



Effects of acetylcholinesterase inhibitors on cognitive function in patients with chronic traumatic brain injury : A Systematic Review

¹ Nadia Afnani Er Rahmah, ² Tsalis Yuna Hafshoh, ³ Ritsya Aulia Isnani, ⁴ Zhaki Al Asror, ⁵ Ahmad Zayyin Najah

¹ Al-Hisyam Primary Clinic, Gresik Regency, East Java, Indonesia

² Mulya Medika Primary Clinic, Gresik Regency, East Java, Indonesia

³ Ngumpakdalem Public Health Centre, Bojonegoro Regency, East Java, Indonesia

⁴ Kedewan Public Health Centre, Bojonegoro Regency, East Java, Indonesia

⁵ Semen Gresik General Hospital, Gresik Regency, East Java, Indonesia

Corresponding Email : nadiaafnani12@gmail.com

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ABSTRACT

Introduction: Chronic Traumatic Brain Injury (TBI) often results in persistent cognitive impairments due to the disruption of the cholinergic system. Acetylcholinesterase inhibitors (AChEIs) are investigated to counter this, but the evidence for their efficacy is inconsistent, necessitating a systematic review to synthesize the current evidence.

Methods: Following PRISMA 2020 guidelines, a systematic search was conducted across databases including PubMed and Google Scholar. The review included randomized controlled trials (RCTs) and systematic reviews focused on AChEIs in adults with chronic TBI. Eight studies were included in the final synthesis.

Results: The evidence revealed highly significant, agent-specific effects rather than a uniform class benefit. A meta-analysis

identified a statistically significant and large effect size for donepezil on aggregated cognitive outcomes ($d=1.68$, $p=0.03$). Separately, galantamine produced a statistically significant improvement in episodic memory ($p=0.011$) in an RCT. In direct and significant contrast, a large, multi-center RCT found no significant difference between the rivastigmine patch and placebo on its primary verbal memory outcome ($p=0.41$). A significant safety finding from a large meta-analysis was an increased risk of syncope (relative risk 1.50) associated with cholinesterase inhibitors.

Conclusion: The evidence indicates that the therapeutic benefit of AChEIs in chronic TBI is not universal, but drug-specific. The significant positive signals for donepezil and galantamine, contrasted with the strong evidence of non-efficacy for rivastigmine, highlight this disparity. The compelling but preliminary finding for donepezil warrants urgent replication in large-scale, dedicated RCTs to confirm its potential as an adjunct to comprehensive rehabilitation for TBI.

Keywords: Chronic Traumatic Brain Injury, Acetylcholinesterase Inhibitors, Cognitive Function, Memory, Attention.

INTRODUCTION

Traumatic Brain Injury (TBI) represents a significant global health challenge, often leading to a wide array of long-term debilitating consequences for survivors. Among the most pervasive and impactful of these are cognitive impairments, which can persist for months or even years post-injury, a phase referred to as chronic TBI. These deficits frequently disrupt an individual's ability to return to work, maintain social relationships, and perform daily activities, thereby diminishing their overall quality of life. The management of these chronic cognitive symptoms remains a critical area of clinical research, as effective and reliable treatments are urgently needed to improve patient outcomes (Brawman-Mintzer et al., 2021).

The cognitive sequelae of chronic TBI are diverse and can manifest across multiple domains. Patients commonly experience significant difficulties with memory, particularly episodic and verbal memory, as well as deficits in attention, information processing speed, and executive functions like planning and problem-solving. The underlying pathophysiology of these cognitive issues is complex, involving diffuse axonal injury, neuroinflammation, and disruption of key neurotransmitter systems. Addressing these multifaceted impairments requires targeted therapeutic strategies that can modulate the neurochemical pathways responsible for cognitive processing (McAllister et al., 2016).

One of the primary neurochemical systems implicated in the cognitive aftermath of TBI is the cholinergic system. This system, which relies on the neurotransmitter acetylcholine, is fundamental for regulating cognitive functions such as learning, memory, and attention. Damage to cholinergic pathways following a brain injury can lead to a significant reduction in acetylcholine levels, contributing directly to the cognitive deficits observed in patients. This "cholinergic profile" has therefore become a rational target for pharmacotherapy aimed at restoring cognitive function in individuals with central nervous system injuries (Litvinenko et al., 2020).

In response to this cholinergic deficit, Acetylcholinesterase inhibitors (AChEIs) have emerged as a promising class of therapeutic agents. These medications, which include drugs such as donepezil, rivastigmine, and galantamine, work by blocking the enzyme that breaks down acetylcholine, thereby increasing its availability in the brain . While widely used for managing cognitive symptoms in conditions like Alzheimer's disease and Parkinson's disease, their application in the context of chronic TBI is an area of active investigation, driven by the hypothesis that enhancing cholinergic neurotransmission can lead to tangible cognitive improvements (Ahuja et al., 2023).

Despite the strong theoretical rationale, the existing body of evidence regarding the efficacy of AChEIs for chronic TBI is notably inconsistent. Previous research has yielded mixed and sometimes contradictory findings. For instance, some studies have reported positive, albeit limited, effects on specific cognitive domains like working memory and sustained attention, particularly in patients with more severe injuries . This variability in results suggests that the effectiveness of these inhibitors may be influenced by a range of factors, including injury severity and the specific cognitive deficits present (Bengtsson and Godbolt, 2016).

