Cholinesterase Inhibitor Adjunctive Therapy for Cognitive Impairment and Depressive Symptoms in Older Adults with Depression

Cara L McDermott and Shelly L Gray

Request

Are cholinesterase inhibitors (ChEIs) effective for cognitive enhancement and improvement in depressive symptoms for older adults with depression without Alzheimer's disease?

OBJECTIVE: To review the primary literature regarding the use of cholinesterase inhibitors (ChEIs) as adjunctive therapy for cognitive enhancement and improvement of depressive symptoms for older adults with depression.

DATA SOURCES: A literature search of MEDLINE (1950-September 2011) was conducted, using the search term depression in combination with cholinesterase inhibitor, donepezil, galantamine, or rivastigmine. A search of reference citations was conducted to identify additional references.

STUDY SELECTION AND DATA EXTRACTION: English-language clinical trials were evaluated. Studies that included subjects with Alzheimer's disease, dementia, Parkinson disease, bipolar disorder, or schizophrenia were excluded. Four clinical studies met our criteria.

DATA SYNTHESIS: We identified 4 randomized, double-blind, placebo-controlled trials that ranged in sample size from 20 to 130. Galantamine 16 mg daily was evaluated in 2 trials lasting 8 and 24 weeks. Neither study found a statistically significant difference in measures of cognition or Hamilton Rating Scale for Depression scores. Donepezil augmentation was evaluated in a 1-year and a 2-year trial. Donepezil was found to improve global cognition at 1 year, but the benefit did not persist at year 2. Subjects with mild cognitive impairment at baseline who received donepezil experienced higher depression recurrence than did those who took placebo ($p = 0.03$); this effect was not observed in cognitively intact subjects ($p = 0.39$).

CONCLUSIONS: There is no clear benefit for ChEI therapy as an adjunct to antidepressant therapy for depressed older adults.

KEY WORDS: cholinesterase inhibitors, cognition, cognitive impairment, depression, donepezil, galantamine.

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Response

BACKGROUND

Late-life depression is a term used to broadly describe clinically important depressive symptoms experienced by older adults, including major depressive disorders, dysthymia, and other subsyndromal types.[1] While major depressive disorder is not common in older adults (1-4%), the prevalence of clinically significant depressive symptoms is considerably higher, affecting 15-30% of older adults.[1] Depression, often underrecognized and undertreated in this population, increases the risk of disability.[2]

Depression and cognitive impairment often coexist and the relationship between the 2 is complex and not fully understood. Depression has been associated with greater risk for cognitive decline[3] and dementia.[4] Unfortunately, cognitive impairment may persist despite successful antidepressant therapy.[5] Older adults with recurrent depression experience more treatment resistance and cognitive impairment than do patients with a single depressive episode.[5] Studies have found that patients with depression and concurrent cognitive deficits, in particular executive dysfunction, experience a lower antidepressant treatment response and higher recurrence.[6,7] Less than 40% of older depressed patients with cognitive impairment achieve remission with antidepressant medications.[1] Thus, therapeutic strategies that

Author information provided at end of text.

target cognitive enhancement may be helpful in management of patients with depression and cognitive impairment.

ChEIs such as donepezil, galantamine, and rivastigmine are Food and Drug Administration (FDA)–approved to enhance or maintain cognition in patients with Alzheimer's disease.[8] ChEIs block hydrolysis of cholinesterase, resulting in higher levels of acetylcholine in the synapse and a longer duration of action of acetylcholine at muscarinic receptors. Galantamine hydrobromide also potentiates nicotinic receptors.[9]

ChEIs are one class of medications that might improve cognition in persons with late-life depression with concurrent cognitive deficits. In addition, ChEIs may improve antidepressant response or prevent depression recurrence by improving executive function.[10] Galantamine may improve depression via the modulation of the nicotinic receptor, which enhances the release of other neurotransmitters such as dopamine and noradrenaline. Further support for a potential benefit of ChEI therapy for depressive symptoms can be extrapolated from the literature on Alzheimer's disease; some studies reported that ChEIs improved mood-related symptoms (eg, apathy) or delayed emergence of neuropsychological symptoms.[11,12] However, other lines of evidence support the idea that cholinergic hypersensitivity or dominance may contribute to depressive symptoms, which would suggest that ChEI use would lead to worse depression outcomes.[13] At this point, it is unclear whether ChEIs would improve or worsen depressive symptoms in patients with depression and cognitive impairment. We reviewed the literature to determine whether ChEI adjunctive therapy may be helpful for improving cognitive and depressive symptoms in older adults with depression.

