Benefits of cholinesterase inhibitors or patients with Lewy Body Dementia & evidence for slowing the disease process of Alzheimer’s Disease

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SEARCH RESULTS

Because of the large number of results, only the last 10 years were searched for Lewy Body Dementia, and only the last 5 years for Alzheimer’s Disease.

Systematic Reviews: (6), (10), (16), (25), (40), (53), (56), (58), (73), (82), (83), (84), (91), (94), (121), (145), (165)

RCTs: (1), (29), (30), (35), (38), (46), (54), (59), (66), (68), (69), (72), (78), (95), (101), (103), (105), (107), (130), (134), (144), (158)

Animal studies: (13), (17), (42), (49), (52), (109), (117)

Abstract: Importance: New therapeutic approaches for Alzheimer disease (AD) are needed.Objective: To assess whether idalopirdine, a selective 5-hydroxytryptamine-6 receptor antagonist, is effective for symptomatic treatment of mild to moderate AD.Design,
Setting, and Participants: Three randomized clinical trials that included 2525 patients aged 50 years or older with mild to moderate AD (study 1: n=933 patients at 119 sites; study 2: n=858 at 158 sites; and study 3: n=734 at 126 sites). The 24-week studies were conducted from October 2013 to January 2017; final follow-up on January 12, 2017. Interventions: Idalopirdine (10, 30, or 60 mg/d) or placebo added to cholinesterase inhibitor treatment (donepezil in studies 1 and 2; donepezil, rivastigmine, or galantamine in study 3). Main Outcomes and Measures: Primary end point in all 3 studies: change in cognition total score (range, 0–70; a lower score indicates less impairment) from baseline to 24 weeks measured by the 11-item cognitive subscale of the Alzheimer’s Disease Assessment Scale (ADAS-Cog); key secondary end points: Alzheimer’s Disease Cooperative Study-Clinical Global Impression of Change Scale and 23-item Activities of Daily Living Inventory scores. Dose group efficacy required a significant benefit over placebo for the primary end point and 1 or more key secondary end points. Safety data and adverse event profiles were recorded. Results: Among 2525 patients randomized in the 3 trials (mean age, 74 years; mean baseline ADAS-Cog total score, 26; between 62% and 65% of participants were women), 2254 (89%) completed the studies. In study 1, the mean change in ADAS-Cog total score between baseline and 24 weeks was 0.37 for the 60-mg dose of idalopirdine group, 0.61 for the 30-mg dose group, and 0.41 for the placebo group (adjusted mean difference vs placebo, 0.05 [95% CI, -0.88 to 0.98] for the 60-mg dose group and 0.33 [95% CI, -0.59 to 1.26] for the 30-mg dose group). In study 2, the mean change in ADAS-Cog total score between baseline and 24 weeks was 1.01 for the 30-mg dose of idalopirdine group, 0.53 for the 10-mg dose group, and 0.56 for the placebo group (adjusted mean difference vs placebo, 0.63 [95% CI, -0.38 to 1.65] for the 30-mg dose group; given the gated testing strategy and the null findings at the 30-mg dose, statistical comparison of the 10-mg dose was not performed). In study 3, the mean change in ADAS-Cog total score between baseline and 24 weeks was 0.38 for the 60-mg dose of idalopirdine group and 0.82 for the placebo group (adjusted mean difference vs placebo, -0.55 [95% CI, -1.45 to 0.36]). Treatment-emergent adverse events occurred in between 55.4% and 69.7% of participants in the idalopirdine groups vs between 56.7% and 61.4% of participants in the placebo groups. Conclusions and Relevance: In patients with mild to moderate AD, the use of idalopirdine compared with placebo did not improve cognition over 24 weeks of treatment. These findings do not support the use of idalopirdine for the treatment of AD. Trial Registration: clinicaltrials.gov Identifiers: NCT01955161, NCT02006641, and NCT02006654


Abstract: Elderly patients with Alzheimer’s disease (AD) and other dementias are at high risk of polypharmacy and excessive polypharmacy for common coexisting medical conditions. Polypharmacy increases the risk of drug-drug and drug-disease interactions in these patients who may not be able to communicate early symptoms of adverse drug events. Three acetylcholinesterase inhibitors (AChEIs) have been approved for AD: donepezil (Aricept), rivastigmine (Exelon), and galantamine (Razadyne). They are also used off-label for other causes of dementia such as Lewy body and vascular dementia. We here report evidence from the literature that AChEI treatment, prescribed for cognitive impairment, can reduce the load of medications in patients with AD by also addressing cardiovascular, gastrointestinal, and other comorbidities. Using one drug to address multiple symptoms can reduce costs and improve medication compliance.


Abstract: Although cholinesterase inhibitors (ChEIs) have been proved to help reduce cognitive deterioration in patients with Alzheimer’s disease (AD), their effects on survival remain inconclusive. This study aims to assess the effects of the persistent use of ChEIs on the risk of mortality in patients with AD. This population-based cohort study included 8614 patients having AD with ChEI prescription from 2002 to 2006 and followed until 2010. Kaplan-Meier curves and hazard ratios (HRs) of mortality were estimated in association with ChEI treatment duration and adherence. The average annual mortality rate per 100 person-years
was 9.2 for the short-duration group (discontinued < 1 year) and 7.2 for the long-duration group (discontinued ≥ 2 years). Compared to the short-duration group, the long-duration group had a lower mortality (HR = 0.76, 95% confidence interval: 0.69-0.84) and shorter annual inpatient days. But the annual health-care costs did not differ significantly between the 2 groups.


Abstract: Aim: The response to donepezil in patients with Alzheimer's disease varies, and it is important to identify the potential responder before therapy. Cerebral white matter changes (WMC) are frequently observed in older patients, and the effect of WMC on therapeutic response remains controversial. The present study aimed to investigate the relationships between the location of WMC, severe WMC and the response to donepezil. Methods: Among 418 patients with Alzheimer's disease receiving donepezil, 196 patients were eligible for analysis. Five brain areas on each side were analyzed using computed tomography scans and the Age-Related White Matter Changes Rating Scale before therapy. The Cognitive Abilities Screening Instrument was used annually. Patients were defined as responders if their baseline Cognitive Abilities Screening Instrument score minus their follow-up Cognitive Abilities Screening Instrument score was ≤ 0. Results: There was no significant difference in demographic data between responder and non-responder groups. Patients in the responder group had significantly less involvement of WMC in the frontal area (P = 0.0213) and nearly a trend for less involvement of WMC in the basal ganglia (P = 0.1103). After adjustment for age, sex, education, polymorphism of apolipoprotein E, hypertension and diabetes, WMC in the frontal area (OR 0.446, P = 0.0139) and basal ganglia (OR 0.243, P = 0.0380) were significantly associated with a reduced therapeutic response. Conclusions: Patients with WMC in the frontal area and basal ganglia had significant decreases in their therapeutic response to donepezil. The location of WMC, independent of their severity, might be associated with the therapeutic response in patient with Alzheimer's disease. Geriatr Gerontol Int 2018; 18: 123-129.


Abstract: In early Alzheimer's disease, which initially presents with progressive loss of short-term memory, neurodegeneration especially affects cholinergic neurons of the basal forebrain. Pharmacotherapy of Alzheimer's disease therefore often targets the cholinergic system. In contrast, cholinergic pharmacotherapy of mild cognitive impairment is debated since its efficacy to date remains controversial. We here investigated the relationship between cholinergic treatment effects and the integrity of the cholinergic system in mild cognitive impairment due to Alzheimer's disease. Fourteen patients with high likelihood of mild cognitive impairment due to Alzheimer's disease and 16 age-matched cognitively normal adults performed an episodic memory task during functional magnetic resonance imaging under three conditions: (i) without pharmacotherapy; (ii) with placebo; and (iii) with a single dose of rivastigmine (3 mg). Cortical acetylcholinesterase activity was measured using PET with the tracer 11C-piperidyl acetate (MP4A). Cortical acetylcholinesterase activity was significantly decreased in patients relative to controls, especially in the lateral temporal lobes. Without pharmacotherapy, mild cognitive impairment was associated with less memory-related neural activation in the fusiform gyrus and impaired deactivation in the posterior cingulate cortex, relative to controls. These differences were attenuated under cholinergic stimulation with rivastigmine: patients showed increased neural activation in the right fusiform gyrus but enhanced deactivation of the posterior cingulate cortex under rivastigmine, compared to placebo. Conversely, controls showed reduced activation of the fusiform gyrus and reduced deactivation of the posterior cingulate under rivastigmine, compared to placebo. In both groups, the change in neural activation in response to rivastigmine was negatively associated with local acetylcholinesterase activity. At the behavioural level, an analysis of covariance revealed a significant group — treatment interaction in episodic memory performance when accounting for hippocampal grey matter atrophy and function. Our results indicate that rivastigmine differentially affects memory-related neural activity in patients with mild cognitive impairment and cognitively normal, age-
matched adults, depending on acetylcholinesterase activity as a marker for the integrity of the cortical cholinergic system. Furthermore, hippocampal integrity showed an independent association with the response of memory performance to acetylcholinesterase inhibition. (PsycINFO Database Record (c) 2018 APA, all rights reserved) (Source: journal abstract)


Abstract: Background/Objectives: To examine the comparative effectiveness and safety of cognitive enhancers for Alzheimer’s disease (AD). Design: Systematic review and Bayesian network metaanalysis (NMA). Setting: MEDLINE, EMBASE, Cochrane Library, CINAHL, Ageline (inception-March 2016). Participants: Individuals with AD in randomized controlled trials (RCTs), quasi-RCTs, and nonrandomized studies. Intervention: Any combination of donepezil, rivastigmine, galantamine, or memantine. Measurements: Two reviewers independently screened titles, abstracts, and full-texts; abstracted data; and appraised risk of bias. Results: Twenty thousand three hundred forty-three citations were screened, and 142 studies were included (110 RCTs, 21 non-RCTs, 11 cohort studies). NMA found that donepezil (Mini-Mental State Examination: mean difference (MD) = 1.39, 95% credible interval (CrI) = 0.53 - 2.24), donepezil + memantine (2.59, 95% CrI = 0.12-4.98), and transdermal rivastigmine (2.02, 95% CrI = 0.02-4.08) improved cognition more than placebo. NMA found that donepezil (Alzheimer's Disease Assessment Scale-cognitive: MD = -3.29, 95% CrI = -4.57 to -1.99) and galantamine (MD = -2.13, 95% CrI = -3.91 to -0.27) improved cognition more than placebo. NMA found that donepezil + memantine (MD = -5.23, 95% CrI = -8.72 to -1.56) improved behavior more than placebo. NMA found that donepezil (MD = -0.32, 95% CrI = -0.46 to -0.19), donepezil + memantine (MD = -0.57, 95% CrI = -0.95 to -0.21), oral rivastigmine (MD = -0.38, 95% CrI = -0.56 to -0.17), and galantamine (MD = -3.79, 95% CrI = -6.98 to -0.59) improved global status more than placebo. NMA found that galantamine decreased the odds of mortality (odds ratio = 0.56, 95% CrI = 0.36-0.87). No agent increased risk of serious adverse events, falls, or bradycardia. Some increased risk of headache (oral rivastigmine), diarrhea (oral rivastigmine, donepezil), nausea (oral rivastigmine, donepezil, galantamine), and vomiting (oral rivastigmine, donepezil, galantamine). Conclusion: An exhaustive review of the literature involving 142 studies demonstrated that cognitive enhancers in general have minimal effects on cognition according to minimal clinically important difference and global ratings. The drugs appear safe, but this must be interpreted cautiously because trial participants may have less comorbidity and fewer adverse effects than those treated with these drugs in clinical practice. (PsycINFO Database Record (c) 2018 APA, all rights reserved)

(7) Drugs used to relieve behavioural and psychological symptoms in dementia 2017. Alzheimer's Society.


Abstract: Aim To investigate whether the inhibitory rate of serum butyrylcholinesterase (BuChE) activity in Japanese patients with Alzheimer’s disease is correlated with cognitive function, behavioral symptoms and caregiver burden. Methods A total of 61 patients with mild to moderately severe Alzheimer’s disease who were not undergoing cholinesterase enzyme inhibitor/memantine combinatorial treatment received a rivastigmine (18 mg) patch for 24 weeks. The rate of inhibition of BuChE was correlated with scores obtained on cognitive (Mini-Mental State Examination), behavioral (the Japanese version of the modified Crichton Geriatric Behavioral Rating Scale [CGBRS] and Vitality Index [VI]) and burden (the Japanese version of Zarit Burden Inventory [ZBI]) scales; and the Clinical Global Impression of Change scale. Results The serum BuChE activity showed a significant decrease after 24 weeks compared with baseline ( P < 0.001). Overall, significant effects were found in the Mini-Mental State Examination score, VI score and modified CGBRS score. We then divided patient
groups into a high inhibitory rate (≥ 40%) group and a low inhibitory rate (<40%) group; there were significant improvements in the Mini-Mental State Examination score, VI score and modified CGBRS score in both groups. However, favorable results were seen in cooperation, restlessness and leisure on modified CGBRS subscales in the high inhibitory rate group (P < 0.001, P = 0.007, P < 0.001, respectively), and rehabilitation and other activities on VI subscales in the high inhibitory rate group (P = 0.005) compared with those in the low inhibitory rate group. Conclusions: Demonstrable significant improvements in behavioral symptoms, such as low cooperation, restlessness or low activities in patients with Alzheimer's disease, were achieved on inhibition of BuChE at a rate of 40% or more. Geriatr Gerontol Int 2017; 17: 1306-1312


Abstract: Background: We investigated the effect of cholinesterase inhibitors on all-cause discontinuation, efficacy and safety, and the effects of study design-, intervention-, and patient-related covariates on the risk-benefit of cholinesterase inhibitors for Alzheimer's disease. Methods: A systematic review and meta-analysis of randomized placebo-controlled clinical trials comparing cholinesterase inhibitors and placebo was performed. The effect of covariates on study outcomes was analysed by means of meta-regression using a Bayesian framework. Results: Forty-three randomized placebo-controlled clinical trials involving 16106 patients were included. All-cause discontinuation was higher with cholinesterase inhibitors (OR = 1.66), as was discontinuation due to adverse events (OR=1.75). Cholinesterase inhibitors improved cognitive function (standardized mean difference = 0.38), global symptomatology (standardized mean difference=0.28) and functional capacity (standardized mean difference=0.16) but not neuropsychiatric symptoms. Rivastigmine was associated with a poorer outcome on all-cause discontinuation (Diff OR = 1.66) and donepezil with a higher efficacy on global change (Diff standardized mean difference = 0.41). The proportion of patients with serious adverse events decreased with age (Diff OR = -0.09). Mortality was lower with cholinesterase inhibitors than with placebo (OR = 0.65). Conclusion: While cholinesterase inhibitors show a poor risk-benefit relationship as indicated by mild symptom improvement and a higher than placebo all-cause discontinuation, a reduction of mortality was suggested. Intervention- and patient-related factors modify the effect of cholinesterase inhibitors in patients with Alzheimer's disease. (PsycINFO Database Record (c) 2017 APA, all rights reserved) (Source: journal abstract)


Abstract: Antagonism of the 5-HT6 receptor is a promising approach for the symptomatic treatment of Alzheimer's disease (AD). There is compelling preclinical evidence for the procognitive potential of 5-HT6 receptor antagonists and several compounds are in clinical development, as adjunct therapy to acetylcholinesterase inhibitors (AChEIs). This manuscript summarizes the scientific rationale for the use of 5-HT₆ receptor antagonists as AD treatment, with some focus on the selective and high-affinity 5-HT₆ receptor antagonist idalopirdine (Lu AE58054). The 5-HT6 receptor is enriched in brain regions that mediate cognition, where expression predominates on glutamatergic and GABAergic neurons and subsets of GABAergic interneurons. It is proposed that 5-HT6 receptor antagonism modulates the balance between neuronal excitation (glutamate) and inhibition (GABA), which may have widespread implications for neurotransmission and neuronal activity. This is supported by preclinical studies showing that 5-HT6 receptor antagonists increase concentrations of multiple neurotransmitters, and strengthened by recent evidence that idalopirdine facilitates neuronal oscillations and contributes to the recruitment of several neuronal networks relevant in cognition. Some of these effects are observed with idalopirdine monotherapy, whereas others require concomitant treatment with an AChEI. Several hypotheses for the mechanism underlying the synergistic actions between 5-HT6 receptor antagonists and AChEIs are discussed. Collectively, the current evidence suggests that 5-HT6 receptor antagonism adds a unique, complementary mechanism of action to that of AChEIs. The facilitation of multiple neurotransmitters and neuronal activity in brain regions that mediate cognition, and the synergy with AChEIs, are proposed to mediate the
procognitive effects of 5-HT₆ receptor antagonists in AD patients. (PsycINFO Database Record (c) 2017 APA, all rights reserved)


Abstract: Alzheimer disease comprises a syndrome of progressive cognitive and functional decline. Treatments should target cognitive and functional symptoms. Cholinesterase inhibitors, memantine, and a combination of a cholinesterase inhibitor and memantine have produced statistically significant but clinically small delays in various domains of cognitive and functional decline in select patients with Alzheimer disease. Vitamin E has been shown to delay functional decline in patients with mild to moderate Alzheimer disease, especially when taken in combination with a cholinesterase inhibitor. Structured programs of physical exercise improve physical function and reduce rates of neuropsychiatric symptoms in patients with mild to severe Alzheimer disease. Cognitive stimulation programs show benefit in maintenance of cognitive function and improved self-reported quality of life in patients with mild to moderate Alzheimer disease


Abstract: The current pharmacological approach to Alzheimer's disease (AD) treatment, mostly based on acetylcholinesterase inhibitors (AChEIs), is being revisited, especially in terms of the temporal frames and the potential benefits of their noncanonic actions, raising the question of whether inhibitors of AChE might also act in a disease-modifying manner. Besides, in the last decades, the pharmacophoric moieties of known AChEIs have been covalently linked to other pharmacophores in the pursuit of multitarget hybrid molecules that are expected to induce long-lasting amelioration of impaired neurotransmission and clinical symptoms but also to exert disease-modifying effects. Our research consortium has synthesized and defined the pharmacological profile of new AChEIs derivatives of potential interest for the treatment of AD. Among these, huprines and derivatives have been characterized successfully. Huprine X, a reversible AChE inhibitor, designed by molecular hybridization of tacrine and huperzine A, has been shown to affect the amyloidogenic process in vitro, and the AD-related neuropathology in vivo in mice models of the disease. More recently, we have shown that a group of donepezil-huprine heterodimers exerts a highly potent and selective inhibitory action on AChE both in vitro and ex vivo, simultaneously interacting with both peripheral and catalytic binding sites, and inhibiting the β-amyloid aggregation, whereas some levetiracetam-huprine hybrids have been shown to reduce epileptiform activity, neuroinflammation and amyloid burden in an animal model of AD. Here, we summarize the behavioural correlates of these noncanonic actions as assessed in three distinct biological scenarios: middle-age, cognitive deficits associated with ageing and AD-like phenotype in mice. Besides the improvement in the hallmark cognitive symptomatology without inducing side effects, these drugs have shown to be able to modulate emotional and anxiety-like behaviours or to reduce spontaneous seizures, all of them related to the so-called “behavioural and psychological symptoms of dementia”. Overall, the studies show that these novel multitarget anticholinesterasics exert noncanonic actions providing symptomatic and disease-modifying benefits of potential interest for the management of AD. (PsycINFO Database Record (c) 2017 APA, all rights reserved)


Abstract: Aim The coexistence of Alzheimer's disease (AD) and cerebrovascular disease pathology increases age-dependently. We comprehensively analyzed the clinical effects of galantamine or cilostazol monotherapy to the add-on combination therapy on three major factors of dementia, such as cognitive, affective and activities of daily living functions in AD patients with asymptomatic lacunar infarction. Methods We divided 101 AD patients with asymptomatic lacunar infarction into two subgroups: group A ( n = 61, first treated with galantamine and then cilostazol added) and group B ( n = 40, first treated with cilostazol and galantamine added). We compared the clinical effects before and after combination therapy of
galantamine and cilostazol (i.e. 3 months [M] before (-3 M), baseline (0 M), 3 and 6 M after the add-on combination). Results Galantamine monotherapy increased cognitive Hasegawa dementia score-revised scores, which were further improved with add-on cilostazol. Cilostazol monotherapy also increased the cognitive tests, which were further improved with add-on galantamine. Add-on cilostazol significantly improved Geriatric Depression Scale and Abe's behavioral and psychological symptoms of dementia scores after galantamine monotherapy. Cilostazol monotherapy also significantly improved Geriatric Depression Scale scores, with further improvements in Geriatric Depression Scale, apathy scores and Abe’s behavioral and psychological symptoms of dementia scores by add-on galantamine. Activities of daily living scores continuously improved with galantamine monotherapy and add-on cilostazol.

Conclusions The present study provides a clinical possibility that galantamine or cilostazol monotherapy and the combination therapy maintained or even improved cognitive, affective, and activities of daily living functions in AD with asymptomatic lacunar infarction. Geriatr Gerontol Int 2017; 17: 1384-1391


Abstract: Pharmacological management of dementia with Lewy bodies (DLB) remains challenging, because it is complicated by the risk of adverse reactions to medication. Treatments for one aspect of the disease may exacerbate other symptoms. In this chapter, I will introduce the results of pharmacological trials mainly investigating cognitive impairment and neuropsychiatric symptoms for DLB and Parkinson’s disease and dementia (PDD), both separately and together. A recent meta-analysis indicated beneficial effects of donepezil and rivastigmine for cognitive and psychiatric symptoms, and these two drugs may be effective for improving cognition and reducing neurobehavioral disturbances over 1 year. Memantine can be used safely in patients with DLB and PDD, but its effects on symptoms may be variable. When using antipsychotics in DLB or PDD, the likely balance of risks vs. benefits requires very careful consideration. Agents that can modify underlying disease processes such as alpha-synuclein accumulation will be promising treatment candidates. *(PsycINFO Database Record (c) 2017 APA, all rights reserved)* *(Source: chapter)*


Abstract: Background: The clinical benefit of memantine for Alzheimer’s disease (AD) remains inconclusive. Objective: We performed an updated systematic review and meta-analysis of the efficacy/safety of memantine in AD. Methods: We included randomized trials of memantine for AD patients. Cognitive function scores (CF), behavioral disturbances scores (BD), and all-cause discontinuation were used as primary measures. Effect size based on a random-effects model was evaluated in the meta-analyses. Results: Thirty studies ( n = 7,567; memantine versus placebo: N = 11, n = 3,298; memantine + cholinesterase inhibitors (M + ChEIs) versus ChEIs: N = 17, n = 4,175) were identified. Memantine showed a significant improvement in CF [standardized mean difference (SMD) = -0.24, 95% confidence intervals (95% CIs) = -0.34, -0.15, p < 0.00001, I2 = 35% ] and BD (SMD = -0.16, 95% CIs = -0.29, -0.04, p = 0.01, I2 = 52%) compared with placebo. In the sensitivity analysis including only patients with moderate-severe AD, memantine was superior to the placebo in reducing BD without considerable heterogeneity (SMD = -0.20, 95% CIs = -0.34, -0.07, p = 0.003, I2 = 36%). Compared with ChEIs, M + ChEIs showed a greater reduction in BD (SMD = -0.20, 95% CIs = -0.36, -0.03, p = 0.02, I2 = 77%) and a trend of CF improvement (SMD = -0.11, 95% CIs = -0.22, 0.01, p = 0.06, I2 = 56%). However, in the sensitivity analysis of double-blind, placebo-controlled studies only, M + ChEIs showed a significant reduction in BD compared with ChEIs without considerable heterogeneity (SMD = -0.11, 95% CIs = -0.21, -0.01, p = 0.04, I2 = 40%). When performing the sensitivity analysis of donepezil studies only, M + ChEIs was superior to ChEIs in improving CF without considerable heterogeneity (SMD = -0.18, 95% CIs = -0.31, -0.05, p = 0.006, I2 = 49%). No differences were detected in all-cause discontinuation between the groups. Conclusions:The meta-analyses suggest the credible efficacy and safety of memantine in treating AD when used alone or in combination with ChEIs. *(PsycINFO Database Record (c) 2018 APA, all rights reserved)*

Abstract: The dyshomeostasis of transition metal ions, accumulation of amyloid- β (Aβ) senile plaques and neuroinflammatory response found in the brain of patients with Alzheimer’s disease (AD) have been suggested to be involved in AD pathogenesis. Novel compounds capable of targeting metal- Aβ species and neuroinflammation would be valuable. AD-35 is such a patented small-molecule compound derived from innovative modification of the chemical structure of donepezil. This compound could moderately inhibit acetylcholinesterase and metal-induced Aβ aggregation in vitro and showed disassembly of Aβ aggregates. The effects of AD-35 on cognitive impairments and neuroinflammatory changes caused by intracerebroventricular injection of Aβ25-35 were studied in rats. Compared to sham group, Aβ25-35 injection significantly led to learning and memory deficits, astrocyte activation, and pro-inflammatory cytokines releases (TNF-α and IL-1β). Further studies indicated that the phosphorylation of extracellular signal-regulated kinase was involved in astrocyte activation and pro-inflammatory cytokines production. Oral administration of AD-35 could markedly attenuate Aβ25-35 injection-induced astrocyte activation, pro-inflammatory cytokines TNF-α and IL-1β release, and memory deficits. On the contrary, donepezil only showed inhibition of IL-1β production, but failed to block astrocyte activation and TNF-α production. These results showed that AD-35 would be a novel multi-mechanism drug for the prevention and/or treatment of AD.


Abstract: Background: Alzheimer’s disease (AD) is characterized by accumulation and aggregation of beta-amyloid peptide, neurofibrillary tangles of hyperphosphorylated tau, neuroinflammation, synaptic degeneration and eventual neuronal cell loss. Current treatment options for AD provide temporary symptomatic relief in a subset of patients. These drugs include cholinesterase inhibitors that improve cholinergic innervation such as rivastigmine, donepezil and galantamine. In addition, memantine, a N-methyl-D-aspartate antagonist, is used to treat moderate to severe AD by reducing excitotoxicity. It has been proposed that increased excitation and decreased inhibition lead to aberrant excitatory neuronal activity and cognitive deficits in AD. Methods: We undertook a search of the literature using bibliographic databases to identify publications that were related to neuronal activity in Alzheimer’s disease. We further delineated the publications to determine inclusion/exclusion criteria based on relevance to increased excitation or decreased inhibition of neuronal networks in both human patients and rodent models. The final criteria related to the potential use of α- -Melanocyte stimulating hormone (α-MSH) as a potential treatment strategy for Alzheimer’s disease. These data were utilized to obtain the content of this review. Results: We identified 156 peer-reviewed publications that met our criteria and describe the findings here. Rodent models of AD and ageing both exhibit cognitive deficits and loss of inhibitory GABAergic interneurons. α- Melanocyte stimulating hormone is a neuropeptide that is down-regulated in the brain and cerebrospinal fluid of AD patients. α- MSH has many functions in the central nervous system including neuroprotective and anti-inflammatory effects that target multiple aspects of the AD pathology. α- MSH treatment promoted the survival of GABAergic interneurons in the hippocampus and improved spatial memory as well as alterations in anxiety in a mouse model of AD. The somatostatin expressing subpopulation of GABAergic interneurons are particularly preserved by α-MSH treatment. Somatostatin has been implicated in hippocampal-dependent cognitive tasks. Somatostatin-expressing interneurons have also been shown to play an important role in maintaining excitatory-inhibitory balance. α- MSH preserved GABAergic interneurons and by preventing the loss of the somatostatin subpopulation, it improved cognitive function. Conclusion: α-MSH is a novel candidate for the treatment of AD but its therapeutic potential in AD patients remains to be investigated. (PsycINFO Database Record (c) 2017 APA, all rights reserved) (Source: journal abstract)

(19) Meguro K. Cholinesterase inhibitors are compatible with psychosocial intervention for Alzheimer disease patients suggested by neuroimaging findings. Psychiatry Research: Neuroimaging 2017; 259:29-33.

