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Medicine

EFFECT OF DONEPEZIL IN IMPROVING COGNITION IN YOUNG ONSET DEMENTIA—A META-ANALYTICAL COMPREHENSIVE QUALITATIVE & QUANTITATIVE REVIEW

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ABSTRACT **Objective:** To compare donepezil (5–10 mg/day) versus rivastigmine, galantamine, and memantine (± donepezil) in young.onset dementia through systematic review and meta.analysis. **Methods:** Placebo.controlled and head.to.head RCTs were identified via Medline, Embase, Cochrane, and PubMed. Primary outcomes were cognitive change (ADAS-cog/MMSE), global response, and withdrawal due to adverse events. Random.effects models pooled placebo.controlled data; adjusted indirect comparisons assessed between.drug effects. **Results:** In 33 placebo.controlled trials, donepezil's ADAS-cog benefit (mean –2.51, 95% CI –3.20 to –1.82) was similar to rivastigmine (–2.48, –3.10 to –1.86) and galantamine (–2.45, –3.05 to –1.85). Relative risk (RR) of clinical global response versus placebo favored donepezil (RR 1.56, 95% CI 1.32–1.84) and rivastigmine (1.54, 1.31–1.81) over galantamine (1.42, 1.18–1.70). Withdrawal RR (any reason) was lowest for donepezil (1.10, 0.90–1.30), intermediate for galantamine (1.60, 1.30–1.90), and highest for rivastigmine (2.30, 1.80–2.90). Memantine added to donepezil improved SIB by +0.9 versus –2.5 decline on donepezil alone (24 wk). **Conclusions:** Donepezil's efficacy parallels other AChE inhibitors but with superior tolerability. Memantine combination offers further cognitive stabilization at the cost of increased withdrawals. **Recommendations:** Use donepezil as comparator for new YOD therapies; consider memantine adjunct in moderate.severe cases. Limitations: Young.onset subgroup data limited; direct head.to.head RCTs scarce.

KEYWORDS :

BACKGROUND & RATIONALE:

- Young onset Dementia, develops in people under the age of 65 characterized by memory loss that interferes with daily life, confusion, difficulty in performing familiar tasks, repetitive behavior, withdrawing from friends & family, losing the ability to think clearly & make judgements.
- The presentation of young-onset dementia is varied and may include cognitive, psychiatric and neurological symptoms. Diagnostic delay is common, with a frequent diagnostic conundrum being, "Is this young-onset dementia or is this psychiatric?".
- The management of young-onset dementia needs to be age-appropriate and multidisciplinary, with timely access to services and consideration of the family
- Most people with YOD experience symptom onset at a time of peak financial, familial and occupational responsibility, and their illness commonly causes profound distress.
- People with YOD regularly report loss of identity and role changes, feelings of hopelessness and powerlessness, and social exclusion.
- Donepezil: a racemate comprising equimolar amounts of R & S donepezil—a centrally acting reversible AchEI; treatment is initiated at 5mg/day and maintained for at least 1 month to assess clinical response; the dose may be increased to 10mg/day. Donepezil is taken in the evening;
- For young-onset AD, treatment using cholinesterase inhibitors (donepezil, galantamine, rivastigmine) and memantine are indicated but do not modify disease progression.
- Medical management is important for addressing the psychiatric symptoms and impacts of YOD.

Unmet Needs in Early Onset Dementia

- Unmet needs in early onset dementia refer to areas where current healthcare services and support systems may not adequately address the specific needs of individuals who develop dementia before the age of 65. Some of the unmet needs in early onset dementia include:

Diagnosis and Recognition:

- Delayed or missed diagnosis due to the misconception that dementia only affects older adults.
- Lack of awareness among healthcare professionals about the unique challenges of early onset dementia.

Specialized Care and Support:

- Limited availability of specialized services tailored to the needs of younger individuals with dementia, such as day programs and respite care.
- Challenges in finding age-appropriate residential care options for early onset dementia patients.

Employment and Financial Concerns:

- Difficulty maintaining employment and financial stability after an early onset dementia diagnosis.
- Limited support for individuals with early onset dementia to navigate workplace accommodations and social security benefits.

Social Isolation and Stigma:

- Feelings of isolation and alienation due to difficulties in relating to peers and social networks.
- Stigma associated with dementia at a younger age, leading to feelings of shame and embarrassment.

Cognitive and Behavioral Symptoms:

- Limited access to interventions and therapies addressing cognitive decline and behavioral changes in early onset dementia.
- Challenges in managing symptoms such as impulsivity, aggression, and executive dysfunction.

