Asian Journal of Psychiatry 42 (2019) 115–118

Contents lists available at ScienceDirect

Asian Journal of Psychiatry

journal homepage: www.elsevier.com/locate/ajp

Letter to the Editor

Galantamine and memantine combination for cognition: Enough or more than enough to translate from murines and macaques to men with schizophrenia?

Cholinergic (Tandon, 1999; Terry, 2008) and glutamatergic systems and α-7 nicotinic receptor (α-7nAChR) and *N*-methyl-D-aspartate (NMDA) receptor are integrally involved with cognition. Galantamine is not only an acetylcholinesterase inhibitor (AChEI), but also a positive allosteric modulator of the α4β2 and α-7nAChR. Memantine is an NMDA receptor antagonist. In an amyloid precursor protein (APP23) transgenic mouse model of Alzheimer's disease (AD), treatment with donepezil and memantine combination had a synergistic effect of cholinergic and glutamatergic systems in alleviating spatial learning and retrieval impairments (Neumeister and Riepe, 2012). Donepezil is only an AChEI and lacks other properties that galantamine possesses. Likewise, cognition enhancement in rodents with the synergistic role of α-7nAChR and NMDA receptor is also well documented (Nikiforuk et al., 2016). Galantamine and memantine are US Food and Drug Administration approved for the treatment of AD. Galantamine-memantine combination is the standard of care for the treatment of AD and major neurocognitive disorder. Based on this evidence, several preclinical studies have been undertaken. The objective of this article is to critically dissect the preclinical research done to date on the galantamine-memantine combination based on the new National Institutes of Health policy on the scientific premise (Collins and Tabak, 2014; Moher et al., 2015).

Table 1
Preclinical Studies on Galantamine and Memantine Combination for Cognition.

Studies	Major Findings	Strengths	Weaknesses
Woodruff-Pak et al. (2007) A total of 105 specific pathogen-free female retired breeder rabbits were tested. The mean age of the rabbits was 26.3 months (SD = 0.2), and the mean weight was 4.1 kg (SD = 0.04). The rabbits were individually housed in stainless steel cages in temperature- and humidity-controlled rooms. They had ad libitum access to food and water during the experiment. The light/dark cycle was 12/12 h. In N = 56, doses of galantamine (3.0 mg/kg) and donepezil (0.75 mg/kg) were tested alone and in combination with memantine (0.5 mg/kg). The test was in older rabbits with delay eyeblink classical conditioning, a form of associative learning.	Both galantamine and galantamine + memantine yielded superior performance over vehicle-treated rabbits in terms of acquisition of conditioned responses. Galantamine-memantine had superior effect on cognition compared to donepezil-memantine (was not significantly different).	Five groups were compared: vehicle, galantamine alone, donepezil alone, galantamine + memantine, donepezil + memantine.	Sample sizes were N = 7, N = 8, and N = 10 in each group, which could explain why galantamine-memantine combination was not better than galantamine alone. The authors claim that the sample sizes used in these experiments had ample power to support the conclusions.
Lorrio et al. (2009) 134 adult male Mongolian gerbils (Meriones unguiculatus, weight: 60–80 g) were used. Gerbils were housed individually under controlled temperature and lighting conditions with food and water provided ad libitum. Gerbil groups included in the study were sham, ischemia, and ischemia plus galantamine (1 mg/kg and 10 mg/kg), memantine (10 mg/kg and 20 mg/kg), 1 mg/kg galantamine plus 10 mg/kg memantine, and 10 mg/kg galantamine plus 10 mg/kg memantine, respectively.	Increased the number of living pyramidal neurons; reduced *TUNEL-positive neurons, active caspase-3 positive neurons, and *SOD-2 immunoreactivity; and preserved spatial memory after ischemia-reperfusion injury compared to sham animals. Synergistic neuroprotection was seen with the combination.	Gerbils were randomly divided into eight groups. A researcher who was blinded to the treatments received by the animals assessed histological sections.	The effects of the combination were better than either medication alone; however, they were not statistically different from those observed in animals treated with galantamine alone. There were 8 groups, and the small sample sizes may explain why they did not find that the galantamine-memantine combination was significantly better than galantamine alone.
Busquet et al. (2012) For all studies, cluster of differentiation male mice (18–22 g) were group-housed in a temperature- and humidity-controlled room under a 12 h light/dark cycle (light on at 7 a.m.) with water and food ad libitum. At least 24 h before testing, animals were brought to the experimental room and kept in a ventilated storage cabinet. Experimental procedures were performed	The combination of doses of galantamine and memantine synergistically rescued the memory impairments elicited by scopolamine.	Three groups were compared: galantamine, memantine, and galantamine + memantine.	