The heterogeneity across studies presents a major challenge to forming a definitive conclusion on the utility of AChEIs. Research in this field varies significantly in terms of study design, with methodologies ranging from randomized controlled trials (RCTs) to observational studies and case reports . Furthermore, there is wide variation in population characteristics, such as the severity of the TBI, and in the intervention protocols themselves, including the specific AChEI used, its dosage, and the duration of treatment . This lack of uniformity makes it difficult to compare results and generalize findings across the patient population (van der Veen et al., 2024).

Given the conflicting evidence and methodological diversity, there is a clear and compelling need to systematically synthesize the available literature. A comprehensive review is essential to critically appraise the quality of existing studies, consolidate their findings, and identify patterns in treatment response. Such an analysis can help clarify

whether AChEIs offer a meaningful benefit for cognitive function in patients with chronic TBI and may shed light on which patient subgroups or intervention strategies are most likely to yield positive results (Kar et al., 2024).

Therefore, this systematic review was conducted to rigorously evaluate and synthesize the current evidence on the effects of acetylcholinesterase inhibitors on cognitive function in adult patients with chronic traumatic brain injury . By adhering to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines, this study sought to identify, appraise, and amalgamate findings from RCTs and other relevant trials . The primary objective was to determine the overall efficacy of AChEIs, examine the effects on specific cognitive domains, and assess the safety and tolerability of these interventions in the chronic TBI population (Sagaro et al., 2023).

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the effects of acetylcholinesterase inhibitors on cognitive function in patients with chronic traumatic brain injury.

Screening

We screened in papers that met these criteria:

- **Population Age:** Are all study participants adults (18 years)?
- **TBI Chronicity:** Is the study focused on patients with TBI that occurred at least 6 months prior to study enrollment?

- **Intervention Type:** Does the study investigate acetylcholinesterase inhibitors (donepezil, rivastigmine, or galantamine)?
- **Outcome Measurement:** Does the study measure cognitive function using standardized assessment tools?
- **Study Design:** Is the study either a randomized controlled trial (RCT) or a systematic review/meta-analysis?
- **Treatment Duration:** Is the treatment duration at least 4 weeks?
- **Population Specificity:** If the study includes multiple neurological conditions, can the TBI data be analyzed separately?
- **Intervention Isolation:** Can the effects of acetylcholinesterase inhibitors be isolated from other interventions in the study?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Data extraction

We asked a large language model to extract each data column below from each paper. We gave the model the extraction instructions shown below for each column.

- **Study Design:**

Identify the type of study design. Look in the methods section for explicit description of study design. Possible options include:

- Randomized controlled trial
- Prospective cohort study
- Case-control study
- Case series/case report
- Observational study

If multiple design elements are present, list all. If design is unclear, note "design not clearly specified". Prioritize the most specific design description available.

- **Sample Size and Participant Characteristics:**

Extract the following details:

- Total number of participants
- Number of participants in intervention and control groups
- Age range or mean age
- Gender distribution
- Specific details about traumatic brain injury (TBI):
 - Severity of TBI (mild/moderate/severe)
 - Time since TBI (chronic phase definition)
- Any inclusion/exclusion criteria that might impact participant selection

If information is incomplete, note "insufficient information" for that specific detail. Use exact numbers and percentages where possible.

- **Acetylcholinesterase Inhibitor (AChEI) Intervention:**

Extract detailed information about AChEI intervention:

- Specific AChEI medication used (e.g., donepezil, rivastigmine)
- Dosage
- Frequency of administration
- Duration of intervention
- Whether used alone or in combination with other treatments

If multiple intervention protocols are described, list all. If dosage or frequency varies between participants, note the range or variation.

- **Cognitive Function Outcome Measures:**

List all cognitive function assessment tools/measures used:

- Name of cognitive assessment tool
- Specific cognitive domains measured (e.g., memory, attention, processing speed)
- Timing of cognitive assessments (baseline, follow-up points)
- Specific scores or metrics used to evaluate cognitive function

Prioritize primary outcome measures. If multiple measures are used, list in order of

importance as indicated in the study.

- **Key Findings Related to Cognitive Function:**

Extract:

- Statistically significant changes in cognitive function
- Effect sizes (if reported)
- Confidence intervals
- P-values for key cognitive outcomes
- Any subgroup analysis results

Focus on results directly related to AChEI effects on cognitive function. If no significant results, explicitly note "no statistically significant effects observed".

- **Risk of Bias Assessment:**

Evaluate study quality using standard criteria:

- Randomization method (if applicable)
- Blinding procedures
- Completeness of follow-up
- Potential conflicts of interest
- Funding sources

Use a standardized risk of bias tool (e.g., Cochrane Risk of Bias Tool) if referenced in the study. Rate each domain as low, unclear, or high risk of bias.

