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Fall-Related Risks with Pharmacological Interventions in Mild-to-Moderate Alzheimer's Disease: A Bayesian Network Meta-Analysis

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BACKGROUND

- The prevalence of falls in Alzheimer's disease (AD) patients is high, which leads to fractures, disability, and further reduction in cognition[1,2]
- Considering the elevated risk of falls among patients with AD, it is essential to perform thorough risk assessments and employ multifactorial interventions to mitigate fall risks and improve the safety and quality of life for such patients[3,4]
- Numerous studies have investigated risk factors for falls in AD. However, there is no direct evidence among available interventions comparing the risk of falls in AD patients

OBJECTIVE

In the absence of head-to-head trials, a network meta-analysis (NMA) was conducted to assess the fall-related risks of pharmacological interventions used in mild-to-moderate AD patients.

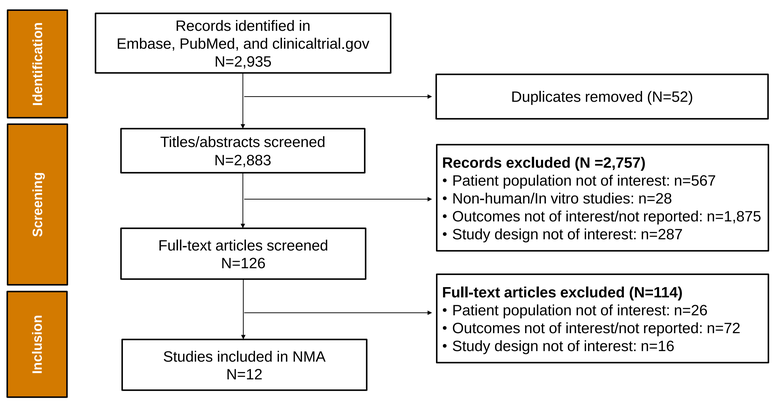
METHODS

- A systematic literature search was conducted in Embase, PubMed, and clinicaltrial.gov (January 1, 2005 to December 21, 2023) to identify randomized controlled trials (RCTs) on approved and in-development interventions among mild-to-moderate AD patients (i.e., donepezil, galantamine, memantine, solanezumab, and semorinemab) reporting fall events
- Random effect Bayesian NMA was performed to calculate the odds ratio (OR) and 95% credible intervals (CrI) using R software (version 4.3.2)
- Network consistency was assessed with node-split model by testing between direct and indirect estimates within treatment loop
- Surface under the cumulative ranking analysis (SUCRA) was performed to determine optimal intervention
- Begg's rank correlation test and Egger's linear regression test were used to assess the presence of publication bias in the analysis

RESULTS

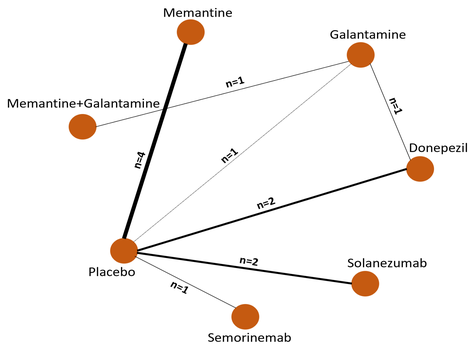
- The literature search yielded 2,935 citations, of which 12 RCTs met the inclusion criteria and were included for NMA. The PRISMA flowchart detailing the literature search process is shown in Figure 1
- The sample size in included studies ranged from 10 to 1,067, with a mean age of 74 years. The follow-up duration of included studies ranged from 12-52 weeks

Figure 1: PRISMA Flowchart



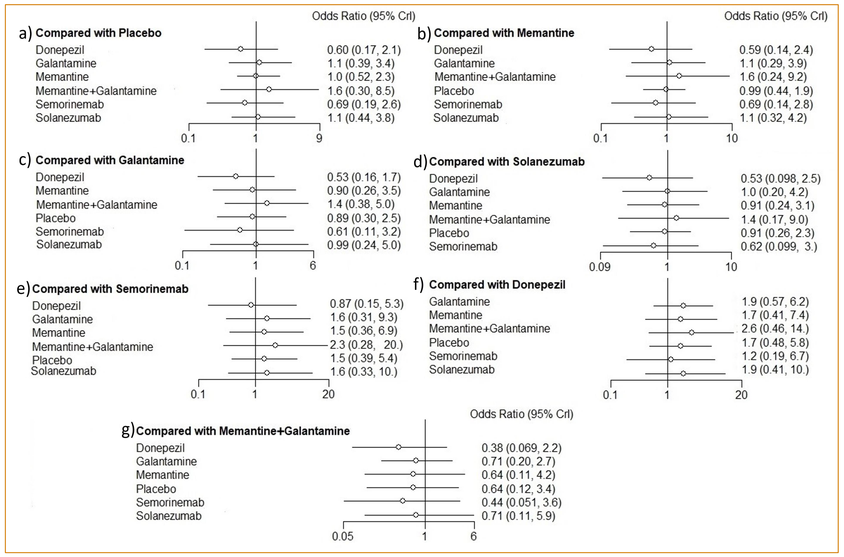
- A network diagram presenting eligible comparators (donepezil, galantamine, memantine, solanezumab, semorinemab, and memantine+galantamine, placebo) from the included trials (n=12) with risk of falls in AD patients is presented in Figure 2