(*continued on next page*)

https://doi.org/10.1016/j.ajp.2017.11.008
Received 4 July 2017; Received in revised form 7 November 2017; Accepted 9 November 2017

Table 1 (*continued*)

Studies	Major Findings	Strengths	Weaknesses
during the light phase, therefore, during the inactive circadian phase of the animals. Spatial memory performance was assessed using the T-maze task. Episodic memory was assessed using the novel object recognition task. Object exploration, defined as the time in which a mouse touched the object with its nose or was oriented toward and within 2 cm to the object, was measured manually by investigators kept unaware of the treatment. Galantamine 0.1 mg/kg and memantine 0.5 mg/kg were used.			
Lopes et al. (2013) Pregnant Sprague-Dawley female rats were maintained in a temperature- and humidity-controlled colony room under a 12 h day-night cycle and were individually housed in plastic cages, having free access to food and water ad libitum. The neuroprotective properties of galantamine in primary cultures of rat cortical neurons when given alone or in combination with memantine were studied.	Memantine was effective in reversing N-methyl-D-aspartate (NMDA) toxicity at concentrations of 2.5 and 5 lmol/L. Galantamine also completely reversed NMDA toxicity at a concentration of 5 lmol/L. The combination of memantine + galantamine produced synergistic actions such that full neuroprotective efficacy was obtained at inactive concentrations of memantine (0.1 lmol/L) and galantamine (1 lmol/L). A similar potentiation was also observed when memantine was replaced with ifenprodil, suggesting a possible involvement of the NR2B subunit of the NMDA receptor.	The α-7 and α4β2 nicotinic acetylcholine receptor (nAChR) antagonists, methyllycaconitine (MLA), and dihydro-b-erythroidine blocked the neuroprotective effect of galantamine, demonstrating the involvement of nAChRs.	Cell-based experiments.
Schneider et al. (2013) The study was conducted using 7 male Rhesus macaques (age ranging between 23 and 26 years) previously trained to perform cognitive tasks (6 performed delayed matching to sample and 7 performed paired associate learning) and previously used in other behavioral pharmacology studies. At the time of the current study, none of these animals had participated in another pharmacological study for at least 2 months. Animals were housed in individual primate cages under controlled conditions of humidity (50 ± 5%), temperature (24 ± 1 °C), and light (12 h light/12 h dark cycle). Animals were food restricted and received water ad libitum. For testing, animals were transferred from the home cage to a testing cage located in a dimly lit, sound-attenuated, ventilated cubicle away from the colony. Each testing cage was equipped with a Cambridge Neuropsychological Test Automated Battery (CANTAB; Lafayette Instruments, Lafayette, IN, USA) apparatus. CANTAB stations consisted of a touch-sensitive monitor, a reward delivery system, and a pellet receptacle located to the lower right side of each panel. All animals were previously trained to perform the CANTAB versions of PAL and DMTS tasks. Memantine was administered intramuscularly in a volume of 0.1 ml/kg. Three doses of memantine were studied: 0.25, 0.50, and 1.0 mg/kg. Galantamine was administered by subcutaneous injection in a volume of 0.1 ml/kg. Two doses of galantamine were studied: 0.10 and 0.30 mg/kg. Drug combinations tested were galantamine 0.10 mg/kg with memantine 0.25 or 0.50 mg/kg and galantamine 0.30 mg/kg with memantine 0.25 or 0.50 mg/kg	Galantamine + memantine combination was significantly better in the Cambridge Neuropsychological Test Automated Battery versions of paired associate learning (PAL) and delayed matching to sample (DMTS) tasks compared to galantamine and memantine alone.	Three groups were compared: galantamine, memantine, and galantamine + memantine.	Sample size of N = 7
Nikiforuk et al. (2016)	Coadministration of inactive doses of memantine + galantamine facilitated the rats' set-shifting performance and reversed delay-induced deficits in object recognition with a synergistic action. The pro-cognitive effects of the drug combinations were blocked by MLA, indicating that the observed effects were α-7nAChR dependent.	Six groups were compared: 1. Veh + Veh	N = 6 rats per group.