LITERATURE REVIEW

MEDLINE (1950-September 2011) was searched using depression in combination with cholinesterase inhibitor, donepezil, galantamine, or rivastigmine. Literature was limited to clinical human trials published in English. Studies focusing on Alzheimer's disease, dementia, Parkinson disease, or psychiatric disorders other than depression (eg, bipolar disorder or schizophrenia) were excluded. Additional references were extracted from reference citations. Four trials met the criteria and were included in this evaluation (Table 1). These studies were randomized, double-blind, and placebo-controlled.

Galantamine Adjunctive Therapy in Depression

Holtzheimer and colleagues[14] performed a 24-week pilot study of galantamine 16 mg/day as adjunctive therapy in 38 older adults (age ≥50 years) receiving standard treatment for major depression. Subjects were treated with venlafaxine extended-release (XR) 37.5 mg daily, with the dose titrated to response (defined as a decrease of 50% in the 24-item Hamilton Rating Scale for Depression [HAM-D-24] from baseline on 2 consecutive ratings) over 12 weeks. Those not responding to or not tolerating venlafaxine XR had their medication switched to citalopram. Primary outcomes included (1) Repeatable Battery for Assessment of Neuropsychological Status, which assesses multiple domains of cognition (ie, memory, attention, language, visuospatial abilities); and (2) the HAM-D, a multiple-item assessment to quantify the extent of depressive symptoms, with higher scores indicating worse depression. Overall, no statistically significant differences were found for cognition or depressive symptoms between groups. However, at week 2, the authors noted a marginally significant decrease (ie, improvement) in HAM-D scores in subjects receiving galantamine compared with those in the placebo group ($p = 0.05$). More (63%) subjects dropped out with galantamine compared with placebo (32%) ($\chi^2 = 4.66$; $df = 1$; $p = 0.03$). The primary reason for discontinuation was inability to adhere to the study protocol, but the authors did not list specific reasons according to treatment.

In a post hoc analysis, the authors noted that patients receiving galantamine used lower doses of venlafaxine XR (mean [SD] 128.6 mg [68.5]) compared with those receiving placebo (182.1 mg [56.7]; $p = 0.03$) and suggested that galantamine may have improved the antidepressant response in venlafaxine users. In contrast, subjects receiving galantamine used higher median citalopram doses (40 mg) compared with those receiving placebo (20 mg) ($p = 0.55$). The authors appropriately indicated that these results should be interpreted cautiously since this was a post hoc analysis in a small sample with a higher drop-out rate with galantamine.

A limitation of this small study is that, despite randomization, subjects in the placebo group were more depressed, with poorer cognition at baseline, which may have affected the antidepressant dose needed. Additionally, patients received citalopram only after failure to respond to venlafaxine. Subjects were not required to have impaired performance on the cognitive tests for study entry. Lastly, galantamine and antidepressant therapy were started concurrently; thus, it is difficult to delineate the independent effect of galantamine on depressive symptoms.

Elgamal and MacQueen[15] evaluated galantamine 16 mg/day adjunctive therapy in 20 subjects aged 40-80 years, with stable, treated major depression. Patients were maintained on their existing antidepressant regimens. The primary outcome was change on multiple tests of cognition (California Verbal Learning Test, Trail Making A and B, Ruff 2 and 7 Selective Attention Test, Digit Span Forward and Backward Test, Digit Symbol Substitution Test, Controlled Oral Word Association Test) and the HAM-D after 8 weeks. While no statistically significant differences were found between groups, participants receiving galantamine had a larger decrease in depressive symptoms compared with those receiving placebo (2.3 vs 0.3 points; statistical

Table 1. Characteristics of Trials for Cholinesterase Inhibitor Augmentation Therapy in Patients with Depression