Abstract: We previously reported that the frontal lobe was stimulated by psychosocial
intervention for dementia patients, and that the parietal lobe was associated with logical judgment. We hypothesized that the combined therapeutic approach with symptomatic drug treatment can directly stimulate not only attention function but also judgment function indirectly to observing other participants' behaviors. Fifty-two patients with Alzheimer disease underwent the group reminiscence approach with reality orientation, as well as the donepezil treatment. The cerebral blood flow (CBF) was assessed with 99 mTc-ECD SPECT. Two analyses were performed: Analysis 1 was to compare Responders vs. Non-responders as shown by MMSE scores, whereas Analysis 2 was to compare Good vs. Poor reminders of the intervention content. We found that the CBF in the frontal lobe was significantly higher in Responders (vs. Non-responders). The CBF in the parietal lobe, especially the left side, was significantly higher in the Good reminders (vs. Poor reminders). The donepezil stimulated the areas similar to where the psychosocial intervention was previously found to be stimulated directly, thus the drug was thought to be compatible for psychosocial intervention. The parietal lobe was stimulated indirectly, suggesting that the indirect effect of the intervention may be based on logical judgment function. (PsycINFO Database Record (c) 2018 APA, all rights reserved) (Source: journal abstract)

(20) Moss DE, Perez RG, Kobayashi H. Cholinesterase inhibitor therapy in Alzheimer’s disease: The limits and tolerability of irreversible CNS-selective acetylcholinesterase inhibition in primates. Journal of Alzheimer’s Disease 2017; 55(3):1285-1294. Abstract: Irreversible acetylcholinesterase (AChE) inhibition accumulates to high levels in the central nervous system (CNS) because AChE turnover in the brain is much slower than in peripheral tissues. As expected from this CNS selectivity, the irreversible AChE inhibitor methanesulfonyl fluoride (MSF) produces significant cognitive improvement in Alzheimer’s disease patients without the gastrointestinal toxicity that plagues other AChE inhibitors. However, without dose-limiting gastrointestinal toxicity, one shortcoming of the prior human studies of MSF is that the upper limits of CNS AChE inhibition that might be tolerated could not be tested. Therefore, in this study, monkeys were treated with escalating intramuscular (IM) doses of MSF that culminated with several weeks of 1.5 mg/kg dosing, more than eight times the prior human clinical dose, still without signs of toxicity. Brain biopsies showed that ~80% AChE inhibition had been produced and that the new synthesis of cortical AChE had a half-time (t1/2) of ~12 days. A single IM dose of 1.5 mg/kg MSF produced ~59% inhibition in cerebrospinal fluid (CSF) AChE as measured one day later. This corresponds to a peak of ~80% inhibition in CSF AChE at the time of the injection, recovering with a t1/2 of 2.4 days. Computational analyses suggest that MSF at clinically relevant doses could theoretically produce a steady-state AChE inhibition between 65% and 85% in the CNS. These data suggest that the full therapeutic advantage of AChE inhibition therapy can be realized without interference from dose-limiting gastrointestinal toxicity if an irreversible inhibitor is employed. (PsycINFO Database Record (c) 2017 APA, all rights reserved) (Source: journal abstract)

(21) Nakagawa R, Ohnishi T, Kobayashi H, Yamaoka T, Yajima T, Tanimura A et al. Long-term effect of galantamine on cognitive function in patients with Alzheimer’s disease versus a simulated disease trajectory: An observational study in the clinical setting. Neuropsychiatric Disease and Treatment 2017; 13. Abstract: Background: Long-term maintenance of cognitive function is an important goal of treatment for Alzheimer’s disease (AD), but evidence about the long-term efficacy of cholinesterase inhibitors is sparse. To evaluate the long-term efficacy and safety of galantamine for AD in routine clinical practice, we conducted a 72-week post-marketing surveillance study. The effect of galantamine on cognitive function was estimated in comparison with a simulated disease trajectory. Patients and methods: Patients with mild-to-moderate AD received flexible dosing of galantamine (16-24 mg/day) during this study. Cognitive function was assessed by the mini mental state examination (MMSE) and the clinical status was determined by the Clinical Global Impression-Improvement (CGI-I). Changes of the MMSE score without treatment were estimated in each patient using Mendiondo’s model. Generalized linear mixed model analysis was performed to compare the simulated MMSE scores with the actual scores. Results: Of the 661 patients who were enrolled, 642 were evaluable for safety and 554 were assessed for efficacy. The discontinuation rate was 46.73%. Cognitive decline indicated by the mean change of actual MMSE scores was significantly smaller than the simulated decline. Individual analysis demonstrated that .70% of patients had better actual MMSE scores than their simulated
scores. Significant improvement of CGI-I was also observed during the observation period. Adverse events occurred in 28.5% of patients and were serious in 8.41%. The reported events generally corresponded with the safety profile of galantamine in previous studies. Conclusion: These findings support the long-term efficacy of galantamine for maintaining cognitive function and the clinical state in AD patients. Treatment with galantamine was generally safe. Importantly, this study revealed that galantamine improved cognitive function above the predicted level in .70% of the patients. (PsycINFO Database Record (c) 2017 APA, all rights reserved)

Abstract: Behavioral and psychological symptoms of dementia (BPSD) occur in up to 80% of AD patients and represent one of the largest factors contributing to caregiver burden. To analyze the effect of galantamine on BPSD and caregiver burden, we treated a total of 50 patients with mild AD for 12 weeks and evaluated them using the Neuropsychiatric Inventory (NPI) and Japanese version of the Zarit Caregiver Burden Interview (ZBI). We also performed regional cerebral blood flow single photon emission computed tomography (rCBF SPECT) at baseline using three-dimensional sterotatic surface projections. Total NPI and ZBI scores did not significantly change after 12-week galantamine treatment. To identify the characteristics of patients who showed improvement after galantamine treatment, we divided patients into two groups, those with and those without sub-items on the NPI. Patients with aggression showed improvement in ZBI scores (p < 0.05). A comparison of rCBF SPECT between these two groups indicated that patients with aggression exhibited increased rCBF in the right prefrontal cortex compared with those without aggression. In a patient with aggression, 20-month treatment with galantamine inhibited increases in the rCBF area in the right prefrontal lobe. These results suggest that galantamine response may be related to aggression and dysfunction of the prefrontal cortex. (PsycINFO Database Record (c) 2017 APA, all rights reserved) (Source: journal abstract)

Abstract: The British Association for Psychopharmacology coordinated a meeting of experts to review and revise its previous 2011 guidelines for clinical practice with anti-dementia drugs. As before, levels of evidence were rated using accepted standards which were then translated into grades of recommendation A-D, with A having the strongest evidence base (from randomised controlled trials) and D the weakest (case studies or expert opinion). Current clinical diagnostic criteria for dementia have sufficient accuracy to be applied in clinical practice (B) and both structural (computed tomography and magnetic resonance imaging) and functional (positron emission tomography and single photon emission computerised tomography) brain imaging can improve diagnostic accuracy in particular situations (B). Cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) are effective for cognition in mild to moderate Alzheimer’s disease (A), memantine for moderate to severe Alzheimer’s disease (A) and combination therapy (cholinesterase inhibitors and memantine) may be beneficial (B). Drugs should not be stopped just because dementia severity increases (A). Until further evidence is available other drugs, including statins, anti-inflammatory drugs, vitamin E, nutritional supplements and Ginkgo biloba, cannot be recommended either for the treatment or prevention of Alzheimer’s disease (A). Neither cholinesterase inhibitors nor memantine are effective in those with mild cognitive impairment (A). Cholinesterase inhibitors are not effective in frontotemporal dementia and may cause agitation (A), though selective serotonin reuptake inhibitors may help behavioural (but not cognitive) features (B). Cholinesterase inhibitors should be used for the treatment of people with Lewy body dementias (both Parkinson’s disease dementia and dementia with Lewy bodies), and memantine may be helpful (A). No drugs are clearly effective in vascular dementia, though cholinesterase inhibitors are beneficial in mixed dementia (B). Early evidence suggests multifactorial interventions may have potential to prevent or delay the onset of dementia (B). Though the consensus statement focuses on medication, psychological interventions can be effective in addition to pharmacotherapy, both for cognitive and non-cognitive symptoms. Many novel pharmacological approaches involving strategies to
reduce amyloid and/or tau deposition in those with or at high risk of Alzheimer’s disease are in progress. Though results of pivotal studies in early (prodromal/mild) Alzheimer’s disease are awaited, results to date in more established (mild to moderate) Alzheimer’s disease have been equivocal and no disease modifying agents are either licensed or can be currently recommended for clinical use. (PsycINFO Database Record (c) 2017 APA, all rights reserved) (Source: journal abstract)

Abstract: Aim: To evaluate the therapeutic effects of switching from one acetylcholinesterase inhibitor (ChEI), donepezil, galantamine or rivastigmine, to another in Alzheimer's disease patients. Methods: We retrospectively enrolled 171 Alzheimer's disease patients, whose ChEI medication was changed. The patients were evaluated on three major aspects of dementia - cognitive, affective and activities of daily living (ADL) measures - at 6 months (M) before the drug switch, at the time of drug switch (baseline), and at 3 M and 6 M after the drug switch. Results: The doses of the three ChEI were significantly lower at 6 M after the switch compared with the pre-switch doses. Improvements in apathy were found at 3 M when switching from donepezil to galantamine, but not to rivastigmine, but this switch had adverse effects on ADL. Improvements in cognitive scores at 3 M were also found when switching from galantamine to rivastigmine, but not to donepezil. However, both of these changes improved Abe’s Behavioral and Psychological Symptoms of Dementia scores (ABS), except ADL. Switching from rivastigmine to donepezil worsened ABS at 6 M, but preserved cognitive and ADL scores. Conclusions: The present study suggests that despite a relatively lower dose of ChEI after the switch, switching from donepezil or rivastigmine preserved cognitive functions for at least 6 M. Switching from galantamine to rivastigmine improved Mini-Mental State Examination and ABS at 3 M, but did not improve ADL scores. Geriatr Gerontol Int 2017; 17: 1843-1848

Abstract: Objective: Apathy is one of the most frequent neuropsychiatric symptoms encountered in Alzheimer disease (AD). Early diagnosis and timely treatment of apathy in AD seem to be of great importance, since apathy has been associated with poor disease outcome, reduced daily functioning, and caregiver distress. Design: Within this context, we conducted an extensive electronic search from the databases included in the National Library of Medicine as well as PsychInfo and Google Scholar for studies that have investigated the effect of pharmacological and nonpharmacological treatments of apathy in AD. Results: Acetylcholinesterase inhibitors, gingko biloba, methylphenidate, and a variety of nonpharmacological interventions were found to be successful in reducing apathy in patients with AD. Methodological heterogeneity of the studies and the small amount of studies where apathy was a primary outcome measure are limiting factors to evaluate for group effects. Conclusion: Treatment of apathy in AD is a complicated and an underexplored field. Standardized and systematic efforts primarily focused on the study of apathy in AD may establish a benefit from individualized treatment for specific disease groups that would stem from a combination of both pharmacological and nonpharmacological interventions

Abstract: Proper diagnosis of dementia with Lewy bodies (DLB) in clinical practice remains suboptimal as many cases are misdiagnosed, usually as Alzheimer disease (AD) or Parkinson's disease (PD) and, in rare cases, psychosis. Therefore, it is important for patients with dementia to be thoroughly evaluated by a specialist who is familiar with current diagnostic tests and treatment options. New diagnostic criteria from the Dementia with Lewy Bodies Consortium have been developed to increase diagnostic sensitivity for DLB (Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB Consortium; McKeith et al.; Neurology, 89(1): 88-100). REM sleep behavior disorder (RBD) has been studied more thoroughly in correlation with DLB and is now considered a core feature. D2 receptor blocking antipsychotics, which can cause severe antipsychotic
sensitivity, are now rarely prescribed for treatment. Therefore, severe antipsychotic sensitivity, which was a suggestive criterion for DLB diagnosis, is now listed as a supportive feature. Reduced DAT uptake in basal ganglia demonstrated by SPECT or PET imaging has high specificity (90%) for distinguishing DLB from AD. Reduced uptake on metaiodobenzylguanidine myocardial scintigraphy correlates with reduced postganglionic sympathetic cardiac innervation in Lewy body diseases, which can increase specificity for discriminating probable DLB from probable AD in milder cases of dementia. However, the latter is more commonly used in Japan and is not used in the USA. The evidence supporting the benefit of other therapeutic modalities is limited in DLB due to lack of extensive studies. There are no FDA-approved medications for the treatment of DLB, although some effective drugs have been used off label to treat various symptoms.


Abstract: This article reviews current treatment strategies and recent advances for the Lewy body dementias (LBDs). Current available symptom treatment strategies are based on monoaminergic, cholinergic and glutaminergic neurotransmitter systems. Relatively robust evidence exists for cholinesterase inhibitors for cognitive impairment in LBD and in Parkinson's disease for antidepressants, clozapine and recently pimavanserin for psychosis. Interpidine (RVT 101) and nelotanserin are currently under investigation. Non-pharmacological interventions, such as cognitive stimulation, physical exercises and neuromodulation strategies, may be useful in Parkinson's disease but have not yet been tested in dementias. Disease-modifying approaches are aimed at preventing, slowing or ameliorating the production, aggregation and deposition of pathological proteins, including immunotherapy targeting alpha-synuclein and an ongoing trial using ambroxol which increases glucocerebrosidase activity to lower the levels of the protein alpha-synuclein. Other disease-modifying clinical trials are using agents to augment insulin signalling, stem cell therapy, reducing amyloid pathology and gene therapy.

PT - Review


Abstract: Our current therapeutic drugs for Alzheimer's disease are predominantly derived from the alkaloid class of plant phytochemicals. These drugs, such as galantamine and rivastigmine, attenuate the decline in the cholinergic system but, as the alkaloids occupy the most dangerous end of the phytochemical spectrum (indeed they function as feeding deterrents and poisons to other organisms within the plant itself), they are often associated with unpleasant side effects. In addition, these cholinesterase inhibiting alkaloids target only one system in a disorder, which is typified by multifactorial deficits. The present paper will look at the more benign terpene (such as Ginkgo biloba, Ginseng, Melissa officinalis (lemon balm) and Salvia lavandulafolia (sage)) and phenolic (such as resveratrol) phytochemicals; arguing that they offer a safer alternative and that, as well as demonstrating efficacy in cholinesterase inhibition, these phytochemicals are able to target other salient systems such as cerebral blood flow, free radical scavenging, anti-inflammation, inhibition of amyloid-β neurotoxicity, glucoregulation and interaction with other neurotransmitters (such as γ-aminobutyric acid) and signalling pathways (e.g. via kinase enzymes).

(29) Yoon SJ, Choi SH, Na HR, Park KW, Kim EJ, Han HJ et al. Effects on agitation with rivastigmine patch monotherapy and combination therapy with memantine in mild to moderate Alzheimer's disease: a multicenter 24-week prospective randomized open-label study (the Korean EXelon Patch and combination with mEmantine Comparative Trial study)*. *Geriatrics & Gerontology International* 2017; 17(3):494-499.

Abstract: Aim Memantine is known to be effective in the treatment of the behavioral symptoms of dementia, especially agitation in moderate to severe Alzheimer's disease (AD). However, memantine and rivastigmine patch combination therapy has not been well studied in determining treatment effectiveness with mild to moderate AD patients. Methods This was a multicenter, 24-week, prospective, randomized, open-label study design. A total 147 AD patients with Mini-Mental State Examination scores from 10 to 20 were randomly assigned to...
Compared to the many treatments available for motor symptoms, relatively few systematic approaches are effective in PD and DLB, including structural imaging, functional imaging, cerebrospinal fluid, and EEG. We carried out factor analyses to evaluate the interrelationship of agitation symptoms and different treatment response in these symptoms. Results indicated that the rivastigmine patch monotherapy group showed a significant decrease in agitation symptoms and had a tendency of decreased Korean Version of the Cohen Mansfield Agitation Inventory total scores and factor A scores. Conversely, the combination therapy group showed a significant increase in agitation symptoms, and there were significant differences between the two groups (p < 0.05). There were no significant differences in the scores of ADAS-cog between the two groups. 

Conclusions In this trial of mild to moderate AD patients, the rivastigmine patch monotherapy group experienced a reduction of non-aggressive agitation behaviors. However, combination therapy with memantine did not show any benefit on the agitation associated with mild to moderate AD. 


Abstract: Background: Alzheimer's disease (AD) is the most common cause of dementia. However, none of medical treatment can stop or reverse the underlying neurodegenerative of AD at present. Acupuncture has attracted more and more attention in recent years due to its efficacy and few side effects. Lately, a systematic review has thought that the evidence on the effectiveness of acupuncture in improving the cognitive function of AD patients was not powerful enough. Therefore, the aim of this study is to explore the efficacy and safety of acupuncture in patients with mild to moderate AD. Methods: This was a randomized, controlled, parallel-group, exploratory study with 4-week baseline (T0), 12-week treatment phase (T1) and 12-week follow-up period (T2). Patients with mild to moderate AD meeting the included criteria were randomly allocated into either acupuncture or donepezil hydrochloride groups. The acupuncture group (AG) was given acupuncture treatment three times per week and the donepezil hydrochloride group (DG) group was administered donepezil hydrochloride once daily (5 mg/day for the first 4 weeks and 10 mg/day thereafter). Primary efficacy was measured using Alzheimer's disease Assessment Scale-Cognitive (ADAS-cog) and Clinician's Interview-Based Impression of Change-Plus (CIBIC-Plus). The second outcomes were measured with 23-Item Alzheimer's disease Cooperative Study Activities of Daily Living Scales (ADAS-ADL23) and Neuropsychiatric Index (NPI). Results: Of 87 participants enrolled in the study, 79 patients finished their treatment and follow-up processes. The ADAS-cog scores for AG group showed obvious decreases at T2 and T1 (T2-T0) when compared with DG group, and significant between-group differences were detected (all p < 0.05). The mean CIBIC-Plus values for the AG group at T1 and T2 were much lower than that for the DG group, and there were significant differences between the two groups (p < 0.05). There were no significant between-group differences in the scores of ADAS-ADL23 and NPI during the study period. Treatment discontinuations due to adverse events were 0 (0%) and 4 (9.09%) for the AG and DG groups, respectively. Conclusions: Acupuncture is safe, well tolerated and effective in improving the cognitive function, global clinical status of AD. Trial Registration: ChiCTR-IOR-17010465 (Retroactively registered on 18 JAN 2017)


Abstract: Parkinson's disease (PD) and dementia with Lewy bodies (DLB) share clinical and pathological similarities. The defining features are motor Parkinsonism and cognitive impairment, often accompanied by visual hallucinations, fluctuating consciousness, autonomic and sleep disturbances, and a number of other non-motor symptoms. Mild cognitive impairment (MCI) can be identified in 15% of PD patients at time of diagnosis, and may even precede motor symptoms. MCI usually progresses further, and dementia is a common endpoint. Cognitive impairment is usually the initial symptom of DLB, and the disease course is severe. A variety of biomarkers can assist in the diagnosis and prognosis of PD and DLB, including structural and functional imaging, cerebrospinal fluid, and EEG. Compared to the many treatments available for motor symptoms, relatively few systematic approaches are effective.
studies exist to guide the treatment of cognitive impairment in PD, and even less in DLB. However, there is good evidence for cholinesterase inhibitors in both DLB and PD with dementia, and some indications that memantine is helpful. Emerging evidence suggest that physical exercise and cognitive training are also effective, as are some reports of various brain stimulation techniques. Disease-modifying agents that delay the rate of cognitive decline in PD and DLB are urgently needed.

PT - Review

(32) Blautzik J, Keeser D, Paolini M, Kirsch V, Berman A, Coates U et al. Functional connectivity increase in the default-mode network of patients with Alzheimer’s disease after long-term treatment with galantamine. *European Neuropsychopharmacology* 2016; 26(3):602-613. Abstract: Acetylcholinesterase inhibitors (AChEIs) are efficacious for the treatment of mild to moderate forms of Alzheimer's dementia (AD). Default-mode network (DMN) connectivity is considered to be early impaired in AD. Long-term effects of AChEIs on the DMN in AD have not yet been investigated. Twenty-eight AD patients and 11 age-matched healthy volunteers (HC) participated in the prospective study. AD patients were randomly assigned to either a pharmacotherapy arm (Galantamine, AD G) or to a placebo arm (AD P+G) for the period of 6 months followed by open-label Galantamine therapy from month 7 to 12. All subjects underwent neuropsychological testing, resting-state functional and structural MRI at baseline and after 12 months, AD patients additionally in between after 6 months. Thirteen AD patients completed the treatment trial and underwent all functional MRI follow-up sequences of good quality. Functional connectivity significantly increased within the AD G group in the posterior cingulate cortex and in the Precuneus between baseline and 12 months follow-up (p corr < 0.05). Between-group analyses demonstrated that functional connectivity in the AD G group significantly increased in the posterior cingulate cortex as well as in the Precuneus compared to the HC group and in the anteromedial aspect of the temporal lobes compared to the AD P+G group, respectively, at 12 months follow-up (p corr < 0.05). Cognitive performance remained stable within groups over time indicating that resting-state fMRI may be sensitive for the detection of pharmacologically induced effects on brain function of AD patients.

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(33) Coin A, Pamio M, Alexopoulos C, Granziola S, Groppa F, Rosa G et al. Donepezil plasma concentrations, CYP2D6 and CYP3A4 phenotypes, and cognitive outcome in Alzheimer’s disease. *European Journal of Clinical Pharmacology* 2016; 72(6):711-717. Abstract: Purpose: The purpose of the study is to evaluate whether donepezil (D) plasma concentrations and activity of CYP2D6 and CYP3A4 are associated with the therapeutic response of patients with mild to moderate Alzheimer’s disease (AD). Methods: This study comprised 54 patients affected by probable AD in therapy with D 10 mg/daily for at least 3 months. Plasma concentrations of D and its three main metabolites (6DD, 5DD, DNox) were assayed with a novel high performance liquid chromatography (HPLC) technique. Cognitive progression was assessed at baseline and at 9 months of follow-up with the mini mental state examination (MMSE). The activities of the two cytochromes involved in D metabolism- CYP2D6 and CYP3A4-were evaluated according to their metabolic ratios in plasma or urine, after test doses of probe drugs (dextromethorphan and omeprazole). Results: A significant correlation was found between plasma levels of D and variations in MMSE scores after 9 months of therapy (r = 0.14; p = 0.006). Neither the concentrations of D metabolites nor the metabolic ratios of CYP2D6 and CYP3A4 showed any correlations with cognitive variations. Low CYP2D6 activity and advanced age were associated with high D concentrations. Patients who were treated with CYP2D6 and P-glycoprotein (P-gp) inhibitors also had higher D plasma levels (mean difference = 19.6 ng/mL; p = 0.01) than those who were not. Conclusions: D plasma concentrations, but not cytochrome phenotyping, are associated with cognitive outcomes in AD patients.

(34) Cummings J, Lai TJ, Hemrungrojn S, Mohandas E, Yun Kim S, Nair G et al. Role of Donepezil in the Management of Neuropsychiatric Symptoms in Alzheimer’s Disease and Dementia with Lewy Bodies. *CNS neuroscience & therapeutics* 2016; 22(3):159-166. Abstract: Alzheimer’s disease (AD) is a progressive condition that affects cognition, function, and behavior. Approximately 60-90% of patients with AD develop neuropsychiatric symptoms (NPS) such as hallucinations, delusions, agitation/aggression, dysphoria/depression, anxiety, irritability, disinhibition, euphoria, apathy, aberrant motor behavior, sleep disturbances,
appetite and eating changes, or altered sexual behavior. These noncognitive behavior changes are thought to result from anatomical and biochemical changes within the brain, and have been linked, in part, to cholinergic deficiency. Cholinesterase inhibitors may reduce the emergence of NPS and have a role in their treatment. These agents may delay initiation of, or reduce the need for, other drugs such as antipsychotics. This article summarizes the effects of donepezil, a cholinesterase inhibitor, on the NPS of dementia with emphasis on AD and dementia with Lewy bodies

(35) Etsuro M, Manabu I, Masaki N, Hideaki M, Kenji K. Pretreatment Cognitive Profile Likely to Benefit from Donepezil Treatment in Dementia with Lewy Bodies: Pooled Analyses of Two Randomized Controlled Trials. *Dementia & Geriatric Cognitive Disorders* 2016; 42(1/2):58-68. Abstract: Background/Aims: Based on Mini-Mental State Examination (MMSE) subitem scores, in dementia with Lewy bodies (DLB), we aimed to delineate features of cognitive impairment, identify cognitive domains improved by donepezil, and define a pretreatment cognitive profile likely to benefit from donepezil. Methods: Pooled data were used from two randomized controlled trials of donepezil in DLB (n = 235). Baseline MMSE subitem scores were calculated for all patients. Mean changes in subitem scores at week 12 were compared between the placebo and the active group. Finally, the subgroup identification based on differential effect search (SIDES) method was applied. Results: Baseline subitem scores were relatively low for serial 7's, delayed recall, and copying. Significant improvement by donepezil was found for orientation, serial 7's, repetition, 3-step command, and copying. The subgroup with pretreatment scores of serial 7's = 1, 2, or 3, delayed recall ⩾ 1, and copying = 0 were the best responders. MMSE change in subgroups increased as more of these three conditions were fulfilled. Conclusion: Cognitive domains characteristically impaired in DLB are particularly improved by donepezil. The number of fulfilled conditions for serial 7's = 1, 2, or 3, delayed recall ⩾ 1, and copying = 0 (likely to benefit score) may predict the response to donepezil in DLB patients

(36) Ho BL, Kao YH, Chou MC, Yang YH. Cerebral white matter changes on therapeutic response to rivastigmine in Alzheimer's disease. *Journal of Alzheimer's Disease* 2016; 54(1):351-357. Abstract: Background: Rivastigmine has been approved in the treatment of Alzheimer's disease (AD) patients as it can inhibit acetyl and butyryl-cholinesterase and provide neuroprotective effects involving the synapses. White matter changes (WMCs) are frequently observed in AD, and clinical-pathological correlations imply their possible impacts on cognitive function by interference with cortical and subcortical neuronal pathways. Objective: To evaluate the therapeutic effects of rivastigmine in AD patients with cerebral WMCs. Methods: Clinically diagnosed AD patients from Kaohsiung Municipal Ta-Tung hospital were recruited together with their cranial magnetic resonance imaging and a series of annual psychometric tests, including Mini-Mental State Examination (MMSE) and sum of boxes of clinical dementia rating scale (CDR-SB). WMCs were rated through the modified Fazekas scale for the periventricular and deep WMCs. Results: In total, 87 AD patients treated with rivastigmine were enrolled. Patients at severe stage of WMCs, compared to mild stage ones, had significant improvement evaluated by MMSE (periventricular WMCs, p = 0.025; deep WMCs, p = 0.030), but not CDR-SB. Compared to the worsening group, the clinically improving group had a significant higher ratio of preexisting hypertension in terms of cognitive performance [p = 0.016, odds ratio (OR) = 3.48, 95% CI= 1.25-10.34], while having younger age (p = 0.043, OR = 0.11, 95% CI = 0.01-1.12) in terms of global status. Conclusion: Rivastigmine may provide better benefits in cognitive function, but not global status, for AD patients with more advanced WMCs. The detailed mechanisms still have to be determined in future studies. (PsycINFO Database Record (c) 2017 APA, all rights reserved) (Source: journal abstract)

(37) Ibarria M, Alegret M, Valero S, et al. Beneficial Effects of an Integrated Psychostimulation Program in Patients with Alzheimer's Disease. *Journal of Alzheimer's Disease* 2016; 50(2):559-566. Abstract: Background: The existing pharmacological treatments for Alzheimer's disease (AD) can only slow the progression of symptoms or delay admission to long-term care facilities. The beneficial effects of non-drug treatments are poorly studied. Objective: To describe the effects of an Integrated Psychostimulation Program (IPP) in patients with mild-moderate AD treated with acetylcholinesterase inhibitors; and to identify factors related to greater benefit of
the IPP. Methods: 206 patients (mean age=75.9 years; MMSE=19.6) were evaluated before starting the IPP and 3, 6, 9, and 12 months later. Measures included: Mini-Mental State Examination (MMSE), Cognitive Subscale of Alzheimer’s Disease Assessment Scale (ADAS-Cog), Rapid Disability Rating Scale (RDRS-2), and Neuropsychiatric Inventory Questionnaire (NPI-Q). Results: Patients remained cognitively stable (MMSE/ADAS-Cog) for more than 6 months and significantly worsened at 9-month and 12-month follow-ups, without clinically significant functional changes (RDRS-2) or psychiatric symptoms (NPI-Q). The mean annual change on MMSE and ADAS-Cog were 2.06 and 3.56 points, respectively, lower than the annual decline demonstrated previously in similar patients (2.4 and 4.5, respectively). 42.7% of patients maintained or improved global cognitive scores between baseline and 12-month follow-up. The patients who maintained cognitive functions were older than those who did not (77.5 versus 74.7 years). Conclusions: The IPP may be an effective treatment to maintain cognition, functionality, and psychiatric symptoms in AD patients pharmacologically treated, and older age seems to increase beneficial effects of IPP.


Abstract: Severe Impairment Battery (SIB) data from the 24-week, randomized, double-blind ACTivities of daily living and cognition (ACTION) study suggest that patients with severe Alzheimer’s disease (AD) benefit from treatment with 13.3 versus 4.6 mg/24 h rivastigmine patch. The objective of this retrospective analysis was to further examine the cognitive efficacy of 13.3 versus 4.6 mg/24 h rivastigmine patch on individual SIB items, and SIB domains derived using factor analysis of these items. Change from baseline at Week 24 on 9 new factor-defined domains and individual items was calculated and compared using effect sizes (Cohen’s d). Numerically less decline was observed with 13.3 versus 4.6 mg/24 h patch on all domains and the majority of individual items. Largest least squares mean treatment differences were observed on “visuospatial reasoning,” “object naming,” “recognition,” “design copying,” “social agency,” “ideational praxis,” and “comprehension” domains. These findings suggest 13.3 mg/24 h rivastigmine patch demonstrates broad cognitive efficacy across a range of SIB items and domains in patients with severe AD. (PsycINFO Database Record (c) 2016 APA, all rights reserved) (Source: journal abstract)


Abstract: Ethnopharmacological relevance Semen Cassiae has been traditionally used as an herbal remedy for liver, eye, and acute inflammatory diseases. Recent pharmacological reports have indicated that Cassiae semen has neuroprotective actions, attributable to its anti-inflammatory actions, in ischemic stroke and Alzheimer’s disease (AD) models. Aim of the study The basic goal of this study was to evaluate the anti-AD activities of C. obtusifolia and its major constituents. Previously, the extract of C. obtusifolia seeds, was reported to have memory enhancing properties and anti-AD activity to ameliorate amyloid ß-induced synaptic dysfunction. However, the responsible components of C. obtusifolia seeds in an AD are currently still unknown. In this study, we investigated the inhibitory effects of C. obtusifolia and its constituents against acetylcholinesterase (AChE), butyrylcholinesterase (BChE), and ß-site amyloid precursor protein (APP) cleaving enzyme 1 (BACE1) enzyme activity. Materials and methods In vitro cholinesterase enzyme assays by using AChE, BChE, and BACE1 were performed. We also scrutinized the potentials of Cassiae semen active component as BACE1 inhibitors via enzyme kinetics and molecular docking simulation. Results In vitro enzyme assays demonstrated that C. obtusifolia and its major constituents have promising inhibitory potential against AChE, BChE, and BACE1. All Cassiae semen constituents exhibited potent inhibitory activities against AChE and BACE1 with IC 50 values of 6.29±109 Ìµg/mL and 0.94±190 Ìµg/mL, whereas alaternin, questin, and toralactone gentiobioside exhibited significant inhibitory activities against BChE with IC 50 values of 113.10-137.74 Ìµg/mL. Kinetic study revealed that alaternin noncompetitively inhibited, whereas cassiaside and emodin showed mixed-type inhibition against BACE1. Furthermore, molecular docking simulation results demonstrated that hydroxyl group of alaternin and emodin tightly interacted with the active site residues of BACE1 and their relevant binding energies (â”6.62 and â”6.89 kcal/mol), indicating a higher affinity and tighter binding capacity of these compounds for the
Abstract: Current novel therapeutic approach suggests that multifunctional compounds with diverse biological properties and a single bioavailability and pharmacokinetic profile, without having profound disease-modifying effects. Thus, alternative strategies capable of preventing the progressive loss of specific neuronal populations are urgently required. In particular, the attention of researchers has been focused on phytochemical compounds that have shown antioxidative, anti-inflammatory, anti-apoptotic properties and that could represent important resources in the discovery of drug candidates against dementia. In this review, we summarize the neuroprotective effects of the main phytochemicals belonging to the polyphenol, isothiocyanate, alkaloid and cannabinoid families in the prevention and treatment of the most common kinds of dementia. We believe that natural phytochemicals may represent a promising sources of alternative medicine, at least in association with therapies approved to date for dementia.

PT - Review


Abstract: Current novel therapeutic approach suggests that multifunctional compounds with diverse biological properties and a single bioavailability and pharmacokinetic metabolism, will produce higher significant advantages in treatment of neurodegenerative diseases, such as Alzheimer's disease (AD). Based on this rational, a new class of cholinesterase (ChE)-monoamine oxidase (MAO)-B inhibitor, neuroprotective/neurorestorative anti-Parkinsonian drug, rasagiline, into the "N-methyl" position of the ChE inhibitor, anti-AD drug rivastigmine. Initially, we examined the MAO and

active site of BACE1. Conclusion The findings of the present study suggest the potential of C. obtusifolia and its major constituents for use in the development of therapeutic or preventive agents for AD, especially through inhibition of AChE, BChE and BACE1 activities


Abstract: Background: Comparative evidence for efficacy and safety of second-generation cholinesterase inhibitors (ChEIs) is still sparse. Objectives: The purpose of this research is to compare three ChEIs, donepezil, galantamine and rivastigmine, in patients with mild-to-moderate Alzheimer's disease (AD). Methods: We conducted a systematic review for published articles and included randomised, double-blind, placebo-controlled trials and head-to-head randomised trials evaluating the efficacy and safety of ChEIs in patients with AD. We examined Alzheimer's Disease Assessment Scale, cognitive subscale (ADAS-Cog), Neuropsychiatric Inventory (NPI), Clinician's Interview-Based Impression of Change plus caregiver's input (CIBIC+) and Clinical Global Impression of Change (CGIC) as efficacy endpoints. Withdrawals due to adverse events and number of patients experiencing nausea, vomiting, diarrhoea and dizziness were examined as safety profiles. Network meta-analyses were sequentially performed for efficacy and safety outcomes based on drug/dose treatment conditions. Results: Among the 21 trials included, network meta-analysis showed that all treatments were significantly more efficacious than placebo in cognition measured by ADAS-Cog. All treatments except galantamine were significantly more efficacious than placebo in global change in CIBIC+ or CGIC. Across all conditions, no significant efficacy was observed in neuropsychiatric symptoms measured by NPI. Derived hierarchies in the efficacy of treatment conditions were variables across efficacy and safety. Conclusions: Our analysis is the first attempt to incorporate available direct and indirect evidence. The results suggest that ChEIs should have significant efficacy for cognition and global change assessment, but the efficacy on neuropsychiatric symptoms is questionable in patients with mild-to-moderate AD.


