-label studies were found in the present review of the literature (table I). Cognitive improvement was found in five of these studies. With the exception of one 48-week study, the length of these studies was relatively short, and the effect on cognitive symptoms appeared to be more rapid than the improvement of cognitive function observed in patients with Alzheimer's disease who were administered cholinesterase inhibitors. On the other hand, these results should be interpreted with caution because these studies were open-label, with no placebo groups, and involved a small number of subjects.

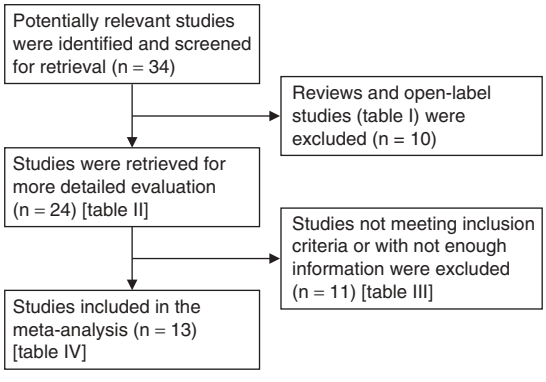

Fig. 1. Study selection process for meta-analysis.

Table III. Double-blind studies excluded from the meta-analysis because of missing data

Study	Reason for exclusion
Friedman et al.[31]	Final mean and SD of the scales not presented
Allen et al.[32]	Final mean and SD of the scales not presented
Stryjer et al.[34]	Final mean and SD of the scales not presented
Erickson et al.[38]	Final mean and SD of the scales not presented
Mazeh et al.[40]	Schizophrenia and co-morbid dementia
Schubert et al.[42]	Final mean and SD of the scales not presented
Lee et al.[43]	Final mean and SD of the scales not presented
Risch et al.[47]	HAM-D not used in other studies (depression was not evaluated in other studies – not possible to compare)
Chouinard et al.[50]	Final mean and SD of the scales not presented
Kohler et al.[52]	Final mean and SD of the scales not presented
Sacco et al.[54]	Final mean and SD of the scales not presented

HAM-D = Hamilton Rating Scale for Depression; **SD** = standard deviation.

Twenty-four double-blind studies were found (table II): 5 with rivastigmine,[37,39,41,46,50] 13 with donepezil[31,33-36,38,40,43-45,47-48,52] and 6 with galantamine.[32,42,49,51,53,54] Fifteen of these studies did not show an improvement in cognition in schizophrenia,[31,33-37,39-40,45-46,48,50,52-54] six found cognitive improvement[32,41-43,49,51] and three[38,44,47] found improvement in psychopathology.

Three studies[24,26,40] selected elderly patients with schizophrenia/schizoaffective disorders and Alzheimer's disease. Only one of these studies[40] was double-blinded (patient mean age of 70.2 years) and no improvements on cognitive measures were found in this trial.

Meta-Analysis

The sample included in the statistical analysis was small. Unfortunately, the reporting of trials