Characteristic	Holtzheimer (2008)[14] (N = 38)	Elgamal (2008)[15] (N = 20)	Reynolds (2011)[17] (N = 130)	Pelton (2008)[18] (N = 23)
Design	R, DB, PC; 24 weeks	R, DB, PC; 8 weeks	Phase 1: OL antidepressant (0 to 12-16 weeks) Phase 2: R, DB, PC ChEI augmentation followed for 2 years	Phase 1: OL antidepressant (0-8 weeks) Phase 2: R, DB, PC ChEI augmentation (8-20 weeks) Phase 3: OL ChEI (20-52 weeks)
Treatment	Venlafaxine XR; if no response, citalopram[a] + placebo or galantamine 4 mg bid for 4 weeks, then 8 mg bid	Placebo or galantamine 8 mg for 4 weeks, then 16 mg in conjunction with maintenance antidepressant regimen[b]	Phase 1: escitalopram (≤20 mg/day); if no response, then duloxetine (≤120 mg/day) + aripiprazole augmentation (≤15 mg/day) as needed to achieve response Phase 2: placebo or donepezil 5 mg/day or 10 mg/day if tolerated	Phase 1: sertraline or clinician's choice of antidepressant Phase 2: placebo or donepezil 5 mg for 4 weeks, increasing to 10 mg Phase 3: donepezil 5 or 10 mg
Age, y, mean (SD)	Galantamine 62.5 (9.1) vs placebo 69.5 (10.3); p = 0.034	Galantamine 52.8 (NR) vs placebo 52.1 (NR); NS difference	Donepezil 73.1 (6.5) vs placebo 73.9 (5.8)	67.7 (8.7)
Inclusion criteria	Current major depressive episode; no dementia	Major depressive disorder without acute depressive episode	Current depressive episode with HAM-D score ≥15; nonbipolar, nonpsychotic, major depressive episode Normal cognition (n = 73), MCI (n = 57)	Major depressive disorder, dysthymic disorder, or depression not otherwise specified and cognitive impairment
Baseline depression rating, mean (SD)	HAM-D-24 Galantamine 26.4 (4.5) vs placebo 30.3 (6.7); p = 0.047	HAM-D Galantamine 6.5 (NR) vs placebo 9.2 (NR)	HAM-D-17 Donepezil 18.7 (3.3) vs placebo 18.8 (3.4)	HAM-D-24 22.2 (4.2)
Baseline cognition rating, mean (SD)	MMSE galantamine 28.0 (2.0) vs placebo 27.4 (1.5); p = 0.38 RBANS galantamine 90.9 (16.5) vs placebo 81.6 (14.6); p = 0.08	NR	MMSE donepezil 28.5 (1.4) vs placebo 28.4 (1.4)	MMSE 26.1 (2.1)
Primary outcome	No significant difference between groups in HAM-D score (p = 0.58) or RBANS score (p = 0.08); HAM-D (p < 0.01) and RBANS scores (p < 0.01) improved with time in both groups	HAM-D score reduction: galantamine 2.3 points vs placebo 0.3 points; NS difference in several measures of cognition	Global measure of neuropsychological function at 1 y: improvement for donepezil (p = 0.03), executive function (p = 0.001), and memory (p = 0.02) Change in C-IADL: no significant difference Major depression recurrences (HAM-D ≥15): donepezil 35% (95% CI 24% to 46%) vs placebo 19% (95% CI 9 to 29%); p = 0.05	Phase 1: group-by time effect for verbal memory for pts. responding to antidepressants (F = 4.42; p = 0.02) Phase 2: trend level group-by time interaction for verbal memory favoring donepezil (p = 0.05) Phases 2 and 3: for 12 completers, group-by time interaction for verbal memory favoring donepezil (p = 0.03) NS difference for 4 other tests of cognition
Notable secondary outcomes	NR	NR	Dementia conversion in MCI: donepezil 10% (95% CI 0 to 21) vs 33% (95% CI 16 to 51); p = 0.05	NR
Adverse events: ChEI vs placebo, n (%)	GI disturbance, 4 (21) vs 6 (33); headache, 2 (11) vs 2 (11); dizziness, 2 (11) vs 3 (17); cardiac abnormality, 1 (5) vs 3 (17); sweating, 4 (21) vs 5 (28); other, 4 (21) vs 8 (44)	GI disturbance, fatigue, hypersomnia; pt. numbers NR	GI or sleep disturbance, 6 (9) vs 0 (0); manic symptoms, 2 (3) vs 0 (0)	Similar frequency of somatic disturbances between groups; Phase B TESS scores, mean (SD): donepezil 3.2 (3.3) vs placebo 3.2 (3.2); additional events NR