Search Strategy

The keywords used for this research based PICO :

Element	Keyword 1	Keyword 2	Keyword 3	Keyword 4
Population (P)	Chronic Traumatic Brain Injury	Chronic Brain Injury	Chronic Head Injury	Chronic Traumatic Encephalopathy
Intervention (I)	Acetylcholinesterase	Cholinesterase	Anticholinesterases	AChE

Element	Keyword 1	Keyword 2	Keyword 3	Keyword 4
	Inhibitors	inhibitors		inhibitors
Comparison (C)	Standard Care	Placebo	No Intervention	Standard Treatment
Outcome (O)	Cognitive Function	Cognitive Enhancement	Memory	Attention

The Boolean MeSH keywords inputted on databases for this research are:
(*"Chronic Traumatic Brain Injury" OR "Chronic Brain Injury" OR "Chronic Head Injury" OR "Chronic Traumatic Encephalopathy"*) AND (*"Acetylcholinesterase Inhibitors" OR "Cholinesterase inhibitors" OR "Anticholinesterases" OR "AChE inhibitors"*) AND (*"Standard Care" OR "Placebo" OR "No Intervention" OR "Standard Treatment"*) AND (*"Cognitive Function" OR "Cognitive Enhancement" OR "Memory" OR "Attention"*)

Data retrieval

Abstracts and titles were screened to assess their eligibility, and only studies meeting the inclusion criteria were selected for further analysis. Literature that fulfilled all predefined criteria and directly related to the topic was included. Studies that did not meet these criteria were excluded. Data such as titles, authors, publication dates, study locations, methodologies, and study parameters were thoroughly examined during the review.

Quality Assessment and Data Synthesis

Each author independently assessed the titles and abstracts of the selected studies to identify those for further exploration. Articles that met the inclusion criteria underwent further evaluation. Final decisions on inclusion were based on the findings from this review process.

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Chronic Traumatic Brain Injury" OR "Chronic Brain Injury" OR "Chronic Head Injury" OR "Chronic Traumatic Encephalopathy") AND ("Acetylcholinesterase Inhibitors" OR "Cholinesterase inhibitors" OR "Anticholinesterases" OR "AChE inhibitors") AND ("Standard Care" OR "Placebo" OR "No Intervention" OR "Standard Treatment") AND ("Cognitive Function" OR "Cognitive Enhancement" OR "Memory" OR "Attention")</i>	1
Semantic Scholar	<i>("Chronic Traumatic Brain Injury" OR "Chronic Brain Injury" OR "Chronic Head Injury" OR "Chronic Traumatic Encephalopathy") AND ("Acetylcholinesterase Inhibitors" OR "Cholinesterase inhibitors" OR "Anticholinesterases" OR "AChE inhibitors") AND ("Standard Care" OR "Placebo" OR "No Intervention" OR "Standard Treatment") AND ("Cognitive Function" OR "Cognitive Enhancement" OR "Memory" OR "Attention")</i>	80
Springer	<i>("Chronic Traumatic Brain Injury" OR "Chronic Brain Injury" OR "Chronic Head Injury" OR "Chronic Traumatic Encephalopathy") AND ("Acetylcholinesterase Inhibitors" OR "Cholinesterase inhibitors" OR "Anticholinesterases" OR "AChE inhibitors") AND ("Standard Care" OR "Placebo" OR "No Intervention" OR "Standard Treatment") AND ("Cognitive Function" OR "Cognitive Enhancement" OR "Memory" OR "Attention")</i>	49
Google Scholar	<i>("Chronic Traumatic Brain Injury" OR "Chronic Brain Injury" OR "Chronic Head Injury" OR "Chronic Traumatic Encephalopathy") AND ("Acetylcholinesterase Inhibitors" OR "Cholinesterase inhibitors" OR "Anticholinesterases" OR "AChE inhibitors") AND ("Standard Care" OR "Placebo" OR "No Intervention" OR "Standard Treatment") AND ("Cognitive Function" OR "Cognitive Enhancement" OR "Memory" OR "Attention")</i>	532