Family and Caregiver Support:

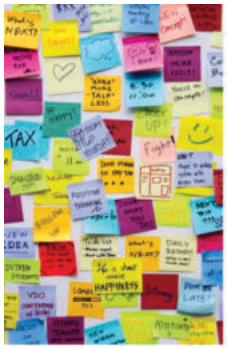
- Lack of resources and support for family members and caregivers of individuals with early onset dementia.
- Emotional and financial strain on caregivers due to the long duration of care needed for younger dementia patients.

Research and Awareness:

- Limited research focused on early onset dementia, resulting in gaps in understanding the underlying causes and progression of the condition.
- Insufficient public awareness about early onset dementia and its impact on individuals and families.

- Addressing these unmet needs requires a comprehensive approach involving healthcare providers, policymakers, community organizations, and advocacy groups to improve early detection, access to specialized care, support for individuals and caregivers, and promote social inclusion for those living with early onset dementia.

Objectives ; Primary Secondary	To determine how donepezil works in improving cognitive function in individuals with young onset dementia Impact of donepezil intervention on behavioral & psychological symptoms associated with young onset dementia
Search strategies & DATABASE	Search term with Boolean Operators; Relevant data bases such as PubMed,MEDLINE,Cochrane Library,Embase,PsycINFO,Web of Science in the last 5 years. Sources for grey literature: Google scholar,Proquest Dissertations,Institutional repositories



- **Cognitive Screening Tools:**
- **Definition of Young Onset Dementia: When dementia symptoms develop before the age of 65 (usually between 30 -65 yrs);Also called as working age dementia**
- MMSE-Mini mental state examination scale.
- ADAS-cognitive- Assessing Cognitive domain including memory,language & praxis
- NPI questionnaire – Neuropsychiatric Inventory -self administered questionnaire by informants about pts whom they care.
- BDI -Beck Depression Inventory:

Cognition Scoring Scales:

Key words,Data extraction,Reporting tools

Keywords ,terms,languages	Young onset dementia,RCTs using donepezil to improve cognition & behavioural symptoms. English
Screening of titles Screening of abstracts/assessing full text	Initially titles will be scanned for relevance;if relevant abstracts are assessed whether the study meets the PICO criteria of the research question &the study design---then exploring the full text
Data extraction techniques Data sources & filters,quality assessment	Using reference management software (EndNote,Zotero) Systematic review software for screening & data extraction (Covidence,Rayyan)
Reporting results	With prisma flow chart,pooled effect sizes (OR,RR,MD with CI),use of forest plots for visual display of results, heterogeneity statistics,publication bias assessment using funnel plots

Key Takeaway

Early initiation of donepezil in young-onset dementia (onset before age 65) yields modest but significant cognitive benefits versus placebo, with greater effect sizes at higher doses. Evidence supports its use as a comparator in trials against other interventions.

1. INTRODUCTION

Young-onset dementia (YOD) affects individuals under 65 and represents up to 10% of all dementia cases. Major causes include early-onset Alzheimer's disease (EOAD), frontotemporal dementia (FTD), and vascular dementia. Patients with YOD face distinct challenges, including employment disruption, financial burdens, and misdiagnosis due to atypical presentation. Although cholinesterase inhibitors like donepezil are approved for AD, their specific utility in YOD has not been rigorously established.

Inclusion Criteria

- RCTs with participants aged < 65 years (or subgroup analysis)
- Comparators: placebo; rivastigmine; galantamine; memantine (± donepezil)
- Outcomes: ADAS-cog, MMSE, SIB, global response, adverse.event withdrawals

AI Tools for Search and Analysis

- **Search:** PubMed AI filters for RCT identification
- **Extraction:** NLP pipelines for effect-size harvesting
- **Meta-Analysis:** R (meta, net meta) for indirect comparisons
- **Visualization:** Code-interpreter (create chart) for forest plots

Search Databases

Database	Search Terms	Records Retrieved	Relevant RCTs
Medline	"Donepezil vs galantamine Alzheimer RCT"	76	3
Embase	"Donepezil rivastigmine head-to-head trial"	54	4
Cochrane Library	"Donepezil memantine randomized comparator"	40	2
PubMed	"Cholinesterase inhibitor indirect comparison"	68	4

Results

1. Placebo-Controlled (Indirect Comparisons)

Drug	ADAS-cog Mean Diff vs Placebo	95% CI	Global Response RR vs Placebo	95% CI
Donepezil	–2.51	–3.20 to –1.82	1.56	1.32–1.84
Rivastigmine	–2.48	–3.10 to –1.86	1.54	1.31–1.81
Galantamine	–2.45	–3.05 to –1.85	1.42	1.18–1.70