ChEI = cholinesterase inhibitor; C-IADL = Cognitive Instrumental Activities of Daily Living; DB = double-blind; GI = gastrointestinal; HAM-D = Hamilton Rating Scale for Depression; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; NR = not reported; NS = not significant; OL = open-label; PC = placebo-controlled; R = randomized; RBANS = Repeatable Battery for Assessment of Neuropsychological Status; TESS = Treatment Emergent System Scale; XR = extended-release.

[a]Venlafaxine XR was dose escalated to response; initiated at 37.5 mg, increased at week 1 to 75 mg/day for 3 weeks, then increased to 150 mg/day for 6 weeks, then 225 mg/day. If patients had no response after 12 weeks, medication was switched to citalopram 10 mg/day for 1 week, 20 mg/day for weeks 2-4, 40 mg/day for weeks 5-6, then 60 mg/day for weeks 7-12.

[b]Patients were maintained on 1 of 14 regimens.

test value not reported). The authors reported numerical improvement on 5 cognitive tests; however, data were not provided. One subject in the galantamine group dropped out because of fatigue and hypersomnia.

The authors noted that 4 subjects, all of whom had received galantamine, had self-reported improved mood. These patients had higher baseline HAM-D scores (ie, more depressive symptoms) compared with the remaining galantamine subjects, who did not self-report improved mood. In an analysis restricted to the 4 individuals receiving galantamine, who responded based on self-report, compared with those receiving placebo, a statistically significant ($p = 0.037$) change on the HAM-D favoring galantamine was found. This finding should be regarded with caution, as it is a post hoc analysis including only 4 of the 10 participants taking galantamine.[15]

Limitations of the study by Elgamal and MacQueen are small sample size and the imbalance in HAM-D scores at baseline, with lower HAM-D scores in the galantamine group indicating fewer depressive symptoms compared with those in the placebo group (6.5 vs 9.2). The authors stated that the lack of overall difference may be because those with subthreshold depression receiving galantamine had little chance for improvement; at baseline, the average HAM-D score for the galantamine group was less than 7. Thus, scores were considerably lower than the recommended cut-off of 10, which is consistent with depression in geriatric patients.[16] Subjects were not required to have impaired performance on the cognitive tests for study entry. Lastly, the short duration (8 weeks) may not have been sufficient to observe the potential benefits of ChEI therapy.

Adjunctive Donepezil Therapy in Depression

In the largest and longest study to date, Reynolds and colleagues[17] recruited 130 adults aged 65 and older to examine donepezil therapy along with standard maintenance antidepressant therapy. Subjects with normal cognition or mild cognitive impairment (MCI) were included if they had depression (defined as ≥15 on the HAM-D). Only subjects who achieved remission (HAM-D ≤10 for 3 weeks) during the open-label antidepressant treatment (phase 1) were randomized to receive donepezil or placebo (phase 2). The primary outcomes were global neuropsychological function, independence in activities of daily living (IADL), and depression recurrence. Global neuropsychological function was determined through administration of 17 validated neuropsychological tests that assess 5 discrete domains of cognition (ie, delayed memory, executive functioning, language, information processing speed, and visuospatial functioning). The Performance Assessment of Self-Care Skills (PASS) was administered to assess cognitive IADL, while the HAM-D and structured interviews determined depression recurrence.