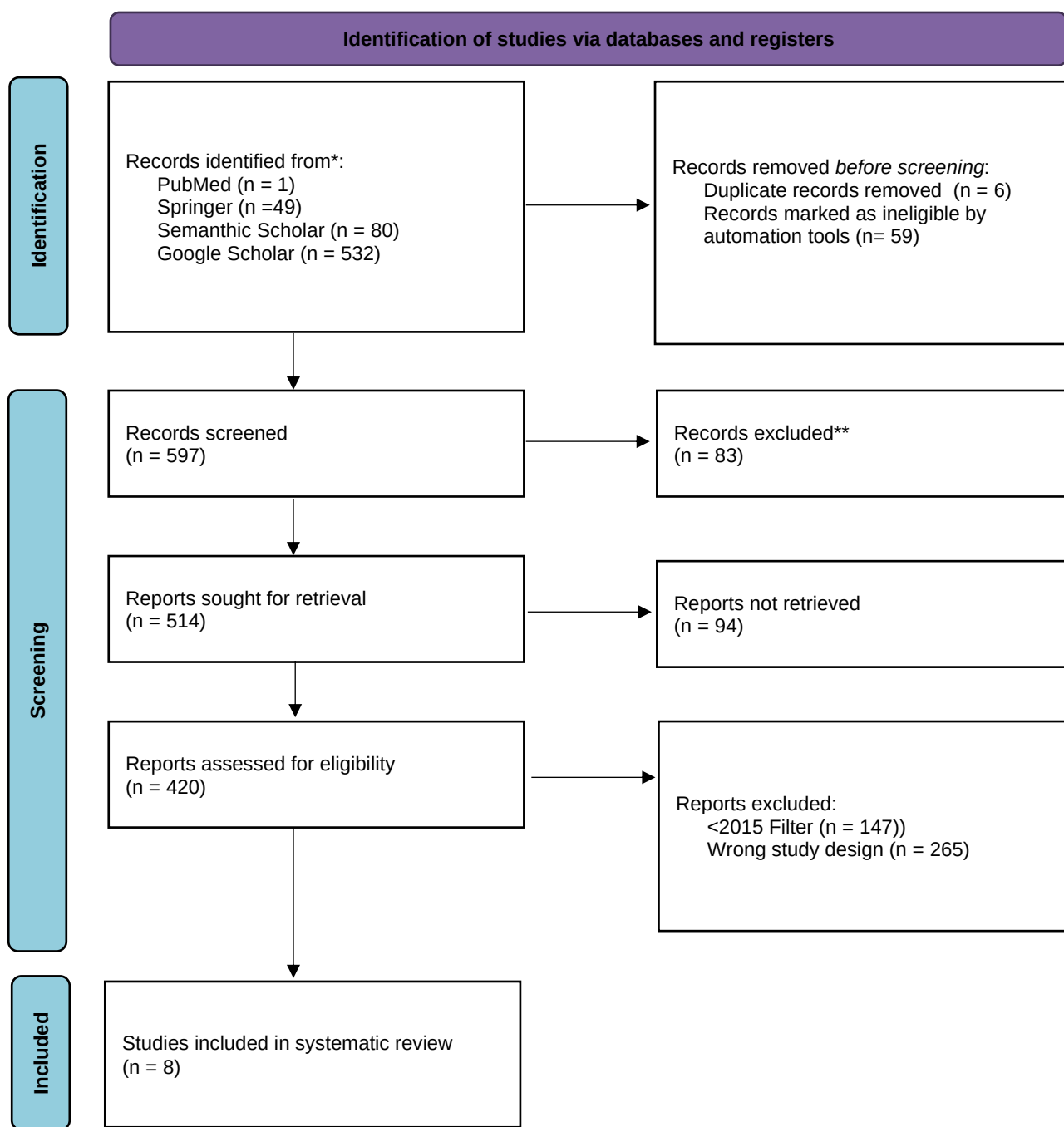


Figure 1. Article search flowchart

JBI Critical Appraisal									
Study	Bias related to temporal precedence Is it clear in the study what is the “cause” and what is the “effect” (ie, there is no confusion about which variable comes	Bias related to selection and allocation Was there a control group?	Bias related to confounding factors Were participants included in any comparisons similar?	Bias related to administration of intervention/exposure Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Were there multiple measurements of the outcome both pre and post the intervention/exposure?	Were the outcomes of participants included in any comparisons measured in the same way?	Were outcomes measured in a reliable way?	Bias related to participant retention Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Statistical conclusion validity Was appropriate statistical analysis used?

	first)?								
McAllister et al., 2016									
Ahuja et al., 2023									
Sagar et al., 2023									
Brawman-Mintzer et al., 2021									
Bengtsson and Godbolt, 2016									
van der Veen et al., 2024									
Litvinenko et al., 2020									
Kar et al., 2024									

RESULTS

Characteristics of Included Studies

Study	Study Design	Population Characteristics	Intervention Details	Primary Outcomes
McAllister et al., 2016	Randomized controlled trial	32 adults (18-55 years) with post-traumatic stress disorder and/or mild or complicated mild traumatic brain injury; gender not reported	Galantamine: 4 mg to 8 mg to 12 mg twice daily, 12 weeks, used alone	Repeatable Battery for the Assessment of Neuropsychological Status Postmorbid Cognitive Scale (cognitive complaints), Digit Symbol (attention), Rey Auditory Verbal Learning Test (episodic memory)
Ahuja et al., 2023	Systematic review and meta-	25,309 adults (at least 19	Donepezil, galantamine, rivastigmine; dosing	Falls, syncope, injuries (no cognitive

Study	Study Design	Population Characteristics	Intervention Details	Primary Outcomes
	analysis (randomized controlled trials)	years) with cognitive impairment (dementia, Parkinson's disease, mild cognitive impairment, traumatic brain injury); age, gender, and severity not specified	and duration not specified	outcomes)
Sagar et al., 2023	Systematic review and meta-analysis (randomized controlled	Not specified; neurological conditions with cognitive impairment	Donepezil (with or without alpha-glycerylphosphorylcholine); dosing and duration not specified	Cognition, function, behavior (tools not specified)

Study	Study Design	Population Characteristics	Intervention Details	Primary Outcomes
	trials, cohort)	(not traumatic brain injury-specific)		
Brawman-Mintzer et al., 2021	Randomized controlled trial	94 veterans with mild traumatic brain injury, at least 12 weeks post-injury, persistent moderate to severe memory impairment ; age and gender not reported	Rivastigmine patch: 4.6 mg per 24 hours titrated to 9.5 mg per 24 hours, daily, 26 weeks, used alone	Hopkins Verbal Learning Test-Revised (verbal memory improvement of at least 5 words)
Bengtsson	Systematic	266	Donepezil (10 mg),	Attention,