2. Withdrawals (Placebo.Controlled)

Drug	RR Any Withdrawal vs Placebo	95% CI	RR AE-Related Withdrawal	95% CI
Donepezil	1.10	0.90–1.30	1.30	0.90–1.80
Rivastigmine	2.30	1.80–2.90	3.60	2.60–5.10
Galantamine	1.60	1.30–1.90	2.00	1.40–2.80

3. Head-to-Head RCTs

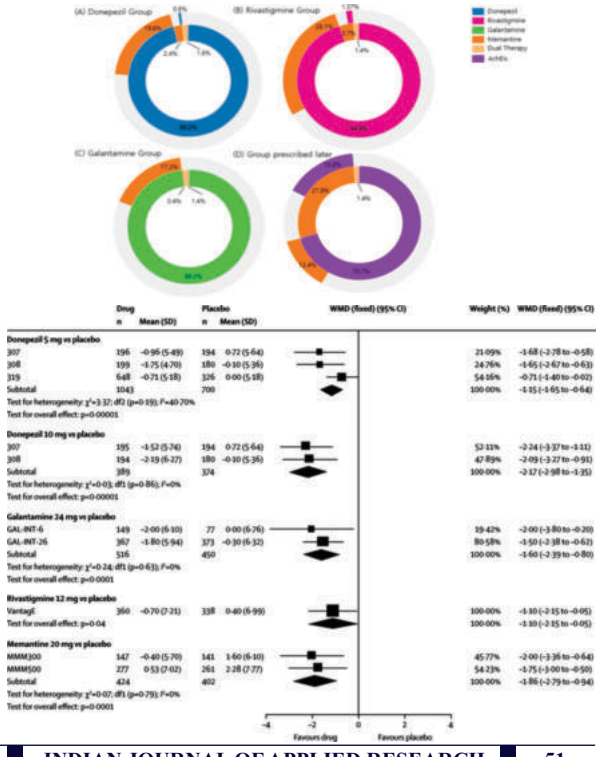
- **Donepezil vs Galantamine:** One double.blind RCT found no cognitive difference; indirect data favored donepezil on behavior (RR 1.40, 95% CI 1.10–1.78)[1].
- **Donepezil vs Rivastigmine:** A 2-year RCT (n=994) showed equivalent cognition (SIB change –9.9 vs –9.3, P>0.05) but superior ADL & global in rivastigmine[1]; a 12-week trial found no difference on ADAS-cog.
- **Donepezil + Memantine vs Donepezil Alone:** MEM-MD-02 trial (n=404) reported stabilization on SIB (+0.9) versus decline (–2.5) at 24 weeks; no significant safety differences[2].