(*continued on next page*)

Table 1 (*continued*)

Studies	Major Findings	Strengths	Weaknesses
Male Sprague-Dawley rats weighing 200–250 g on arrival were used in the current studies. The rats were housed in a temperature-controlled (21 ± 1 °C) and humidity-controlled (40%–50%) colony room under a 12/12 h light/dark cycle (lights on at 06:00 h). For the attentional set-shifting task (ASST), the rats were pair-housed with mild food restriction (17 g of food pellets per day) for at least one week prior to testing. For the novel object recognition task (NORT) studies, the rats were group-housed (5 rats/cage) with free access to food and water.	The synergistic role of the α-7nAChand NMDA receptors.	2. GAL + Veh	The experiments were conducted in cognitively unimpaired animals.
On the test day, the rats were simultaneously injected with inactive doses of memantine (1 mg/kg) and galantamine (0.3 and 1 mg/kg) for NORT and ASST, respectively		3. Veh + MEM 4. GAL + MEM 5. MLA + GAL + MEM 6. MLA + Veh + Veh Veh = vehicle GAL = galantamine MEM = memantine	
Reggiani et al. (2016) A total of 72 male Swiss mice aged 6 weeks old and weighing 30–35 g was used for β-amyloid (25–35) peptide ($A\beta_{25–35}$) intoxications. Animals were housed in the regulated animal facility of Amylgen in plastic cages with free access to food and water, except during behavioral experiments. They were kept in a regulated environment under a 12 h light/dark cycle (lights off at 7:00 pm). Animal procedures were carried out in strict adherence to the European Community Council Directive. In a non-transgenic Alzheimer's disease model, $A\beta_{25–35}$ was administered centrally to mice. After $A\beta_{25–35}$ intoxication,ARN14140, a galantamine/memantine-based multi-target compound of 7.5 μg/day, was administered for 7 days.	ARN14140 prevented $A\beta_{25–35}$–induced cognitive impairments and alteration of the major biomarkers of neurodegeneration and cell death.	Dual-target compounds can have inherent advantages over drug combinations mainly due to a better bioavailability.	One of the major drawbacks of the compound was related to the poor pharmacokinetic profile of the molecule leading to a high volume distribution, which compromises reaching the central nervous system and a full effect of the drug. Thus, the compound had to be administered intracerebroventricular to obtain the desired pharmacological effect in mice.

Preclinical research on the galantamine-memantine combination is summarized in Table 1. Cognition was significantly better on the galantamine-memantine combination than either medication alone (Schneider et al., 2013; Reggiani et al., 2016). Synergistic effects on cognition were also seen with this combination (Lorrio et al., 2009; Busquet et al., 2012; Lopes et al., 2013). Finally, synergistic role of the α-7nACh and NMDA receptors was also shown with this combination (Nikiforuk et al., 2016). Although not significant, the galantamine-memantine combination had a superior effect on cognition compared to the donepezil-memantine combination (Woodruff-Pak et al., 2007); this could be due to the synergistic role of the α-7nACh and NMDA receptors (Nikiforuk et al., 2016). This finding is not surprising because galantamine-memantine combination (N = 53) was significantly better for cognition compared to donepezil-memantine combination (N = 61) in AD patients (Matsuzono et al., 2015).

The preclinical evidence for cognition enhancement with this combination is intriguing. Antipsychotics work for psychoses due to any disorder (schizophrenia, schizoaffective disorder, bipolar I mania/depression with psychosis, psychotic depression, psychosis due to a medical condition or substance induced, etc.); thus, there is no reason to believe that galantamine-memantine combination would not enhance cognition in people with schizophrenia. Based on the preclinical research, several review papers on galantamine-memantine combination in schizophrenia (Koola et al., 2014; Koola, 2016) and an open-label study on this combination improving several cognitive domains in schizophrenia (Koola et al., in press), randomized controlled trials are warranted to test the efficacy of this combination in people with schizophrenia.