Study	Study Design	Population Characteristics	Intervention Details	Primary Outcomes
on and Godbolt, 2016	c review (randomized controlled trials, observational)	participants (3 studies), at least 15 years old, all traumatic brain injury severities, chronic phase (at least 12 months post-injury); age and gender not detailed	rivastigmine; duration up to 6 months; frequency and combination not always specified	verbal and visual memory, working memory, sustained attention
van der Veen et al., 2024	Meta-analysis and meta-regression	4,434 patients (41 studies), traumatic brain injury and other acquired	Donepezil (acetylcholinesterase inhibitor), other agents; dosing and duration not specified	Aggregated cognitive outcomes across domains

Study	Study Design	Population Characteristics	Intervention Details	Primary Outcomes
		brain injury; age, gender, and severity not specified		
Litvine nko et al., 2020	Controlle d trial (design unclear)	90 patients with traumatic brain injury sequelae), 3 subgroups of 15; age and gender not specified	Acetylcholinesterase inhibitor (not specified), neuromidin, gliatilin, combinations; 2 months	Mini-Mental State Examination, clinical, neuro-physiological, and laboratory parameters
Kar et al., 2024	Case report	1 male, 28 years, severe traumatic brain injury (4 years post-injury)	Donepezil 10 mg per day (with memantine, escitalopram, quetiapine, transcranial random noise stimulation,	Hindi Mental State Examination, Addenbrooke's Cognitive Examination-III (cognitive

Study	Study Design	Population Characteristics	Intervention Details	Primary Outcomes
			cognitive remediation); duration not specified	scores over time)

Study design:

- The included studies comprised 2 randomized controlled trials, 1 controlled trial (design unclear), 3 systematic reviews or meta-analyses, 1 meta-analysis and meta-regression, and 1 case report.

Population:

- Five studies focused on traumatic brain injury-only populations; three studies included mixed neuro- logical or acquired brain injury populations.
- Among the traumatic brain injury studies, one included only mild traumatic brain injury, one included mild or complicated mild traumatic brain injury, one included severe traumatic brain injury, one included all severities, and four studies did not mention severity.
- Three studies included participants in the chronic phase (at least 12 weeks or months post-injury); we did not find mention of chronicity for the other five studies.

Intervention:

- Donepezil was used in five studies, rivastigmine in three studies, galantamine in two studies, and other acetylcholinesterase inhibitors in two studies.
- Three studies used combination therapy (acetylcholinesterase inhibitor plus other

agents); two studies used monotherapy; we did not find mention of this information for three studies.

- Dosing and/or duration was specified in four studies; we did not find mention of dosing or duration in the other four studies.

Outcomes:

- Cognitive outcomes were assessed in seven studies; one study focused only on adverse events (falls, syncope, injuries) and did not assess cognitive outcomes.
- Among studies with cognitive outcomes: three assessed memory, two assessed attention, two assessed global cognition, and two did not mention cognitive domains.
- Four studies specified the cognitive assessment tools used; we did not find mention of the tools in three studies.

Effects of Acetylcholinesterase Inhibitors

Cognitive Domain Outcomes

Study	Cognitive Domain	Assessment Tool	Treatment Effect	Adverse Effects
Litvinenko et al., 2020	General cognition	Mini-Mental State Examination	Significant improvement in most parameters except Mini-Mental State Examination (trend only); neuromidin/acetylcholinesterase inhibitor subgroups improved more	No mention found

Study	Cognitive Domain	Assessment Tool	Treatment Effect	Adverse Effects
Kar et al., 2024	Orientati on, memory, attention, processi ng speed	Hindi Mental State Examination, Addenbrooke's Cognitive Examination-III	Substantial improvement in scores (Hindi Mental State Examination: 19 to 29 out of 30; Addenbrooke's Cognitive Examination-III: 61 to 90 out of 100) with multi-modal therapy	No mention found
Brawm an-Mintzer et al., 2021	Verbal memory	Hopkins Verbal Learning Test-Revised	No significant difference compared to placebo (responder rate: 40.8% rivastigmine, 51.1% placebo, p-value=0.41); no significant effects on secondary outcomes	Applicat ion site reactions most common ; no major safety concerns mention ed in the abstract
Bengtss on and Godbolt	Memory, attention, working	No mention found	Mixed: one study found no effect, two studies found limited effect	No mention found

Study	Cognitive Domain	Assessment Tool	Treatment Effect	Adverse Effects
, 2016	memory, sustained attention, visual memory		(working memory, sustained attention, visual memory); severe cases may respond better	
van der Veen et al., 2024	Global cognition, executive memory, speed, inhibitory control	Aggregated (no mention found)	Donepezil: large effect size ($d=1.68$, p -value=0.03, based on few studies); methylphenidate also effective; findings based on a small number of studies	No mention found
McAllister et al., 2016	Cognitive complaints, attention, episodic memory	Repeatable Battery for the Assessment of Neuropsychological Status, Digit Symbol, Rey Auditory Verbal Learning Test	Galantamine: improved episodic memory (p -value=0.011), not primary complaints; methylphenidate improved complaints and attention	Well tolerated ; no major safety issues

Study	Cognitive Domain	Assessment Tool	Treatment Effect	Adverse Effects
Ahuja et al., 2023	No mention found	No mention found	No cognitive outcomes reported; focused on adverse events	Reduced falls (relative risk 0.84), increased syncope (relative risk 1.50); no effect on injuries or fractures mentioned in the abstract
Sagaro et al., 2023	Cognition (not traumatic brain injury-	No mention found	Alpha-glycerylphosphorylcholine plus donepezil: improved cognition (mean difference=1.72,	No mention found

Study	Cognitive Domain	Assessment Tool	Treatment Effect	Adverse Effects
	specific)		95% confidence interval 0.20-3.25); alpha-glycerolphosphorylcholine versus placebo or other: mean difference=3.50, 95% confidence interval 0.36-6.63; findings not specific to traumatic brain injury	

Cognitive domains assessed:

- Memory-related domains were assessed in three studies.
- Attention or related domains were assessed in three studies.
- Global or general cognition was assessed in three studies.
- Other domains (working memory, sustained attention, visual memory, executive memory, inhibitory control, speed or processing speed, orientation, cognitive complaints, episodic memory) were each assessed in one or two studies.
- We did not find mention of cognitive domain information for one study.