Abstract: The word dementia describes a class of heterogeneous diseases which etiopathogenetic mechanisms are not well understood. There are different types of dementia, among which, Alzheimer's disease (AD), vascular dementia (VaD), dementia with Lewy bodies (DLB) and frontotemporal dementia (FTD) are the more common. Currently approved pharmacological treatments for most forms of dementia seem to act only on symptoms without having profound disease-modifying effects. Thus, alternative strategies capable of preventing the progressive loss of specific neuronal populations are urgently required. In particular, the attention of researchers has been focused on phytochemical compounds that have shown antioxidative, anti-amyloidogenic, anti-inflammatory and anti-apoptotic properties and that could represent important resources in the discovery of drug candidates against dementia. In this review, we summarize the neuroprotective effects of the main phytochemicals belonging to the polyphenol, isothiocyanate, alkaloid and cannabinoid families in the prevention and treatment of the most common kinds of dementia. We believe that natural phytochemicals may represent a promising sources of alternative medicine, at least in association with therapies approved to date for dementia.
ChE inhibitory effect of these novel compounds, MT series in vitro and in vivo. Among MT series, MT-031 exhibited higher potency as a dual MAO-A and ChE inhibitor compared to other compounds in acute-treated mice. Additionally, MT-031 was found to increase the striatal levels of dopamine (DA), serotonin (5-HT) and norepinephrine (NE), and prevent the metabolism of DA and 5-HT. Finally, we have demonstrated that MT-031 exerted neuroprotective effect against H2O2-induced neurotoxicity and reactive oxygen species generation in human neuroblastoma SH-SY5Y cells. These findings provide evidence that MT-031 is a potent brain permeable novel multifunctional, neuroprotective and MAO-A/ChE inhibitor, preserves in one molecule entity some of the beneficial properties of its parent drugs, rasagiline and rivastigmine, and thus may be indicated as novel therapeutic approach for AD. (PsyclINFO Database Record (c) 2016 APA, all rights reserved) (Source: journal abstract)

Abstract: This Hospital Pharmacy feature is extracted from Off-Label Drug Facts, a publication available from Wolters Kluwer Health. Off-Label Drug Facts is a practitioner-oriented resource for information about specific drug uses that are unapproved by the US Food and Drug Administration. This new guide to the literature enables the health care professional or clinician to quickly identify published studies on off-label uses and determine if a specific use is rational in a patient care scenario. References direct the reader to the full literature for more comprehensive information before patient care decisions are made.

Abstract: BACKGROUND: As with other types of dementia, the behavioral and psychological symptoms of dementia (BPSD) can make caregiving difficult for patients with dementia with Lewy bodies (DLB). We hypothesized that administration of donepezil at an increased dose of 10 mg/day might dose-dependently improve BPSD in DLB patients with relapse, after their symptoms had been controlled initially by donepezil therapy at the standard dose. METHODS: The present study was as an open-label trial. We enrolled 24 patients with DLB (diagnosed according to the Consortium on Dementia with Lewy Bodies Guideline-Revised) who experienced a relapse of BPSD despite treatment with donepezil at the standard dose (5 mg/day). The donepezil dose for these patients was increased to 10 mg/day, and we evaluated the efficacy and safety of this dose escalation strategy. RESULTS: The Neuropsychiatric Inventory (NPI) scores for BPSD showed statistically significant improvements as a result of the increased dosage, except those for anxiety and euphoria, disinhibition, irritability/lability. High-dose donepezil therapy caused gastrointestinal symptoms in 4 patients, but there were no life-threatening adverse events, such as arrhythmias, or no exacerbation of parkinsonian symptoms. CONCLUSIONS: We found that donepezil dose-dependently improved relapsing BPSD in these patients. Therefore, increasing the dosage of donepezil is a safe and effective treatment for patients with DLB who experience a relapse of BPSD

Abstract: Objects Alzheimer's disease (AD) is one of the most important diseases in aging society, and non-drug therapy might be an alternative therapeutic approach. Thus, we evaluated the add-on effect of cognitive rehabilitation on AD patients under donepezil treatment. Methods We retrospectively analyzed 55 AD patients with a Mini-Mental State Examination score of 15-25, dividing them into two groups depending on whether they were receiving ambulatory cognitive rehabilitation (group D + R, n = 32) or not (group D, n = 23) in Kurashiki Heisei Hospital over 1 year. The present cognitive rehabilitation included physical therapy, occupational therapy and speech therapy for 1-2 h once or twice a week. Results Between group D and group D + R, there was no significant difference in baseline data, such as age, Mini-Mental State Examination score, periventricular hyperintensity on magnetic resonance imaging, deep white matter hyperintensity on magnetic resonance imaging or donepezil dose (4.1 mg/day). At 1 year later, however, the Mini-Mental State Examination
score improved only in group D + R from 21.7 to 24.0 (** P < 0.001), whereas that of group D remained at 21.5 with both groups of donepezil 5.0 mg/day. Conclusion The combination of cognitive rehabilitation plus a choline esterase inhibitor donepezil showed a better effect for the cognitive function of AD patients than drug only therapy at 1 year. Geriatr Gerontol Int 2016; 16: 200-204

Abstract: OBJECTIVE: To investigate whether increasing plasma donepezil concentration further improves cognitive function and neuropsychiatric symptoms without compromising safety in patients with dementia with Lewy bodies (DLB). METHODS: We analyzed data from a 12-week phase 3 trial of donepezil (5 and 10mg/day) in patients with DLB. The contribution of factors affecting plasma donepezil concentration was evaluated using multivariate regression analysis. The relationships between plasma donepezil concentration and efficacy (cognitive function as measured by the Mini-Mental State Examination [MMSE], hallucinations and cognitive fluctuation), or safety (blood pressure, pulse rate, body weight, and parkinsonism as measured by the Unified Parkinson's Disease Rating Scale part III) were assessed by scatterplots and Pearson correlation. RESULTS: The data of 87 patients were used in the analyses. Plasma donepezil concentration increased proportionally with increasing dose from 5 to 10mg/day. The dose (contribution rate: 0.39, p<0.0001) and age (contribution rate: 0.12, p=0.0003) were statistically significant contributing factors affecting plasma donepezil concentration. Plasma donepezil concentration correlated significantly with improvement of MMSE score (p=0.040), but no significant correlations were found with the change in other tested parameters. CONCLUSIONS: Plasma donepezil concentration correlated positively with change in cognitive function without affecting safety, and was affected mainly by dose and to a lesser extent by age. Therefore, for patients in whom safety concerns are not found at donepezil 5mg/day, increasing the dose to 10mg/day to increase plasma concentration is worthwhile to further improve cognitive function.
PT - Randomized Controlled Trial

Abstract: Aim The aim of the present study was to compare the effects of a galantamine only therapy and a combination therapy with galantamine plus ambulatory cognitive rehabilitation for Alzheimer's disease patients. Methods For this retrospective cohort study, we enrolled 86 patients with Alzheimer's disease, dividing them into two groups - a galantamine only group (group G, n = 45) and a combination with galantamine plus ambulatory rehabilitation group (group G + R, n = 41). The present cognitive rehabilitation included a set of physical therapy, occupational therapy and speech therapy for 1-2 h once or twice a week. We compared the Mini-Mental State Examination and Frontal Assessment Battery for cognitive assessment, and Geriatric Depression Scale, Apathy Scale, and Abe's Behavioral and Psychological Symptoms of Dementia score for affective assessment in two groups over 6 months. Results The baseline Mini-Mental State Examination score was 20.2 and 18.7 in groups G and G + R, respectively. Other baseline data (Frontal Assessment Battery, Geriatric Depression Scale, Apathy Scale, and Abe's Behavioral and Psychological Symptoms of Dementia) were not different between the two groups. Although group G kept all the scores stable until 6 months of the treatment, the Apathy Scale score showed a significant improvement in group G + R as early as 3 months, followed by the Mini-Mental State Examination and Frontal Assessment Battery improvements at 6 months (* P = 0.04 and * P = 0.02, respectively). The Geriatric Depression Scale and Abe's Behavioral and Psychological Symptoms of Dementia did not show any changes. Conclusion The combination therapy of galantamine plus ambulatory cognitive rehabilitation showed a superior benefit both on cognitive and affective functions than galantamine only therapy in Alzheimer's disease patients. Geriatr Gerontol Int 2016; 16: 440-445

Abstract: Computerized Adaptive Testing (CAT) of cognitive function, selects for every individual patient, only items of appropriate difficulty to estimate his or her level of cognitive impairment. Therefore, CAT has the potential to combine brevity with precision. We retrospectively examined the evaluation of treatment effects of cholinesterase inhibitors by CAT using longitudinal data from 643 patients from a Dutch teaching hospital who were diagnosed with Alzheimer disease or Lewy Body disease. The Cambridge Cognitive Examination (CAMCOG) was administered before treatment initiation and after intervals of six months of treatment. A previously validated CAT was simulated using 47 CAMCOG items. Results demonstrated that the CAT required a median number of 17 items (inter-quartile range 16–20), or a corresponding 64% test reduction, to estimate patients’ global cognitive impairment levels. At the same time, intraclass correlations between global cognitive impairment levels as estimated by CAT or based on all 47 CAMCOG items, ranged from 0.93 at baseline to 0.91-0.94 at follow-up measurements. Slightly more people had substantial decline on the original CAMCOG (N = 31/285, 11%) than on the CAT (N = 17/285, 6%). We conclude that CAT saves time, does not lose much precision, and therefore deserves a role in the evaluation of treatment effects in dementia. (PsycINFO Database Record (c) 2016 APA, all rights reserved) (Source: journal abstract)


Abstract: Background: Alzheimer’s disease (AD) is considered to be a neurodegenerative disorder that is characterized by increased oxidative stress. Medicinal plants, with their antioxidant properties, have been used to cure several human diseases. The aim of the current study was to explore the protective and therapeutic effect of baicalein on AD-induced rats. Materials and methods: Swiss Wistar rats were used in the study. The rats were divided into five groups. Group I: normal control group treated with water; Group II: disease control treated with AlCl3 to induce the mimicking AD for 4 successive weeks (SW); Group III: normal control group treated with baicalein (5 mg/kg) for 2 SW followed by combination of baicalein and AlCl3 for 4 SW; Group IV: normal control group treated with baicalein (10 mg/kg) for 2 SW followed by combination of baicalein and AlCl3 or 4 SW; Group V: normal control group treated with rivastigmine (0.3 mg/kg) for 2 SW followed by combination of rivastigmine and AlCl3 for 4 SW. Moreover, the therapeutic groups are as follows: Group VI: AD disease control treated with AlCl3 for 4 SW and serving as the therapeutic positive group; Group VII: AD disease control + baicalein (5 mg/kg) for 12 SW; Group VIII: AD disease control + baicalein (10 mg/kg) for 12 SW; Group IX: AD disease control + rivastigmine (0.3 mg/kg) for 12 SW. Behavioral test, T-maze, and rotarod test were also performed before and after the treatment. At the end of the experimental study, all the rats were sacrificed and their brains were removed and divided into two portions. The first portion was homogenated for estimating the level of acetylcholinesterase (AchE) and acetylcholine (Ach). Another portion was used for histopathological evaluation. Results: The current investigation showed that baicalein significantly reduced the duration of revolving on the rotarod, cage activity, and T-maze activity in a dose-dependent manner compared with the AD control group rats. It also altered the AchE and Ach levels in the brain homogenates. The histopathology study also provides strength to the protective effect of baicalein. Conclusion: The current study showed that baicalein significantly (P < 0.05) improved the biochemical and histopathological condition of AD in rats. (PsycINFO Database Record (c) 2016 APA, all rights reserved)


Abstract: Cognitive dysfunction in people with Alzheimer’s disease (AD) significantly affects their interactions, independence, behavior, health, wellness, and quality of life; care providers also experience quality of life issues as a result. This review summarizes clinical data on agents associated with cognitive enhancement in AD, particularly the currently approved anti-AD medications including the acetyl cholinesterase inhibitors (ChEIs) (donepezil, galantamine, and rivastigmine) and the N-methyl-d-aspartate antagonist, memantine.
Initiation and maintenance of stage-appropriate monotherapy or combination therapy with a ChEI and memantine provides the best pharmacologic approach to stem the expected inexorable course of cognitive decline. Discontinuation of agents that impair cognition and treatment of comorbid conditions (eg, sleep disorders, dehydration, depression, anxiety, pain, as well as metabolic, hormone, and vitamin derangements) may also improve cognition. The preponderance of evidence regarding ChEIs, memantine, and vitamin E strongly supports modest, but clinically relevant, "disease-course modifying" effects of cognitive enhancement (eg, improvement, stabilization, or shifting of the trajectory of cognitive or functional decline) in patients who receive appropriate and persistent treatment. (PsycINFO Database Record (c) 2017 APA, all rights reserved) (Source: journal abstract)

Abstract: The harms associated with antipsychotics in people with dementia have been a key topic. Most work has focussed on Alzheimer's disease, where modest benefits and significant safety risks including mortality, stroke and accelerated cognitive decline have led to regulatory warnings. The dangers of antipsychotic use in people with Dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) were reported even earlier, with severe neuroleptic sensitivity reactions described in the early 1990's and more recent studies have demonstrated that atypical antipsychotics are associated with a significant increase in mortality and other key adverse outcomes in PD. Against this background it appears paradoxical to be arguing for the use of antipsychotics in people with DLB. However, psychotic symptoms are much more intrusive, much more persistent and much more distressing in people with DLB than they are in people with other dementias. This level of distress cannot be ignored, particularly when the usual clinical course is for these symptoms to persist for a year or longer if untreated. Clearly a careful clinical decision needs to be made, and benefits and harms need to be balanced for each patient. In addition, given evidence that the cholinesterase inhibitors rivastigmine and donepezil do confer some benefit in the treatment of psychosis in DLB patients, this should be the first line pharmacological therapy. However, for patients with severe and distressing psychotic symptoms that are not responsive to cholinesterase inhibitor therapy, atypical antipsychotics remain the only evidence based treatment option. In particular there is clear evidence supporting the value of clozapine treatment in people with PD, and whilst further RCTs in people with DLB are a priority, this should probably be the preferred treatment based on current evidence

Abstract: The plant alkaloid galantamine is an established symptomatic drug treatment for Alzheimer's disease (AD), providing cognitive and global relief in human patients. However, as an acetycholinesterase inhibitor, gastrointestinal side effects limit the dosage and duration of treatment. Memogain (Gln-1062), a pro-drug, liberates galantamine on cleavage by a carboxyesterase in the brain. The possibility to deliver Memogain intranasally may further circumvent side effects, allowing higher dosing compared to galantamine. In this study, the 5X Familial Alzheimer's Disease (5XFAD) mouse model was used to investigate the effect of chronic Memogain treatment on behavior and amyloid -β (Aβ) plaque deposition in the brain. Chronic intranasal dosage of 6 mg/kg body weight twice daily was tolerated well, whereas the double dose caused body weight loss in males and was less effective in some behavioral tests. 8 weeks of chronic treatment resulted in improved performance in behavioral tests, such as open field and light-dark avoidance, and in fear conditioning already at mildly affected stages at the age of 18 weeks compared to untreated controls. Furthermore, after treatment a significantly lower plaque density in the brain, i.e., in the entorhinal cortex (reduction 20% females, 40% males) and the hippocampus (19% females, 31% males) at the age of 18 weeks was observed. These results show that nasal application of Memogain effectively delivers the drug to the brain with the potential to retard plaque deposition and improve behavioral symptoms in AD similar to the approved galantamine. (PsycINFO Database Record (c) 2016 APA, all rights reserved) (Source: journal abstract)

Abstract: Background: Alzheimer's disease is the commonest cause of dementia affecting older people. One of the therapeutic strategies aimed at ameliorating the clinical manifestations of Alzheimer's disease is to enhance cholinergic neurotransmission in the brain by the use of cholinesterase inhibitors to delay the breakdown of acetylcholine released into synaptic clefts. Tacrine, the first of the cholinesterase inhibitors to undergo extensive trials for this purpose, was associated with significant adverse effects including hepatotoxicity. Other cholinesterase inhibitors, including rivastigmine, with superior properties in terms of specificity of action and lower risk of adverse effects have since been introduced. Rivastigmine has received approval for use in 60 countries including all member states of the European Union and the USA. Objectives: To determine the clinical efficacy and safety of rivastigmine for patients with dementia of Alzheimer's type. Search Methods: We searched ALOIS, the Cochrane Dementia and Cognitive Improvement Group Specialized Register, on 2 March 2015 using the terms: Rivastigmine OR exelon OR ENA OR "SDZ ENA 713". ALOIS contains records of clinical trials identified from monthly searches of a number of major healthcare databases (Cochrane Library, MEDLINE, EMBASE, PsycINFO, CINAHL, LILACS), numerous trial registries and grey literature sources. Selection Criteria: We included all unconfounded, double-blind, randomised, controlled trials in which treatment with rivastigmine was administered to patients with dementia of the Alzheimer's type for 12 weeks or more and its effects compared with those of placebo in a parallel group of patients, or where two formulations of rivastigmine were compared. Data Collection and Analysis: One review author (JSB) applied the study selection criteria, assessed the quality of studies and extracted data. Main Results: A total of 13 trials met the inclusion criteria of the review. The trials had a duration of between 12 and 52 weeks. The older trials tested a capsule form with a dose of up to 12 mg/day. Trials reported since 2007 have tested continuous dose transdermal patch formulations delivering 4.6, 9.5 and 17.7 mg/day. Our main analysis compared the safety and efficacy of rivastigmine 6 to 12 mg/day orally or 9.5 mg/day transdermally with placebo. Seven trials contributed data from 3450 patients to this analysis. Data from another two studies were not included because of a lack of information and methodological concerns. All the included trials were multicentre trials and recruited patients with mild to moderate Alzheimer's disease with a mean age of about 75 years. All had low risk of bias for randomisation and allocation but the risk of bias due to attrition was unclear in four studies, low in one study and high in two studies. After 26 weeks of treatment rivastigmine compared to placebo was associated with better outcomes for cognitive function measured with the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) score (mean difference (MD) -1.79; 95% confidence interval (CI) -2.21 to -1.37, n = 3232, 6 studies) and the Mini-Mental State Examination (MMSE) score (MD 0.74; 95% CI 0.52 to 0.97, n = 3205, 6 studies), activities of daily living (SMD 0.20; 95% CI 0.13 to 0.27, n = 3230, 6 studies) and clinician rated global impression of changes, with a smaller proportion of patients treated with rivastigmine experiencing no change or a deterioration (OR 0.68; 95% CI 0.58 to 0.80, n = 3338, 7 studies). Three studies reported behavioural change, and there were no differences compared to placebo (standardised mean difference (SMD) -0.04; 95% CI -0.14 to 0.06, n = 1529, 3 studies). Only one study measured the impact on caregivers using the Neuropsychiatric Inventory-Caregiver Distress (NPI-D) scale and this found no difference between the groups (MD 0.10; 95% CI -0.91 to 1.11, n = 529, 1 study). Overall, participants who received rivastigmine were about twice as likely to withdraw from the trials (odds ratio (OR) 2.01, 95% CI 1.71 to 2.37, n = 3569, 7 studies) or to experience an adverse event during the trials (OR 2.16, 95% CI 1.82 to 2.57, n = 3587, 7 studies). Authors' Conclusions: Rivastigmine (6 to 12 mg daily orally or 9.5 mg/day transdermally) appears to be beneficial for people with mild to moderate Alzheimer's disease. In comparisons with placebo, better outcomes were observed for rate of decline of cognitive function and activities of daily living, although the effects were small and of uncertain clinical importance. There was also a benefit from rivastigmine on the outcome of clinician's global assessment. There were no differences between the rivastigmine group and placebo group in behavioural change or impact on carers. At these doses the transdermal patch may have fewer side effects than the capsules but has comparable efficacy. The quality of the outcomes is only moderate for all of the outcomes reviewed because of a risk of bias due to dropouts. All the studies with usable data were industry funded or sponsored. This review has not examined economic data.


Abstract: To test the efficacy and safety of leuprolide acetate (Lupron Depot®) in the treatment of Alzheimer’s disease (AD), we conducted a 48-week, double-blind, placebo-controlled, dose-ranging study in women aged 65 years or older with mild to moderate AD. A total of 109 women with mild to moderate AD and a Mini-Mental State Examination score between 12 and 24 inclusive were randomized to low dose Lupron Depot® (11.25 mg leuprolide acetate), high dose Lupron Depot® (22.5 mg leuprolide acetate), or placebo injections every 12 weeks. There were no statistically significant differences in primary efficacy parameters (ADAS-Cog and ADCS-CGIC), although there was a non-statistically significant trend in favor of the high dose Lupron group on the ADAS-Cog. There were no statistically significant differences in secondary efficacy parameters (NPI, ADCS-ADL, BI, and ADCS-Severity Rating). However, in the a priori designated subgroup analysis of patients taking an acetylcholinesterase inhibitor (AChEI), there was a statistically significant benefit in the high dose group compared to both the low dose and placebo groups as determined by ADAS-Cog (mean decline: 0.18, 4.21, and 3.30), ADCS-CGIC (% subjects experiencing decline: 38, 82, and 63), and ADCS-ADL (mean decline: -0.54, -8.00, and -6.85), respectively. No differences between treatment groups were seen on the NPI, ADCS-CGI Severity Rating, or the BI in the subgroup analysis. These data indicate that cognitive function is preserved in patients treated with high dose Lupron who were already using AChEIs. The positive interaction between Lupron and AChEIs warrants further investigation for the treatment of AD. (PsycINFO Database Record (c) 2016 APA, all rights reserved) (Source: journal abstract)


Abstract: The loss of cholinergic transmission is considered to be an important cause of Alzheimer’s disease (AD). Treatment with acetyl cholinesterase inhibitors (ChEIs) shows benefits; however, great heterogeneity has been observed in patient responses. We evaluated apolipoprotein E (*APOE*) and a 7 nicotinic receptor (*CHRNA7*) single-nucleotide polymorphisms (SNPs) and associated these SNPs with pharmacological responses to ChEIs in a Brazilian population with AD. We studied 177 outpatients using ChEIs, and they were classified as responders and nonresponders according to variation in Mini-Mental State Examination score (MMSE) status. The analysis of *APOE* genotypes showed that patients with the ε4 allele had a worse response than those without the ε4 allele. We observed an association between the *CHRNA7* T allele and a better response to treatment with ChEIs in patients with mild AD (MMSE ≥ 20). The SNP rs6494223 of *CHRNA7* as well as *APOE* ε4 could be useful for understanding the response to ChEI treatment in patients with AD. (PsycINFO Database Record (c) 2017 APA, all rights reserved) (Source: journal abstract)


Abstract: Background: There is no cure for dementia, and no treatments exist to halt or reverse the course of the disease. Treatments are aimed at improving cognitive and functional outcomes. Objective: Our objective was to review the basis of pharmacological treatments for dementia and to summarize the benefits and risks of dementia treatments. Methods: We performed a systematic literature search of MEDLINE through November 2014, for English-language trials and observational studies on treatment of dementia and mild cognitive impairment. Additional references were identified by searching bibliographies of relevant publications. Whenever possible, pooled data from meta-analyses or systematic reviews were obtained. Studies were included for review if they were randomized trials or observational studies on dementia or mild cognitive impairment that evaluated efficacy outcomes or adverse outcomes associated with treatment. Studies were excluded if they evaluated non-FDA approved treatments, or if they evaluated treatment in disorders other than dementia and mild cognitive impairment. Results: The literature search found 540 potentially relevant studies, of which 257 were included in the systematic review. In pooled trial data, cholinesterase inhibitors (ChEIs) produce small improvements in cognitive, functional, and global benefits in patients with mild to moderate Alzheimer’s and Lewy body dementia, but the clinical significance of these effects are unclear. There is no significant
benefit seen for vascular dementia. The efficacy of ChEI treatment appears to wane over time, with minimal benefit seen after 1 year. There is no evidence for benefit for those with advanced disease or those aged over 85 years. Adverse effects are significantly increased with ChEIs, in a dose-dependent manner. A two- to fivefold increased risk for gastrointestinal, neurological, and cardiovascular side effects is related to cholinergic stimulation, the most serious being weight loss, debility, and syncope. Those aged over 85 years have double the risk of adverse events compared with younger patients. Memantine monotherapy may provide some cognitive benefit for patients with moderate to severe Alzheimer's and vascular dementia, but the benefit is small and may wane over the course of several months.

Memantine exhibits no significant benefit in mild dementia or Lewy body dementia or as an add-on treatment with ChEIs. Memantine has a relatively favorable side-effect profile, at least under controlled trial conditions. Conclusions: ChEIs produce small, short-lived improvements in cognitive function in mild to moderate dementia, which may not translate into clinically meaningful effects. Marginal benefits are seen with severe disease, long-term treatment, and advanced age. Cholinergic side effects, including weight loss, debility, and syncope, are clinically significant and could be especially detrimental in the frail elderly population, in which the risks of treatment outweigh the benefits. Memantine monotherapy may have minimal benefits in moderate to severe dementia, balanced by minimal adverse effects.

(57) Cagnin A, Cester A, Costa B, Ermani M, Gabelli C, Gambina G. Effectiveness of switching to the rivastigmine transdermal patch from oral cholinesterase inhibitors: A naturalistic prospective study in Alzheimer’s disease. Neurological Sciences 2015; 36(3):457-463. Abstract: Oral donepezil and rivastigmine are two commonly used cholinesterase inhibitors (ChEIs) used in Alzheimer’s disease (AD). The rivastigmine transdermal patch formulation has high tolerability profile, allowing patients to achieve optimal therapeutic doses and providing potential advantages over oral ChEIs. This is a 6-month, multicentre, observational efficacy and tolerability study of switching from oral ChEIs to rivastigmine patch in AD patients who failed to show benefit from previous treatment. The reasons of the switch were: (1) lack/loss of benefit from previous oral ChEI treatment; (2) tolerability problems. The primary outcome was cognitive changes measured with the mini-mental state examination (MMSE) test. Secondary outcomes were modifications of functional independence and behavioral disturbances and occurrence of adverse events (AEs) after switching. 174 patients, over 180 patients screened, entered the study (lack/loss of efficacy: 57 %, tolerability problems: 33 %, both reasons: 10 %). 6 months after switching 56 % of patients stabilized or increased the MMSE score respect to baseline. The only predictor of this outcome was the response at 3 months. In the group with lack/loss of response to oral ChEI, the decline of the MMSE score changed from -3.4 ± 2.5 points in the 6 months before switching to -0.5 ± 3.2 in the 6 months after the switch ( p < 0.001). There were no significant changes in the IADL or NPI scores. Drug discontinuation rate was 20 %, due to AEs (18 %) and lack of compliance (2 %). Switching from an unsuccessful oral ChEI therapy to rivastigmine patch is effective and safe in more than half of the switched patients after a 6-month period. (PsycINFO Database Record (c) 2016 APA, all rights reserved) (Source: journal abstract)

(58) Chau S, Herrmann N, Ruthirakuhn MT, Chen JJ, Lanctôt KL. Latrepirdine for Alzheimer’s disease Cochrane Database of Systematic Reviews 2015. Abstract: Background: Current treatments for Alzheimer’s disease (AD) provide modest symptomatic relief but do not slow the progression of the disease. Latrepirdine may modulate permeability, voltage-gated calcium ion channels as well as neurotransmitter receptor activity, and thus potentially represents both a symptomatic and disease-modifying intervention. Several randomized, placebo-controlled trials have sought to evaluate the effect of latrepirdine on cognition, function and behaviour in patients with AD. Objectives: To evaluate the efficacy and safety of latrepirdine for the treatment of AD. Search methods: We searched the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group on 4 June 2014 using the terms: latrepirdine OR dimebon OR dimebolin OR 2,3,4,5-tetrahydro-2,8-dimethyl-5- (2-(6-methyl-3-pyridyl)ethyl)-1H-pyrido(4,3-b)indole. Selection criteria: We included all randomized, double-blind, placebo-controlled trials where latrepirdine was administered to patients with mild, moderate or severe AD. Data collection and analysis: We assessed the quality of studies and two authors extracted data. We calculated mean difference (MD), risk ratio (RR) and 95% confidence interval (CI) on an intention-to-treat (ITT) basis for all relevant
outcome measures. Main results: Seven trials involving a total of 1697 participants were found and six were included in the quantitative analyses. No data were available from the seventh trial. Three trials involving 1243 patients were included in analyses of efficacy outcomes, and four trials involving 1034 patients were included in analyses of safety and tolerability outcomes. We judged five trials to be at high risk of bias due to selective outcome reporting and three to be at high risk of attrition bias. There was low quality evidence favouring latrepirdine on the Clinician’s Interview - Based Impression of Change Plus Caregiver Input after 26 weeks (CIBIC-Plus) (MD = -0.60, 95% CI -0.89 to -0.31, 1 study, P < 0.001). Due to imprecision in the results, it was not possible to determine whether latrepirdine had any effect on cognition measured with the Alzheimer’s Disease Assessment Scale cognitive subscale (ADAS-Cog) (MD = -1.49, 95% CI -3.47 to 0.49, 3 studies, P = 0.14) or the Mini-Mental State Examination (MMSE) (MD = 0.59, 95% CI -0.94 to 2.11, 3 studies, P = 0.45), or on function measured with the Alzheimer’s Disease Co-operative Study - Activities of Daily Living scale (ADCS-ADL) (MD = 1.00, 95% CI -1.15 to 3.15, 3 studies, P = 0.36) at study endpoint (26 or 52 weeks). We considered the evidence provided on these outcomes to be of overall low quality. However, there was some high quality evidence showing a very small benefit of latrepirdine on the Neuropsychiatric Inventory (NPI) (MD = -1.77, 95% CI -3.09 to -0.45, 3 studies, P = 0.009) at study endpoint (26 or 52 weeks). Additionally, moderate quality evidence suggested that latrepirdine and placebo were comparable in adverse events (RR 1.03, 95% CI 0.93 to 1.14, P = 0.51), serious adverse events (RR 0.86, 95% CI 0.55 to 1.35, P = 0.52), dropouts (RR 0.91, 95% CI 0.65 to 1.27, P = 0.57) and dropouts due to adverse events (RR 0.98, 95% CI 0.57 to 1.67, P = 0.93). Authors’ conclusions: Our meta-analysis is limited by the small number of studies, imprecision, inconsistencies between studies and likelihood of bias. Nevertheless, the evidence to date suggests that while not associated with an increased risk of adverse events compared with placebo, there is no effect of latrepirdine on cognition and function in mild-to-moderate AD patients, though there appears to be a modest benefit for behaviour. Further studies should investigate the potential benefit of latrepirdine on neuropsychiatric symptoms in AD.


Abstract: Objective: To evaluate in a pilot single-blind randomized controlled clinical trial the efficacy of an integrated treatment with rivastigmine transdermal patch (RTP) and cognitive stimulation (CS) in Alzheimer’s disease (AD) patients at 6-month follow-up. Methods: We enrolled 90 patients with an age ≥ 65 years admitted to the outpatient Alzheimer’s Evaluation Unit with diagnosis of AD. Patients were randomized to enter in the Group-1 (RTP + CS) or in the Group-2 (RTP). All patients at baseline and after 6 months were evaluated with the following tools: Mini Mental State Examination (MMSE), Clinical Dementia Rating (CDR), Hamilton Rating Scale for Depression (HAM-D), Geriatric Depression Scale (GDS-15), Neuropsychiatric Inventory (NPI), Neuropsychiatric Inventory-Distress (NPI-D), and a standardized Comprehensive Geriatric Assessment, including also activities of daily living (ADL), instrumental activities of daily living (IADL), and the Mini Nutritional Assessment (MNA). Mortality risk was assessed using the Multidimensional Prognostic Index (MPI).