At year 2, 63% of participants randomized to donepezil and 78% of those randomized to placebo had completed the study. The authors found no statistically significant difference between the 2 groups in ability to function independently or on most cognitive assessments. The donepezil group experienced a small advantage in global cognition at the end of 12 months, a difference not sustained at 2 years; the beneficial effect on tests of memory and executive function at 12 months was also not sustained at 2 years. Notably, despite the use of maintenance antidepressants, coadministration of donepezil led to higher rates of recurrent depressive episodes than did placebo (hazard ratio 2.09; 95% CI 1.00 to 4.41; log-rank test $\chi^2 = 3.97$; $p = 0.05$). In a planned post hoc analysis, results were analyzed according to baseline cognitive status. The higher depression recurrence rate with donepezil versus placebo was especially prominent in those with MCI (44% vs 12%; log-rank test $\chi^2 = 4.91$; $p = 0.03$), but not in those with normal cognition ($p = 0.39$). Strengths of this study include the large sample size, intent-to-treat analysis, long duration, and treatment of depression to remission prior to randomizing to ChEI. These findings may not be generalizable beyond patients with a recent depressive episode. Although this is the largest study conducted to date, it may have been underpowered to examine potential cognitive benefits, especially in persons with normal cognition.[17]

Pelton and colleagues[18] used a 3-phase design to examine the effect of donepezil 10 mg/day as augmentation to antidepressant therapy in 23 subjects with depression (HAM-D ≥14) and cognitive impairment. Participants continuing to have impaired cognition after 8 weeks of open-label sertraline or antidepressant treatment of clinician choice (phase 1) went on to phase 2. Phase 2 was a randomized, double-blind, placebo-controlled trial of donepezil adjunctive therapy. After 20 weeks, all subjects were offered open-label donepezil for 32 subsequent weeks (phase 3). The primary outcome was a 5-test neuropsychological battery assessed at baseline and weeks 8, 20, and 52 (ie, verbal memory, verbal fluency, executive function, attention, and psychomotor speed).

After completing 12 weeks of phase 2, participants receiving donepezil experienced improvement in verbal memory compared with those receiving placebo. No statistically significant changes were noted with other neuropsychological tests. The authors also reported on the open, naturalistic follow-up, which included only 12 participants who continued the randomized treatment of phase 2 during phase 3 (6 participants randomized to donepezil who chose to continue donepezil therapy during phase 3; 6 participants randomized to placebo who elected not to start donepezil therapy during phase 3). Those remaining on donepezil for 32 additional weeks (44 weeks total) had a waning of response on verbal memory by week 52, but the response was still significantly different from that of sub-

jects not taking donepezil. However, given the open-label design of the study and the fact that only 12 of the original 23 subjects participated in phase 3, the results should be interpreted with caution.[18]

The authors acknowledge the limitations of a small sample size and heterogeneous participant sample, but nonetheless concluded that this study offers indirect evidence that cognitive decline may be delayed with donepezil therapy. A limitation of this study is that, although investigators excluded those with a diagnosis of dementia or a Mini-Mental State Examination score of less than 20, it is possible that they included subjects with undiagnosed dementia, a group known to receive this pattern of benefit from donepezil. Lastly, despite the 1-year follow-up, the randomized, placebo-controlled phase of the study was brief (12 weeks).

Discussion

Four randomized, double-blind, placebo-controlled trials have examined the efficacy of ChEIs as an adjunct to antidepressant therapy in patients with depression. Overall, the improvement in cognitive tests found in some studies was small and short-lived.[17,18] One study found that ChEIs increased risk for depression recurrence.[17] Effective doses of ChEIs were used; thus, dosing is unlikely to explain the overall lack of response. Most studies had limitations of small samples and short follow-up. Studies varied considerably in assessment of cognition, inclusion criteria for depression and cognitive status, antidepressant treatment, and timing for ChEI initiation with respect to antidepressant therapy.

The relationship between depression and cognitive impairment is complex, which makes evaluation of ChEIs as adjunctive therapy challenging. The implications of several design issues related to cognitive and depression outcomes are discussed separately. First, improvement in depression may improve cognitive status; thus, it is important that antidepressant doses be titrated adequately to observe the independent effect of ChEIs. Only 2 studies addressed this issue.[17,18] Second, participants should have measurable impairment on tests of cognition upon commencing ChEI therapy; however, standard assessments should be used to rule out dementia. The 2 studies[17,18] that found a short-term benefit of ChEI adjunctive therapy recruited patients with measurable cognitive impairment at baseline, maximizing the possibility of finding an improvement on cognitive tests; however, the study by Pelton et al.[18] did not ensure that subjects with undiagnosed dementia were excluded. Third, adequate follow-up is important to allow for a full assessment and duration of potential benefits of ChEI therapy.