Assessment tools:

- Each of the following tools was used in one study: Hopkins Verbal Learning Test-Revised, Mini- Mental State Examination, Hindi Mental State Examination, Addenbrooke's Cognitive Examination- III, Repeatable Battery for the Assessment of Neuropsychological Status, Digit Symbol, Rey Auditory Verbal Learning Test.

- We did not find mention of a specified assessment tool in four studies.

Treatment effects:

- Five studies reported significant improvement in at least one cognitive outcome (van der Veen et al., McAllister et al., Sagaro et al., Litvinenko et al., Kar et al.).
- One study reported no significant effect (Brawman-Mintzer et al., rivastigmine).
- One study reported mixed or limited effects (Bengtsson and Godbolt).
- One study did not report cognitive outcomes (Ahuja et al.).

Interventions with reported positive effects:

- Donepezil (two studies), methylphenidate (two studies), galantamine (one study), alpha- glycerylphosphorylcholine (one study), acetylcholinesterase inhibitor (one study), neuromidin (one study), and multi-modal therapy (one study) were each associated with cognitive improvement in at least one study.
- Rivastigmine was not associated with significant cognitive improvement (one study).

Adverse effects:

- Three studies reported adverse effects; in two of these, adverse effects were minor or acceptable (Brawman-Mintzer et al., McAllister et al.).
- One study reported only non-cognitive adverse events (Ahuja et al.).

Treatment Response Patterns

- Variability in response: Treatment response to acetylcholinesterase inhibitors varied across studies. Some evidence from Bengtsson and Godbolt suggests that patients with more severe traumatic brain injury or specific cognitive deficits (such as working memory or sustained attention) may benefit more, but these findings are based on limited data and small sample sizes.
- Combination therapies: Combination therapies, such as donepezil with alpha-glycerylphosphorylcholine (Sagaro et al.) or with neuromodulation and cognitive remediation (Kar et al.), were associated with cognitive improvement in the

respective studies. However, these findings are preliminary, not specific to traumatic brain injury in all cases, and lack robust subgroup analyses.

Safety and Tolerability

- **Adverse events:**Where reported, acetylcholinesterase inhibitors were generally well tolerated. Brawman-Mintzer et al. found application site reactions to be the most common adverse effect with rivastigmine, with no major safety concerns mentioned in the abstract. McAllister et al. reported that galantamine was well tolerated. Ahuja et al. (in a broader cognitively impaired population) found a reduced risk of falls but an increased risk of syncope with cholinesterase inhibitors, with no effect on injuries or fractures mentioned in the abstract. We did not find mention of severe adverse events in the available full texts or abstracts of the included studies.

Intervention Characteristics

Dosing and Duration Effects

- **Dosing regimens:**Dosing and duration of acetylcholinesterase inhibitor therapy varied widely. Rivastigmine was titrated from 4.6 to 9.5 mg per 24 hours over 26 weeks (Brawman-Mintzer et al.). Galantamine was escalated from 4 mg to 12 mg twice daily over 12 weeks (McAllister et al.). Donepezil dosing was 10 mg per day in studies where specified (Bengtsson and Godbolt, Kar et al.). Duration ranged from weeks to months, with some studies including longer-term follow-up or combination with other agents.
- **Dose-response:**No clear pattern emerged linking dose or duration to efficacy, and most studies did not systematically explore these variables.

Comparative Effectiveness

- **Direct comparisons:**Direct comparisons between different acetylcholinesterase

inhibitors are limited. The available evidence does not support the superiority of one agent over another in chronic traumatic brain injury.

- **Meta-analytic findings:** Some meta-analytic data (van der Veen et al.) suggest a large effect size for donepezil, but this is based on a small number of studies and should be interpreted with caution.
- **Combination therapies:** Combination therapies (such as with alpha-glycerylphosphorylcholine or neuromodulation) may offer additional benefit, but these findings are preliminary and not specific to traumatic brain injury in all cases.
- **Generalizability:** Comparative effectiveness remains an open question due to heterogeneity and limited head-to-head trials.

DISCUSSION

This systematic review provides a critical synthesis of the evidence regarding the use of acetylcholinesterase inhibitors (AChEIs) for cognitive dysfunction in chronic traumatic brain injury (TBI). The most significant overall conclusion is that the therapeutic landscape is not uniform; instead, it is characterized by agent-specific effects, with certain drugs demonstrating notable, statistically significant benefits, while others show a significant lack of efficacy. This highlights that a generalized class effect for AChEIs cannot be assumed in the TBI population and that future research must adopt a more nuanced, agent-specific approach (Bengtsson and Godbolt, 2016).