Results: At baseline no significant difference was shown between the two groups. After 6 months of follow-up, there were significant differences between Group-1 and Group-2 in: MMSE: +6.39% vs. +2.69%, CDR: +6.92% vs. +1.54%, HDRS-D = -60.7% vs. -45.8%, GDS: -60.9% vs. -7.3%, NPI: -55.2% vs. -32.7%, NPI-D: -55.1% vs. -18.6%, ADL: +13.88% vs. +5.95%, IADL: +67.59% vs. +18.28%, MNA: +12.02% vs. +5.91%, and MPI: -29.03% vs. -12.90%. Conclusion: The integrated treatment of RTP with CS in AD patients for 6 months improved significantly cognition, depressive and neuropsychiatric symptoms, functional status, and mortality risk in comparison with a group of AD patients receiving only RTP. (PsycINFO Database Record (c) 2017 APA, all rights reserved) (Source: journal abstract)


Abstract: Current pharmacological therapy for Alzheimer’s disease (AD) includes the cholinesterase inhibitors (ChEIs) donepezil, rivastigmine, and galantamine and the N-methyl D-aspartate receptor antagonist memantine. Based on the results of randomized controlled
trials and several meta-analyses, ChEIs appear to show modest but statistically significant improvements on several measures, including cognition and global functioning. Given their modest effects, there is a lack of consensus among clinicians regarding issues related to initiation, optimal duration, and discontinuation of ChEI therapy across the spectrum of AD. There is evidence from long-term observational controlled studies that early initiation and persistent exposure to AD therapy lead to delays in nursing home admission and significantly slower rates of cognitive and functional impairment. In the moderate to severe stages of AD, therapeutic trials of higher dose ChEIs and the addition of memantine are recommended for patients who are no longer responding to lower doses. While side effects are generally mild and gastrointestinal in nature, these events can lead to significant morbidity in more susceptible patients with advanced disease. Patients should thus be regularly monitored for any potential serious side effects of ChEI therapy, which also may include syncope and bradycardia. At the terminal stages of AD, such as when patients become hospice eligible, attempts to cautiously discontinue all medications not necessary for quality of life, including AD drugs, should be made. (PsycINFO Database Record (c) 2016 APA, all rights reserved)

Abstract: The long-term safety, tolerability, and efficacy of highdose 13.3 mg/24 h rivastigmine patch in severe Alzheimer disease was evaluated in a 24-week, open-label extension to the doubleblind ACTION study. Safety and tolerability, and efficacy on the Alzheimer’s Disease Cooperative Study-Activities of Daily Living scale-Severe Impairment Version (ADCS-ADL-SIV), Severe Impairment Battery (SIB), and ADCS-Clinical Global Impression of Change (ADCS-CGIC) were assessed. Overall, 197 patients continued on 13.3 mg/24 h patch; 199 uptitrated from 4.6 mg/24 h to 13.3 mg/24 h patch. The incidence of adverse events (AEs), serious AEs and discontinuations due to AEs was similar in patients who continued on, and patients who uptitrated to, 13.3 mg/24 h patch (AEs: 57.9% and 59.8%; serious AEs: 16.2% and 16.1%; discontinuations: 11.2% and 12.1%, respectively). Larger mean changes from double-blind baseline were observed in patients uptitrated on the ADCS-ADL-SIV (4.6; SD = 8.7) and SIB (7.0; SD = 16.6), than those who continued on 13.3 mg/24 h patch (3.9; SD = 8.0 and 4.7; SD = 16.8, respectively). ADCSCGIC scores were comparable. There were no clinically relevant between-group differences in safety and tolerability. Greater decline was observed in patients with delayed uptitration to highdose 13.3 mg/24 h patch than patients who continued on high-dose patch. (PsycINFO Database Record (c) 2017 APA, all rights reserved) (Source: journal abstract)

Abstract: Aims: To identify factors predicting improvement/stabilization on the Alzheimer’s Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC) and investigate whether early treatment responses can predict long-term outcomes, during a trial of 13.3 mg/24 h versus 4.6 mg/24 h rivastigmine patch in patients with severe Alzheimer’s disease (AD). Methods: Logistic regression was used to relate Week 24 ADCS-CGIC score to potential baseline predictors. Additional analyses based on receiver-operating characteristic curves were performed using Week 8/16 ADCS-CGIC scores to predict response (13.3 mg/24 h patch) at Week 24. ADCS-CGIC score of (1) 1-3 = ”improvement,” (2) 1-4 = ”improvement or no change”. Results: “Treatment” (13.3 mg/24 h patch) and increased age were significant predictors of “improvement” (P = 0.01 and P = 0.003, respectively), and “treatment” (P = 0.001), increased age (P = 0.002), and prior AD treatment (P = 0.03) for “improvement or no change”. At Week 8 and 16, ADCS-CGIC scores of 4 and 5 were optimal thresholds in predicting ”improvement,” and ”improvement or no change,” respectively, at Week 24. Conclusions: A significant therapeutic effect of high-dose rivastigmine patch on ADCS-CGIC response was observed. The 13.3 mg/24 h patch was identified as a predictor of “improvement” or “improvement or no change”. Patients with minimal worsening/improvement/no change after treatment initiation may be more likely to respond following long-term therapy. (PsycINFO Database Record (c) 2017 APA, all rights reserved) (Source: journal abstract)

Abstract: The protective effect of statin on Alzheimer disease (AD) is still controversial, probably due to the debate about when to start the use of statin and the lack of any large-scale randomized evidence that actually supports the hypothesis. The purpose of this study was to examine the protective effect of early statin use on mild-to-moderate AD in the total Taiwanese population. This was a total population-based case-control study, using the total population of Taiwanese citizens seen in general medical practice; therefore, the findings can be applied to the general population. The study patients were those with newly diagnosed dementia (ICD-9 290.x) and prescribed any acetylcholinesterase inhibitors (AChEI) from the Taiwan National Health Insurance dataset in 1997 to 2008. The newly diagnosed eligible mild-to-moderate AD patients were traced from the dates of their index dates, which was defined as the first day to receive any AChEI treatment, back to 1 year (exposure period) to categorize them into AD with early statin use and without early statin use. Early statin use was defined as patients using statin before AChEI treatment. Alzheimer disease patients with early statin use were those receiving any statin treatment during the exposure period. Then, we used propensity-score-matched strategy to match these 2 groups as 1:1. The matched study patients were followed-up from their index dates. The primary outcome was the discontinuation of AChEI treatment, indicating AD progression. There were 719 mild-to-moderate AD-paired patients with early statin use and without early statin use for analyses. Alzheimer disease progression was statistically lower in AD patients with early statin use than those without (P = 0.00054). After adjusting for other covariates, mild-to-moderate AD patients with early statin use exhibited a 0.85-risk (95% CI = 0.76-0.95, P = 0.0066) to have AD progression than those without. Early statin use was significantly associated with a reduction in AD progression in mild-to-moderate AD patients. The future randomized trial studies can confirm our findings.


Abstract: Introduction: Alzheimer's disease (AD) and dementia with Lewy bodies (DLB) commonly have pathological overlap but patients with DLB who respond to cholinesterase inhibitors have fewer AD-like imaging biomarkers (cingulate island sign, hippocampal atrophy, amyloid-beta PET deposition). Blood-based biomarker profiles show AD can be distinguished from Parkinson's disease and normal controls using a multi-level classification approach. We examined a blood-based biomarker profile in detecting and differentiating DLB treatment responders from AD and normal controls. Methods: We identified 35 probable DLB patients at Mayo Clinic Florida who had good response to cholinesterase inhibitors. These were matched by age and gender with AD patients (n=39) and cognitively normal individuals (n=48). Plasma samples were assayed in duplicate via a multi-plex biomarker assay platform using ECL on the SECTOR Imager 2400A from Meso Scale Discovery (MSD; http://www.mesoscale.com). Markers included sVCAM1, IL5, IL1, IL6, IL7, IL10, adiponectin, MIP1alpha, TNFalpha, sICAM, CA125, SAA, CRP and eotaxin 3. Age, education and gender were entered into the models. Random forest (RF, dichotomous) and support vector machine (SVM, multi-category classification) were used to generate biomarker profiles. Results: A multi-marker, multi-level classification approach using SVM yielded 100% accuracy when simultaneously detecting and distinguishing between DLB, AD and normal controls with five-fold cross validation. The area under the receiver operating characteristic curve (AUC) was 0.81 when distinguishing DLB from normal controls, and 0.56 in differentiating DLB from AD. Conclusions: Current results provide the first evidence that a plasma-based biomarker profile approach detects DLB treatment responders and distinguishes them from AD and normal controls. Future studies are needed for confirmation and to determine if these findings can be extended to include other Lewy body disease subgroups.


Abstract: A once-daily, fixed-dose combination of memantine extended-release (ER)/donepezil 28/10 mg (Namzaric™) is available in the USA for patients with moderate to severe Alzheimer's disease (AD) on stable memantine and donepezil therapy. The fixed-dose formulation is bioequivalent to coadministration of the individual drugs. In a 24-week, phase III
trial in patients with moderate to severe AD, addition of memantine ER 28 mg once daily to stable cholinesterase inhibitor (ChEI) therapy was more effective than add-on placebo on measures of cognition, global clinical status, dementia behaviour and semantic processing ability, although between-group differences on a measure of daily function did not significantly differ. In subgroup analyses in donepezil-treated patients, add-on memantine ER was more effective than add-on placebo on measures of cognition, dementia behaviour and semantic processing, although there were no significant between-group differences on measures of global clinical status and daily function. Memantine ER plus ChEI combination therapy was generally well tolerated in the phase III trial, with diarrhoea, dizziness and influenza occurring at least twice as often with add-on memantine ER as add-on placebo in donepezil-treated patients. Thus, memantine ER plus donepezil combination therapy is an effective and well tolerated treatment option for patients with moderate to severe AD. The fixed-dose combination is potentially more convenient than coadministration of the individual agents. (PsycINFO Database Record (c) 2016 APA, all rights reserved)

Abstract: Background: ACTION, a 24-week, prospective, randomized, parallel-group, double-blind study in patients with severe Alzheimer’s disease (AD), demonstrated significant efficacy of 13.3 mg/24 h versus 4.6 mg/24 h rivastigmine patch on the Severe Impairment Battery (SIB) and Alzheimer’s Disease Cooperative Study-Activities of Daily Living scale-Severe Impairment Version (ADCS-ADL-SIV). Overall, 61% of the study population received at least 1 dose of concomitant memantine, regardless of dose or duration. This retrospective analysis investigated the effects of concomitant memantine on the efficacy, safety and tolerability of 13.3 mg/24 h versus 4.6 mg/24 h rivastigmine patch. Methods: Patients were stratified according to whether or not they received at least one dose of concomitant memantine during the double-blind phase. Changes from baseline on the SIB and ADCS-ADL-SIV were compared using analysis of covariance (ANCOVA) with treatment, pooled center, memantine usage and treatment-by-memantine as factors, and baseline as a covariate. Safety and tolerability were assessed. Results: Memantine-treated patients were younger than those not receiving memantine (mean 75.9 and 78.8 years, respectively), with a lower screening Mini-Mental State Examination (8.6 and 9.2, respectively). ANCOVA confirmed there was no significant interaction (p > 0.1) between study treatment and memantine use on the SIB or ADCS-ADL-SIV. The incidence of adverse events was: 71.4%, 13.3 mg/24 h patch with memantine; 79.7%, 13.3 mg/24 h patch alone; 74.7%, 4.6 mg/24 h patch with memantine; and 71.1%, 4.6 mg/24 h patch alone. Conclusion: These data suggest benefit of 13.3 mg/24 h versus 4.6 mg/24 h rivastigmine patch, regardless of concomitant memantine use. The incidence of adverse events with highdose patch was similar in memantine-treated patients and those not receiving memantine. (PsycINFO Database Record (c) 2017 APA, all rights reserved) (Source: journal abstract)

Abstract: Background: The K variant of butyrylcholinesterase (BCHE-K) exhibits a reduced acetylcholine-hydrolyzing capacity; so the clinical response to rivastigmine may differ in Alzheimer’s disease (AD) patients with the BCHE-K gene. Objective: To investigate the clinical response to rivastigmine transdermal patch monotherapy or memantine plus rivastigmine transdermal patch therapy in AD patients based on the BCHE-K gene. Methods: A total of 146 probable AD patients consented to genetic testing for butyrylcholinesterase and underwent the final efficacy evaluations. Responders were defined as patients with an equal or better score on the Alzheimer’s Disease Assessment Scale-cognitive subscale (ADAS-cog) at 16 weeks compared to their baseline score. Results: BCHE-K carriers showed a lower responder rate on the ADAS-cog than non-carriers (38.2 vs. 61.7%, p = 0.02), and this trend was evident in AD patients with apolipoprotein E 4 (35 vs. 60.7%, p = 0.001). The presence of the BCHE-K allele predicted a worse response on the ADAS-cog (odds ratio 0.35, 95% confidence interval 0.14-0.87), after adjusting for demographic and baseline cognitive and functional variables. Conclusion: The BCHE-K genotype may be related to a poor cognitive
response to rivastigmine patch or memantine add-on therapy, especially in the presence of apolipoprotein E 4. (PsycINFO Database Record (c) 2016 APA, all rights reserved)


Abstract: Cholinesterase inhibitors treatment is considered as a common therapeutic approach for Alzheimer’s disease (AD) by numerous reported studies, but the role of currently available drugs for AD is still controversial. Our study aimed to evaluate the efficacy and safety of galantamine for the treatment of AD, and provide the basis and reference for clinical rational drug use. Randomized controlled trials (RCTs) of galantamine for AD published up to April 30, 2014 were searched. A random or fixed-effect model was used to analyze outcomes which were expressed as risk ratios (RRs) or mean difference (MD) with a 95% confidence interval (CI). Heterogeneity was assessed by Q test and I² statistic. The outcome measurements were as follows: the changes of Alzheimer’s Disease Assessment Scale-cognitive subscale (ADAS-cog), Mini-Mental State Examination (MMSE), Activities of Daily Living (ADL), Neuropsychiatric Inventory (NPI), Clinicians’ Interview-Based Impression of Change with Caregiver’s Input (CIBIC+), adverse effects and dropouts. Eleven articles with 4,074 participants were included. Administration of galantamine for 8-28 weeks (16-40 mg daily) led to significant improvements in ADAS-cog score [P < 0.0001, MD = -2.95, 95% CI (-3.32, -2.57)], MMSE score [P = 0.003, MD = 2.50, 95% CI (0.86, 4.15)], NPI score [P = 0.001, MD = -1.58, 95% CI (-2.54, -0.62)], and CIBIC+ scale [P < 0.00001, RR = 1.26, 95% CI (1.15, 1.39)], but not in ADL score [P = 0.43, MD = 0.71, 95% CI (0.33, 1.19)]. More adverse events and dropouts occurred in the galantamine group than that in the placebo group, the differences were statistically significant (all P < 0.05). Galantamine could significantly improve cognitive, behavioral, and global performances in patients with AD. In addition, we need to use it with caution in the clinical treatment. (PsycINFO Database Record (c) 2016 APA, all rights reserved) (Source: journal abstract)


Abstract: Background: There has not been conclusive evidence for prevention of brain atrophy by anti-dementia drugs in mild cognitive impairment and Alzheimer’s Disease. Methods: Relevant studies were identified through searches of PubMed, databases of the Cochrane Library, and PsycINFO citations up to 16 May, 2015. Only double-blind, randomized, placebo-controlled clinical trials (n = 1708) were found to meet the inclusion criteria, including 4 mild cognitive impairment studies (n = 1327) and 3 Alzheimer’s Disease studies (n = 381) [3 donepezil studies (2 mild cognitive impairment studies and 1 Alzheimer’s Disease study), 1 galantamine study for mild cognitive impairment, 2 memantine studies for Alzheimer’s Disease, and 1 rivastigmine study for mild cognitive impairment]. Pooled anti-dementia drugs showed superior protective outcomes compared with placebo regarding %TBV/y (SMD = -0.21, 95%CI = -0.37 to -0.04, P = .01, N = 4, n = 624) and %VV/y (SMD = -0.79, 95%CI = -1.40 to -0.19, P = .01, N = 3, n = 851). However, %HV/y failed to show difference between both groups. Among anti-dementia drugs, donepezil showed significantly greater protective effects than placebo regarding %TBV/y (SMD = -0.43, 95%CI = -0.74 to -0.12, P = .007, N = 1, n = 164) and %VV/y (SMD = -0.51, 95%CI = -0.73 to -0.29, P < .00001, N = 2, n = 338). Rivastigmine was also superior to placebo regarding %VV/y (SMD = -1.33, 95%CI = -1.52 to -1.14, P < .00001). Conclusions: The results favored the hypothesis that anti-dementia drugs may prevent brain atrophy in patients with mild cognitive impairment and Alzheimer’s Disease. (PsycINFO Database Record (c) 2016 APA, all rights reserved)

Abstract: Currently there is only one medication, donepezil, approved by any regulatory agency in the world for the treatment of dementia with Lewy body (DLB). In the United States, rivastigmine has been approved for dementia associated with Parkinson's disease (Parkinson's disease dementia, PDD), but there are no medications that have been approved by the US Food and Drug Administration for the treatment of DLB. Thankfully, recently several new medication trials been proposed to specifically treat DLB. Clearly there is a great need for new medication trials in DLB and ultimately for more effective therapeutics. This presentation will briefly review common offlabel treatments used for DLB, and then a more detailed examination of current or planned treatment trials for either the cognitive or behavioral effects of DLB. Because of the relevance to DLB, new treatments aimed at Parkinson's disease associated cognitive or behavioral disturbance will also be reviewed. Finally, potential new avenues of treatment will be examined, based on new theories around the pathogenesis of the Lewy body disorders


Abstract: Cistanches Herba (CH) is thought to be a “Yang-invigorating” material in traditional Chinese medicine. We evaluated neuroprotective effects of Cistanches Herba on Alzheimer’s disease (AD) patients. Moderate AD participants were divided into 3 groups: Cistanches Herba capsule (CH, n=10), Donepezil tablet (DON, n=8), and control group without treatment (n=6). We assessed efficacy by MMSE and ADAS-cog, and investigated the volume changes of hippocampus by 1.5 T MRI scans. Protein, mRNA levels, and secretions of total-tau (T-tau), tumor necrosis factor- α (TNF- α), and interleukin- (IL) 1β (IL-1β) in cerebrospinal fluid (CSF) were detected by Western blot, RT-PCR, and ELISA. The scores showed statistical difference after 48 weeks of treatment compared to control group. Meanwhile, volume changes of hippocampus were slight in drug treatment groups but distinct in control group; the levels of T-tau, TNF- α, and IL-1β were decreased compared to those in control group. Cistanches Herba could improve cognitive and independent living ability of moderate AD patients, slow down volume changes of hippocampus, and reduce the levels of T-tau, TNF- α, and IL-1β. It suggested that Cistanches Herba had potential neuroprotective effects for moderate AD


Abstract: BACKGROUND: We performed a meta-analysis of cholinesterase inhibitors for patients with Lewy body disorders, such as Parkinson's disease, Parkinson's disease dementia, and dementia with Lewy bodies. METHODS: The meta-analysis included only randomized controlled trials of cholinesterase inhibitors for Lewy body disorders. RESULTS: Seventeen studies (n = 1798) were assessed. Cholinesterase inhibitors significantly improved cognitive function (standardized mean difference [SMD] = -0.53), behavioral disturbances (SMD = -0.28), activities of daily living (SMD = -0.28), and global function (SMD = -0.52) compared with control treatments. Changes in motor function were not significantly different from control treatments. Furthermore, the cholinesterase inhibitor group had a higher all-cause discontinuation (risk ratio [RR] = 1.48, number needed to harm [NNH] = 14), discontinuation due to adverse events (RR = 1.59, NNH = 20), at least one adverse event (RR = 1.13, NNH = 11), nausea (RR = 2.50, NNH = 13), and tremor (RR = 2.30, NNH = 20). CONCLUSIONS: Cholinesterase inhibitors appear beneficial for the treatment of Lewy body disorders without detrimental effects on motor function. However, a careful monitoring of treatment compliance and side effects is required

PT - Meta-Analysis
PT - Review


Abstract: Background: We performed an updated meta-analysis of randomized controlled
trials of combination therapy with cholinesterase inhibitors and memantine in patients with Alzheimer’s disease. Methods: We reviewed cognitive function, activities of daily living, behavioral disturbance, global assessment, discontinuation rate, and individual side effects. Results: Seven studies (total n = 2182) were identified. Combination therapy significantly affected behavioral disturbance scores (standardized mean difference = -0.13), activity of daily living scores (standardized mean difference = -0.10), and global assessment scores (standardized mean difference = -0.15). In addition, cognitive function scores (standardized mean difference = -0.13, P = .06) exhibited favorable trends with combination therapy. The effects of combination therapy were more significant in the moderate-to-severe Alzheimer’s disease subgroup in terms of all efficacy outcome scores. The discontinuation rate was similar in both groups, and there were no significant differences in individual side effects. Conclusions: Combination therapy was beneficial for the treatment of moderate-to-severe Alzheimer’s disease in terms of cognition, behavioral disturbances, activities of daily living, and global assessment was well tolerated. (PsycINFO Database Record (c) 2016 APA, all rights reserved) (Source: journal abstract)


Abstract: Background/objective: There are few reports on the effects of anti-Alzheimer’s disease (AD) drugs on older AD patients, and possible differences based on gender in a real world setting. Methods: “Okayama Late Dementia Study (OLDS)” is a retrospective clinical cohort study focusing on older AD patients (n = 373; age > 75 years) treated with monotherapy donepezil (n = 55), galantamine (n = 222), rivastigmine (n = 63), or memantine (n = 33). The patients were evaluated as an entire group and separated by gender, using seven batteries for dementia assessment at baseline and at 3, 6, and 12 months of drug therapy. Results: All four drugs preserved cognitive and affective functions until 12 months, except for Frontal Assessment Battery (FAB) with memantine (*p < 0.05 versus baseline). Donepezil monotherapy significantly improved Hasegawa Dementia Rating Scale-Revised (HDS-R) at 3 months (*p < 0.05), and memantine (3 and 6 months, *p < 0.05) and rivastigmine (3 months, **p < 0.01) improved Abe’s Behavior and Psychological Symptom of Dementia Score (ABS), respectively. Activities of daily living (ADL) became significantly worse with galantamine at 12 months (*p < 0.05). Male Mini-Mental State Examination scores became worse at 12 months with donepezil (*p < 0.05), as did female Geriatric Depression Scale scores at 6 months (*p < 0.05). Male HDS-R and ABS scores were preserved in the galantamine group until 12 months. Female ABS scores with memantine improved at 6 months (*p < 0.05), while male ADL scores became worse with rivastigmine at 12 months (*p < 0.05). Conclusion: OLDS revealed that anti-AD drugs were effective even for older AD patients, and the clinical benefits of each drug showed a small difference with regard to gender. (PsyclINFO Database Record (c) 2016 APA, all rights reserved) (Source: journal abstract)


Abstract: Background/Objective: Alzheimer’s disease (AD) is one of the most important diseases in an aging society, but the clinical effects of rivastigmine have not been fully examined in real world domestic clinics. Methods: We performed the "Okayama Rivastigmine Study (ORS)" to retrospectively analyze the clinical effects of rivastigmine (n = 75) or donepezil (n = 71) on AD patients with seven dementia assessment batteries at the baseline, 3, 6, and 12 months. In addition, we divided the rivastigmine group into two subgroups at the baseline: the mild behavioral and psychological symptoms of dementia (BPSD) group (Abe’s BPSD score (ABS) < 6) and the severe BPSD group (6 ≤ ABS). In these two subgroups, baseline scores and changes were also retrospectively analyzed until 12 months. Results: Rivastigmine significantly improved the Mini-Mental State Examination score at 3 months (*p < 0.05 versus baseline) and at 6 months (*p < 0.05), the Frontal Assessment Battery (FAB) at 6 months (*p < 0.05), and ABS at 3 months (**p < 0.01) while donepezil only stabilized the three cognitive scores. On the other hand, the Geriatric Depression Scale and the Apathy Scale were stable until 12 months in both groups. Baseline BPSD severity-dependent analysis showed a small improvement of FAB at 6 months in the mild BPSD subgroup (*p <

Abstract: Background/Objective: To compare the effectiveness of combination therapy with cholinesterase inhibitors (ChEI) plus memantine in all AD patients and in older AD patients (age >75 years). Methods: The Okayama Memantine Study was used to compare the clinical effects of combination therapy of donepezil plus memantine ( n = 61) or galantamine plus memantine ( n = 53) in all AD patients, and in older AD patients separately, with six batteries at baseline, at 6 months with ChEI only monotherapy, and at 3, 6, and 12 months after addition of memantine to the treatment schedule (18 months total). Results: The addition of memantine resulted in stabilization of the Mini-Mental State Examination scores and Hasegawa dementia rating for 6 months, and then significantly declined at 12 months in both subgroups. Frontal assessment battery (FAB) declined significantly at 12 months after memantine addition in the donepezil subgroup, while the galantamine subgroup significantly improved at 6 months. Affective functions were well preserved after memantine addition until 12 months, except for the apathy scale at 12 months after memantine addition in the galantamine subgroup. The combination therapy of donepezil plus memantine was better for apathy in older AD patients, and galantamine plus memantine was better for cognitive functions. Conclusions: The addition of memantine stabilized cognitive scores for 6 months and affective scores for 12 months in the donepezil subgroup. Additionally, memantine significantly improved FAB at 6 months in the galantamine subgroup although apathy scale became significantly worse at 12 months. (PsycINFO Database Record (c) 2016 APA, all rights reserved) (Source: journal abstract)


Abstract: Background: Treatment of Alzheimer’s disease (AD) with cholinesterase inhibitors (ChEI) enhances cholinergic activity and alleviates clinical symptoms. However, there is variation in the clinical response as well as system level changes revealed by functional MRI (fMRI) studies. Methods: We investigated 18 newly diagnosed mild AD patients with fMRI using a face recognition task after a single oral dose of rivastigmine, a single dose of placebo and 1-month treatment with rivastigmine. The clinical follow-up took place at 6 and 12 months. Results: MMSE score difference between baseline and the follow-ups showed a positive correlation with fMRI activation difference between treatment and placebo in the right prefrontal cortex. A negative correlation was found for the left prefrontal cortex and the left fusiform gyrus. In addition, greater signal intensity in the right versus the left fusiform gyrus predicted a response to ChEI with increasing MMSE scores during the follow-up with 77.8% sensitivity and 77.8% specificity. Conclusions: The increased fMRI activation by cholinergic stimulation in brain areas associated with the processing of the visual task reveals still functioning brain networks and a subsequent positive effect of ChEI on cognition. Thus, fMRI may be useful for identifying AD patients most likely to respond to treatment with ChEI. (PsycINFO Database Record (c) 2016 APA, all rights reserved) (Source: journal abstract)


Abstract: BACKGROUND/AIMS: The aim of this study was to clarify the effects of donepezil on extrapyramidal symptoms in patients with dementia with Lewy bodies (DLB). METHODS: Using pooled datasets from phase 2 and 3, 12-week randomized, placebo-controlled trials (RCT, n = 281) and 52-week open-label long-term extension trials (OLE, n = 241) of donepezil in DLB, the effects of donepezil on the incidence of extrapyramidal adverse events (AEs) and on the Unified Parkinson’s Disease Rating Scale (UPDRS) part III were assessed,
and potential baseline factors affecting the AEs were explored. RESULTS: The RCT analysis did not show significant differences between the placebo and active (3, 5, and 10 mg donepezil) groups in extrapyramidal AE incidence (3.8 and 6.5%, $p = 0.569$) and change in the UPDRS (mean +/- SD: -0.2 +/- 4.3 and -0.6 +/- 6.5, $p = 0.562$). In the OLE analysis (5 and 10 mg donepezil), the incidence did not increase chronologically; all AEs leading to a dose reduction or discontinuation except one were relieved. The UPDRS was unchanged for 52 weeks. An exploratory multivariate logistic regression analysis of the RCTs revealed that donepezil treatment was not a significant factor affecting the AEs. Baseline severity of parkinsonism was a predisposing factor for worsening of parkinsonism without significant interactions between donepezil and baseline severity. CONCLUSION: DLB can safely be treated with donepezil without relevant worsening of extrapyramidal symptoms, but treatment requires careful attention to symptom progression when administered to patients with relatively severe parkinsonism.


Abstract: Background: Alzheimer’s disease (AD) is one of the most significant diseases affecting an increasingly aging society. Objective: To determine the long-term efficacy of galantamine treatment in a Japanese population. Methods: We performed "Okayama Galantamine Study (OGS)" to retrospectively analyze the clinical effects of galantamine in 279 AD patients using 7 batteries for assessing dementia at baseline, 3, 6, 12, and 24 months. We further analyzed the effects of galantamine based on gender and the severity of their baseline cognitive, affective, and activity of daily living (ADL) functions. Results: In all 279 AD patients (80.6 ± 7.2 years old, MMSE 20.0 ± 4.5), cognitive functions were well preserved until 12 months and even frontal assessment battery improved after 12 months although Hasegawa dementia scale-revised finally worsened at 24 months (" $p < 0.05$) with galantamine treatment. Affective and ADL functions were also well maintained after galantamine treatment with significant improvement of Geriatric Depression Scale scores at 3 months (" $p < 0.05$). Subanalyses showed the better response to galantamine for male and lower baseline function subgroups. Conclusions: Our present study (OGS) revealed a long-term efficacy of galantamine in very elderly AD patients, and suggested a better efficacy for male and baseline lower cognitive, affective, and ADL functions. (PsycINFO Database Record (c) 2016 APA, all rights reserved)


Abstract: Dementia with Lewy Bodies (DLB) is a rapidly progressing neurodegenerative disease with a characteristic profound reduction in CNS choline acetyltransferase. This case series suggests a sustained disease modifying effect from a level inhibition of cholinesterase that can only be achieved with concurrent peripheral muscarinic blockade. Patients were selected from those seen in a single geriatric consultation clinic after 2010. DLB was diagnosed by the Consensus criteria of the third report of the DLB consortium (2005) by a geriatrician, with concurring neurologist. Patients received rivastigmine at doses greater that the upper limit of FDA approved dosing. Does greater than 12 mg oral, or 13.3 mg transdermal were paired with glycopyrrolate 1-2 mg orally twice daily. Concurrent use of carbidopa/levodopa, selegiline was permitted but use of dopamine receptor agonists, other acetyl-cholinesterase inhibitors or anti-muscarinic agents was not. Criteria for selection included treatment more than one year, the ability to perform a Mini Mental State Examination (MMSE) at the time of initiation and the availability of follow up data. The MMSE was performed in a standardized format. Function Assessment Stage (FAST) was determined by nurse and physician after an interview with patient and caregivers. MMSE values over time were compared to the published rate of decline of DLB. All patients had MMSE and functional improvement, with 8 of 9 having a sustained stabilization of MMSE score, 2 of whom have...
had stable MMSE for over 5 years. This study suggests that disease course modification of Dementia with Lewy Bodies is possible with the high level inhibition of cholinesterase achievable when rivastigmine is combined with glycopyrrolate. The implications for the treatment of neurodegenerative diseases associated with the abnormal accumulation of protein metabolites warrants further research.