Table IV. Scales used in each study for the meta-analysis

Study	ChEI	Executive function	Language	Memory	Extrapyramidal symptoms	Psychopathology
Nahas et al.[33]	Donepezil		Verbal fluency, COWAT			Total PANSS, positive PANSS, negative PANSS
Tuğal et al.[35]	Donepezil	Trail Making test part A/B, verbal fluency, WCST, digit span forward, digit span backward	Verbal fluency			Total PANSS, positive PANSS, negative PANSS
Freudenreich et al.[36]	Donepezil	Trail Making test part B, grooved pegboard test, digit span forward, digit span backward		HVLT, BOWAT		
Aasen et al.[37]	Rivastigmine				AIMS, SAS	Total PANSS, positive PANSS, negative PANSS
Kumari et al.[39]	Rivastigmine				AIMS, SAS	Total PANSS, positive PANSS, negative PANSS
Guillem et al.[41]	Rivastigmine					Total PANSS, positive PANSS, negative PANSS
Risch et al.[44]	Donepezil					Negative PANSS
Keefe et al.[45]	Donepezil					Positive PANSS, negative PANSS
Sharma et al.[46]	Rivastigmine	Trail Making test part A/B, finger tapping, WCST, spatial working memory average distance, letter, number scaled score (WAIS-III), digit span scaled score (WAIS-III)	Verbal fluency letter, verbal fluency categories			
Fagerlund et al.[48]	Donepezil					Total PANSS, positive PANSS, negative PANSS
Buchanan et al.[49]	Galantamine	CPT, grooved pegboard, WAIS-III digit symbol and symbol search, WAIS III letter-number sequencing, BACS number sequencing		CVLT, BVMT	AIMS, SAS	
Lee et al.[51]	Galantamine	Digit span, DSST, stroop, Trail Making test part A	Verbal fluency, BNT	HVLT, RCFT		
Dyer et al.[53]	Galantamine	CPT, three-card stroop, letter-number span (WAIS-III), grooved pegboard				

AIMS = Abnormal Involuntary Movement Scale; **BACS** = Brief Assessment of Cognition in Schizophrenia number sequencing score; **BNT** = Boston Naming Test; **BOWAT** = Benton Oral Word Association Test; **BVMT** = Brief Visuospatial Memory Test; **ChEI** = cholinesterase inhibitor; **COWAT** = Controlled Oral Word Association Test; **CPT** = Continuous Performance Test; **CVLT** = California Verbal Learning Test; **DSST** = digit symbol substitution test; **HVLT** = Hopkins Verbal Learning Test; **PANSS** = Positive and Negative Syndrome Scale; **RCFT** = Rey Complex Figure Test; **SAS** = Simpson-Angus Scale; **WAIS-III** = Wechsler Adult Intelligence Scale-Third Edition; **WCST** = Wisconsin Card Sorting Test.

was often incomplete and, therefore, extracting the required data from all trials was impossible. Adherence to a recommendation for the reporting of clinical trials would have increased the datasets available.

Only 13 trials (in a total of 564 subjects) met the inclusion criteria (table IV). The heterogeneity of the instruments used in the studies restricted the analysis: there were different scales evaluating the same cognitive function (e.g. for

memory: the Hopkins Verbal Learning Test, Benton Oral Association Test, California Verbal Learning Test, Brief Visuospatial Memory Test, Rey Complex Figure Test) or symptom (e.g. for extrapyramidal symptoms: AIMS, SAS).

Extrapyramidal Symptoms

For extrapyramidal symptoms, a significant improvement was found when we analysed the first two studies[37,39] (two scales for each study), with a total of 72 patients. When we included the third study,[49] no significant improvement was found (table V).

There is a possibility that the use of a cholinesterase inhibitor reduces extrapyramidal symptoms, which are a frequent adverse event of antipsychotics. A net improvement of dopaminergic function produced by a combination of cholinergic and nicotinic actions may be one speculative hypothesis.[42] At this stage, conclusions should be considered preliminary.

Psychopathology

Six studies provided data for total PANSS analysis (total sample = 119), seven contributed to the analysis of positive symptoms from PANSS (n = 364) and eight met the inclusion criteria for negative PANSS analysis (n = 377). Statistical analysis found that positive symptoms were significantly more intense (28.2%, p = 0.010) in the group that received a cholinesterase inhibitor than in the group that received placebo. This result must be interpreted with caution as one trial[45] provided >50% of the total sample (245). No statistical difference was found in the total PANSS or negative PANSS analysis. In many studies, the clinical stability of the patients who had been receiving antipsychotic treatment could explain the lack of change in positive and negative symptoms.[35]

Cognitive Functions

Similar to a previous meta-analysis,[55] no improvement in executive function or language was found. Analysis of one specific test of motor speed and attention (Trail Making test part A) found a significant improvement in the drug group in relation to the placebo group. Contrary to a previous meta-analysis,[56] memory results also showed a significant improvement. Nevertheless, caution should be taken in interpreting these results, as one of the studies[49] contributed >50% of the total number of patients in the analysis.