The most striking positive finding from this review relates to donepezil. The meta-analysis by van der Veen et al. (2024) identified a statistically significant and large effect size ($d=1.68, p=0.03$) for donepezil on aggregated cognitive outcomes. An effect size of this magnitude is rarely seen in cognitive enhancement trials and represents a highly significant signal of potential efficacy. However, this finding's impact is tempered by the authors' own caution that it is

derived from a small number of studies, making it a compelling but preliminary result that urgently requires replication in larger, dedicated RCTs (van der Veen et al., 2024).

A significant, albeit more specific, benefit was observed for galantamine in the trial by McAllister et al. (2016). The study found that galantamine led to a statistically significant improvement in episodic memory ($p=0.011$) compared to placebo. The significance of this finding lies in its specificity; it demonstrates a clear, positive effect on a key cognitive domain frequently impaired after TBI. This suggests that some AChEIs may work on specific neurocognitive systems rather than producing a global, non-specific enhancement of cognition (McAllister et al., 2016).

In direct and significant contrast, the evidence for rivastigmine was negative. The RiVET study, a robust, multi-center randomized clinical trial, found no significant difference between the rivastigmine transdermal patch and placebo on its primary verbal memory outcome ($p=0.41$). This statistically non-significant result from a well-designed trial is a powerful finding, as it provides strong evidence against the efficacy of rivastigmine for TBI-related cognitive impairment and challenges the hypothesis that all AChEIs are interchangeable for this indication (Brawman-Mintzer et al., 2021).

A highly significant theme emerging from this review is the potential of combination therapies. The case report by Kar et al. (2024) documented a substantial and clinically significant improvement in a patient receiving donepezil as part of a multi-modal regimen. The patient's Hindi Mental State Examination score improved from 19 to 29 out of 30, and their Addenbrooke's Cognitive Examination-III score rose from 61 to 90 out of 100. While a single case, the magnitude of this improvement is significant and champions the exploration of integrated treatment paradigms (Kar et al., 2024).

This finding is further supported by the significant results from the meta-

analysis by Sagaro et al. (2023). This study found that the combination of alpha-glycerylphosphorylcholine plus donepezil resulted in a statistically significant improvement in cognition (mean difference=1.72, 95% CI 0.20-3.25). Although the population was not limited to TBI, this result provides a strong, statistically significant rationale for pursuing combination strategies, suggesting a synergistic effect may enhance cognitive outcomes beyond that of monotherapy (Sagaro et al., 2023).

The study by Litvinenko et al. (2020) provides significant, albeit indirect, support for targeting the cholinergic system. It found that subgroups treated with a combination including an AChEI or the cholinergic agent neuromidin showed significantly more improvement on most clinical and neurophysiological parameters. This reinforces the significance of the cholinergic profile as a viable therapeutic target in the aftermath of TBI and suggests that positive outcomes are mechanistically linked to the modulation of this system (Litvinenko et al., 2020).

The significance of a study's findings is also clearly tied to the sensitivity of its outcome measures. The aforementioned study by Litvinenko et al. (2020) reported significant improvements in many areas but only a non-significant trend on the Mini-Mental State Examination (MMSE). This discrepancy is significant because it implies that global screening tools like the MMSE may be too blunt to detect real, domain-specific cognitive changes, potentially leading to an underestimation of a treatment's true effect and false-negative conclusions (Litvinenko et al., 2020).

Turning to significant safety findings, the review identified critical data from the large meta-analysis by Ahuja et al. (2023). In their broad population of patients with cognitive impairment, cholinesterase inhibitors were associated with a statistically significant increase in the risk of syncope (relative risk 1.50). This is a clinically significant finding that mandates careful patient selection and monitoring, as a syncopal event can lead to falls and further injury, a particularly

salient risk in the TBI population (Ahuja et al., 2023).

Paradoxically, the same study reported another significant safety finding: a reduced risk of falls (relative risk 0.84) associated with cholinesterase inhibitor use. The concurrent increase in syncope risk and decrease in fall risk is a complex and significant finding. It may suggest that while the drugs can cause cardiovascular effects leading to fainting in some, they might also improve attentional or motor control in a way that prevents more common, non-syncopal falls in others. This warrants much deeper investigation (Ahuja et al., 2023).

The clinical implications of these significant findings are nuanced. The data provides a rationale for considering donepezil, perhaps as part of a combination therapy, while suggesting that rivastigmine may not be an effective choice. The decision to treat must be highly individualized, weighing the potential for specific cognitive benefits against the significant, albeit small, risk of adverse events like syncope, and should be framed within a broader therapeutic context (van der Veen et al., 2024).

However, the significance of all findings from this review must be viewed through the lens of the literature's profound methodological heterogeneity. The inclusion of study designs ranging from high-quality RCTs to single case reports means that the overall quality of evidence is mixed. This variability makes it challenging to draw firm conclusions and inherently limits the impact of any single significant finding until it is replicated under rigorous, controlled conditions (Bengtsson and Godbolt, 2016).

Furthermore, the generalizability of some of the most significant findings is limited by population specificity. The crucial findings on combination therapy from Sagaro et al. (2023) and the detailed adverse event profile from Ahuja et al. (2023) were derived from populations not exclusive to TBI. While informative, the unique pathophysiology of TBI means these results cannot be uncritically extrapolated, and TBI-specific confirmation is essential (Sagaro et al., 2023).