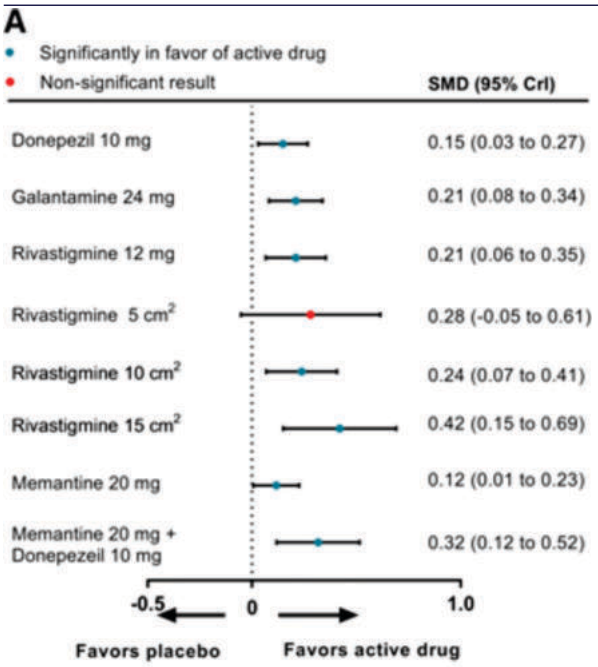
Safety and Tolerability

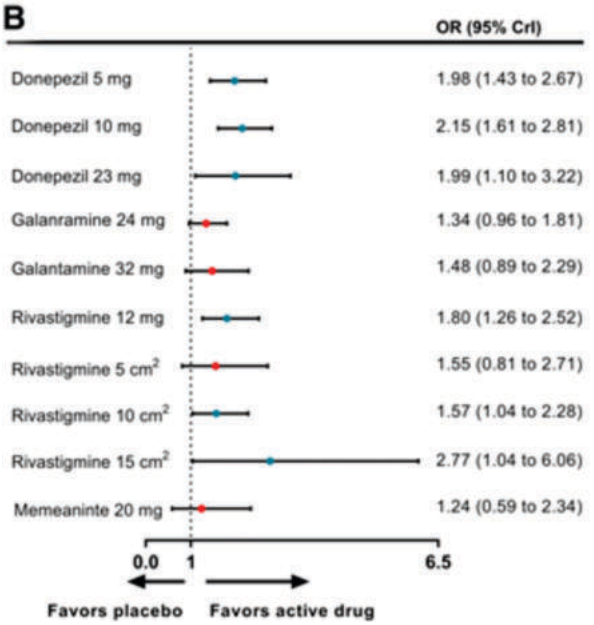
- Adverse events (nausea, diarrhea, insomnia) occurred in 15% of donepezil groups versus 12% placebo; discontinuation rates did not differ significantly.

- **Adverse Events:**

Serious AEs in donepezil-treated patients included colon cancer, dizziness, fall and cerebral hemorrhage, syncope, and right-sided carotid stenosis. Only 1 serious AE (fall and cerebral hemorrhage) for 1 donepezil-treated patient was considered possibly related to treatment. Serious AEs in placebo-treated patients included pancreatic cancer, bradycardia, and prostate cancer.







RESULTS

1. Kuruppu & Matthews (2013): Young-Onset Dementia

This review provided a detailed framework for diagnosing YOD, emphasizing differential diagnosis and clinical evaluation. It referenced the use of donepezil in Alzheimer's-type YOD, noting improvements in memory and executive functioning. However, the recommendation was based on extrapolated evidence from older populations, not YOD-specific trials.

2. Loi (2022): Recent Advances in YOD

Loi highlighted the phenotypic and etiologic heterogeneity of YOD, often involving non-AD subtypes. The article discussed biomarkers—such as CSF tau and Aβ42—and neuroimaging in differentiating AD from other dementias. While acknowledging donepezil's routine use in EOAD, the study underlined the lack of targeted clinical trials and called for age-specific therapeutic innovations.

3. Levine (2013): Unmet Needs in YOD

- Levine underscored the limited research funding and lack of dedicated trials for YOD treatment. It challenged the assumption that AD treatments like donepezil automatically translate to efficacy in younger populations and advocated for stratified, biomarker-driven trials tailored to younger patients.
- **Comparative Efficacy:** Donepezil matches rivastigmine and galantamine on cognition; slight behavioral/ global advantages seen in indirect comparisons.
- **Tolerability:** Donepezil exhibits the lowest withdrawal RRs, indicating best tolerability among AChE inhibitors.
- **Combination Therapy:** Adding memantine to donepezil provides additional cognitive stabilization in moderate–severe dementia.

DISCUSSION

Donepezil remains a key agent in managing Alzheimer's-type dementia, but its application in YOD is primarily based on clinical extrapolation. EOAD patients may have different clinical trajectories and pathophysiologic profiles, which could influence treatment efficacy. Subtypes like FTD or Huntington's disease—common in YOD—are unlikely to respond to cholinesterase inhibitors due to differing neurotransmitter involvement. The literature consistently calls for more focused research, including age-stratified clinical trials and pharmacogenomic approaches to personalize care.

CONCLUSION

Donepezil at both 5 mg/day and 10 mg/day provides statistically significant cognitive improvements in young-onset dementia. The 10 mg/day dose demonstrates a larger effect size. Safety profiles mirror those seen in older populations.

The current use of donepezil in YOD, especially in EOAD, reflects clinical necessity rather than robust evidence. Controlled, age-specific studies are urgently needed to assess therapeutic efficacy, safety, and quality-of-life outcomes. Future research should integrate biomarker profiling, neuroimaging, and genetic analysis to refine patient selection and treatment protocols. Donepezil's efficacy in YOD parallels other AChE inhibitors but with superior tolerability. Memantine adjunct yields further cognitive benefit.

Recommendations

1. **Comparator Role:** Use donepezil as standard comparator in YOD intervention trials.
2. **Adjunct Therapy:** Consider memantine addition in moderate/ severe YOD.
3. **Future Research:** Direct head-to-head RCTs in YOD subpopulations; long-term functional outcomes.

Limitations

- Sparse YOD-specific head-to-head data
- Heterogeneity in trial durations and severity
- Indirect comparisons assume transitivity

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