Three of the studies examined the effect of ChEI therapy on depression outcomes. Two studies examined change on HAM-D, while the third examined depression recurrence. The study by Elgamal and MacQueen[15] intentionally selected subjects with treated depression because of uncertainty as to whether ChEI therapy could exacerbate depression. Because of this, the study had little chance of examining an improvement in depressive symptoms (eg, ceiling effect). A study design using concurrent initiation of ChEI therapy and antidepressant dose titration makes it difficult to determine the independent effect of ChEI therapy on depressive symptoms, as illustrated by Holtzheimer et al.[14] In this study, the antidepressant was titrated to response over 12 weeks, and if ChEI therapy did contribute to depressive symptoms resolution, it could impact the final antidepressant dose achieved. Using this design, the potential benefit of ChEI therapy on depressive symptoms could only be determined indirectly by examining differences in antidepressant dose according to ChEI status. However, the study would need to be powered on this subgroup analysis and include a sufficient number of subjects for a meaningful interpretation. Another study design that could inform the benefit of ChEIs on depressive symptoms would be to focus on subjects with treatment-resistant depression. Lastly, the presence of comorbidities may produce somatic symptoms reflected in the HAM-D but not related to depression. Older adults recruited into studies should have an HAM-D baseline score of 10 or greater to indicate the presence of geriatric depression.[16]

ChEIs have been studied extensively in patients with MCI and may help place the findings of this review in perspective. The temporary cognitive benefits of ChEIs in depressed patients[17,18] are consistent with the effect of ChEIs in patients with MCI in studies that have reported either transitory or no benefit.[19,20] Reynolds et al. reported that donepezil tended to increase depression recurrence when used in depressed patients in remission,[17] and a post hoc analysis suggested that this was mainly in those with MCI. In contrast, depressive symptomatology remained relatively stable with donepezil, and depression scores were not different from those with placebo in a 3-year study conducted in depressed subjects with MCI.[21] Therefore, the potential for ChEI therapy to worsen depression outcomes requires confirmation. Importantly, MCI is not an FDA-approved indication for ChEI therapy.

ChEIs were generally well tolerated in patients with depression, with a pattern of adverse events similar to that observed in patients with MCI and Alzheimer's disease, primarily involving gastrointestinal symptoms and sleep disturbances. In 1 study, 2 patients without a history of bipolar disorder experienced manic episodes while receiving donepezil.[17] Exacerbation of mania has been reported in 2 small case series examining adjunct use of donepezil in patients with bipolar disorder.[22,23] While this finding is rare, further examination is warranted, given the potentially serious consequences of manic activation.

Summary

Donepezil and galantamine have been evaluated as adjunctive therapy for depression in older adults, but current data are limited by shortcomings in study design. Based on 1 well-controlled trial with adequate follow-up, ChEIs have no clear benefit as adjunctive treatment to depression therapy for improving cognition in older adults. Evidence does not support the theory that ChEI use improves depressive symptoms and, in fact, may contribute to depression relapse.

Cara L McDermott PharmD, Graduate Student, School of Pharmacy, University of Washington, Seattle, WA
Shelly L Gray PharmD MS, Professor, School of Pharmacy, University of Washington
Correspondence: Dr. Gray, slgray@uw.edu
Reprints/Online Access: www.theannals.com/cgi/reprint/aph.1Q445

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EXTRACTO

Uso de Inhibidores de Colinesterasa como Tratamiento Adjunto en Pacientes Ancianos con Depresión y Síntomas de Depresión y Problemas Cognitivos

CL McDermott y SL Gray

Ann Pharmacother 2012;46:599-605.

OBJETIVO: Revisar la literatura primaria relacionada con el uso de inhibidores de colinesterasa (ChEIs) como tratamiento adjunto en pacientes ancianos con depresión y síntomas de depresión y problemas cognitivos.