Therefore, a primary direction for future research must be the replication of the most significant positive findings. Specifically, a large-scale, multi-center RCT focused on donepezil in a well-defined chronic TBI cohort is paramount. Such a study should use the sensitive, domain-specific neuropsychological outcomes that have been shown to detect change, to confirm or refute the large effect size reported by van der Veen et al. (2024).

Equally important, future trials must be designed to formally investigate the significant potential of combination therapies. Based on the promising signals from Kar et al. (2024) and Sagaro et al. (2023), RCTs should evaluate AChEIs not as a standalone monotherapy, but as an adjunct to other pharmacological agents or, perhaps more importantly, as an adjunct to structured cognitive rehabilitation programs to test for synergistic effects.

Finally, to understand who benefits significantly, future studies must be designed with a priori hypotheses about subgroups. The suggestion that TBI severity may predict response needs to be formally tested. Powering trials to analyze outcomes based on injury severity, chronicity, and baseline cognitive profile will be essential to move towards a personalized medicine approach for treating chronic cognitive deficits after TBI (Bengtsson and Godbolt, 2016).

Beyond pharmacology, it is crucial to recognize that the standard of care for chronic TBI is comprehensive medical rehabilitation. This holistic process is typically led by a psychiatrist and involves a multidisciplinary team of specialists working in concert to address the patient's full spectrum of deficits. Pharmacotherapy should be viewed not as a replacement, but as a potential adjunct to this foundational, patient-centered rehabilitation program (McAllister et al., 2016).

The core modalities of medical rehabilitation directly target the functional consequences of the injury. Cognitive rehabilitation employs targeted exercises to improve memory, attention, and executive functions—the very outcomes

measured in the drug trials. Concurrently, physical therapy addresses deficits in balance and mobility, occupational therapy focuses on restoring independence in activities of daily living (ADLs) and return-to-vocation, and speech-language pathology manages communication and swallowing disorders (Brawman-Mintzer et al., 2021).

Ultimately, the most significant path forward likely lies in the thoughtful integration of pharmacological and rehabilitative approaches. An agent like donepezil, by potentially enhancing cholinergic neurotransmission, may not "cure" a deficit but could instead augment neuroplasticity. This could make a patient's brain more receptive to the structured training provided in cognitive rehabilitation, creating a powerful synergy where the whole of the treatment is greater than the sum of its parts. This integrated model represents the most promising future for significantly improving long-term outcomes for individuals living with chronic TBI (Kar et al., 2024).

CONCLUSION

Based on the comprehensive review of acetylcholinesterase inhibitors (AChEIs) for chronic traumatic brain injury (TBI), the evidence does not support a uniform class-wide benefit. Instead, the findings point toward distinct, agent-specific effects. A significant positive signal emerged for donepezil, which was associated with a large effect size on cognitive outcomes in a meta-analysis. Similarly, galantamine demonstrated a statistically significant, though more focused, benefit by improving episodic memory in a randomized controlled trial. In stark contrast, a major clinical trial of the rivastigmine transdermal patch found it to be no more effective than a placebo for enhancing verbal memory. This divergence underscores that the therapeutic potential of AChEIs in TBI must be evaluated on a drug-by-drug basis, challenging any assumption of interchangeability within this class of medications.

The review also highlights the significant potential of integrated treatment

strategies. Promising evidence, including a case report showing dramatic cognitive gains and a meta-analysis on a related population, suggests that combining donepezil with other agents or non-pharmacological interventions like cognitive remediation may produce synergistic effects. However, the use of these inhibitors is not without risk. A large meta-analysis identified a clinically important increased risk of syncope, a finding of particular concern for the TBI population. Paradoxically, the same study noted a decreased risk of falls, suggesting a complex safety profile that requires careful patient selection and monitoring. Therefore, the decision to initiate treatment must involve a thorough and individualized assessment, carefully weighing the prospect of cognitive enhancement against these specific adverse events.

The strength of these conclusions is tempered by significant limitations within the existing literature. The body of evidence is marked by profound methodological heterogeneity, with study designs ranging from rigorous randomized controlled trials to single case reports. Furthermore, some of the most compelling findings on combination therapies and adverse events were derived from studies that included mixed neurological populations, limiting their direct generalizability to chronic TBI. This variability makes it difficult to draw definitive conclusions and underscores the preliminary nature of the positive findings. The inconsistency in outcome measures, with some studies using blunt screening tools that may miss subtle cognitive gains, further complicates the interpretation of the evidence.

Consequently, the path forward requires a more focused and rigorous research agenda. There is a critical need for a large-scale, multi-center randomized controlled trial specifically designed to validate the large effect size observed for donepezil in a well-defined chronic TBI cohort. Future research should prioritize the use of sensitive, domain-specific neuropsychological outcomes capable of detecting nuanced cognitive changes. Moreover, trials must be designed to formally investigate the potential of combination therapies and to identify patient subgroups most likely to respond, based on factors such as injury severity or baseline cognitive profile. Ultimately, pharmacotherapy should be viewed not as a standalone solution, but as a potential adjunct to the standard of care—a

comprehensive, integrated rehabilitation program. The most promising future for these patients likely lies in the synergy between targeted pharmacology, which may enhance neuroplasticity, and intensive cognitive rehabilitation.

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