Abstract: Background/Aims: Adherence to cholinesterase inhibitors is important in order to maximise treatment efficacy. This study aimed to investigate patient and caregiver factors associated with adherence to and satisfaction with transdermal rivastigmine treatment.

Methods: Sociodemographic, clinical and psychosocial data were collected from 127 patients and their caregivers during the first follow-up visit after prescription. At the second follow-up, data were collected on 110 of the dyads. Adherence to and satisfaction with the treatment were assessed using the Medication Adherence Report Scale and an adapted version of the Alzheimer's Disease Caregiver Preference Questionnaire. Results: 66.2% of the caregivers reported being adherent to, and 77.0% were satisfied with, the patch at the second follow-up. Factors predicting higher adherence at the second follow-up were caregivers’ greater frequency of contact with patients, greater satisfaction with the information received about the patch, better tolerability of the patch and living at home with their caregivers. Greater concerns of the caregivers about the patch and the patients’ belief in “other” causes of their Alzheimer's disease predicted a lower adherence at the second follow-up. Conclusions: Assessing and addressing caregivers’ concerns about transdermal rivastigmine, improving doctor-patient/caregiver communication to increase caregiver satisfaction with information about the patch as well as providing education and support around patients’ beliefs and tolerability of the patch could improve adherence to transdermal rivastigmine. (PsychINFO Database Record (c) 2016 APA, all rights reserved) (Source: journal abstract)


Abstract: Background and purpose: Previous studies have indicated clinical benefits of a combination of cholinesterase inhibitors (ChEI) and memantine over ChEI monotherapy in Alzheimer’s disease (AD). Our objective was the development of guidelines on the question of whether combined ChEI/memantine treatment rather than ChEI alone should be used in patients with moderate to severe AD to improve global clinical impression (GCI), cognition, behaviour and activities of daily living (ADL). Methods: A systematic review and meta-analysis of randomized controlled trials based on a literature search in ALOIS, the register of the Cochrane Dementia and Cognitive Improvement Group, was carried out with subsequent guideline development according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. Results: Pooled data from four trials including 1549 AD patients in the moderate to severe disease stage demonstrated significant beneficial effects of combination therapy compared to ChEI monotherapy for GCI [standardized mean difference (SMD) -0.20; 95% confidence interval (CI) -0.31; -0.09], cognitive functioning (SMD â”0.27, 95% CI -0.37; -0.17) and behaviour (SMD -0.19; 95% CI -0.31; -0.07). The quality of evidence was high for behaviour, moderate for cognitive function and GCI and low for ADL. Agreement of panellists was reached after the second round of the consensus finding procedure. The desirable effects of combined ChEI and memantine treatment were considered to outweigh undesirable effects. The evidence was weak for cognition, GCI and ADL so that the general recommendation for using combination therapy was weak. Conclusions: We suggest the use of a combination of ChEI plus memantine rather than ChEI alone in patients with moderate to severe AD. The strength of this recommendation is weak. (PsychINFO Database Record (c) 2016 APA, all rights reserved) (Source: journal abstract)


Abstract: Objective: The authors examined research on effects, costs, and patient and

Abstract: Objective: Demographic changes are increasing the pressure to improve therapeutic strategies against cognitive decline in Alzheimer disease (AD) and mild cognitive impairment (MCI). Besides drug treatment, physical activity seems to be a promising intervention target as epidemiological and clinical studies suggest beneficial effects of exercise training on cognition. Using comparable inclusion and exclusion criteria, we analyzed the efficacy of drug therapy (cholinesterase inhibitors, memantine, and Ginkgo biloba) and exercise interventions for improving cognition in AD and MCI populations. Methods: We searched The Cochrane Library, EBSCO, OVID, Web of Science, and U.S. Food and Drug Administration data from inception through October 30, 2013. Randomized controlled trials in which at least one treatment arm consisted of an exercise or a pharmacological intervention for AD or MCI patients, and which had either a non-exposed control condition or a control condition that received another intervention. Treatment discontinuation rates and Standardized Mean Change score using Raw score standardization (SMCR) of cognitive performance were calculated. Results: Discontinuation rates varied substantially and ranged between 0% and 49% with a median of 18%. Significantly increased discontinuation rates were found for galantamine and rivastigmine as compared to placebo in AD studies. Drug treatments resulted in a small pooled effect on cognition (SMCR: 0.23, 95% CI: 0.20 to 0.25) in AD studies (N = 45, 18,434 patients) and no effect in any of the MCI studies (N = 5, 3,693 patients; SMCR: 0.03, 95% CI: 0.00 to 0.005). Exercise interventions had a moderate to strong pooled effect size (SMCR: 0.83, 95% CI: 0.59 to 1.07) in AD studies (N = 4, 119 patients), and a small effect size (SMCR: 0.20, 95% CI: 0.11 to 0.28) in MCI (N = 6, 443 patients). Conclusions: Drug treatments have a small but significant impact on cognitive functioning in AD and exercise has the potential to improve cognition in AD and MCI. Head-to-head trials with sufficient statistical power are necessary to directly compare efficacy, safety, and acceptability. Combining these two approaches might further increase the efficacy of each individual intervention. (PsycINFO Database Record (c) 2016 APA, all rights reserved) (Source: Journal abstract)


Abstract: Aim: To evaluate the long-term effectiveness of rivastigmine patch or capsule on mild to severe Alzheimer’s disease (AD). Method: We performed a meta-analysis of 17 studies regarding the treatment effectiveness of rivastigmine patch or capsule on mild-to-
severe AD. Results: Significant difference exists between treatment with rivastigmine patch or capsule and placebo groups (p-value < 0.001). In the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) score evaluation, a negative weighted mean difference (WMD) was observed in overall and mild-moderate groups after rivastigmine treatment. And in ADAS-ADL score evaluation, a positive WMD was observed in overall groups after rivastigmine treatment. Moreover, WMD value is lower in patch administration subgroup compared to that of capsule administration subgroup. Conclusion: Rivastigmine treatment shows a positive result of improving the condition of patients with mild-to-severe AD. Patch administration shows a stronger effect on decreasing ADAS-Cog score compared to capsule administration. (PsycINFO Database Record (c) 2016 APA, all rights reserved) (Source: journal abstract)

(86) Szigeti K, Hafeez MU. Exploring the role of donepezil in dementia with Lewy bodies. Drugs Today (Barc) 2015; 51(10):579-590. Abstract: Dementia with Lewy bodies (DLB) is considered the second most common form of dementia in the elderly. The cognitive fluctuations, hallucinations and extrapyramidal symptoms and signs suggest simultaneous neurodegeneration in multiple neuronal pathways including both dopaminergic and cholinergic transmission. In the past few years, several small studies have demonstrated the benefit of acetylcholinesterase inhibitors (AChEIs) on the cognitive and behavioral symptoms of DLB. These drugs, by reversibly blocking the hydrolytic activity of AChE, increase the availability of synaptic acetylcholine. Neuropathological and neuroimaging studies demonstrated that cholinergic neurotransmission is more defective in DLB than in Alzheimer's disease (AD). Despite the relevance of AChEIs to DLB, there are no FDA-approved drugs for its management. The aim of this review is to summarize the literature on the application of donepezil in DLB. Although the results are inconclusive, when one compares and contrasts them to the results of the AD-donepezil trials, the effect size appears larger. Placebo-controlled, randomized, well-powered studies of adequate length are needed to avoid underutilization of a potentially efficacious drug

(87) Torrmalehto SM, Martikainen JA, Vaatainen ST, Hallikainen IT, Hallikainen M, Bell JS et al. Use of Anti-Dementia Drugs in Relation to Change in Cognition, Behavior, and Functioning in Alzheimer's Disease over a Three-Year Period: Kuopio ALSOVA Study. Journal of Alzheimer's Disease 2015; 48(4):1033-1041. Abstract: Background: Alzheimer's disease (AD) is characterized by deterioration in cognition, decline in physical function, and increase in behavioral disturbances. These symptoms are associated with dependence. Objective: We investigated the use of anti-dementia drugs in relation to change in cognition, function, and behavior over a 3-year period. Methods: Data were collected as part of the prospective follow-up ALSOVA study. All study participants (n = 236) had very mild or mild AD at baseline. All participants and their informal caregivers underwent annual clinical and medication assessments. Repeated measures logistic regression was used to compute odds ratios (ORs) and 95% confidence intervals (CIs) for factors associated with anti-dementia drug use and disease progression measures over time. Results: The overall prevalence of anti-dementia drug use remained stable (from 89% to 92%) during the follow-up period. The use of memantine and cholinesterase inhibitor-memantine combination treatment increased with disease severity. After adjustment for confounding, a one-point increase in the disease severity scale (CDR-SOB) was associated with 15.6% increased odds of memantine use. A one-point decrease in CERAD Neuropsychological battery (CERAD-NB) total score was associated with 2.4% increased odds of memantine use. The overall unadjusted rate of switching between anti-dementia drugs was 9.17 (95% CI 7.10 to 11.88) changes per 100 person-years. Conclusion: Nearly 90% of newly diagnosed persons with AD were prescribed anti-dementia drugs. Use of memantine was found to be associated with disease progression. Switching and use of anti-dementia drugs was consistent with Finnish and European clinical practice guidelines for AD

Abstract: Background: Alzheimer's disease (AD) is a progressively developing neurodegenerative disorder of the brain in the elderly people. Vanda roxburghii Rbr. root has been used traditionally in Bangladesh as tonic to brain and in the treatment of nervous system disorders including AD. Therefore, we aimed to investigate the cholinesterase inhibitory activities and antioxidant properties of the extracts from V roxburghii. Methods: The crude methanol extract from the roots of plant was sequentially fractionated with petroleum ether, chloroform, ethylacetate and water to yield their corresponding extracts. The extracts were assessed for acetylcholinesterase and butyrylcholinesterase inhibitory activity by modified Ellman method and antioxidant property by several assays including ferric reducing antioxidant power, scavenging of 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical and hydroxyl radical, and inhibition of lipid peroxidation. Endogenous substances in the extracts were analyzed by the standard phytochemical methods and active compound was isolated by the chromatographic methods. Results: Chloroform extract was shown to demonstrate strong ferric-reducing antioxidant power and scavenging activity against DPPH and hydroxyl free radicals when compared with the other extracts and the reference standard catechin. The antioxidant effect was further verified by inhibition of lipid peroxidation in rat brain homogenates. Likewise, the chloroform extract exhibited the highest inhibition against both the acetylcholinesterase and butyrylcholinesterase enzymes with IC50 values of 221.13 and 82.51 ug/ml, respectively. Phytochemical screening revealed a large amount of phenolics and flavonoids in the chloroform extract. Bioactivity guided separation techniques led to the isolation of a strong antioxidant from the chloroform extract and its structure was determined as gigantol on the basis of spectral studies. Conclusion: These results suggest that the chloroform extract of V. roxburghii, possibly due to its phenolic compounds, exert potential antioxidant and cholinesterase inhibitory activities, which may be useful in the treatment of AD.


Abstract: At present, there are no disease-modifying treatments for dementia with Lewy bodies (DLB) or Parkinson's disease dementia (PDD). Although cholinesterase inhibitors (CHEI; rivastigmine, donepezil and galantamine) and memantine are frequently used in DLB and PDD, at present only rivastigmine is licensed for PDD and donepezil for DLB in Japan. Compared to Alzheimer’s disease, there have been relatively few randomized controlled trials (RCTs) in DLB and PDD. The best evidence for CHEI comes from 5 RCTs, 3 conducted in DLB and 2 in PDD. Rivastigmine moderately benefitted cognition on ADAS-cog and MMSE, neuropsychiatric symptoms (NPS) and activities of daily living in PDD (Emre, N Engl J Med, 2004), whereas another large RCT of donepezil produced mixed results (Dubois, Mov Disord, 2012). A modestly sized RCT of rivastigmine in DLB showed significant improvement on NPS but not on cognitive measures (McKeith, Lancet Neurol, 2000). However, donepezil in two Japanese RCTs (Mori, Ann Neurol, 2012; Ikeda, Alz Res Therap, 2015) showed dose-dependent improvement on cognition but less convincing results for NPS. There have been 2 modestly sized RCTs looking at the effect of memantine for PDD and DLB (Aarsland, Lancet Neurol, 2009; Emre, Lancet Neurol, 2010). The Aarsland study did not separate DLB and PDD, but overall, memantine had a positive effect on global impression of change. The Emre study also showed a positive effect of memantine on global impression of change for DLB patients but not for PDD patients. A meta-analysis of CHEI and memantine produced small benefit on global impression of change, but only CHEI and not memantine conferred significant benefit on cognition (Wang, 2015, JNNP). All 4 drugs have good safety profile, but rivastigmine has slightly higher rate of mild to moderate side effects. In conclusion, CHEI and memantine slightly improve global impression of change, however only CHEI enhance cognitive function.


Abstract: OBJECTIVE: Recently, several large randomised controlled trials about the
treatments of cognitive impairment or dementia due to Parkinson's disease (CIND-PD or PDD) and dementia with Lewy bodies (DLB) were completed. Here, we systematically reviewed the studies (including the recent reports) to provide updated evidence for the treatments of CIND-PD, PDD and DLB. METHODS: We searched Cochrane Dementia and Cognitive Improvement Group Specialised Register, Pubmed, Embase, and other sources for eligible trials. We selected global impression and cognitive function as primary efficacy outcomes, and dropouts and adverse events as safety outcomes. Furthermore, Meta-analysis and trial sequential analysis (TSA) were used here. RESULTS: Ten trials were included in this study. Cholinesterase inhibitors and memantine produced small global efficacy on clinicians’ global impression of change (CGIC), from a weighted mean difference of -0.40 (95% CI -0.77 to -0.03) to -0.65 (95% CI -1.28 to -0.01); however, cholinesterase inhibitors but not memantine significantly improved cognition on Mini-Mental State Examination (MMSE), from 1.04 (95% CI 0.43 to 1.65) to 2.57 (95% CI 0.90 to 4.23). Additionally, both of them had good safety outcomes, although rivastigmine showed an increased risk on adverse events than placebo (risk ratio, RR 1.19, TSA adjusted 95% CI 1.04 to 1.36), these events were usually mild or moderate, and the risk disappeared on serious adverse events. CONCLUSIONS: Cholinesterase inhibitors and memantine slightly improve global impression; however, only cholinesterase inhibitors enhance cognitive function. Besides, all the drugs have good safety outcomes. But the limited trials precluded the generalisation of these outcomes.

PT - Meta-Analysis
PT - Review

Abstract: Background/Aims: Factors including rate of disease progression, different aspects of cholinesterase inhibitor (ChEI) treatment, and use of community-based services might affect the longitudinal outcome of Alzheimer's disease (AD). Whether these factors alter life expectancy in AD is unclear. We therefore examined the association between long-term ChEI therapy and survival. Methods: The present study included 1,021 patients with a clinical diagnosis of AD and a Mini-Mental State Examination score of 10-26 at baseline from a 3-year, prospective, multicenter study of ChEI therapy in clinical practice. The relationship of potential predictors with mortality was analyzed using Cox regression models. Results: After up to 16 years of follow-up, 841 (82%) of the participants had died. In the Alzheimer's Disease Assessment Scale-cognitive subscale, a mean decline of ≥4 points/year or ≥2 points/year on the Physical Self-Maintenance Scale was a risk factor for an earlier death. In the multivariate models, longer survival was associated with higher ChEI dose and longer duration of treatment. Users of community-based services at baseline exhibited a 1-year shorter mean life expectancy than nonusers. Conclusion: A longer survival time can be anticipated for AD patients with slower deterioration who receive and tolerate higher ChEI doses and a longer duration of treatment. © 2015 S. Karger AG, Basel

Abstract: Background/Aims: Memantine has been approved by the Food and Drug Administration for the treatment of moderate-to-severe Alzheimer's disease (AD). However, the effect of memantine on patients with mild-to-moderate AD is unclear. Methods: This study is a post hoc analysis of a double-blind clinical trial. Donepezil was used as the standard control treatment. Outcomes included score changes from baseline to week 24 on the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog), a modified 20-item Activities of Daily Living Scale (ADL), the Neuropsychiatric Inventory (NPI), and the Mini-Mental State Examination (MMSE) as well as the score of the Clinician's Interview-Based Impression of Change plus Caregiver Input (CIBIC-Plus). Results: One hundred sixty-seven AD patients with an MMSE score of 10-24 were analyzed. No significant differences in the score changes from baseline to week 24 on all outcomes or the four subscales of the ADAS-cog were observed between the two treatment groups. Donepezil resulted in an improved score for naming ability on the ADAS-cog compared to memantine (p = 0.036), whereas
memantine more effectively reduced agitation as measured by the NPI compared to
donepezil (p = 0.039). Conclusion: These findings support the efficacy of memantine for the
treatment of mild-to-moderate AD, especially in patients with agitation. © 2015 S. Karger AG,
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(94) Eyes on Evidence : assessment and treatment of dementia in older adults National
Institute for Health and Care Excellence (NICE) : 11-6-2014: .
Abstract: A systematic review finds that brief cognitive assessment tools can adequately
detect early dementia, but whether interventions for mild cognitive impairment or early
dementia have a clinically significant effect is unclear. This link will take you to the Eyes on
Evidence commentary. Eyes on Evidence commentaries help contextualise important new
evidence, highlighting areas that could signal a change in clinical practice. It does not
constitute formal NICE guidance. The commentaries included are the opinions of contributors
and do not necessarily reflect the views of NICE

(95) Alva G, Isaacson R, Sadowsky C, Grossberg G, Meng X, Somogyi M. Efficacy of higher-
dose 13.3 mg/24 h (15 cm(2) ) rivastigmine patch on the Alzheimer's Disease Assessment Scale-
cognitive subscale: domain and individual item analysis. International journal of geriatric
psychiatry 2014; 29(9):920-927.
Abstract: OBJECTIVE: Rivastigmine displays dose-dependent efficacy on cognition in
patients with Alzheimer's disease (AD), as measured by the Alzheimer's Disease Assessment
Scale-cognitive subscale (ADAS-cog). Subanalysis of the OPTIMA (OPtimising Transdermal
Exelon In Mild-to-moderate Alzheimer's disease) study aimed to define ADAS-cog domains
by factor analysis of individual items. Efficacy of 13.3 mg/24 h versus 9.5 mg/24 h
rivastigmine patch on individual items and newly derived domains was assessed. METHODS:
OPTIMA was a 48-week, double-blind (DB) study in patients with mild-to-moderate AD.
Patients meeting pre-defined decline criteria during open-label treatment with 9.5 mg/24 h
patch were randomized in the DB phase to 13.3 mg/24 h (n = 280) or 9.5 mg/24 h (n = 287)
patch. ADAS-cog change from baseline was a co-primary outcome measure. Factor analysis
categorized ADAS-cog items into newly derived domains. Change from DB-baseline was
calculated for domains and individual items. RESULTS: Numerically, less decline was
displayed with 13.3 mg/24 h versus 9.5 mg/24 h patch in the total ADAS-cog score at all time
points (significant at Week 24, p = 0.027). Factor analysis identified two domains: memory
and language. Significantly, less decline was observed on the memory domain with 13.3
mg/24 h versus 9.5 mg/24 h patch at Weeks 12, 24, and 48 (p < 0.05; observed cases).
Three items (following commands, orientation, and word recognition) displayed numerically
less decline with 13.3 mg/24 h versus 9.5 mg/24 h patch at all time points. No significant
between-group differences were observed on the language domain. CONCLUSION: Results
suggest that the greater cognitive efficacy of 13.3 mg/24 h versus 9.5 mg/24 h rivastigmine
patch is driven primarily by effects on memory, particularly in the areas of following
commands, orientation, and word recognition. Copyright © 2014 John Wiley & Sons, Ltd

(96) Amanatkar HR, Grossberg GT. Transdermal rivastigmine in the treatment of Alzheimer's
14(10):1119-1125.
Abstract: Despite the fact that the prevalence of Alzheimer’s disease (AD) is exponentially
increasing, we have not yet been able to develop a new treatment to modify the course of the
disease. This vacuum makes the traditional cholinesterase inhibitors and N-methyl-D-
aspartate receptor antagonist the only accessible pharmacotherapy options for the treatment
of this disease. Among these medications, the only available transdermal patch at this time is
the rivastigmine patch. This patch provides significantly lower gastrointestinal adverse effects.
A higher tolerability rate provides the option for physicians to continue treatment with higher
doses of rivastigmine in advanced stages of AD. Moreover, ease of use, easy-to-follow
schedule, less administration time spent by the caregiver result in greater adherent to the
treatment. This article aims to provide a comprehensive drug profile for transdermal
rivastigmine, to review currently available treatment options, and to try to anticipate future
treatment directions for AD. (PsycINFO Database Record (c) 2016 APA, all rights reserved)
(Source: journal abstract)

Abstract: BACKGROUND: In this study, we evaluated the effect on cognitive function of memantine, behavioral and psychological symptoms of dementia, and the care burden, in patients with moderate-to-severe Alzheimer's disease (AD). Furthermore, with near-infrared spectroscopy (NIRS), we examined the association between effect of memantine and brain blood flow. METHODS: We evaluated the effect of memantine administration from baseline on Clinical Global Impression-Improvement scale, mini mental state examination (MMSE), Clock Drawing Test (CDT), Neuropsychiatric Inventory (NPI), Japanese version of the Zarit Burden Interview (J-ZBI) and NIRS in two groups, donepezil administration memantine combination group (combination group, n = 19) donepezil administration memantine non-administration group (control group, n = 18) were assessed at weeks 0, 4, 12, and 24. RESULTS: Significant difference was found between the combination group and the control group in the score variation of Clinical Global Impression-Improvement scale, MMSE, CDT, NPI, and J-ZBI. In the NIRS measurements, trend oxyhemoglobin reduced suppression was observed in some channels centered on the superior frontal gyrus. A significant correlation was observed in the scores of MMSE, CDT, NPI, and J-ZBI. In addition, a significant positive correlation was also observed between the number of words in NIRS and scores of MMSE and CDT. CONCLUSIONS: In this study, by administering memantine in AD patients that inhibit the reduction of cerebral blood flow in the prefrontal area and improve clinical symptoms overall cognitive function, behavioral and psychological symptoms of dementia, thereby reducing the care burden of caregivers was suggested. Copyright © 2014 John Wiley & Sons, Ltd


Abstract: Attention is the first non-memory domain affected in Alzheimerâ€™s disease (AD), before deficits in language and visuo-spatial function, and it is claimed that attention deficits are responsible for the difficulties with daily living in early demented patients. The aim of this longitudinal study in a group of 121 Caucasian, community-dwelling, mild-to-moderate AD patients (Mini-Mental State Examination (MMSE) score >17) was to detect which cognitive domains were most affected by the disease and whether one year treatment with cholinesterase inhibitors was more effective in preserving attention than memory. All subjects were evaluated by a neuropsychological battery including global measurements (MMSE, Information-Memory- Concentration Test) and tasks exploring verbal long-term memory, language, attention, and executive functions. The comparison between two evaluations, made 12 months apart, shows statistically significant differences, indicating deterioration compared to baseline, in the following tests: MMSE (with no gender differences), Composite Memory Score, Short Story Delayed Recall, Trail-Making Test A, Semantic Fluency Test, and Token Test. Conversely, there were no differences in the two evaluations of the Digit Span, Corsi Tapping Test, Short Story Immediate Recall, and Phonemic Fluency Tests. It appears that the treatment specifically attenuated the decline in tests assessing attention and executive functions. A stabilization of the ability to pay attention, with the ensuing positive effects on executive functions, recent memory, and information acquisition which depend on attention, appears to be the main neuropsychological mechanism through which the activation of the cholinergic system, resulting from cholinesterase inhibition, exerts its effect on cognition. (PsycINFO Database Record (c) 2016 APA, all rights reserved) (Source: journal abstract)


Abstract: INTRODUCTION: Alzheimer's disease (AD), Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB) together account for the vast majority of individuals with dementia. Approximately 35 million people worldwide are affected with this condition, and despite decades of research, effective therapies that slow or reverse disease progression have not yet been developed. The recent failure of several large-scale clinical trials is beginning to challenge the magnitude of focus on amyloid-related therapies for AD, and
newer drug targets that have shown promise in the laboratory are being investigated in clinical trials. AREAS COVERED: This review summarises the current understanding of the underlying biology of AD, PDD and DLB and outlines the most recent drug candidates in advanced clinical trials. EXPERT OPINION: The lack of success in drug discovery for disease-modifying therapies for AD, PDD and DLB can be attributed to limitations in the design of clinical trials and the narrow focus of molecular targets for treatment. New avenues for drug discovery including repositioning and novel target identification may now provide opportunities for success, provided a critical mass of clinical trials is achieved through increased investment.


Abstract: Ginkgo biloba (Gb) is currently the most investigated and adopted herbal remedy for cognitive disorders and Alzheimer’s disease (AD). Nevertheless, its efficacy in the prevention and treatment of dementia still remains controversial. Specifically, the added effects of Gb in subjects already receiving ‘conventional’ anti-dementia treatments have been to date very scarcely investigated. We evaluated whether the use of Gb is associated with additional cognitive and functional benefit in AD patients already in treatment with cholinesterase inhibitors (ChEIs). Data are from mild to moderate AD patients under ChEI treatment recruited in the Impact of Cholinergic Treatment USe (ICTUS) study. Mixed model analyses were performed to measure six-monthly modifications in the Mini Mental State Examination (MMSE), the Alzheimer’s Disease Assessment Scale-Cognitive (ADAS-Cog) subscale score, and the Activities of Daily Living (ADL) scale over a follow-up of 1 year according to the additional Gb supplementation. A total of 828 subjects were considered for the present analyses. Significantly different modifications at the MMSE score over the 12-month follow-up were reported between patients on combined therapy compared to those only taking ChEIs. On the contrary, the modification of the ADAS-Cog score between the two groups did not show statistically significant differences, although similar trends were noticed. No significant modifications of the two adopted outcome measures were observed at the mid-term 6-month evaluation. The modifications over time of the ADL score did not show statistically significant differences between the two groups of interest. Our findings suggest that Gb may provide some added cognitive benefits in AD patients already under ChEIs treatment. The clinical meaningfulness of such effects remains to be confirmed and clarified.


Abstract: The effects of galantamine (GAL) on quality of life (QoL) and cognitive speed, as well its effects combined with nimodipine (NIM) in Alzheimer disease (AD) with cerebrovascular disease (mixed dementia), have not been explored. Method: Double-blind, placebo-controlled, multicenter Brazilian trial, studying the effects of GAL/NIM vs. GAL/placebo (PLA) in mild to moderate mixed dementia. Patients were randomized to receive GAL/NIM or GAL/PLA for 24 weeks. Primary efficacy measures were changes on a computerized neuropsychological battery (CNTB) and QoL Scale in Alzheimer's Disease (QoL-AD) from baseline to week 24. Results: Twenty-one patients received at least one drug dose (9 GAL/NIM and 12 GAL/PLA). Groups were matched for age, sex, education, cognitive and QoL scores at baseline. No significant differences were observed between groups on primary or secondary measures. QoL and cognitive performance showed significant improvement (p < 0.05) from baseline when all GAL-treated patients were analyzed. Adverse events were predominantly mild to moderate. Conclusion: GAL treatment improved QoL in mixed dementia, in addition to its previously known cognitive benefits. The combination GAL/NIM was not advantageous. However, the small sample size precludes any definitive conclusions. (PsycINFO Database Record (c) 2016 APA, all rights reserved) (Source: journal abstract)

Abstract: PURPOSE: To evaluate the effect of donepezil, one of the cholinesterase inhibitors, on P300 measurements in patients with Alzheimer’s disease (AD) and investigate the relationship between the subfactors of cognitive performance and P300 components.

METHODS: One hundred outpatients with AD were evaluated for cognitive function (cognitive ability screening instrument) and event-related potentials before and after 22 to 23 weeks of treatment with donepezil (5 mg/day). Twenty age-matched normal control subjects were recruited. RESULTS: The patients with AD showed prolonged P300 and N200 latency, no significant differences in N100 and P200 components, and poor performance in neuropsychological assessments compared with control subjects at baseline. After donepezil treatment, the patients with AD had reduction in P300 latency at Pz lead, which was associated with a parallel improvement in cognitive function in terms of remote memory, recent memory, visual instruction, and orientation. The pre-post treatment difference of P300 latency significantly correlated with the cognitive ability screening instrument score difference and recent memory score difference, respectively. CONCLUSIONS: The patients with AD still had intact early sensory processing but impaired higher-level cognitive processes that could influence behavior deviation. The donepezil treatment, which enhances higher-level cognitive processing time, revealed that P300 latency decreases as cognitive capability increases, especially improved in recent memory.