Erickson et al.[38] pointed out that as neurocognitive deficits are the most difficult symptoms to treat in schizophrenia/schizoaffective disorders, even modest improvements in this area may have a profound influence on overall functional and psychiatric stabilization. It is possible that the short duration of these studies was the reason that the analysis did not provide strong evidence of the efficacy of cholinesterase inhibitors for cognitive enhancement in schizophrenia/schizoaffective disorders. Cholinesterase inhibitors significantly benefit cognitive functions in patients with Alzheimer's disease for up to 6 months,[57] and many studies investigating the effects of galantamine on cognitive function were

Table V. Results of meta-analysis of randomized, controlled trials of cholinesterase inhibitors in patients (pts) with schizophrenia or schizoaffective disorder

Outcome domain	Studies (no.)	Effect size	95% CI	p-Value	Pts (no.)	Analysis (Hedge's Q/*df*/p-value)
Executive function	6	0.049	−0.256, 0.355	0.751	199	4.85/25/1
Trail Making test part A	4	−0.686	−1.1391, −0.2337	0.003	93	3.41/3/0.332
Language	4	0.237	−0.117, 0.592	0.190	63	4.78/6/0.573
Memory	3	0.280	0.0577, 0.5029	0.014	146	12.82/8/0.118
Extrapyramidal symptoms	3	−0.5676	−1.1588, −0.0236	0.059	158	19.85/5/0.001
Total PANSS	6	0.0892	−0.3193, 0.4976	0.669	119	1.05/5/0.958
Positive PANSS	7	0.282	0.0673, 0.4968	0.010	364	1.91/6/0.927
Negative PANSS	8	−0.1741	−0.6795, 0.3312	0.499	377	21.47/7/0.003

df = degrees of freedom; **PANSS** = Positive and Negative Syndrome Scale.

conducted for 6 months.[58,59] The heterogeneity of baseline characteristics of the samples (diagnostic inclusion criteria, age, education, severity of cognitive impairment, years of disease, antipsychotic drug used, smoking status, use of adjunctive anticholinergic medication) and of the neuropsychological assessments[60] made comparison difficult and confounded the results.

Concomitant use of psychotropics, including benzodiazepines, valproate and antidepressants, is a possible confounder of the results of the administration of cholinesterase inhibitors,[34] but few trials described the concomitant psychotropic drugs used. Most of the trials did not control the use of anticholinergic drugs, which may worsen cognition. Anticholinergic drugs interact with the cholinergic augmentation and are known to impair cognitive and information processing functions in both healthy and schizophrenic populations.[51] Antipsychotic medication should not be considered a causative factor in the cognitive impairment because several studies have concluded that antipsychotic drugs tend to improve performance in schizophrenic patients, except when they have anticholinergic effects.[61-63] Nevertheless, most of the studies did not control the use of antipsychotics and patients could receive typical and/or atypical antipsychotics.

To better analyse the use of cholinesterase inhibitors in schizophrenia/schizoaffective disorder patients, there must be homogeneity of the assessment instruments used in the studies. Furthermore, if possible, patients should receive specific drugs (especially atypical antipsychotics) or follow an algorithm to minimize the use of drugs with a potential to cause cognitive damage (e.g. those with cholinergic effects).

