Acetylcholinesterase Inhibitors and Effects on Behaviors in Alzheimer's Disease: A Review

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Alzheimer's Disease (AD) is characterized by the degeneration of cholinergic neurons and reduced synaptic acetylcholine. Acetylcholinesterase inhibitors (AChEIs; donepezil, rivastigmine, galantamine, and benzgalantamine) are a cornerstone of symptomatic treatment for AD. A literature review was conducted to evaluate the impact of AChEIs on behavioral and psychological symptoms in AD utilizing the Neuropsychiatric Inventory (NPI). The data revealed galantamine treatment resulted in significant reductions in total NPI scores as well as NPI subdomains compared to placebo; no significant effects were observed for donepezil or rivastigmine versus placebo. The reduction in behavioral and psychological symptoms in AD may be due to the unique dual mechanism of action of galantamine/benzgalantamine as an AChEI and positive allosteric modulator of nicotinic cholinergic receptors.

INTRODUCTION

Alzheimer's Disease (AD) is characterized by the degeneration of cholinergic neurons and reduced synaptic acetylcholine (ACh).[1] One of the primary pharmacologic treatment strategies for alleviating the symptoms of AD involves the use of acetylcholinesterase inhibitors (AChEIs; donepezil, rivastigmine, galantamine, and benzgalantamine, which enhance cholinergic neurotransmission by preventing the breakdown of ACh in the synaptic cleft.[2,3] This mechanism helps mitigate the cholinergic deficits observed in AD and has been shown to provide symptomatic benefits in terms of cognition, daily functioning, and behavior.[2,4] Importantly, behavioral and psychological symptoms of dementia (BPSD) affect up to 80% of AD patients, including those in the early stages.[5,6] BPSD can worsen over time, contributing significantly to patient distress, caregiver burden, and earlier institutionalization.[7] As a result, behavioral symptom management has become a critical domain of AD care, alongside cognitive and functional outcomes. The objective of this review is to examine the utilization of AChEIs and their impact on BPSD in AD.

METHODS

A literature search was conducted to identify relevant peer-reviewed articles published between 1995-2025 examining the impact of AChEIs on BPSD as measured by the Neuropsychiatric Inventory (NPI).[8] The NPI has demonstrated reliability across languages and cultures, making it a validated tool for assessing BPSD in diverse populations, including AD; it assesses the frequency and severity of symptoms in 10 or 12 domains, plus caregiver's distress.

RESULTS

Meta-Analysis (13 RCTs)

Pooled NPI data from three galantamine studies,[9-11] nine donepezil studies,[12-20] and one rivastigmine study[21] were evaluated. Galantamine was the only AChEI to demonstrate statistically significant and consistent improvements in behavioral symptoms, as measured by the NPI, standardized mean differences [MD] = –0.15; 95% Confidence Interval [CI]: –0.24, –0.06 (*P*=0.001).[22] No significant effect was observed for donepezil (SMD = –0.14, 95% CI: –0.29, 0.01); *P*=0.06) or rivastigmine (MD = –0.50, 95% CI: –2.68, 1.68; *P*=0.65).[22]

Cochrane Systematic Reviews

Galantamine showed the most consistent benefit, with high levels of evidence supporting improvement in behavioral symptoms, as measured by the NPI, compared to placebo (MD = –1.63, 95% CI: –3.07, –0.20; 2 studies, 1043 participants).[23] Donepezil did not show behavioral improvements in NPI scores versus placebo (MD = –1.62, 95% CI: –3.43, 0.19; 4 studies, 1035 participants).[24] Rivastigmine demonstrated no meaningful NPI-behavioral benefit compared to placebo across three studies (SMD = –0.04; 95% CI: –0.14, 0.06; 1529 participants).[25]

Prospective Switching: from Donepezil to Galantamine

Patients with mild to moderate AD (N=32) were switched from donepezil to galantamine without a washout period. The mean NPI score exhibited a statistically significant improvement 3 months after the switch (*P*=0.027). Among the individual NPI domains, delusions (*P*=0.018), agitation (*P*=0.034), and aberrant motor activity (*P*=0.045) showed significant improvement after switching. The average NPI-Q scores were significantly improved in terms of both the severity of disease (*P*=0.009) and caregiver distress (*P*=0.012).[28]

Galantamine: Data from a Randomized Trial and Post-Hoc Analyses

A large 5-month, randomized, multicenter, placebo-controlled trial (N=978) demonstrated galantamine improved behavioral symptom scores, with statistically significant differences observed in total NPI scores at 16 and 24 mg/day doses (*P*<0.05).[9] Post-hoc analyses revealed that among patients with behavioral symptoms at baseline, galantamine (16, 24 or 32 mg/day) significantly improved symptoms across multiple NPI domains, including aberrant motor behavior, agitation/aggression, anxiety, apathy, delusions, disinhibition, and hallucinations, compared to placebo.[26,27]

CONCLUSIONS

Among the available AChEIs, galantamine demonstrated significant reductions in total NPI scores compared to placebo; no significant effects were observed for either donepezil or rivastigmine. In addition, galantamine was shown to significantly improve several NPI domains including aberrant motor behavior, agitation/aggression, anxiety, apathy, delusions, disinhibition, and hallucinations.[26-28]

The benefits of galantamine/ benzgalantamine in BPSD may be due to their unique dual mechanism of action, acting as both AChEI and positive allosteric modulation of nicotinic cholinergic receptors.[2] It is hypothesized that the dual mechanism may improve limbic and frontal lobe function, and influence secondary neurotransmitter pathways, potentially leading to behavioral stabilization or improvement.[26]

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