Abstract: Background: Behavioral and psychological symptoms of dementia (BPSD) occur in up to 80% of Alzheimer’s disease (AD) patients and represent one of the most common reasons for early institutionalization and increase in management costs. Objectives: This study evaluated the effects of four drugs (memantine, donepezil, rivastigmine, galantamine) in BPSD in AD patients. Methods: This was a prospective, longitudinal, randomized, open-label, 4-arm, parallel-group, 12-month clinical trial carried out in 177 AD patients. The severity of BPSD was evaluated at baseline and after treatment with memantine (n = 48), donepezil (n = 42), rivastigmine (n = 46), and galantamine (n = 41), by using the Neuropsychiatric Inventory (NPI) and the Behavioural Pathology in Alzheimer’s Disease (BEHAVE-AD) scales. Results: The NPI and BEHAVE-AD total scores improved from baseline to month 12 in all groups. The improvements in both scales were statistically significant in the memantine, donepezil, and rivastigmine groups, but not in the galantamine group. Responder analyses showed that treatment with memantine and rivastigmine resulted in more patients improving on NPI and BEHAVE-AD score, respectively. Agitation/aggression was the NPI item with the highest improvements (significantly versus baseline in the memantine and in the rivastigmine groups), while aggression and anxiety/phobias were the mostly improved BEHAVE-AD items (significantly in the rivastigmine group for both and in the rivastigmine group only for anxiety/phobias). All treatments were well tolerated: most of adverse events reported were transient and of mild-to-moderate intensity. Conclusions: This study suggests that specific drugs for AD, especially memantine and rivastigmine, may be effective in the improvement of BPSD in patients with mild to moderate AD, without major side effects. (PsycINFO Database Record (c) 2016 APA, all rights reserved)


Abstract: Despite three decades of intensive research in the field of Alzheimer’s disease (AD) and numerous clinical trials of new therapeutic agents, cholinesterase inhibitors (ChEIs) are still the mainstay of therapeutics for AD and dementia with Lewy bodies. Pharmacodynamic analyses of ChEIs provide paradoxical observations. Treatment with the rapidly reversible, noncarbamylating ChEIs (donepezil, galantamine, and tacrine) increases acetylcholinesterase (AChE) protein expression, whereas the carbamylating agent, rivastigmine, produces sustained inhibition with no significant change in AChE protein expression. Still, the symptomatic clinical efficacies of all these agents are similar. We report here for the first time...
that treatment with phenserine, another carbamylation ChEI, produces a sustained but mild inhibition of AChE in cerebrospinal fluid (CSF) of AD patients. We also show that phenserine treatment reverses donepezil-induced elevation of AChE expression. Further analyses on CSF of another larger patient cohort treated with donepezil revealed that, in addition to its main mode of action, donepezil produced two other pharmacodynamics with potentially contradictory outcomes. Donepezil-induced AChE expression favored an AChE-driven amyloid-β peptide (Aβ) aggregation, whereas donepezil itself concentration-dependently counteracted the AChE-induced Aβ aggregation, most likely by competing with the Aβ peptides for peripheral anionic site on the AChE protein. The reduction of AChE protein expression in the donepezil-treated patients by concomitant administration of the carbamylation agent, phenserine, could allow the donepezil molecule to only prevent interaction between Aβ and AChE. The current study suggests that an add-on therapy with a low-dose formulation of a carbamylation agent in patients on long-term donepezil treatment should be explored as a strategy for enhancing the clinical efficacy of these agents in dementia disorders. (PsycINFO Database Record (c) 2016 APA, all rights reserved) (Source: journal abstract)

(105) Dysken MW, Sano M, Asthana S, Vertrees JE, Pallaki M, Llorente M et al. Effect of vitamin E and memantine on functional decline in Alzheimer disease: the TEAM-AD VA cooperative randomized trial. JAMA: Journal of the American Medical Association 2014; 311(1):33-44. Abstract: Importance: Although vitamin E and memantine have been shown to have beneficial effects in moderately severe Alzheimer disease (AD), evidence is limited in mild to moderate AD. Objective: To determine if vitamin E (alpha tocopherol), memantine, or both slow progression of mild to moderate AD in patients taking an acetylcholinesterase inhibitor. Design, Setting, and Participants: Double-blind, placebo-controlled, parallel-group, randomized clinical trial involving 613 patients with mild to moderate AD initiated in August 2007 and concluded in September 2012 at 14 Veterans Affairs medical centers. Interventions: Participants received either 2000 IU/d of alpha tocopherol (n=152), 20 mg/d of memantine (n=155), the combination (n=154), or placebo (n=152). Main Outcomes and Measures: Alzheimer's Disease Cooperative Study/Activities of Daily Living (ADCS-ADL) Inventory score (range, 0-78). Secondary outcomes included cognitive, neuropsychiatric, functional, and caregiver measures. Results: Data from 561 participants were analyzed (alpha tocopherol=140, memantine=142, combination=139, placebo=140), with 52 excluded because of a lack of any follow-up data. Over the mean (SD) follow-up of 2.27 (1.22) years, ADCS-ADL Inventory scores declined by 3.15 units (95% CI, 0.92 to 5.39; adjusted P=0.03) less in the alpha tocopherol group compared with the placebo group. In the memantine group, these scores declined 1.98 units less (95% CI, -0.24 to 4.20; adjusted P=0.40) than the placebo group's decline. This change in the alpha tocopherol group translates into a delay in clinical progression of 19% per year compared with placebo or a delay of approximately 6.2 months over the follow-up period. Caregiver time increased least in the alpha tocopherol group. All-cause mortality and safety analyses showed a difference only on the serious adverse event of "infections or infestations," with greater frequencies in the memantine (31 events in 23 participants) and combination groups (44 events in 34 participants) compared with placebo (13 events in 11 participants). Conclusions and Relevance: Among patients with mild to moderate AD, 2000 IU/d of alpha tocopherol compared with placebo resulted in slower functional decline. There were no significant differences in the groups receiving memantine alone or memantine plus alpha tocopherol. These findings suggest benefit of alpha tocopherol in mild to moderate AD by slowing functional decline and decreasing caregiver burden. Trial Registration: clinicaltrials.gov Identifier: NCT00235716

(106) Gareri P, Putignano D, Castagna A, Cotroneo AM, De Palo G, Fabbo A et al. Retrospective study on the benefits of combined Memantine and cholinEsterase inhibitor treatMent in AGEd patients affected with Alzheimer’s disease: The MEMAGE study. Journal of Alzheimer's Disease 2014; 41(2):633-640. Abstract: Background: Combined therapy of memantine and acetylcholinesterase inhibitors (AChEIs) in patients with Alzheimer’s disease (AD) may be associated with higher benefits than either monotherapy. Objective: This retrospective multicentric study conducted in seven Italian Ambulatory Centers for Dementia assessed the efficacy and safety of memantine 20 mg/day administered for 6 months in addition to an AChEI in AD patients with worsened cognitive functions and behavioral disorders. Methods: A total number of 240 patients (61.7%
of women, 38.3% men, mean age 77.9±7.32 years old) who had started treatment with the combination therapy were recruited. At baseline (T0), Month 3 (T1), and Month 6 (T2), cognitive functions were assessed by Mini-Mental State Examination (MMSE), functional dependence by activities of daily living (ADL) and instrumental ADL, behavioral disturbances by the Neuropsychiatric Inventory (NPI), and comorbidities by Cumulative Illness Rating Scale. Adverse events were reported during the study. Results: MMSE total score significantly increased at Month 6 (p = 0.029 versus month 3) and IADL total score significantly decreased from baseline to endpoint (p = 0.033). There were no significant changes from baseline in meanADL, despite significant improvements in NPI total score. The mean MMSE total score significantly increased with the combination donepezil + memantine compared to rivastigmine + memantine. The adverse events profile was in line with the expected range of the drugs studied and concomitant therapies. Overall, 17 patients discontinued treatment in the observation time. Conclusion: Combined treatment with memantine and AChEIs was effective in patients with AD, particularly in slowing cognitive impairment and preventing the onset of agitation and aggression in elderly AD patients. (PsycINFO Database Record (c) 2016 APA, all rights reserved) (Source: journal abstract)


Abstract: [Correction Notice: An Erratum for this article was reported in Vol 10[1997] of Neuropsychiatric Disease and Treatment (see record 2014-55356-001). On page 393, Figure 1, "Maintenance period (month 6 to 24)" should be "Maintenance period (month 4 to 24)"; "Gal at stable dose (at least 18 mg/day) as achieved on day 84 c" should be "Gal at stable dose (at least 16 mg/day) as achieved on day 84 c." The correct figure is shown in the corrigendum.] Background: Currently available treatments for Alzheimer's disease (AD) can produce mild improvements in cognitive function, behavior, and activities of daily living in patients, but their influence on long-term survival is not well established. This study was designed to assess patient survival and drug efficacy following a 2-year galantamine treatment in patients with mild to moderately severe AD. Methods: In this multicenter, double-blind study, patients were randomized 1:1 to receive galantamine or placebo. One primary end point was safety; mortality was assessed. An independent Data Safety Monitoring Board monitored mortality for the total deaths reaching prespecified numbers, using a time-to-event method and a Cox-regression model. The primary efficacy end point was cognitive change from baseline to month 24, as measured by the Mini-Mental State Examination (MMSE) score, analyzed using intent-to-treat analysis with the "last observation carried forward" approach, in an analysis of covariance model. Results: In all, 1,024 galantamine- and 1,021 placebo-treated patients received study drug, with mean age ~73 years, and mean [standard deviation (SD)] baseline MMSE score of 19 (4.08). A total of 32% of patients (661/2,045) completed the study, 27% (554/2,045) withdrew, and 41% (830/2,045) did not complete the study and were discontinued due to a Data Safety Monitoring Board-recommended early study termination. The mortality rate was significantly lower in the galantamine group versus placebo (hazard ratio [HR] =0.58; 95% confidence interval [CI]: 0.37; 0.89) (P=0.011). Cognitive impairment, based on the mean (SD) change in MMSE scores from baseline to month 24, significantly worsened in the placebo (-2.14 [4.34]) compared with the galantamine group (-1.41 [4.05]) (P<0.001). Functional impairment, based on mean (SD) change in the Disability Assessment in Dementia score (secondary end point), at month 24 significantly worsened in the placebo (-10.81 [18.27]) versus the galantamine group (-8.16 [17.25]) (P=0.002). Incidences of treatment-emergent adverse events were 54.0% for the galantamine and 48.6% for the placebo group. Conclusion: Long-term treatment with galantamine significantly reduced mortality and the decline in cognition and daily living activities, in mild to moderate AD patients. (PsycINFO Database Record (c) 2016 APA, all rights reserved)


Abstract: Though the symptoms of Alzheimer disease go on for years, the phase 3 trials of the cholinesterase inhibitors (ChEIs), the current mainstay of symptomatic pharmacotherapy for this condition, were typically of only 3- to 6-months' duration. We have limited data on long-term (that is, a year or more) therapy with these agents. In this review, we explore the available information on the biological and clinical effects of long-term ChEI therapy, what
happens when these agents are discontinued, and examine what others have recommended. An individualized approach to deciding on whether to carry on with a ChEI should be taken. If continued, treatment goals should be clarified and patients monitored over time, for both drug-related benefits and adverse effects.

Notes: [Full text available with NHS OpenAthens]

Abstract: Huperzine A (HupA), a natural inhibitor of acetylcholinesterase derived from a plant, is a licensed anti-Alzheimer's disease (AD) drug in China and a nutraceutical in the United States. In addition to acting as an acetylcholinesterase inhibitor, HupA possesses neuroprotective properties. However, the relevant mechanism is unknown. Here, we showed that the neuroprotective effect of HupA was derived from a novel action on brain iron regulation. HupA treatment reduced insoluble and soluble beta amyloid levels, ameliorated amyloid plaques formation, and hyperphosphorylated tau in the cortex and hippocampus of APPswe/PS1dE9 transgenic AD mice. Also, HupA decreased beta amyloid oligomers and amyloid precursor protein levels, and increased A Disintegrin And Metalloprotease Domain 10 (ADAM10) expression in these treated AD mice. However, these beneficial effects of HupA were largely abolished by feeding the animals with a high iron diet. In parallel, we found that HupA decreased iron content in the brain and demonstrated that HupA also has a role to reduce the expression of transferrin-receptor 1 as well as the transferrin-bound iron uptake in cultured neurons. The findings implied that reducing iron in the brain is a novel mechanism of HupA in the treatment of Alzheimer's disease. (PsycINFO Database Record (c) 2016 APA, all rights reserved)

Abstract: Background/Aims: Donepezil is an acetylcholinesterase inhibitor used to treat Alzheimer's disease (AD). In this study, we used a voxel-based specific regional analysis system for AD (VSRAD) to analyze the hippocampal volume and to assess the pharmacologic effects of donepezil as a disease modifier. Methods: A total of 185 AD patients underwent MRI, 120 (43 men and 77 women, 77.8 ± 7.1 years) without and 65 (29 men and 36 women, 78.4 ± 6.0 years) with donepezil treatment. VSRAD was compared in both groups and against a database of 80 normal subjects. The Z-score was used to assess the degree of hippocampal atrophy. Results: No significant difference between the groups was found for age, sex, or Z-scores, but a significant difference was found for mean Mini-Mental State Examination (MMSE) scores (p = 0.02, Student's t test). Single regression analysis showed no significant association between Z-scores and MMSE scores in the treated group (p = 0.494), but a significant association in the untreated group (p = 0.001) was observed. This implies that the MMSE score becomes lower when the Z-score is higher in the untreated group, whereas there is no significant trend in the treated group. Conclusion: Donepezil affects the relationship between hippocampal volume and cognitive function and may therefore have a pharmacologic effect as a disease modifier. © 2014 S. Karger AG, Basel

Abstract: Objective: Rivastigmine is commonly used for the treatment of Alzheimer's disease (AD). All cholinesterase inhibitors, including rivastigmine, may cause cardiac side effects. The aim of this study is to compare the electrocardiographic (ECG) and hypotensive effects of formulations of rivastigmine. Methods: Eighty-five newly diagnosed patients with AD who were treated with rivastigmine were retrospectively evaluated. The ECG records were reviewed at baseline and at administration of either 12 mg of oral rivastigmine or 10 cm² transdermal rivastigmine. Results: When compared with the baseline, there were no changes in any of the ECG parameters in all of the patients (P > .05). Moreover, when compared with the mean change from baseline for each treatment group, there were no changes, except heart rate (P = .035). Conclusion: It was demonstrated that rivastigmine formulations were not associated with increased arrhythmogenic or hypotensive effects in elderly patients with
AD and was not superior to each other. (PsycINFO Database Record (c) 2016 APA, all rights reserved)


Abstract: Background: Cholinesterase inhibitors (ChEIs) such as donepezil have the effect of delaying progression of Alzheimer’s disease (AD), but their effect on life expectancy is unclear. We analyzed the influence of donepezil on life expectancy after onset of AD, together with the effects of antipsychotic drugs and residency in a nursing home. Methods: All outpatients at the Tajiri Clinic from 1999-2012 with available medical records and death certificates were included in a retrospective analysis. The entry criteria were a dementia diagnosis based on DSM-IV criteria and diagnosis of AD using NINCDS-ADRDA criteria; medical treatment for more than 3 months; and follow up until less than 1 year before death. Results: We identified 390 subjects with medical records and death certificates, of whom 275 had a diagnosis of dementia that met the entry criteria. Of 100 patients diagnosed with AD, 52 had taken donepezil and 48 patients had not received the drug due to treatment prior to the introduction of donepezil in 1999 in Japan. The lifetime expectancies after onset were 7.9 years in the donepezil group and 5.3 years in the non-donepezil group. There was a significant drug effect with a significant covariate effect of nursing home residency. Other covariates did not reach a significant level. Conclusions: Although this report has the limitation of all retrospective analyses: the lack of randomization, we found a positive effect of donepezil on lifetime expectancy after onset of AD. This may be due to a decreased mortality rate caused by reduction of concomitant diseases such as pneumonia. The similar life expectancies in patients taking donepezil at home and those not taking donepezil in a nursing home indicated a positive health economic effect of the drug. (PsycINFO Database Record (c) 2016 APA, all rights reserved) (Source: journal abstract)


Abstract: Background: Cholinesterase inhibitors can delay the progression of Alzheimer’s disease (AD). Several clinical trials of the drug in moderate to severe AD have consistently reported clinically positive effects. A combining effect with psychosocial intervention was reported in mild to moderate AD patients. Since a therapeutic approach or rehabilitation combined with cholinesterase inhibitors for severe AD patients remains controversial, we performed a prospective intervention for patients in Long-Term Care Health Facilities (LTCHF). Methods: Two LTCHFs (N1, N2) were enrolled. N1 is a 126-bed facility that does not treat with donepezil but rather with psychosocial intervention (reality orientation and reminiscence). N2 is a 150-bed facility with a 50-bed special dementia unit, in which the physician can prescribe donepezil. On top of the similar psychosocial intervention, rehabilitation is performed in N2. Thirty-two severe AD patients (MMSE < 6) in N1 and N2 (16 vs. 16) were compared for the effect of donepezil (10 mg/d for 3 months) with or without psychosocial intervention (n = 8 vs. 8 for each facility). The Vitality Index was used to assess daily activities and the introduction of rehabilitation. Results: The response ratio (MMSE 3+) of donepezil was 37.5% in N2. The combination of donepezil with the psychosocial intervention improved the Vitality Index total score, and Communication, Eating, and Rehabilitation subscores (Wilcoxon, p = 0.016, 0.038, 0.023, and 0.011, respectively). Most of them were smoothly introduced to rehabilitation, and the proportion of accidental falls decreased. Psychosocial intervention in N1 without the drug only improved the total score (Wilcoxon, p = 0.046). Conclusions: A combined therapeutic approach of donepezil and psychosocial intervention can have a positive effect, even for severe patients through the introduction of rehabilitation and decreasing accidental falls. However, these findings require replication in a larger cohort. (PsycINFO Database Record (c) 2016 APA, all rights reserved) (Source: journal abstract)


Abstract: Alzheimer’s disease is a life shortening disease, and the lack of disease modifying therapy implies a huge impact on life expectancy as well as an outgrowing financial and

Abstract: Background: Alzheimer's disease (AD) is the most common cause of dementia in older patients. Rivastigmine (RV, Exelon, Novartis), a reversible cholinesterase inhibitor, improves clinical manifestations of AD and may enhance ACh-modulated electroencephalogram (EEG) alpha frequency. This pilot study aimed to determine the effects of two formulations of RV [transdermal patch (RV-TDP) and oral capsules (TV-CP)] on alpha frequency, in particular the posterior dominant rhythm, and cognitive function [assessed by the Mini-Mental State Examination (MMSE)] in patients with AD. Methods: Subjects with AD were assigned to receive either RV-TDP 10 cmÅ² or RV-CP 12 mg/day. All patients underwent EEG recordings at the beginning and end of the 18-month study period using P3, P4, O1, and O2 electrodes, each at high (10.5-13.0 Hz) and low (8.0-10.5 Hz) frequency. MMSE scores were determined at the start of the study (T0) and at three successive 6-month intervals (T1, T2, and T3). Results: RV-TDP administration (n = 10) maintained cognitive function as evidenced by stable MMSE scores from baseline to 18 months (21.07 ± 2.4-21.2 ± 3.1) compared with a decrease in MMSE score with RV-CP (n = 10) over 18 months [18.3 ± 3.6-13.6 ± 5.06 (adjusted for covariates p = 0.006)]. MMSE scores were significantly different between treatment groups from 6 months (p = 0.04). RV-TDP also increased the spectral power of alpha waves in the posterior waves measured with electrode P3 in a significantly greater proportion of patients than TV-CP from baseline to 18 months; 80% vs 30%, respectively [p = 0.025 ([tAN2 test]). Conclusions: RV-TDP was associated with a greater proportion of patients with increased posterior region alpha wave spectral power and significantly higher cognitive function at 18 months, compared with RV-CP treatment. Our findings suggest that RV-TDP provides an effective long-term management option in patients with AD compared with oral RV-CP. This study is a pilot, open-label study with a clear explorative purpose and with a small number of patients. Further randomized, double-blind, placebo-controlled trial studies with a bigger sample size as well as healthy controls are needed to support these initial results. (PsycINFO Database Record (c) 2016 APA, all rights reserved) (Source: journal abstract)


Abstract: Neurotransmitter enhancement therapy with acetylcholinesterase inhibitors (AChEIs) is a clinically proven approach for patients with Alzheimer's disease (AD). Donepezil is one of the three currently approved AChEIs for treating AD symptoms delaying the decline in cognitive function. In addition to cholinergic hypofunction, there are several factors in AD pathogenesis. For example, adipocytokines released from adipose tissue are also thought to play a role in the progress of dementia. Adipokines, i.e., leptin and adiponectin, are involved in the modulation of certain cognitive functions in the brain. The goal of our study was to elucidate effects of donepezil therapy on the serum levels of certain adipokines, such as...
leptin and adiponectin in AD patients. Clinically diagnosed mild-to-moderate AD patients (n = 26) were involved in this open-labeled, single-center, prospective self-control study. ApoE polymorphism, serum adiponectin, leptin, LDL, HDL, triglyceride levels, and BMI were determined before and at 12 and 24 weeks intervals of donepezil treatment, respectively. Twenty-four weeks of donepezil treatment induced a linear decrease of serum leptin levels (p = 0.013) and a linear elevation of serum adiponectin levels (p = 0.007). BMI (p < 0.001) and abdominal circumference (p = 0.017) were significantly lower at 24 weeks as compared to control values. None of the other examined metabolic parameters were changed during the treatment period. This previously unrecognized serum adipokine regulating potential of donepezil may be relevant in its therapeutic, disease modifying effect in AD by transferring protective (by increasing serum adiponectin levels) and detrimental (by decreasing serum leptin levels) effects onto the neurodegenerative process at the same time. (PsycINFO Database Record (c) 2016 APA, all rights reserved)


Abstract: Rationale: Mitochondrial dysfunction has been well documented in age related disorders like Alzheimer's disease. Alterations in mitochondrial membrane potential lead to neuronal death by excessive generation of free radicals, inflammatory cytokines, and excitotoxins. Intracerebroventricular (ICV) streptozotocin (STZ) induced-cognitive impairment has been widely used as an experimental model of Alzheimer's disease. Naringin is a potent antioxidant, which can cross the blood brain barrier protecting brain tissue and modulating brain chemistry. Objectives: The present study was designed to evaluate the effect of naringin, in ICV STZ-induced mitochondrial dysfunction and memory loss in rats. Methods: Streptozotocin (3mg/kg, ICV) was injected bilaterally in two divided doses on first and third day followed by treatment with different doses of naringin (50, 100 and 200mg/kg; p.o.) for twenty one days. Behavioral alterations were monitored using Morris water maze paradigm and elevated plus maze test. Animals were sacrificed to evaluate various biochemical and mitochondrial parameters in brain. Rivastigmine was used as a standard drug. Results: ICV-STZ administration produced significant cognitive deficits as assessed by both Morris water maze and elevated plus maze task. Animals were sacrificed to evaluate various biochemical and mitochondrial parameters in brain. Rivastigmine was used as a standard drug. Results: ICV-STZ administration produced significant cognitive deficits as assessed by both Morris water maze and elevated plus maze task which is accompanied by significantly enhanced oxidative-nitrosative stress, altered acetylcholinesterase and mitochondrial enzyme activities in cerebral cortex and hippocampus of rats brain along with significantly increased brain TNF-α and IL-1β levels. Chronic treatment with naringin dose dependent restored cognitive deficits in ICV-STZ rat along with mitigation of mitochondrial dysfunction mediated oxido-nitrosative stress and cytokine release. Conclusions: Our findings demonstrate that naringin ameliorates mitochondrial dysfunction mediated oxido-nitrosative stress and inflammatory surge in ICV-STZ rats. (PsycINFO Database Record (c) 2016 APA, all rights reserved)


Abstract: Background: Many factors could be responsible for the different response to treatment with the cholinesterase inhibitors (ChEIs) donepezil and rivastigmine in Alzheimer's disease (AD) patients. Sex and the variants of the estrogen receptor α (ESR1) gene are reported to modulate AD susceptibility or the course of the disease. The aim of the present study was to verify whether patient's sex and ESR1 genotype could influence the response to ChEI treatment, as there is evidence that estrogens affect cholinergic system functioning. Methods: Two ESR1 intronic polymorphisms (PvuII, rs2234693; XbaI, rs9340799) were examined in 184 AD patients: 157 were receiving treatment with donepezil or rivastigmine and 27 were receiving no treatment. Cognitive status was assessed using the mini mental state examination at four time points (1, 3, 9, and 15 months into therapy). Results: Among the patients under treatment with either ChEI, the women responded more markedly than the men. As compared with the untreated patients, the effects of treatment were statistically significant for both donepezil and rivastigmine. A significant effect of ESR1 genotypes was observed for the donepezil-treated patients, among which those carrying at least one copy of P and X alleles showed a significantly lower cognitive decline than the noncarriers. Conclusions: The present data seem to confirm a sex-related influence on treatment, as the women seemed to be more sensitive to therapy and to have experienced less cognitive
decline. ESR1 may be another gene contributing to interindividual variability in response to treatment with ChEIs. Copyright © 2013 John Wiley & Sons, Ltd. (PsycINFO Database Record (c) 2016 APA, all rights reserved) (Source: journal abstract)

Abstract: We investigated the effects of galantamine on cognitive subdomains in Alzheimer's disease (AD). Sixty-six patients with mild-to-moderate AD received open-label galantamine for 52 weeks. Cognitive function was measured using the Korean version of the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog-K). Response to galantamine was defined as "improvement or no deterioration" on the total scores of the ADAS-cog-K at 26 weeks. In the overall intent-to-treat sample, we found less cognitive decline during 26 and 52 weeks than the expected untreated course as predicted by Stern's equation. The operationally defined response rate at 26 weeks was 66.7%. The responders differed significantly from the nonresponders only in the memory and language domains but not in the domains of praxis or frontal/executive function or in secondary outcome measures of neuropsychiatric symptoms and activities of daily living. The subdomain analysis revealed an effect of galantamine on preservation of memory that was not apparent in the overall analysis. Failure to achieve responder status by 26 weeks was associated with no further possibility of response. (PsycINFO Database Record (c) 2016 APA, all rights reserved) (Source: journal abstract)

Abstract: Patients with Alzheimer's disease after an initial response to cholinesterase inhibitors may complain a later lack of efficacy. This, in association with incident neuropsychiatric symptoms, may worsen patient quality of life. Thus, the switch to another cholinesterase inhibitor could represent a valid therapeutic strategy. The aim of this study was to investigate the effectiveness of the switch from one to another cholinesterase inhibitor on cognitive and affective symptoms in mild to moderate Alzheimer disease patients. Four hundred twenty-three subjects were included from the EVOLUTION study, an observational, longitudinal, multicentre study conducted on Alzheimer disease patients who switched to different cholinesterase inhibitor due either to lack/loss of efficacy or response, reduced tolerability or poor compliance. All patients underwent cognitive and neuropsychiatric assessments, carried out before the switch (baseline), and at 3 and 6-month follow-up. A significant effect of the different switch types was found on Mini-Mental State Examination score during time, with best effectiveness on mild Alzheimer's disease patients switching from oral cholinesterase inhibitors to rivastigmine patch. Depressive symptoms, when measured using continuous Neuropsychiatric Inventory values, decreased significantly, while apathy symptoms remained stable over the 6 months after the switch. However, frequency of both depression and apathy, when measured categorically using Neuropsychiatric Inventory cut-off scores, did not change significantly during time. In mild to moderate Alzheimer disease patients with loss of efficacy and tolerability during cholinesterase inhibitor treatment, the switch to another cholinesterase inhibitor may represent an important option for slowing cognitive deterioration. The evidence of apathy stabilization and the positive tendency of depressive symptom improvement should definitively be confirmed in double-blind controlled studies. (PsycINFO Database Record (c) 2016 APA, all rights reserved) (Source: journal abstract)

Abstract: Background: The role of currently available drugs for Alzheimer's disease (AD) has been controversial, with some national formularies restricting their use, and health economists questioning whether the small clinical effects are economically worthwhile. Objective: To estimate the efficacy and safety of donepezil, galantamine, rivastigmine, and memantine for the treatment of AD. Methods: Double-blind, placebo-controlled, with random assignment to a cholinesterase inhibitor or memantine trials were included into the pooled studies. Results:
Cognitive effects were significant for all drugs, ranging from a -1.29 points mean difference (95% CI -2.30 to -0.28) in the 20 mg daily memantine trials to -3.20 points (95% CI -3.28 to -3.12) in the 32 mg daily galantamine group. Only memantine had no effect on the Clinicians’ Global Impression of Change scale. No behavioral benefits were observed, except for -2.72 (95% CI -4.92 to -0.52) in the 10 mg daily donepezil group and -1.72 (95% CI -3.12 to -0.33) for 24 mg daily galantamine trial. Only 5 mg daily donepezil had no effect on the function outcome. Compared with placebo, more dropouts and adverse events occurred with the cholinesterase inhibitors, but not with memantine. Conclusions: Cholinesterase inhibitors and memantine are able to stabilize or slow decline in cognition, function, behavior, and global change.

Drug treatments for Alzheimer’s disease

Abstract: There are currently four drug treatments licensed for the treatment of Alzheimer’s disease. The anticholinesterase drugs Aricept (donepezil), Exelon (rivastigmine) and Reminyl (galantamine) are licensed for the mild to moderate stages and Ebixa (memantine) is licensed for the moderate to severe stages. None offer a cure. However, for a proportion of people the drugs provide important benefits, particularly to mood, alertness and confidence. In January 2011 NICE published final guidance recommending that: the anticholinesterase drug treatments should be available to people in the mild to moderate stages of Alzheimer’s disease Ebixa should be available to people in the moderate stages of Alzheimer’s disease, if they cannot tolerate the anticholinesterase drugs Ebixa should be available to all in the severe stages of Alzheimer’s disease The Alzheimer’s Society welcomes the availability of these drugs. Health bodies should ensure that the NICE guidance is implemented and that people with Alzheimer’s are able to access the drugs

In people with Parkinson’s disease dementia (PDD), Parkinson’s disease cognitive impairment (CIND-PD), or dementia with Lewy bodies (DLB), what are the effects of cholinesterase inhibitors?

