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Letter to the Editor

Galantamine-memantine combination effective in dementia: Translate to dementia praecox?

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Cholinergic and glutamatergic systems, alpha-7 nicotinic acetylcholine receptor (α-7nAChR) and *N*-methyl-D-aspartate (NMDA) receptor are strongly implicated with cognitive impairments in Alzheimer's disease (AD). Donepezil, a frequently used drug in the treatment of AD, is only an acetylcholinesterase inhibitor (AChEI), whereas galantamine is an AChEI and a positive allosteric modulator of the α4β2 and α-7nAChR. Memantine is an NMDA receptor antagonist. Donepezil (Aricept), galantamine (Razadyne), memantine (Namenda), and donepezil-memantine combination (Namzaric) are US Food and Drug Administration (FDA)–approved medications for the treatment of AD. Several randomized controlled trials (RCTs) and meta-analyses have shown that the donepezil-memantine combination was better than either drug alone for cognition in AD. Based on these data and the unique properties of galantamine, several studies were conducted evaluating the efficacy of galantamine-memantine combination in AD.

In a 1-year RCT with 232 participants with mild-to-moderate AD, a galantamine-memantine combination was not superior to galantamine alone for cognition (Peters et al., 2015). However, this combination was effective in AD prodrome (Peters et al., 2012) and AD (Matsuzono et al., 2015). These studies are summarized in Table 1.

This letter sheds light on the galantamine-memantine combination, which showed significantly better cognitive improvements compared to galantamine alone in prodrome AD and donepezil-memantine combination in AD. The recommended daily dose of galantamine in AD is 16–24 mg. Peters and colleagues used galantamine 16 mg daily; 24 mg would have enhanced cognition even further. The studies described in Table 1 used the maximum dose of memantine 20 mg. In schizophrenia, studies have been done with the maximum dose of 20 mg; one study used memantine XR 21 mg (Koola et al., in press). In AD, the new FDA-approved treatment dose of memantine is 28 mg, which may further enhance cognition in schizophrenia. Galantamine-memantine combination was effective for cognition in "rabbits, rodents, and rhesus"; hence, these findings could be translated to all "races" with schizophrenia (Koola, in press).

Kynurenine pathway (KP) metabolites are abnormal in AD and are associated with cognitive impairments. Kynurenic acid (KYNA) is an antagonist to α-7nAChR and NMDA receptor. Galantamine and memantine via α-7nACh and NMDA receptors, respectively, may counteract the effects of KYNA, thereby improving cognition in schizophrenia (Koola et al., in press). In the Matsuzono study (Table 1), the concurrent action of galantamine-memantine combination on the α-7nAChR and NMDA might have modulated the KP metabolites. This is an additional benefit of this combination and is the most parsimonious explanation for its effects. Because of the involvement of cholinergic and glutamatergic systems, α-7nAChR, NMDA receptor, and KP in schizophrenia, the galantamine-memantine combination may be effective in schizophrenia as well. In fact, in a small open-label study, the galantamine-memantine combination improved several cognitive domains with concurrent improvement in KP metabolites (Koola et al., in press). If these findings are validated in RCTs, this may address the clinically unmet need in schizophrenia—treatment for cognitive impairments. If this combination is effective in schizophrenia, the FDA may be able to approve it for both dementia and dementia praecox.

Conflict of interest

Authors declare no conflict of interest.

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Contributors

Koola prepared the manuscript; Parsaik prepared the table. All authors contributed, edited and approved the final version.

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Table 1
Characteristics of studies with the galantamine and memantine combination for cognitive impairments in elderly people.

Studies	Age (years) Mean ± SD	Target population	Sample size	Study design	Intervention dose	Outcome
Peters et al., 2012 Germany	67.4 ± 7.8	Subjects with amnestic mild cognitive impairments	232 (placebo = 79, galantamine = 75, galantamine + memantine = 78)	Randomized controlled trial (2 years)	Galantamine 8 mg BID + memantine 10 mg BID versus galantamine 8 mg BID versus placebo	At 6 months, only the subgroup of AD prodrome (N = 39) treated with the combination treatment showed significant benefit from medications; cognitive decline occurred after discontinuation of galantamine. Cognitive improvement was numerically larger in the combination treatment group than in the galantamine group. Placebo: − 4.5/1/0.5[a] Galantamine: − 1.25/1/1.25[a] Combination: 0.75/2.5/4.75[a] (ADAS-cog presented as P25/median/P75) P < 0.05
Matsuzono et al., 2015 Japan	78.9 ± 7.1	Subjects with a diagnosis of AD	Among 123 patients, 64 (52%) were treated with donepezil plus memantine and 59 (48%) with galantamine plus memantine. Nine patients dropped out due to side effects.	Retrospective cohort study (1.5 years follow-up)	All received ChEI for 6 months. Then, memantine 5–20 mg was added for 12 weeks. The average daily dose of donepezil was 7 ± 2.5 mg, memantine was 16.7 ± 5.2 mg (average of 2 groups), and galantamine was 17.8 ± 4.6 mg.	ChEI reduced the MMSE score by 1.7 (P < 0.001), HDS-R by 1.8 (P < 0.05), and FAB by 0.8 (P < 0.05). After the addition of memantine, the galantamine + memantine group showed significantly better preservation of cognitive function compared to donepezil + memantine in MMSE score at 3 months (21 versus 14, P < 0.05), HDS-R score at 12 months (11 versus, 9, P < 0.05), and FAB score at 3 months (15 versus 9, P < 0.05).

AD: Alzheimer disease.
ADAS-cog: Alzheimer's Disease Assessment Scale-Cognitive.
BID = twice daily.
ChEI: cholinesterase inhibitor.
FAB: Frontal Assessment Battery.
HDS-R: Hasegawa Dementia Rating Scale-Revised.
MMSE: Mini-Mental State Examination.
[a] P25 is 25th percentile and P75 is 75th percentile.

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