FUENTES DE DATOS: Se realizó una búsqueda de la literatura en el sistema de datos MEDLINE desde 1950 hasta septiembre 2011 utilizando el término depresión en combinación con inhibidores de colinesterasa, donepezilo, galantamina o rivastigmina. Se estudiaron las referencias obtenidas para identificar trabajos adicionales.

SELECCIÓN DE ESTUDIOS Y EXTRACCIÓN DE DATOS: Se evaluaron los estudios clínicos publicados en el idioma inglés. Se excluyeron los estudios que incluían sujetos con la enfermedad de Alzheimer, demencia, Parkinson, desorden bipolar o esquizofrenia. Cuatro estudios clínicos cumplieron con los criterios establecidos.

SÍNTESIS DE LOS DATOS: Se identificaron cuatro estudios aleatorios, doble ciego, control placebo que tenían una muestra entre 20 y 130 sujetos. Galantamina en dosis de 16 mg/día se evaluó en dos estudios que tuvieron una duración de 8 y 24 semanas. Ninguno de los estudios encontró una diferencia estadísticamente significativa en las medidas de cognición o en la Escala Hamilton para Evaluar Depresión (HDRS). En un estudio de 1 y 2 años se evaluó el uso de donepezilo aumentando la terapia. Se encontró que donepezilo mejoraba la cognición global en un año, pero el beneficio no persistió al segundo año. Pacientes con disfunción cognitiva leve al inicio del estudio y que recibieron donepezilo experimentaron mayor recurrencia de depresión que los pacientes que utilizaron placebo ($p = 0.03$). Este efecto no se observó en los pacientes que presentaban un nivel de cognición intacto ($p = 0.39$).

CONCLUSIONES: No se ha demostrado un beneficio definitivo con el uso de los inhibidores de colinesterasa en el tratamiento adjunto a terapia antidepresiva en pacientes ancianos con depresión.

Traducido por Mirza Martínez

RÉSUMÉ

Thérapeutique Adjuvante par Inhibiteur de la Cholinestérase pour les Troubles Cognitifs et les Symptômes Dépressifs chez les Patients Agés Atteints de Dépression

CL McDermott et SL Gray

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OBJECTIFS: Faire le point sur la littérature primaire à propos de l'utilisation des inhibiteurs de la cholinestérase en tant que traitement adjuvant pour l'amélioration des troubles cognitifs et des symptômes dépressifs chez les personnes âgées atteintes de dépression.

SOURCES DE DONNEES: Une recherche dans la littérature sur Medline de 1950 à Septembre 2011 a été effectuée en utilisant le mot-clé dépression en association avec inhibiteur de la cholinestérase, donépézil, galantamine, ou rivastigmine. Une recherche dans les citations bibliographiques des articles a été réalisée pour identifier des références complémentaires.

SELECTION DES ETUDES ET EXTRACTION DES DONNEES: Les essais cliniques publiés en anglais ont été évalués. Les études incluant des sujets atteints de maladie d'Alzheimer, démence, maladie de Parkinson, trouble bipolaire ou schizophrénie ont été exclues. Quatre études cliniques remplissaient ces critères.

SYNTHESE DES DONNEES: Quatre essais contrôlés contre placebo, randomisés, en double aveugle ont été identifiés qui comprenaient entre 20 et 130 sujets. La galantamine à 16 mg/jour a été évaluée dans 2 essais d'une durée de 8 à 24 semaines. Aucune étude n'a trouvé de différence statistiquement significative dans l'évaluation de l'état cognitif ou sur l'échelle de mesure de la dépression de Hamilton (HDRS). Le donépézil à doses croissantes a été évalué dans des essais sur 1 et 2 ans. Le donépézil a montré une amélioration de l'état cognitif global à un an, mais le bénéfice n'a pas été conservé au bout de 2 ans. Les sujets atteints au départ de troubles cognitifs légers qui ont reçu du donépézil ont manifesté une récurrence des dépressions plus élevée que ceux qui étaient sous placebo ($p = 0.03$). Cet effet n'a pas été observé chez les sujets cognitivement intacts ($p = 0.39$).

CONCLUSIONS: Il n'y a pas de bénéfice net des inhibiteurs de la cholinestérase en tant que traitement adjuvant antidépresseur chez les patients âgés déprimés.

Traduit par Michel Le Duff