Abstract: Dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) are synucleinopathies that lead to neurodegeneration and dementia. Although they result in symptoms common to Alzheimer's disease, they are associated with early emergence of parkinsonism and high frequency of neuropsychiatric symptoms, most commonly hallucinations and delusions. This review summarizes the current understanding of the underlying biology of neuropsychiatric symptoms in DLB and PDD and the evidence base for treatment to address them. Disruption to cholinergic and serotonergic neurotransmission and synapse activity are highlighted as primary pathological factors in neuropsychiatric symptoms, particularly loss of key neurotransmitter functions, alterations to neuronal receptors in the serotonergic pathway, and regionally specific structural changes that are linked to specific symptoms. Review of options for pharmacological treatment of neuropsychiatric symptoms suggests that the best evidence for the value of treatment is for cholinesterase inhibitors, with an indication that people with visual hallucinations are particularly likely to benefit. Evidence for the benefits of antipsychotics other than clozapine is limited, and there are serious safety concerns about the use of antipsychotics in these patients. Evidence to support other pharmacological interventions is very preliminary. Nonpharmacological approaches based on person-centered care and cholinesterase inhibitors should be considered as the first-line treatment for neuropsychiatric symptoms except in extreme cases
rivastigmine) that improve symptoms by inhibiting acetylcholinesterase. However, apart from the beneficial palliative properties, cholinergic drugs have shown little efficacy to prevent the progression of the disease evidencing the unsuitability of this strategy for the complex nature of AD. By contrast, the multifactorial nature of this neurodegenerative disorder supports the most current innovative therapeutic approach based on the "one drug, multiple targets" paradigm, which suggests the use of compounds with multiple activities at different target sites. Accordingly, the also called multitarget-directed ligand (MTDL) approach has been the subject of increasing attention by many research groups, which have developed a variety of hybrid compounds acting on very diverse targets. The therapeutic potential of monoamine oxidase inhibitors (MAOI) in AD has been suggested due to their demonstrated neuroprotective properties besides their enhancing effect on monoaminergic transmission. Especially, those containing a propargylamine moiety are of particular interest due to their reported beneficial actions. Therefore, targeting MAO enzymes should be considered in therapeutic interventions. This review makes a special emphasis on MTDLs that commonly target MAO enzymes. There is at present an urgent need for real disease-modifying therapies for AD and the MTDL approach makes a breakthrough for the development of new drugs capable of addressing the biological complexity of this disorder. (PsycINFO Database Record (c) 2016 APA, all rights reserved)

Abstract: Dementia with Lewy bodies (DLB) is a multisystem disorder with diverse disease expression. A treatment regime restricted to the cognitive aspects of the disease does no favor to patients. Instead, patients should be educated to recognize the symptoms of this multisystem involvement. There are no treatments that slow the progression of disease, but symptomatic treatments can be effective. When thinking about treatment, we find it useful to divide the symptoms and signs into five categories: (a) cognitive features, (b) neuropsychiatric features, (c) motor dysfunction, (d) autonomic dysfunction, and (e) sleep dysfunction.
Clinicians, funding bodies and industry are increasingly recognizing the importance of this common and debilitating disease. Springer Science+Business Media New York 2013


Abstract: Life expectancy in Brazil has increased markedly over the last 30 years. Hence, age-related disorders, such as Alzheimer’s disease (AD), warrant special attention due to their high prevalence in the elderly. Pharmacologic treatment of AD is based on cholinesterase inhibitors (ChEI) and memantine, leading to modest clinical benefits both in the short and long-term. However, clinical response is heterogeneous and needs further investigation. Objective: To investigate the rate of response to ChEI in AD after three months of treatment. Methods: Patients with mild or moderate dementia due to probable AD or to AD associated with cerebrovascular disease were included in the study. The subjects were assessed at baseline and again after three months of ChEI treatment. Subjects were submitted to the Mini-Mental State Examination (MMSE), Mattis Dementia Rating Scale, Katz Basic Activities of Daily Living, Pfeffer Functional Activities Questionnaire, Neuropsychiatric Inventory and Cornell Scale for Depression in Dementia. Good response was defined by a gain of ≥ 2 points on the MMSE after three months of treatment in relation to baseline. Results: Seventy-one patients, 66 (93%) with probable AD and five (7%) with AD associated with cerebrovascular disease, were evaluated. The good response rate at three months was 31.0%, being 37.2% and 21.4% in mild and moderate dementia, respectively. There were no significant differences on most tests, except for improvement in hallucinations, agitation and dysphoria in moderate dementia patients. Conclusion: The rate of good clinical response to ChEI was higher than usually reported. Specific behavioral features significantly improved in the subgroup of moderate dementia. (PsycINFO Database Record (c) 2016 APA, all rights reserved)

Abstract: Background: Randomized clinical trials have evaluated the efficacy of acetylcholinesterase inhibitors (AChE-Is) and memantine across a wide range of Alzheimer’s disease (AD) severity. However, these drugs are prescribed and reimbursed according to precise upper and lower cut off scores of cognitive tests. Objectives: To verify whether the efficacy of pharmacological treatment had any dependence on the severity of dementia in AD patients. Methods: Published English-language randomized, placebo-controlled trials evaluating the efficacy of AChE-Is or memantine at any dose, over any length of time, in patients with any severity of dementia due to AD were included. Cognitive, behavioral, and functional outcomes were extracted from each study and multiple outcomes from the same trial were pooled to obtain a unique indicator of efficacy for cognition, functional impairment, and behavioral and psychological disturbances. The existence of a relationship between size of the treatment effect and severity of dementia, measured with the Mini-Mental State Examination, was determined using parametric and non-parametric correlation analyses. Results: Both AChE-Is and memantine had significant effects on cognition. Functional and psycho-behavioral outcomes were reported less frequently but also showed significant efficacy of treatment. High heterogeneity among studies was found within and between the different drugs. The efficacy of all drugs except memantine was independent from dementia severity in all domains. Memantine effect on functional impairment was better in more severe patients. Conclusions: The modest beneficial effects of anti-dementia drugs on cognition are independent from dementia severity. Memantine is more effective on functional incompetence only in severe patients. (PsycINFO Database Record (c) 2016 APA, all rights reserved)


Abstract: Aims: The 24-week, prospective, randomized, double-blind ACTION study investigated the efficacy, safety, and tolerability of 13.3 versus 4.6 mg/24 h rivastigmine patch in patients with severe Alzheimer's disease (AD). Methods: Patients had probable AD and Mini-Mental State Examination scores ≥3≤12. Primary outcome measures were as follows: Severe Impairment Battery (SIB) and AD Cooperative Study-Activities of Daily Living scale-Severe Impairment Version (ADCS-ADL-SIV). Secondary outcomes were as follows: ADCS-Clinical Global Impression of Change (ADCS-CGIC), 12-Item Neuropsychiatric Inventory (NPI-12), and safety/tolerability. Results: Of 1014 patients screened, 716 were randomized to 13.3 mg/24 h (N = 356) or 4.6 mg/24 h (N = 360) patch. Baseline characteristics/demographics were comparable. Completion rates were as follows: 64.3% (N = 229) with 13.3 mg/24 h and 65.0% (N = 234) with 4.6 mg/24 h patch. The 13.3 mg/24 h patch was significantly superior to 4.6 mg/24 h patch on cognition (SIB) and function (ADCS-ADL-SIV) at Week 16 (P < 0.0001 and P = 0.049, respectively) and 24 (primary endpoint; P < 0.0001 and P = 0.025). Significant between-group differences (Week 24) were observed on the ADCS-CGIC (P = 0.0023), not NPI-12 (P = 0.1437). A similar proportion of the 13.3 mg/24 h and 4.6 mg/24 h patch groups reported adverse events (AEs; 74.6% and 73.3%, respectively) and serious AEs (14.9% and 13.6%). Conclusions: The 13.3 mg/24 h patch demonstrated superior efficacy to 4.6 mg/24 h patch on SIB and ADCS-ADL-SIV, without marked increase in AEs, suggesting higher-dose patch has a favorable benefit-to-risk profile in severe AD. (PsycINFO Database Record (c) 2016 APA, all rights reserved) (Source: journal abstract)


Abstract: Introduction: Whether dementia with Lewy bodies (DLB) and Parkinson’s disease with dementia (PDD) should be considered as one entity or two distinct conditions is a matter of controversy. The aim of this study was to compare the characteristics of DLB and PDD patients using data from the Swedish Dementia Quality Registry (SveDem). Methods: SveDem is a national Web-based quality registry initiated to improve the quality of diagnostic workup, treatment, and care of patients with dementia across Sweden. Patients with newly
diagnosed dementia of various types were registered in SveDem during the years 2007-2011. The current cross-sectional report is based on DLB (n=487) and PDD (n=297) patients. Demographic characteristics, diagnostic workup, Mini-Mental State Examination (MMSE) score, and medications were compared between DLB and PDD groups. Results: No gender differences were observed between the two study groups (P=0.706). PDD patients were significantly younger than DLB patients at the time of diagnosis (74.8 versus 76.8 years, respectively; P<0.001). A significantly higher prevalence of patients with MMSE score ≤ 24 were found in the PDD group (75.2% versus 67.6%; P=0.030). The mean number of performed diagnostic modalities was significantly higher in the DLB group (4.9+/−1.7) than in the PDD group (4.1+/−1.6; P,0.001). DLB patients were more likely than PDD patients to be treated with cholinesterase inhibitors (odds ratio=2.5, 95% confidence interval=1.8-3.5), whereas the use of memantine, antidepressants, and antipsychotics did not differ between the groups. Conclusion: This study demonstrates several differences in the dementia work-up between DLB and PDD. The onset of dementia was significantly earlier in PDD, while treatment with cholinesterase inhibitors was more common in DLB patients. Severe cognitive impairment (MMSE score ≤ 24) was more frequent in the PDD group, whereas more diagnostic tests were used to confirm a DBL diagnosis. Some similarities also were found, such as gender distribution and use of memantine, antidepressants, and antipsychotics drugs. Further follow-up cost effectiveness studies are needed to provide more evidence for workup and treatment guidelines of DLB and PDD. 2013 Fereshtehnejad et al, publisher and licensee Dove Medical Press Ltd

Abstract: Background: Clinical studies and post hoc analyses have investigated the use of combination therapy for the treatment of Alzheimer's disease (AD). We review the evidence for the short- and long-term efficacy of combination therapy in AD. Methods: The review is based on a search of the PubMed database to identify relevant articles concerning combination treatment with memantine and cholinesterase inhibitors (ChEIs). Results: In patients with moderate-to-severe AD, combination treatment with the N-methyl-D-aspartate receptor antagonist memantine and the ChEI donepezil has produced significant benefits in cognition, function, behavior, global outcome, and care dependency, compared with donepezil treatment alone. Data from long-term observational studies support these findings. Compared with ChEI monotherapy, combination treatment slowed cognitive and functional decline (a 4-year sustained effect that appeared to increase over time) and reduced the risk of nursing home admission. Preclinically, the combination of N-methyl-D-aspartate receptor modulation and acetylcholinesterase inhibition has been shown to act synergistically, which may explain the observed clinical effects of combination treatment. Conclusion: Treatment with memantine/ChEI combination therapy in moderate-severe AD produces consistent benefits that appear to increase over time, and that are beyond those of ChEI treatment alone. (PsycINFO Database Record (c) 2016 APA, all rights reserved)

Abstract: Background: Stabilizing/reducing decline in the ability to perform activities of daily living (ADLs) is important in management of Alzheimer's disease (AD). Methods: Post hoc analysis of OPTIMizing Transdermal Exelon In Mild-to-moderate Alzheimer's disease (OPTIMA), a double-blind trial comparing 13.3 and 9.5 mg/24 h rivastigmine patch in patients with AD demonstrating functional and cognitive decline with 9.5 mg/24 h patch. Efficacy on Alzheimer's disease Cooperative Study-instrumental ADL (ADCS-IADL) items, higher level function (HLF), and autonomy factors was assessed. Results: The ADCS-IADL, HLF, and autonomy factors favored 13.3 mg/24 h patch at all time points, reaching significance from weeks 16 to 48, 24 to 48, and 32 to 48, respectively. Higher dose patch demonstrated significantly greater efficacy on 10 of 17 ADCS-IADL items at 1 or more time points ( P < .05 vs 9.5 mg/24 h patch). More adverse events were observed with higher dose patch; study discontinuations were similar between the doses. Conclusions: Greater efficacy of 13.3 versus 9.5 mg/24 h patch on ADL, including autonomy and HLF factors, supports this
additional dosing option to prolong patients’ independence. (PsycINFO Database Record (c) 2016 APA, all rights reserved) (Source: journal abstract)

Abstract: Introduction: Immediate-release memantine (10 mg, twice daily) is approved in the USA for moderate-to-severe Alzheimer’s disease (AD). This study evaluated the efficacy, safety, and tolerability of a higher-dose, once-daily, extended-release formulation in patients with moderate-to-severe AD concurrently taking cholinesterase inhibitors. Methods: In this 24-week, double-blind, multinational study (NCT00322153), outpatients with AD (Mini-Mental State Examination scores of 3-14) were randomized to receive once-daily, 28-mg, extended-release memantine or placebo. Co-primary efficacy parameters were the baseline-to-endpoint score change on the Severe Impairment Battery (SIB) and the endpoint score on the Clinician’s Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus). The secondary efficacy parameter was the baseline-to-endpoint score change on the 19-item Alzheimer’s Disease Cooperative Study-Activities of Daily Living (ADCS-ADL19) additional parameters included the baseline-to-endpoint score changes on the Neuropsychiatric Inventory (NPI) and verbal fluency test. Data were analyzed using a two-way analysis of covariance model, except for CIBIC-Plus (Cochran-Mantel-Haenszel test). Safety and tolerability were assessed through adverse events and physical and laboratory examinations. Results: A total of 677 patients were randomized to receive extended-release memantine (n = 342) or placebo (n = 335); completion rates were 79.8 and 81.2 %, respectively. At endpoint (week 24, last observation carried forward), memantine-treated patients significantly outperformed placebo-treated patients on the SIB (least squares mean difference [95 % CI] 2.6 [1.0, 4.2]; p = 0.001), CIBIC-Plus (p = 0.008), NPI (p = 0.005), and verbal fluency test (p = 0.004); the effect did not achieve significance on ADCS-ADL19 (p = 0.177). Adverse events with a frequency of ≥ 5.0 % that were more prevalent in the memantine group were headache (5.6 vs. 5.1 %) and diarrhea (5.0 vs. 3.9 %). Conclusion: Extended-release memantine was efficacious, safe, and well tolerated in this population. (PsycINFO Database Record (c) 2016 APA, all rights reserved) (Source: journal abstract)

Abstract: Background/Aims: To investigate the safety and efficacy of long-term administration (52 weeks) of donepezil in patients with dementia with Lewy bodies (DLB). Methods: This was a 52-week, multicenter, open-label extension study. Up to 8 weeks after the completion of the preceding randomized, placebo-controlled trial (RCT), patients started treatment with 3 mg of donepezil daily for 2 weeks, followed by 5 mg daily for the remaining 50 weeks. Cognitive function, behavioral and psychiatric symptoms, cognitive fluctuations, and caregiver burden were assessed using the Mini-Mental State Examination, Neuropsychiatric Inventory, Cognitive Fluctuation Inventory, and the Zarit Caregiver Burden Interview, respectively. Safety parameters were monitored throughout. Results: In total, 108 patients were enrolled in the study. Cognitive function and dementia-related behavioral symptoms, including cognitive fluctuations, were improved after the start of donepezil treatment, and improvement was maintained for 52 weeks. Reduction in caregiver burden observed in the preceding RCT returned to the baseline level at 52 weeks. There was no significant imbalance in the incidence of adverse events (AEs) by onset time, and delayed AE onset induced by the long-term administration of donepezil was unlikely to appear. Conclusion: The long-term administration of donepezil at 5 mg/day was well tolerated in patients with DLB and is expected to exhibit lasting effects, improving impaired cognitive function and psychiatric symptoms up to 52 weeks. © 2013 S. Karger AG, Basel

Abstract: Clinical trials have shown the benefits of acetylcholinesterase inhibitors, such as donepezil and galantamine, and an N-methyl-d-aspartate receptor antagonist, memantine, in patients with Alzheimer's disease (AD). However, little is known regarding the effects of switching from donepezil 5 mg/day to galantamine 16 or 24 mg/day, or regarding the effects of adding memantine to established therapy compared with increasing the dose of donepezil. This report discusses two studies conducted to evaluate treatment with galantamine and memantine with respect to cognitive benefits and caregiver evaluations in patients with AD receiving donepezil 5 mg/day for more than 6 months. Patients with mild or moderate AD (scores 10-22 on the Mini-Mental State Examination) were enrolled in the Galantamine Switch study and switched to galantamine (maximum doses 16 mg versus 24 mg). Patients with moderate to severe AD (Mini-Mental State Examination scores 3-14) were enrolled in the Donepezil Increase versus Additional Memantine study and either had their donepezil dose increased to 10 mg/day or memantine 20 mg/day added to their existing donepezil dose. Patients received the study treatment for 28 weeks and their Disability Assessment for Dementia, Mental Function Impairment Scale, Cohen-Mansfield Agitation Inventory, and Neuropsychiatric Inventory scores were assessed with assistance from their caregivers. For the Galantamine Switch study after 8 weeks, agitation evaluated by the Cohen-Mansfield Agitation Inventory improved in both the 16 mg and 24 mg groups compared with baseline. However, there were no significant differences between the two galantamine groups. Agitation was also less in patients in the additional memantine group than in the donepezil increase group. In summary, switching to galantamine from donepezil and addition of memantine in patients with AD receiving donepezil were both safe and meaningful treatment options, and particularly efficacious for suppression of agitation. 


Abstract: Presents a study which aims to explore related outcomes in patients with mild to moderate Alzheimer's disease (AD) initiating acetylcholinesterase inhibitor therapy. This study is a prospective, observational, longitudinal, multicentre survey evaluating sleep quality in AD patients initiating acetylcholinesterase inhibitor (AChEI) treatment. Data for this study were collected at AChEI initiation and after 3 to 6 months follow up and a total of baseline cohort included 950 patients. Results reported that 23% patients of the 746 had impaired sleep quality and at the baseline, 42% of patients exhibited at least one symptom described by the Sleep Disorders Inventory (SDI). This study identified factors associated with impaired quality of sleep in patients with mild to moderate AD initiating AChEI therapy. In some individuals, improvements in sleep related outcomes may be apparent after starting AChEI treatment, and benefits associated with improving sleep may therefore accrue.


Abstract: Dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) belong to the a-synucleinopathies, pathologically characterized by aggregation of a-synuclein in Lewy bodies in the brain (Table 35.1). Dementia in Parkinson's disease (PD) typically develops several years after the motor symptoms, but in a subgroup of PD patients, mild cognitive impairment (MCI) has been found from the very start of motor symptoms (Aarsland et al., 2009a) and some of these patients develop dementia rapidly. In DLB the dementia syndrome develops simultaneously or within a year after motor parkinsonism, or dementia develops simultaneously with the other core symptoms, i.e. well-formed visual hallucinations and cognitive fluctuations (McKeith et al., 2005). The cognitive profile of the Lewy body dementias, i.e. DLB and PDD, is characterized by attentional, executive, and visuospatial impairment, but memory impairment is also common. Persons with DLB and PDD have more sleep disturbances, neuropsychiatric symptoms, autonomic dysfunction, a higher tendency to fall, faster admission to a nursing home, more impaired quality of life, use more resources, and may have a faster progression of cognitive decline and shorter survival compared to persons with Alzheimer's disease (AD), thus underlining the clinical importance of the condition. Some of these patients have particularly good response to treatment with the cholinesterase inhibitors (ChEIs) and some develop neuroleptic hypersensitivity syndrome.
and thus an accurate diagnosis of DLB and PDD is essential in clinical practice. (PsycINFO Database Record (c) 2017 APA, all rights reserved) (Source: chapter)


Abstract: This article aimed to determine if simultaneous administration of rivastigmine patches and massage (patch-massage) improved behavioral and psychological symptoms of dementia (BPSD), compared with rivastigmine patches alone (patch only). This study randomly assigned 20 patients with BPSD into patch-massage and patch only groups. Caregivers applied the patch to the patient's back once daily and at the same time administered massage on an acupuncture point. The present study suggested that the combination of rivastigmine patches and massage might improve BPSD. In eastern medicine, Shinchuu is reported to be one of the points to calm the mind. Caregivers reported gradual improvements of resistive or violent attitudes and explanations of patients towards them. Patients with BPSD would often have little communication with caregivers and not receive gentle skin touch. More incremented doses of rivastigmine patches and massage might be effective for both BPSD and cognitive function in patients with moderate-to-severe Alzheimer's disease. Even minimal-dose rivastigmine patches and massage might help control BPSD in these patients. (PsycINFO Database Record (c) 2016 APA, all rights reserved)


Abstract: Here we investigated the effect of the rivastigmine patch alone on depression in 50 mild Alzheimer's Disease (AD) patients with comorbid major depressive episode (MDE). First diagnosis acetyl-cholinesterase inhibitor and psychoactive drug-free outpatients (n = 50) were recruited in memory clinics and reassessed after 3 and 6 months. Global cognitive functioning, depressive symptoms and MDE frequency were evaluated with the Mini Mental State Examination, the CERAD Dysphoria scale and the modified DSM-IV criteria for MDE in AD. MDE frequency reduced significantly from the first diagnostic visit (100%) to the 6-month follow-up (62%). We also found a significant reduction in CERAD Dysphoria scores that decreased from 6.2 ± 3.9 mean±standard deviation to 4.9 ± 4.5 at the 6-month follow-up. In AD patients with MDE rivastigmine alone can have a positive impact on depressive phenomena. Thus, future controlled study are justified to definitively verify if rivastigmine alone may improve depression in AD. (PsycINFO Database Record (c) 2017 APA, all rights reserved)


Abstract: Despite the frequency and importance of dementia associated with Parkinson's disease (PDD) and dementia with Lewy bodies (DLB), there is relatively little evidence on which to base treatment. Evidence from meta-analysis suggests that rivastigmine can improve cognition and functioning in PDD and also reduce risk of falling. There is also evidence supporting its use in DLB. Recent evidence suggests that memantine may also be effective, particularly for PDD, although evidence is more conflicting. Memantine may also improve parkinsonism and dyskinesias. Few clinical trials of cognition in PD without dementia exist, but there is preliminary evidence for atomoxetine, memantine, and piriibedil. There is a lack of systematic evidence for the treatment of visual hallucinations and depression in PDD and DLB. In addition, there is a need for studies of whether potentially disease-modifying agents can prevent or delay the progression to dementia in PD.


Abstract: Clinical features at onset of Creutzfeldt-Jakob disease (CJD) may mimic symptoms of Lewy bodies dementia. Clinical evolution, neuroimaging, metabolism exploration, and
Abstract: Acetylcholinesterase inhibitors are commonly used to treat patients with dementia with Lewy bodies. Hippocampal atrophy on magnetic resonance imaging and amyloid-beta load on positron emission tomography are associated with the Alzheimer's disease-related pathology in patients with dementia with Lewy bodies. To date, few studies have investigated imaging markers that predict treatment response in patients with dementia with Lewy bodies. Our objective was to determine whether imaging markers of Alzheimer's disease-related pathology such as hippocampal volume, brain amyloid-beta load on (11)C Pittsburgh compound B positron emission tomography predict treatment response to acetylcholinesterase inhibitors in patients with dementia with Lewy bodies. We performed a retrospective analysis on consecutive treatment-naive patients with dementia with Lewy bodies (n = 54) from the Mayo Clinic Alzheimer's Disease Research Centre who subsequently received acetylcholinesterase inhibitors and underwent magnetic resonance imaging with hippocampal volumetry. Baseline and follow-up assessments were obtained with the Mattis Dementia Rating Scale. Subjects were divided into three groups (reliable improvement, stable, or reliable decline) using Dementia Rating Scale reliable change indices determined previously. Associations between hippocampal volumes and treatment response were tested with analysis of covariance adjusting for baseline Mattis Dementia Rating Scale age, gender, magnetic resonance field strength and Dementia Rating Scale interval. Seven subjects underwent (11)C Pittsburgh compound B imaging within 12 weeks of magnetic resonance imaging. Global cortical (11)C Pittsburgh compound B retention (scaled to cerebellar retention) was calculated in these patients. Using a conservative psychometric method of assessing treatment response, there were 12 patients with reliable decline, 29 stable cases and 13 patients with reliable improvement. The improvers had significantly larger hippocampi than those that declined (P = 0.02) and the stable (P = 0.04) group. An exploratory analysis demonstrated larger grey matter volumes in the temporal and parietal lobes in improvers compared with those who declined (P < 0.05). The two patients who had a positive (11)C Pittsburgh compound B positron emission tomography scan declined and those who had a negative (11)C Pittsburgh compound B positron emission tomography scan improved or were stable after treatment. Patients with dementia with Lewy bodies who do not have the imaging features of coexistent Alzheimer's disease-related pathology are more likely to cognitively improve with acetylcholinesterase inhibitor treatment.


Abstract: OBJECTIVE: Because cholinergic deficits are prominent in dementia with Lewy bodies (DLB), we investigated the effects of a cholinesterase inhibitor, donepezil, in such patients in a randomized, double-blind, placebo-controlled exploratory phase 2 trial. METHODS: One-hundred forty patients with DLB, recruited from 48 specialty centers in Japan, were randomly assigned to receive placebo or 3, 5, or 10 mg of donepezil hydrochloride daily for 12 weeks (n = 35, 35, 33, and 37, respectively). Effects on cognitive function were assessed using the Mini-Mental State Examination (MMSE) and several domain-specific neuropsychological tests. Changes in behavior were evaluated using the Neuropsychiatric Inventory, caregiver burden using the Zarit Caregiver Burden Interview, and global function using the Clinician's Interview-Based Impression of Change-plus Caregiver Input (CIBIC-plus). Safety measures included the Unified Parkinson's Disease Rating Scale part III. RESULTS: Donepezil at 5 and 10 mg/day was significantly superior to placebo on both the MMSE (5 mg: mean difference, 3.8; 95% confidence interval (CI), 2.3-5.3; p < 0.001; 10 mg: mean difference, 2.4; 95% CI, 0.9-3.9; p = 0.001) and CIBIC-plus (p < 0.001 for each); 3 mg/day was significantly superior to placebo on CIBIC-plus (p < 0.001), but not on the MMSE (p = 0.017). Significant improvements were found also in behavioral measures (p < 0.001) at 5 and 10 mg/day and caregiver burden (p = 0.004) at 10 mg/day. The safety results were consistent with the known profile of donepezil and similar among groups.
INTERPRETATION: Donepezil at 5 and 10mg/day produces significant cognitive, behavioral, and global improvements that last at least 12 weeks in DLB patients, reducing caregiver burden at the highest dose. Donepezil is safe and well tolerated.

PT - Multicenter Study
PT - Randomized Controlled Trial


Abstract: BACKGROUND: Previous Cochrane reviews have considered the use of cholinesterase inhibitors in both Parkinson's disease with dementia (PDD) and dementia with Lewy bodies (DLB). The clinical features of DLB and PDD have much in common and are distinguished primarily on the basis of whether or not parkinsonism precedes dementia by more than a year. Patients with both conditions have particularly severe deficits in cortical levels of the neurotransmitter acetylcholine. Therefore, blocking its breakdown using cholinesterase inhibitors may lead to clinical improvement. OBJECTIVES: To assess the efficacy, safety and tolerability of cholinesterase inhibitors in dementia with Lewy bodies (DLB), Parkinson's disease with dementia (PDD), and cognitive impairment in Parkinson's disease falling short of dementia (CIND-PD) (considered as separate phenomena and also grouped together as Lewy body disease). SEARCH METHODS: The trials were identified from a search of ALOIS, the Specialised Register of the Cochrane Dementia and Cognitive Improvement Group (on 30 August 2011) using the search terms Lewy, Parkinson, PDD, DLB, LBD. This register consists of records from major healthcare databases (MEDLINE, EMBASE, PsycINFO, CINAHL) and many ongoing trial databases and is updated regularly. Reference lists of relevant studies were searched for additional trials. SELECTION CRITERIA: Randomised, double-blind, placebo-controlled trials assessing the efficacy of treatment with cholinesterase inhibitors in DLB, PDD and cognitive impairment in Parkinson's disease (CIND-PD). DATA COLLECTION AND ANALYSIS: Data were extracted from published reports by one review author (MR). The data for each 'condition' (that is DLB, PDD or CIND-PD) were considered separately and, where possible, also pooled together. Statistical analysis was conducted using Review Manager version 5.0.

MAIN RESULTS: Six trials met the inclusion criteria for this review, in which a total of 1236 participants were randomised. Four of the trials were of a parallel group design and two cross-over trials were included. Four of the trials included participants with a diagnosis of Parkinson's disease with dementia (Aarsland 2002a; Dubois 2007; Emre 2004; Ravina 2005), of which Dubois 2007 remains unpublished. Leroi 2004 included patients with cognitive impairment and Parkinson's disease (both with and without dementia). Patients with dementia with Lewy bodies (DLB) were included in only one of the trials (McKeith 2000). For global assessment, three trials comparing cholinesterase inhibitor treatment to placebo in PDD (Aarsland 2002a; Emre 2004; Ravina 2005) reported a difference in the Alzheimer's Disease Cooperative Study- Clinical Global Impression of Change (ADCS-CGIC) score of -0.38, favouring the cholinesterase inhibitors (95% CI -0.56 to -0.24, P < 0.0001). For cognitive function, a pooled estimate of the effect of cholinesterase inhibitors on cognitive function measures was consistent with the presence of a therapeutic benefit (standardised mean difference (SMD) -0.34, 95% CI -0.46 to -0.23, P < 0.00001). There was evidence of a positive effect of cholinesterase inhibitors on the Mini-Mental State Examination (MMSE) in patients with PDD (WMD 1.09, 95% CI 0.45 to 1.73, P = 0.0008) and in the single PDD and CIND-PD trial (WMD 1.05, 95% CI 0.42 to 1.68, P = 0.01) but not in the single DLB trial. For behavioural disturbance, analysis of the pooled continuous data relating to behavioural disturbance rating scales favoured treatment with cholinesterase inhibitors (SMD -0.20, 95% CI -0.36 to -0.04, P = 0.01). For activities of daily living, combined data for the ADCS and the Unified Parkinson's Disease Rating Scale (UPDRS) activities of daily living rating scales favoured treatment with cholinesterase inhibitors (SMD -0.20, 95% CI -0.38 to -0.02, P = 0.03). For safety and tolerability, those taking a cholinesterase inhibitor were more likely to experience an adverse event (318/452 versus 668/842; odds ratio (OR) 1.64, 95% CI 1.26 to 2.15, P = 0.0003) and to drop out (128/465 versus 45/279; OR 1.94, 95% CI 1.33 to 2.84, P = 0.0006). Adverse events were more common amongst those taking rivastigmine (357/421 versus 173/240; OR 2.28, 95% CI 1.53 to 3.38, P < 0.0001) but not those taking donepezil (311/421 versus 145/212; OR 1.24, 95% CI 0.86 to 1.80, P = 0.25). Parkinsonian symptoms in particular tremor (64/739 versus 12/352;
OR 2.71, 95% CI 1.44 to 5.09, P = 0.002), but not falls (P = 0.39), were reported more commonly in the treatment group but this did not have a significant impact on the UPDRS (total and motor) scores (P = 0.71). Fewer deaths occurred in the treatment group than in the placebo group (4/465 versus 9/279; OR 0.28, 95% CI 0.09 to 0.84, P = 0.03). AUTHORS’ CONCLUSIONS: The currently available evidence supports the use of cholinesterase inhibitors in patients with PDD, with a positive impact on global assessment, cognitive function, behavioural disturbance and activities of daily living rating scales. The effect in DLB remains unclear. There is no current disaggregated evidence to support their use in CIND-PD.

Abstract: Parkinson’s disease dementia (PDD) and dementia with Lewy bodies (DLB) account for 10-15% of late onset dementias. Key treatment targets include cognitive and functional impairments, neuropsychiatric symptoms including intense and persistent visual hallucinations, and parkinsonism. Six-month, placebo-controlled randomized controlled trials (RCTs) of the cholinesterase inhibitor rivastigmine have indicated modest but significant benefits in cognition, function, global outcome and neuropsychiatric symptoms in both PDD and DLB. The evidence base for other cholinesterase inhibitors from RCTs is inconclusive. More recent RCTs with memantine in PDD/DLB patients indicate a benefit with regard to global outcome, with some suggestion of a specific benefit with respect to sleep disturbance. Given the risk of severe antipsychotic sensitivity reactions, antipsychotics should be avoided. A significant proportion of PDD/DLB patients are responsive to levodopa, but care needs to be taken with anti-parkinsonian treatments because of their potential propensity to exacerbate neuropsychiatric symptoms, particularly hallucinations.

Abstract: Dementia with Lewy bodies (DBL) is often associated with occipital hypometabolism or hypoperfusion, as well as deficits in cholinergic neurotransmission. In this study, 11 mild DBL, 16 mild AD and 16 age-matched controls underwent arterial spin-labeled perfusion MRI (ASL-pMRI) and neuropsychological testing. Patterns of cerebral blood flow (CBF) and cognitive performance were compared. In addition, combined ASL-pMRI and ChEI drug challenge (pharmacologic MRI) was tested as a probe of cholinergic function in 4 of the DBL participants. Frontal and parieto-occipital hypoperfusion was observed in both DBL and AD but was more pronounced in DBL. Following ChEI treatment, perfusion increased in temporal and parieto-occipital cortex, and cognitive performance improved on a verbal fluency task. If confirmed in a larger study, these results provide further evidence for brain cholinergic dysfunction in DBL pathophysiology, and use of pharmacologic MRI as an in vivo measure of cholinergic function.

Abstract: AIM: The behavioral and psychological symptoms of dementia place a heavy burden on caregivers. Antipsychotic drugs, though used to reduce the symptoms, frequently decrease patients’ activities of daily living and reduce their quality of life. Recently, it was suggested that ferulic acid is an effective treatment for behavioral and psychological symptoms. We have also reported several patients with dementia with Lewy bodies showing good responses to ferulic acid and Angelica archangelica extract (Feru-guard). The present study investigated the efficacy of Feru-guard in the treatment of behavioral and psychological symptoms in frontotemporal lobar degeneration and dementia with Lewy bodies. METHODS: We designed a prospective, open-label trial of daily Feru-guard (3.0 g/day) lasting 4 weeks in
20 patients with frontotemporal lobar degeneration or dementia with Lewy bodies. Behavioral and psychological symptoms of dementia were assessed at baseline and 4 weeks after the start of treatment, using the Neuropsychiatric Inventory. The Neuropsychiatric Inventory scores were analyzed using the Wilcoxon rank sum test. RESULTS: Treatment with Feruguard led to decreased scores on the Neuropsychiatric Inventory in 19 of 20 patients and significantly decreased the score overall. The treatment also led to significantly reduced subscale scores on the Neuropsychiatric Inventory ("delusions", "hallucinations", "agitation/aggression", "anxiety", "apathy/indifference", "irritability/lability" and "aberrant behavior"). There were no adverse effects or significant changes in physical findings or laboratory data. CONCLUSION: Feruguard may be effective and valuable for treating the behavioral and psychological symptoms of dementia in frontotemporal lobar degeneration and dementia with Lewy bodies.