Heavy cigarette smoking has been associated with the normalization of the sensory motor gating and eye tracking abnormalities[64,65] and desensitization of the α_7-nicotinic receptor,[66,67] which may render the nicotinic receptors of the patients insensitive to the effects of increased acetylcholine produced by cholinesterase inhibitors.[68] Desensitized nicotinic receptor channels are closed and refractory to agonist activation. Smoking behaviour was analysed in only 11 studies (2 open-label and 12 double-blind) and, in most of these studies, cigarette smoking was a very prevalent behaviour (table II) that must be considered one of the major confounders. It should be controlled in further studies. Few trials included a specific test related to nicotine dependence to control for potential group differences in this variable.[41,53]

An alternative to a pure cholinesterase inhibitor such as donepezil should be considered. Galantamine acts as both a cholinesterase inhibitor and a nicotinic receptor modulator. In animals with memory and learning deficits, treatment with cholinesterase inhibitors can reverse cognitive deficits.[69] The cognitive effects of galantamine may be accentuated by its nicotinic allosteric agonist action, which can improve attention and memory.[70,71] Furthermore, galantamine appears to more powerfully elevate frontal cortical dopamine levels than cholinesterase inhibitors such as donepezil.[42] This biological effect may be significant since frontal dopaminergic deficits have been proposed to underlie cognitive impairment in schizophrenia.[42] Three studies that met the inclusion criteria used galantamine.[49,51,53] Only selective benefits for processing speed and verbal memory and improvement in the score for recognition on the Rey Complex Figure Test were found. Recently, studies using a partial α_7-nicotinic cholinergic receptor agonist (GTS-21; DMXB-A) in patients with schizophrenia have found a significant neurocognitive improvement compared with placebo.[72] This strategy may be promising for improving cognition and psychopathology in patients with schizophrenia.

The placebo response found in some studies may reflect the increased clinical care offered to all patients. The small sample size of the reviewed studies is an important limitation and likely prevents more definite conclusions about a significant drug effect on cognition.

It is possible that less sensitive tests were wrongly chosen to evaluate effects of cholinergic activity in this specific population. All double-blind studies that used functional MRI found enhanced neuronal activity in some regions.[33,37,39] Nahas et al.[33] found that the addition of donepezil provided a functional normalization, with an increase in left frontal lobe and cingulated

gyrus activity when compared with placebo from baseline scans. Aasen et al.[37] found an increase in regional brain activity in the cerebellum in the rivastigmine group, which was partially explained by changes in behavioural measures. Kumari et al.[39] found increased activity in the extrastriate visual cortex in areas associated with visual and spatial attention. It is possible that the functional MRI technique was more sensitive for detecting differences than the cognitive and behavioural measures used in other studies.

This apparent lack of effect on the cognitive function of patients with psychosis compared with the effect on patients with Alzheimer's disease may be due to the chronicity of schizophrenic illness or, alternatively, may be related to the distinct pathophysiological nature of the two illnesses.[49] Another reason for this difference could be that cognitive impairment in schizophrenia is more likely to be related to other transmitter systems. The roles of the dopaminergic, serotonergic and noradrenergic systems should be further studied.[10] It is important to note that we only included published trials in this analysis, which led to a publication bias as trials with positive results tend to be more frequently published than those with negative results. Therefore, active treatment effect sizes may be less than those reported in this review.

Few studies met inclusion criteria because of methodological problems. More double-blind trials (with homogeneous samples and longer duration) are needed to determine the clinical utility of cholinesterase inhibitors as cognitive enhancers in patients with schizophrenia and schizoaffective disorder.

Conclusions

There seems to be little effect of cholinesterase inhibitors on cognitive and psychopathological symptoms in schizophrenic patients. Cholinergic dysfunction underlying cognitive deficits in schizophrenic patients likely exists for those with co-morbid dementia. Open-label studies that evaluated patients with co-morbid dementia found cognitive improvement; however, the effect was smaller in double-blind studies.

The reviewed studies suggest that specific cognitive deficits (memory and motor speed/attention) of schizophrenic patients may be responsive to adjunctive rivastigmine, donepezil and galantamine.

Additional studies with larger samples are needed to clarify these issues. Few studies met the meta-analysis inclusion criteria. New trials should include methodological improvements such as a careful randomization of the patients treated; apply a more homogeneous set of scales and tests to assess drug effects; and standardize the primary antipsychotic drugs used in the treatment of schizophrenia.

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