Figure 2: Network diagram of eligible comparisons from included trials



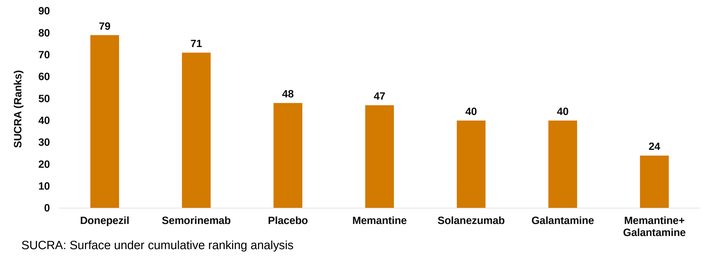
- No significant difference was observed with the risk of falls in AD patients between different interventions compared to placebo (Figure 3a)
- Numerically lower odds (95%CrI) of falls were observed with donepezil vs. memantine (0.59 [0.14-2.40]), galantamine (0.53 [0.16-1.70]), and solanezumab (0.53 [0.098-2.50]) (Figure 3b, 3c, 3d)
- Similar lower odds of falls were observed with semorinemab as compared to memantine (0.69 [0.14-2.80]), galantamine (0.61 [0.11-3.20]), and solanezumab (0.62 [0.099-3.00]) (Figure 3b, 3c, 3d)
- Further, it was observed that the combination of memantine and galantamine did not reduce the risk of falls as compared to the individual therapies assessed (donepezil, galantamine, memantine, semorinemab, and solanezumab) (Figure 3g)

Figure 3: Forest plots of the effect of interventions on risk of falls among AD patients included in NMA



- Overall, in terms of SUCRA values, donepezil (79%) and semorinemab (71%) were more effective in reducing falls than other interventions (Figure 4)

Figure 4: SUCRA ranks



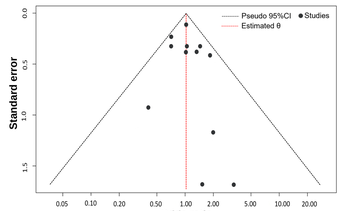
SUCRA: Surface under cumulative ranking analysis

- Node-splitting analysis indicated no notable inconsistencies, suggesting that the treatment effects of interventions remained consistent within the treatment loop across both direct and indirect evidence (Table 1)
- Rank correlation and linear regression test did not find any significant publication bias (p=0.27 and p=0.54, respectively) in the current analysis
- Lastly, the funnel plots presented a symmetrical distribution, with most of the studies (n=9) having sample size >100 indicating no small-sample effects for the risk of falls in AD patients (Figure 5)

Table 1: Node-splitting analysis of inconsistency

Comparison	Evidence	P value	OR (95%CrI)
Donepezil vs. Galantamine	Direct	0.74	0.74 (-0.73, 2.30)
	Indirect		0.33 (-2.00, 2.50)
	Network		0.63 (-0.48, 1.80)
Donepezil vs. Placebo	Direct	0.81	0.40 (-1.40, 2.30)
	Indirect		0.69 (-1.30, 2.70)
	Network		0.51 (-0.81, 1.80)
Galantamine vs. Placebo	Direct	0.78	-0.05 (-1.40, 1.40)
	Indirect		-0.42 (-2.80, 2.00)
	Network		-0.10 (-1.10, 0.91)

Figure 5: Funnel plot



CI: Confidence interval; θ: Overall effect estimate
Studies with higher precision (i.e., larger sample sizes or smaller standard errors) are located near the top of the plot, while studies with lower precision are located closer to the bottom

CONCLUSIONS

- The findings of this NMA revealed that none of the interventions was associated with reduced risk of falls among mild-to-moderate AD patients
- However, the results favoured donepezil and semorinemab in reducing risk of falls among mild-to-moderate AD patients as compared to other interventions studied
- These results should be interpreted cautiously as the risks and benefits alter with underlying disease progression and change in symptoms, which were not assessed in the present analysis
- Considering the association between movement and cognition in AD the intervention studied in the present NMA could be further explored targeting motor-cognitive interface along with disease progression, as a strategy to reduce the risk of falls in AD patients

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