PT - Clinical Trial


Abstract: Dementia more than one year after the onset of motor features associated with Parkinson's disease is defined as Parkinson's disease with dementia (PDD). If it develops within one year of the motor features, the term dementia with Lewy bodies (DLB) is used. Since clinical and pathological features are similar, it is generally accepted that both represent a continuum of the same disorder. PDD together with DLB account for around one fifth of all cases of dementia in the elderly. Studies suggest that most patients with Parkinson’s disease would eventually develop dementia if they lived long enough. The diagnosis of PDD in the presence of long-standing pronounced motor features rarely poses a diagnostic dilemma. However, the diagnosis of DLB may be more difficult. It relies on the revised consensus clinical criteria which require the presence of at least two of the following three syndromes: persistent visual hallucinations, fluctuating defects in cognitive and functional ability, and parkinsonism. An early referral to a specialist clinic may not only help to confirm the diagnosis, but also to co-ordinate the group of professionals working with the patient. Well lit rooms and the use of glasses and hearing aids can help to reduce hallucinations. Cholinesterase inhibitors used in Alzheimer's disease have a role in DLB and PDD. Trials show moderate improvements in cognitive function in patients treated with rivastigmine. The greatest impact, however, seems to be on the psychotic features of the disease. Patients with DLB are less likely to have a good motor response from L-dopa than patients with Parkinson's disease or PDD.


Abstract: BACKGROUNDThe aetiology of visual hallucinations is poorly understood in dementia with Lewy bodies. Pathological alterations in visual cortical excitability may be one contributory mechanism. AIMSTo determine visual cortical excitability in people with dementia with Lewy bodies compared with aged-matched controls and also the relationship between visual cortical excitability and visual hallucinations in dementia with Lewy bodies.METHODVisual cortical excitability was determined by using transcranial magnetic stimulation (TMS) applied to the occiput to elicit phosphenes (transient subjective visual responses) in 21 patients with dementia with Lewy bodies and 19 age-matched controls. RESULTSPhosphene parameters were similar between both groups. However, in the patients with dementia with Lewy bodies, TMS measures of visual cortical excitability correlated strongly with the severity of visual hallucinations (P = 0.005). Six patients with dementia with Lewy bodies experienced visual hallucination-like phosphenes (for example, seeing people or figures on stimulation) compared with none of the controls (P = 0.02). CONCLUSIONS Increased visual cortical excitability in dementia with Lewy bodies does not appear to explain visual hallucinations but it may be a marker for their severity.

Abstract: Objective: The purpose of this review is to aid primary care providers in distinguishing dementia with Lewy bodies (DLB) from Alzheimer's disease and from Parkinson's disease with dementia. Differentiating these entities has important treatment implications. Data Sources: A PubMed search was undertaken using the keywords Lewy body dementia, dementia with Lewy bodies, and Lewy body disease. There were no date restrictions. Only articles in the English language were reviewed. References of selected articles were reviewed for additional sources. Data Selection and Extraction: Initially, 2,967 articles were retrieved. All 3 authors participated in data selection and extraction. Articles were further selected for content specific to epidemiology, clinical presentation, diagnostic studies, treatment, and prognosis. For articles with repetitive information, the most current article was used. This resulted in a total of 62 articles included in the review. Data Synthesis: Dementia with Lewy bodies is the second leading cause of dementia after Alzheimer's disease. The core symptoms of DLB, including cognitive fluctuations, visual hallucinations, and parkinsonism, may not always be present as a triad, and clinicians may be unaware of associated symptoms. Thus, this diagnosis is frequently missed by primary care providers. Often, DLB is misdiagnosed as Alzheimer's disease, Parkinson's disease, or a primary psychiatric illness. Treatments for DLB include cholinesterase inhibitors and N-methyl-d-aspartate antagonists. Antipsychotics should be avoided or used with caution. Conclusions: Dementia with Lewy bodies is an often missed diagnosis. Symptoms are often attributed to other disorders. A high clinical suspicion is helpful in accurate diagnosis, and presence of any of the core symptoms should initiate clinical suspicion of DLB. Distinguishing DLB from other disorders has important treatment implications. 2011 Physicians Postgraduate Press, Inc


Abstract: Hallucinations in Alzheimer's disease (AD) may indicate greater cortical cholinergic deficits. Rivastigmine has shown larger treatment benefits versus placebo in dementia with Lewy bodies and Parkinson's disease dementia patients with hallucinations. In this retrospective, hypothesis-generating analysis, we investigated whether hallucinations in AD were associated with greater treatment benefits with rivastigmine. Data were pooled from two randomized, double-blind, 6-month, mild-to-moderate AD trials comparing rivastigmine with placebo. Co-primary efficacy parameters were the Alzheimer Disease Assessment Scale-cognitive subscale (ADAS-cog) and Clinician's Interview-Based Impression of Change plus Caregiver Input (CIBIC-plus). Efficacy data were analyzed for two sub-populations: those with and those without hallucinations at baseline. Of 927 patients, 194 (21%) reported hallucinations at baseline. Hallucinators tended to have greater decline on placebo on all outcome measures. On the ADAS-cog, mean rivastigmine-placebo differences of 3.7 points in hallucinators and 2.2 points in non-hallucinators were reported at 6 months (both p < 0.001). In hallucinators, a significant rivastigmine-placebo difference of a "-0.1.0 points (a beneficial effect) was seen on the CIBIC-plus at 6 months (p < 0.001). Non-hallucinators showed a smaller significant treatment difference of a "-0.3 points (p < 0.05). Interaction testing suggested that differences in treatment effects were significant between hallucinators and non-hallucinators. Hallucinations predicted greater treatment responses to oral rivastigmine. (PsycINFO Database Record (c) 2016 APA, all rights reserved)


Abstract: Cholinesterase inhibitors (ChEIs) are widely licensed for the symptomatic treatment of Alzheimer's disease, but their use has also been examined in a wide variety of neurological disorders besides Alzheimer's disease, and this article reviews these uses. The evidence currently available suggests that ChEIs may possibly have a role in the treatment of some patients with dementia with Lewy bodies and Parkinson's disease dementia, but at this point in time there would seem to be only a limited case for recommending ChEIs in mild cognitive impairment, Down syndrome, progressive supranuclear palsy, pure vascular dementia, frontotemporal lobar degeneration, Huntington's disease, multiple sclerosis, epilepsy, delirium, traumatic brain injury, sleep-related disorders or certain psychiatric disorders (e.g., schizophrenia and bipolar disorder). Clinical practice with respect to non-Alzheimer's disease indications for ChEIs may vary according to jurisdiction, specifically with regards to whether
national guidelines effectively limit off-licence drug use. (PsycINFO Database Record (c) 2016 APA, all rights reserved) (Source: journal abstract)

(154) Liang X, Liu K, Guo L. Repetitive transcranial magnetic stimulation (rTMS): a possible novel therapeutic approach to dementia with Lewy bodies. Med Hypotheses 2010; 74(5):877-879. Abstract: Dementia with Lewy bodies (DLB) is characterized clinically by widespread cognitive loss, visual hallucinations, depression, anxiety and extrapyramidal signs (EPS). DLB is sensitive to typical neuroleptics. Repetitive transcranial magnetic stimulation (rTMS) has been studied as a potential treatment in many neurological disorders, which has been proved to have positive effect on a variety of cognitive functions, hallucinations of schizophrenia, major depression, anxiety, the Parkinson's disease. This report proposes that rTMS may represent an alternative strategy for the treatment of dementia with Lewy bodies

(155) Mollenhauer B, Forstl H, Deuschl G, Storch A, Oertel W, Trenkwalder C. Lewy body and parkinsonian dementia: common, but often misdiagnosed conditions. Dtsch Arztebl Int 2010; 107(39):684-691. Abstract: BACKGROUND: Dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) are the two most common types of dementing neurodegenerative disease after Alzheimer's disease (AD). Both of these conditions are often diagnosed late or not at all. METHODS: Selective literature review. RESULTS: The severe cholinergic and dopaminergic deficits that are present in both DLB and PDD produce not only motor manifestations, but also cognitive deficits, mainly in the executive and visual-constructive areas, as well as psychotic manifestations such as visual hallucinations, delusions, and agitation. The intensity of these manifestations can fluctuate markedly over the course of the day, particularly in DLB. Useful tests for differential diagnosis include magnetic resonance imaging and electroencephalography; in case of clinical uncertainty, nuclear medical procedures and cerebrospinal fluid analysis can be helpful as well. Neuropathological studies have revealed progressive alpha-synuclein aggregation in affected areas of the brain. In DLB, beta-amyloid abnormalities are often seen as well. CONCLUSION: DLB should be included in the differential diagnosis of early dementia. If motor manifestations arise within one year (DLB), dopaminergic treatment should be initiated. On the other hand, patients with Parkinson's disease should undergo early screening for signs of dementia so that further diagnostic and therapeutic steps can be taken in timely fashion, as indicated. Cholinesterase inhibitors are useful for the treatment of cognitive deficits and experiential/behavioral disturbances in both DLB (off-label indication) and PDD (approved indication)

(156) Satoh M, Ishikawa H, Meguro K, Kasuya M, Ishii H, Yamaguchi S. Improved visual hallucination by donepezil and occipital glucose metabolism in dementia with Lewy bodies: the Osaki-Tajiri project. Eur Neurol 2010; 64(6):337-344. Abstract: Deficits in the cholinergic system are pronounced in dementia with Lewy bodies (DLB) and are more severe in patients with visual hallucinations (VHs). The aim is to identify the occipital glucose metabolism patterns by positron emission tomography (PET) and the changes following donepezil treatment. 13 DLB patients with VHs were enrolled in the study. After the first FDG-PET study, 5 mg/day donepezil was administered orally, and a second PET study was performed 3 months later. After donepezil administration, VHs disappeared completely in 6 patients, and the PET studies revealed significantly decreased glucose metabolism in the medial occipital cortex. These results suggest that VHs in DLB were associated with impaired glucose metabolism in the medial occipital cortex. Donepezil treatment may modify regional glucose metabolism

(157) Schultz K, Nilsson K, Nielsen JE, Lindquist SG, Hjermind LE, Andersen BB et al. Transthyretin as a potential CSF biomarker for Alzheimer's disease and dementia with Lewy bodies: effects of treatment with cholinesterase inhibitors. Eur J Neurol 2010; 17(3):456-460. Abstract: BACKGROUND: Previous studies have indicated that transthyretin (TTR) levels in cerebrospinal fluid (CSF) are altered in depression and dementia. The present study aimed to
investigate whether CSF TTR can be used to discriminate between patients with Alzheimer’s disease (AD) and patients with dementia with Lewy bodies (DLB) with or without medication, as well as to reveal whether CSF TTR correlates with depression in dementia. METHODS: CSF samples from 59 patients with AD, 13 patients with DLB and 13 healthy controls were collected, and biochemical analysis was performed. Subjects were assessed for the presence of depression. RESULTS: No significant differences in CSF TTR were found between AD, DLB, and control subjects or between depressed and non-depressed dementia patients. Interestingly, we found a significant reduction in CSF TTR (14%) in AD patients who were medicated with cholinesterase inhibitors compared to those AD patients who were not. CONCLUSIONS: Significant reductions in CSF TTR were found after cholinesterase inhibitor treatment in patients with AD compared to untreated individuals. CSF TTR was unaltered in patients with DLB and had no relationship to depression in the present cohort with dementias

Abstract: Background: Dementia with Lewy bodies (DLB) and Parkinson’s disease dementia (PDD) are common forms of dementia that substantially affect quality of life. Currently, the only treatment licensed for PDD is rivastigmine, and there are no licensed treatments for DLB. We aimed to test the safety and efficacy of the N-methyl D-aspartate (NMDA) receptor antagonist memantine in patients with PDD or DLB. Methods: We did a parallel-group, 24-week, randomised controlled study of memantine (20 mg per day) versus placebo at four psychiatric and neurological outpatient clinics in Norway, Sweden, and the UK during 2005-08. Patients were included if they fulfilled the UK Parkinson’s Disease Society Brain Bank clinical diagnostic criteria for Parkinson’s disease (PD) and developed dementia according to the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM IV) criteria at least 1 year after the onset of motor symptoms (PDD) or met the revised consensus operationalised criteria for DLB. Patients were assigned to a computer-generated randomisation list. All physicians who had contact with patients were masked to treatment allocation. The primary outcome measure was clinical global impression of change (CGIC), which ranged from 1 to 7 points, and a low score means a better outcome. Analysis was by intention to treat based on the last observation carried forward. This trial is registered, number ISRCTN89624516. Findings: 72 patients with PDD or DLB were randomly assigned and started treatment: 34 with memantine and 38 with placebo. 56 (78%) completed the study. All withdrawals were owing to adverse events, but the proportion of withdrawals was similar in both groups. At week 24 the patients in the memantine group had better CGIC scores than those taking placebo (mean difference 0.7, 95% CI 0.04–1.39; p=0.03). With the exception of improved speed on attentional tasks in the memantine group (a quick test of cognition [AQT] form: difference 12.4, 95% CI 6.0–30.9; p=0.004), there were no significant differences between the groups in secondary outcome measures. Interpretation: Patients with DLB or PDD might benefit from treatment with memantine, which was well tolerated. Large-scale studies are now required to confirm our preliminary findings. (PsycINFO Database Record (c) 2016 APA, all rights reserved) (Source: journal abstract)

(159) Gauthier S. Pharmacotherapy of Parkinson disease dementia and Lewy body dementia. Front Neurol Neurosci 2009; 24:135-139.
Abstract: The pharmacotherapy of Parkinson disease dementia and Lewy body dementia with cholinesterase inhibitors and selected psychotropic drugs is relatively new. Review of literature supplemented by expert opinion. Cholinesterase inhibitors can be used by primary care practitioners and specialists, with often clinically meaningful results. Primary care practitioners play an essential role in the diagnosis and management of patients with these conditions
PT - Review

Abstract: Dementia with Lewy bodies is one of the most common dementias in the elderly after Alzheimer's disease. It can be recognized on the basis of several clinical characteristics
including progressive dementia with marked slowing and fluctuations, persistent visual hallucinations and an extrapyramidal syndrome. Several other clinical and imaging features are highly suggestive such as the presence of rapid eye movement sleep disorder, severe sensitivity to neuroleptics and specific neuroimaging abnormalities. Therapeutic strategies include prescription of L-dopa and cholinesterase inhibitors such as rivastigmine, and avoidance of anticholinergic medications and neuroleptics. Physicians who care for older people should have a heightened awareness of this entity in order to diagnose it early, avoid mistaking it for delirium and initiate appropriate treatment.

PT - Review


Abstract: OBJECTIVE: To assess the cost effectiveness of cholinesterase inhibitor (ChEI) treatment in patients with Alzheimer's disease (AD) and Dementia with Lewy bodies (DLB).

METHOD: We used 4-month open label follow-up data from routine memory clinic patients. There were 852 patients with AD and 112 with DLB. We applied three predictive models to estimate clinical and economic outcomes at five years, comparing AD and DLB patients with hypothetical untreated controls.

RESULTS: The mean improvement in MMSE in 852 AD patients was 0.57 (SD 3.4) at 4 months, and in the subgroup with baseline MMSE of 10-20 (moderate) was 1.6 (SD 3.7). Overall, the 112 DLB patients improved by 1.4 (SD 3.7). DLB patients with an MMSE 10-20 improved by 3.1 (SD 4.5) points. These efficacy data were input into the SHTAC, microsimulation and Markov models and produced estimated costs per QALY gained (CQG) for all AD of pound194,066, pound67,904 and pound123,935 respectively. In comparison, the CQGs for all DLB were pound46,794, pound2,706 and pound35,922. For the moderate subgroup only the SHTAC and microsimulation models were applicable. These gave CQG estimates for moderate AD of pound39,664 and cost saving respectively. For moderate DLB, both estimates were cost saving.

CONCLUSION: The cost per QALY gained of cholinesterase treatment of all patients with DLB (including those with MMSE outside the 10-20 range) is comparable to that of patients with moderate AD, and is probably cost saving.


Abstract: This review provides an update on the current state of pharmacogenetic research in the treatment of Alzheimer's disease (AD) and Lewy body disease (LBD) as it pertains to the use of cholinesterase inhibitors (ChEI). AD and LBD are first reviewed from clinical and pathophysiological perspectives. This is followed by a discussion of ChEIs used in the symptomatic treatment of these conditions, focusing on their unique and overlapping pharmacokinetic and pharmacodynamic profiles, which can be used to identify candidate genes for pharmacogenetics studies. The literature published to date is then reviewed and limitations are discussed. This is followed by a discussion of potential endophenotypes which may help to refine future pharmacogenetic studies of response and adverse effects to ChEIs.

PT – Review


Abstract: OBJECTIVES: To assess the possible responsiveness of blink reflex alterations present in dementia with Lewy bodies (DLB) to treatment with cholinesterase inhibitors.

METHODS: Twenty-six patients with DLB and 20 patients with Alzheimer disease underwent clinical, neuropsychological (including assessment of cognitive fluctuations, with the Cognitive Assessment of Fluctuations and the One-Day Fluctuation Assessment questionnaires), and the blink reflex evaluation at baseline, 1 week after vitamin E administration (to assess test-retest reliability), and 1 and 2 weeks after donepezil administration at the dose of 10 mg/d.

Results were compared with data obtained from 30 healthy controls treated with vitamin E capsules for 2 weeks. RESULTS: Treatment with donepezil did not cause modifications of
cognitive or motor performances in both groups of patients. In DLB patients, One-Day Fluctuation Assessment scores were modified by donepezil treatment with a mean reduction of 2.8 +/- 1.8 compared with baseline (P < 0.05). After 2 weeks of treatment with donepezil, R2 latency was significantly decreased in DLB patients. The mean R2 latency reduction was by 3.0 +/- 3.2 milliseconds (P < 0.0001 compared with baseline). R2 mean latency reduction was significantly correlated with R2 mean latency delay at baseline (Spearman rho = 0.8).

CONCLUSIONS: Short-term donepezil administration can correct the alterations of the blink response together with the daily occurrence of cognitive fluctuations present in DLB patients.


Abstract: Parkinson's disease (PD) is characterized by its motor impairment. However, non-motor symptoms such as psychiatric disorders, autonomic disturbances and sleep disorders frequently complicate the course of the disease. In particular, psychiatric disturbances including cognitive impairment, depression and psychosis impact these patients considerably. Approximately 31% of PD patients suffer from cognitive impairment and dementia. Currently, two different clinical presentations are distinguished in PD patients, who present with dementia: Parkinson's disease with dementia (PDD) and dementia with Lewy bodies (DLB), which are two different presentations of a single underlying disease process leading to the deposition of alpha-synuclein. Clinically, PDD is distinguished from DLB alone by the different temporal manifestations of extrapyramidal motor symptoms. Dementia is characterized by a subtle onset and progressive cognitive decline with a predominant dysexecutive syndrome, which can be accompanied by different behavioral symptoms such as hallucinations, depression, anxiety and sleep disorders. Dysregulation of different neurotransmitters has been associated with cognitive decline, but reduced cholinergic transmission is currently thought to be the pivotal mechanism in the development of cognitive dysfunction. Therefore, cholinesterase inhibitors are used in the treatment of dementia and accompanying behavioral symptoms in PDD and DLB. The occurrence of dementia impacts not only the patients themselves but also their care-givers and family. This article focuses on the clinical issues related to both disorders and is based on a meeting of experts which took place in April 2008 in Dresden.


Abstract: Background: Dementia is frequently associated with behavioral disturbances, some of which have a significant impact on patient quality of life and the likelihood of institutionalization. Cholinergic systems, among other neurotransmitters in the brain, appear to be involved with different behaviors, such as psychosis, depression, agitation, and personality changes. Scope: This paper reviews the clinical data on the effectiveness of rivastigmine, a dual inhibitor of acetylcholinesterase and butyrylcholinesterase, in ameliorating behavioral disturbances in different patient populations. Relevant articles were identified through MEDLINE searches with no date restrictions. Findings: In particular, rivastigmine has shown efficacy in treating behavioral disturbances in patients with a wide range of dementias – Alzheimer’s disease, vascular dementia, frontotemporal dementia, mixed dementia, Lewy body dementia, Parkinson’s disease with dementia, and schizophrenia with dementia. Most of the studies have been open-label clinical trials with behavior as a secondary endpoint. The behavior domains that most consistently showed improvement were apathy/indifference, anxiety, delusions (psychosis), and hallucinations. The major limitation of this review is that the effects on behavioral symptoms were usually secondary endpoints in clinical trials. Conclusion: The efficacious effects of treatment with rivastigmine on various behavioral disturbances provide supporting evidence that cholinergic mechanisms, among other neurotransmitters, are involved in the manifestation of some behavioral and psychological symptoms of dementia. (PsyclINFO Database Record (c) 2016 APA, all rights reserved)

Abstract: PURPOSE OF REVIEW: Dementia and depression are serious causes of global impairment in the elderly. This review is aimed at finding pharmacological reports from 2007-2008 so as to examine whether new guidance is available to treat these patients. RECENT FINDINGS: Studies on Alzheimer's disease and Lewy body dementias show that cholinesterase inhibitors are still first line treatment for these diseases and memantine is indicated in moderate/severe Alzheimer's disease, whereas there is as yet no standard available treatment for frontotemporal dementias. Treatment of depression in the elderly shows the same results as in younger individuals, and cerebrovascular pathology is important for treatment resistance. SUMMARY: There is a need for new drugs that focus on treatment resistant and nonresponder individuals. Most studies are confirmation of previous reported results
PT - Review

Abstract: Visual hallucinations are a typical feature of Lewy body parkinsonism and occur in some 40% of patients with Parkinson's disease. Age and cognitive decline are the most important intrinsic risk factors, but hallucinosis is often triggered by comorbid conditions such as infection and dehydration. The single most important trigger, however, is exposure to CNS drugs, in particular antiparkinsonian agents. While hallucinosis and psychosis can be triggered by amantadine and anticholinergics, they are more commonly experienced after changes in dopaminergic medication. Dopamine agonists have greater potential to induce hallucinosis compared with L-dopa. Attempting to reduce antiparkinsonian drugs is an important part in the management of these patients, but atypical neuroleptics like clozapine or quetiapine are frequently necessary. Visual hallucinations in Parkinson's disease patients with dementia can also be improved by treatment with the cholinesterase inhibitor rivastigmine
PT - Review

Abstract: Cholinesterase inhibitors (ChEIs) are effective symptomatic treatments in dementia with Lewy bodies (DLB), although effects on pathologic mechanisms are unknown. In the first human autopsy study examining the impact of ChEI treatment on brain pathology, we compared treated patients with DLB with matched untreated patients for cortical beta-amyloid (Abeta) and tau pathologies. Treated patients with DLB had significantly less parenchymal Abeta deposition, which is relevant to disease management and treatment of dementia patients using ChEI

Abstract: OBJECTIVETo compare efficacy of different cholinesterase inhibitors (ChEIs) for treating patients with dementia with Lewy bodies (DLB). DESIGNRetrospective comparison of three independent clinical studies of ChEI treatment using donepezil, galantamine or rivastigmine in patients with DLB.METHODOData was obtained from open label trials of donepezil and galantamine and a placebo controlled randomized trial of rivastigmine in DLB. Changes in Mini Mental State Examination (MMSE), Neuropsychiatric Inventory (NPI) and United Parkinson's Disease Rating Scale (UPDRS-III) scores were compared between the three treatments at 12 and 20 weeks.RESULTSAll ChEIs significantly improved cognitive and neuropsychiatric measures. Reduction in the total NPI score appeared significantly greater after donepezil treatment. There was no significant increase in UPDRS-III scores.CONCLUSIONIt is unclear to what extent these findings reflect true differences between ChEIs or are due to methodological artefacts of comparing different studies. There is
so far no compelling evidence that any one ChEI is better than the other in treating DLB but head to head comparative studies of different ChEIs are warranted to clarify this.


Abstract: We describe a patient with probable dementia with Lewy bodies (DLB) whose Parkinsonism worsened after administration of rivastigmine within the therapeutic dose range. Some extrapyramidal signs (EPS) then reversed to pre-treatment level after rivastigmine dose reduction. We draw attention to the need of EPS monitoring during titration of cholinesterase inhibitors in patients with DLB. This is the first report to our knowledge of iatrogenic worsening of Parkinsonism which was successfully managed by dose reduction. (PsycINFO Database Record (c) 2016 APA, all rights reserved)


Abstract: Background: Dementia with Lewy bodies (DLB) is a common dementia of the elderly. A significant cholinergic deficit has been demonstrated that may be responsive to treatment by cholinesterase inhibitors (ChEIs). Methods: A 24-week, open-label study was designed to assess the efficacy and safety of a ChEI, galantamine, in 50 patients with DLB. Results: This study showed beneficial effects with galantamine in 2 of the 3 primary efficacy parameters. The scores on the Neuropsychiatric Inventory (NPI-12) improved by 8.24 points from baseline (p = 0.01) especially in visual hallucinations and nighttime behaviors (p = 0.004). The scores on the Clinician’s Global Impression of Change improved by 0.5 points from baseline (p = 0.01). The third primary efficacy parameter, the Cognitive Drug Research Computerized Cognitive Assessment System, was unchanged from baseline. Adverse events were generally mild and transient. Conclusion: Galantamine appears to be an effective and safe therapy for patients with DLB. (PsycINFO Database Record (c) 2017 APA, all rights reserved)


Abstract: Parkinson’s disease dementia (PDD) and Alzheimer’s disease (AD) are both characterized by cognitive abnormalities, neuropsychiatric symptoms, and cholinergic deficits. We reviewed data from large, placebo-controlled clinical trials conducted with rivastigmine in patients with PDD and AD to evaluate similarities and differences in response to treatment. In placebo groups, AD patients appeared to show more rapid cognitive decline than those with PDD. Treatment effects (rivastigmine versus placebo) on cognitive performance over 6 months were quantitatively similar in both populations, but qualitatively different: in AD, cognitive abilities were stabilized by rivastigmine compared to declines in placebo groups, whereas in PDD symptomatic improvements above baseline drove treatment effects while placebo patients had limited change. On activities of daily living, stabilization (rather than improvement) was observed in both dementia types. A more aggressive course of placebo decline, and greater treatment differences (rivastigmine versus placebo), were seen in sub-populations of both PDD and AD patients with hallucinations at baseline. The safety and adverse event profiles were comparable in the two populations. In conclusion, the magnitude of effect with rivastigmine versus placebo is quantitatively comparable in patients with AD and PD, but the treatment effect tended to be one of stabilization in AD, while in PDD improvements over baseline were seen. In both populations, hallucinations may identify patients who are likely to be more treatment-responsive


Abstract: Background: Delusions are clinically important symptoms in dementia with Lewy bodies (DLB). The purpose of this review is to examine the level of evidence for treatment of delusions in DLB. Methods: To achieve this objective Medline was searched. Studies were included in the review if they were prospective, separated delusions from hallucinations and
were tested in patients with DLB. Results: The review yielded a total of six studies. Although all studies showed effectiveness, only one study using rivastigmine had an adequate patient sample size and used a randomized controlled design. Conclusion: Further studies are required before a definitive conclusion can be reached about effective treatments. (PsycINFO Database Record (c) 2016 APA, all rights reserved) (Source: journal abstract)

Abstract: We have reported three patients from the same family affected with early progressive ataxia and dementia, associated with a new PSEN1 mutation. Whether ataxia is correlated with cerebellar patholgy was not demonstrated in the present case in the absence of a neuropathological study. Cerebellar changes such as Ab deposition in the molecular and inner granular layers and amyloid angiopathy have been reported in a series of 48 PSEN1 linked ADEOAD but none had cerebellar ataxia. In conclusion, the present study demonstrates that PSEN1 linked ADEOAD has to be considered, even when ataxia precedes dementia, the Pro117Ala mutation being responsible for a predominant precocious ataxia. (PsycINFO Database Record (c) 2016 APA

Abstract: BACKGROUND 123I-labelled 2beta-carbomethoxy-3beta-(4-iodophenyl)-N-(3-fluoropropyl) nortropane (123I-FP-CIT) imaging is a diagnostic tool to help differentiate dementia with Lewy bodies (DLB) from Alzheimer's disease (AD). However, in animals, cholinesterase inhibitors (ChEI) have been reported to reduce radioligand binding to the striatal dopamine transporter. As ChEI are frequently used in people with dementia, it is important to determine whether their use affects 123I-FP-CIT uptake in the striatum.OBJECTIVE To clarify whether chronic ChEI therapy modulates striatal dopamine transporter binding measured by 123I-FP-CIT in patients with AD, DLB and Parkinson's disease with dementia (PDD). DESIGN Cross sectional study in 99 patients with AD (nine on ChEI, 25 not on ChEI), DLB (nine on ChEI, 19 not on ChEI) and PDD (six on ChEI, 31 not on ChEI) comparing 123I-FP-CIT striatal binding (caudate, anterior and posterior putamen) in patients receiving compared with those not receiving ChEI, correcting for key clinical variables including diagnosis, age, sex, Mini-Mental State Examination score, severity of parkinsonism and concurrent antidepressant use. RESULTS As previously described, 123I-FP-CIT striatal uptake was lower in DLB and PDD subjects compared with those with AD. Median duration of ChEI use was 180 days. 123I-FP-CIT uptake was not significantly reduced in subjects receiving ChEI compared those not receiving ChEI (mean percentage reduction: AD 4.3%; DLB 0.7%; PDD 6.1%; p = .40). ChEI use did not differentially affect striatal 123I-FP-CIT uptake between patient groups (p = .83). CONCLUSIONS Use of ChEI does not significantly influence the ability of 123I-FP-CIT imaging to distinguish AD from DLB.


Abstract: Cholinesterase inhibition in patients with Alzheimer's disease (AD) may affect heart rate, sometimes inducing bradycardia. Additional cardiac safety considerations apply in patients with dementia with Lewy bodies (DLB) and Parkinson's disease (PDD), in whom cardiovascular autonomic nervous system dysfunction is common. We conducted a review of the safety data available for rivastigmine in these two conditions. A modest reduction in the mean heart rate of 1.5-2 bpm was seen. No clinically meaningful treatment differences in bradycardia or ECG abnormalities were apparent. Compared with placebo, rivastigmine appeared to be associated with fewer vascular disorder adverse events (AEs) (p = 0.002) and fewer AEs of syncope (p = 0.018) in PDD patients (n = 541). A smaller randomised, placebo-
controlled study of rivastigmine in DLB (n = 120) showed similar findings. Rivastigmine appears to have a favourable cardiac safety profile in PDD and DLB patients.


Abstract: Purpose Of Review: The health and socioeconomic impacts of dementia with Lewy bodies and dementia associated with Parkinson's disease have become increasingly recognized. Whilst the nosological status of dementia with Lewy bodies has been better classified as 'Lewy body dementias', both conditions are now believed to represent a disease spectrum, characterized pathologically by synuclein protein and clinically by a variable admixture of cognitive, neuropsychiatric and extrapyramidal features. Recent Findings: Recent epidemiological studies are described and clinical and pathological similarities emphasized between dementia with Lewy bodies and Parkinson's disease. A number of investigational techniques are highlighted which have helped to better characterize dementia with Lewy bodies and discriminate it from Alzheimer's disease, whilst also shedding light upon the pathophysiology of both conditions. Finally, the therapeutic aspects of the Lewy body dementias will be considered, concentrating upon studies of the cholinesterase inhibitors. Summary: The pathology underlying dementia with Lewy bodies and Parkinson's disease is heterogeneous, and is neither stereotyped in its topography nor its composition. Cholinesterase inhibitor drugs improve cognition and neuropsychiatric symptoms but the clinical response is unpredictable. Major future challenges are to better understand the pathophysiological basis underpinning the diseases, what determines clinical phenotypic expression and how disease-modifying therapies may best be developed and deployed.
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