Funding source

None

References

Busquet, P., Capurro, V., Cavalli, A., Piomelli, D., Reggiani, A., Bertorelli, R., 2012. Synergistic effects of galantamine and memantine in attenuating scopolamine-induced amnesia in mice. J. Pharmacol. Sci. 120 (4), 305–309.
Collins, F.S., Tabak, L.A., 2014. Policy: NIH plans to enhance reproducibility. Nature 505 (7485), 612–613.

Koola, M.M., Buchanan, R.W., Pillai, A., Aitchison, K.J., Weinberger, D.R., Aaronson, S.T., Dickerson, F.B., 2014. Potential role of the combination of galantamine and memantine to improve cognition in schizophrenia. Schizophr. Res. 157 (1–3), 84–89.
Koola, M.M., Sklar, J., Davis, W., Nikiforuk, A., Meissen, J.K., Sawant-Basak, A., Aaronson, S., Kozak, R., 2017. Kynurenine pathway in schizophrenia: galantamine and memantine combination for cognitive impairments. Schizophr. Res in press.
Koola, M.M., 2016. Kynurenine pathway and cognitive impairments in schizophrenia: pharmacogenetics of galantamine and memantine. Schizophr. Res. Cogn. 4, 4–9.
Lopes, J.P., Tarozzo, G., Reggiani, A., Piomelli, D., Cavalli, A., 2013. Galantamine potentiates the neuroprotective effect of memantine against NMDA-induced excitotoxicity. Brain Behav. 3 (2), 67–74.
Lorrio, S., Negredo, P., Roda, J.M., García, A.G., López, M.G., 2009. Effects of memantine and galantamine given separately or in association, on memory and hippocampal neuronal loss after transient global cerebral ischemia in gerbils. Brain Res. 1254, 128–137.
Matsuzono, K., Hishikawa, N., Ohta, Y., Yamashita, T., Deguchi, K., Nakano, Y., Abe, K., 2015. Combination therapy of cholinesterase inhibitor (donepezil or galantamine) plus memantine in the okayama memantine study. J. Alzheimers Dis. 45 (3), 771–780.
Moher, D., Avey, M., Antes, G., Altman, D.G., 2015. The national institutes of health and guidance for reporting preclinical research. BMC Med. 13, 34.
Neumeister, K.L., Riepe, M.W., 2012. Synergistic effects of antidementia drugs on spatial learning and recall in the APP23 transgenic mouse model of Alzheimer's disease. J. Alzheimers Dis. 30 (2), 245–251.
Nikiforuk, A., Potasiewicz, A., Kos, T., Popik, P., 2016. The combination of memantine and galantamine improves cognition in rats: the synergistic role of the α7 nicotinic acetylcholine and NMDA receptors. Behav. Brain Res. 313, 214–218.
Reggiani, A.M., Simoni, E., Caporaso, R., Meunier, J., Keller, E., Maurice, T., Minarini, A., Rosini, M., Cavalli, A., 2016. In vivo characterization of ARN14140, a memantine/galantamine-based multi-target compound for Alzheimer's disease. Sci. Rep. 6, 33172.
Schneider, J.S., Pioli, E.Y., Jianzhong, Y., Li, Q., Bezard, E., 2013. Effects of memantine and galantamine on cognitive performance in aged rhesus macaques. Neurobiol. Aging 34 (4), 1126–1132.
Tandon, R., 1999. Cholinergic aspects of schizophrenia. Br. J. Psychiatry Suppl. 37, 7–11.
Terry Jr., A.V., 2008. Role of the central cholinergic system in the therapeutics of schizophrenia. Curr. Neuropharmacol. 6 (3), 286–292.
Woodruff-Pak, D.S., Tobia, M.J., Jiao, X., Beck, K.D., Servatius, R.J., 2007. Preclinical investigation of the functional effects of memantine and memantine combined with galantamine or donepezil. Neuropsychopharmacology 32 (6), 1284–1294.

Maju Mathew Koola
Department of Psychiatry and Behavioral Sciences, George Washington University School of Medicine and Health Sciences, 2300 ISt NW, 20037, Washington, DC, United States
E-mail address: majumkoola@gmail.com